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Sulfonyl Chloride Resins and Associated Supported Reagents

One volume

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For Sarah, with love.

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ABSTRACT

FACULTY OF SCIENCE

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Sulfonyl Chloride Resins and Associated Supported Reagents

by Robert M. Hughes

The use of sulfonyl chloride resins in organic synthesis and as precursors for supported reagents has been well documented, and has highlighted shortcomings in using currently available commercial resins. The aim of this study has been to investigate the synthesis of novel sulfonyl chloride and sulfonyl containing resins and their uses in synthesis and for supported reagents.

A number of supported reagents have been identified as useful targets. Solid-supported reagents can remove any associated hazards involved in using their solution-phase counterparts. Examples include a supported version of sulfonyl azide, used in diazo-transfer reactions and supported *O*-sulfonyl hydroxylamines as an alternative to reagents such as MSH (Mesitylenesulfonyl hydroxylamine).

Thesis Contents

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A special commendation I save for my family, Richard my brother and Lucy my sister, a great set of siblings and thanks for the support. But special thanks are due to my parents, Kenneth and Christine Hughes, who have been excellent role models to me over the years, offering much support in many ways, I owe you a large debt, I hope you can be proud of my achievements.

Finally, a heartfelt thank you and much love I express to my wife Sarah, someone whom I am proud to be married to. There have been many ups and downs in the last few years and I thank you for your continued support, help and unconditional love. I look forward to a long, happy and fulfilling marriage with you, wherever we end up in the future.

Abbreviations

Ac	Acetyl
AcOH	Acetic acid
Boc	*tert*-butoxycarbonyl
Bu	Butyl
$CDCl_3$	Chloroform-*d*
CI	Chemical ionisation
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DIC	1,3-Diisopropylcarbodiimide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane (Ethylene glycol dimethyl ether)
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DVB	Divinylbenzene
EI	Election-impact ionisation
eq.	Equivalents
ES	Electrospray ionisation
EtOH	Ethanol
EtOAc	Ethyl acetate
Fmoc	9-Fluorenylmethoxycarbonyl
GC	Gas Chromatography
h	Hour/s
HPLC	High pressure liquid chromatography
IR	Infrared
MAS	Magic angle spin probe (NMR)
*m*CPBA	3-Chloroperbenzoic acid
min	Minute/s
Ms	Mesyl (methane sulfonyl)

MSH	*O*-Mesitylenesulfonyl hydroxylamine
o-	ortho
NaHMDS	Sodium hexamethyldisilazane (Sodium bis(trimethylsilyl)amide)
NaOAc	Sodium acetate
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance
Pd/C	Palladium on activated carbon
$Pd(OAc)_2$	Palladium acetate
P-*o*-Tol_3	Tri-*o*-tolylphosphine
PPh_3	Triphenylphosphine
PTSA	*p*-Toluenesulfonic acid
pyr	Pyridine
rt	Room temperature
Tf	Triflate (Trifluoro acetyl)
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMOF	Trimethylorthoformate
TMS	Trimethylsilyl
TMSOK	Potassium trimethylsilanolate
Tol	Tolyl
Ts	Tosyl (*p*-toluenesulfonyl)

Chapter 1. Introduction

The work discussed within this thesis is concerned with the synthesis and use of supported reagents derived from sulfonyl chloride resins. In particular, the synthesis of sulfonyl azide resins that can be used as diazo-transfer reagents and supported *O*-sulfonyl hydroxylamine moieties, which can be used for Beckmann rearrangements with carbonyl substrates.

As an introduction to these respective areas, reviews are given respectively within this chapter of supported reagents and their uses (section 1.1), the synthesis and use of diazo-containing compounds (section 1.2) and the Beckmann rearrangement (section 1.3). Section 1.4 will outline some of the aims and objectives of the research carried out.

1.1 Applications of solid-phase chemistry

1.1.1 Background of solid-phase chemistry

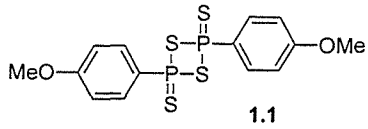
The use of polymeric resins in organic synthesis has been a part of research for decades, ever since work pioneered by Merrifield.[1] However, the early work in this area involved the stepwise assembly of peptides, by sequential reaction with amino acids and oligonucleotides.[2] The advantage of using molecules tethered to a solid-support means that they can be easily removed from any reaction mixture by filtration, and the solution reagents can be used in large excess in order to force reactions to completion.

Despite these advantages, the difficulty in analysing the reaction products on the solid-support means that the optimisation of a reaction on the solid-phase is particularly demanding. As a result, multi-step syntheses on the solid-phase become particularly challenging, and recently alternative methodologies have been developed utilising supported reagents with target molecules in solution.[3] This allows the effective analysis of the target molecule and optimisation of the reaction, using excess reagents (in an ideal situation all by-products and excess reagent remain attached to the solid-phase), and simple purification by filtration.

A flavour of the chemistries possible using solid-supported reagents is outlined below. However, given the extensive variety of reagents available commercially, the discussion has been limited to a number of interesting examples to illustrate the general principles.

1.1.2 Examples of supported reagents and selected applications

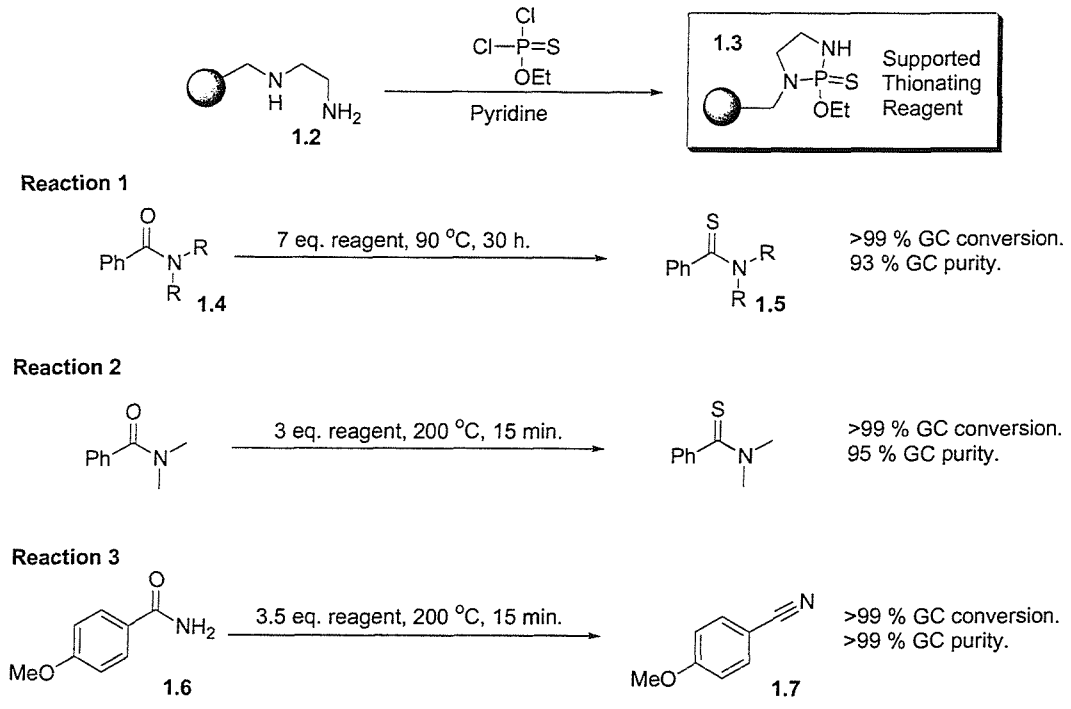
The development of supported reagents for use in organic synthesis is often undertaken for a specific reason. Many reagents used in solution are often dangerous, toxic or malodorous for example, and in most cases the supported analogue is much easier to handle. Alternatively, the problem sometimes is the isolation of the target molecule from any remaining excess reagent or reagent by-products. An example of such a reagent that embodies many of these traits is Lawesson's reagent (**1.1**, scheme 1.1).



1.1

Scheme 1.1 Lawesson's reagent.

Lawesson's reagent (2,4-*bis*[4-methoxyphenyl]-1,3-dithia-2,4-diphosphetane 2,4-disulfide) is used for the conversion of amides to thioamides.[4,5] Unfortunately, a number of drawbacks to using this reagent exist, including the high toxicity and malodorous nature of the reagent and by-products, harsh reaction conditions and protracted reaction times, and difficulty in the isolation of the target thioamide from the reaction mixture. To overcome these adversities, a supported thionating reagent has recently been developed.[6] Although a direct use of Lawesson's reagent immobilised on a resin was not possible, an alternative supported aminothiophosphate **1.3** was synthesised from commercially available diamine resin **1.2** using ethyl dichlorothiophosphate.

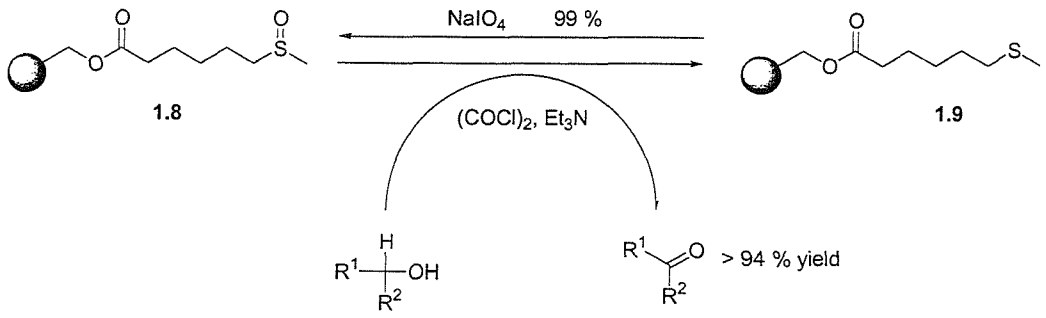


Scheme 1.2 Supported thionating reagent and selected examples.

Excellent results were obtained for the conversion of a number of amides (**1.4**) to thioamides (**1.5**), carried out thermally (reaction 1, scheme 1.2). However, using microwave chemistry, a much-improved methodology was developed, only taking 15 minutes with reduced amounts of reagent (reaction 2, scheme 1.2). Examples of the dehydration of primary amides (**1.6**) to nitriles (**1.7**) were also carried out (reaction 3, scheme 1.2).

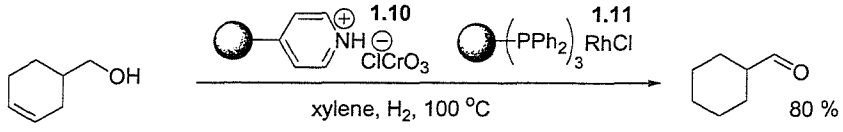
Another well known reaction that has a malodorous by-product is the Swern oxidation.[7,8] Traditionally, the oxalyl chloride activation of dimethyl sulfoxide (DMSO) in order to oxidise primary and secondary alcohols eventually results in a volatile and malodorous by-product (dimethyl sulfide). Vederas and coworkers used a polymer-supported sulfoxide **1.8** (using either polystyrene or poly(ethylene glycol) support) and determined that the Swern oxidation of a variety of alcohols using their supported reagent proceeded with excellent yield (scheme 1.3).[9]

After reaction, the sulfide resin **1.9** could be regenerated by oxidation back to the sulfoxide using sodium periodate, and indeed with the poly(ethylene glycol) supported-reagent no drop in activity was observed for subsequent Swern oxidations.



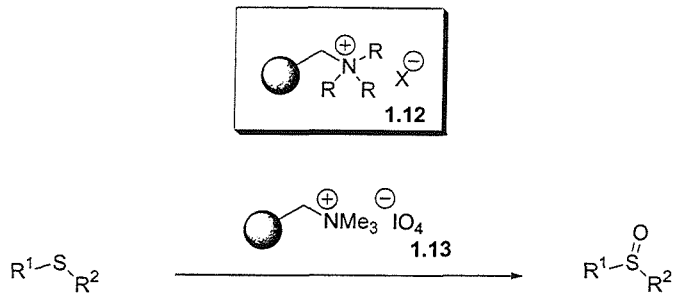
Scheme 1.3 Swern oxidations with supported sulfoxide reagent **1.8**.

A number of other examples exist in the literature for supported oxidising reagents. Bergbreiter and Chandran demonstrated the use of a polymer-supported chromium (VI) oxidant **1.10**, concurrently with polymeric supported Wilkinson's catalyst **1.11** for olefin reduction, reagents which would not normally be compatible.[10] Utilising a poly(vinylpyridine) support in order to synthesise a supported version of PCC (pyridinium chlorochromate) previously determined by Frechert *et al*,[11] the oxidation of an alcohol and reduction of an olefin in one pot was possible, in the majority of cases with good yield (scheme 1.4).



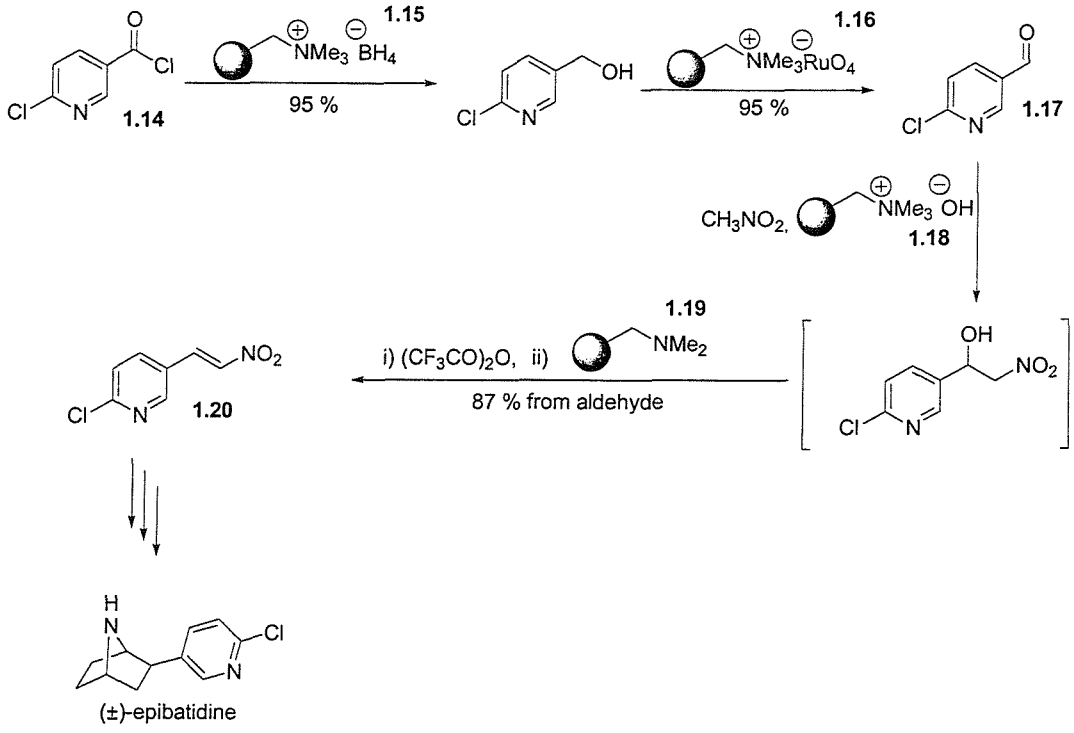
Scheme 1.4 Concurrent alcohol oxidation and olefin reduction.

The use of ammonium resins has become a very important tool in the making of supported reagents. Perhaps the most commonly used resin is the ammonium anion exchange resin **1.12**. A whole plethora of supported reagents can be accessed from these resins, where R is usually methyl. Scheme 1.5 depicts work by Harrison and Hodge, using such a resin to form a supported periodate oxidant **1.13**.[12] Their investigations showed that a number of substrates could be oxidised using the supported reagent **1.13**, including a variety of aryl alcohols to quinones, sulfides to sulfoxides and phosphines to phosphine oxides.



Scheme 1.5 Supported periodate reagent **1.13** as an oxidant.

Anion exchange resins can also be used in order to access a supported perruthenate oxidant. Indeed, Ley and coworkers have used this supported oxidant on a number of occasions in the synthesis of a variety of substrates. In 1999, towards the synthesis of (±)-epibatidine, they used the perruthenate resin in conjunction with a variety of other reagents derived from amine or ammonium anion exchange resin **1.12**.[13]

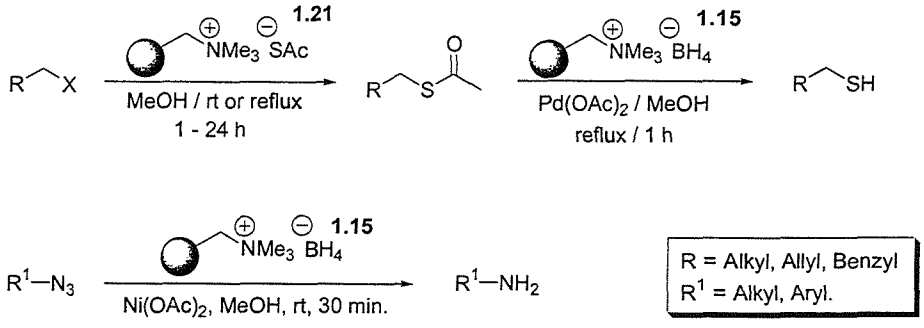


Scheme 1.6 Early steps towards the synthesis of (±)-epibatidine.

Initially, the starting acid chloride **1.14** was reduced using the supported borohydride reagent **1.15** to the corresponding alcohol, which was subsequently oxidised using the supported perruthenate reagent **1.16** to pyridyl aldehyde **1.17**. A subsequent Henry reaction with supported hydroxide **1.18** and nitromethane, followed by conversion to a

trifluoroacetate and elimination with dimethylaminomethyl polystyrene **1.19**, gave exclusively the *trans*-alkene **1.20**. Another 5 steps, 4 of which used supported reagents, gave the desired product (±)-epibatidine.

The supported borohydride reagent **1.15** used in the synthesis of (±)-epibatidine (scheme 1.6) has been shown to be a very useful supported reagent for the reduction of a number of functional groups other than carbonyls. Yoon *et al* utilised the borohydride resin **1.15** in order to carry out methanolysis of thioacetate moieties to the corresponding thiols, in the presence of a palladium catalyst (scheme 1.7).[14] Interestingly, the thioacetate functionalities themselves were synthesised from the corresponding halides, using thioacetate exchange resin **1.21**. It was found that both steps could be carried out in one pot. Yields greater than 87 % for the thiol products over two steps from the halide starting material were obtained.

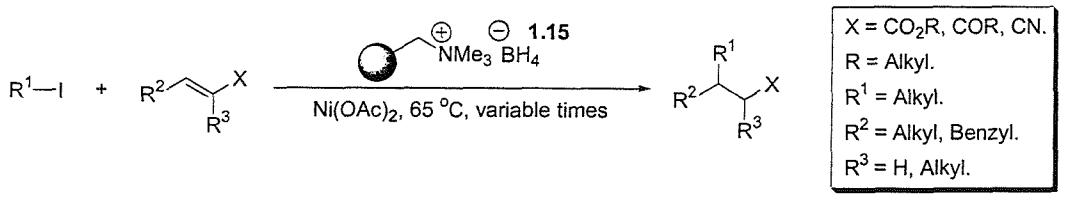


Scheme 1.7 Uses of supported borohydride reagent **1.15** shown by Yoon *et al.*

The Yoon group also showed that the borohydride resin **1.15** could be used with nickel acetate catalyst in order to reduce azides to amines (scheme 1.7).[15] Both aliphatic and aromatic azides were reduced with greater than 90 % yields in all cases. Better yields are reported for the reduction of aliphatic azides with supported borohydride reagent **1.15** than for the equivalent reaction with sodium borohydride. The reaction conditions are also tolerant of ester, chloro, acetal, nitrile, aliphatic epoxide, and tosylate groups. However carbon-carbon multiple bonds, ketone and iodo groups were reduced.

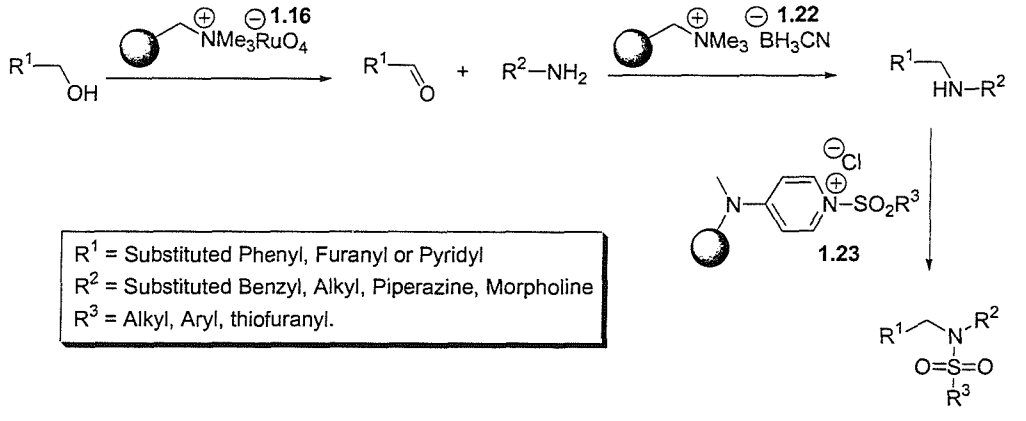
Supported borohydride resin **1.15** has also been used with nickel acetate catalyst for other applications. The coupling of alkyl halides with electron deficient alkenes has been demonstrated using the supported borohydride reagent **1.15** in conjunction with nickel acetate catalyst (scheme 1.8).[16]

Alkyl iodides were used with olefins such as α,β-unsaturated esters (12 examples), α,β-unsaturated nitriles (13 examples) and α,β-unsaturated ketones (13 examples) and the coupling product obtained in good yield for the majority of cases.



Scheme 1.8 Coupling of electron deficient olefins with alkyl halides.

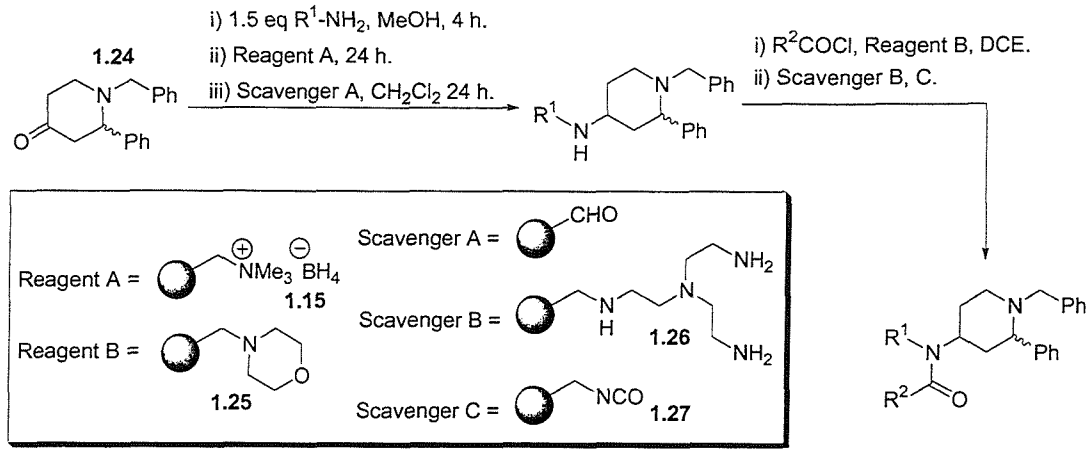
Perhaps one of the more usual uses of borohydrides in synthesis is their application in carrying out reductive amination reactions. Indeed, a number of examples exist in the literature for the use of supported borohydride reagents in order to carry out reductive aminations. The Ley group utilised supported cyanoborohydride reagent **1.22** in order to carry out reductive aminations, as a step towards the synthesis of a library of sulfonamides (scheme 1.9).[17]



Scheme 1.9 Sulfonamide library synthesis using reductive amination.

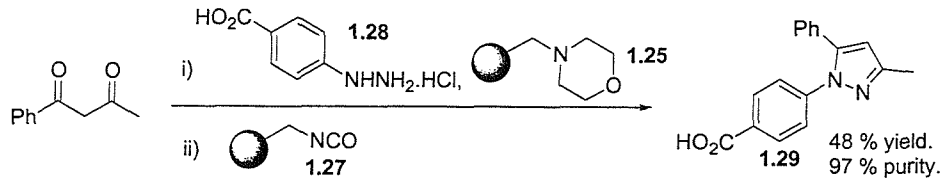
Initially a selection of twelve alcohols were oxidised to the corresponding aldehydes using supported perruthenate reagent **1.16**, which were then condensed with a variety of amines and reduced with cyanoborohydride resin **1.22** to give a library of secondary amines. Treatment of the amines with a selection of amino sulfonylpyridinium chloride resins (**1.23**) accessed the desired library of sulfonamides.

Of course, reductive amination reactions are not the exclusive reserve of cyano borohydride reagents. Creswell and coworkers demonstrated the synthesis of a library of dihydropiperidones.[18] Starting from piperidone **1.24**, condensation with 10 different amines followed by reduction with borohydride resin **1.15** gave a collection of 4-aminopiperidines (scheme 1.10). These were subsequently reacted with a selection of eight acid chlorides in the presence of a supported morpholine base **1.25** after which scavenger resins were employed in order to remove excess acid chloride (amine resin **1.26**) and any unreacted amine (isocyanate resin **1.27**).



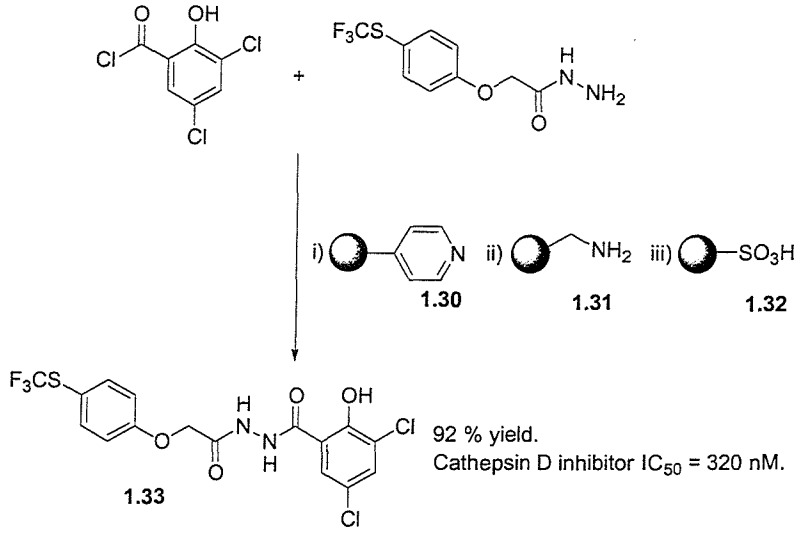
Scheme 1.10 Synthesis of a library of dihydropyridones by Creswell *et al.*

Apart from the supported borohydride reagent **1.15** used in this synthesis, the other reagent used was the supported morpholine base **1.25**. Such a resin has been used to good effect in a number of cases in the literature. Blackburn *et al* demonstrated the use of a supported morpholine base in order to form tertiary amides from an amine and acid chloride in this case in order to form a library of aminoimidazo pyridines and pyrazines.[19] Booth and Hodges showed that a supported morpholine base can be used in order to synthesise pyrazoles (scheme 1.11). [20] A 1,3 diketone is condensed with excess hydrazine **1.28** in the presence of morpholine resin **1.25**. Subsequent removal of the excess hydrazine **1.28** with isocyanate scavenger **1.27** gives the desired pyrazole in 48 % yield with excellent purity.



Scheme 1.11 Pyrazole synthesis with supported base **1.25** by Booth and Hodges.

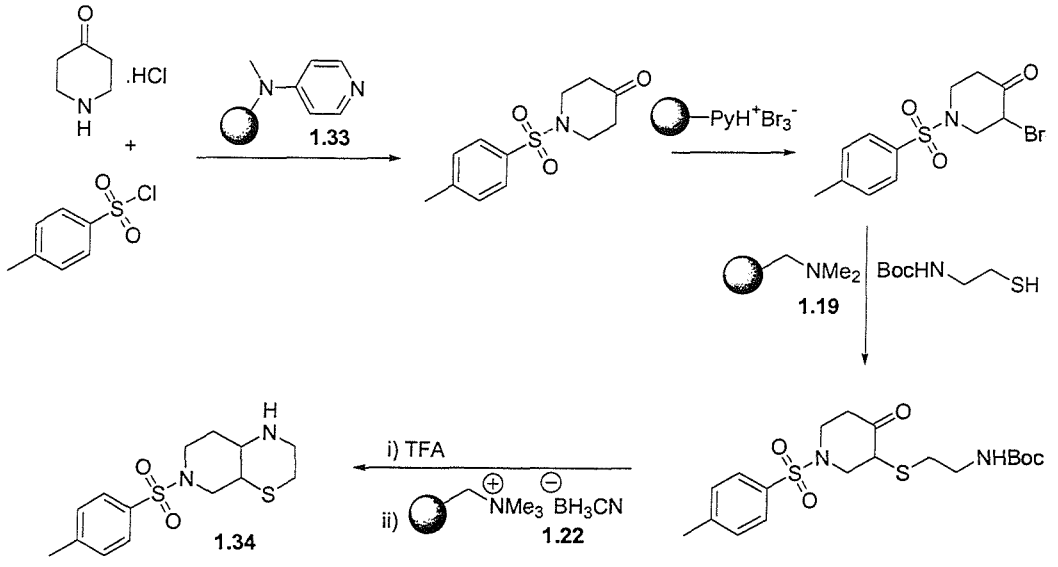
Other polymer-supported bases are available and are used in synthesis. Trialkylamine bases such as **1.19** (scheme 1.6) have been used regularly and also supported pyridine bases are widely utilised. In scheme 1.4, supported pyridine was used in order to access supported pyridinium chlorochromate reagent **1.10**. Pyridine resin **1.30** can also be simply used as a base, demonstrated to good effect by Chen *et al* during the synthesis of a library of cathepsin D inhibitors (scheme 1.12).[21] A selection of acid chlorides or sulfonyl chlorides were coupled to either anilines or hydrazines.



Scheme 1.12 Synthesis of a Cathepsin D inhibitor.

Scheme 1.12 shows the synthesis of the most effective inhibitor of Cathepsin D **1.33** that was forthcoming from the library of compounds that were produced. The coupling of the hydrazide and acid chloride segments was carried out in the presence of supported pyridine base **1.30**. In this instance, any unreacted acid chloride was scavenged from the reaction mixture using aminomethyl resin (**1.31**) and any remaining nitrogen nucleophiles were removed with sulfonic acid resin **1.32**.

As mentioned, the use of trialkyl amine resins as bases has been widely demonstrated, and also the use of a supported version of DMAP. Work by Ley *et al* demonstrates the use of these base resins in the synthesis of a library of piperidino-thiomorpholines (scheme 1.13).[22]

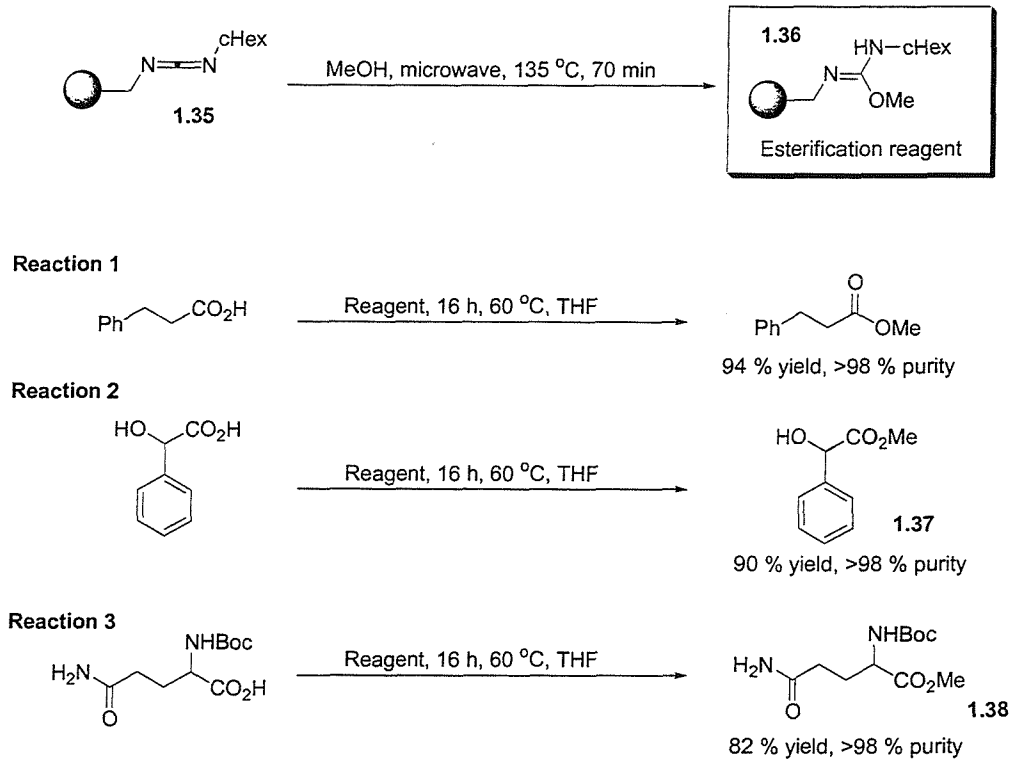


Scheme 1.13 Synthesis of a piperidino-thiomorpholine library using supported reagents.

A sulfonamide was formed using sulfonyl chloride and piperidine mediated by polymer-supported DMAP reagent **1.33**, followed by bromination with a supported pyridinium tribromide reagent. Halide displacement with a *N*-Boc-amino thiol using dimethylaminomethyl polystyrene **1.19** as base, followed by deprotection of the amine and reductive amination with supported cyanoborohydride reagent **1.22** gave the desired morpholine **1.34**. Variation was introduced by reaction of the morpholine nitrogen with a variety of isocyanate and isothiocyanates in order to access ureas and thioureas respectively.

Along with amide and sulfonamide bond formation, esterification reactions are possible with a number of supported reagents, including sulfonyl chloride resin.[23] Perhaps one of the more interesting examples of esterification uses a supported isourea, which does not require the use of scavenger resins.[24] Commercially available carbodiimide resin **1.35** was exploited in a reaction with an alcohol (methanol in this case) in order to access the supported *O*-methylisourea **1.36**. Reaction of the resin with

a number of carboxylic acids afforded the desired methyl esters with excellent yields and purities, the urea by-product remaining immobilised on the solid support (reaction 1, scheme 1.14). Interestingly, the resin was shown to selectively react with an acid over an alcohol, and reaction 2 (scheme 1.14) only affords the hydroxy ester product **1.37**. Also, the reaction is selective for ester formation in the presence of primary amides and Boc protected amines (reaction 3, scheme 1.14) to give **1.38**.

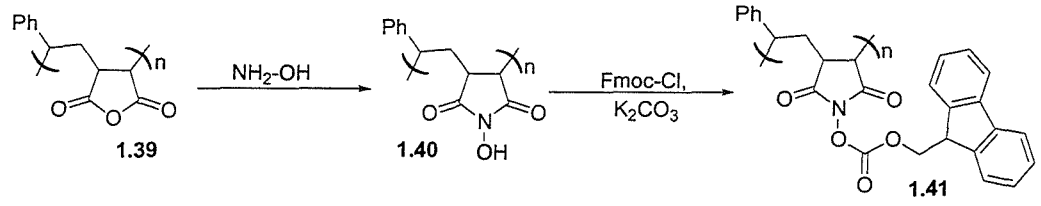


Scheme 1.14 Selective methylation of carboxylic acids.

The versatility of such an approach is self-evident. The coupling of any alcohol could be used to access the desired supported *O*-alkylisourea after reaction with the supported carbodiimide and allow subsequent selective reaction with a carboxylic acid. In this way the strategy could be used in order to attach various ester protecting groups.

Protecting group chemistry for other functional groups has also been exploited by a number of other research groups. One area of study has included the use of supported reagents in order to synthesise carbamate protecting groups for amines. Recently, Nájera and co-workers turned their attention to the use of a supported reagent to generate Fmoc (9-fluorenylmethoxycarbonyl) protected amines.[25]

Traditionally, the reagent of choice to enable Fmoc protection is the chloroformate ester Fmoc-Cl. However problems with the undesired formation of "Fmoc-dipeptides" and stability issues have been raised with this reagent. Another commonly used reagent used is Fmoc-N_3 however there are problems handling such a potentially explosive oxycarbonyl azide. Viable alternatives are more stable carbonates, and in particular Fmoc-Su (Su = succinimidyl).[26] As such, Nájera and colleagues synthesised a supported Fmoc-Su reagent. Starting with styrene/maleic anhydride co-polymer (**1.39**), reaction with hydroxylamine gives the corresponding hydroxy maleimide **1.40**. Subsequent reaction with Fmoc-Cl gives the desired polymer-bound Fmoc-OSu **1.41** (scheme 1.15).



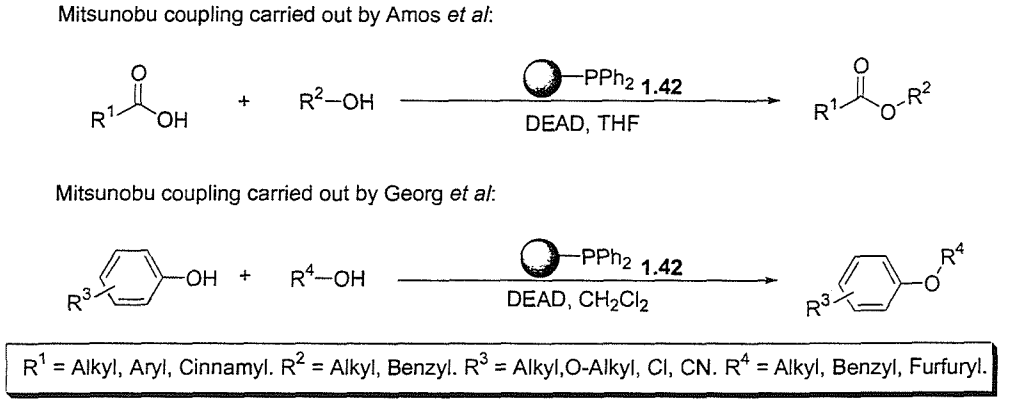
Scheme 1.15 Supported carbonate for Fmoc protection of amines.

Using supported reagent **1.41**, the Fmoc protection of a number of amino acids was carried out, including alanine, glycine, valine, proline, and leucine, with good yields.

Protection of alcohol functionalities has also been achieved by using a variety supported reagents. Perhaps one of the more unusual examples was shown by Hon *et al.* Supported ATPB (acetonyltriphenylphosphonium bromide, from triphenyl phosphine resin) can be used in order to allow the protection and deprotection of alcohols as THP (tetrahydropyranyl), EE (ethoxyethyl) or THF (tetrahydrofuranyl) ethers with yields in the majority of cases of greater the 90%.[27]

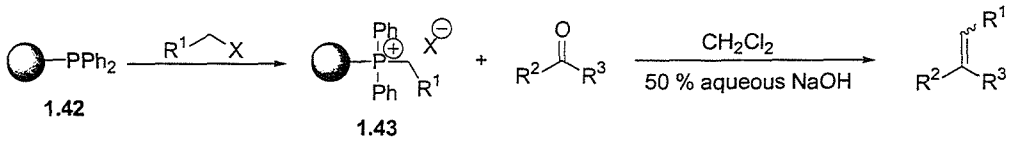
However, more common uses for supported triphenylphosphine equivalents have been employeded extensively in synthesis, particularly where the resulting by-product in solution would be triphenylphosphine oxide. The application of a supported version therefore eases purification. Mitsunobu chemistry has been used to good effect with supported phosphine resin **1.42**. Amos and coworkers showed that the effective esterification of alcohols with acids under Mitsunobu conditions, could be carried out with excellent yields substituting supported phosphine resin **1.42** for triphenylphosphine (scheme 1.16).[28] Georg *et al* later showed that the same reagent

could be used effectively for the synthesis of aryl ethers from a phenol and another alcohol, also utilising Mitsunobu coupling conditions (scheme 1.16).[29]



Scheme 1.16 Mitsunobu couplings carried out with supported phosphine **1.42.**

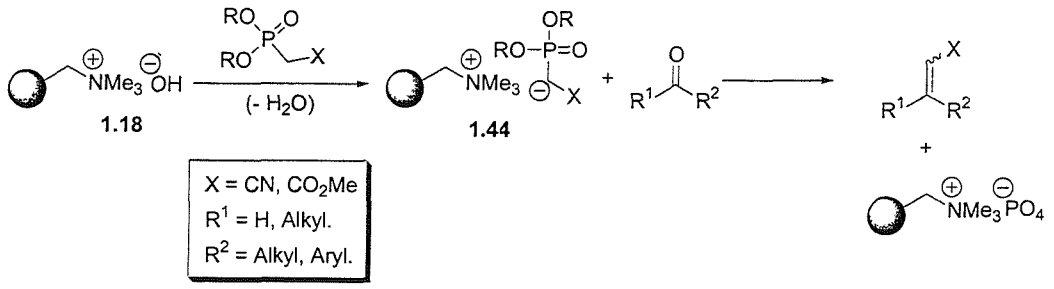
Other coupling reactions often associated with triphenylphosphine are also possible with the supported reagent **1.42.** Supported phosphine reagents have also been used in Wittig couplings.[30] As far back as 1980, Hodge and coworkers reported the use of supported reagents in Wittig olefination reactions under phase-transfer conditions.[31] Starting with phosphine reagent **1.42**, reaction with a selection of halides gave the corresponding phosphonium salts **1.43** (scheme 1.17). These were then used to treat a variety of aldehydes under phase-transfer conditions with aqueous sodium hydroxide in order to form the reactive intermediate phosphonium ylide species, giving the desired olefin products.



Scheme 1.17 Wittig olefination reactions carried out by Hodge *et al.*

In some cases it was found that a phase-transfer catalyst was required to expediate the reaction. They also reported that the ratio of *cis:trans* olefin products as a result of reaction with supported phosphonium salts **1.43**, were comparable with conventional Wittig olefination reactions reported previously in the literature.

In similar reactions, Cainelli *et al* reported the use of supported reagents in Horner-Wittig variant olefination reactions.[32] In this case, hydroxy ion exchange resin **1.18** was reacted with a phosphonate in order to give polymer-supported phosphonate **1.44** (scheme 1.18).

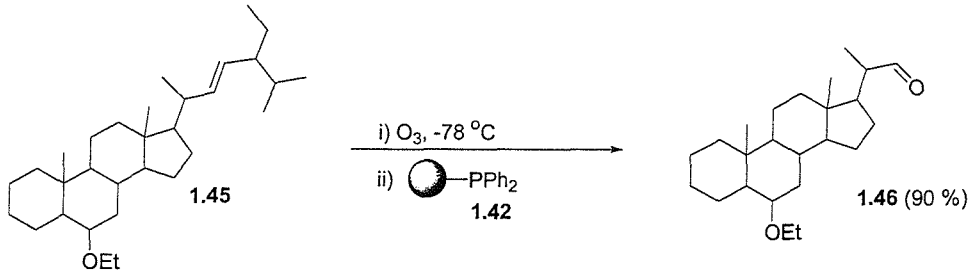


Scheme 1.18 Olefination with a supported phosphonate reagent **1.44**.

Subsequent reaction of the phosphonate resin **1.44** with a variety of aldehydes gave the desired olefins in excellent yield. It was noted that in the majority of cases investigated, the predominant product was the E-isomer olefin product. In fact, in many cases the E-isomer was the only product observed. Interestingly, the methodology was to perform the reaction using a column technique. Using the phosphonate resin **1.44** (where X = CN) packed in a column, slow percolation of a solution of the aldehyde substrate through the column directly obtained the corresponding olefin product. This method could be used in a continuous fashion using one aldehyde after another until the resin was exhausted. Regeneration of the active phosphonate resin **1.44** could be achieved by sequential washing with aqueous hydrochloric acid, sodium hydroxide and a final wash with phosphonate solution. However, this method could only be used with phosphonate resins where X = CN as the other resins were not reactive enough.

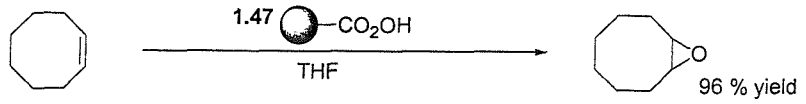
The use of phosphine resins is by no means limited to coupling reactions. Supported phosphine reagent **1.42** has been used to carry out ozonolysis reactions. The phosphine resin **1.42** is utilised to carry out the reductive cleavage of the ozonide intermediate in place of the more traditional triphenylphosphine. This application was reported by Santaniello *et al* when synthesising the steroid derivative **1.46** *via* an ozonolysis reaction with a stigmasterol derivative **1.45**.[33] Using the conventional method with triphenylphosphine, the isolation of aldehyde **1.46** was not forthcoming,

as it was always poisoned with traces of triphenylphosphine (due to similar polarities). In using supported triphenylphosphine reagent **1.42** purification problems were no longer an issue and the aldehyde **1.46** was achieved in 90 % yield without need for purification (scheme 1.19). A number of other alkenes were investigated using the supported reagent under ozonolysis conditions, with similarly good yields.



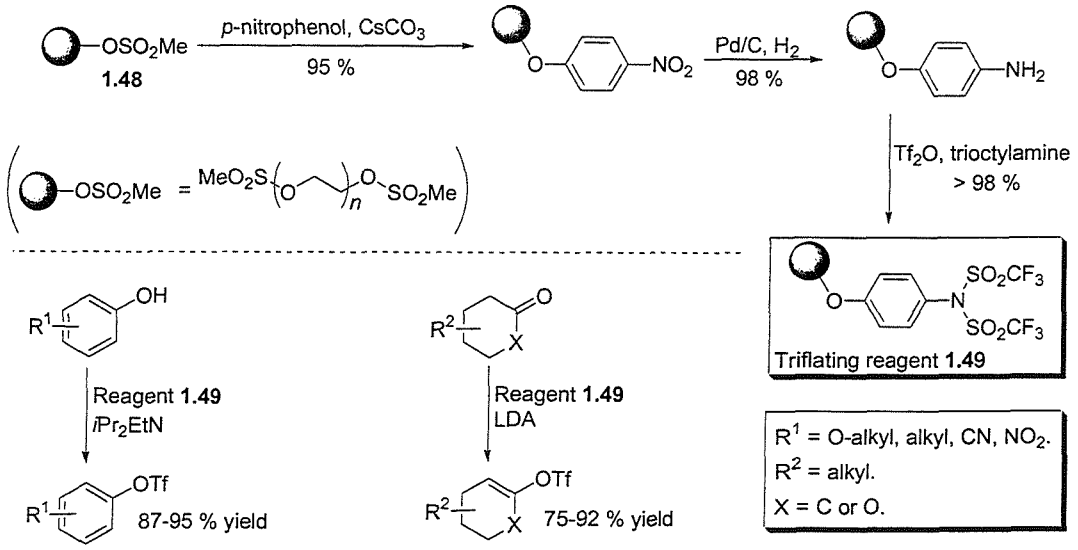
Scheme 1.19 Ozonolysis reaction using a supported phosphine reagent.

Supported phosphine **1.42** has been shown to be a very versatile reagent, with a number of different uses in a variety of synthetic pathways. Some groups synthesise supported reagents that have a specific remit. In the mid-1970s, Hodge and Harrison reported the synthesis of peroxy acid resin **1.47**, which they used in order to epoxidise a number of different alkenes.[34] The resin was synthesised in 2 steps from an aldehyde resin, and their investigations showed that the selected olefins could be converted to the corresponding epoxides (scheme 1.20). They noted that reaction yields and ratios of stereoisomers with the resin supported peroxy acid **1.47** were comparable to those obtained when the same reactions were carried out with 3-chloroperbenzoic acid and perbenzoic acid. When acidic substrates are used, a recognised side reaction occurs, whereby the carboxylic acid by-product (from the spent peroxy-acid) reacts with the epoxide product to form a hydroxy ester. This is an unfortunate problem with conventional reagents but when the resin is used, any hydroxy ester that is formed is bound to the resin, and is therefore removed by filtration of the resin. In addition, the resin is very safe, as attempts to detonate the peroxyacid resin **1.47** by impact failed to explode the resin.



Scheme 1.20 An example of an epoxidation using a supported peroxyacid.

Another specific reagent that has been attached to the solid-phase is one used as a triflating agent. Triflate moieties are routinely used in carbon-carbon or carbon-heteroatom bond forming reactions and *N*-phenyl triflimide is a commonly used reagent for the conversion of aromatic alcohols to aromatic triflates and enolates to enol triflates. To this end, a supported triflimide reagent was synthesised and used to good effect by Janda *et al.*[35] Using soluble homopolymer PEG (poly(ethylene glycol)), the triflimide resin **1.49** was synthesised in three steps from the corresponding mesylate resin **1.48** (scheme 1.21).

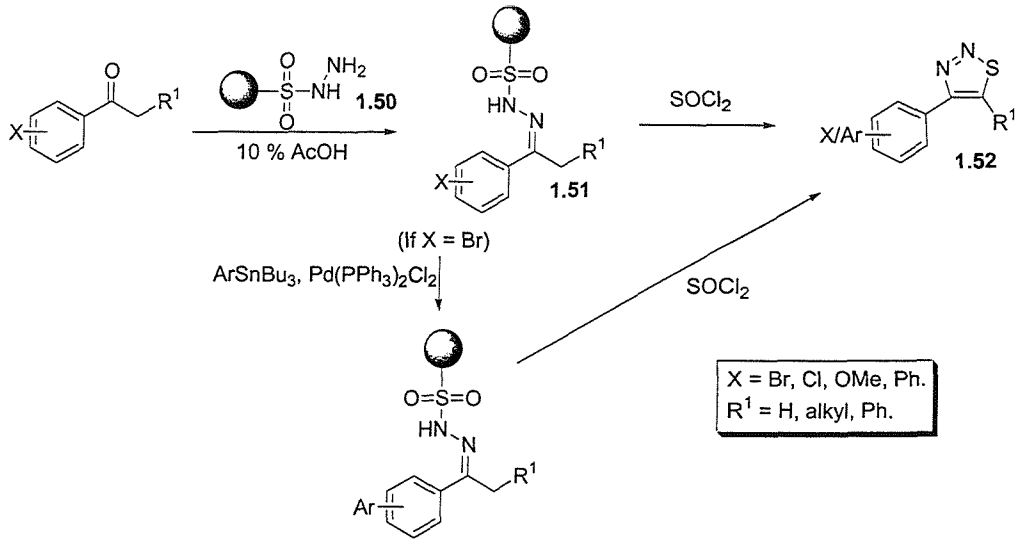


Scheme 1.21 Synthesis and application of a supported triflating agent.

In each example investigated, the identical reaction was carried out using the solution reagent equivalent. The triflating reagent resin **1.49** performed with comparable yields to the solution equivalent. The polymer resin is isolated as a mono triflamide after the reaction and can be converted back to the triflimide reagent resin **1.49** by treatment with Tf_2O, allowing the resin to be reused.

Many of the resins outlined above are used as discreet reagents that are removed from the reaction mixture by filtration after completion. However, in some cases the

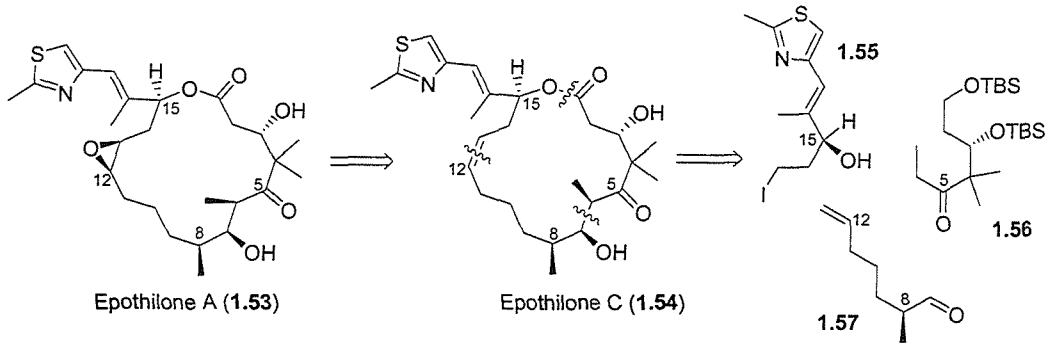
reagents can be used in a "catch and release" method, whereby the substrate reacts with the resin to form a resin bound intermediate, and the resin can then be treated with another reagent to release the target molecule into solution. This usually allows multiple steps to be carried out while purification issues are avoided. An attractive example of such a route is that presented by Porco and colleagues in the synthesis of a small library of thiadiazoles.[36] A number of ketones were reacted with sulfonyl hydrazide resin **1.50** accessing a supported sulfonyl hydrazone intermediate **1.51**. At this point, where aryl halides are present in the supported sulfonyl hydrazide **1.51**, a tin-mediated Stille coupling was possible on the support to add further variation to the library. Finally, a Hurd-Mori cyclisation[37] using thionyl chloride was utilised in order to cleave the products from the support as the desired thiadiazoles **1.52**.



Scheme 1.22 Sulfonyl hydrazide resin for "catch and release" synthesis of a thiadiazole library.

In the majority of cases, the resulting 1,2,3-thiadiazoles were returned from the resin with greater than 80 % yield, and in all cases excellent purity. Molecules of particular interest are those where R^1 is an aryl group as examples of antithrombotic agents have been found to possess aryl groups at the 4 and 5 positions of 1,2,3-thiadiazole moieties.

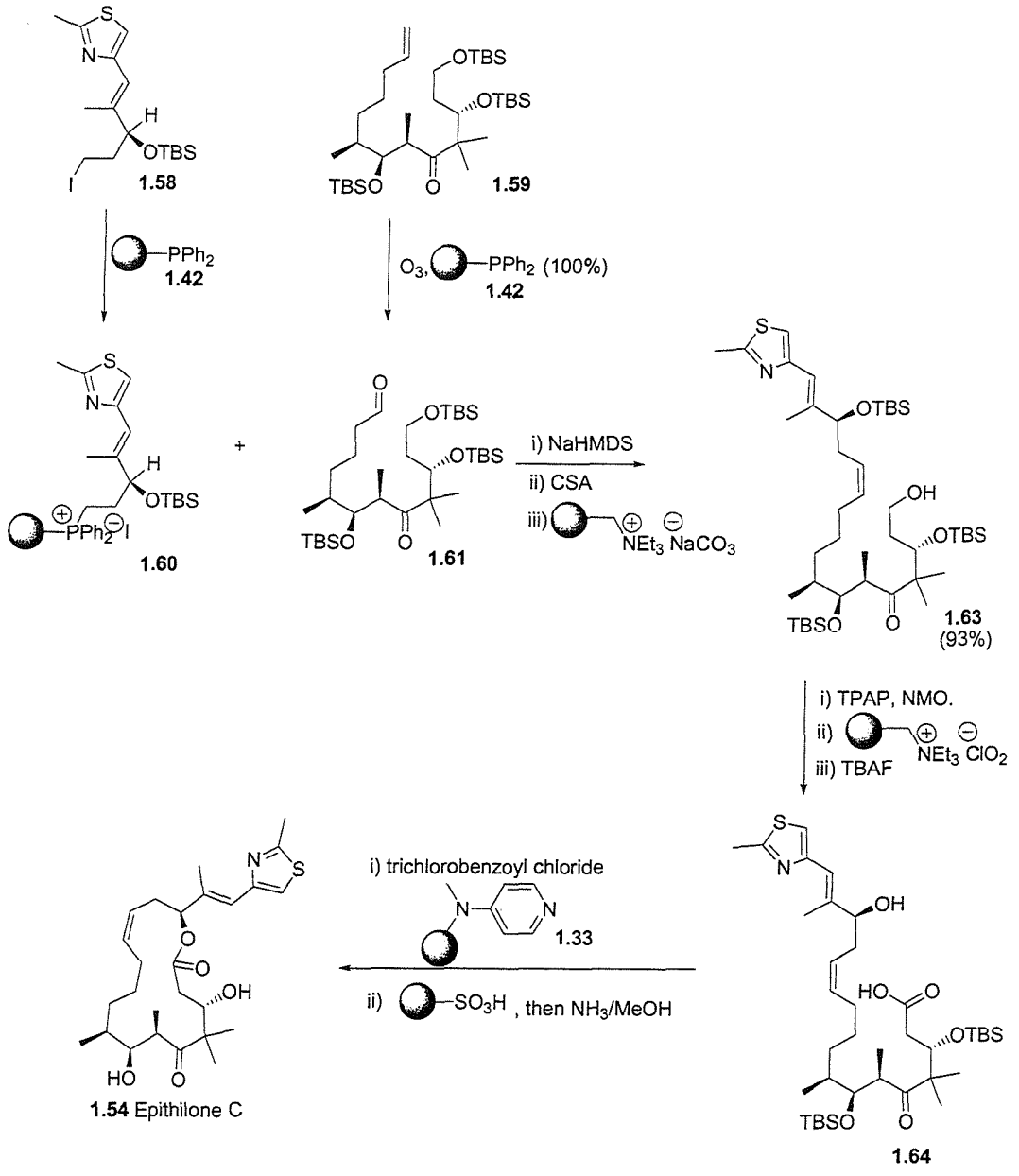
Many of the papers outlined above and published in the literature have been based on the development of methodology illustrated by applications of the reagents on test substrates, or part of a short library synthesis. However, they do not give an idea of the usefulness of supported reagents as a part of more complex synthetic pathways, within organic synthesis. An excellent example demonstrating the power of supported reagents in synthesis was reported recently by Ley and co-workers, their aim being the total synthesis of Epithilones only using supported reagents.[38]



Scheme 1.23 Retrosynthetic analysis of Epothilones by Ley *et al.*

In the synthesis of epothilones, Ley *et al* identified fragments **1.55**, **1.56**, **1.57** (scheme 1.23) as key intermediates, which could be linked together using Wittig, aldol and macrolactonisation chemistries. Epothilone C (**1.54**) was in fact synthesised in 29 steps overall (shortest linear sequence being 17 steps) with every step involving the use of supported reagents and/or scavenger methodologies. The high selectivities and overall yields were comparable with previous conventional syntheses.

The use of commercially available supported phosphine reagent **1.42** [29] plays a major role in this synthesis in order to carry out the Wittig olefination step in order to couple two major fragments (scheme 1.24). Immobilised phosphonium salt (**1.60**) was obtained by reaction of supported phosphine **1.42** with the previously synthesised iodide **1.58**.



Scheme 1.24 Selected reactions by Ley and co-workers to synthesise Epothilone C.

The synthesis of the required aldehyde **1.61** to allow the Wittig coupling was completed by the use of supported phosphine **1.42** *via* ozonolysis from olefin **1.59**. Subsequent treatment of the supported phosphonium salt **1.60** with NaHMDS gives the desired ylide and addition of the aldehyde fragment **1.61** led to exclusively the *cis*-olefin with excellent yield. Subsequent selective deprotection of the primary TBS ether using a supported carbonate afforded alcohol **1.63**. A sequential 2 step oxidation process using TPAP/NMO followed by polymer-supported chlorite allowed oxidation of the primary alcohol to the corresponding acid. Selective deprotection of the allylic

TBS ether moiety with TFA accessed the hydroxy acid **1.64** required for macrolactonisation. Indeed, lactonisation proceeded smoothly under Yamaguchi conditions, using polymer supported DMAP **1.33** as base. Finally, a sulfonic acid resin was utilised to remove the remaining TBS protecting groups and also to protonate the thiazole nitrogen thereby sequestering the target molecule on the resin as an ion-exchanged salt. This allowed any unbound impurities to be removed by washing and after, the target epithilone C (**1.54**) was returned by washing the resin with ammonia solution.

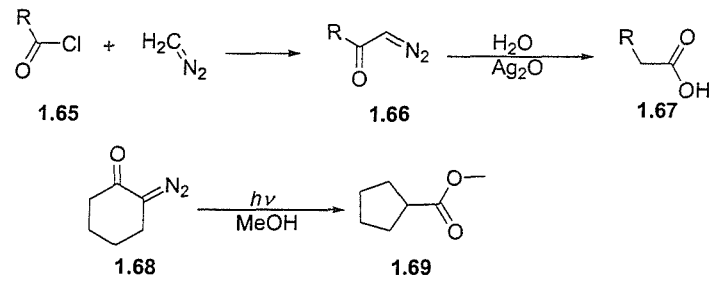
The synthesis of epithilone C represents a significant achievement, and shows the use of many of the supported reagents outlined above, culminating in the total synthesis of a complicated target.

1.2 Synthesis and uses of diazo compounds

Compounds containing diazo functionality are well known to be synthetically useful substances.[39] As such, much work has been carried out and published in the literature into the synthesis and use of such compounds. They have become a useful synthetic tool for many key transformations and therefore their synthesis is an important objective.

1.2.1 Classical approaches to the synthesis of diazo compounds

The synthesis of diazo compounds has been reported as far back as the late 1800s.[40] However, pioneering work by Arndt and Eistert brought diazo chemistry to the attention of a greater audience and allowed such compounds to be readily synthesised (scheme 1.25).[41,42] The Arndt Eistert reaction involves the conversion of an acyl halide (**1.65**) to a homologated carboxylic acid or ester (the use of water gives the acid and an alcohol yields an ester), *via* a diazoketone (**1.66**). The diazo ketone is prepared from reaction of an acyl halide with diazomethane. The rearrangement of the diazo ketone occurs in the presence of water and silver oxide to afford carboxylic acid **1.67** with an additional methylene. The rearrangement is known as the Wolff rearrangement.



Scheme 1.25 Rearrangements of diazo ketones.

Photolysis can be used to carry out ring contraction of cyclic diazo ketones such as compound **1.68** accessing the corresponding ester such as **1.69**.[43,44] The important point is that the use of diazomethane with acid chlorides remains to this day a synthetically significant and reliable route to access terminal diazo compounds. Unfortunately, by virtue of the requirement of an acid chloride, such methodology can only be applied to acyclic systems and subsequently, many groups have worked on methodologies in order to determine routes that are more universally applicable to the synthesis of diazo compounds. One of the most notable is the Bamford-Stevens procedure.[45]

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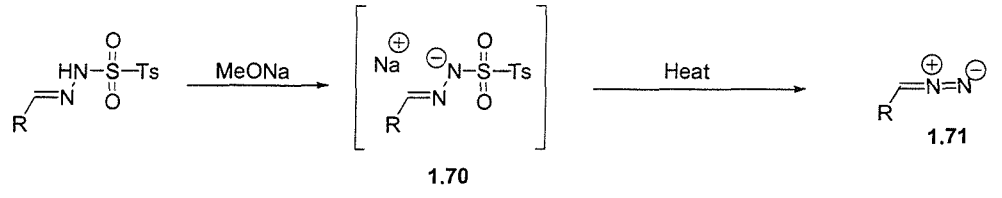
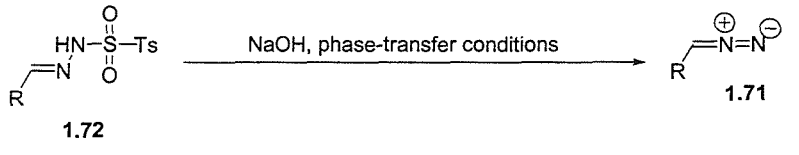


Wulfman *et al*:

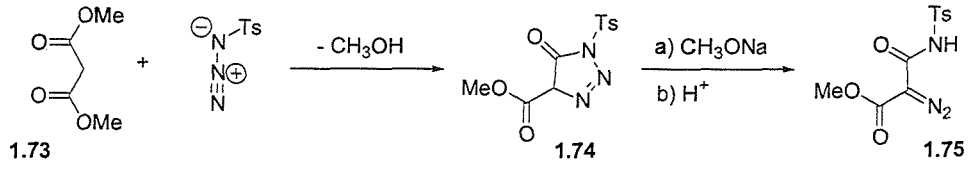


Scheme 1.26 Modified Bamford-Stevens reactions to give diazo compounds.

The Bamford-Stevens reaction utilises a tosyl hydrazone intermediate in the presence of base in order to access diazo compounds. Further improvements have subsequently been reported by Creary,[46] utilising tosylhydrazone salts (**1.70**) and also by Wulfman *et al* who reacted tosylhydrazones (**1.72**) with aqueous base under phase-transfer conditions in order to access the desired diazo products **1.71** (scheme 1.26).[47]

1.2.2 Diazo-transfer reactions with sulfonyl azides

The use of diazo transfer reagents has become an integral part of the preparation of diazo compounds.[48,49] Curtius and Klaveln reported the first preparation of a diazo compound by diazo transfer in 1926.[50] They showed that using tosyl azide, dimethyl malonate (**1.73**) could be converted to the corresponding methyl diazomalonate amide **1.75** (scheme 1.27). They proposed that the reaction proceeded *via* an intermediate triazolone (**1.74**).



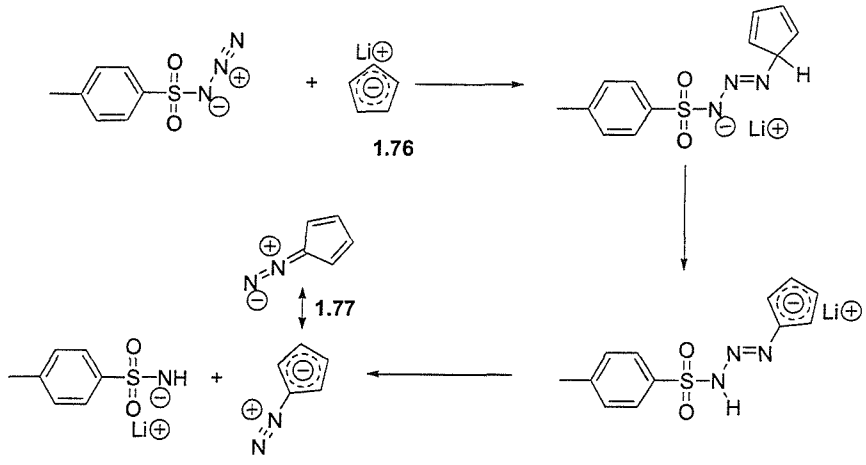
Scheme 1.27 Use of tosyl azide as diazo-transfer reagent.

In 1953 Doering and Depuy published work they had carried out in this area, having apparently not been aware of the previous work by Curtius and Kalvehn.[51] In attempting to synthesise diazocyclopentadiene (**1.77**), their initial approach involved using the dimer of cyclopentadienone oxime, which was eventually proved unsuccessful and was abandoned. An alternative route utilising cyclopentadienyllithium (**1.76**) was proposed whereby a reagent of formula N=N=A was required. Key attributes of A were determined to be:

- The ability to stabilise the negative charge introduced by the addition of the carbanion to the terminal nitrogen.
- The loss of a proton from the C_1 position of the cyclopentadiene ring of the intermediate to an atom in A.

- The ability of AH- to leave as a relatively stable anion breaking its bond to the second nitrogen atom.

A number of different variations of A were considered, however a *p*-toluenesulfonyl group was determined to be the most viable, satisfying all the theoretical conditions, as well as being readily accessible. They were able to carry out a diazo-transfer isolating diazocyclopentadiene (**1.77**) in 35 % yield, and the corresponding *p*-toluenesulfonamide by-product in 29 % yield (scheme 1.28).

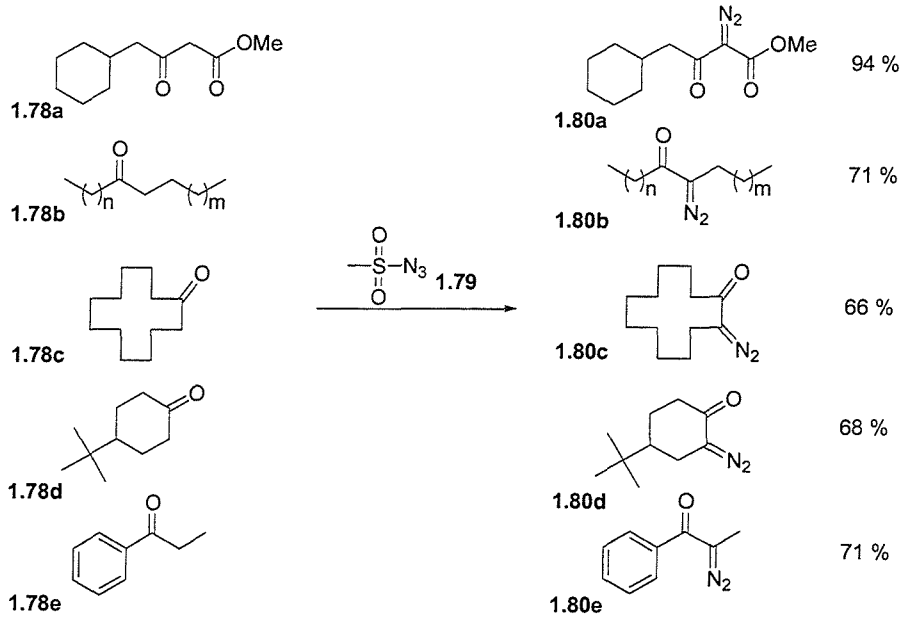


Scheme 1.28 Preparation of diazocyclopentadiene by diazo-transfer.

The sulfonyl azide family of compounds have subsequently become very important for the synthesis of diazo compounds. Since the discovery of the use of sulfonyl azides as diazo-transfer reagents their use has become common place. Regitz published an extensive study in the area in 1967.[39] In 1968 Hendrickson and Wolf reported the use of tosyl azide and *p*-carboxybenzenesulfonyl azide to introduce diazo functionality at methylene positions flanked by carbonyl groups.[52] Also reported was the reaction with methylene groups flanked by phenyl and carbonyl groups, giving predominantly the diazo compounds, but also Wolff rearrangement products.

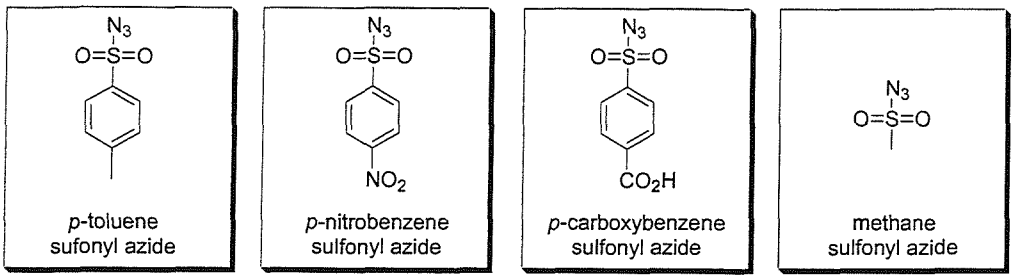
In 1986, Taber *et al.* introduced the use of methanesulfonyl azide as a diazo-transfer reagent that could not only introduce diazo functionality to dicarbonyls, but monocarbonyls could also be used as substrates (scheme 1.29).[53] Their one-pot methodology was limited to symmetrical ketones or ketones that favour the formation of one enolate (**1.78a-e**).

The problems demonstrated prior to publication of this work were that the diazo products were difficult to separate by chromatographic means from the sulfonyl azide and sulfonamide by-product. Using methanesulfonyl azide (**1.79**), Taber found that the purification was greatly simplified and the desired products (**1.80a-e**) could be separated from the by-products by washing with aqueous NaOH solution. Also, methanesulfonyl azide reagent was easily synthesised from methylsulfonyl chloride and sodium azide (however warnings were given about the potential explosive nature of mesyl azide).



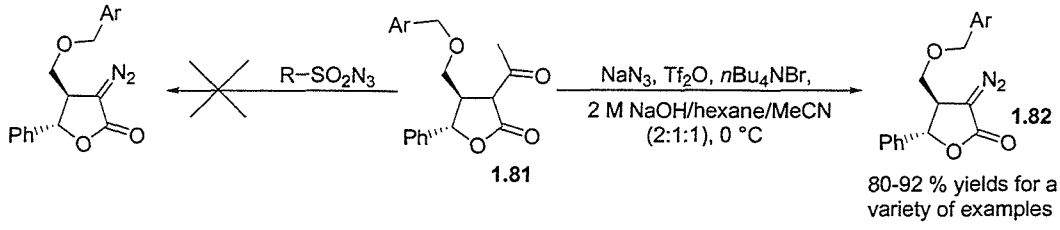
Scheme 1.29 The use of mesyl azide in diazo-transfer reactions.

It is clear that the sulfonyl azides are effective diazo-transfer reagents, and are still used routinely to access diazo compounds in synthesis. Scheme 1.30 depicts a number of sulfonyl azide reagents that are used to carry out diazo-transfer reactions.



Scheme 1.30 Commonly used sulfonyl azide diazo-transfer reagents.

More recently however, the shortcomings of commonly employed sulfonyl azide diazo-transfer reagents has been exposed. Brown *et al* showed that despite repeated attempts, it was not possible to carry out deacylative diazo-transfer reactions using sulfonyl azide reagents with their substrate **1.81** (scheme 1.31).[54] A more reactive alternative methodology was required in order to carry out the desired deacylative diazo-transfer.

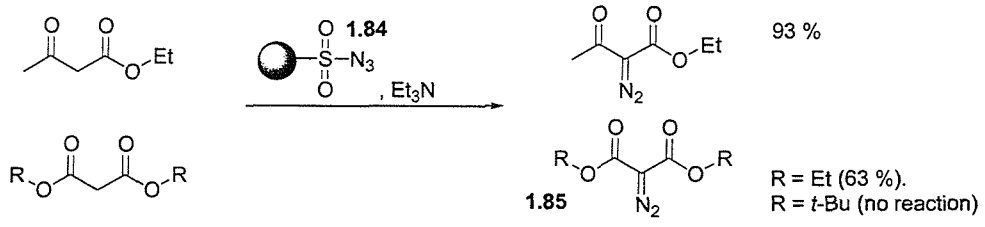


Scheme 1.31 Use of triflyl azide under phase-transfer conditions.

Their investigations showed that *in situ* generation of triflyl azide under phase-transfer conditions provided a solution. The procedure was both facile and highly reactive, giving a variety of diazo products **1.82** (with variation of the aryl group) *via* deacylative diazo-transfer with excellent yields.

Despite great efforts to overcome some of the shortcomings of the sulfonyl azide reagents, one major handling problem still remains. The explosive nature of sulfonyl azides has been highlighted and in fact, *p*-toluenesulfonyl azide has been shown to be on a par with TNT. A number of incidents have been reported with this reagent.[55] As a result, protocols to carry out diazo-transfer reactions more safely have been investigated, with variable success. These include solid-state reactions at low temperature[56] and the immobilisation of a sulfonyl azide moiety on polymer bead.[57]

Recently, Metz and co-workers have shown that a solid-supported diazo-transfer reagent can be used effectively in order to convert a number of carbonyl containing compounds to their corresponding diazo compounds (scheme 1.32).[58] They reported using a sulfonyl azide resin **1.84**, synthesised from commercially available sulfonyl chloride resin, could be used with excellent results for diazo-transfer to various β-keto esters and diketones. However, diminished yields were observed for reaction with diethyl malonate giving **1.85** (R = Et), and no diazo-transfer was possible with the more hindered di-*t*-butylmalonate, returning only starting.



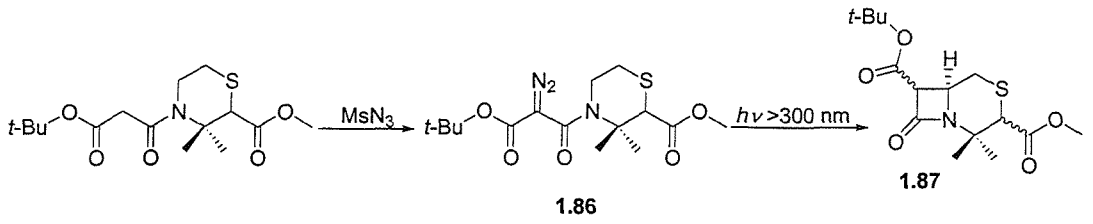
Scheme 1.32 Examples used by Metz *et al.* with a solid-supported sulfonyl azide.

Despite some of the shortcomings of sulfonyl azide reagents, they remain an important part of the synthetic chemist's tool kit and are still widely used in order to access diazo containing compounds. However, there remains room for improvement to avoid the problems outlined above, including potential hazards and purification issues.

1.2.3 Selected syntheses and applications of diazo compounds

Diazo compounds are excellent precursors to carbenes, and photolysis has long been used with diazo species in order to access carbenes. An interesting example of such a reaction was demonstrated by Lowe and Ramsay in 1973 to perform a C-C bond formation during the synthesis of penicillin and cephalosporin type bicyclic β-lactam analogues.[59] In the case of such antibacterial compounds, the essential elements are an acyl-dipeptide structure along with the β-lactam ring. The required diazo compound **1.86** was synthesised from the corresponding β-keto ester by diazo-transfer using methanesulfonyl azide. Irradiation of **1.86** with 300 nm in carbon tetrachloride gave the desired β-lactam ring **1.87** as a mixture of 4 diastereomers. The lack of

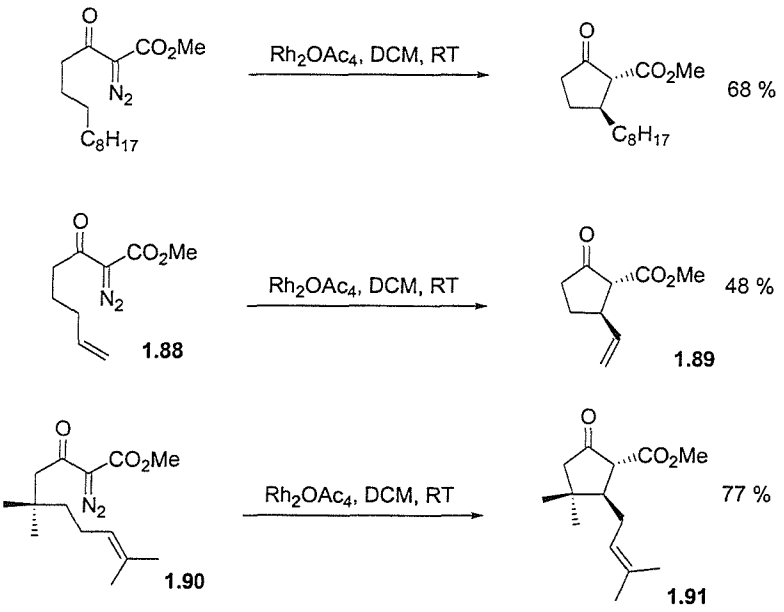
stereoselectivity is to be expected as the existing asymmetric centre offers little in the way of stereo control at the reacting centre.



Scheme 1.33 β-Lactam ring formation by C-H insertion.

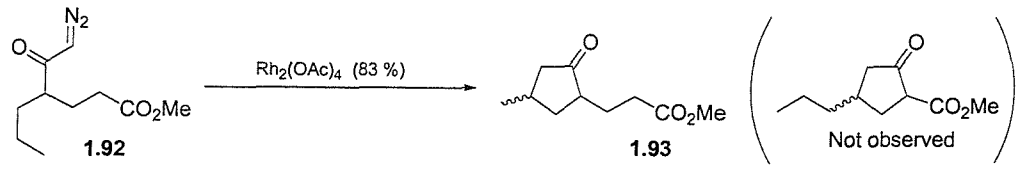
The generation of metal carbenoids from diazo species has come to the fore in recent years; in particular Rh (II) complexes have shown to be very effective in the production of electrophilic metal carbenoids from the corresponding diazo species.[60] One of the most generally applicable metal catalysts for the decomposition of diazo substrates has proved to be dirhodium (II) tetraacetate, following on from work carried out by Teyssié *et al.*[61] The development of this catalyst and various other analogues of rhodium (II) and their use to generate carbenoids from diazo compounds has meant that diazo species have found a niche area and become very important for C-H insertion reactions.[62]

Ground-breaking work by Taber and co-workers showed that an intramolecular C-H insertion was possible using a rhodium catalyst in order to synthesise cyclopentanones (scheme 1.34).[63] Starting with diazocarbonyl species, treatment with a rhodium catalyst led to the formation of the corresponding cyclopentanone ring systems with good yield. Previous work in this area had been carried out with constrained systems whereby the diazo moiety is held in close proximity to the C-H bond to be inserted. Taber's group showed that C-H insertions were possible with acyclic freely rotating systems, and that the process was quite general.



Scheme 1.34 Examples of C-H insertion reactions carried out by Taber *et al.*

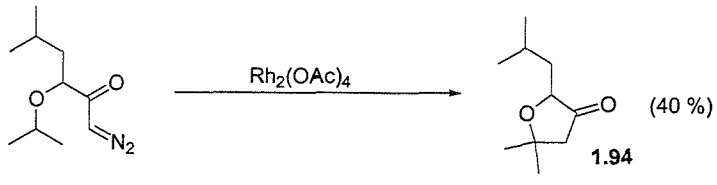
Their work with α-diazo-β-ketoesters (scheme 1.34) in the synthesis of cyclopentanones also demonstrated regiochemical properties of the rhodium-catalysed reactions, along with the electronic influences of the substrates. Firstly, the stereoselectivity across the newly formed C-C bond favours the *trans*-products (scheme 1.34). Secondly, the formation of **1.89** from **1.88** showed that the C-H insertion reaction proceeds preferentially over the usually efficient intramolecular cyclopropanation,[64] although they reported the isolation of the cyclopropane as a by-product in 10 % yield. Finally, the formation of **1.91** from **1.90** showed that the C-H insertion into a methylene group is much favoured over insertion into a methyl C-H bond. They also showed that the insertion into methine C-H bonds was preferential to methylene groups. Further work in this area determined that not only was 5-membered ring formation preferred, but also electronic effects were indeed a very important variable in determining the course of such C-H insertions.[65] The reasoning behind why reactivity decreases with reduced substitution of the aliphatic C-H centre undergoing insertion, is due to the electron donating effect of the alkyl substituent groups. Greater substitution heightens the electron density of the C-H bond and increases its reactivity towards electrophilic carbenoid attack. Therefore the order of reactivity is methyl<methylene<methine.[65]



Scheme 1.35 Electronic deactivation of C-H bonds to Rhodium carbenoid insertion.

Later work showed that an even greater inductive effect could be observed using esters. Stork and Nakatani showed that no C-H insertion was observed α to the carboxyl group when diazoketone **1.92** was treated with rhodium acetate, only insertion was observed at the proximal aliphatic chain to give cyclopentanone **1.93** (scheme 1.35).[66]

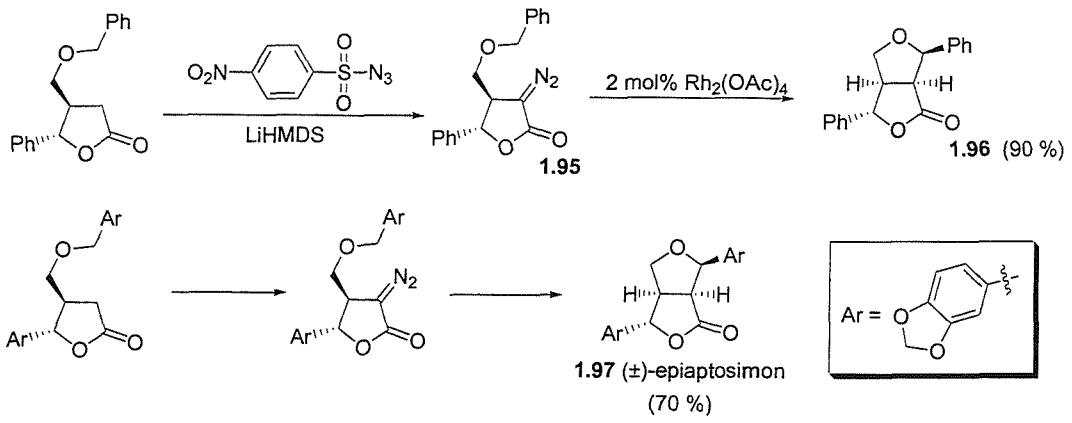
Conversely, the idea of increased reactivity of electron rich C-H bonds to insertion from rhodium carbenoids was demonstrated by work carried out by Adams and coworkers.[67,68]



Scheme 1.36 Influence of a heteroatom on carbenoid C-H insertion.

They utilised an α-heteroatom ether to control the selective C-H insertion α to the oxygen, to give the furanone product **1.94** without any regioisomer being observed (scheme 1.36).

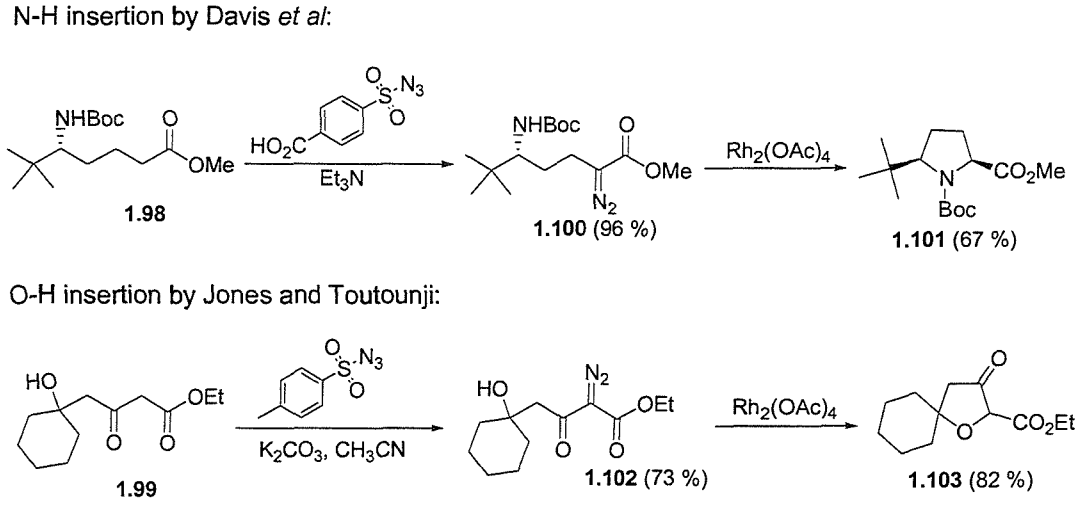
Brown and coworkers exploited some of the observed electronic properties outlined above in total synthesise of furofuranones.[69] Initially synthesising a diazolactone substrate **1.95** by diazo-transfer from the starting lactone using 4-nitrobenzenesulfonyl azide (scheme 1.37), the application of rhodium (II) acetate dimer gave the desired ring closed furofuranone **1.96** with excellent yield. Indeed the same methodology was applied to the synthesis of (±)-epiaptosimon (**1.97**) to equally good effect.



Scheme 1.37 Synthesis of furofuranone lactones using a C-H insertion ring closing.

Brown *et al* later elaborated the chemistry in order to synthesise some other furofurans (±)-fargesin and (±)-epimagnolin A, a major subclass of lignan natural product.[70]

As well as C-H insertion reactions catalysed by rhodium complexes, the insertion into other bonds has been achieved. Davis *et al* demonstrated that N-H bond insertions were possible using rhodium carbenoids generated from diazo intermediates such as **1.100**, leading to proline derivatives such as **1.101** (scheme 1.38).[71] In this case, the intermediate diazo compound **1.100** was generated from a diazo-transfer reaction with **1.98** using carboxybenzene sulfonyl azide with excellent yield.

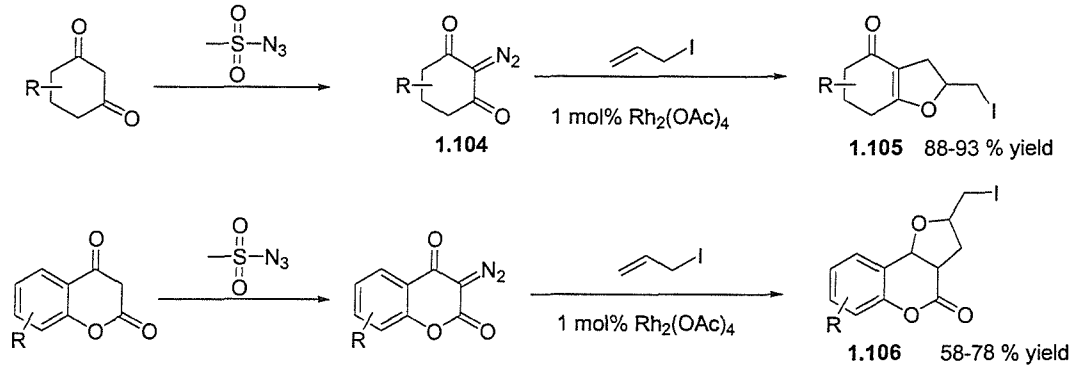


Scheme 1.38 N-H and O-H insertion reactions with generated rhodium carbenoids.

Also, the insertion into an O-H bond has been demonstrated by a number of groups[72] but more recently by Jones and Toutounji.[73] In their approach to spirocyclic

tetrahydrofurans, the desired diazo intermediate **1.102** was synthesised from **1.99** by using tosyl azide with potassium carbonate as base. Subsequent treatment of the diazo ester **1.102** with $Rh_2(OAc)_4$ afforded the desired spirocycle **1.103** in good yield (scheme 1.38).

The use of a rhodium catalyst in conjunction with diazo containing compounds has also been used with allyl halides. Lee and Suk reacted diazo-intermediates with a rhodium catalyst, and with allyl halides in order to access dihydrofuran products.[74] Their work showed that a variety of diazodicarbonyl substrates (**1.104**) could be synthesised easily using mesyl azide as a diazo-transfer reagent. Subsequent treatment with allyl iodide and rhodium acetate accessed a variety of iodomethyldihydrofurans **1.105** (scheme 1.39) *via* a 1,3-dipolar cycloaddition. Also, their work showed that the same methodology could be applied to similar substrates accessing biologically interesting iodomethyldihydrofurocoumarin derivatives (**1.106**).[75] After further treatment with DBU, the dihydrofurocoumarins (**1.106**) afforded only the 2-methyl furans, however using iodomethyldihydrofurans (**1.105**), either an *exo*-olefin or a 2-methyl furan product was obtained depending on the reaction conditions.

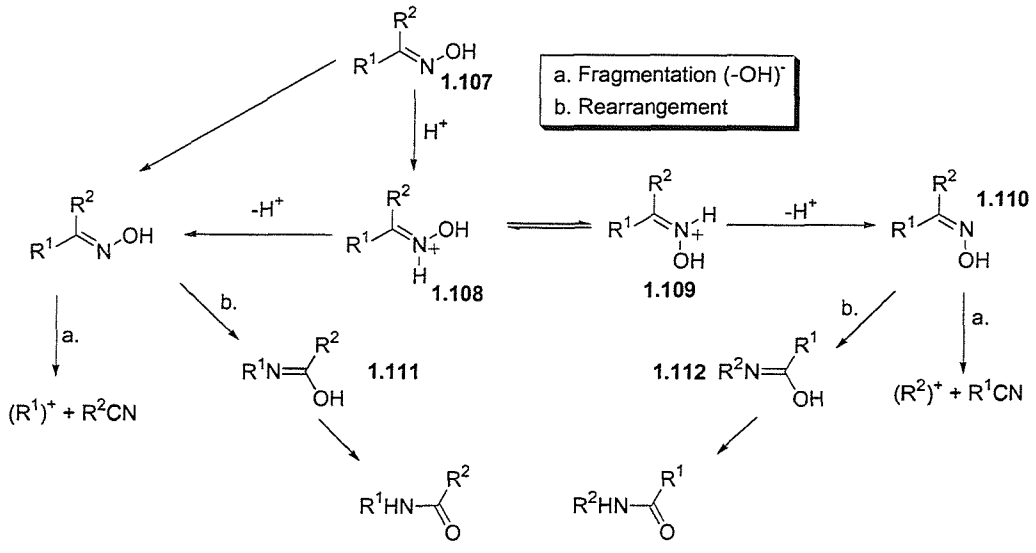


Scheme 1.39 Dihydrofuran derivatives from diazodicarbonyl intermediates.

1.3 The Beckmann rearrangement

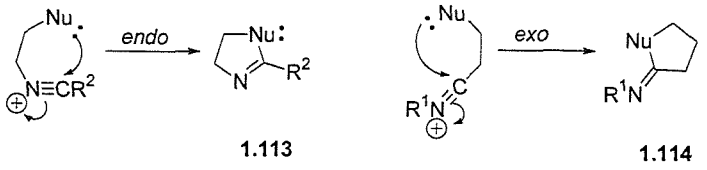
The Beckmann rearrangement, one of the oldest reactions in organic chemistry, was discovered by Beckmann in 1886.[76] It can be generally described as the acid-catalysed isomerisation of an oxime species to the corresponding amide. This transformation can be achieved a number of ways. For example, certain oximes that

are not acid stable and fragment under acidic conditions can undergo a Beckmann rearrangement when photolyzed. As shown in scheme 1.40, the attack of the acid on the nitrogen of **1.107** leads to **1.108**, this can then isomerise to **1.109**. The fact that isomerisation is possible accounts for the occurrence of nonstereospecificity in some Beckmann rearrangements. The subsequent breaking of the nitrogen-oxygen bond can occur by one of two routes. Simultaneous migration gives the rearrangement products **1.111** and **1.112**, cleavage gives the fragmentation products. The imidates **1.111** and **1.112** formed as a result of rearrangement may then either hydrolyse directly to give the final amide product or undergo a Chapman rearrangement[77] to give an *N*-substituted amide, which is hydrolysed on workup.



Scheme 1.40 Acid mediated Beckmann rearrangement.

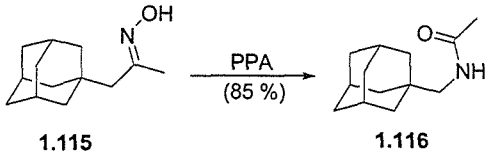
The formation of the imidate is not the only route that can be taken, in some cases the formation of free nitrilium ions results. In instances where a nucleophile is present in the starting oxime, ring closure is possible (scheme 1.41). The mode by which this is achieved, and therefore the product obtained, depends on the position of the nucleophile within the starting oxime. If the nucleophile is *anti* to the hydroxyl of the oxime (R^1) the cyclisation proceeds by an *endo* route to afford a heterocycle such as **1.113**. When the nucleophile is *syn* the cyclisation goes by an *exo* route and results in an *N*-alkylcycloalkanimine such as **1.114**.[76]



Scheme 1.41 Cyclisation resulting from oxime starting material.

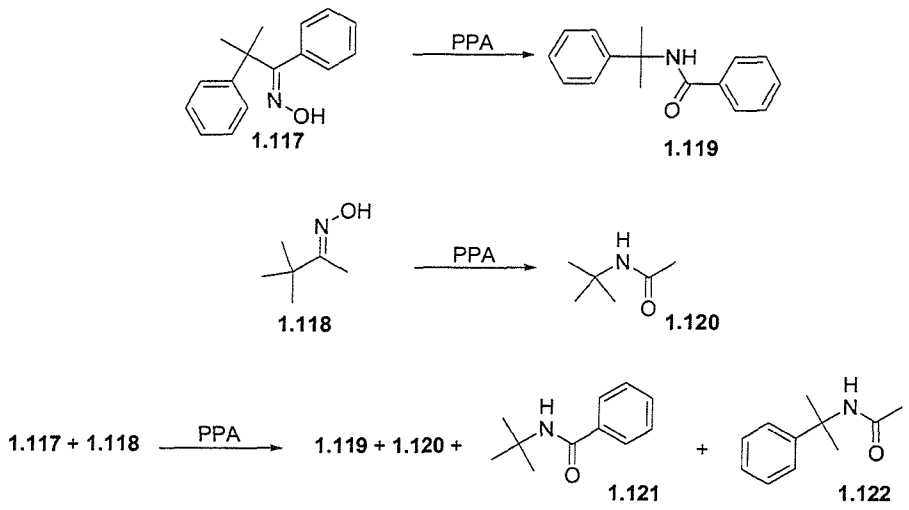
1.3.2 Reagents used to induce Beckmann rearrangements

Popular reagents used to induce the Beckmann rearrangement include phosphorus pentachloride, and for substrates that are not acid sensitive, polyphosphoric acid (PPA). A good example of the use of PPA is the rearrangement of **1.115**, adamantylacetone oxime (scheme 1.42).[78]



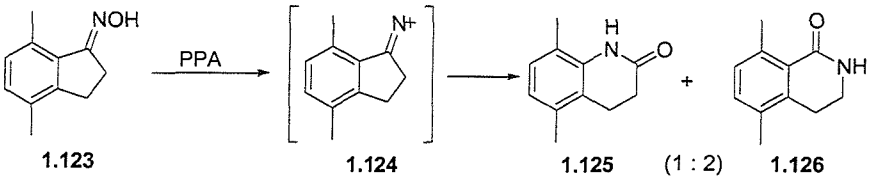
Scheme 1.42 Polyphosphoric acid induced Beckmann rearrangement.

In the case of the reaction of PPA with adamantylacetone oxime (**1.115**) the conversion to the corresponding amide **1.116** is very good, however it has been shown that such a reagent is not ideal for the conversion of unsaturated oxime substrates. A number of acid-catalysed rearrangements using PPA have been shown to proceed *via* a fragmentation-recombination route and hence there is no retention of configuration. In experiments using a pair of oximes **1.117** and **1.118** (scheme 1.43), it was shown that individually the oximes gave their respective amides (**1.119** and **1.120**) in good yield. However, when the two oximes were reacted in the same pot, crossover products **1.121** and **1.122** were also observed.[79]



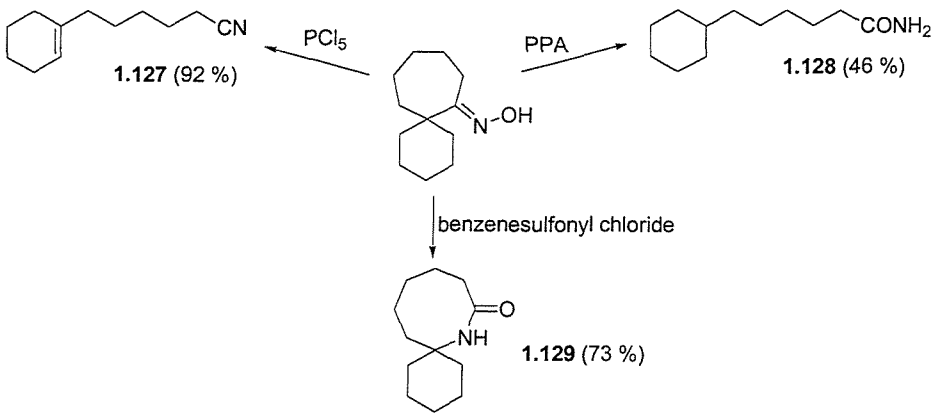
Scheme 1.43 Fragmentation-recombination mechanism using PPA.

Early literature discussing the mechanism of the Beckmann rearrangement suggests a free nitrenium ion as an intermediate (scheme 1.44). Such a mechanism is often used in order to explain the observation of *syn* migration. The action of PPA on dimethylindanone oxime (**1.123**) gives a 1:2 mixture of lactams **1.125** and **1.126** in 48 % yield and is thought to proceed *via* a nitrenium ion such as **1.124**.[80]



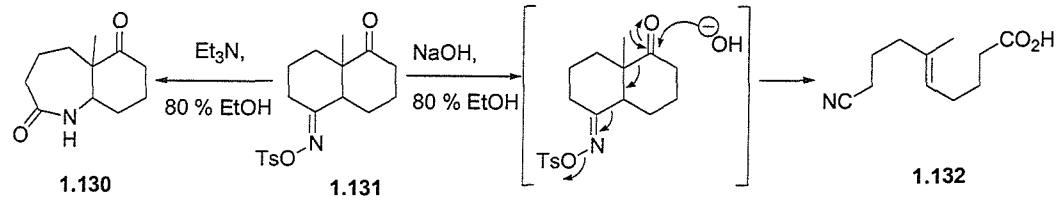
Scheme 1.44 Nitrenium ion intermediate in the Beckmann rearrangement.

In many cases the fragmentation of oximes to give a nitrile product is usually an unwanted side-reaction. The synthesis of lactam spirocycle **1.129** could not be achieved using phosphorus pentachloride, which only afforded the alkenyl nitrile **1.127** (scheme 1.45). [81] Use of polyphosphoric acid yielded amide **1.128** as a product, however the desired spirocycle **1.129** could be accessed by reaction of the oxime with benzenesulfonyl chloride.



Scheme 1.45 Spirolactam synthesis by Beckmann rearrangement.

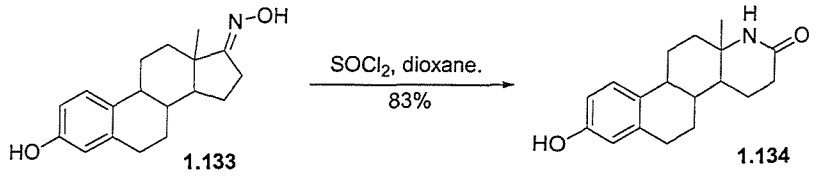
To reduce fragmentation as a side reaction, rearrangement can be carried out using sulfonyl chloride reagents, although some examples of fragmentation have also been demonstrated with oxime tosylates (scheme 1.46). Exposure of compound **1.131** to triethylamine results in the formation of lactam **1.130**. By contrast, the use of sodium hydroxide in 80 % ethanol gave the nitrile fragmentation product **1.132**.[82]



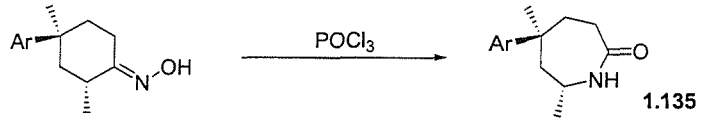
Scheme 1.46 Oxime fragmentation.

Other commonly used reagents employed to facilitate the Beckmann rearrangement of oximes are thionyl chloride and phosphorus oxychloride. Regan and Hayes showed that estrone oxime (**1.133**) could be treated with thionyl chloride in order to access the corresponding lactam **1.134**.[83] Phosphorus oxychloride has also been used to good effect on a number of occasions and here the example by Sainsbury *et al* of a ring expansion from a cyclohexyl oxime derivative to give **1.135** is depicted (scheme 1.47).[84]

Regan and Hayes:

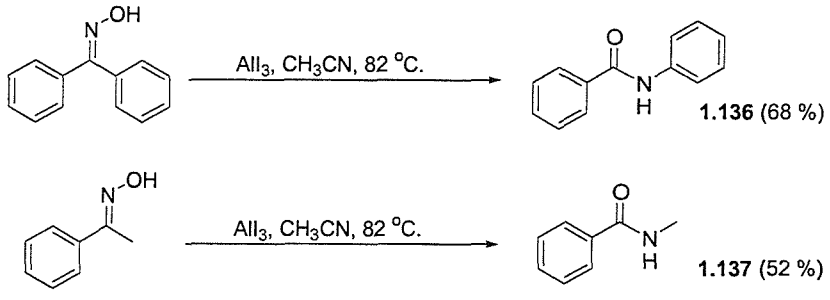


Sainsbury *et al*:



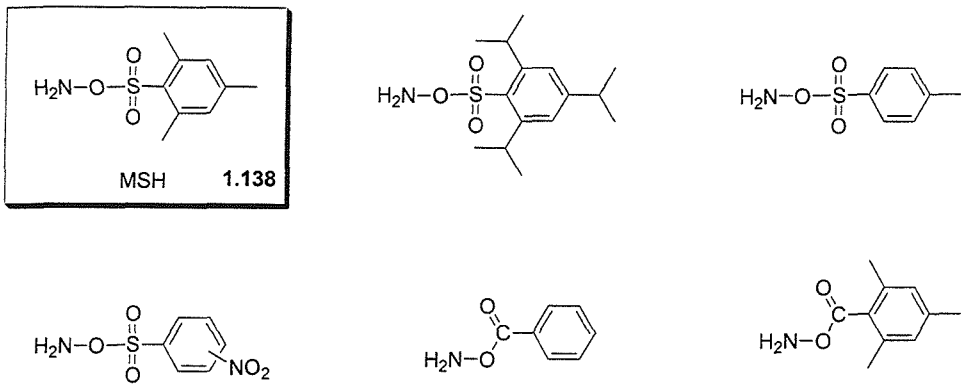
Scheme 1.47 Beckmann rearrangements using $SOCl_2$ and $POCl_3$.

One of the more unusual examples of a reagent being used in order to carry out a Beckmann rearrangement was published by Sandhu and co-workers.[85] In their investigation into the dehydration of oximes to give nitriles, they reported the isolation of amide product **1.136** and surprisingly **1.137**. They have therefore shown that AlI_3 can be used in order to carry out Lewis acid promoted Beckmann rearrangements (scheme 1.48).



Scheme 1.48 Beckmann rearrangements promoted by aluminium iodide.

Despite there being many reagents that can be used to rearrange oximes to amides, probably the most useful and interesting class of compounds used as Beckmann reagents is the *O*-sulfonylhydroxylamines, a simple example being hydroxylaminesulfonic acid (H_2NOSO_3H). These reagents are used in order to convert ketones directly to amides and lactams under mild conditions. Scheme 1.49 shows a number of different reagents that have been used to effect direct Beckmann rearrangement of ketones.[86]



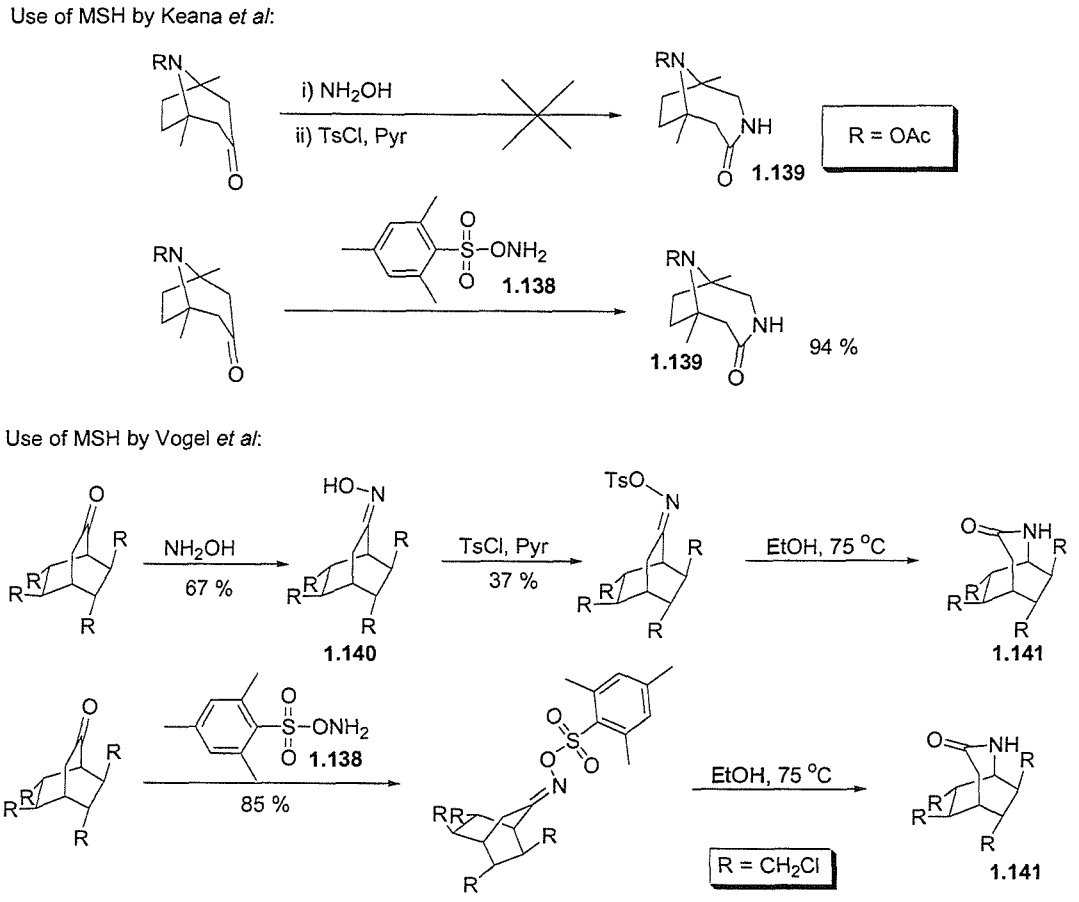
Scheme 1.49 Some examples of hydroxylamine Beckmann reagents.

The reagent that has emerged as the reagent of choice for the direct Beckmann rearrangement of ketone substrates is MSH (mesitylene-*O*-sulfonyl hydroxylamine, **1.138**).

1.3.3 Selected applications of mesitylene-*O*-sulfonyl hydroxylamine (MSH)

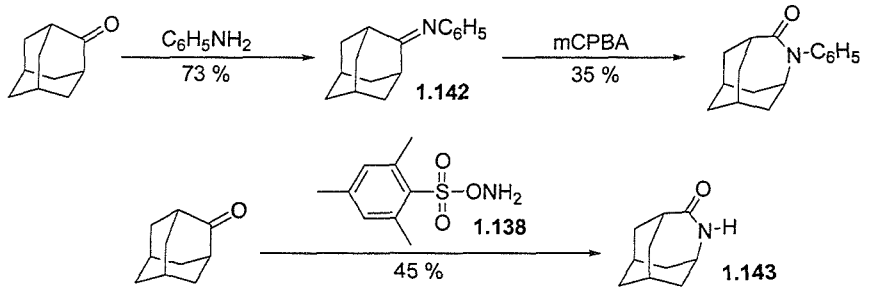
The use of MSH (**1.138**) has been shown by a number of research groups to be a superior means to carry out the direct Beckmann rearrangement of ketone substrates. During the course of their research, Keana and coworkers attempted to carry out a Beckmann rearrangement by a standard route *via* an oxime and then treatment with tosyl chloride to promote rearrangement to amide product **1.139** (scheme 1.50).[87] However, the two-step procedure failed whereas direct reaction of the ketone with MSH gave the amide product **1.139** in 94 % yield.

The Keana group were not the only researchers to expose the shortcomings of using tosyl chloride to rearrange oximes. Vogel and colleagues showed that the use of MSH gave much higher yield of amide product **1.141** than conversion of the ketone to oxime **1.140** and rearrangement with tosyl chloride (scheme 1.50).[88]



Scheme 1.50 Use of MSH in the direct Beckmann rearrangement of ketones.

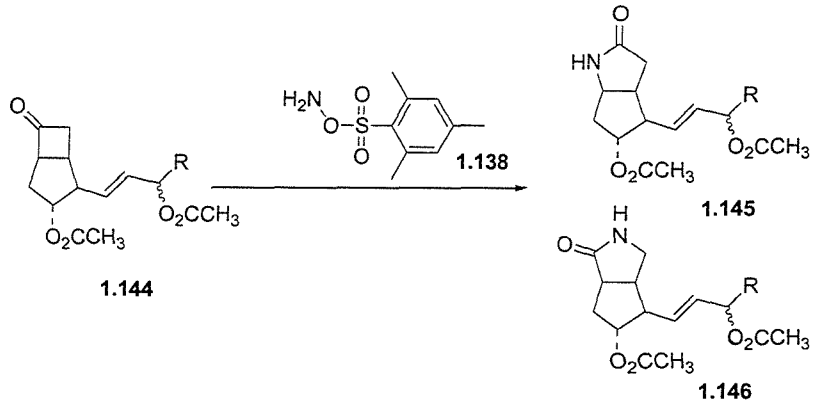
Indeed MSH has been used to overcome problems with other reactions in order to access amide products. Towards the synthesis of adamantane derivatives, Sasaki *et al* initially attempted to access the required amide by reaction of the ketone starting material with aniline to form an intermediate imine, which was subsequently treated with *m*CPBA in order to afford the desired amide (scheme 1.51).[89]



Scheme 1.51 Synthesis of adamantane derivatives using MSH.

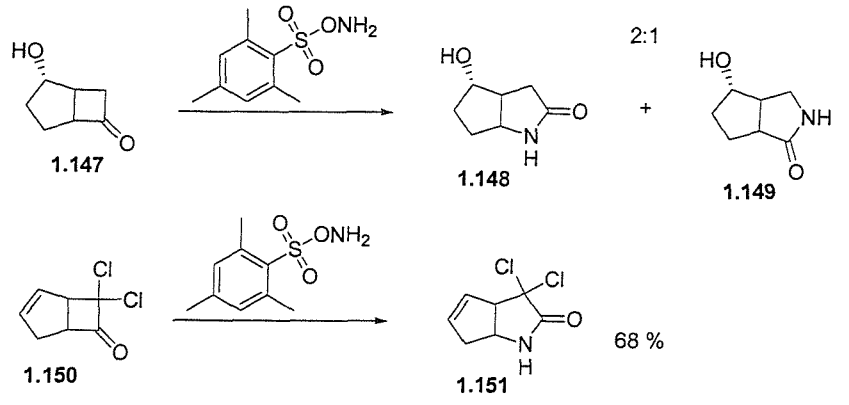
The route had problems in that the intermediate adamantylideneaniline **1.142** was very unstable. In order to circumvent this problem, MSH was used and the amide product **1.143** was accessed directly from the ketone instead.

As shown above, the conversion of symmetrical ketone substrates can be achieved with good yield. However, when the Beckmann rearrangement is undertaken with unsymmetrical ketones like **1.144** using MSH, the result is a mixture of lactams **1.145** and **1.146** in a ratio of 4:1 (scheme 1.52).[90] This ring expansion of cyclobutanone **1.144** is not especially selective the synthesis of a single regioisomer and the synthesis of pyrrolidone rings by this route has therefore been investigated thoroughly to try and improve the reaction.



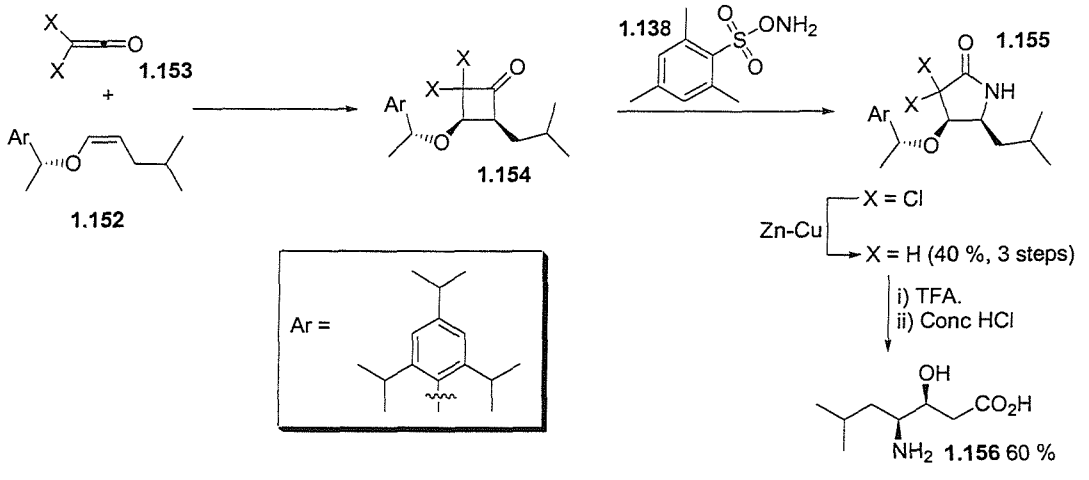
Scheme 1.52 An example of limited regioselectivity of the Beckmann reagent.

Investigations by Luh *et al* have developed a regioselective synthesis of pyrrolidones using MSH (scheme 1.53).[91] Initial reactions showed that little selectivity was observed with a standard cyclobutanone **1.147**, the pyrrolidinone products **1.148** and **1.149** being obtained in a ratio of 2:1. However, they hypothesised that the use of electronegative groups on one flank of the carbonyl functionality of the cyclobutanone could control which group migrates to nitrogen, by influencing the stereochemistry of the intermediate sulfonyl oxime. Indeed their results showed that the electronic effects had a marked effect on the regioselectivity of the reaction, only giving a single regioisomer.



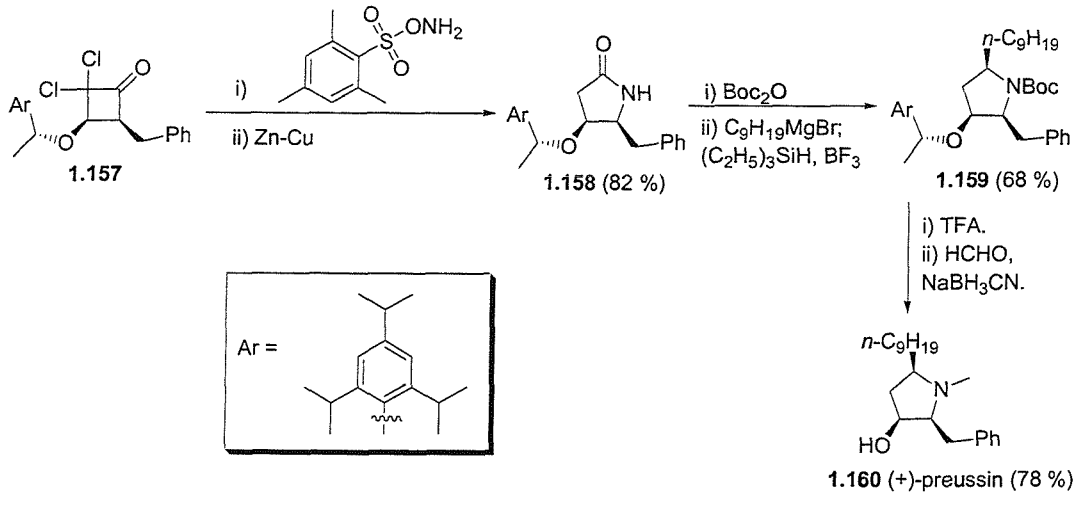
Scheme 1.53 Regioselective Beckmann rearrangement using MSH.

The modified regioselective reaction was a huge improvement and has been used subsequently to good effect. Nebois and Greene employed the method in the synthesis of (-)-statine (**1.156**), which is an important intermediate in the synthesis of several acid protease inhibitors.[92] Many previously reported syntheses of this hydroxy amino acid had failed to yield stereochemically pure material. In this case, starting with enol ether **1.152**, cycloaddition with dichloroketene **1.153** gave the required dichlorocyclobutanone **1.154**, as a 94:6 ratio of diastereomeric cycloadducts (scheme 1.54). Regioselective Beckmann rearrangement of this substrate was then possible with MSH (**1.138**) followed by treatment with zinc/copper to remove the chlorine atoms. Final treatment of the lactam with acid gives (-)-statine (**1.156**).



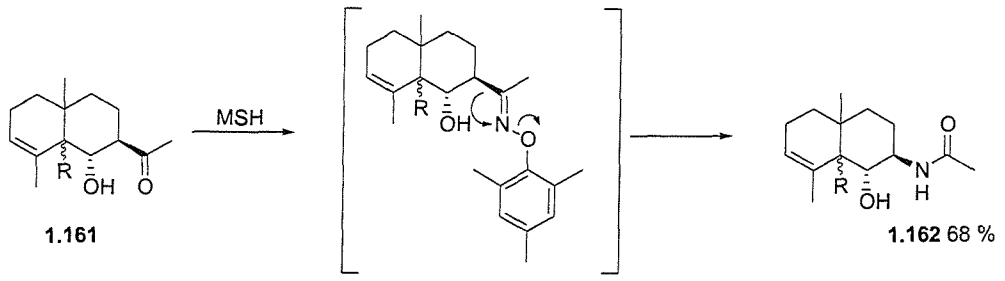
Scheme 1.54 Stereoselective synthesis of (-)-statine using a Beckmann rearrangement.

Indeed, the Greene group went on to show the chemistry to work superbly well in the synthesis of (+)-preussin, an antifungal agent (scheme 1.55). Previous syntheses of this compound had been achieved by using a chiral pool starting material. Here, the substituted dichlorobutanone intermediate **1.157** was synthesised as for the previous route to (-)-statine by [2+2] cycloaddition. Beckmann reaction and reduction gave the pyrrolidone **1.158** with excellent yield, and subsequent Boc protection, Grignard reaction and reduction afforded cyclic amine **1.159**. Deprotection and reductive alkylation gave (+)-preussin (**1.160**) in overall 15 % in 10 steps.[93]



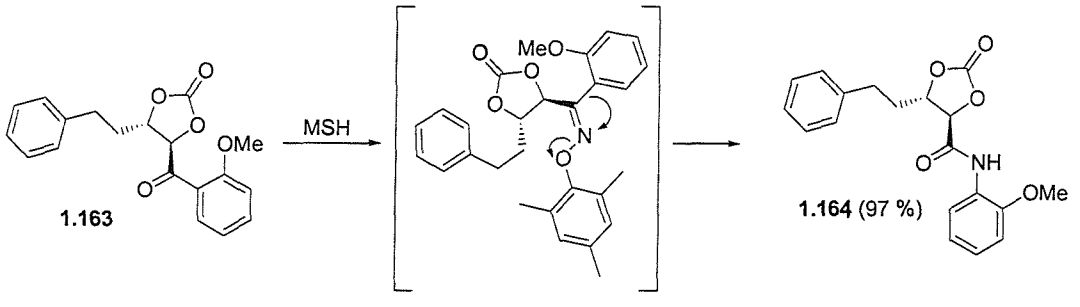
Scheme 1.55 Synthesis of (+)-preussin using a Beckmann rearrangement with MSH.

The rearrangement of unsymmetrical oximes can also be influenced by steric interactions. If there is a large difference in the size of the substituents flanking the starting carbonyl functionality, the formation of the sulfonyl oxime is influenced *anti* to the larger group, which means when rearrangement occurs, the larger group migrates to nitrogen. This is demonstrated by research carried out by Nagano and coworkers who selectively synthesised amide **1.162** from ketone **1.161** using MSH (scheme 1.56).[94]



Scheme 1.56 Selective oxime rearrangement influenced to substituent size.

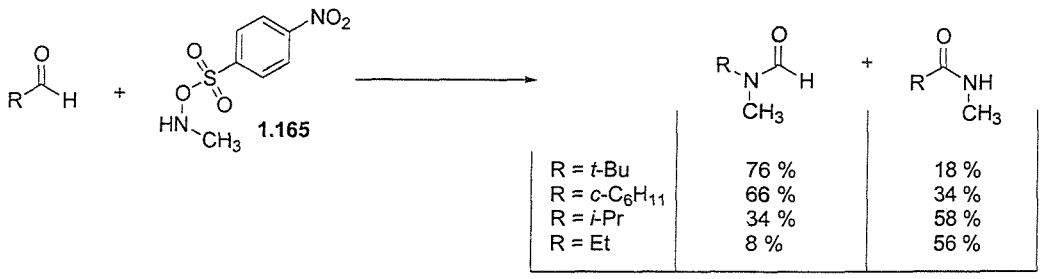
Selective rearrangement was also achieved by Shibasaki *et al.*[95,96] In this case, using MSH in order to effect the Beckmann rearrangement of ketone **1.163**. Amide **1.164** is formed with the aryl group migrating to nitrogen, again with excellent regioselectivity (scheme 1.57).



Scheme 1.57 Example of a selective Beckmann rearrangement.

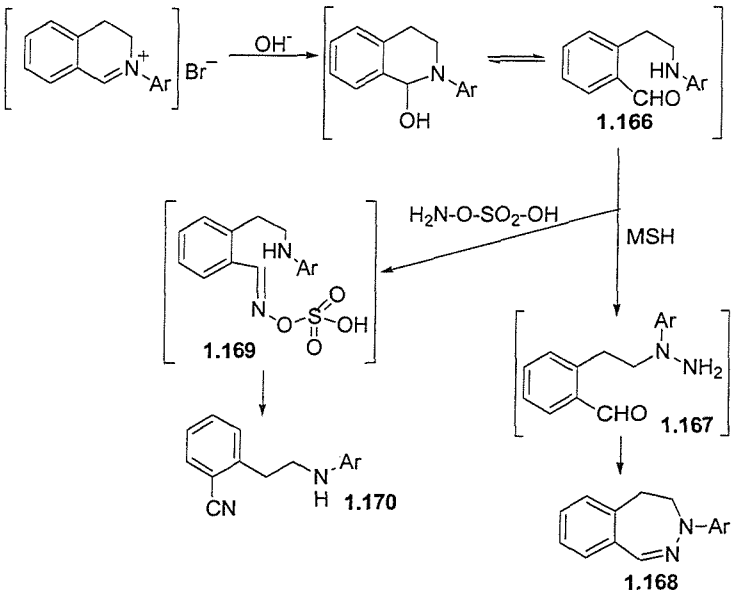
In the cases outlined above, a secondary amine product is observed as the returned product. Interesting work published by Hoffman and Salvador, employed an *N*-alkylated *O*-sulfonylhydroxylamine reagent **1.165** which was reacted with aldehydes in order to access more substituted amide products (scheme 1.58). [97]

Undoubtedly the principal use for *O*-sulfonyl hydroxylamines, and MSH in particular, is for the synthesis of amides from ketones by Beckmann rearrangement. However, these reagents have been used for a number of other applications.



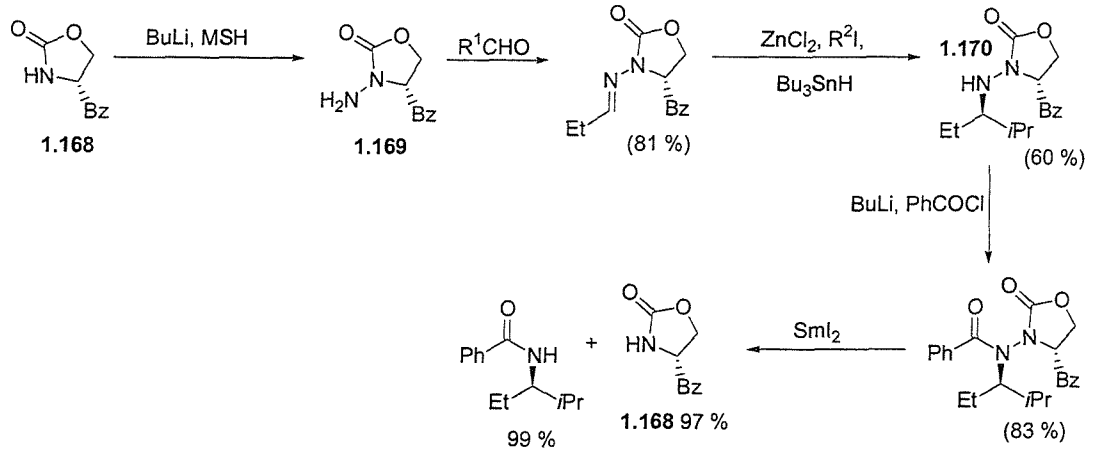
Scheme 1.58 The use of an *N*-alkylsulfonyl hydroxylamine.

An interesting use of MSH came in the synthesis of benzodiazepines (scheme 1.59).[98] MSH is actually being used as a nitrogen transfer reagent involved in the ring closure step to form the heterocyclic ring. This is thought to occur *via* a hydrazine intermediate **1.167**, which is then able to undergo an intramolecular condensation with the adjacent aldehyde to close the ring giving benzodiazepine **1.168**. A number of *N*-aromatic substituents have been tried for this reaction and all seem to give between 47 and 57 % yield. It is interesting to note that in the presence of hydroxylamine *O*-sulfonic acid rather than MSH the benzodiazepine product is not observed. The hydroxylamine is thought to react first with the aldehyde **1.166** and the resulting oxime intermediate **1.169** is then able to fragment to give nitrile **1.170**.



Scheme 1.59 Synthesis of benzdiazepines using MSH.

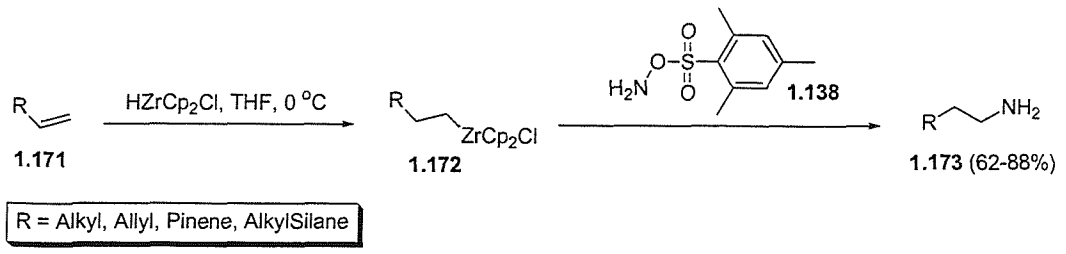
Freistad and Qin have also used MSH as a nitrogen-transfer reagent to synthesise *N*-amino derivatives of oxazolidinones (scheme 1.60).[99] The chiral oxazolidinone **1.168** was used as an auxillary intermediate for stereoselective syntheses of amines or amides, the starting oxazilidinone **1.168** being returned at the end.



Scheme 1.60 *N*-Amino oxazolidinone synthesis using MSH.

The reaction of oxazolidinone **1.168** with MSH gave the desired *N*-amino oxazolidinone **1.169**, which after condensation with an aldehyde and alkylation gave intermediate **1.170** in 60 % yield. Cleavage of the N-N bond was possible to return oxazolidinone **1.168** and the amide or amine product.

Amines can be synthesised using MSH by other routes as well. The reaction of MSH with organoboranes to access primary amines has been reported.[86] However more recently Zheng and Srebnik have demonstrated the effective reaction of MSH with Zirconocene alkyl chlorides in order to synthesise primary amines.[100] Reacting alkene **1.171** with $HZrCp_2Cl$ accessed the required organozirconocene **1.172** by hydrozirconation (scheme 1.61). Treatment of **1.172** with MSH afforded the desired primary amine **1.173**. Yields of between 62 to 88 % were observed for a number of examples determined over both steps.



Scheme 1.61 Reaction of MSH with organozirconocenes to give amines.

All the reactions reviewed above, using the *O*-sulfonylhydroxylamine reagents have the benefit of proceeding under very mild conditions and in many cases the yields are very good. Many other compounds react in different ways with this class of reagent and so it is clear how valuable such reagents can be for synthesis. However, the *O*-sulfonyl hydroxylamine class of compounds (including MSH) do suffer from stability and handling issues and are sometimes explosive in nature. The development of more stable equivalents of MSH would therefore be highly desirable.

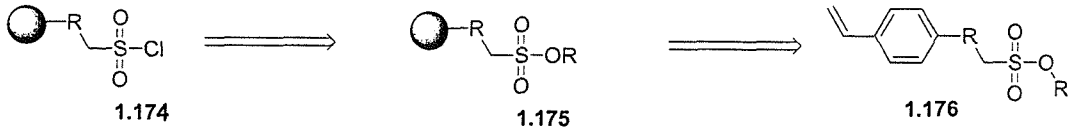
1.4 Aims and Objectives

1.4.1 Why investigate sulfonyl chloride functionalised resins?

Currently, sulfonyl chloride resins are commercially available however only aryl sulfonyl chloride resins are provided. These resins are produced by the chlorosulfonation of unfunctionalised polystyrene, which is not an ideal way to synthesise sulfonyl chloride resins, as it is difficult to control and get reproducible loadings of sulfonyl chloride.[101-104] Limitations have been determined with such resins. To use an analogy, tosyl chloride is not as reactive as mesyl chloride and the aryl nature of the resins means that they are unsuitable for certain applications. This could be due to their reactivity or indeed it may be due to steric effects as the reactive functionality of the resin is in very close proximity to the resin backbone of the resin or more likely a combination of the two factors. Therefore, a number of routes to synthesise a variety of sulfonyl chloride resins have been determined for investigation. These approaches are introduced briefly below, with an overview of some of the investigations undertaken.

1.4.2 Synthesis of a monomer to access sulfonyl chloride resins by copolymerisation.

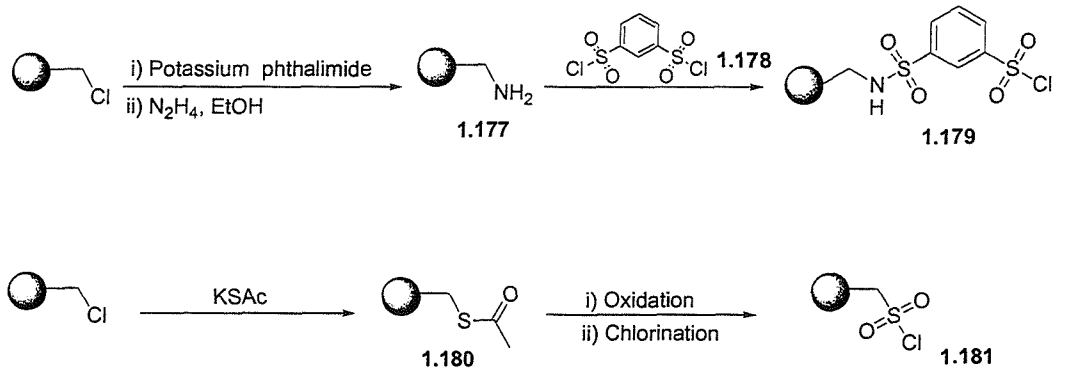
A number of different routes have been devised in order to obtain a reliable sulfonyl chloride resin reproducibly. The most radical being the use of a sulfonate monomer **1.176** in a copolymerisation reaction with styrene and divinyl benzene in order to give the corresponding polystyrene resin functionalised with sulfonate groups **1.175**. The sulfonate moiety could then be deprotected to give the sulfonic acid salt, allowing facile conversion to the active sulfonyl chloride resin **1.175** (scheme 1.62).



Scheme 1.62 Retrosynthetic analysis of resin **1.174**.

1.4.3 Sulfonyl chloride resin from Merrifield resin

Merrifield resin (chloromethyl polystyrene) has been a convenient starting point for the synthesis of a variety of functionalised resins in the past.[1] One of the proposed routes to access sulfonyl chloride resins would be to use Merrifield resin as a starting point and convert to aminomethyl resin (**1.177**) as an intermediate (scheme 1.63).



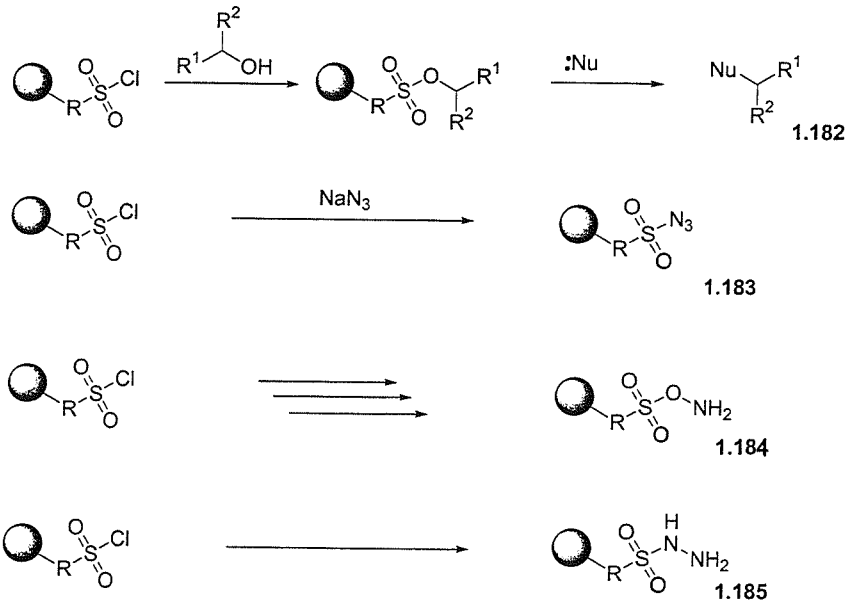
Scheme 1.63 Proposed syntheses of sulfonyl chloride resins.

The synthesis of aminomethyl resins in this way is well documented in the literature.[105] The amine resin could be used with a disulfonyl chloride compound in order to access a sulfonamide-linked sulfonyl chloride resin **1.179**. The most viable option for the disulfonyl chloride being 1,3-benzenedisulfonyl chloride (**1.178**), which is commercially available and very cheap (scheme 1.63). An anticipated potential problem is crossing-linking between the disulfonyl chloride and two resin-bound amine moieties, however this should be overcome easily by using an excess of 1,3-benzenedisulfonyl chloride (**1.178**).

An alternative sulfonyl chloride resin could be synthesised from Merrifield resin *via* thioacetate resin intermediate **1.180** (scheme 1.63). Reaction of potassium thioacetate with Merrifield resin would give the thioacetate resin **1.180** by a facile route, and subsequent oxidation to a sulfonic acid, followed by chlorination, would furnish alkyl sulfonyl chloride resin **1.181**. Variations on these outlined themes could be used in order to synthesise related resins with different spacer groups.

1.4.4 Synthesis and use of supported reagents

Having synthesised a variety of sulfonyl chloride resins, a number of different reagent targets will be investigated. Firstly, the use of the resins as supported "tosylating" agents will be examined by reacting with alcohols and displacement with a nucleophile to give **1.182** (scheme 1.64). Other potential uses include sulfonyl azide resin (**1.183**) and its subsequent use as a diazo-transfer reagent; the synthesis of a supported *O*-sulfonyl hydroxylamine (**1.184**) analogous to MSH (**1.138**) and its use in Beckmann rearrangements of carbonyl compounds; a supported sulfonyl hydrazine (**1.185**) which could be a potential source of diimide in order to carry out olefin reductions, or an intermediate in the synthesis of potentially synthetically important supported hydrazones.



Scheme 1.64 Proposed supported reagents containing sulfonyl functionality.

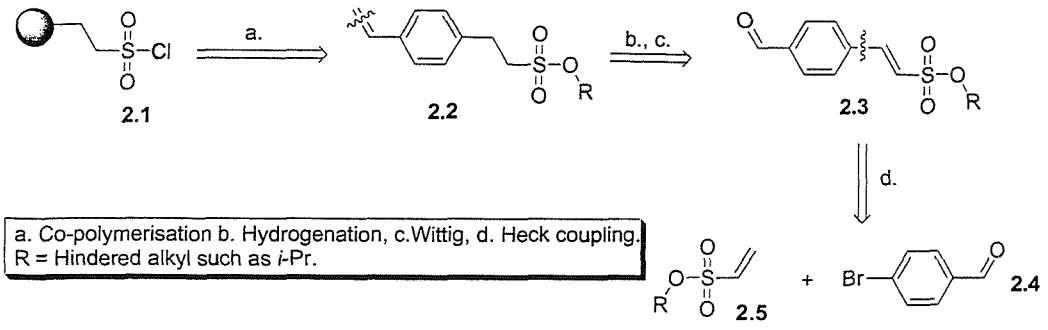
Chapter 2. Results and discussion

Monomer Synthesis

One of the routes to be investigated for the synthesis of novel sulfonyl chloride resins was the use of a co-polymerisation strategy. This involves the use of styrene, divinylbenzene (DVB) and a specifically synthesised monomer in order to access a resin loaded with the desired functionality. Here, a sulfonate ester was designed as a monomer to use in a co-polymerisation reaction, as the resulting sulfonate ester resin could be deprotected and chlorinated to afford the desired sulfonyl chloride.

2.1 Retrosynthetic analysis of Monomer (2.2)

The structure of monomer (**2.2**) was determined retrosynthetically for a co-polymerisation route to access an alkyl sulfonyl chloride resin **2.1** (scheme 2.1). Bertini and coworkers showed that sulfonate monomers are stable to co-polymerisation reactions.[106] The major retrosynthetic disconnections initially would be at the styryl double bond, back to an aldehyde **2.3** and disconnection of **2.3** where shown (scheme 2.1). In order to arrive at the desired monomer **2.2** it can be envisaged using a palladium catalysed Heck coupling. Starting from a vinyl sulfonate **2.5** and 4-bromobenzaldehyde (**2.4**) in order to give **2.3**, followed by reduction of the resulting double bond. The styrene functionality could then be installed by Wittig olefination of the aldehyde functionality, giving the desired monomer **2.2**. The palladium coupling of 4-bromobenzaldehyde with methyl acrylate has been reported by Heck *et al.* with the aldehyde moiety unprotected, chemistry which could be reasonably assumed to be applicable to the vinyl sulfonate **2.5**.[107] Indeed, precedent for palladium couplings of aryl bromides with vinyl sulfonates does exist.[108]

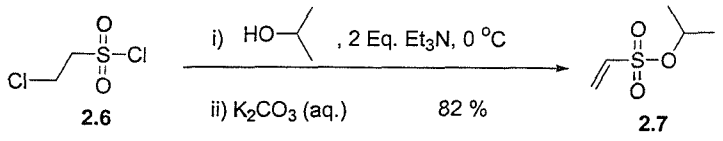


Scheme 2.1 Retrosynthetic analysis for the desired monomer.

2.2 Initial attempted synthesis of the desired monomer (2.2)

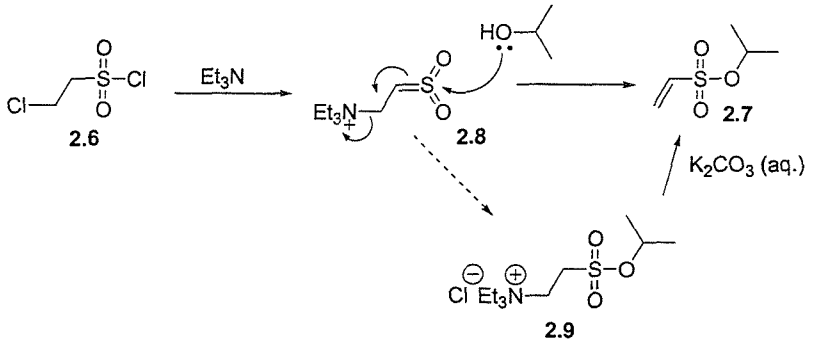
In 1982 King *et al.* showed that it was possible to use chloroethanesulfonyl chloride (**2.6**) and an appropriate alcohol to produce the corresponding vinyl sulfonate esters.[109] Their method involved the use of between 3 and 4 equivalents of trimethylamine, which was condensed in a cooled dropping funnel at 0 °C and excess chloroethanesulfonyl chloride. We reasoned that the reaction could be simplified by using 2 equivalents of triethylamine (with respect to the sulfonyl chloride) and a slight excess of alcohol (in this case *iso*propyl alcohol), performing the reaction at 0 °C and then a further period of stirring at room temperature. *Iso*propyl sulfonate was chosen as the target substrate because Roush and co-workers had previously demonstrated the deprotection of *iso*propyl sulfonate to the corresponding sulfonate on the solid-phase.[110] This would of course be necessary after co-polymerisation of the monomer in order to access the sulfonyl chloride resin.

The reaction to form *iso*propylvinylsulfonate (**2.7**) resulted in good conversion to the product by dropwise addition of triethylamine, but attempts to purify the product by distillation failed and the product decomposed. However, the rapid addition of triethylamine to the reaction mixture improved the result and gave *iso*propylvinylsulfonate **2.7** in 82 % yield without the need for further purification.



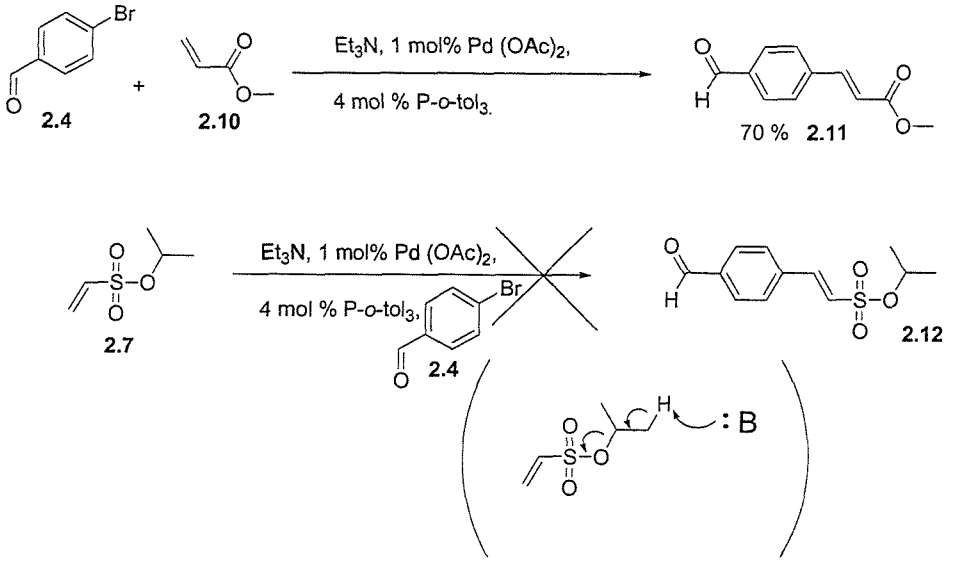
Scheme 2.2 Synthesis of *iso*propylvinyl sulfonate.

The reaction between the sulfonyl chloride and triethylamine is thought to proceed *via* a sulfene intermediate **2.8** and the introduction of the alcohol gives the desired ethenesulfonate **2.7** (scheme 2.3). In the process a significant amount of betylate **2.9** is also formed. The use of aqueous potassium carbonate at the end of the reaction converts the betylate intermediate into the desired product **2.7**.[111,112]



Scheme 2.3 King's proposed mechanism for the synthesis of vinyl sulfonates.

Having made the *iso*propyl ethenesulfonate **2.7** the next step was to carry out a palladium-catalysed vinylic substitution using 4-bromobenzaldehyde. Previous work by Heck *et al.* has shown that the protection of the aldehyde functionality is not necessary.[107] In order to verify the procedure outlined by Heck, 4-Bromobenzaldehyde (**2.4**) was coupled to methyl acrylate (**2.10**) as a model reaction (scheme 2.4) and the product **2.11** was obtained in 70 % yield after recrystallisation.



Scheme 2.4 Attempted Heck reaction of vinyl sulfonate **2.7**.

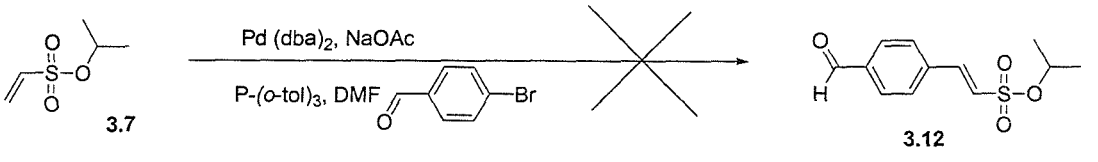
Therefore, the reaction was attempted with a mixture of the vinyl sulfonate **2.7** and 4-bromobenzaldehyde **2.4**. It was clear however from ^{1}H NMR of the crude recovery that the reaction had not proceeded to give the desired sulfonate **2.12** (scheme 2.4). The basic conditions of the reaction had caused the elimination of the *iso*propyl group from the sulfonate. Evidence could be found in the ^{1}H NMR spectrum, where the complete absence of signals from the *iso*propyl group was obvious.

2.3 Alternative Heck coupling for the synthesis of the monomer

Initially the *iso*propyl group had been chosen because as outlined earlier, previous work by Roush and Hunt had shown that the group could be removed on the solid-phase to give the sulfonate sodium salt.[110] They showed that such a group could be cleaved on the solid-phase with iodide in acetone. Unfortunately, the *iso*propyl sulfonate was found to be unstable to the Heck coupling conditions employed. There were therefore two possible solutions, use of an alternative protecting group, or use of an alternative strategy performing the reaction under milder coupling conditions. Indeed the Heck coupling has been intensively studied and reviewed.[113] A number of reports exist of Heck couplings under milder conditions[114] and even for α,β-

unsaturated sulfoxides with aryl halides.[115] In particular, Hartwig *et al.* showed that milder Heck coupling conditions can be used to couple an electron deficient aryl halide and an activated vinyl group, even at room temperature.[116,117] The method involves using $Pd(dba)_2$, NaOAc, and either P(*o*-Tol)$_3$ or P(*t*-Bu)$_3$ as ligands in DMF (scheme 2.5).

However, several attempts at carrying out the Heck coupling with the *iso*propyl vinyl sulfonate **2.7** with bromobenzaldehyde proved unsuccessful using various temperatures, $Pd(dba)_2$ and the chloroform adduct of $Pd(dba)_2$ as catalyst, and with a number of phosphines as ligands.

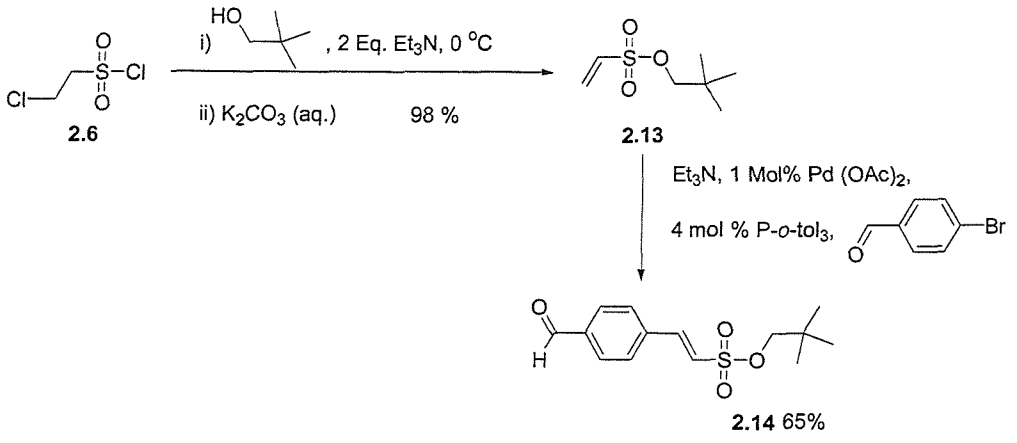


Scheme 2.5 Attempted Heck coupling under milder reaction conditions.

2.4 An alternative sulfonate protecting group

It has been shown that an *iso*propylsulfonate group was not useful in the synthesis of the desired monomer due to its instability during the Heck coupling reaction (section 1.2, 1.3), thus the use of an alternative sulfonate protecting group was investigated.

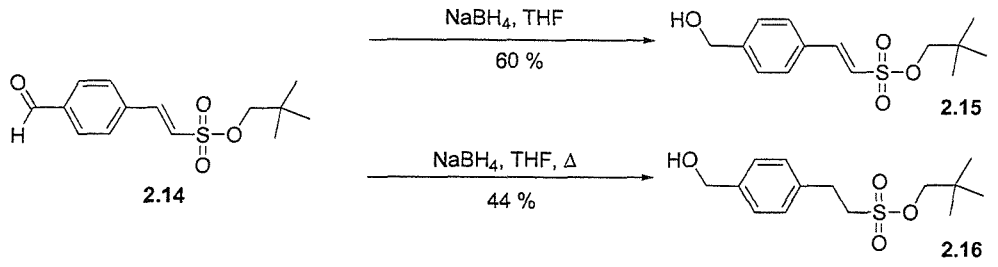
The group chosen was a *neo*pentyl sulfonate moiety, in the hope of overcoming the problem of elimination observed with the *iso*propyl group. The *neo*pentyl sulfonate **2.13** was obtained in 98 % yield using the conditions employed previously (scheme 2.6). Sulfonate **2.13** and 4-bromobenzaldehyde were then exposed to the Heck reaction conditions used and the desired *neo*pentyl sulfonate **2.14** was obtained in a respectable yield of 65%.



Scheme 2.6 Revised sulfonate synthesis and Heck coupling to give aldehyde **2.14**.

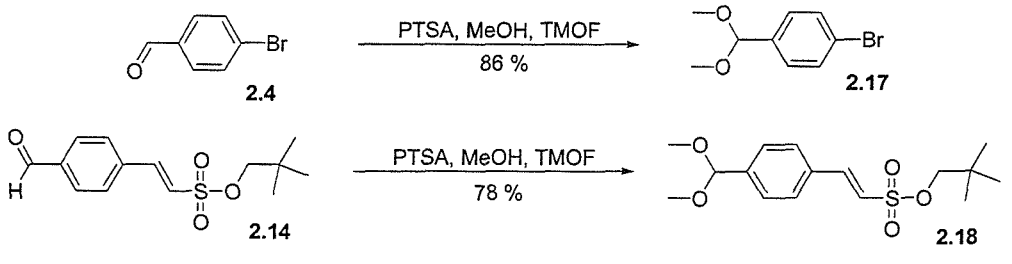
Having achieved the coupling of the vinyl sulfonate **2.13** to 4-bromobenzaldehyde the next step was the reduction of the double bond. Previous work has shown that a double bond can be selectively reduced in the presence of unprotected benzaldehyde functionalities, using Pd/C and H_2.[118-122] Such a reaction could not be achieved with substrate **2.14**, in all cases the reduction of the aldehyde was observed.

An alternative methodology was sought in order to reduce the double bond that results from the coupling. Examples of the reduction of similar substrates includes the use of a copper hydride complex $[(Ph_3P)CuH]_6$, which has also been used in the past in order to reduce α,β unsaturated sulfonates.[123,124] Widlanski and co-workers reported the use of sodium borohydride in order to reduce a vinyl sulfonate similar to substrate **2.14**, but no experimental procedure was provided with the report.[125] Initially, reduction of compound **2.14** was attempted with 2 equivalents (allowing for the reduction of the carbonyl) of sodium borohydride at room temperature. After stirring for 30 minutes, TLC analysis of the reaction showed the complete conversion of the substrate to a more polar compound, assumed to be the alcohol. After stirring for a further 48 hours to allow the slower reduction of the olefin moiety, no change was observed by TLC. As expected, the corresponding alcohol **2.15** was obtained in 60 % yield with the double bond remaining intact (scheme 2.7).



Scheme 2.7 Reduction of the vinyl sulfonate.

The experiment was repeated, this time under reflux conditions and it was possible to follow the reduction of the aldehyde as for the previous experiment and after a further 48 hours the conversion to the saturated compound **2.16** was observed, albeit in disappointing yield. Having determined that the double bond could be reduced using sodium borohydride the next step was to choose an appropriate protecting group for the carbonyl functionality. A dimethoxy acetal protecting group was chosen because it could be easily removed by an aqueous acid wash after the borohydride reduction. [126] The initial approach was to protect the aldehyde functionality at the beginning of the synthesis prior to the Heck coupling. The treatment of 4-bromobenzaldehyde (**2.4**) with *p*-toluenesulfonic acid (PTSA) in methanol gave the corresponding dimethoxy acetal **2.17** in 86 % yield (scheme 2.8). The protected bromobenzaldehyde **2.17** was carried forward to the Heck coupling reaction with vinylsulfonate **2.13**. The coupling proved to be much less effective compared to the coupling using the unprotected aldehyde.

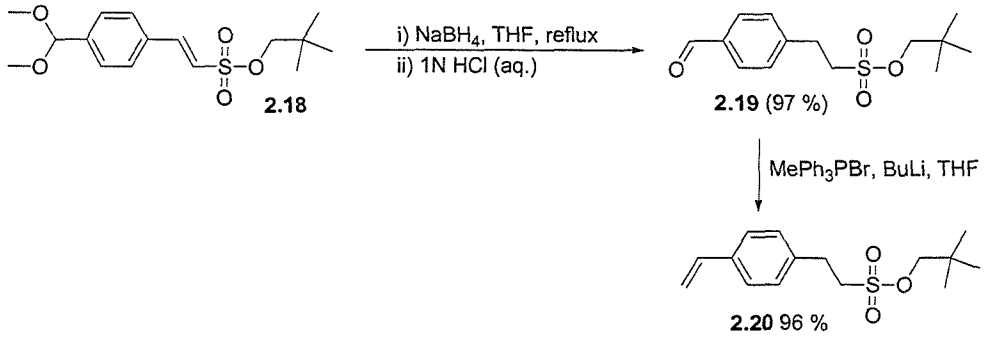


Scheme 2.8 Aldehyde protection steps.

The ^{1}H NMR of the crude reaction mixture showed that the dimethoxy acetal protecting group was in fact not stable to the Heck coupling reaction conditions given that there was a significant amount of the free aldehyde present.

As the Heck coupling was therefore much cleaner between the unprotected bromobenzaldehyde and vinyl sulfonate **2.13**, the aldehyde product **2.14** could be protected after the Heck coupling, using acid/methanol. Initially, it was thought prudent to avoid this scenario for the reason that the vinyl sulfonate moiety has the potential to be a Michael acceptor under these conditions. Nevertheless, the protection reaction with *p*-toluenesulfonic acid and methanol was carried out using vinyl sulfonate **2.14** and the reaction was found to be exceptionally clean, providing the protected product **2.18** in 78 % yield.

Having accessed protected sulfonate **2.18** the reduction of the double bond was attempted with sodium borohydride. The slow reaction to reduce the double bond was observed (manifesting in the appearance of a less polar compound by TLC) and the final TLC sample was shaken with 1N HCl (aq.) and reanalysed by TLC. This showed a more polar spot than the original starting material and was presumed to be that of the free aldehyde **2.19** (scheme 2.9). After 36 hours the reaction was quenched with 1N HCl (aq.) and **2.19** was obtained with no need for further purification by ^{1}H NMR in 97 % yield.

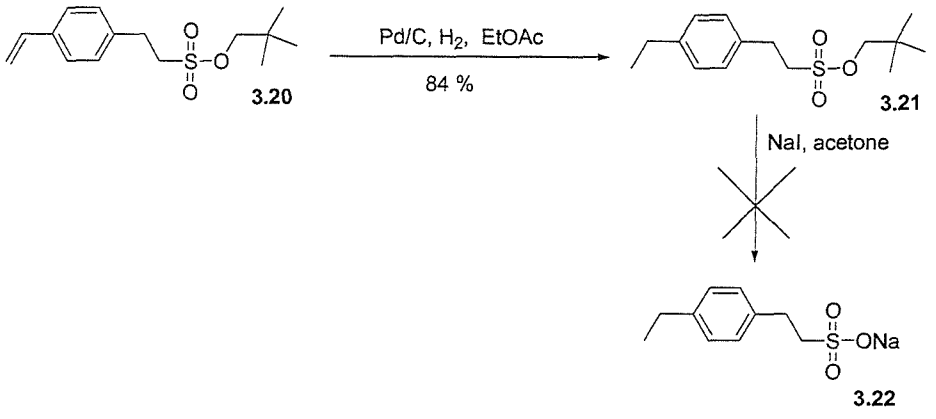


Scheme 2.9 Final steps to desired monomer **3.20**.

The final step for the synthesis of the desired monomer **2.20** was a Wittig olefination to introduce the styryl functionality at the aldehyde position.[127,128] As one might expect for well defined and used chemistry, the Wittig olefination proceeded with no problems giving the desired monomer product **3.20** in 96 % yield (scheme 2.9).

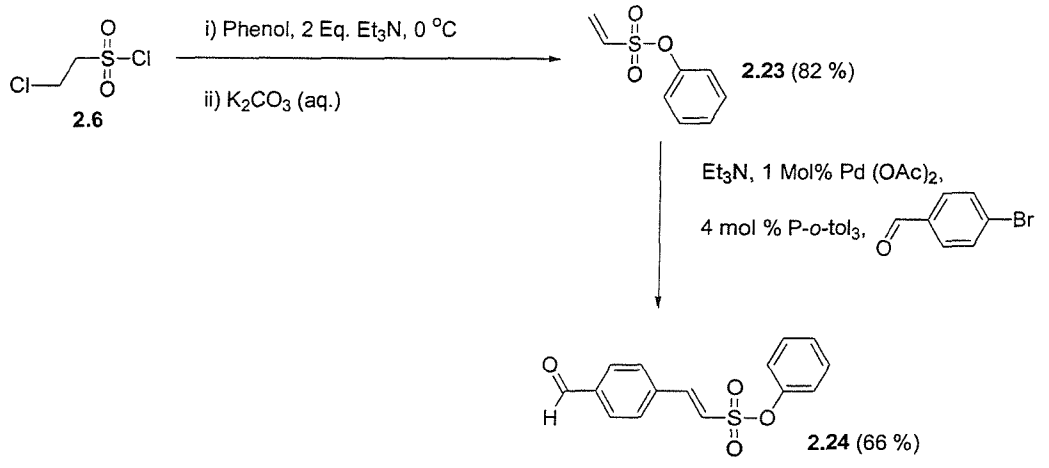
If scale up and subsequent co-polymerisation was to be undertaken, it is essential the protecting group can be removed. In order to ascertain whether the removal of the *neo*pentyl group was to be possible on the solid-phase, a test substrate was synthesised. The styryl double bond of **2.20** was reduced out using Pd/C and

hydrogen gas, affording the saturated product **2.21** in 84 % yield (scheme 2.10). Deprotection was attempted under the conditions described by Roush and Hunt using sodium iodide, developed for the cleavage of *iso*propyl sulfonate esters in the solid support.[110]



Scheme 2.10 Styryl reduction and attempted sulfonate deprotection.

The *neo*pentyl sulfonate protecting group was found to be resistant to the sodium iodide/acetone deprotection reaction conditions. The reaction was repeated in dimethylformamide, which also failed to yield sulfonate **3.22**. Taylor and coworkers reported the removal of a *neo*pentyl group from a fluorinated sulfonate ester using either TFA in acetonitrile/water (1:1) or lithium bromide in butanone.[129] These conditions were also investigated, however neither of these methods were successful in removing the *neo*pentyl group from **3.21**. This was an unfortunate setback, meaning that despite the final monomer **2.20** being synthesised, it could not be used, as the sulfonate functionality was too stable to be removed after co-polymerisation. An alternative protecting group was therefore investigated. A phenyl group was chosen, as there was precedent for phenyl sulfonate cleavage in the literature.[130,131] The desired phenylvinyl sulfonate was synthesised using the route described for the previous examples and the desired vinyl sulfonate **2.23** (scheme 2.11) was obtained in 82 % yield.



Scheme 2.11 Synthesis of phenylvinylsulfonate and subsequent Heck coupling.

Application of the sulfonate **2.23** in the Heck coupling with bromobenzaldehyde proceeded in similar yield to those reactions carried out with previous substrates and the required product **2.24** was obtained with 66 % yield. Although this methodology worked as expected up until this point, unfortunately attempts to reduce the olefin in the manner previously utilised, with sodium borohydride failed, as the phenyl group was not stable to this reductive step, and phenol was recovered in large quantities (35%). It may be possible to access the desired reduced sulfonate using an alternative reduction such as diimide, however at this point the synthesis of a monomer by this route was abandoned in favour of approaches that focussed on the modification of commercial resins.

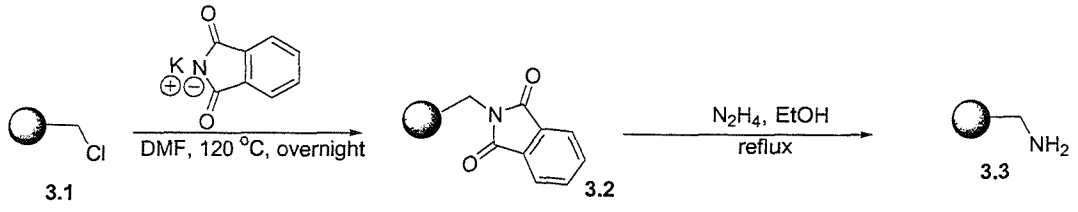
The chemistry had demonstrated nevertheless that a variety of vinyl sulfonates can be synthesised by a facile route, and these vinyl sulfonate esters can be effectively utilised in Heck coupling reactions with aryl halides, giving the aryl vinyl sulfonates in good yield. Further work in this area should focus on solving the problems associated with the sulfonate protecting group.

Chapter 3. Results and Discussion

Sulfonyl Chloride Resins Synthesised from Merrifield Resin

3.1 Synthesis of an aryl sulfonyl chloride resin from aminomethyl polystyrene

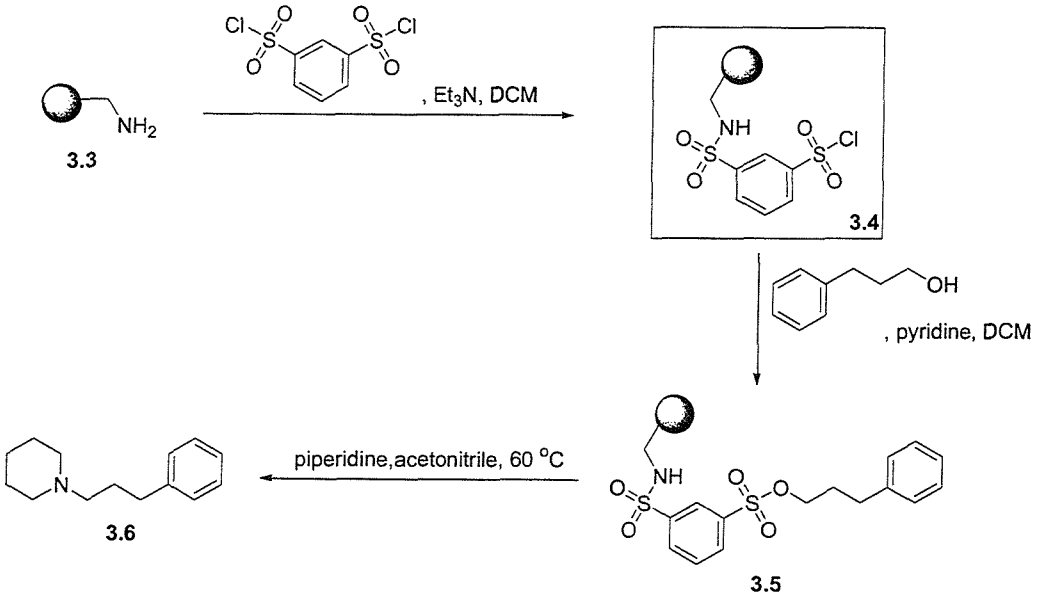
Merrifield resin (chloromethyl functionalised resin) is a relatively cheap and classical starting point for the synthesis of other resins.[1] This resin was chosen as the starting point and employed a well-established route in order to access an amino methyl resin.[105] Merrifield resin (**3.1**, 1.6 mmol/g) was reacted with potassium phthalimide to give a phthalimide resin (**3.2**) with a theoretical loading of 1.36 mmol/g.



Scheme 3.1 Synthesis of amino methyl resin **3.3** from Merrifield resin

IR spectroscopy of the phthalimide resin **3.2** confirmed the presence of the carbonyl stretch (1710 cm $^{-1}$) corresponding to the phthalimide group. Hydrolysis of the phthalimide using the Ing-Manske procedure with hydrazine and heating (scheme 3.1) gave the desired amine resin, with a theoretical loading of 1.65 mmol/g. IR spectroscopy showed the disappearance of the carbonyl functionality. The presence of a carbonyl peak in the IR spectrum is diagnostic of the presence of the by-products, however further thorough washing of the resin with hot solvents (DMF and water) removed all by-products. Elemental analysis of the amino methyl resin showed the complete disappearance of chlorine and 2.53 % nitrogen by weight, agreeing with the theoretical loading. Having accessed the amino methyl resin by a reliable route the next step was the reaction of the resin with 1,3-benzenedisulfonyl chloride in order to create the sulfonyl chloride resin **3.4** linked by a sulfonamide bond (scheme 3.2). A

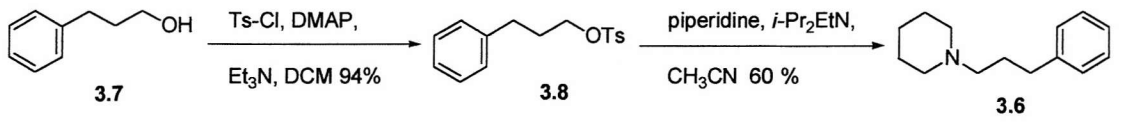
potential side reaction was cross-linkage. In order to limit this undesired reaction, we used the 1,3-benzenedisulfonyl chloride in excess (5 equivalents). The resulting resin was shown to have IR peaks corresponding to sulfonamide and sulfonyl chloride stretches (1384, 1168 cm $^{-1}$). Elemental analysis shows that the resin had undergone very little or no crosslinking at all and is in agreement with the theoretical resin loading of 1.18 mmol/g.



Scheme 3.2 Synthesis of a sulfonyl chloride resin **3.4** and loading assessment.

In order to confirm the actual loading of the sulfonyl chloride resin **3.4** and also to assess the reactivity of the resin, dihydrocinnamyl alcohol (3-phenylpropan-1-ol) was immobilised giving sulfonate resin **3.5**. The reaction was carried out at three different reaction times of 5, 27 and 48 hours. Identical reactions were carried out using commercially available resins from Argonaut® (2.56 mmol/g) and from Aldrich® (1.5-2 mmol/g). Cleavage of the sulfonate resins using piperidine to give the tertiary amine **3.6** allowed the product to be quantified in order to determine the loading of the resin using GC analysis. The product **3.6** was also synthesised in solution in order to make standard solutions to aid analysis of the cleavage solutions by GC. 3-Phenylpropanol (**3.7**) was treated with tosyl chloride (*p*-toluenesulfonyl chloride), a catalytic amount of DMAP and triethylamine in order to afford the tosylate product **3.8** in 96% yield

(scheme 3.3). Subsequent treatment of the tosylate with piperidine and Hünig's base in acetonitrile afforded the tertiary amine **3.6** in 60 % isolated yield.

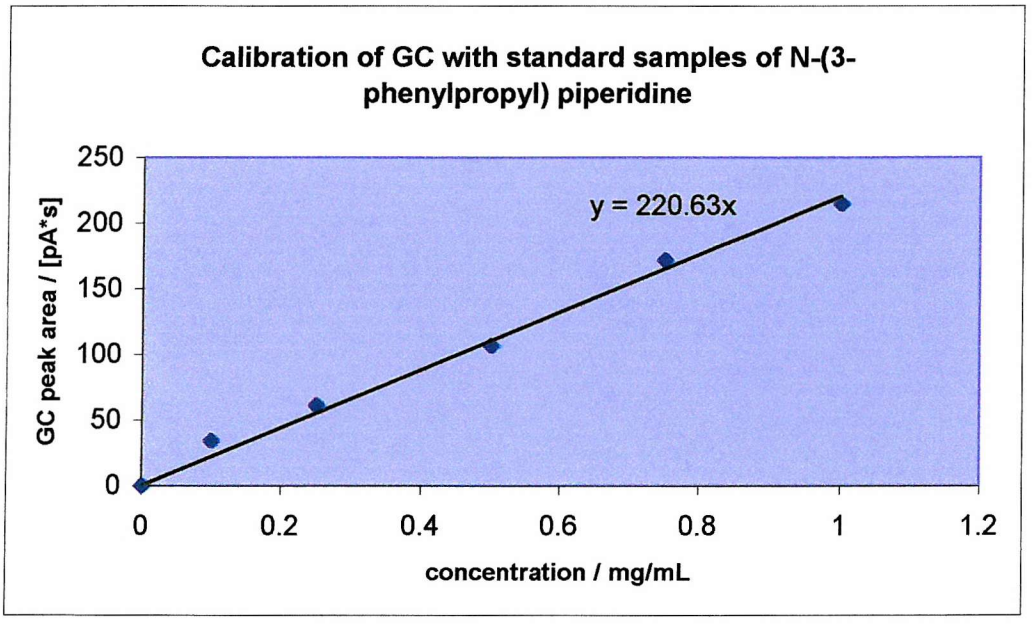


3.7 3.8 3.6

Scheme 3.3 Solution-phase synthesis of tertiary amine product from resin cleavage.

As can be seen from the graph of results (Figure 3.1), calibration of the GC was carried out effectively using the authentic sample of the tertiary amine **3.6**, allowing the conversion of the GC results into percentage yield data.

Figure 3.1 Calibration curve for tertiary amine **3.6**.



The results obtained from this investigation were disappointing. Figure 3.2 shows the plot for each of the resins (having been reacted to give the sulfonate resins for 5 hours) against the expected peak for a quantitative recovery of the tertiary amine product **3.6**. All resins failed to deliver the theoretical yield of **3.6**, in particular resin **3.5** gave a very low yield of compound **3.6**. Figure 3.3 translates the data into percentage yields for the cleavages.

Figure 3.2 Cleavage yields obtained from the respective resins determined by GC.

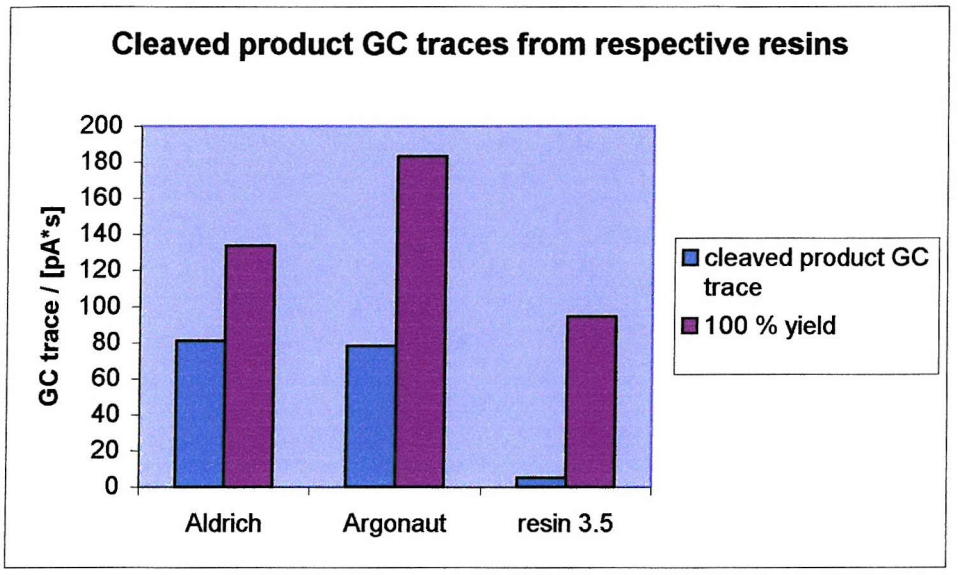
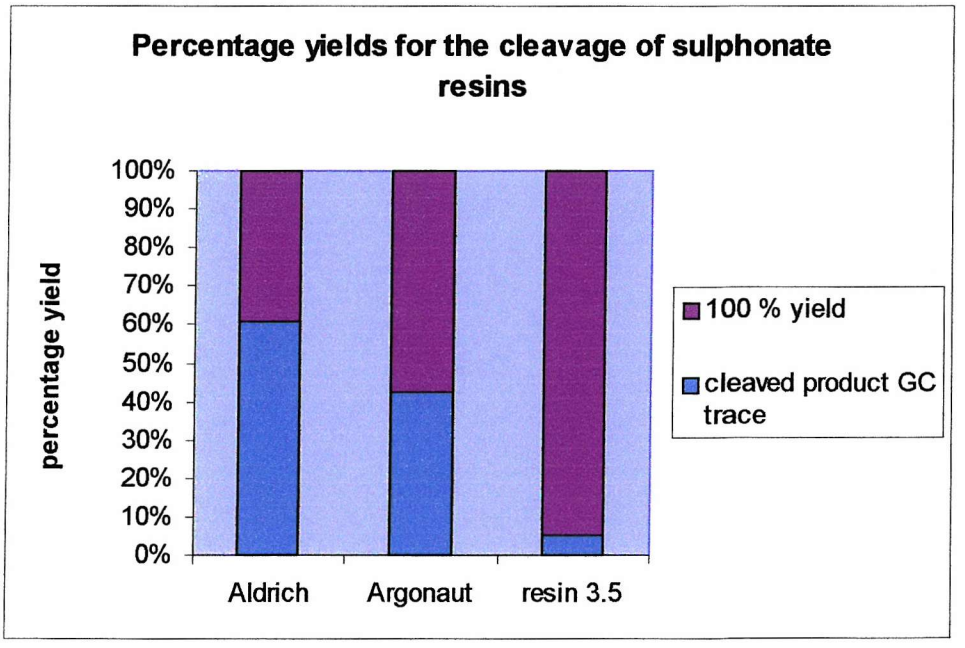


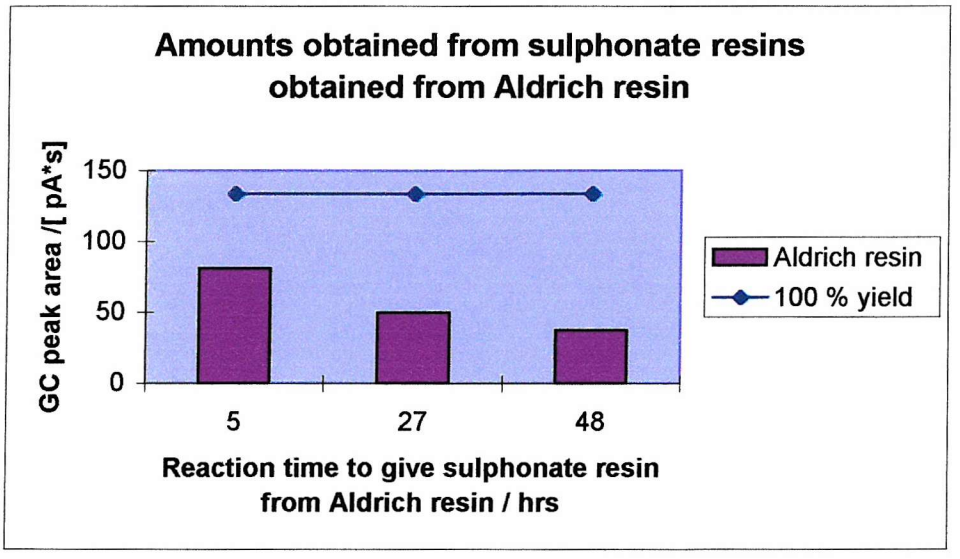
Figure 3.3 Percentage yields of amine **3.6** from the respective resins



A yield of around 5 % was obtained from the cleavage of resin **3.5**. Initially it was thought that this was possibly due the degradation of the resin as it was stored for some time before use in the reactions. However, reactions carried out with freshly prepared batches of resins give similarly disappointing results.

Curiously, the cleavage yields from resins where immobilisation reactions were carried out over 5 hours were greater than for those resins where reactions were carried out over a greater amount of time. Indeed, the longer the reaction time to give the sulfonate resin from the sulfonyl chloride, the less product was obtained from the subsequent cleavage. This is demonstrated by figure 3.4 showing the yields determined for the Aldrich® resin.

Figure 3.4 Cleavage yields obtained from commercial sulfonyl chloride resin.

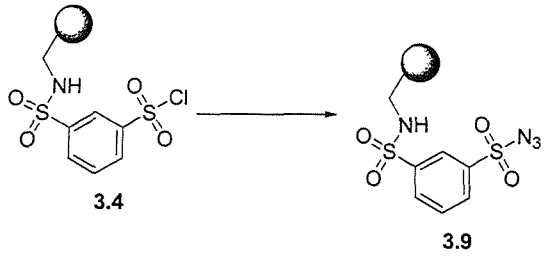


It was clear from these results that the synthesised resin **3.5** was not performing well as a supported tosylating agent.

3.2 Qualitative investigations into the conversion of sulfonyl chloride to sulfonyl azide resin

Reaction of sodium azide with sulfonyl chloride resins has been used to access the sulfonyl azide diazo-transfer reagents.[58] One problem with this route is that sodium

azide is only effectively soluble in water and therefore there exists an obvious incompatibility with gel-type polystyrene resin. The first attempt to react sodium azide with the sulfonyl chloride resin **3.4** used dichloromethane as a solvent in order to swell the resin effectively and sodium azide in water. The mixture was shaken very vigorously overnight and after filtering the resin and washing, the IR spectrum of the resin showed a peak at 2130 cm^{-1} corresponding to a sulfonyl azide stretch. However, elemental analysis of the sulfonyl azide resin **3.9** showed that the loading of nitrogen was lower than expected. A number of other conditions were therefore investigated in order to increase the efficiency of the displacement reaction (scheme 3.4).



Investigated conditions

1) DCM, H_2O, NaN_3

2) DMF, H_2O, NaN_3

3) DCM, H_2O, NaN_3, Bu_4NHSO_4

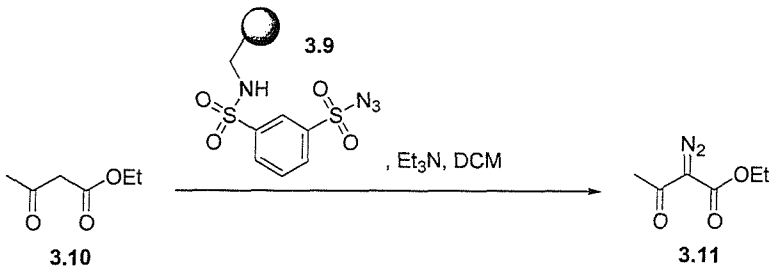
4) DMF, H_2O, NaN_3, Bu_4NHSO_4

5) DCM, NaN_3, Bu_4NHSO_4

6) DMF, NaN_3, Bu_4NHSO_4

Scheme 3.4 Synthesis of supported sulfonyl azide.

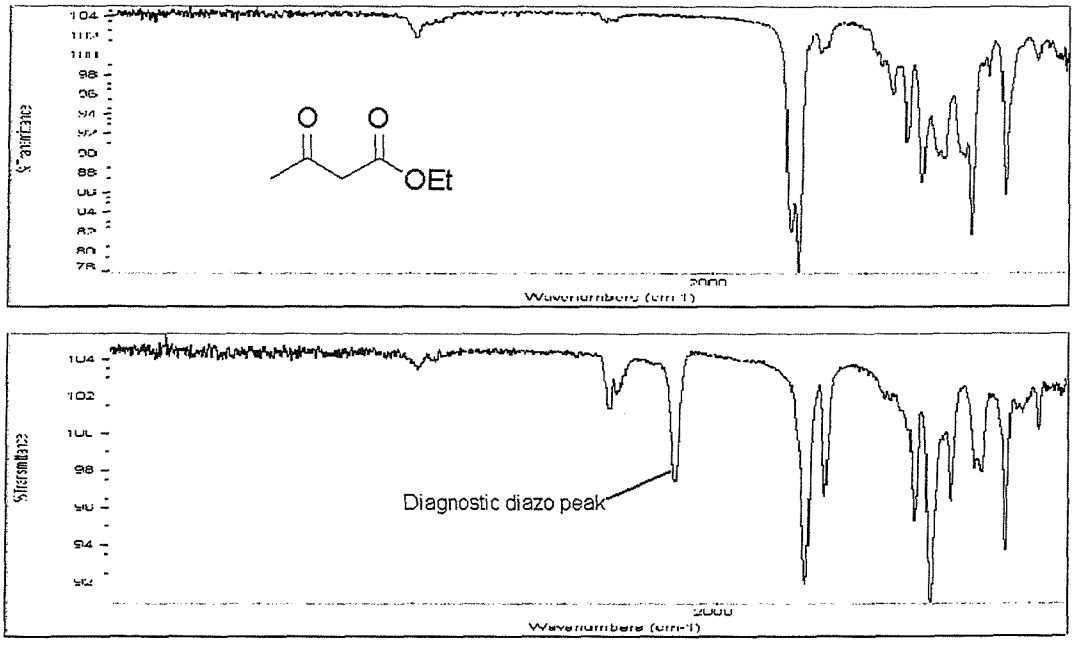
It was decided to use DMF as an alternative solvent. DMF is known to swell polystyrene resins and it has the added advantage of being miscible with water. Two experiments were also carried out with dichloromethane and DMF with the sodium azide dissolved in water and 10 mol% of the phase transfer catalyst tetrabutylammonium hydrogensulfate. The same reactions were also carried out with the phase-transfer catalyst and solid sodium azide without water. All the reactions were analysed in the same manner, by IR spectroscopy (grinding the resin to make a KBr disc) to get a comparison for the azide loading. The best method was found to involve the use of DMF or dichloromethane as solvent with solid sodium azide and 10 mol% of the phase-transfer reagent. Initial attempts to use the solid supported sulfonyl azide as a diazo-transfer reagent (scheme 3.5) proved to be very encouraging.



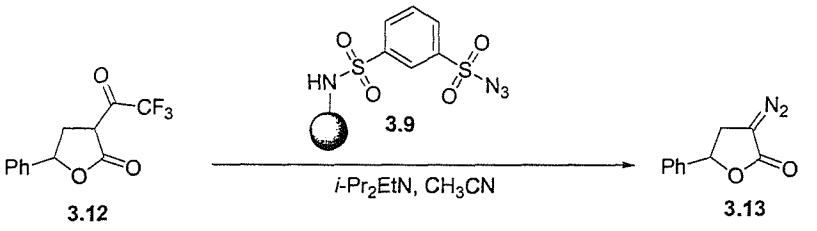
Scheme 3.5 The use of the solid supported sulfonyl azide as a diazo-transfer reagent.

Ethyl acetoacetate (**3.10**) was chosen as the substrate for the initial diazo-transfer experiment. The reaction was carried out on a small scale and the reaction mixture was analysed by IR spectroscopy. The appearance of a diazo stretching band corresponding to the desired product **3.11** in the IR spectrum (2141 cm^{-1}, figure 3.5) indicated that resin **3.9** was indeed successfully acting as a diazo-transfer reagent.

Figure 3.5 Infrared spectra for the initial diazo-transfer.



Encouraged by this result, a revised methodology was used in conjunction with a sulfonyl azide resin **3.9** with a more demanding substrate to allow comparison with results from a reaction carried out in solution. The conditions used were Hünig's base instead of triethylamine, with acetonitrile as solvent (scheme 3.6).



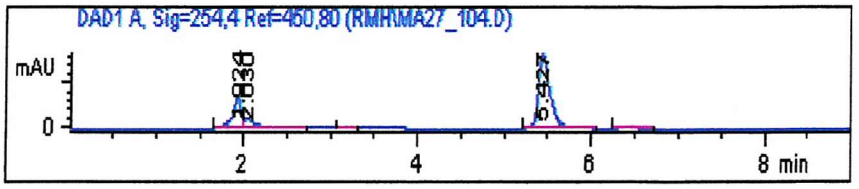
Scheme 3.6 Diazo-transfer reaction *via* revised methodology.

It has been noted in the past that purification of diazo products such as **3.13** is complicated as the product, sulfonamide by-product and the sulfonyl azide reagent are difficult to separate by flash chromatography.

The reaction mixture was monitored by HPLC and as can be seen from the HPLC trace (figure 3.6), provided a significant advantage over the reaction using *p*-nitrobenzenesulfonyl azide (figure 3.7).[132] The supported reagent means the sulfonamide by-product is also supported and both are filtered off easily from diazo product **3.13**. The lack of any by-products should be noted and when compared to the figure 3.7[132], where using a solution reagent the presence of the by-products can be observed.

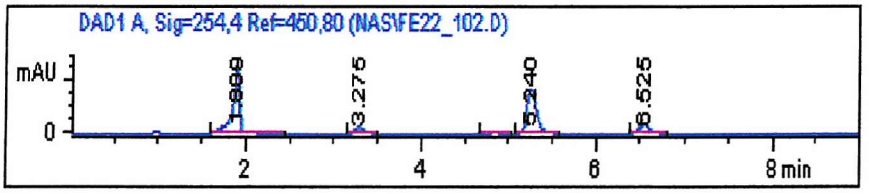
The advantage of using a supported reagent for these transformations has therefore been shown as the absence of the by-products in solution means purification of the diazo product can be made more facile.

Figure 3.6 HPLC trace obtained from Diazo-transfer with resin **3.9**.



5.427 = diazo product **3.13**, 1.924 = starting lactone **3.12**.

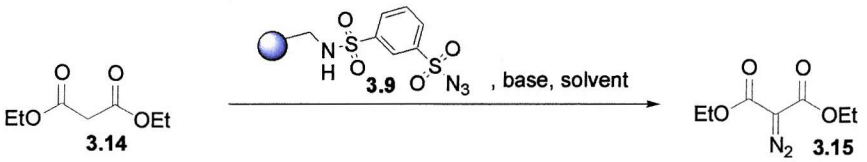
Figure 3.7 HPLC trace obtained from Diazo-transfer reaction carried out using *p*-nitrobenzenesulfonyl azide.



3.275 = Sulfonamide by-product, 5.427 = diazo product **3.13**, 6.525 = Sulfonyl azide reagent.

3.3 Investigation into the optimal conditions for the diazo-transfer reactions with supported reagent.

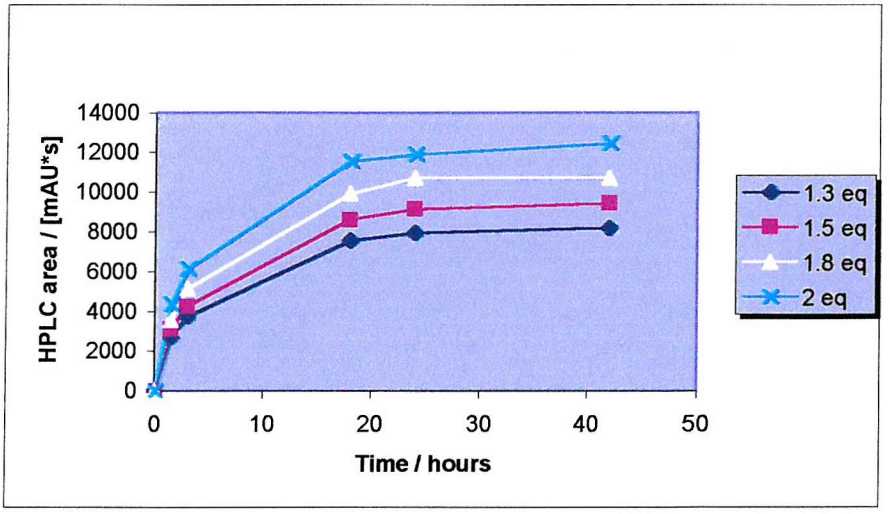
Having synthesised a solid-supported diazo-transfer reagent, it was necessary to ascertain the best conditions for performing the diazo-transfer reactions. For this purpose, diethylmalonate **3.14** was chosen as a substrate (scheme 3.7). A semi-quantitative study was embarked on using reverse-phase HPLC analysis in order to monitor the appearance of the diazo products over time, to allow the methodology to be applied effectively to the solid-phase. Variation of the number of theoretical equivalents of resin, equivalents of base, type of base and solvents used were investigated systematically.



Scheme 3.7 Optimisation of the diazo-transfer reaction using a supported reagent.

Initially, an investigation was carried out into the variation of the number of equivalents of resin based on the theoretical loading (1.17 mmol/g) of resin **3.9**. Diisopropylethylamine was used as base and acetonitrile as solvent (figure 3.8). All reactions were treated identically and aliquots were taken periodically for HPLC analysis.

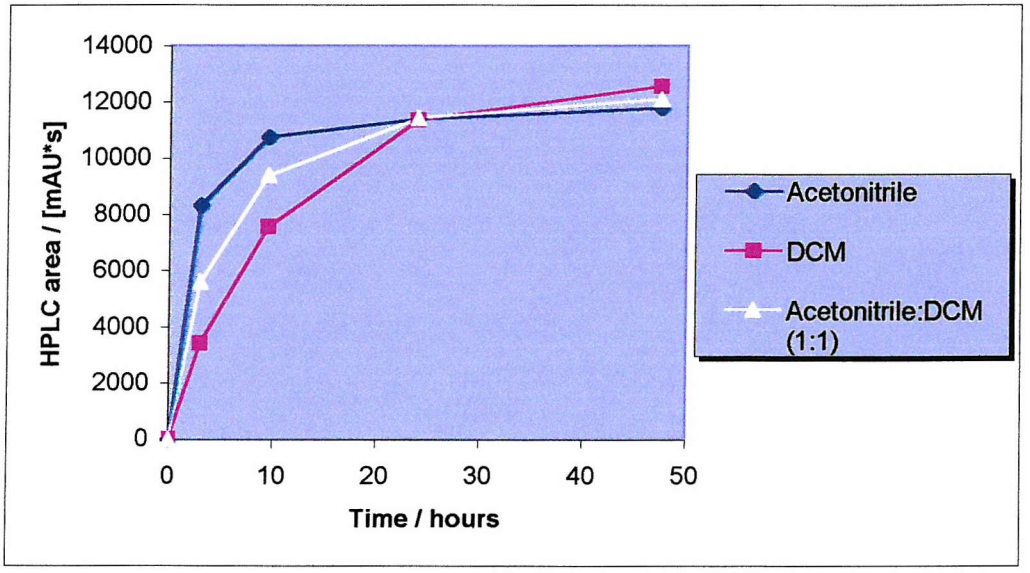
Figure 3.8 Variation of resin equivalents.



As shown from figure 3.8, the use of greater the number of equivalents of resin **3.9** results in a significant rise in the amount of product detected by HPLC. It is therefore possible to assume that either the sulfonyl azide functionality is not as highly loaded on resin **3.9** as the theoretical loading, or that the resin is not swollen fully in acetonitrile leaving some of the functionality inaccessible. It was therefore decided to investigated the possibility of changing the solvent in order to increase the extent of resin swelling. Identical reactions were carried out using acetonitrile, dichloromethane

and also a 1:1 mixture of acetonitrile:dichloromethane as solvents. In each case, two (theoretical) equivalents of resin were used along with 1 equivalent of Hünigs base.

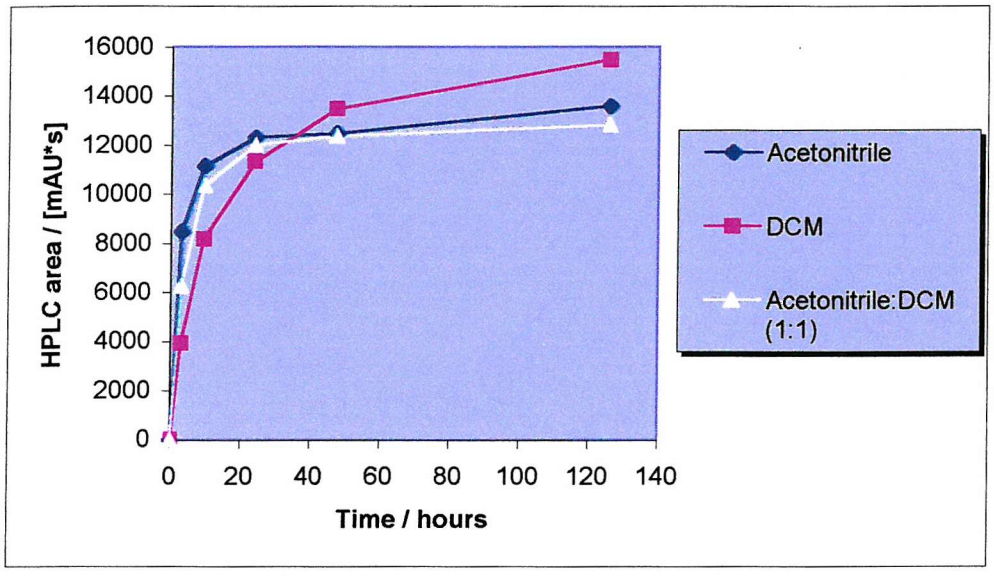
Figure 3.9 Variation of solvents (iPr$_2$EtN as base)



As shown in figure 3.9, the reaction carried out in acetonitrile initially proceeds significantly faster over the first 10 hours of reaction and then tails off. By contrast the reaction in dichloromethane is more sluggish over the same period and is similar to the reaction in acetonitrile after about 24 hours. Over an extended period of time, the reaction in dichloromethane actually goes marginally further, believed to be as a result of improved swelling of the resin. The reaction that employed a 1:1 mixture of acetonitrile:dichloromethane, as might be expected, performed somewhat the same as the other solvents.

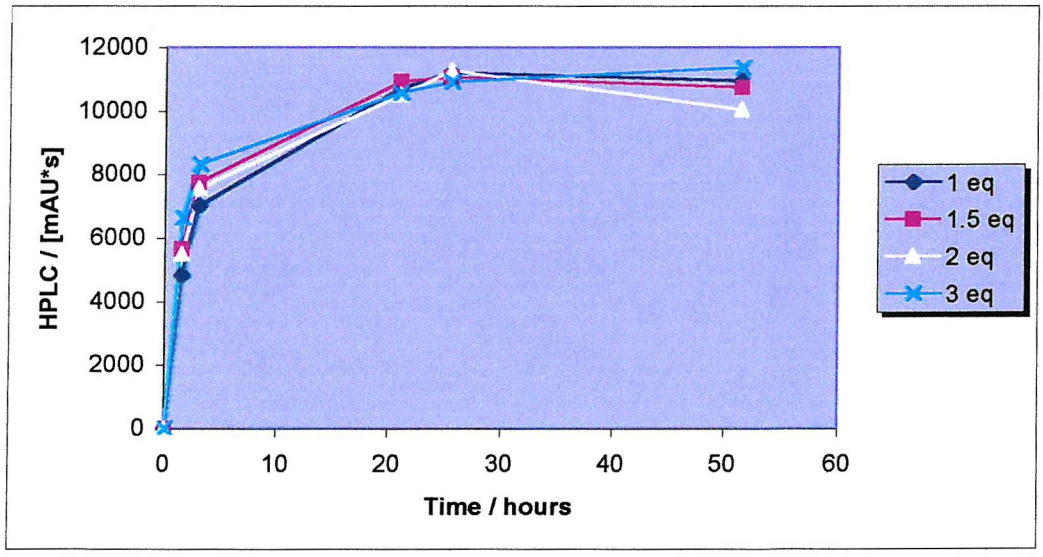
Identical reactions were carried out using triethylamine as base. The reactions with triethylamine as base showed a similar trend to those reactions for the variation of solvent (figure 3.10) using Hünigs base (figure 3.9).

Figure 3.10 Variation of solvent (triethylamine as base).



Finally, an investigation into the number of equivalents of base (in this case Hünigs base) was carried out. Figure 3.11 indicates that there is no significant advantage to be gained from using a large excess of base.

Figure 3.11 Variation of base equivalents



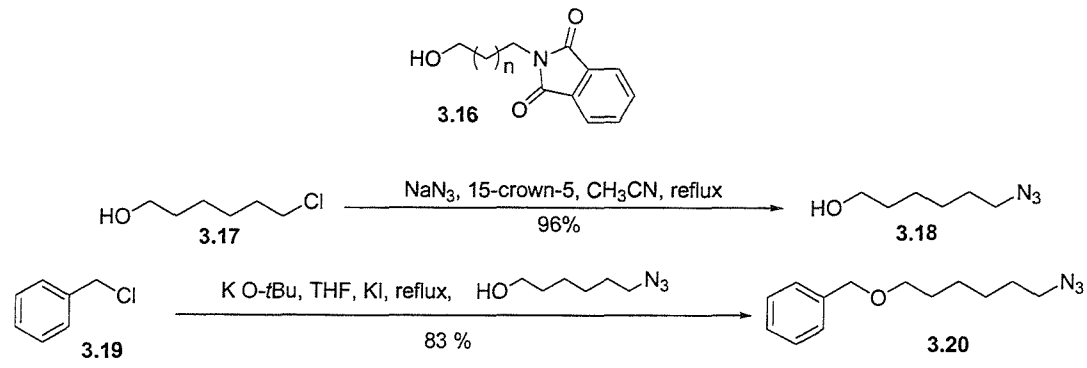
A final conclusion that can be drawn from the reactions represented by figures 3.8 to 3.11 is that reactions are reproducible. A number of reactions in the 4 sets of results were repeated (reactions with dichloromethane required more solvent in order to allow for greater swelling and so the comparible reactions in acetonitrile were adjusted accordingly). For example, the result for 2 equivalents of resin **3.9** in figure 3.8, the result for the acetonitrile reaction in figure 3.9, and the result for 1 equivalent of base in figure 3.11 are identical reactions except for the volume of solvent used. Encouragingly, the HPLC traces for these reactions are very similar, demonstrating reproducibility.

However, given that the extent of conversion was highly dependent on the amount of resin used, it seems likely that the loading of the resin is significantly lower than the theoretical value. It has been determined that this is not due to any other factors (swelling of the resin, base, etc). Allied with the poor results for the use of the sulfonyl chloride intermediate resin **3.4** as a tosylation reagent (section 3.1, chapter 3), a conclusion can be drawn that the sulfonyl chloride resin **3.4** would not be good to use to synthesise supported reagents from. Further investigation was therefore carried out to assess whether this was due to steric interactions from the resin bulk, by preparing other sulfonyl chloride resins containing spacer groups (see below).

3.4 Synthesis of a sulfonyl chloride resin with a spacer

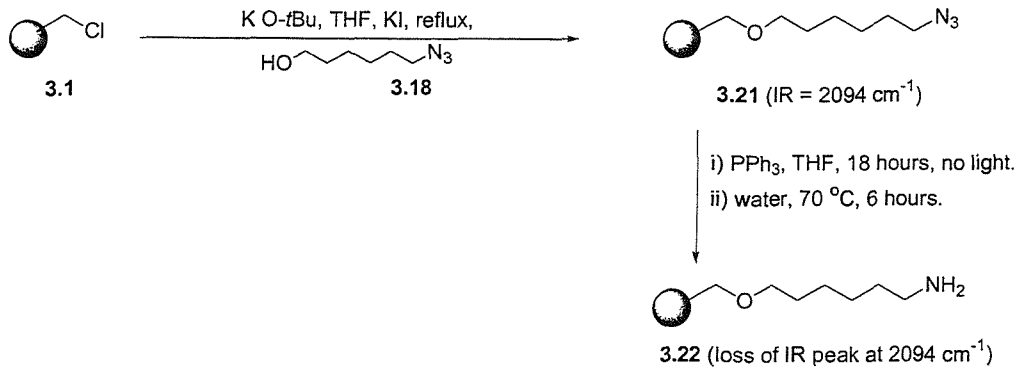
To assess the effect of the steric bulk of the resin on its activity as a solid-supported reagent, the use of a spacer was investigated to see whether any benefit could be derived from removing the active functionality away from the bulk of the resin. The effect of steric interactions from the resin backbone has been an issue for other groups in the past.[110] In order to maintain continuity, the final reactions to install the sulfonyl chloride functionality were to be kept the same, i.e. the use of 1,3-benzenedisulfonyl chloride with an amine functionalised resin. In order to install the spacer, the proposal was to use an ether linkage by reacting Merrifield resin (**3.1**) with an alcohol, containing a protected amine moiety. Deprotection of the amine would then allow reaction with 1,3-benzenedisulfonyl chloride.

Initial thoughts were to use a similar method to that employed for the synthesis of aminomethyl resin **3.3**, whereby the amine is protected as a phthalimide group. Compound **3.16** could be attached to the resin, followed by deprotection with hydrazine to give the amine. However, it was believed that this method would be flawed because the alkoxide ion could undergo intramolecular attack at the carbonyl centres of the phthalimide functionality causing a competing cyclisation product. A revised method was therefore decided upon, using an azide group in order to access the free amine group.



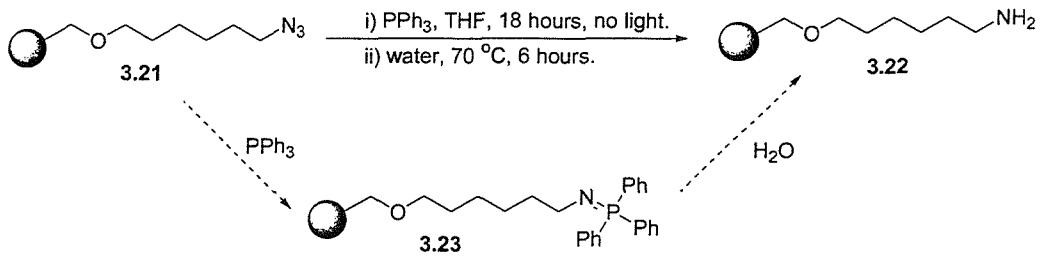
Scheme 3.8 Solution model reactions involving the proposed spacer.

6-Chlorohexanol (**3.17**) was chosen as a 6-carbon spacer unit as it was available commercially and cheap (scheme 3.8). Conversion to the corresponding azide was performed using methodology previously employed by Kusumoto and coworkers.[133] The reaction of chloride **3.17** with sodium azide, 15-crown-5 in acetonitrile at reflux gave the desired azide **3.18** in excellent yield (96 %) with no need for further purification (scheme 3.8). By means of an initial test, azidoalcohol **3.18** was coupled to benzyl chloride (**3.19**), which afforded the azido ether **3.20** in 83 % yield, using potassium *t*-butoxide as base and potassium iodide as a catalyst. The reaction worked equally well with sodium hydride as base, however potassium *t*-butoxide is more compatible with reactions on the solid-phase. The use of potassium *t*-butoxide as base in order to attach alcohols to Merrifield resin has been documented in the past however reaction times are generally long (3.5 days).[134] This is not ideal and as such, some improvement is required to increase the speed of the reaction.



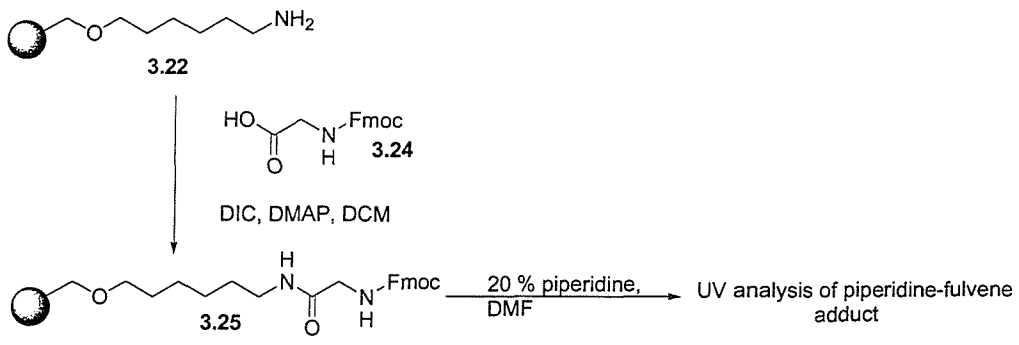
Scheme 3.9 Synthesis of amino resin **3.22** with a spacer.

The use of potassium iodide was initially employed in the reaction to create a better leaving group (iodide) by employing the Finkelstein reaction (scheme 3.9). The IR spectrum of resin **3.21** showed a very strong peak at 2094 cm^{-1} corresponding to the azide functionality immobilised on the resin and a reduction method was therefore sought. Typical solution-phase methods for the reduction of azides to amines include the use of lithium aluminium hydride[135,136] and Pd/C.[137] Unfortunately, these methods are not generally compatible with solid-phase chemistry. The azide group was therefore reduced to the amine group employing a Staudinger reaction,[138] followed by hydrolysis of the intermediate phosphazo compound **3.23** to give the desired amine **3.22** (scheme 3.10). This is confirmed by the loss of the azide stretch in the IR spectrum at 2094 cm^{-1}. Such a reaction was reported by Poirier *et al.*[139] in order to access an amine from an azide on solid-support and in the presence of a benzylic ether linkage, following solution-phase work carried out by Vaultier and co-workers.[140] As well as using triphenylphosphine and water, Poirier and colleagues have also carried out a similar reduction using $SnCl_2$, thiophenol and triethylamine.[141]



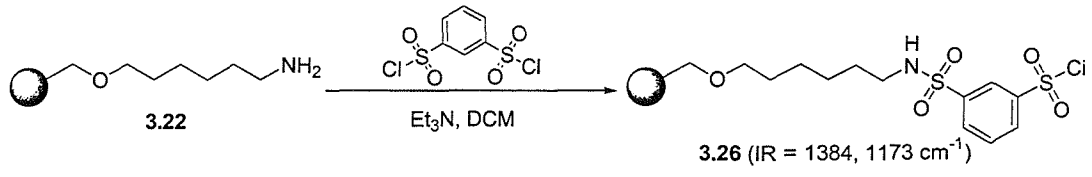
Scheme 3.10 Azide reduction using the Staudinger reaction.

Having accessed the ether-linked aminohexyl resin **3.22**, elemental analysis showed a 1.96 % mass nitrogen content, compared to the expected mass of nitrogen of 1.99 %. This indicated a resin loading consistent with the theoretical load of 1.42 mmol/g. In order to reinforce this result an Fmoc test was carried out with amine resin **3.22** (scheme 3.11). Fmocglycine (**3.24**) was coupled to the resin repeatedly until a qualitative ninhydrin test[142] for free amines was negative. After repeated couplings the ninhydrin test was still positive (weakly), however no improvement on this result was possible, possibly due to inaccessible nitrogen reactive sites. The cleavage of the Fmoc group from resin **3.25** with 20 % piperidine in DMF and quantification by UV analysis translated to a loading of 0.72 mmol/g. Although a low result, the complete addition of the amino acid was not possible and so the result was expected to be lower than it should have been.



Scheme 3.11 Fmoc cleavage test on aminohexyl resin **3.22**.

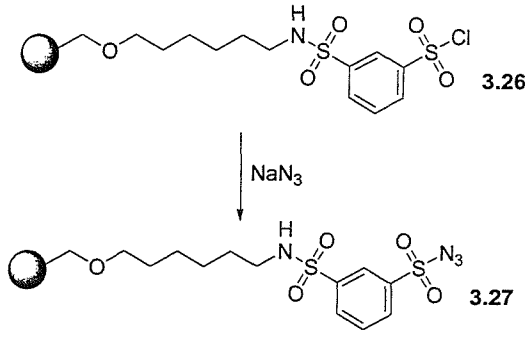
The coupling to give the sulfonamide linked sulfonyl chloride resin **3.26** (scheme 3.12) was carried out using 10 equivalents (based on the theoretical loading of the amine resin) of 1,3-benzenedisulfonyl chloride and was confirmed by the presence of IR peaks at 1384 and 1173 cm^{-1}.



Scheme 3.12 Synthesis of the sulfonyl chloride resin with a spacer.

However, the potential for cross-linking to occur where one molecule of the disulfonyl chloride reacts with two resin-bound amine functions, is greater now that the flexible spacer is in place. Elemental analysis of the resin appears to show that cross-linking has mostly been avoided in that the nitrogen:sulfur ratio (theoretically 1:2) is 1:1.7.

Also, the reaction of the sulfonyl chloride resin **3.26** with sodium azide appears to proceed giving sulfonyl azide resin **3.27**. IR analysis showing the appearance of an azide stretch (2129 cm^{-1}).



Scheme 3.13 Conversion to the corresponding azide resin.

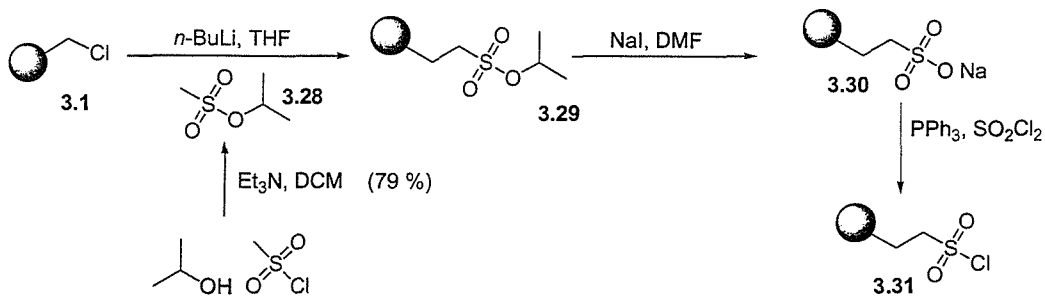
Despite the qualitative analysis of the azide resin, further reactions carried out to establish the viability of the resin, using the same procedures as for the previous sulfonyl chloride resin **3.4** (section 3.1, chapter 3) by the synthesis and analysis of the tertiary amine **3.6**, showed that the spacer resin was as ineffective as its predecessor. As such, it can be determined that the methodology using 1,3-benzenesulfonyl chloride with an amine resin is flawed, either due to being unreactive or unstable and degrading. At this point it was decided not to pursue the use of the disulfonyl chloride linker any further. However, the alkyl azide chemistry that has been carried out has shown to be very effective in the synthesis of an amino resin with a spacer, such as **3.22**.

3.5 Synthesis of an alkyl sulfonyl chloride resin

The synthesis of an alkyl sulfonyl chloride resin could have a number of advantages over commercially available resins. Existing resins are aryl sulfonyl

chloride moieties produced by the sulfonation of polystyrene (the loading of which is difficult to control) and have some shortcomings.[110]

The first route explored, starting from Merrifield resin (**22**), utilised work originally carried out by Roush *et al.* involving the use of a methanesulfonate.[110] *Iso*propyl methanesulfonate (**3.28**) was synthesised from 2-propanol and mesyl chloride in 79 % yield (scheme 1.14). The resulting sulfonate **3.28** was treated with *n*-butyllithium to give the corresponding anion, which was added to Merrifield resin (**3.1**) to afford sulfonate resin **3.29**. Elemental analysis of the resin for sulfur showed the reaction proceeded in 83 % yield (Calculated: S = 4.38 %. Found: S = 3.66 %, Cl = 0.49 %). Subsequent deprotection of the sulfonate resin **3.29** with sodium iodide to give the sulfonate salt resin **3.30**, was followed by conversion to sulfonyl chloride resin **3.31** using triphenyl phosphine and sulfuryl chloride.

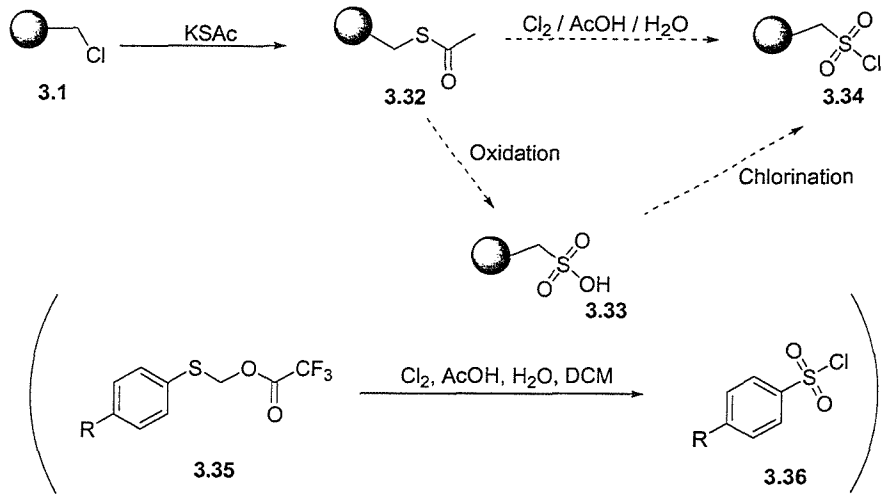


Scheme 3.14 Synthesis of resin **3.31** used originally by Roush *et al.*

Elemental analysis of resin **3.31** for sulfur and chlorine content indicates a yield of around 72 % overall (Calculated: S = 4.54 %, Cl = 5.04 %. Found: S = 3.28 %, Cl = 3.89 %), consistent with the yield reported by Roush and co-workers.

Although the reactions have been shown to work effectively by IR and elemental analysis, the major drawback to the methodology is that the first step has to be carried out under nitrogen at low temperature (–78 °C), premixing the sulfonate and butyl lithium and adding to Merrifield resin at –78 °C by cannula and stirring overnight at –30 °C. Apart from being inconvenient, it is very problematic and the results can be quite variable due to the complexities of using the resin at these low temperatures for prolonged periods of time.

An alternative and more facile methodology was sought. One proposed pathway was the use of Merrifield resin (**3.1**) and reaction with potassium thioacetate to produce the thioacetate resin **3.32** as an intermediate. Preliminary work showed that the reaction is effective with Merrifield resin giving a characteristic thioacetate IR peak at 1690 cm^{-1}. Work by Spaltenstein *et al.* showed that thioacetates could be converted to sulfonyl chlorides using chlorine gas bubbled through an aqueous acetic acid solution.[143] This followed work shown by Stewart and Cordts in 1952.[144] Clearly such a reaction would not be suitable for use with gel-phase resins as it takes place in aqueous media. However, more recent work using a Pummerer type product (**3.35**) in 20 % (v/v) H_2O in DCM with acetic acid was used effectively to access the corresponding sulfonyl chloride **3.36.**[145] It is also true that the existing methodology could be employed but using a macroporous resin that would lend itself more easily to aqueous reaction conditions.



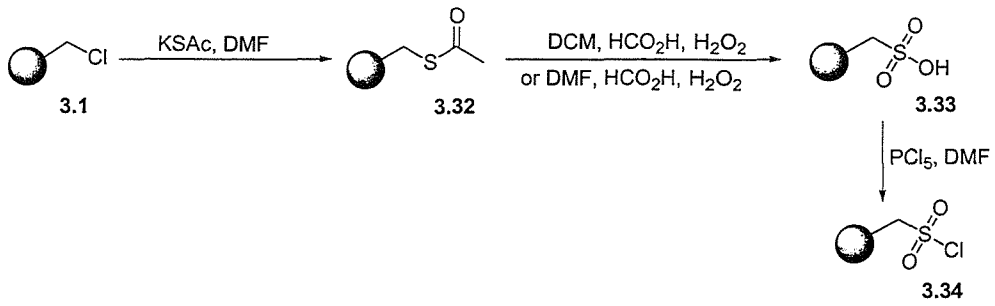
Scheme 3.15 Proposed sulfonyl chloride resin syntheses.

Attempts to effect the conversion of the thioacetate resin **3.32** to the sulfonyl chloride resin using chlorine gas and acetic acid with DCM was unsuccessful with gel-type thioacetate resins due to its tri-phasic nature. Alternative routes were therefore investigated by sequential oxidation to a sulfonic acid/salt such as **3.33** followed by chlorination (scheme 3.15).

The first route undertaken involved the use of Oxone® (potassium monoperoxosulfate) which has been used in the past for the oxidation of thioacetates to sulfonate salts.[146-148] The method of Reddie *et al* was employed by using a solution

a salt-reduced Oxone®, made by precipitating out the majority of unactive potassium sulfate and bisulfate salts from the commercially available Oxone®.[149] Although this method is usually carried out in an aqueous reaction media, the possibility of using co-solvents to allow reaction with resins was explored. The first reaction investigated used DMF as a co-solvent in order to attempt the conversion from thioacetate to sulfonate salt. However, when applied to the resin bound thioacetate the conversion failed to occur (IR analysis indicating the presence of the C=O stretch of the acetate group). Alternative reactions using a DCM/DMF mix as co-solvent also failed.

An alternative oxidation methodology was therefore found to oxidise thioacetate resin **3.32** using a neat mixture of formic acid and aqueous peroxide.[150,151] Adapting the chemistry slightly, samples of thioacetate resin were pre-swollen in DCM and DMF respectively, and each treated with a premixed (and stirred) formic acid/hydrogen peroxide mixture (scheme 3.16).



3.1 **3.32** **3.33** **3.34**

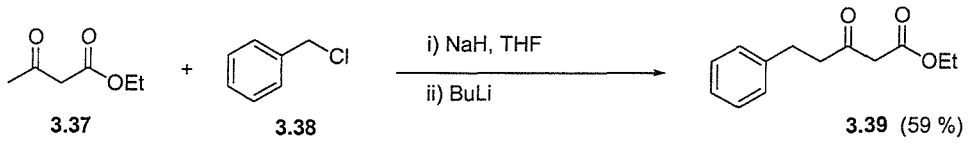
Scheme 3.16 Synthesis of alkyl sulfonyl chloride resin **3.34**.

The IR spectra of each resin showed that both reactions had been successful as no trace of the thioacetate carbonyl could be detected, although the reaction using DCM as solvent proved to be marginally faster (presumably due to increased swelling of the resin). The final conversion of the sulfonic acid resin to the corresponding sulfonyl chloride was carried out initially using phosphorus pentachloride, a reaction that has precedent in the literature on the solid support.[152] Indeed, such a reaction has been employed previously to access benzylic sulfonyl chlorides in solution-phase chemistry.[153]

3.6 Benzylic sulfonyl azide resin as diazo-transfer reagent

In order to test the viability of the sulfonyl chloride resin **3.34** synthesised above, its use as a precursor to a potential supported diazo-transfer reagent was given preliminary investigation.

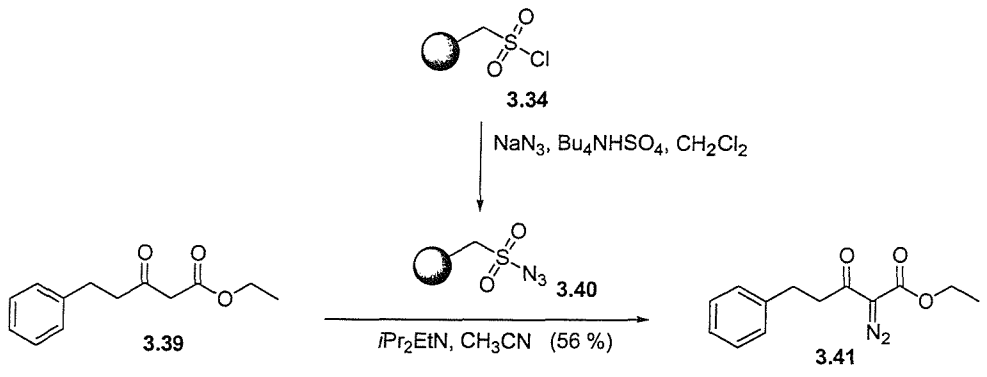
The next step was to determine the yields obtained from the reactions in order to quantify the amount of diazo product obtained from diazo-transfer reactions. Reactions with ethyl acetoacetate and diethyl malonate with previously synthesised resins allowed qualitative analysis of the resins, however, in order to get reliable isolated yields for the products, a substrate with a greater relative molecular weight was required. For this reason, β-keto ester **3.39** was chosen as it was readily prepared using dianion chemistry.[154] Starting from ethyl acetoacetate (**3.37**) and benzyl chloride (**3.38**) the β-keto ester **3.39** was afforded in 59 % yield (scheme 3.17).



3.37 **3.38** **3.39** (59 %)

Scheme 3.17 Dianion chemistry to make a less volatile β-keto ester.

Sulfonyl chloride resin **3.34** was reacted with sodium azide under phase-transfer conditions to provide the sulfonyl azide resin **3.40** (scheme 3.18). β-Keto ester **3.39** was then exposed to 2 equivalents of the sulfonyl azide resin **3.40** based on its theoretical loading of 1.45 mmol/g. The corresponding diazo compound **3.41** was returned in reasonable yield, with the mass balance being accounted for by recovered starting material. This result is very encouraging in that only product and starting material are recovered. However disappointingly, increasing the amounts of resin used could not improve the reaction any further. This resin would therefore have limited applications as a supported reagent, as large excesses of resin would be required to force reactions to completion.



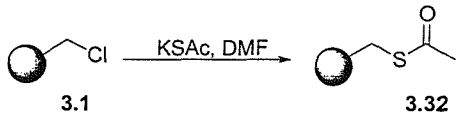
Scheme 3.18 Diazo transfer achieved using the new resin **3.40**.

3.7 Optimisation of the synthesis of the benzylic sulfonyl chloride resin

Although qualitative analyses of the synthesised alkyl resins have been favourable (IR), the use of the final resins has given variable results. Optimisation of the synthetic route was therefore required. The formation of the thioacetate resin was studied first. Initially, the reactions with potassium thioacetate had been carried out at room temperature with shaking for 20 hours in DMF. However, elemental analysis of the resin showed chlorine remaining (see table 3.1). Modification of the reaction conditions was undertaken such that one reaction was carried out having pre-swollen the Merrifield resin with DCM before suspension in DMF to carry out the reaction (reaction 2) and a second reaction was performed at elevated temperature (reaction 3) to try to improve the result (table 3.1).

As shown in table 3.1, it appears that the best reaction conditions involved heating to elevated temperature. Indeed, subsequent oxidation as previously discussed (section 3.5) with performic acid solution gave sulfonic acid resin **3.33**, with an optimal sulfur content, determined by elemental analysis (calculated: S = 4.77 %, found: S = 4.99 %). Therefore, no further improvement to the methodology was attempted with the oxidation step.

Table 3.1 Variation of reaction to form thioacetate resin **3.32**.



3.1 3.32

Reaction	Conditions (KSAc, DMF)	Chlorine content of thioacetate resin / %
1	20 hrs, rt.	1.60
2	20 hrs, rt, preswell DCM	2.25
3	20 hrs, 80 °C	0.00

The final step involved the conversion of the sulfonic acid to sulfonyl chloride. IR spectra of the resulting resins obtained from reactions using PCl_5/DMF have been variable in terms of the intensities of the required IR peaks. A number of procedures have therefore been investigated including PCl_5/DCM, SO_2Cl_2/PPh_3,[110,155] phosgene (triphosgene)[151,156] and thionyl chloride[157,158] (result discussed later). The IR spectra for some of the synthesised resins were compared (figure 3.12 and 3.13), offering some insight into the reacions. Figure 3.12 shows a typical result for the reactions using phosphorus pentachloride in DMF (weak SO_2Cl peaks). However, reactions using phosphorus pentachloride in DCM showed a small improvement. The reaction using sulfuryl chloride/triphenylphosphine was more encouraging showing much stronger SO_2Cl peaks in the IR spectrum (figure 3.13).

In order to evaluate quantitatively the effectiveness of the resins produced, the coupling of 3-phenylpropanol and subsequent cleavage with piperidine was employed, as used to evaluate previously synthesised sulfonyl chloride resins (section 3.1, chapter 3). The respective resins were reacted with 3-phenylpropanol to form the resin bound sulfonate **3.42**, which was subsequently cleaved with piperidine to form tertiary amine **3.6** in solution, which was quantified by GC as used previously (section 3.1, chapter 3). The results from these reactions were unfortunately very disappointing (for selected examples, table 3.2).

Figure 3.12 Typical infrared spectrum from chlorination reactions with PCl_5.

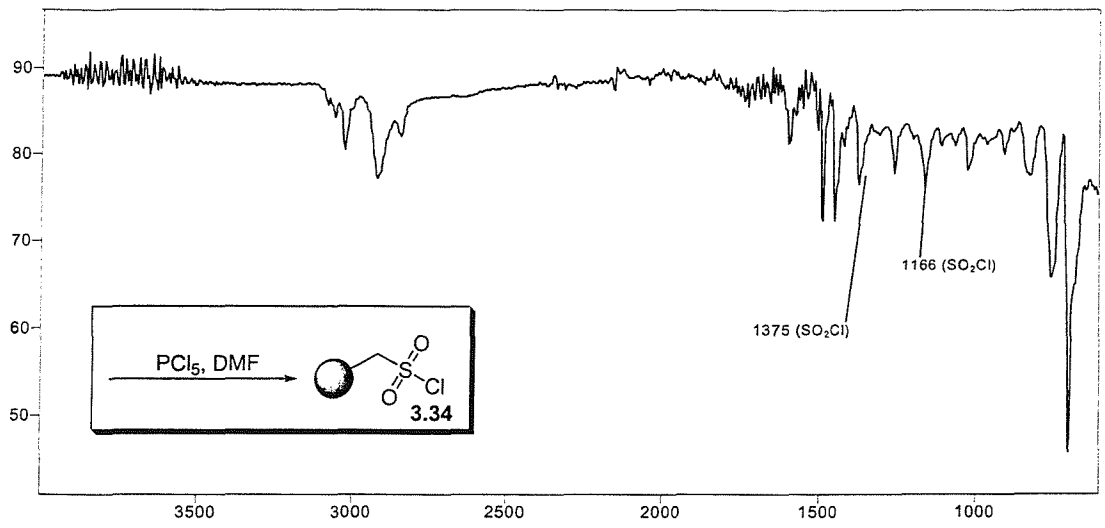


Figure 3.13 Typical infrared spectrum from chlorination reactions with SO_2Cl_2/PPh_3.

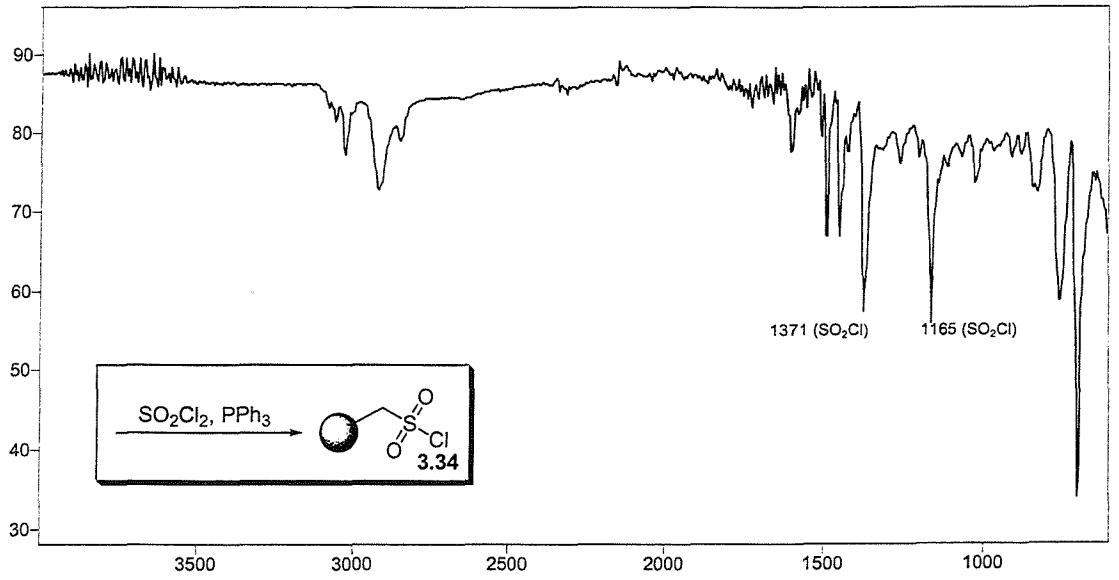
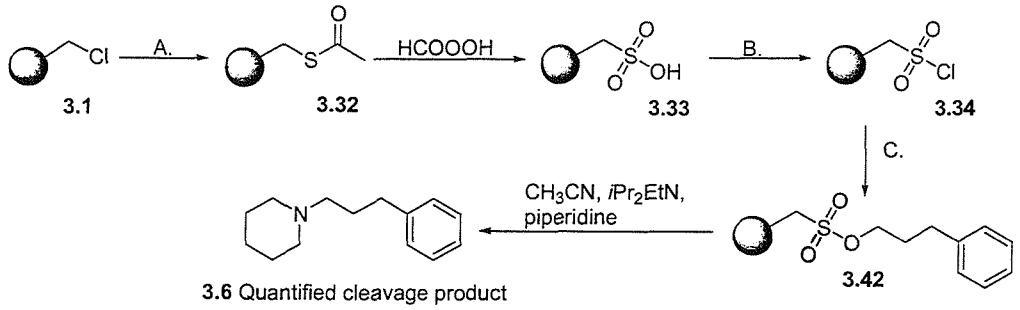


Table 3.2 Assessment of the sulfonyl chloride resins.



	Reaction A – conditions[a]	Reaction B – conditions[b]	Reaction C – time / hrs[c]	Cleavage yield / %[d]
1	DMF, 25 °C	PCl_5, DMF	5	< 5
2		PCl_5, DMF	20	< 5
3	DMF, 80 °C	PCl_5, DMF	5	< 5
4		PCl_5, DMF	20	< 5
5		PCl_5, DCM	5	16
6		SO_2Cl_2, PPh_3, DCM	5	14
7	DMF, 25 °C. Pre-swell with DCM before reaction	PCl_5, DMF	5	< 5
8		PCl_5, DCM	5	< 5
9		SO_2Cl_2, PPh_3, DCM	5	6

a). Equal amounts of potassium thioacetate used in each reaction. b). All reactions at 25 °C, for 18 hours. c). All reactions with 3-phenylpropanol, DCM:pyridine (1:1). d). Reactions yielding under 5 % are unquantifiable.

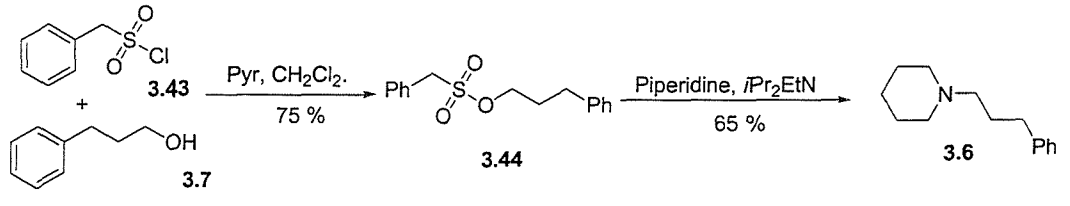
Most of the reactions showed little or no recovery of the desired tertiary amine (the dilution of the products is such that any yield under 5 % is not quantifiable). To be sure this was not due to the procedure for the formation of the sulfonate, reactions were carried out with triethylamine as base in place of pyridine, without significant improvement (table 3.3).

Table 3.3 Assessment of the sulfonyl chloride resins with alternative method.

	Reaction A – conditions[a]	Reaction B – conditions[b]	Reaction C – time / hrs[c]	Cleavage yield / %[d]
1	DMF, 80 °C	PCl_5, DMF	5	< 5
2		PCl_5, DCM	5	< 5
3		SO_2Cl_2, PPh_3, DCM	5	< 5
4	DMF, 25 °C. Pre-swell with DCM before reaction	PCl_5, DMF	5	< 5
5		PCl_5, DCM	5	< 5
6		SO_2Cl_2, PPh_3, DCM	5	< 5
7[e]	N/A	N/A	5	32

a). Equal amounts of potassium thioacetate used in each reaction. b). All reactions at 25 °C, for 18 hours. c). All reactions with 3-phenylpropanol, Et_3N in DCM. d). Reactions yielding under 5 % are unquantifiable. e.) reaction carried out with commercial sulfonyl chloride resin.

In order to be sure that the problem did not lie with the benzylic nature of the resin and that the resin was able to perform adequately in forming a sulfonate ester, an analogous system was investigated as a solution model. A commercial source of benzylsulfonyl chloride **3.43** was used and reacted with 3-phenylpropanol to give the corresponding sulfonate ester **3.44** in 75 % yield (scheme 3.19).

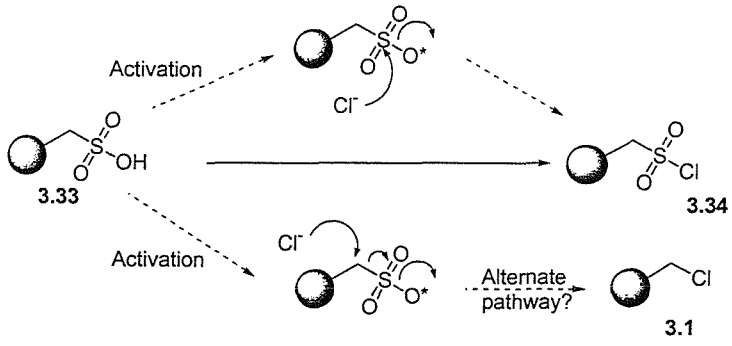


Scheme 3.19 Model reactions with benzylsulfonyl chloride **3.43**.

Nucleophilic displacement with piperidine gave the tertiary amine product **3.6** in 65 % yield. With these results we were satisfied the resin, once formed would behave as expected.

The problem could therefore only be with the chlorination reactions as all the other synthetic steps had been shown to be effective. Typically, conversion of sulfonic acid

groups to the corresponding sulfonyl chlorides works very well, but usually with aryl sulfonic acid moieties. Mechanistically, formation of the sulfonyl chloride can be described as activation of the –OH, followed by displacement with Cl^- (scheme 3.20). However, in this case it is conceivable that a different displacement is possible whereby the chloride ion attacks at the benzylic position eliminating the sulfonate group completely and regenerating the chloromethyl functionality.

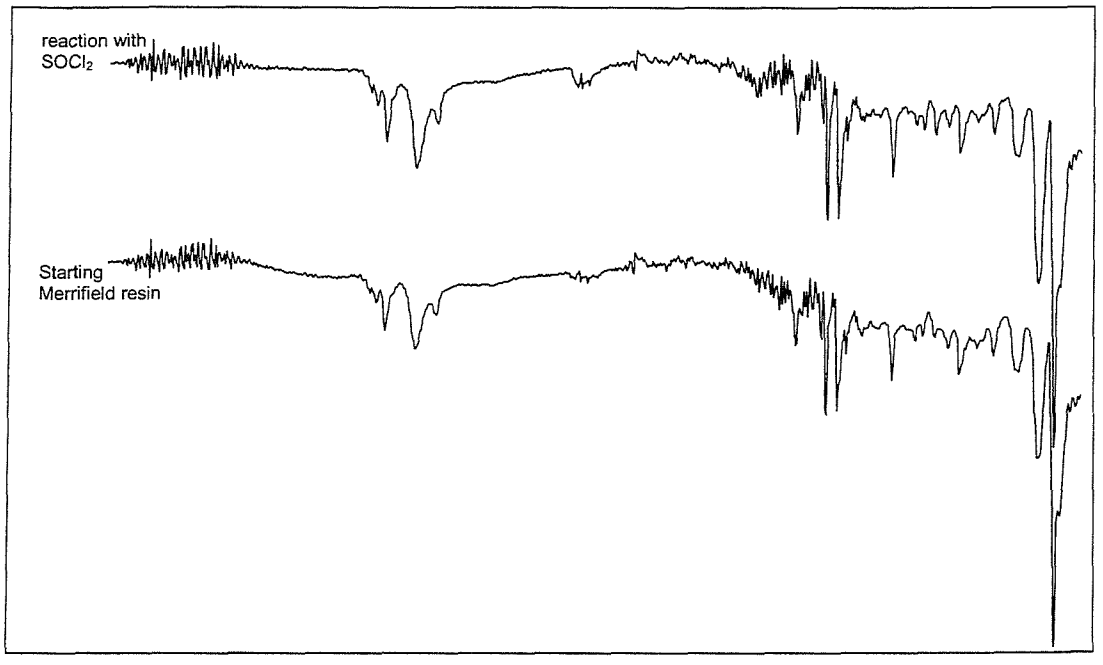


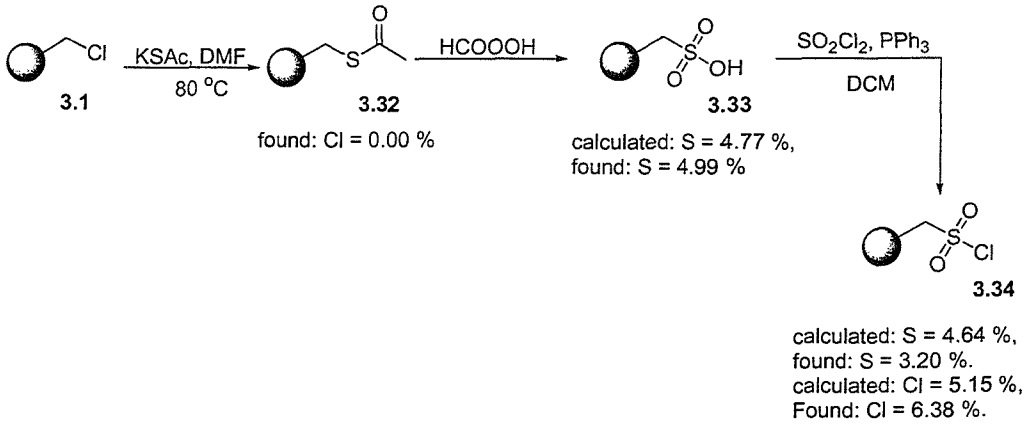
Scheme 3.20 Generalised mechanistic proposal for chlorination and proposed side-reaction.

This appears to be confirmed when the sulfonic acid resin was exposed to harsher conditions using thionyl chloride in DCM with DMF present. When the IR spectrum is compared to the spectrum of the starting Merrifield resin, it can be seen they are identical (figure 3.14). This would explain the low returns of tertiary amine **3.6** in the assessment of the previous resins, the sulfonyl chloride peaks in the IR spectra being present from the remaining sulfonyl chloride functionality.

Indeed, inspection of the elemental analysis data for the resin made *via* the route shown in scheme 3.21, which was in fact the best route determined by assessment through amine displacement of the corresponding sulfonate, a reduced level of sulfur compared to the theoretical value. In addition, inflated levels of chlorine were observed as would be expected if the side-reaction had taken place. This is despite the reliable synthesis to the point of the sulfonic acid resin **3.33**.

Figure 3.14 IR spectra of Merrifield (chloromethyl) resin and resin after treatment with thionyl chloride.

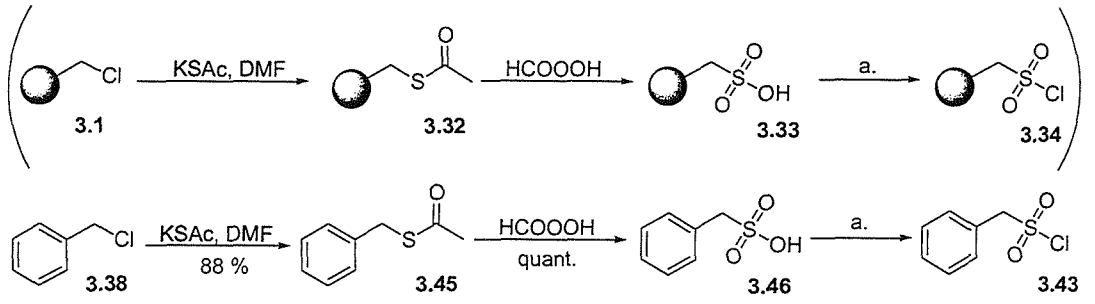




Scheme 3.21 Elemental analysis data obtained from the various steps in the synthesis of a benzylic sulfonyl chloride resin.

3.8 Solution model proof of the undesired chlorination reaction

In order to confirm the nature of the undesired side reaction, studies using a solution model were undertaken (scheme 3.22).



Scheme 3.22 Resin synthesis and the corresponding solution study.

Benzyl chloride (**3.38**) was chosen as an analogue for Merrifield resin. An added advantage was that the sulfonyl chloride product **3.43** was amenable to GC analysis so all the potential products from the chlorination reactions could be analysed quickly against commercial sources.

As expected, the synthesis of the thioacetate **3.45** was trivial yielding the desired material in 88 % yield. The conversion to the corresponding sulfonic acid **3.46** proceeded as expected without need for purification. The acid was however very hygroscopic and as such had to be handled carefully prior to use in the water sensitive chlorination reactions.

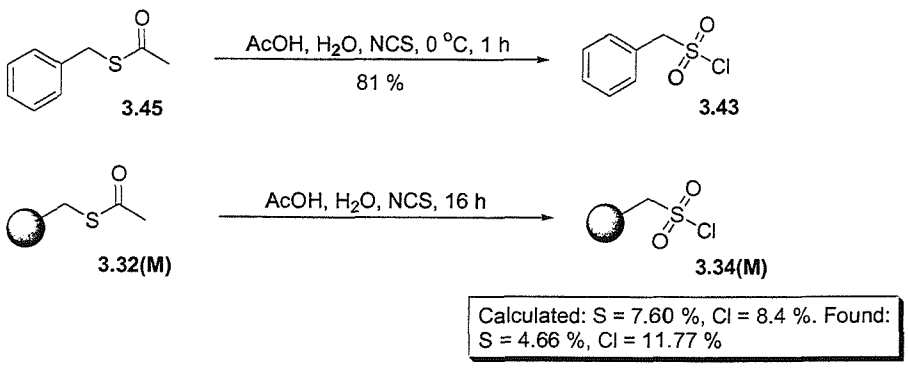
The GC studies carried out on the acid proved very useful. Shown in figure 3.15 is one of the GC traces obtained from the chlorination reactions, using PCl_5 in dichloromethane. This was the best ratio of sulfonyl chloride product to chloride by-product observed from any of the methods used (including thiophosgene, SO_2Cl_2/PPh_3, PCl_5/DMF etc.) after 15 minutes reaction time. Indeed the prolonged reaction time showed that the ratio appears to worsen with time, eventually only showing benzyl chloride (**3.38**) and no sulfonyl chloride **3.43**. As the sulfonic acid starting material **3.46** cannot be detected by GC, it could not be determined whether this meant the acid gave a mixture of benzyl chloride (**3.38**) and benzylsulfonyl chloride **3.43** directly, or whether the desired sulfonyl chloride product **3.43** was formed first and then underwent conversion to the benzyl chloride. However, the latter

was proven to be the case when a commercial sample of sulfonyl chloride **3.43** was exposed to chlorination conditions, the product observed was benzyl chloride (**3.38**), showing the desired sulfonyl chloride product **3.43** was indeed unstable to the reaction conditions.

Figure 3.15 GC trace observed from reaction with PCl_5 in CH_2Cl_2 after 15 minutes.

It was clear from these results that conventional chlorination reactions were not going to be useful to produce the desired resin **3.34**. Indeed, a solution study using the benzyl thioacetate **3.45** also showed that the reaction with Cl_2 gas in acetic acid and water was also ineffective, giving the same displacement product (benzyl chloride). Nonetheless, following work by Kim *et al* using acetic acid and water with *N*-chlorosuccinimide as a chlorine source,[159] a respectable yield of the desired sulfonyl chloride product **3.43** was obtained from thioacetate **3.45** (scheme 3.23). As a result, using macroporous Merrifield resin (designated with an "M" in brackets) the thioacetate resin **3.32(M)** was synthesised using the optimised procedure outlined above (section 3.7, chapter 3). However, when the chlorination method using *N*-chlorosuccimide was initially applied to the thioacetate macroporous resin, the reaction failed. After some investigation it was shown that much longer reaction times were required and at room temperature, the elemental analysis results for this resin

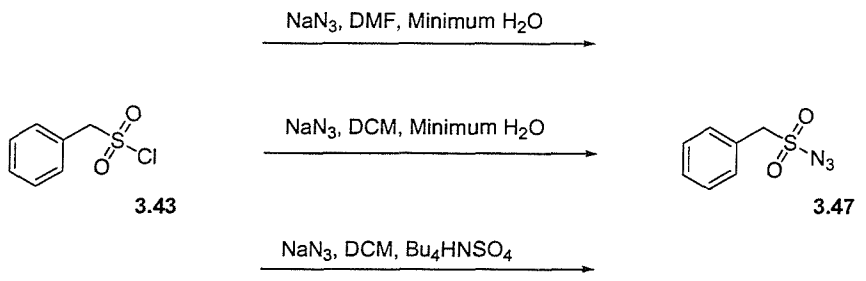
however show that the same displacement problem was occurring with this method (scheme 3.23).



Scheme 3.23 Chlorination reactions with *N*-chlorosuccinimide in solution and with macroporous thioacetate resin (**3.32(M)**).

Having shown that chloride ions acted as a nucleophile at the benzylic carbon position to give benzyl chloride moieties from sulfonic acids, it was wondered whether the same problems would be observed when reacting benzylic sulfonyl chloride resins with other nucleophiles, such as azide. A number of trials were carried out reacting benzyl sulfonyl chloride **3.43** with an azide. Studies indicated that the desired sulfonyl azide was obtained as the only product (scheme 3.24). All three reactions gave the desired product however under markedly different reaction times.

The reaction using phase-transfer conditions (with Bu_4HNSO_4) gave the most rapid transformation, and indeed these conditions had been made use of with gel-type (microporous) sulfonyl chloride resins in work reported above. Next fastest was that of the reaction with DMF, which required overnight reaction and the slowest, the reaction with DCM/H_2O (not altogether unexpected from this bi-phasic system), which took 24 hours. Interestingly, when the phase-transfer conditions were applied to macroporous sulfonyl chloride resin, no reaction was observed. However, reaction was possible in DMF with the minimum amount of water.



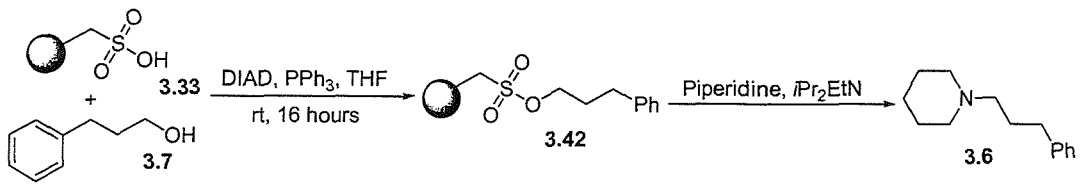
Scheme 3.24 Reactions of benzylsulfonyl chloride **3.43** with azide.

Unfortunately, the side-reactions involving displacement to give chloromethyl functionality could not be solved, despite all the other steps being shown to be very reliable.

3.9 Sulfonic acid resin and Mitsunobu chemistry.

Alternative methodologies were sought in order to perform chemistry with the sulfonic acid resin **3.33** that had been synthesised with a view to removing the need for conversion to the sulfonyl chloride moiety. Perhaps the most interesting and useful route would be to use Mitsunobu chemistry.[160-162] Indeed, the use of Mitsunobu chemistry on the solid-phase is well documented with a variety of substrates.[163-166] The use of sulfonic acids as the acidic portion of a Mitsunobu coupling has precedent in the literature.[167-169] This also has stereochemical implications that are complementary to direct tosylation conditions, which may become important for chiral secondary alcohols.

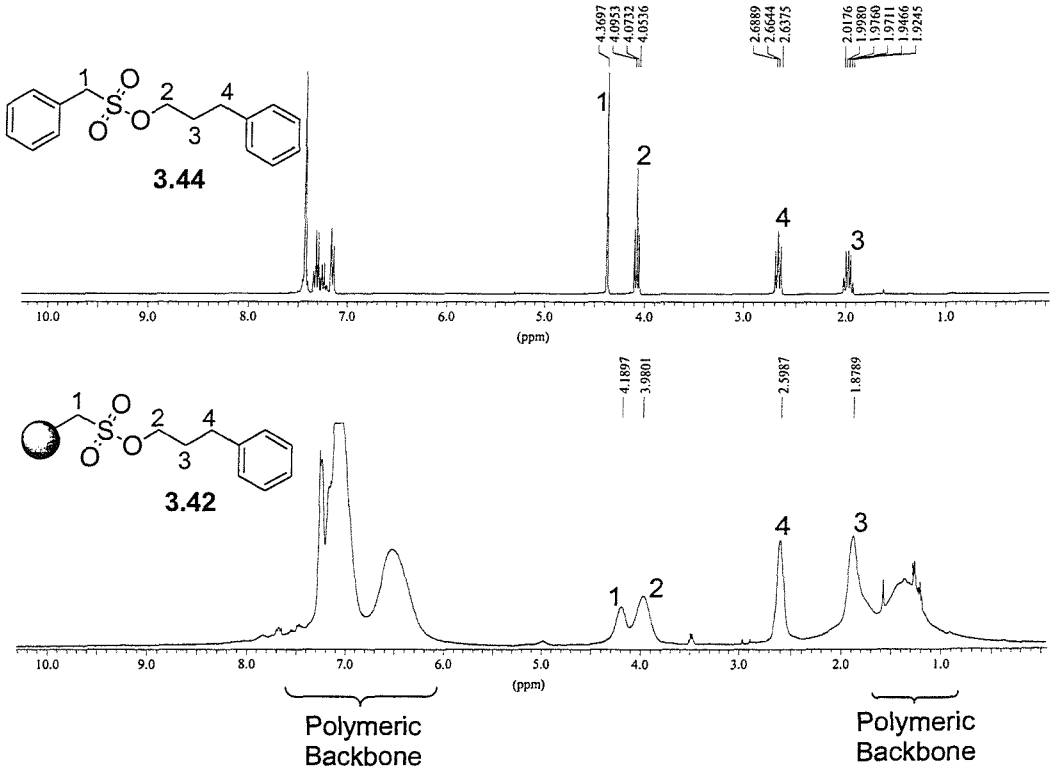
In order to investigate this route, a preliminary reaction was carried out, using 3-phenylpropanol (**3.7**) under standard Mitsunobu conditions with a sulfonic acid resin **3.33** stirring overnight at room temperature (scheme 3.25). The IR analysis of the resulting resin **3.42** indicated the presence of sulfonate groups.



Scheme 3.25 Initial Mitsunobu chemistry carried out with sulfonic acid resin **3.33**.

A known weight of the resulting resin **3.42** was then taken and exposed to the usual cleavage conditions with piperidine as nucleophile in order to give the tertiary amine **3.6**. GC analysis of a standard sample taken from the cleavage reaction revealed a 49 % yield based on the theoretical loading of the sulfonate resin **3.42**, assuming 100 % conversion for each step up to that point.

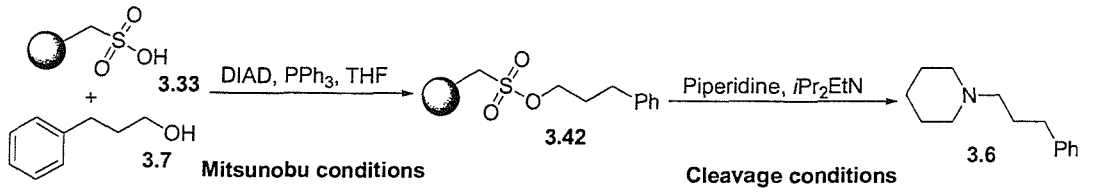
Figure 3.16 Comparison of MAS ^{1}H NMR for resin **3.42** against model **3.44**.



The synthesis of sulfonate resin by this route appeared to be more effective and in fact allowed the successful analysis of the resin by MAS ^{1}H-NMR. Figure 3.16 shows a comparison of the on-bead MAS ^{1}H-NMR against the corresponding

conventional NMR of the solution model **3.44** synthesised previously. The results are excellent and the spectra are in strong agreement with each other.

Table 3.4 Results from Mitsunobu reactions with sulfonic acid resin **3.33** in the microwave reactor.



Rxn	Mitsunobu reaction					Cleavage reaction					
	eq. R-OH	eq. reagents	eq. Resin	Time/ min	Temp./ °C	eq. Amine	eq. Base	Time/ min	Temp./ °C	Mass[a]/ mg	% yield
1	6	6	1	10	80	3	6	15	120	11.25	43.6
2	6	6	1	10	100	3	6	15	120	9.82	38.0
3	6	6	1	20	100	3	6	15	120	9.94	38.5
4	6	6	1	10	120	3	6	15	120	8.65	33.5
5	1	1	1	10	80	3	6	15	120	5.49	21.3
6	1	1	1	10	100	3	6	15	120	4.04	15.7
7	1	1	1	20	100	3	6	15	120	4.28	16.6
8	1	1	1	10	120	3	6	15	120	4.48	17.3
9	6	6	1	10	90	3	6	15	120	9.65	37.4
10	6	6	1	10	70	3	6	15	120	9.55	37.0
11	6	6	1	10	60	3	6	15	120	10.46	40.5
12	6	6	1	10	80	3	6	15	120	10.45	40.5
13	6	6	1	15	80	3	6	15	120	9.72	37.6
14	6	6	1	20	80	3	6	15	120	10.64	41.2
15	6	6	1	25	80	3	6	15	120	12.51	48.4
16	6	6 [b]	1	25	80	3	6	15	120	4.29	16.6

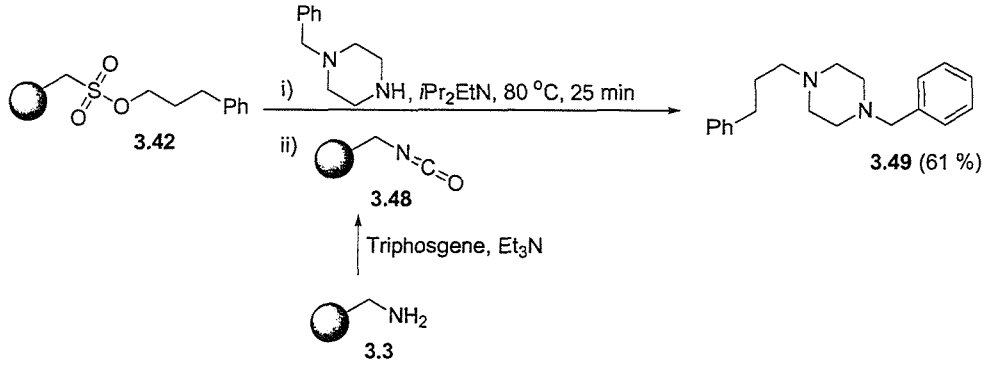
a) Mass determined from the calibrated GC spectra b) Reaction cooled to 0 °C on addition of DIAD.
NB. After reaction under Mitsunobu conditions, a 100 mg sample of the resulting sulfonate resin was taken and exposed to the cleavage conditions. Percentage yields are therefore based in theoretical loading of the sulfonate resin **3.42** determined by assuming 100 % conversion of each step from starting Merrifield resin.

As the result using Mitsunobu chemistry was very encouraging, a microwave-assisted study was embarked upon whereby the reaction shown in scheme 3.25 was studied in depth. Table 3.4 shows the results obtained from the reactions carried out.

The use of the microwave reactor (Smith Synthesiser® from Personal Chemistry) allowed the expediation of this study.[170,171] Reactions 1 and 12 show that the reaction can be carried out reproducibly with fairly good correlation between the results. The initial variation in temperature for the Mitsunobu step showed that better results were obtained at 80 °C (reaction 1-4). This was also the case for reactions carried out with just 1 equivalent of alcohol and reagents (reactions 5-8). Little variation was observed with reactions below 80 °C (reactions 10 and 11) and indeed this microwave reactor would not accept reaction temperatures below 60 °C. Finally, reactions 13-15 show that at 80 °C longer reaction times led to improved yields.

Although the yield for the thermal Mitsunobu reaction could not be improved, a comparable yield could be obtained for the reaction at 80 °C in the microwave with the advantage of a reaction time of only 25 min (entry 15, table 3.4).

Using this method, additional examples were investigated, substituting an alternative amine in the microwave-assisted cleavage step (scheme 3.26). *N*-benzyl piperazine was reacted with resin **3.42**. The resulting amine product **3.49** was obtained with a yield of 60 %.



Scheme 3.26 Synthesis of amine **3.49** using an isocyanate scavenger.

In this case, the reacting piperazine is non-volatile and so in order to remove the excess amine, an isocyanate scavenger resin was employed.[172] Starting from aminomethyl resin **3.3** and treating with phosgene and base, isocyanate resin **3.48** can be accessed, as reported by Booth and Hodges.[20]

A number of examples exist in the literature for the synthesis of a variety of sulfonate precursors by Mitsunobu chemistry involving sulfonic acids in solution

phase chemistry,[167-169] and so one might imagine a number of uses for this methodology using sulfonic acid resins in synthesis.

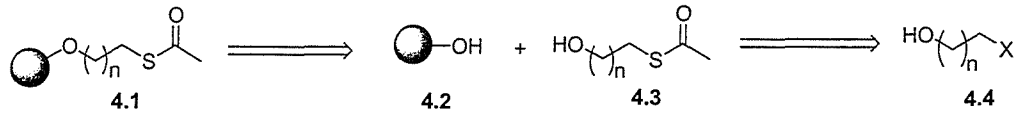
Chapter 4. Results and Discussion

Sulfonyl Chloride Resins Synthesised from a Phenolic Resin

4.1 Synthesis of a sulfonyl chloride resin from phenolic resin

Problems experienced with the resins synthesised from Merrifield resin called for an alternative route to be investigated. The reactions to synthesise the benzylic sulfonyl chloride had shown that the final chlorination step was flawed, due to displacement occurring at the benzylic position. An alternative alkyl resin was therefore required to be able to carry out the final chlorination step satisfactorily. The thioacetate chemistry and subsequent oxidation to sulfonic acid along with Mitsunobu chemistry on the solid-phase have all worked well and a conscious effort was made to include these methods.

Scheme 4.1 gives a retrosynthetic analysis of the proposed resin. Using an hydroxy thioacetate moiety such as **4.3**, which can be synthesised from the corresponding hydroxy halide **4.4**, it can be envisaged that Mitsunobu reaction with a phenolic resin **4.2** would provide an ether-linked alkyl thioacetate resin **4.1**. Subsequent conversion to sulfonic acid and then translation to the sulfonyl chloride would then be possible by the routes explored previously.

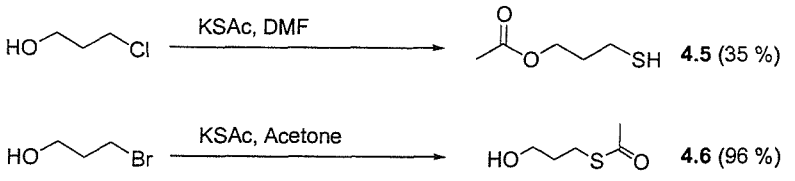


4.1 4.2 4.3 4.4

Scheme 4.1 Retrosynthetic analysis of an alternative alkyl sulfonyl chloride resin.

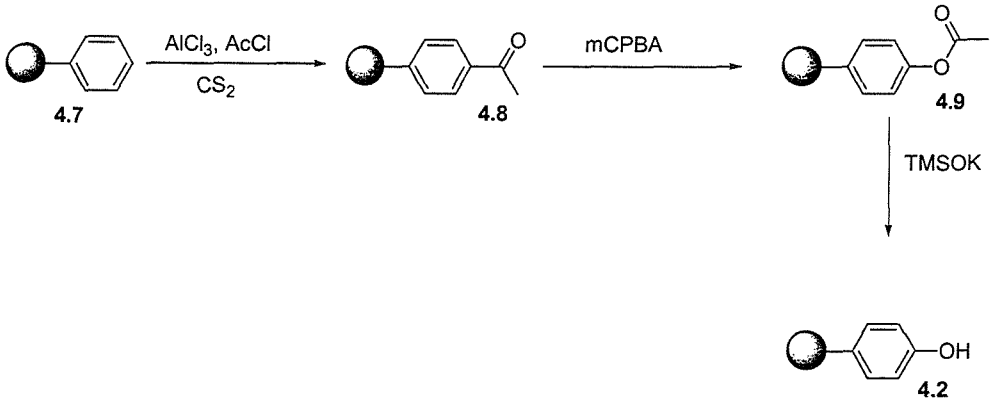
Synthesis of a hydroxy thioacetate was the first step. A three carbon hydroxy halide was chosen (scheme 4.2). Initially, 3-chloropropanol was used, however, reaction at elevated temperature gave mostly an undesired trans-acetylated thiol ester **4.5**. An alternative, milder route was required and in fact the use of more reactive 3-bromopropanol had been utilised by Richardson and co-workers in order to access the

desired hydroxy thioester **4.6**.[173] Using this method, the displacement could be carried out at room temperature and the desired thioacetate was obtained in excellent yield.



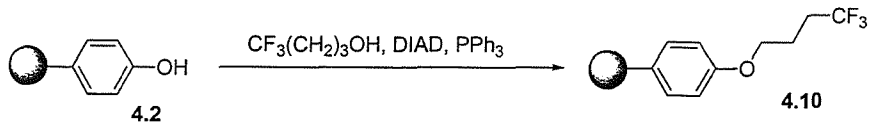
Scheme 4.2 Synthesis of the desired hydroxy thioacetate.

Despite a number of phenolic resins being commercially available, they are relatively expensive. For this reason, it was decided to synthesise the phenolic resin by the method described by Brown and Fisher, in three steps from unfunctionalised polystyrene resin (Scheme 4.3).[165] Freidel-Crafts acylation of unfunctionalised polystyrene backbone gave acyl resin **4.8**; Baeyer-Villiger oxidation of resin **4.8** gave acetate intermediate **4.9**, which underwent hydrolysis to provide the desired phenolic resin **4.2**.



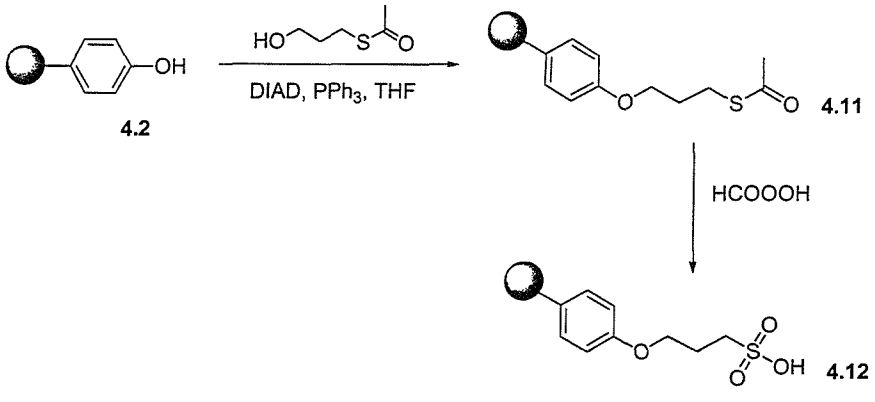
Scheme 4.3 Synthesis of phenolic resin **4.2**.

In order to determine the loading of the phenolic resin **4.2**, a Mitsunobu coupling of the resin with 4,4,4-trifluorobutanol was carried out (scheme 4.4) to give resin **4.10**. Elemental analysis for fluorine of the resulting ether resin showed that the loading of fluorine was 9.91 %, corresponding to a loading of 1.74 mmol/g.



Scheme 4.4 Mitsunobu coupling to determine phenolic resin loading.

From the elemental analysis data, the loading for phenolic resin **4.2** was determined to be 2.15 mmol/g. This figure is in agreement with the loading value determined by Brown and Fisher using a different method.[165] The Mitsunobu coupling of phenol resin **4.2** with hydroxy thioacetate **4.6** was carried out to obtain the desired ether-linked thioacetate resin **4.11** (scheme 4.5). Theoretical loading of the thioacetate resin **4.11** was calculated to be 1.67 mmol/g from the determined loading for the phenol resin **4.2**. Elemental analysis results for sulfur for reactions on a small scale showed the reaction gave thioacetate resin **4.11** with a loading of 1.60 mmol/g (S = 5.13 %), demonstrating that the reaction had worked very effectively. After scale-up, the resin was exposed to the oxidation reaction to give the sulfonic acid resin **4.12**. Elemental analysis for sulfur showed a much-reduced loading of sulfur than was expected based on the theoretical loading. The only difference between the small-scale and large-scale reactions to give the thioacetate **4.11** was that for the small-scale reactions, the exothermic Mitsunobu reaction was not controlled and DIAD reagent was added carefully.

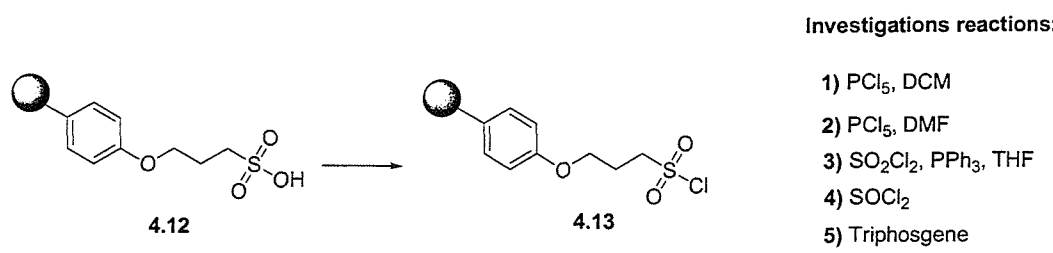


Scheme 4.5 Synthesis of the ether-linked sulfonic acid resin **4.12**.

When scaled up, in the interests of safety, carrying out the addition of DIAD was done at 0 °C to control the exotherm. Further reactions showed that much improved yields

for the Mitsunobu reaction with phenolic resin **4.2**, could be achieved when the reaction mixture is allowed to warm, the exotherm being controlled by slow and careful addition of DIAD. A similar result was observed for the reaction between the benzylic sulfonic acid and an alcohol (see entry 16, table 3.4, chapter 3). This has proved to be a very important observation for the Mitsunobu reaction on the solid-phase.

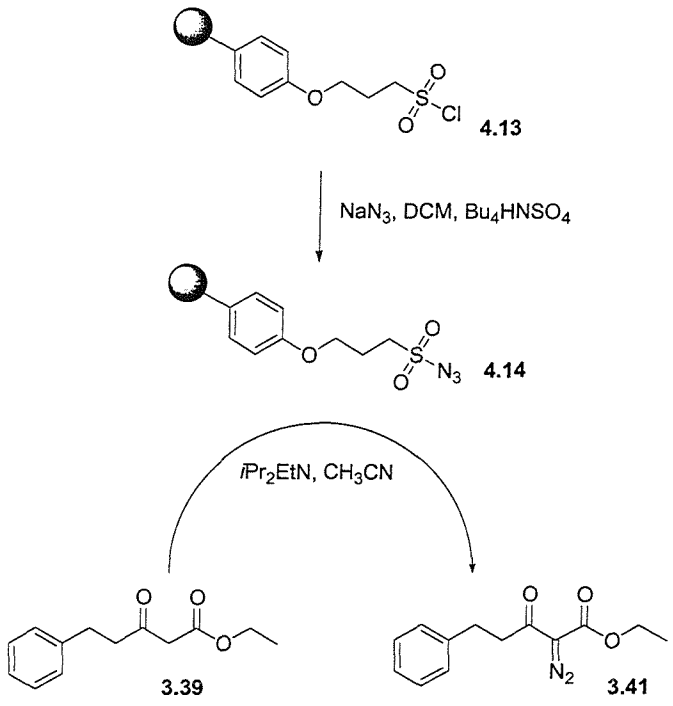
Despite a slightly low loading, further investigation of the sulfonic acid resin **4.12** was undertaken. In order to determine the best chlorination conditions to afford the desired sulfonyl chloride resin **4.13**, a number of reactions were carried out with resin **4.12** (scheme 4.6).



Scheme 4.6 Chlorination reactions of sulfonic acid resin **4.12**.

4.2 Evaluation of the ether-linked sulfonyl chloride resin

Assessment of the synthesised sulfonyl chloride resins **4.13** was carried out by converting each respective resin into the corresponding sulfonyl azide resin **4.14** using the phase-transfer methodology previously determined. Each sulfonyl azide resin **4.14** was then employed in diazo-transfer reactions with β-ketoester **3.39** (scheme 4.7).



Scheme 4.7 Assessment of the sulfonyl chloride resin in diazo-transfer reactions.

In each case the amount of sulfonyl azide resin **4.14** used was based upon the theoretical loading, and they were all made from the same batch of sulfonic acid resin **4.12**. Determination of the conversion of a known amount of β-ketoester **3.39** to the diazo product **3.41** was carried out utilising GC analysis, allowing indirect determination of the loading of the sulfonyl azide resin to be calculated.

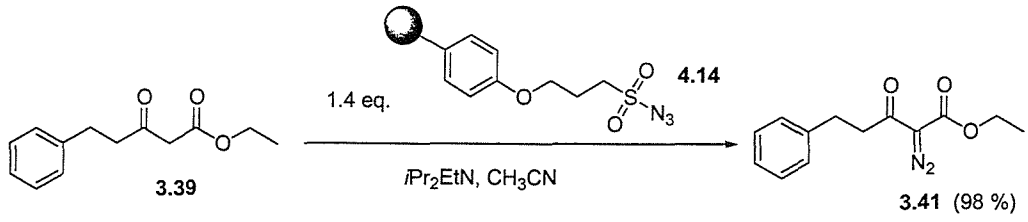
Table 4.1 Assessment of sulfonyl azide resin **4.14**.

Reaction	**Chlorination method used to prepare resin 4.13**	**Calculated loading of sulfonyl azide resin 4.14**
1	$SOCl_2$	0.50 mmol/g
2	SO_2Cl_2/PPh_3	0.91 mmol/g
3	Triphosgene	0.45 mmol/g

Table 4.1 shows the three best reaction results. Reactions using PCl_5 as chlorinating agent, in either DCM or DMF over various reaction times were proved to be inferior to

the entries shown. By far the most effective chlorination conditions involved the use of sulfuryl chloride/triphenyl phosphine. Comparison of elemental analysis results for sulfur on the intermediate sulfonic acid resin **4.12** (S = 2.84 %, translates to a loading of 0.89 mmol/g), represented quantitative conversion for the ensuing steps to the sulfonyl azide **4.14**.

Increasing the number of equivalents of sulfonyl azide resin **4.14** with respect to the β-ketoester substrate **3.39**, with the revised loading of 0.91 mmol/g (from table 4.1) showed that using 1.4 equivalents, the reaction could be forced to completion. The product was obtained pure without need for further purification (only filtration through a silica plug was required), in 98 % yield (scheme 4.8).

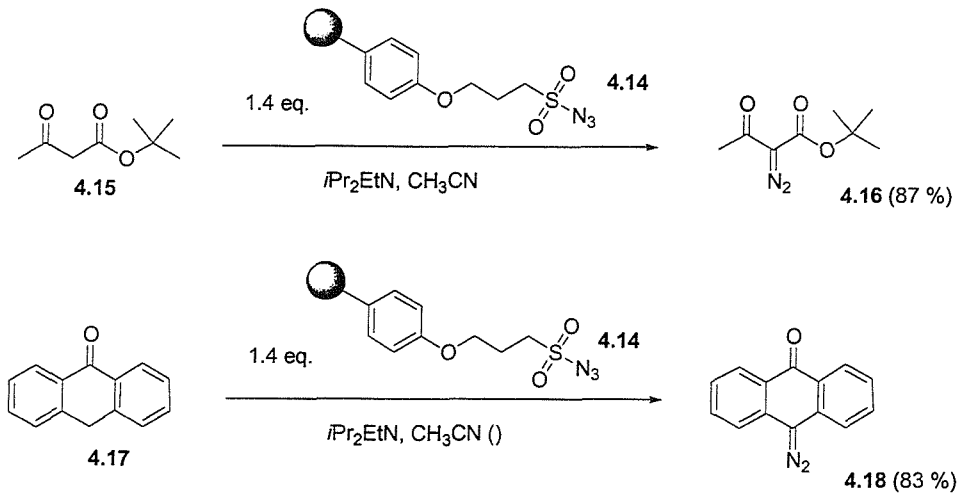


Scheme 4.8 Optimised diazo-transfer reaction with sulfonyl azide resin **4.14**.

The sulfonyl azide resin was also tested for its stability. A sample of resin was left in a screw top vial in air, on the bench at room temperature for 6 weeks. The diazo-transfer reaction was carried out again using β-keto ester **3.39** substrate and no deterioration in the yield of the reaction was observed and as such it can be declared that the resin diazo-transfer reagent **4.14** exhibits a much improved stability over its solution-phase counterparts used in the literature.

4.3 Diazo-transfer reactions with a supported sulfonyl azide

The results outlined above represent an excellent outcome and it was therefore prudent to investigate the diazo-transfer reaction using a number of other substrates. Another more hindered β-ketoester (**4.15**) was used with equal success in order to give the diazo product **4.16** in 87 % yield, again with no need for formal purification (scheme 4.9).

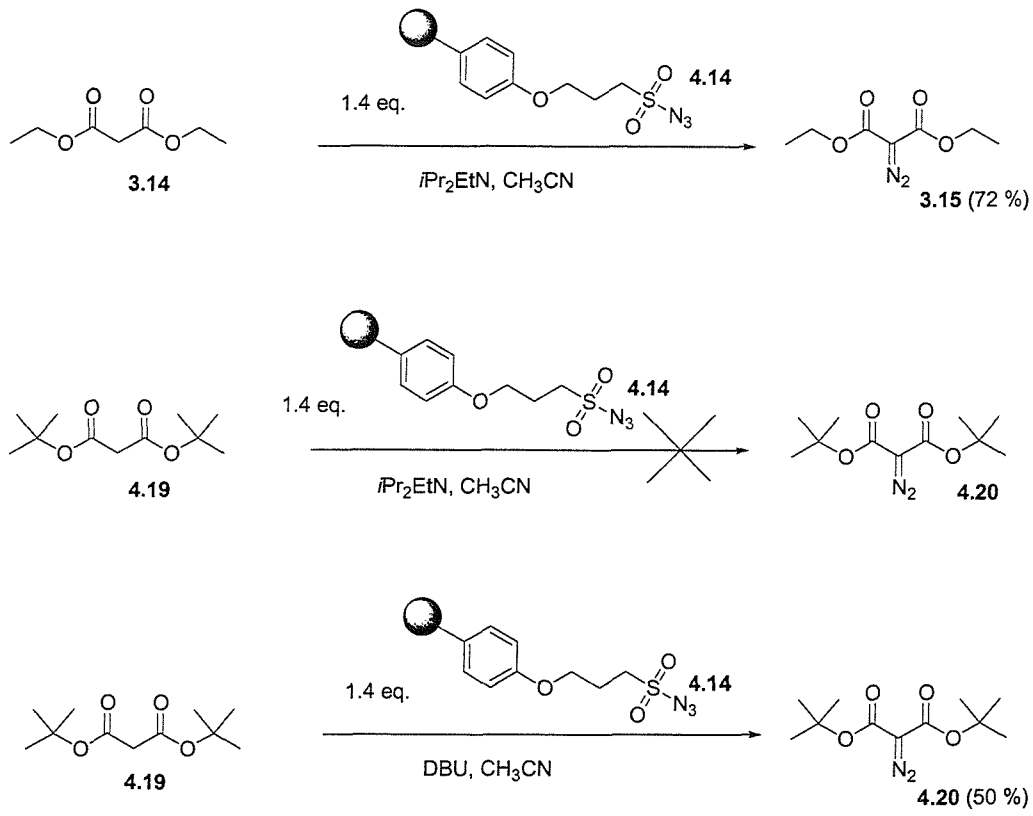


Scheme 4.9 Follow up diazo-transfer reactions.

A reaction carried out with anthrone (**4.17**) gave the corresponding diazo product **4.18**, however in this case purification was necessary to separate the product from remaining starting material.

The use of the reaction with malonates proved to be slightly more problematic. Reaction with diethyl malonate (**3.14**) was less successful in comparison with previous results with a yield of 72 % (scheme 4.10), the mass balance being made up by returned starting material. However, no reaction was observed with di-*tert*-butyl malonate (**4.19**) under these reaction conditions. A similar trend was observed with the work of Metz *et al.*[58]

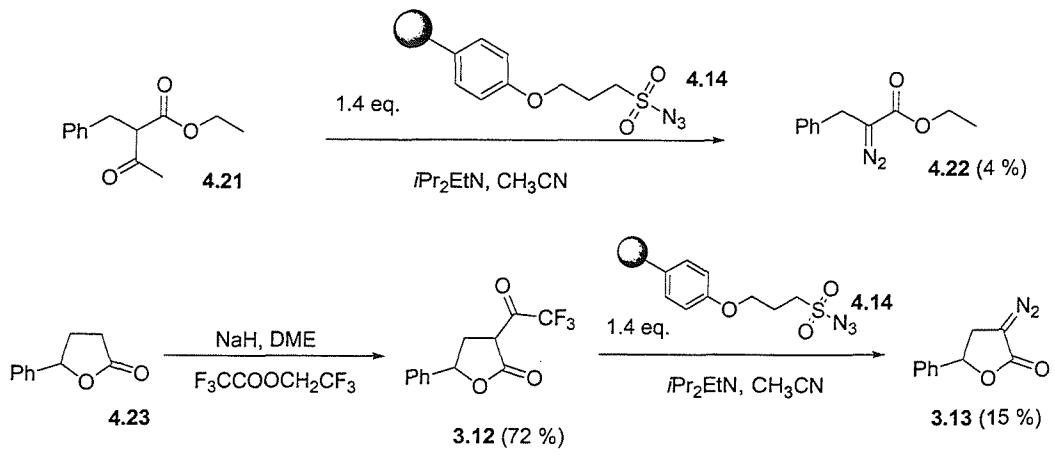
However, despite this setback further investigation into this reaction showed that a change of base to DBU made it possible to obtain the di-*tert*-butyl malonate diazo product **4.20** with 50 % yield, with the mass balance made up by starting material.



Scheme 4.10 Diazo-transfer reactions with malonate substrates.

Reactions have also been carried out with more challenging substrates. These involve a sacrificial deacylative diazo-transfer reaction (scheme 4.11). The first reaction carried out on such a substrate was with β-ketoester **4.21**. This substrate represents quite a challenge to the methodology and in fact only a very small amount (4 %) of the corresponding diazo product **4.22** was recovered after reaction with resin **4.14**, with no returned starting material.

This perhaps was to be expected, as the substrate is not especially activated, therefore another more activated system was investigated. Starting with commercially available γ-phenyl-γ-butyrolactone **4.23**, conversion to the corresponding trifluoroacyl lactone intermediate **3.13** was achieved by reaction with NaH and trifluoroethyl trifluoroacetate with 72 % yield.

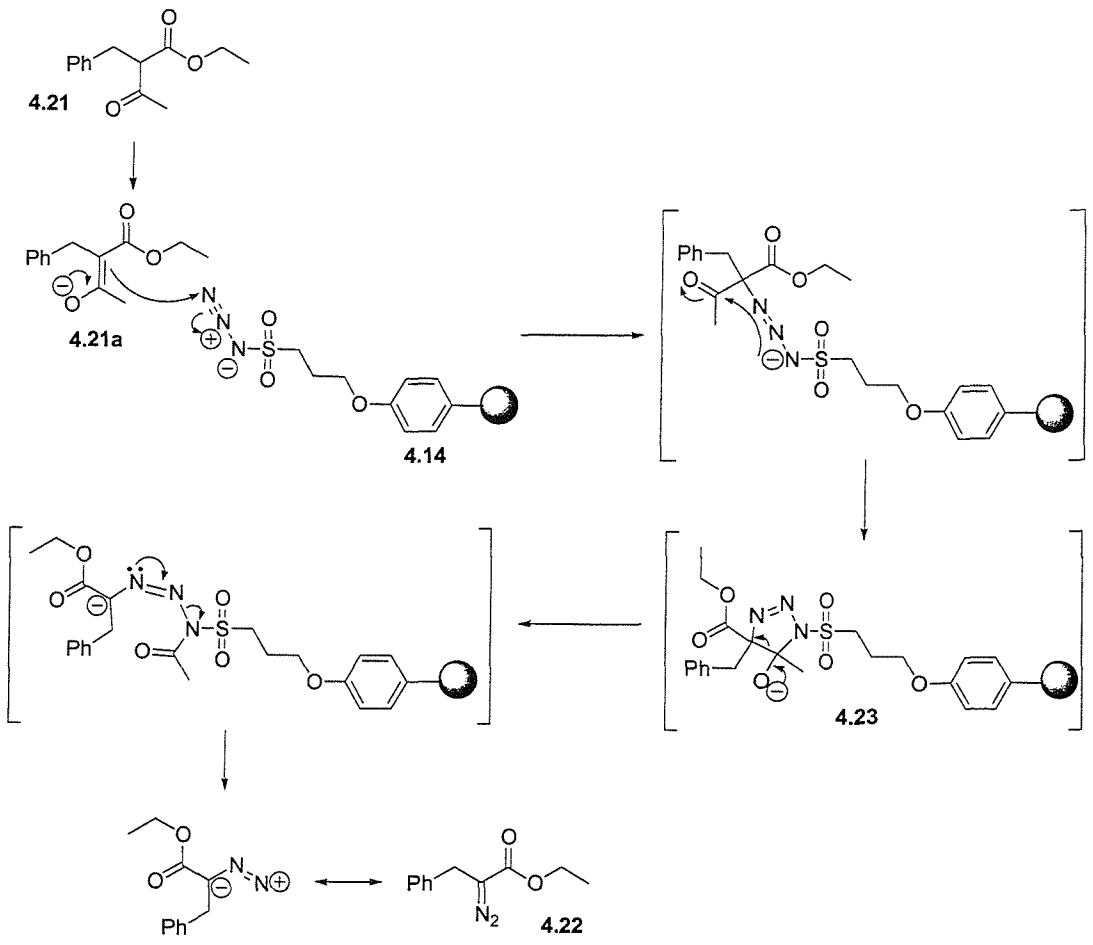


Scheme 4.11 Attempted sacrificial deacylative diazo-transfer reactions.

However, when the diazo-transfer reaction conditions were applied to trifluoroacyl substrate **3.12**, diazo product **3.13** was observed with an increased yield of 15 %. Although an improvement in yield over that obtained for diazo ester **4.22**, this is still far from satisfactory. Indeed, repeated attempts to improve the yields from diazo-transfer reactions carried out with substrates **4.21** and **3.12** using DBU as base gave similar results. No improvement was observed from reactions carried out over an extended amount of time either. Interestingly, virtually no starting material was returned from the reactions carried out.

Hendrickson and Wolf proposed mechanisms that account for diazo-transfer reactions with activated methylene groups and a mechanism for the formation of Wolff rearrangement products. They proposed a mechanistic route for the formation of diazo products from deacylative diazo-transfer reactions *via* a triazene intermediate.[52] When their mechanism is applied to the reaction carried out with the supported reagent **4.14** and β-keto ester **4.21** (scheme 4.12), the formation of an enolate, followed by reaction with the sulfonyl azide would lead to triazene intermediate **4.23**. The subsequent acyl cleavage should then give the desired diazo product **4.22**. However, given the stability of the sulfonyl azide resin **4.14**, it is conceivable that the triazene intermediate **4.23** may well either be stable enough not to collapse to give the diazo product **4.22**, or rearrange *via* an alternative route, in either case possibly affording an alternate resin-bound product. This would account for the lack of recovered starting material from the reactions. Indeed, given that a greater yield was observed for the diazo-transfer reaction with trifluoroacetate **3.12** than the reaction with acetate **4.21**, a

hypothesis could be proposed that this substrate is more highly activated towards acyl cleavage, and hence more diazo product is returned. However, further work would be required in order to determine whether or not this is the case.

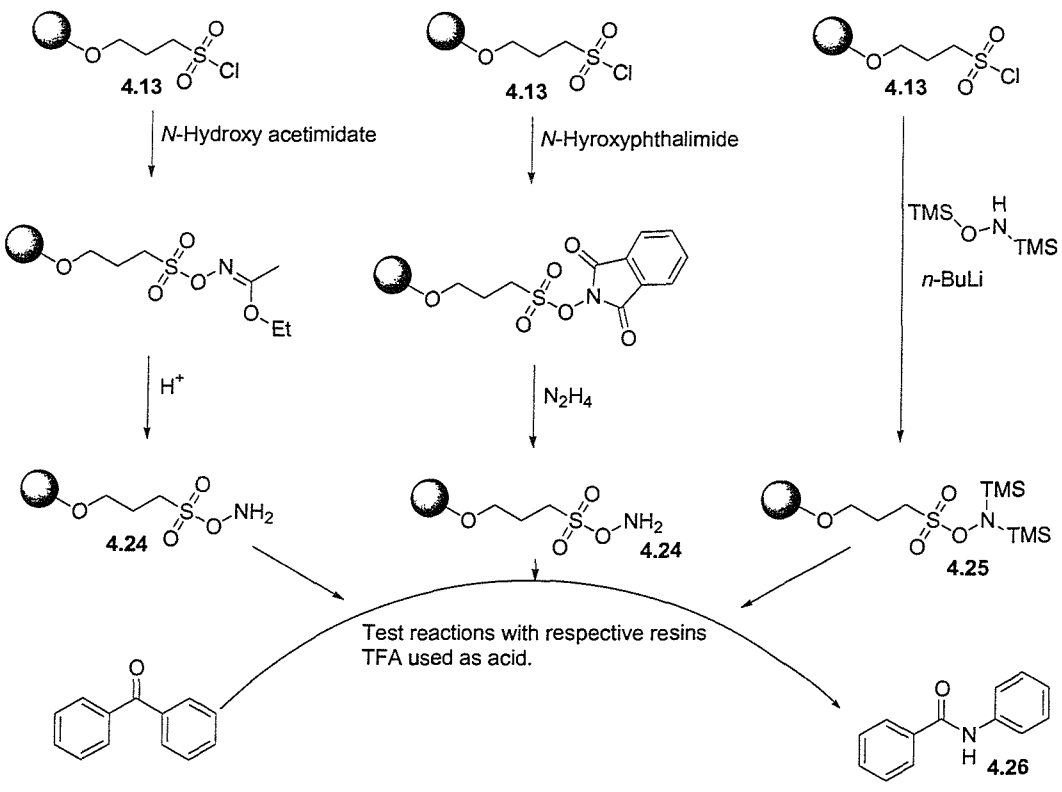


Scheme 4.12 Proposed mechanism for the deacylative diazo-transfer reaction of **4.21**.

4.4 Attempted syntheses of Beckmann reagents

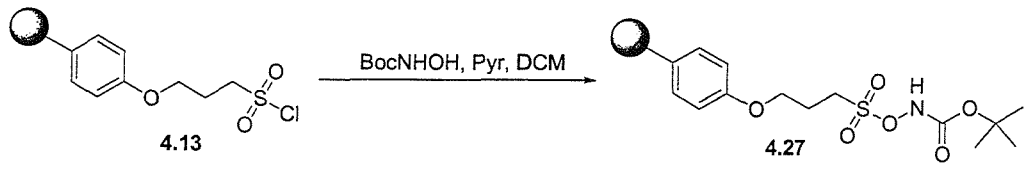
Given the success shown with the phenolic-linked sulfonyl azide resin **4.14** as a diazo-transfer reagent, attempts were made to use the sulfonyl chloride precursor **4.13** in order to synthesise a Beckmann reagent analogous to MSH (*O*-sulfonylhydroxylamine). A number of routes were investigated in order to access the desired hydroxylamine resin. To determine the activity of the resin, benzophenone was used as a test, determining the amount of amide product **4.26** obtained by GC analysis of the reaction mixtures. Initially, reactions of the sulfonyl chloride resin **4.13** with *N*-

hydroxyacetimidate and then hydrolysis,[174] or reaction with hydroxyphthalimide and deprotection with hydrazine failed to provide access to the desired *O*-sulfonylhydroxylamine **4.24**,[175,176] with no return of the amide product being obtained from reactions (see scheme 4.13). Also, a more adventurous route using bis-(TMS)hydroxylamine in the presence of base was attempted in order to give the *N,N*-disilylated *O*-sulfonyl hydroxylamine resin **4.25**.[177-179] In this case the resin was used directly as the TMS groups would be removed *in situ*, however again this method was unsuccessful.



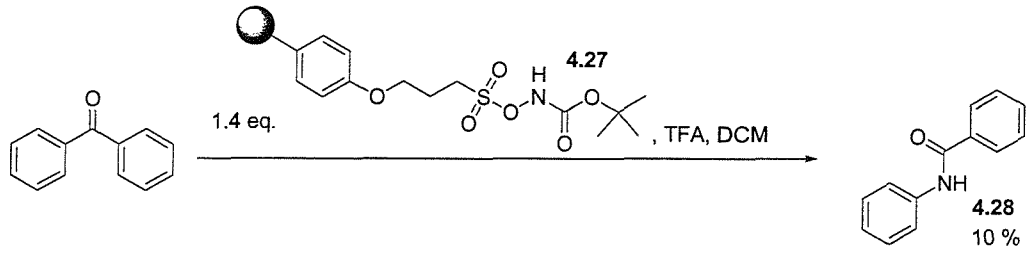
Scheme 4.13 Unsuccessful attempts to make supported Beckmann reagents.

An alternative route was therefore proposed. Previously, work by Endo *et al* showed that the synthesis of MSH could be achieved by the reaction of mesitylenesulfonyl chloride with a Boc protected hydroxylamine.[180] In order to apply this route to the solid-phase, commercially available *N*-Boc-hydroxylamine[181,182] was reacted with sulfonyl chloride resin **4.13** to provide *N*-Boc-*O*-sulfonyl hydroxylamine resin **4.27** (scheme 4.14).



Scheme 4.14 Synthesis of Boc-protected supported *O*-sulfonyl hydroxylamine.

Due to the acid-lability of the Boc group it was hoped that resin **4.27** could be used directly in an acid catalysed Beckmann rearrangement. Using benzophenone as a substrate, resin **4.27** was used under acidic conditions to effect the Beckmann rearrangement to afford the corresponding amide product **4.26**. In this case, the amide product **4.26** was obtained albeit in poor yield. GC analysis of the reaction mixture showed that product **4.26** was formed in a very modest 10 % yield, the mass balance being made up of the starting benzophenone (scheme 5.14).



Scheme 4.15 Initial Beckmann rearrangement with a supported reagent.

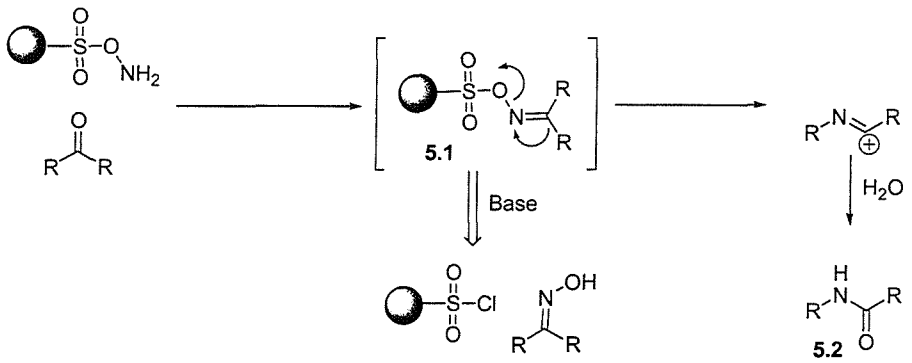
This represents a very encouraging starting point and this route should prove very useful for work carried out in the future (see conclusions and further work).

Chapter 5. Results and Discussion

Miscellaneous Reactions with commercially available Resins

5.1 The Beckmann rearrangement of oximes using sulfonyl chloride resin

The ultimate goal of this work, in terms of Beckmann rearrangement chemistry was the synthesis of a supported sulfonyl hydroxylamine that could be used for the direct one pot transformation of ketones to amides. Reaction of a sulfonyl hydroxylamine with a ketone gives a tosyl oxime equivalent **5.1** which undergoes a bond migration and final addition of water to give the amide product **5.2** (scheme 5.1).

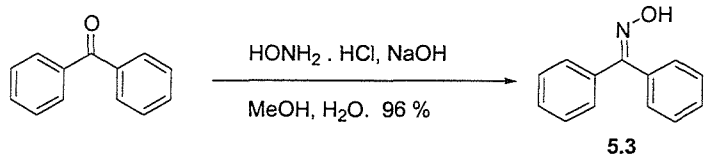


Scheme 5.1 Proposed alternative route to oxime tosylate.

In order to access the Beckmann amide product *via* intermediate supported oxime tosylate **5.1**, the reaction of sulfonyl chloride resin with a pre-formed oxime in the presence of a base could be used. This would provide a good test of methodology for a reliable route to a resin-bound *O*-sulfonyl hydroxylamine. The reactions of oximes are well documented[183] and indeed their reaction with sulfonyl chlorides to effect the Beckmann rearrangements is well known, albeit with solution-phase chemistry.[184-191] Reactions are typically carried out in polar solvents such as acetone or neat pyridine. In order to achieve the same transformation using solid-supported sulfonyl chlorides,

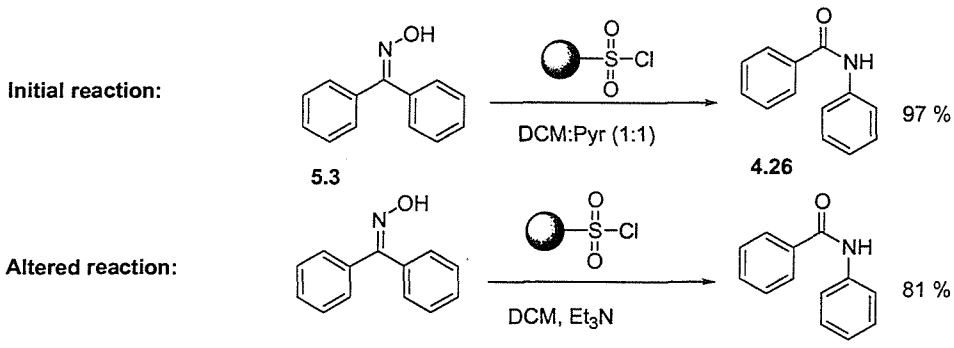
some adjustments to the reaction conditions would be required to be compatible with gel-type resins.

The synthesis of oximes from the corresponding ketones using hydroxylamine hydrochloride is a well-known and efficient process.[192-195] Benzophenone oxime (**5.3**) was chosen as a test substrate. Benzophenone oxime (**5.3**) was prepared from benzophenone in 96 % yield (scheme 5.2).[196]



Scheme 5.2 Preparation of benzophenone oxime (**5.3**).

Having accessed the starting oxime, a Beckmann rearrangement was attempted using three equivalents of sulfonyl chloride resin to force the reaction to completion.

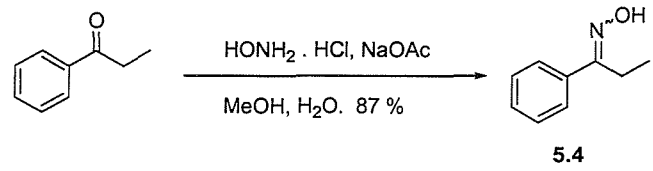


Scheme 5.3 Beckmann rearrangements with commercial sulfonyl chloride.

In view of the fact that the solution reactions in the past had been carried out in neat pyridine, the initial resin reaction (scheme 5.3) was carried out in dichloromethane:pyridine (1:1). The crude recovery from the reaction after filtering off the resin required purification by flash chromatography, however the desired amide product **4.26** was obtained with an excellent yield of 97 %. Although a high yielding reaction, the need for purification means that there is no advantage to using this route over existing solution reactions. It was hypothesised that a change of base to triethylamine and subsequent water wash after filtering off the resin should remove

any need for purification. A reaction with 1.5 equivalents of resin and 5 equivalents of triethylamine followed by washing the organic layer with dilute acid gave the desired amide product **4.26** with 81 % yield and no need for further purification. No starting material was recovered. It is possible that warming the reaction mixture could well speed up the reaction and allow the rearrangement to occur with similar yields to that obtained from the reaction with pyridine in dichloromethane.

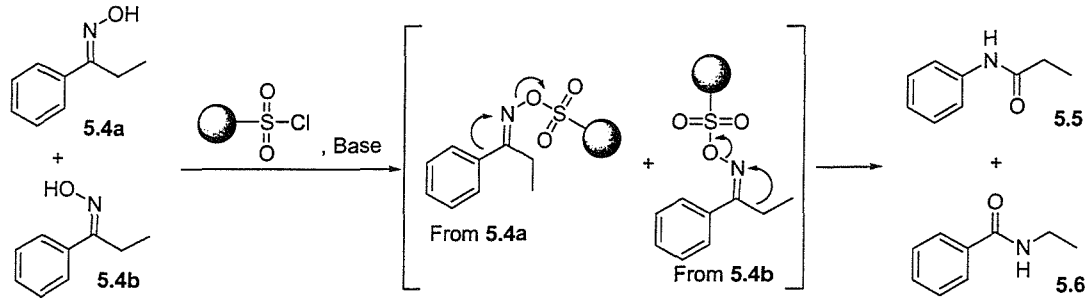
Having shown that using benzophenone oxime (**5.3**) the quantitative conversion to the amide product **4.26** could be achieved with pyridine as base and commercially available sulfonyl chloride resin, it was therefore decided to investigate the reaction of an unsymmetrical oxime. In order to do this, propiophenone oxime (**5.4**) was synthesised using the revised method of Hansen *et al* affording the desired oxime **5.4** in 87 % yield.[188]



5.4

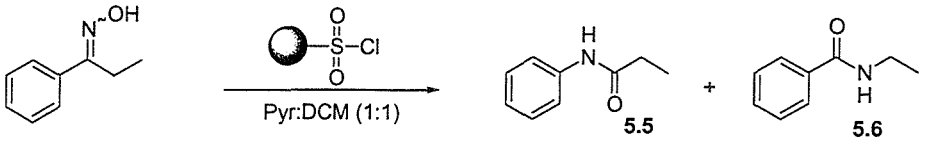
Scheme 5.4 Preparation of propiophenone oxime (**5.4**).

The formation of the oxime in this case would give rise to a mixture of *syn* and *anti* isomers (**5.4a**, **5.4b**) and as a result a mixture of amide products **5.5** and **5.6** would therefore be expected, by the bond migration of the group *anti* to the SO_3R leaving group (scheme 5.5).



Scheme 5.5 Expected amide products using propiophenone oxime (**5.4**) as substrate.

However, when propiophenone oxime (**5.4**) was exposed to the same reaction conditions as for benzophenone oxime (**5.3**) only amide **5.5** was obtained with a disappointing yield of 30 % with no trace of amide **5.6** (scheme 5.6). The rearrangement of unsymmetrical oximes when starting from the ketone and sulfonyl hydroxylamine (such as MSH) favours the bond migration to nitrogen from the larger group (as the conformation of the tosyl group is *anti* to the larger group due to steric interactions), which in this case would favour the formation of amide **5.5** as observed.[90] However, in this case, as the oxime is formed first, both geometric isomers would be expected and so as none of amide **5.6** is given, it is possible that geometric isomer **5.4b** is either reluctant to rearrange causing it to remain on the resin, does not react with the resin at all, or is isomerised. The hypothesis was therefore that by putting more energy into the system, the yield of both amide products might be increased. The Smith synthesiser microwave reactor was used to carry out the same reaction at 120 °C for 10 minutes.[170] The reaction gave amide **5.5** with a 42 % yield and again no trace of amide **5.5**. Repeating the experiment with 20 minutes reaction time and 3 equivalents of water gave roughly the same amount of amide **5.5** and 5 % yield of amide **37**. Although an improvement has been achieved in the yield for this reaction it is still far from acceptable.



Conditions	Yields: 5.5	5.6
room temperature, 16 h.	30 %	None observed
microwave, 120 °C, 10 minutes.	42 %	None observed
microwave, 120 °C, 20 minutes.	40 %	5%

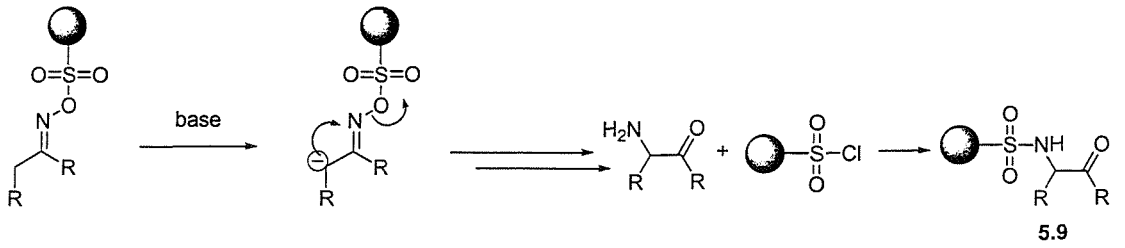
Scheme 5.6 Beckmann rearrangements of propiophenone oxime (**5.4**).

One possible reason for the low yield of the amide products is that it is conceivable that a Neber rearrangement is occurring, whereby the tosylate is displaced by a carbanion and not by bond migration, resulting in an azirine intermediate **5.7** (which in some cases can be isolated) with hydrolysis giving an α-aminoketone **5.8** main product

along side the Beckmann amide products (scheme 5.7).[43,190] Also, it should be noted that the excellent yields shown with benzophenone oxime **5.3** would not be affected by this rearrangement as no carbanion can be formed.

Scheme 5.7 Neber rearrangement as a possible undesired side reaction.

Indeed, van Vliet *et al.* showed that in solution reactions using pyridine as a base, the tosylate of an oxime can be isolated and thereafter, treatment with butoxide in ethanol gave the Neber α-aminoketone product.[197] If this alternative rearrangement is applied to reactions with a resin-bound sulfonyl chloride the resulting α-amino ketone is then free to react under the basic conditions with excess sulfonyl chloride resin to form resin-bound sulfonamide **5.9** (scheme 5.8).



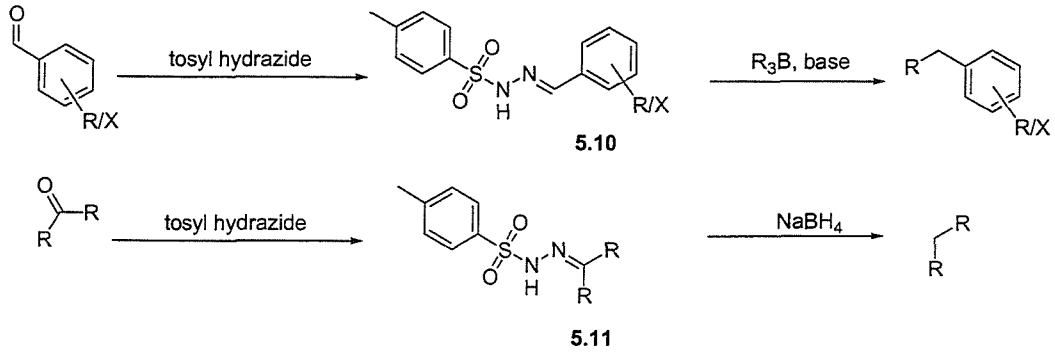
Scheme 5.8 Possible side reaction outcome.

In order to try and determine whether or not this was the case, IR spectroscopy of the recovered resin was undertaken. It showed the absence of carbonyl stretch you would expect to see if indeed a product such as **5.9** was obtained. However, the presence of a typical imine peak in the IR spectrum seems to show that there appears to be resin bound oxime still present which has not rearranged to give the amide products.

5.2 Synthesis and use of sulfonyl hydrazide resins

Sulfonyl hydrazide moieties have found a multitude of uses in organic synthesis. Some examples of the uses of sulfonyl hydrazides in synthesis are the reaction with acid chlorides,[198] formation of disulfones,[199] homocoupling to form stilbenes,[200] alkylation with alkyl halides to form sulfones,[201] condensation with aldehydes (or ketones) in order to give hydrazones such as **5.10** and **5.11** (scheme 5.9),[202] which can then be used as intermediates to the synthesis of alkyl diazo compounds,[203,204] or for decomposition using sodium ethoxide, borohydride bases, or potassium cyanide giving alkenes, alkanes or nitriles respectively.[205]

The use of sulfonyl hydrazides directly as a reagent is the reaction of aryl sulfonyl hydrazides with base, acting as diimide precursors for the reduction of olefins. In fact a few examples exist in the literature for the use of solid-supported sulfonyl hydrazines as diimide precursors.[206,207] A sulfonyl hydrazide resin would therefore have many potential uses.



5.10

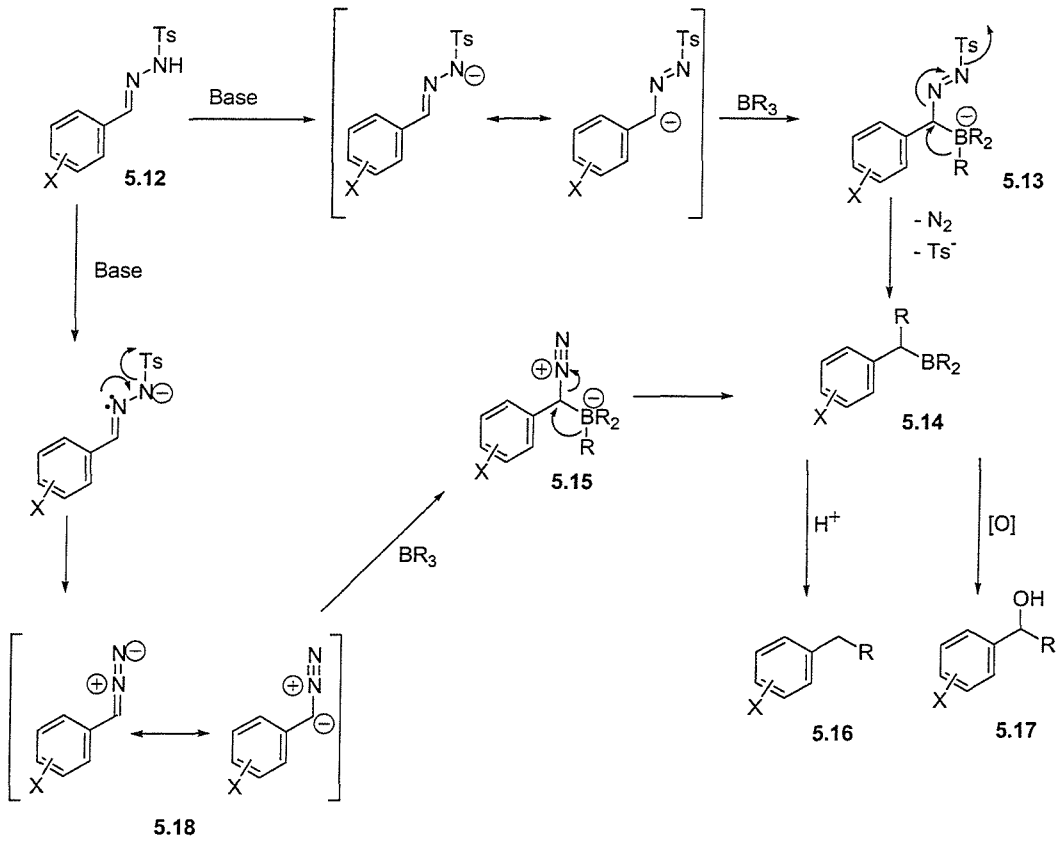
5.11

Scheme 5.9 Decomposition of some hydrazones.

Kalbalka *et al* have worked extensively on the alkylation of hydrazone intermediates with trialkylboranes (scheme 5.9).[208,209] The mechanisms they propose (scheme 5.10) for such reactions involve the deprotonation of the hydrazone **5.12** in order to form a resonance stabilised anion, which then reacts with the trialkylborane to form an electron rich organoborane intermediate **5.13**. This intermediate then undergoes a spontaneous 1,2-boratropic shift, the driving force being for the formation of nitrogen

gas and sulfinate anion, giving a new organoborane moiety **5.14**. This can be hydrolysed to the corresponding alkane **5.16** or oxidised to give alcohol **5.17**.

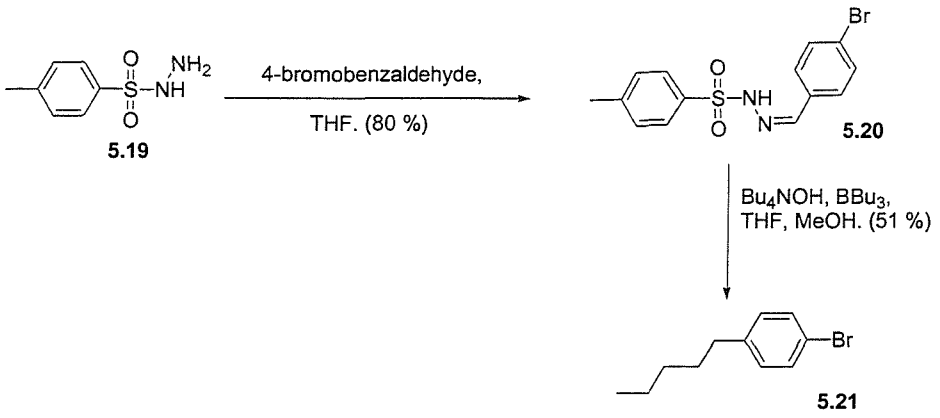
An alternate mechanism involves the decomposition of the hydrazone anion to give a diazo intermediate **5.18**, which then reacts with the alkyl borane and the ensuing 1,2-boratropic shift then liberates nitrogen to give the organoborane intermediate **5.15**. Both routes are plausible, however, the treatment of hydrazones with base to give the corresponding diazo species is well known.[204]



Scheme 5.10 Mechanisms proposed by Kabalka *et al* for the decomposition of hydrazones with trialkylboranes.

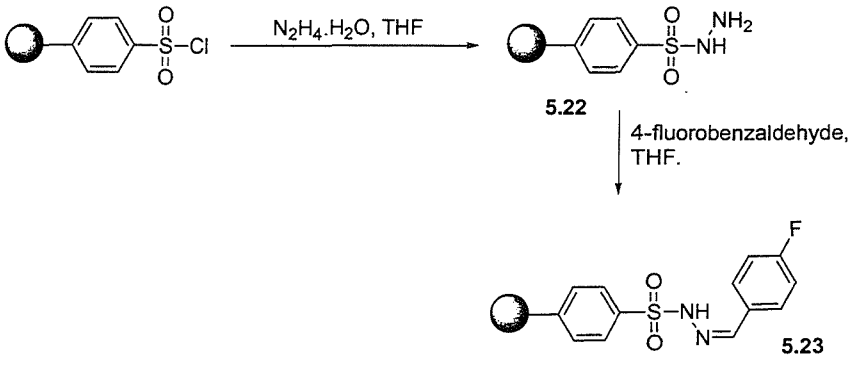
An initial study in solution was carried out to test the viability of such chemistry. Tosyl hydrazide (**5.19**) was reacted with 4-bromobenzaldehyde in order to access the corresponding hydrazone **5.20** (scheme 5.11). Subsequent treatment of hydrazone **5.20** with base and tributylborane accessed product **5.21** in moderate yield.

It was wondered whether similar results could be observed with a solid-supported version using a resin bound sulfonyl hydrazide.



Scheme 5.11 Solution study of the alkylation of hydrazones.

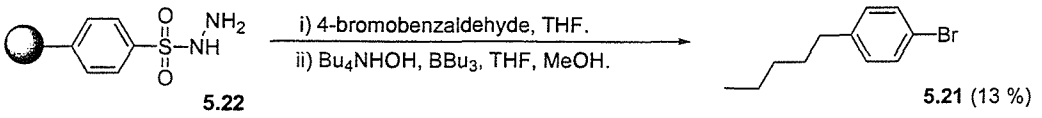
Using commercial sulfonyl chloride resin, treatment with hydrazine hydrate accessed the corresponding sulfonyl hydrazide resin **5.22** (scheme 5.12).[201] Condensation of this resin with 4-fluorobenzaldehyde gave the desired hydrazone resin **5.23** with quantitative yield (determined by mass difference of the final resin). The condensation was carried out with 4-fluorobenzaldehyde initially in order to be able to carry out ^{19}F NMR Gel-Phase NMR of the resulting resin **5.23**.



Scheme 5.12 Supported sulfonyl hydrazide and the synthesised supported hydrazone.

As all the chemistry appeared to be working well, the use of the sulfonyl hydrazide resin **5.22** with 4-bromobenzaldehyde and subsequent reaction with tributylborane was attempted. The reaction gave the desired product **5.21** with a disappointing yield of 13

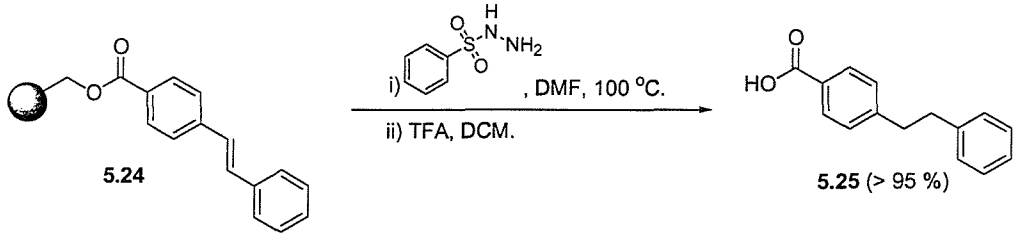
% (scheme 5.13). Although the yield of the product was low, further investigation of the chemistry by variation of the conditions may well show significant improvement on this result.



5.22 **5.21** (13 %)

Scheme 5.13 Alkylation of supported hydrazone from sulfonyl hydrazide resin **5.22**.

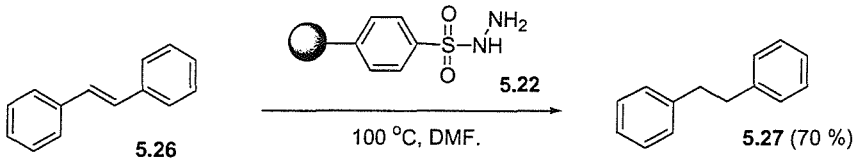
As outlined earlier, the use of supported sulfonyl hydrazide as a diimide precursor has been outlined in the past. Work by Emerson *et al.* in the late 1970s showed that these resins can by used as such a reagent, however, their methodology involved the utilisation of traditional solution phase reaction conditions, using base to remove a proton and eliminate the sulfinate anion.[207] Later work by Lacombe *et al.* involved the reduction of Wang resin-bound electron rich and deficient stilbenes (**5.24**) using a sulfonyl hydrazide in solution.[210] Subsequent cleavage with TFA afforded the reduced products in excellent yield (scheme 5.14). This work was of interest as the diimide is generated thermally in DMF at 100 °C without any need for a base.



5.24 **5.25** (> 95 %)

Scheme 5.14 Diimide reduction carried out by Lacombe *et al.*

It was conceivable that this chemistry could be applied with a supported sulfonyl hydrazide instead. Using 5 equivalents sulfonyl hydrazide resin **5.22**, *trans*-stilbene (**5.26**) was used as substrate and heated in DMF to 100 °C (scheme 5.15).



Scheme 5.15 Test reaction using sulfonyl hydrazide resin as a diimide precursor.

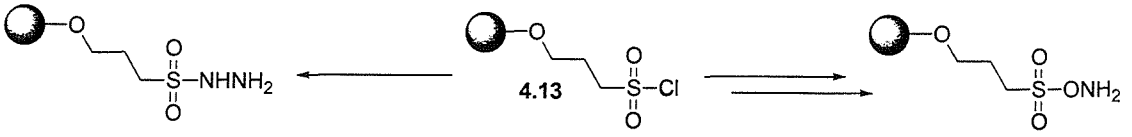
The initial results are encouraging, and the reduced product **5.27** was returned in 70 % yield. The mass balance was that of recovered starting material.

It is believed that this reaction can possibly be optimised in order to drive reactions to completion, utilising a change in the amount of resin and the microwave reactor. If the microwave reactor is used, care should be taken to determine the amount of N_2 gas formed during the reaction as the microwave reactions are carried out in closed vessels and the change in pressure has to be considered. Alternatively, the use of other sulfonyl chloride resins synthesised previously, once converted to the sulfonyl hydrazide, may well provide a much more efficient source of diimide. Such a reaction would be very useful as a number of reductions using sulfonyl hydrazide derivatives in solution often involve difficult purification steps.

Chapter 6. Conclusions and Further Work

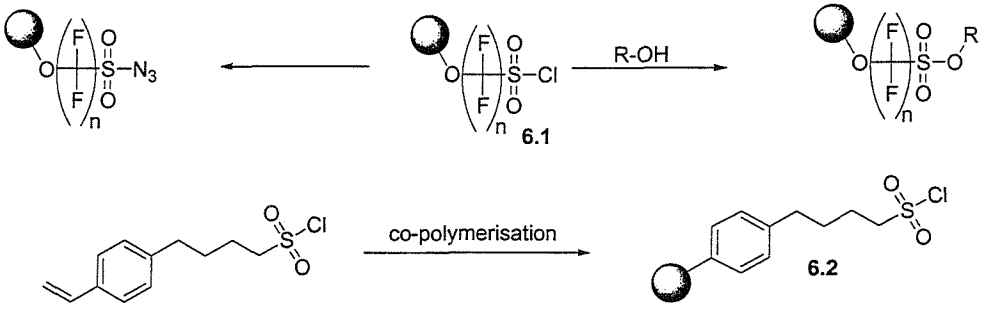
A number of sulfonyl chloride resins have been prepared and evaluated for their use in synthesis. Sulfonyl chloride resin **4.13** was shown to be effective and has been used to prepare an effective supported-sulfonyl azide diazo-transfer reagent. The use of resin **4.13** to access a Beckmann reagent has also been investigated and initial results have shown that amide products can be obtained.

Further work would include the synthesis of an *O*-sulfonyl hydroxylamine resin for use as a Beckmann reagent. An alternative use of resin **4.13** could be the synthesis of a sulfonyl hydrazide resin that could be used for the synthesis of hydrazones or as a diimide precursor (scheme 6.1).



Scheme 6.1 Proposed further work with sulfonyl chloride resin **4.13**.

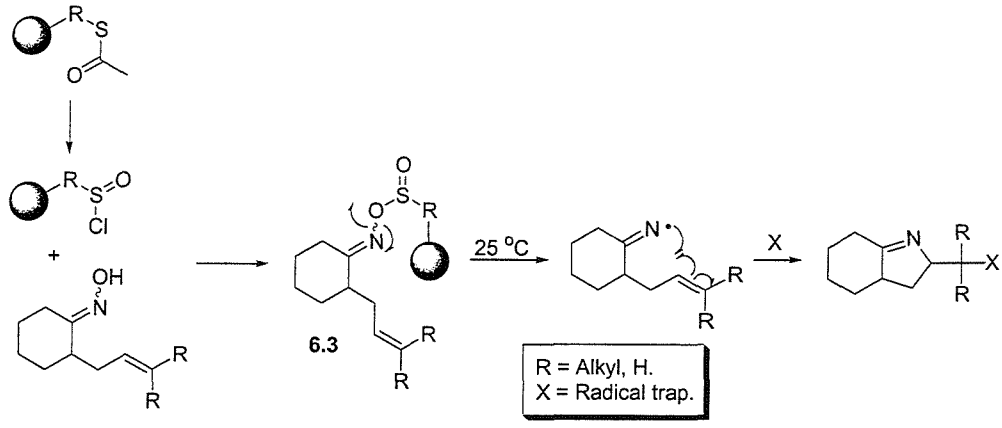
One might also envisage the synthesis of analogous resins, for example a perfluorinated resin **6.1** [211] that might be used as a supported triflating agent or a more reactive fluorosulfonyl azide diazo-transfer reagent that has been shown to be more reactive for deacylative diazo-transfer reactions (scheme 6.2).[54]



Scheme 6.2 Proposed resin analogues that could be synthesised in the future.

An alternative approach, which warrants further investigation would be the synthesis of resin **6.2** by a co-polymerisation route with no heteroatom in the linking chain (scheme 6.2).

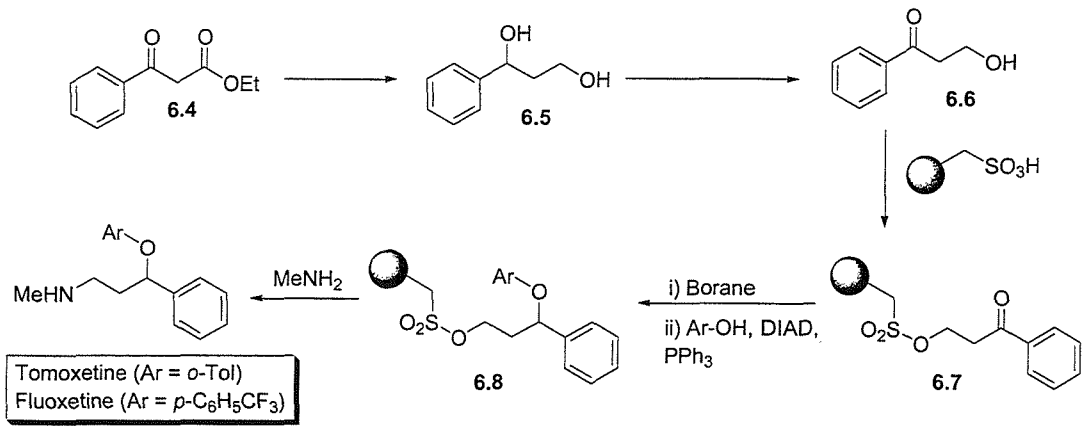
The synthesis of a sulfinyl chloride could be carried out from the intermediate thioacetate resin (scheme 6.3).[212,213] Sulfinyl chlorides have a number of uses[214] and recently Weinreb and coworkers have used sulfinyl chloride moieties in order to carry out Hudson reactions with oximes. This involves the formation of a sulfinate ester such as **6.3**, which on warming fragments to a diradical. Weinreb *et al* showed that the iminyl radical could be used in order to carry out intramolecular cyclisations with olefins, trapping with a radical trap.[215-217] If the sulfinyl chloride portion were immobilised on the solid-phase, then any unwanted radical reactions that might take place and give unwanted by-products would be trapped on the resin, aiding purification of the target molecule.



Scheme 6.3 Possible use of a supported sulfinyl chloride.

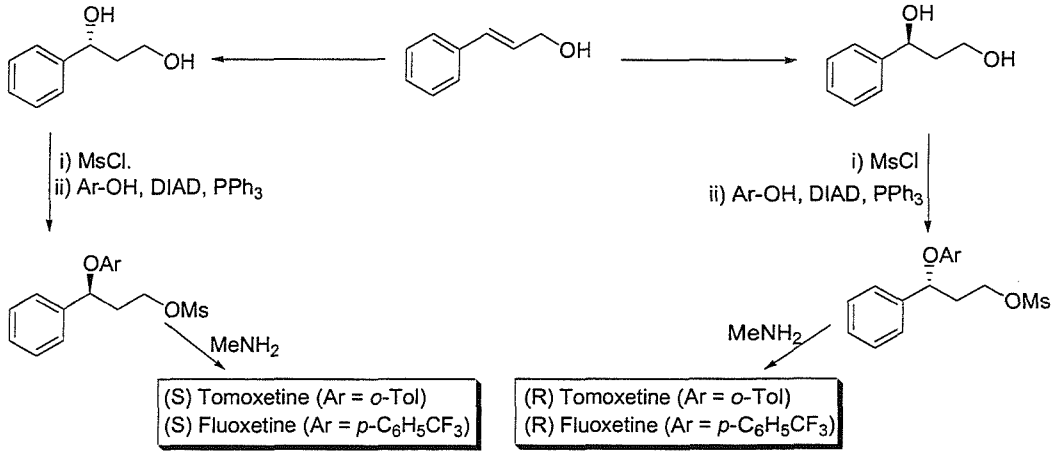
The use of sulfonic acid resins in Mitsunobu reactions has proven to be a viable route in order to use the resins as a tosylating reagent. This chemistry might be used in order access sulfonate esters as a linker in multistep syntheses of drug molecules. Ideal targets that have been identified for such a route are Fluoxetine and Tomoxetine. Many syntheses exist in the literature for these targets through a variety of routes.[218-221] One might imagine the possible synthesis of hydroxyketone **6.6** from reduction of commercially available β-ketoester **6.4** to the corresponding diol **6.5** (scheme 6.4).[222] Selective oxidation with barium manganate, which has precedent in the literature, would then give the desired hydroxyketone **6.6**.[223] Immobilisation on the solid-phase

as sulfonate ester **6.7** would then allow the completion of the synthesis. Reduction of ketones in the presence of sulfonate esters has precedence in the literature using boranes.[224] The resulting resin-bound alcohol could then be converted by Mitsunobu chemistry to aryl ether **6.8** and final cleavage from the resin by methylamine should give the drug target.



Scheme 6.4 Possible synthesis of Tomoxetine and Fluoxetine.

An alternative route to these drug targets could be the adaptation of chemistry employed by Sharpless *et al.*[221] Cinnamyl alcohol was used as the starting material and the benzylic oxygen installed using asymmetric epoxidation and then reduction giving the desired diol (scheme 6.5). Similar steps as outlined above gave the desired target molecules. One might imagine this route being adapted to the solid-phase.



Scheme 6.5 Synthesis of Tomoxetine and Fluoxetine by Sharpless *et al.*

Chapter 7. Experimental

7.1 General Information

All air and/or moisture sensitive reactions were carried out in oven-dried glassware under an atmosphere of nitrogen unless otherwise stated. "Brine" refers to a saturated aqueous solution of sodium chloride. Dichloromethane was dried by distillation from CaH_2 and THF was distilled from Na/benzophenone prior to use. Where appropriate, all other solvents and reagents were purified according to standard methods.[225] Reactions were monitored by TLC using aluminium-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm. Microwave reactions were carried out in a sealed tube (either 6 or 2 mL) on a SmithSynthesiser® from personal chemistry with autosampler handling.

All ^{1}H-NMR and ^{13}C-NMR spectra were recorded in a $CDCl_3$ solution unless otherwise stated. The machines used were a Bruker AC300 (300 MHz), a Bruker AM300 (300 MHz) and a Bruker DPX400 (400 MHz). ^{1}H-NMR and ^{13}C-NMR spectra of resins were carried out using a magic angle spin (MAS) probe. Chemical shifts are given in δ units. Abbreviations used for reporting data are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet) and m (multiplet). Coupling constants (J) are given in Hz. All spectra are reported uncorrected.

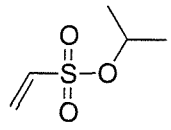
IR spectra were recorded on a Mattson Satellite fitted with a Specac Golden Gate ATR sampling platform, Bio-rad FTS 135 spectrometer on a Nicolet impact 400 spectrometer fitted with a Thunderdome ATR sampling platform. Abbreviations used for reporting data are s (strong), m (medium), w (weak) and br (broad). Where appropriate, the corresponding functionality is designated.[226]

GC analysis was carried out using a Hewlett Packard 6890 instrument with autosampler, using helium carrier gas, flame ionisation detector, passing through a 5 % phenylmethylsiloxane column with the oven programmed from 50-250 °C over 10 minutes. HPLC analysis was carried out using an HP 1090 Series II LC system, with a reverse-phase Phenomenex sphereclone C_{18} column with 254, 230 and 215 nm detection.

Low-resolution mass spectra were recorded by a GC-MS method on a Thermoquest trace MS single Quadrupole mass spectrometer. The GC column used a RTX5 capillary column with helium carrier gas, the reagent gas being ammonia and the source temperature 200 °C for the chemical ionisation and election impact ionisation modes used. For electrospray ionisation methods, a Micromass platform mass analyser with used. All mass spectrometry data reported was carried out with chemical ionisation (CI) unless otherwise specified.

Melting points were obtained in open capillary tubes and are uncorrected.

2.7 *i*-Propyl ethenesulfonate



A mixture of 2-chloro-1-ethanesulfonyl chloride (5.00 g, 30.6 mmol) and propan-2-ol (2.36 mL, 30.8 mmol) in CH_2Cl_2 (45 mL) was cooled to 0 °C under nitrogen. Et_3N (8.55 mL, 61.3 mmol) was added rapidly and the resulting mixture allowed to warm to ambient temperature and stirred for 2 h. The reaction was quenched with saturated aqueous Na_2CO_3 solution (50 mL) and stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (30 mL) and the combined organic fractions washed with Na_2CO_3 (1 x 30 mL), water (2 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford the title compound as a brown oil (3.79 g, 25.3 mmol, 82 %).

CAS registry number [3851-91-0]

IR (cm^{-1}) 2986 (w), 1353 (s), 1168 (s), 1096 (m), 979 (w), 917 (s), 881 (s).

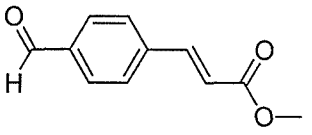
^{1}H-NMR ($CDCl_3$, δ ppm) 6.56 (1H, dd, J = 16.4 and 9.9 Hz, =C**H**-S), 6.39 (1H, d, J = 17.8 Hz, C**H**$_2$=), 6.08 (1H, d, J = 9.4 Hz, **CH**$_2$=), 4.80 (1H, quin, J = 6.3 Hz, O-C**H**), 1.40 (6H, d, J = 5.9 Hz, CH(C**H**$_3$)$_2$).

^{13}C-NMR ($CDCl_3$, δ ppm) 133.7 (=**C**H-S), 129.4 (**C**H$_2$=), 77.9 (O-**C**H), 22.9 (CH(**C**H$_3$)$_2$).

Mass Spec. *m/z* (relative intensity and ion) 168 (100, $[M + NH_4]^+$), 126 (4).

Spectroscopic data in agreement with literature.[109]

2.11 Methyl (*E*)-3-(4-formylphenyl)-2-propenoate



4-Bromobenzaldehyde (1.00 g, 5.4 mmol) and methyl acrylate (0.54 mL, 6.0 mmol) in Et_3N (0.84 mL, 6.0 mmol) were stirred with palladium acetate (12.1 mg, 54.0 μmol) and tri-*o*-tolyl phosphine (67 mg, 0.22 mmol) and heated to 100 °C in reflux apparatus under a nitrogen atmosphere. The mixture was stirred for 18 h and quenched with excess aqueous HCl (1M), instantly forming a yellow solid. The solid was broken up and stirred for a further 10 min after which the solid was filtered off and washed with hexane. Purification was by repeated recrystallisation from CH_2Cl_2/hexane to afford the title compound as a yellow solid (720 mg, 3.8 mmol, 70 %).

CAS registry number [7560-50-1]

Melting point: 80-82 °C.

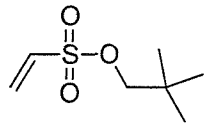
IR (cm^{-1}) 1717 (m), 1689 (s), 1639 (m), 1434 (m), 1312 (s), 1210 (m), 1198 (s), 1170 (s), 1160 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 10.04 (1H, s, C**H**O), 7.91 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.73 (1H, J = 17.7 Hz, Ar-C**H**=), 7.69 (2H, d, J = 8.1 Hz, Ar C-**H**), 6.57 (1H, d, J = 16.2 Hz, =C**H**-COO), 3.84 (3H, s, O-COC**H**$_3$).

^{13}C-NMR ($CDCl_3$, δ ppm) 191.6 (**C**HO), 166.8 (**C**OO), 143.3 (Ar-**C**H=), 140.3 (**C**-CH=), 137.3 (CHO-**C**), 130.3 (Ar **C**-H), 128.7 (Ar **C**-H), 121.1 (=**C**HCOO), 52.1 (O-**C**H$_3$).

Spectroscopic data in agreement with literature.[107]

2.13 Neopentyl ethenesulfonate

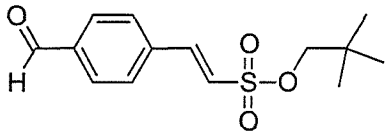


A mixture of chloroethanesulfonyl chloride (5.00 g, 30.6 mmol) and neopentyl alcohol (2.72 g, 30.8 mmol) in CH_2Cl_2 (45 mL) was cooled to 0 °C under nitrogen. Et_3N (8.55 mL, 61.3 mmol) was added rapidly and the resulting mixture allowed to warm to ambient temperature and stirred for 2 h. The reaction was quenched with saturated aqueous Na_2CO_3 solution (50 mL) and stirred for 20 min. The aqueous layer was extracted with CH_2Cl_2 (30 mL) and the combined organic fractions washed with Na_2CO_3 (1 x 20 mL), water (2 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford the title compound as a pale brown oil (5.46 g, 30.5 mmol, 99 %).

CAS registry number [75391-24-1]
IR (cm^{-1}) 2966 (w), 2828 (w), 1481 (w), 1358 (s), 1174 (s), 963 (s), 851 (s), 738 (m).
^{1}H-NMR ($CDCl_3$, δ ppm) 6.53 (1H, dd, J = 16.4 and 9.9 Hz, =C**H**-S), 6.40 (1H, d, J = 16.9 Hz, C**H**$_2$=), 6.13 (1H, d, J = 9.9 Hz, C**H**$_2$=), 3.76 (2H, s, -C**H**$_2$), 0.98 (9H, s, C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 132.4 (=**C**H-S), 130.4 (**C**H$_2$=), 80.0 (O-**C**H$_2$), 31.8 (**C**(CH$_3$)$_3$), 26.1 (C(**C**H$_3$)$_3$).
Mass Spec. *m/z* (relative intensity and ion) 196 (100, $[M + NH_4]^+$), 126 (3).

Spectroscopic data in agreement with literature.[109]

2.14 Neopentyl (*E*)-2(4-formylphenyl)-1-ethene-1-sulfonate



4-Bromobenzaldehyde (1.55 g, 8.4 mmol) and neopentylethene sulfonate **2.13** (1.5 g, 8.4 mmol) in Et_3N (1.25 mL, 9.0 mmol) were stirred with palladium acetate (18.9 mg,

84.0 μmol) and tri-*o*-tolyl phosphine (102 mg, 0.34 mmol) and heated to 100 °C in reflux apparatus and stirred for 20 h. The mixture was diluted with CH_2Cl_2 (30 mL) and quenched with excess aqueous HCl (1M). The organic layer was washed with aqueous 1M HCl (3 x 20 mL), water (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a brown waxy solid. Purification by recystallisation from EtOAc/hexane and flash chromatography eluting with CH_2Cl_2 afforded to title compound as a crystalline solid (1.54 g, 5.4 mmol, 65 %).

Melting point: 95-97 °C.

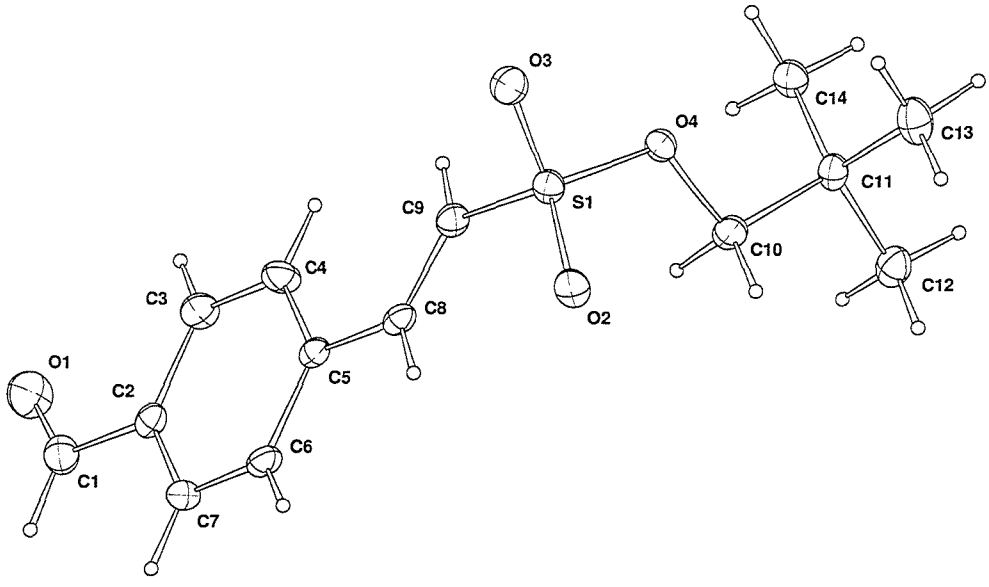
IR (cm^{-1}) 2960 (w), 1701 (m), 1619 (w), 1568 (w), 1476 (w), 1352 (s), 1194 (m), 1163 (s), 953 (s), 856 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 10.05 (1H, s, C**H**O), 7.95 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.69 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.64 (1H, d, J = 15.4 Hz, Ar-C**H**=), 6.90 (1H, d, J = 15.4 Hz, =C**H**-S), 3.84 (2H, s, O-C**H**$_2$), 0.99 (9H, s, C(C**H**$_3$)$_3$).

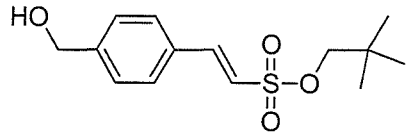
^{13}C-NMR ($CDCl_3$, δ ppm) 191.4 (**C**HO), 142.9 (Ar-**C**H=), 138.1 (**C**-CH=), 137.6 (CHO-**C**), 130.5 (Ar **C**-H), 129.1 (Ar **C**-H), 124.5 (=**C**H-S), 80.1 (O-**C**H$_2$), 31.9 (**C**(CH$_3$)$_3$), 26.2 (C(**C**H$_3$)$_3$).

Elemental analysis Calculated: C = 59.55 %, H = 6.43 %, S = 11.35 %. Found: C = 59.82 %, H = 6.40 %, S = 11.21 %.

X-ray crystal structure



2.15 Neopentyl 2-[4-(hydroxymethyl) phenyl]-1-ethene-1-sulfonate



To a stirred solution of sodium borohydride (57 mg, 1.5 mmol), in THF (5 mL) under a nitrogen atmosphere at 0 °C was added the vinyl sulfonate **2.14** (200 mg, 0.7 mmol). The reaction was monitored by TLC and the complete conversion of all starting material was observed after 1 hour. The reaction was quenched with excess aqueous HCl (1 M) and diluted with Et_2O (20 mL). The aqueous layer was extracted further with Et_2O (3 x 10 mL) and the combined organic fractions washed with water (2 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* in order to give a pale yellow solid. Purification by recrystallisation from Et_2O /hexane afforded the title compound as a cream coloured solid (154 mg, 0.54 mmol, 75 %)

Melting point: 119-121 °C.

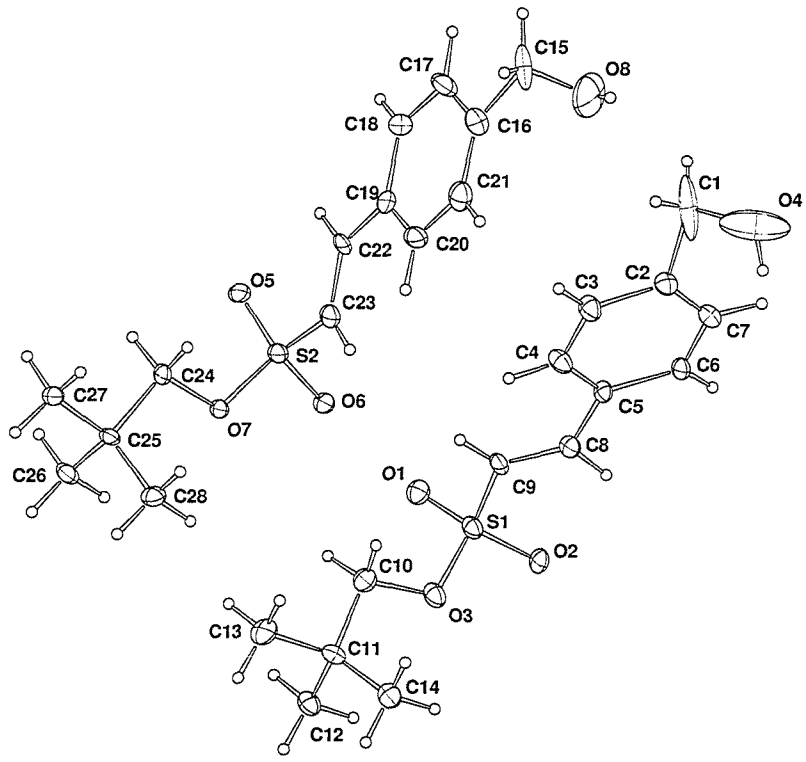
IR (cm^{-1}) 2955 (w), 1624 (w), 1340 (s), 1159 (s), 962 (s), 938 (m), 879 (s), 797 (m).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.58 (1H, d, J = 15.5 Hz, Ar-C**H**=), 7.51 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.43 (2H, d, J = 8.1 Hz, Ar C-**H**), 6.73 (1H, d, J = 15.4 Hz, =C**H**-S), 4.75 (2H, s, CH_2OH), 3.79 (2H, s, S-OC**H**$_2$), 0.98 (9H, s, O-$CH_2(CH_3)_3$).

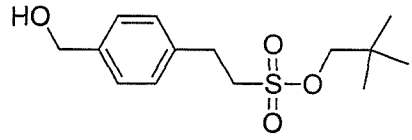
^{13}C-NMR ($CDCl_3$, δ ppm) 144.7 (**C**-CH_2OH), 144.5 (Ar-**C**H=), 131.5 (**C**-CH=), 128.8 (Ar **C**-H), 127.5 (Ar **C**-H), 120.9 (=**C**H-S), 79.7 (S-O**C**H_2), 64.7 (**C**H_2OH), 31.1 (**C**$(CH_3)_3$), 26.2 (C(**C**$H_3)_3$).

Elemental analysis Calculated: C = 59.02 %, H = 7.04 %. Found: C = 59.36 %, H = 6.87 %.

X-ray crystal structure (two views shown)



2.16 Neopentyl 2-[4-(hydroxymethyl) phenyl] ethane-1-sulfonate



To a stirred solution of sodium borohydride (27 mg, 0.7 mmol), in THF (4 mL) under a nitrogen atmosphere was added the vinyl sulfonate **2.14** (100 mg, 0.36 mmol), heated to reflux and stirred for 50 h. The reaction was quenched with excess aqueous HCl (1 M) and diluted with Et_2O (30 mL). The aqueous layer was extracted further with Et_2O (3 x 10 mL) and the combined organic fractions washed with water (2 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* in order to furnish a pale yellow solid. Purification by recrystallisation from Et_2O /hexane afforded the title compound as a white solid (45 mg, 0.16 mmol, 44 %).

Melting point: 64.5-66 °C.

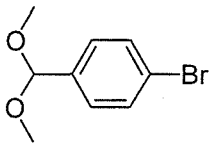
IR (cm^{-1}) 3391 (br), 2955 (w), 2909 (w), 2873 (w), 1352 (s), 1166 (s), 1014 (m), 962 (s), 939 (m), 855 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.35 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.22 (2H, d, J = 8.1 Hz, Ar C-**H**), 4.69 (2H, s, CH_2OH), 3.87 (2H, s, S-OCH_2), 3.37 (2H, dd, J = 4.8 and 9.2 Hz, S-CH_2), 3.16 (2H, dd, J = 5.5 and 11.4 Hz, Ar-CH_2CH_2), 0.9 (9H, s, O-$CH_2(CH_3)_3$).

^{13}C-NMR ($CDCl_3$, δ ppm) 140.0 (**C**-CH_2OH), 137.0 (**C**-CH_2CH_2-S), 128.7 (Ar **C**-H), 127.7 (Ar **C**-H), 78.9 (S-OCH_2), 65.1 (CH_2OH), 51.6 (CH_2-S), 31.9 ($C(CH_3)_3$), 29.6 (Ar-CH_2CH_2) 26.2 ($C(CH_3)_3$).

Elemental analysis Calculated: C = 58.73 %, H = 7.70 %. Found: C = 58.78 %, H = 7.65 %.

2.17 *p*-Bromobenzaldehyde dimethyl acetal



A stirred mixture of *p*-toluenesulfonic acid (571 mg, 3.0 mmol), trimethylorthoformate (0.77 mL, 7.0 mmol) and 4-bromobenzaldehyde (500 mg, 2.5 mmol) in MeOH (8 mL) was heated to 65 °C under a nitrogen atmosphere. After stirring for 4 h the reaction was quenched carefully with excess solid $NaHCO_3$ and stirred for a further 10 min. The excess solids were filtered off and washed with CH_2Cl_2 (20 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), water (2 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* in order to furnish a pale yellow oil. Purification by Kugelrohr distillation (125 °C, 9 mmHg) afforded the title compound as a colourless oil (489 mg, 2.11 mmol, 86 %).

CAS registry number [24856-58-4]

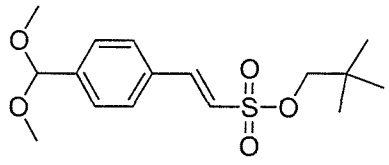
IR (cm^{-1}) 2991 (w), 2945 (w), 2889 (w), 2827 (w), 1592 (w), 1485 (m), 1351 (m), 1205 (m), 1100 (s), 1054 (s), 1012 (s), 985 (m), 804 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.51 (2H, d, J = 8.8 Hz, Ar C-**H**), 7.33 (2H, d, J = 8.8 Hz, Ar C-**H**), 5.37 (1H, s, Ar-C**H**), 3.32 (6H, s, $CH(OCH_3)_2$).

^{13}C-NMR ($CDCl_3$, δ ppm) 137.3 (**C**-CH(OCH_3)$_2$), 131.5 (Ar **C**-H), 128.7 (Ar **C**-H), 122.6 (**C**-Br), 102.4 (**C**H(OCH_3)$_2$), 52.6 (O-**C**H_3).

Spectroscopic data in agreement with literature.[227]

2.18 Neopentyl (*E*)-2-(4-dimethoxymethylphenyl)-1-ethene-1-sulfonate



A stirred mixture of *p*-toluenesulfonic acid (571 mg, 3.0 mmol), trimethylorthoformate (1.4 mL) and aldehyde **2.14** (700 mg, 2.5 mmol) in MeOH (14 mL) under a nitrogen atmosphere was warmed to reflux. After stirring for 16 h at this temperature the reaction was quenched carefully with excess solid $NaHCO_3$ and stirred for a further 10 min. The excess solids were filtered off and washed with CH_2Cl_2 (20 mL). The organic layers were combined and washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), water (2 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow solid. Purification by recrystallisation from Et_2O /hexane afforded the title compound as a yellow crystalline solid (635 mg, 1.93 mmol, 78 %).

Melting point: 74-76 °C.

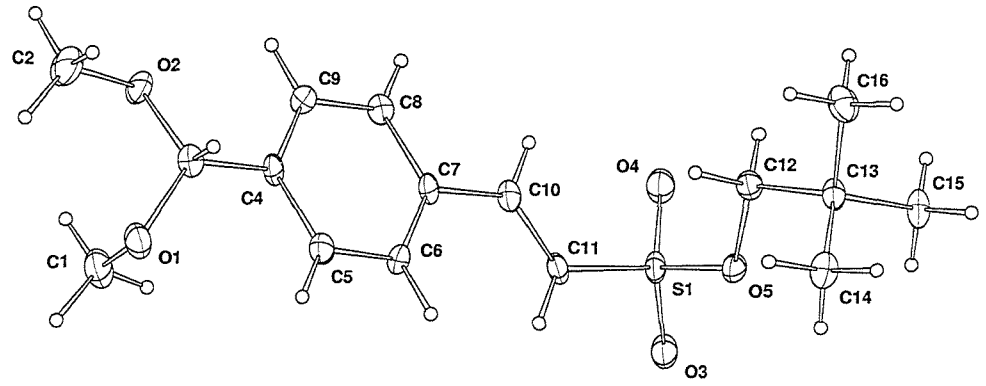
IR (cm^{-1}) 2960 (w), 1614 (w), 1475 (w), 1351 (s), 1164 (s), 1102 (m), 1054 (s), 985 (m), 960 (s), 871 (s), 845 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.60 (1H, d, J = 15.44 Hz, Ar-C**H**=), 7.54 (4H, m, Ar C-**H**), 6.75 (1H, d, J = 15.44 Hz, =C**H**-S), 5.43 (1H, s, C**H**(OMe)$_2$), 3.81 (2H, s, S-O**CH**$_2$), 3.35 (6H, s, CH(O**CH**$_3$)$_2$), 0.99 (9H, s, C(**CH**$_3$)$_3$).

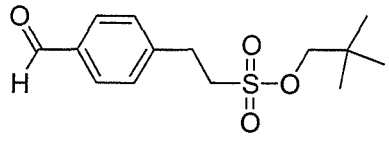
^{13}C-NMR ($CDCl_3$, δ ppm) 144.3 (Ar-**C**H=), 141.7 (**C**-CH(OMe)$_2$), 132.2 (**C**-CH=), 128.5 (Ar C-H), 127.8 (Ar C-H), 121.5 (=**C**H-S), 102.4 (**C**H(OMe)$_2$), 79.7 (**C**H$_2$O-S), 52.9 (CH(O**CH**$_3$)$_2$), 31.9 (**C**(CH$_3$)$_3$), 26.2 (C(**CH**$_3$)$_3$).

Elemental analysis Calculated: C = 58.51 %, H = 7.37 %, S = 9.76 %. Found: C = 58.81 %, H = 7.16 %, S = 9.67 %.

X-ray crystal structure



2.19 Neopentyl 2-(4-formylphenyl)-1-ethane-1-sulfonate



To a stirred solution of alkene **2.18** (100 mg, 0.30 mmol) in THF (4 mL) was added sodium borohydride (23.1 mg, 0.6 mmol) and the mixture heated to reflux. After 36 h, the mixture was allowed to cool and excess aqueous HCl (1M) was added with further stirring for 3 h. The aqueous layer was then extracted with Et_2O (1 x 20 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a white crystalline solid (83 mg, 29.1 mmol, 97 %).

Melting point: 59 – 61 °C.

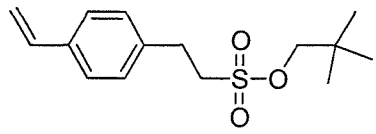
IR (cm^{-1}) 2955 (w), 2935 (w), 2863 (w), 1680 (s), 1606 (m), 1351 (s), 1214 (m), 1167 (s), 959 (s), 938 (m), 851 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 10.00 (1H, s, C**H**O), 7.86 (2H, d, J = 7.3 Hz, Ar C-**H**), 7.41 (2H, d, J = 8.1 Hz, Ar C-**H**), 3.87 (2H, s, O-C**H**$_2$), 3.41 (2H, m, C**H**$_2$CH$_2$-S), 3.26 (2H, m, C**H**$_2$-S), 0.97 (9H, s, C(C**H**$_3$)$_3$).

^{13}C-NMR ($CDCl_3$, δ ppm) 191.8 (**C**HO), 144.6 (Ar **C**), 135.6 (Ar **C**), 130.5 (Ar **C**-H), 129.3 (Ar **C**-H), 79.1 (O-**C**H$_2$), 51.0 (**C**H$_2$-S), 31.9 (**C**(CH$_3$)$_3$), 30.1 (**C**H$_2$CH-S), 26.2 (C(**C**H$_3$)$_3$).

Elemental analysis Calculated: C = 59.13 %, H = 7.09 %. Found: C = 59.25 %, H = 6.84 %.

2.20 Neopentyl 2-(4-styryl)-1-ethane-1-sulfonate



To a stirred solution of methyltriphenylphosphonium bromide (377 mg, 1.1 mmol) in THF (5 mL) was added rapidly *n*-BuLi (0.42 mL of a 2.5 M solution in hexane, 1.1 mmol) and stirred for 20 min under a nitrogen atmosphere. The mixture was cooled to 0 C and aldehyde **2.19** (200 mg, 0.7 mmol) dissolved in THF (2 mL) was added dropwise and the reaction mixture allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with excess aqueous HCl (1 M) and diluted with Et_2O (30 mL). The organic layer was washed with water (2 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow crude solid (414 mg). Purification by flash chromatography on silica eluting with CH_2Cl_2 afforded the title compound as a pale yellow crystalline solid (190 mg, 0.67 mmol, 96 %).

Melting point: 42-44 °C

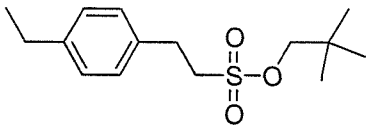
IR (cm^{-1}) 2955 (w), 2870 (w), 1352 (s), 1339 (s), 1161 (s), 962 (s), 845 (s), 831 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.38 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.19 (2H, d, J = 8.1 Hz, Ar C-**H**), 6.70 (1H, dd, J = 11.0, 17.7 Hz, CH_2=C**H**), 5.74 (1H, d, J = 17.6 Hz, C**H**H=CH), 5.26 (1H, d, J = 11.0 Hz, CH**H**=CH), 3.86 (2H, s, O-C**H**$_2$), 3.37 (2H, m, Ar-C**H**$_2$), 3.16 (2H, m, C**H**$_2$-S), 0.98 (9H, s, C(C**H**$_3$)$_3$).

^{13}C-NMR ($CDCl_3$, δ ppm) 137.1 (**C**-CH_2CH-S), 136.7 (CH_2=CH**C**), 136.4 (CH_2=**C**H), 128.7 (Ar **C**-H), 126.9 (Ar **C**-H), 114.2 (**C**H_2=CH), 79.0 (O-**C**H_2), 51.5 (**C**H_2-S), 31.9 (**C**(CH_3)$_3$), 29.6 (Ar-**C**H_2), 26.2 (C(**C**H_3)$_3$).

Mass Spec. *m/z* (relative intensity and ion) 300.3 (18, $[M + NH_4]^+$), 283.3 (1, $[M + H]^+$), 44 (100).

2.21 Neopentyl 2-(4-ethylphenyl)-1-ethane-1-sulfonate



To a stirred solution of styryl sulfonate **2.20** (97 mg, 0.34 mmol) in EtOAc (5 mL) was added palladium on activated carbon (748 mg, 34 μmol of palladium). The reaction vessel was evacuated and flushed with nitrogen 3 times and finally evacuated and flushed with H_2 twice. The reaction was stirred vigorously under H_2 atmosphere for 1 h after which the reaction vessel was evacuated and flushed three times with nitrogen, the solids filtered off through celite and washed with CH_2Cl_2 (4 x 20 mL) and the combined organic layers concentrated *in vacuo* to afford the title compound as a white crystalline solid (81 mg, 0.28 mmol, 84 %).

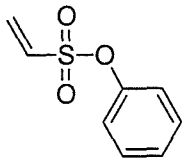
Melting point: 46-48 °C.

IR (cm^{-1}) 2954 (w), 2870 (w), 1352 (s), 1162 (s), 956 (s), 936 (s), 865 (s), 836 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.17 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.14 (2H, J = 8.1 Hz, Ar C-**H**), 3.87 (2H, s, O-C**H**$_2$), 3.38 (2H, m, Ar-C**H**$_2$), 3.15 (2H, m, C**H**$_2$-S), 2.64 (2H, q, J = 7.6 Hz, CH_3C**H**$_2$), 1.24 (3H, t, J = 7.4 Hz, C**H**$_3$$CH_2$), 0.92 (9H, s, C(C**H**$_3$)$_3$).

^{13}C-NMR ($CDCl_3$, δ ppm) 143.3 (Ar **C**), 134.7 (Ar **C**), 128.6 (Ar **C**-H), 128.5 (Ar **C**-H), 78.9 (O-**C**H$_2$), 51.7 (**C**H$_2$-S), 31.9 (**C**(CH$_3$)$_3$), 29.5 (**C**H$_2$-Ph), 28.6 (**C**H$_2$-Ph), 26.2 (C(**C**H$_3$)$_3$), 15.8 (**C**H$_3$CH$_2$).

2.23 Phenyl ethenesulfonate



A mixture of chloroethanesulfonyl chloride (3.0 g, 18.4 mmol) and phenol (1.73 g, 18.4 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C under a nitrogen atmosphere. Et_3N (5.16 mL, 37 mmol) was added rapidly and the resulting mixture allowed to warm to

room temperature and stirred for 2 h. The reaction was quenched with saturated aqueous Na_2CO_3 solution (50 mL) and stirred for 20 min. The aqueous layer was extracted with CH_2Cl_2 (30 mL) and the combined organic fractions washed with Na_2CO_3 (1 x 20 mL), water (2 x 20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a brown oil. Purification by flash chromatography eluting with Et_2O:hexane (1:1) afforded the title compound as a pale yellow oil (2.78 g, 15.1 mmol, 82 %.)

CAS registry number [1562-34-1]

IR (cm^{-1}) 3115 (w), 3069 (w), 1587 (m), 1487 (m), 1368 (s), 1169 (s), 1140 (s), 980 m), 858 (s).

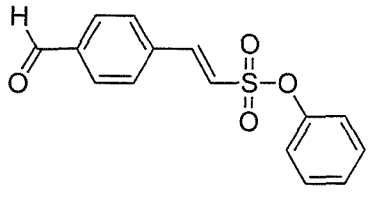
^{1}H-NMR ($CDCl_3$, δ ppm) 7.40-7.21 (5H, m, Ph-**H**), 6.67 (1H, dd, J = 16.5 and 9.9 Hz, =C**H**-S), 6.31 (1H, d, J = 16.9 Hz, C**H**$_2$=), 6.13 (1H, d, J = 10.3 Hz, C**H**$_2$=).

^{13}C-NMR ($CDCl_3$, δ ppm) 149.6 (Ar **C**-O), 132.2 (=**C**H-S), 132.1 (Ar C-H), 130.1 (**C**H_2=), 127.6 (Ar C-H), 122.5 (Ar C-H).

Mass Spec. *m/z* **(relative intensity and ion)** 202 (3, $[M + NH_4]^+$), 184 (78, $[M]^+$), 94 (90, $[Ph\text{-}O + H]^+$), 65 (100).

Spectroscopic data in agreement with literature.[228]

2.24 Phenyl (*E*)-2-(4-formylphenyl)-1-ethene-1-sulfonate



4-Bromobenzaldehyde (1.51 g, 8.15 mmol) and phenylethene sulfonate **2.23** (1.50 g, 8.15 mmol) in Et_3N (1.25 mL, 9.0 mmol) were stirred with palladium acetate (37 mg, 0.16 mmol) and tri-*o*-tolyl phosphine (198 mg, 0.65 mmol) and heated to 100 °C in reflux apparatus under a nitrogen atmosphere. After stirring for 20 h, the mixture was diluted with CH_2Cl_2 (30 mL) and quenched with excess aqueous HCl (1M). The organic layer was washed with aqueous 1 M HCl (3 x 20 mL), water (2 x 20 mL),

dried ($MgSO_4$) and concentrated *in vacuo* to give a brown waxy solid. Purification by flash chromatography eluting with Et_2O:hexane (2:98, 4:96, 1:9) afforded the title compound as a crystalline solid (1.55 g, 5.4 mmol, 66 %).

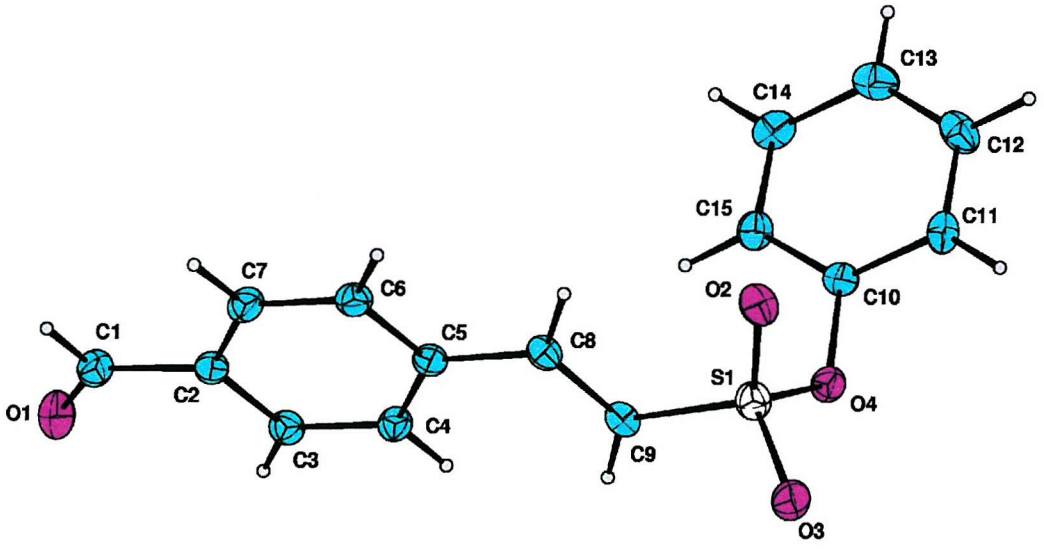
IR (cm^{-1}) 2847 (w), 2747 (w), 1701 (s), 1618 (w), 1569 (w), 1485 (m), 1363 (s), 1196 (m), 1163 (s), 1146 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 10.07 (1H, s, C**H**O), 7.95 (2H, d, *J* = 8.1 Hz, Ar C-**H**), 7.65 (2H, d, *J* = 8.1 Hz, Ar C-**H**), 7.58 (1H, d, *J* = 15.4 Hz, Ar-C**H**=), 7.41-7.25 (5H, m, O-**Ph**), 7.02 (1H, d, *J* = 15.4 Hz, =C**H**-S).

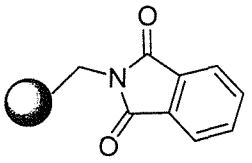
^{13}C-NMR ($CDCl_3$, δ ppm) 191.3 (**C**HO), 149.5 (SO_2-O-**C**), 144.4 (**C**H=), 138.2 (**C**-CH=), 137.2 (CHO-**C**), 130.5 (Ar **C**-H), 130.1 (Ar **C**-H), 129.3 (Ar **C**-H), 127.6 (Ar **C**-H), 124.0 (=**C**H-S), 122.5 (Ar **C**-H).

Mass Spec. *m/z* (relative intensity and ion) 289 (0.1, $[M+H]^+$), 224 (17, $[M - SO_2]^+$), 195 (5, $[C_9H_7O_3S]^+$), 131 (30, $[C_9H_7O]^+$), 94 (100, $[Ph\text{-}O + H]^+$).

X-ray crystal structure



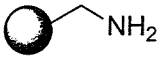
3.2 Poly (styryl-DVB) – *N*-methylphthalimide resin



Merrifield resin (3.0 g, 4.8 mmol, 1.6 mmol/g) was stirred very slowly in DMF (25 mL). Potassium phthalimide (4.45 g, 24 mmol) was added portionwise over 10 min and the resulting mixture stirred gently at 120 °C for 16 h. The resin was filtered off and washed with DMF, DMF:water (1:1), water, dioxane, MeOH, Et_2O (200 mL of each) and dried in a vacuum oven (40 °C) in order to give a pale yellow resin.

IR (cm^{-1}) 3022 (w), 2918 (w), 2847 (w), 1769 (w, C=O), 1710 (s, C=O), 1491 (m), 1450 (m), 1427 (m), 1389 (s).

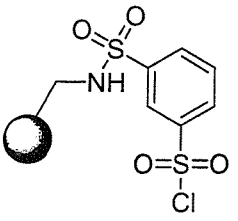
3.3 Poly (styryl-DVB) – amino methyl resin



N-Phthalimide resin **3.2** (1 g, 1.36 mmol, 1.36 mmol/g) was suspended in ethanol (16 mL) and hydrazine hydrate added (0.75 mL, 24 mmol). The resulting mixture was heated to reflux and allowed to react for 18 h. The resin was filtered off and washed thoroughly with hot DMF, hot DMF:H_2O (1:1), hot H_2O, dioxane, MeOH, Et_2O and dried in a vacuum oven (40 °C) to give a pale yellow resin.

IR (cm^{-1}) 3022 (w), 2916 (w), 2845 (w), 1599 (w), 1491 (m), 1449 (m).
Elemental Analysis Calculated: N = 2.31 %. Found: N = 2.53 %, Cl = 0.0 %.

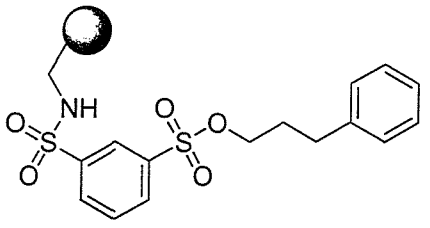
3.4 Poly (styryl-DVB) – sulfonamide-linked sulfonyl chloride resin



Aminomethyl resin **3.3** (500 mg, 1.65 mmol) was swollen in CH_2Cl_2 (6 mL) for 15 min after which Et_3N (0.44 mL, 3.2 mmol) was added. The resulting mixture was shaken for 10 min and 1,3-benzenedisulfonyl chloride (880 mg, 3.2 mmol) subsequently added. The mixture was shaken for 16 h and the resin filtered off and washed with CH_2Cl_2, dioxane, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 1384 (m, SO_2R), 1168 (m, SO_2R).

3.5 Poly (styryl-DVB) – sulfonamide-linked (3-phenylpropyl) sulfonate resin

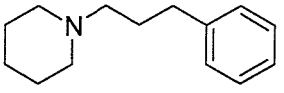


General method for the assessment against commercial resin

Either sulfonyl chloride resin **3.4**, sulfonyl chloride resin from Aldrich, or sulfonyl chloride resin from Argonaut, (100 mg, for amounts and loadings see table below) were swollen in dry CH_2Cl_2:pyridine (1:1, 1 mL) for 15 min under a nitrogen atmosphere. To the respective resin suspensions was added 3-phenylpropanol (for amounts see table below) and the reaction mixtures shaken at room temperature, for the desired reaction time (see table below). All resins were filtered off and washed with CH_2Cl_2, DMF, DMF:water (1:1), DMF, CH_2Cl_2, Et_2O (50 of each) and dried in a vacuum oven (40 C).

Rxn	Starting sulfonyl chloride resin	Resin amount /mmol (loading)	Amount of 3-phenylpropanol	Reaction time / h
1	Resin **3.4**	0.12 (1.17 mmol/g)	64 μL, (0.47 mmol)	5
2	Resin **3.4**	0.12 (1.17 mmol/g)	64 μL, (0.47 mmol)	27
3	Resin **3.4**	0.12 (1.17 mmol/g)	64 μL, (0.47 mmol)	48
4	Aldrich Resin	0.18 (1.5-2 mmol/g)	95 μL, (0.7 mmol/g)	5
5	Aldrich Resin	0.18 (1.5-2 mmol/g)	95 μL, (0.7 mmol/g)	27
6	Aldrich Resin	0.18 (1.5-2 mmol/g)	95 μL, (0.7 mmol/g)	48
7	Argonaut Resin	0.26 (2.56 mmol/g)	138 μL, (1.02 mmol)	5
8	Argonaut Resin	0.26 (2.56 mmol/g)	138 μL, (1.02 mmol)	27
9	Argonaut Resin	0.26 (2.56 mmol/g)	138 μL, (1.02 mmol)	49

3.6 *N*-(3-Phenylpropyl) piperidine



General method for the assessment of sulfonyl chloride resin 3.4 against commercial resins

Sulfonate resin **3.5** or the analogs synthesised from commercial resins (100 mg, see table below for amounts) were swollen in dry CH_3CN (1.5 mL) under a nitrogen atmosphere for 15 min. Piperidine (see table below for amounts) and iPr$_2$EtN (see table below for amounts) were added to the respective reactions and each stirred using the quest® auto synthesiser for 16 h at 60 C. Each resin was filtered off and washed with CH_2Cl_2 (30 mL) and the combined filtrates diluted to 50 mL (in volumetric flasks) with further CH_2Cl_2. Each sample was analysed by GC.

Sulfonate Resin	Amount of resin / mmol	Amount of piperidine / μL (mmol)	Amount of *i*Pr$_2$EtN / μL (mmol)
Aldrich resin	0.149	29 (0.30)	156 (0.89)
Argonaut resin	0.204	40 (0.41)	213 (1.22)
Resin **3.5**	0.105	21 (0.21)	110 (0.63)

Method for synthesis from tosylate 3.8

To a stirred solution of tosylate **3.8** (200 mg, 0.69 mmol) in dry CH_3CN (3 mL) under a nitrogen atmosphere was added piperidine (136 μg, 1.38 mmol) and *i*Pr$_2$EtN (240 μL, 1.38 mmol). The reaction was heated to 60 ° C, stirred for 4 h and the crude reaction mixture was concentrated *in vacuo* to give a dark brown slurry. Purification by flash chromatography eluting with CH_2Cl_2, CH_2Cl_2:EtOAc (9:1, 7:3, 1:1) and CH_2Cl_2:MeOH (95:5) afforded the title compound as a pale yellow oil (85 mg, 0.42 mmol, 60 %).

General method for results for table 3.3 and 3.2 from sulfonate resin 3.42

Sulfonate resin **3.42** or the analogs synthesised from commercial resins (100 mg, see table below for amounts) were swollen in dry CH_3CN (1.5 mL) under a nitrogen atmosphere for 15 min. Piperidine (see table below for amounts) and *i*Pr$_2$EtN (see table below for amounts) were added to the respective reactions and stirred gently for 16 h at 60 C. Each resin was filtered off and washed with CH_2Cl_2 (30 mL) and the combined filtrates diluted to 50 mL (in volumetric flasks) with further CH_2Cl_2. Each sample was analysed by GC.

Sulfonate resin	Amount of resin / mmol	Amount of piperidine / μL (mmol)	Amount of *i*Pr$_2$EtN / μL (mmol)
Resin **3.42**	0.13	25 (0.25)	133 (0.75)
Aldrich Resin	0.15	30 (0.3)	157 (0.9)

Method for synthesis from tosylate 3.44

To a solution of sulfonate **3.44** (50 mg, 0.17 mmol) in dry CH_3CN (2 mL) under a nitrogen atmosphere was added *i*Pr$_2$EtN (35 μL, 0.2 mmol) and piperidine (20 μL, 0.2

mmol). The reaction was heated to 60 C, stirred for 4 h and the crude reaction mixture was concentrated *in vacuo* to give a brown slurry. Purification by flash chromatography eluting with CH_2Cl_2, CH_2Cl_2:EtOAc (9:1, 7:3, 1:1) and CH_2Cl_2:MeOH (95:5) afforded the title compound as a pale yellow oil (23 mg, 0.11 mmol, 65 %).

Method for synthesis from tosylate resin 3.42 (after Mitsunobu coupling to sulfonic acid resin 3.33)

Sulfonate resin **3.42** (100 mg, 127 μmol, based on theoretical loading of 1.27 mmol/g) was swollen in dry CH_3CN (1.5 mL) under a nitrogen atmosphere for 15 min. Piperidine (38 μL, 381 μmol) and *i*Pr_2EtN (133 μL, 762 μmol) were added to the resin and the resulting mixture stirred gently for 16 h at 60 °C. The resin was filtered off and washed with CH_2Cl_2 (30 mL) and concentrated *in vacuo* to give a yellow oil, which was the title compound with some impurity. Purification by flash chromatography, to determine an isolated yield, eluting with CH_2Cl_2, CH_2Cl_2:EtOAc (9:1, 7:3, 1:1) and CH_2Cl_2:MeOH (95:5) afforded the title compound as a pale yellow oil (13 mg, 62 μmol, 49 %).

General method for microwave-assisted synthesis from sulfonate resin 3.42

Sulfonate resin **13** (100 mg, 127 μmol, based on theoretical loading of 1.27 mmol/g) was swollen in dry CH_3CN (1.5 mL) under a nitrogen atmosphere for 15 min in a oven-dried microwave reaction vessel. Piperidine (38 μL, 381 μmol) and *i*Pr_2EtN (133 μL, 762 μmol) were added to the resin suspension and the resulting mixture placed in the Smith synthesiser microwave reactor for 15 min at 120 °C. Each resin was filtered off and washed with CH_2Cl_2 (30 mL) and the combined filtrates diluted to 50 mL (in volumetric flasks) with further CH_2Cl_2. Each sample was analysed by GC.

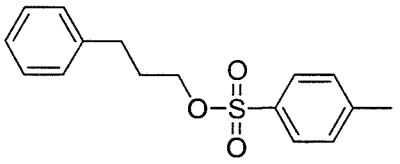
CAS registry number [2905-57-9]

^{1}H-NMR ($CDCl_3$, δ ppm) 7.21-7.08 (5H, m, Ar C-**H**), 2.55 (2H, t, J = 7.8 Hz, Ph**C**H_2), 2.31-2.25 (6H, m, **C**H_2N(**C**H_2)**C**H_2), 1.77 (2H, quin, J = 5.6 Hz, PhCH_2**C**H_2), 1.52 (4H, quin, J = 5.6 Hz, **C**H_2), 1.38-1.35 (2H, m, **C**H_2).

^{13}C-NMR ($CDCl_3$, δ ppm) 144.7 (Ar **C**), 130.8 (Ar **C**-H), 130.7 (Ar **C**-H), 128.1 (Ar **C**-H), 61.3 (N-**C**H_2), 57.0 (N(**C**H_2)CH_2), 36.3 (Ph**C**H_2), 31.0 (PhCH_2**C**H_2), 28.3 (**C**H_2 x 2), 26.9 (**C**H_2).

Spectroscopic data in agreement with literature.[229]

3.8 3-Phenylpropyl tosylate



To a stirred solution of 3-phenylpropanol (**3.7**, 150 μL, 1.1 mmol) in dry CH_2Cl_2 (5 mL) under a nitrogen atmosphere, was added DMAP (13.4 mg, 0.11 mmol) and Et_3N (0.31 mL, 2.2 mmol). After 20 min and cooling to 0 C, tosyl chloride (286 mg, 1.1 mmol) was added carefully and the reaction was allowed to warm to room temperature and stirred for 2 h. The mixture was quenched with excess aqueous HCl (1 M) and diluted with CH_2Cl_2 (15 mL). The organic layer was washed with aqueous HCl (1 M, 2 x 10 mL), water (2 x10 mL), brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound a colourless oil (310 mg, 1.0 mmol, 94 %).

CAS registry number [3742-75-4]

IR (cm^{-1}) 1598 (w), 1496 (w), 1454 (w), 1359 (s, SO_3R), 1189 (m), 1175 (s, SO_2R), 1097 (m), 998 (m), 966 (m), 929 (s).

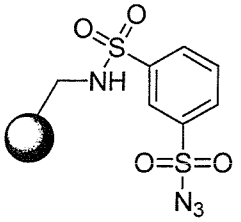
^{1}H-NMR ($CDCl_3$, δ ppm) 7.80 (2H, d, J = 8.1 Hz, Ar C**H**-C-SO_3), 7.36 (2H, d, J = 8.1 Hz, Ar C**H**-C-CH_3), 7.35-7.16 (4H, m, Ar C-**H**), 7.08 (1H, d, J = 6.6 Hz, Ar C-**H**), 4.04 (2H, t, J = 6.3 Hz, C**H**$_2$-O-SO_2), 2.66 (2H, t, J = 7.7 Hz, Ph-C**H**$_2$), 2.47 (3H, s, S-C_6H_4 -C**H**$_3$), 2.02-1.89 (2H, m, CH_2C**H**$_2$$CH_2$-O).

^{13}C-NMR ($CDCl_3$, δ ppm) 144.9 (**C**-CH_3), 140.5 (Ar **C**-CH_2), 133.2 (**C**-SO_2-O), 130.0 (Ar **C**-H), 128.6 (Ar **C**-H), 128.6 (Ar **C**-H), 128.1 (Ar **C**-H), 126.3 (Ar **C**-H), 69.8 (**C**H_2-O), 31.6 (Ph-**C**H_2), 30.6 (CH_2**C**$H_2$$CH_2$-O), 21.8 (S-$C_6H_4$-**C**$H_3$).

Mass Spec. *m/z* **(relative intensity and ion)** 308 (10, $[M + NH_4]^+$), 200 (5, $[Tol\text{-}SO_3CH_2CH_2 + H]^+$), 118 (100, $[SO_2\text{-}OCH_2 + Na + H]^+$), 91 (92, $[C_6H_5\text{-}CH_3]^+$ or $[C_6H_5\text{-}CH_2]^+$).

Spectroscopic data in agreement with literature.[230]

3.9 Poly (styryl-DVB) – sulfonamide linked sulfonyl azide resin



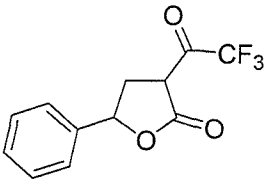
General Method

Sulfonyl chloride resin **3.4** (300 mg, 1.17 mmol/g) was swollen in 5 mL of organic solvent (DMF or CH_2Cl_2) for 10 min. Sodium azide (91 mg, 1.4 mmol) was then added in all cases and where appropriate the sodium azide was dissolved in the minimum amount of water prior to addition (see table below). Bu_4NHSO_4 (12mg, 35 μmol) was added to the appropriate reactions (see table below). All mixtures were then agitated by shaking for 16 h and all resins were filtered off and washed with CH_2Cl_2, DMF, water, DMF, water, DMF, CH_2Cl_2, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C). All the resins were analysed by IR spectroscopy (KBr discs).

Reaction	Solvent	Solvation of NaN_3 in water before addition?	Phase-transfer reagent (Bu_4NHSO_4)?
1	CH_2Cl_2	Yes	No
2	DMF	Yes	No
3	CH_2Cl_2	Yes	Yes
4	DMF	Yes	Yes
5	CH_2Cl_2	No	Yes
6	DMF	No	Yes

Typical IR (cm^{-1}) 2131 (m, N_3), 1484 (w), 1455 (w), 1383 (s, SO_2), 1167 (s, SO_2), 1117 (m).

3.12 5-Phenyl-3-(2,2,2,-trifluoroacetyl)tetrahydrofuran-2-one



NaH (160 mg, 4 mmol, 60 % dispersion in mineral oil) was washed with dry hexane (2 x 5 mL) and suspended in DME (4 mL) under a nitrogen atmosphere. The suspension was cooled to 0 °C and γ-phenyl-γ-butyrolactone (162 mg, 1 mmol) solution in DME (1 mL) added dropwise. After stirring for 10 min, 2,2,2-trifluoroethyl trifluoroacetate (201 μL, 1.5 mmol) solution in DME (1 mL) was added dropwise and the resulting mixture allowed to warm to room temperature and stirred for a further 3 h. The reaction mixture was acidified with aqueous HCl (1 M) to pH 4 and diluted with Et_2O (10 mL). The aqueous layer was extracted with Et_2O (2 x 15 mL) and the combined organic fractions dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography eluting with Et_2O:hexane (3:7) afforded the title compound as a cream coloured solid as a mixture of diastereoisomers in a ratio of approximately 1:1.5 (185 mg, 0.72 mmol, 72%).

CAS registry number [371969-06-1]

IR (cm^{-1}) 1738 (s), 1346 (w), 1217 (m), 1193 (s), 1141 (s), 1105 (s), 1013 (m), 981 (m).

Spectroscopic data reported for the mixture of diastereoisomers.

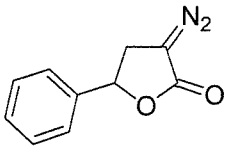
^{1}H-NMR ($CDCl_3$, δ ppm) 7.47-7.27 (2 x 5H, m, Ph-**H**), 5.69 (1H, dd, J = 6.6, 8.8 Hz, Ph-C**H**), 5.45 (1H, dd, J = 6.3, 10.7 Hz, Ph-C**H**), 3.59-3.51 (2 x1H, m, COC**H**), 3.24 (1H, dd, J = 8.5, 12.1 Hz, C**H**H), 3.13-3.01 (1H, m, CH**H**), 2.86-2.77 (1H, m, C**H**H), 2.57 (1H, q, J = 12.3 Hz, CH**H**).

^{13}C-NMR ($CDCl_3$, δ ppm) 177.2 and 175.6 (OC=O), 138.8 and 137.5 (Ar **C**), 129.4 (Ar **C**-H), 129.2 (Ar **C**-H), 129.1 (Ar **C**-H), 126.2 (Ar **C**-H), 125.6 (Ar **C**-H), 124.9 (Ar **C**-H), 81.1 and 80.1 (Ph-**C**H), 44.1 and 41.5 (COCH), 33.6 and 32.6 (**C**H_2). No CF_3 observed.

Mass Spec. *m/z* **(relative intensity and ion)** 258 (35, $[M]^{\bullet+}$), 105 (100).

Spectroscopic data in agreement with literature.[70]

3.13 3-Diazo-5-phenyltetrahydrofuran-2-one



Sulfonyl azide resin **4.14** (162 mg, 148 μmol, 0.91 mmol/g) was swollen in CH_3CN (1 mL) for 10 min. To the resin suspension was added *i*Pr_2EtN (73 μL, 0.42 mmol) and trifluoroacetate **3.12** (27 mg, 105 μmol) and the resulting mixture shaken for 16 h. The resin was filtered off and washed CH_2Cl_2 (80 mL) and the combined filtrates concentrated *in vacuo* to give a crude yellow oil. The crude mixture was dissolved in CH_2Cl_2 (3 mL) and the mixture passed through a silica plug, which afforded the title compound as a yellow oil (3 mg, 16 μmol, 15 %).

CAS registry number [371969-07-2]

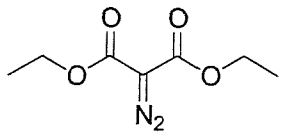
IR (cm^{-1}) 2970 (w), 2935 (w), 2093 (s, C=N_2), 1727 (s), 1456 (w), 1373 (m), 1275 (w), 1227 (m), 1098 (m), 1011 (m).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.45-7.36 (5H, m, Ph-**H**), 5.57 (1H, dd, J = 6.8, 8.8 Hz, PhC**H**), 3.76 (1H, dd, J = 8.5, 13.1 Hz, C**H**H), 3.28 (1H, dd, J = 6.5, 13.1 Hz, CH**H**).

^{13}C-NMR ($CDCl_3$, δ ppm) 169.7 (**C**=O), 139.3 (Ar **C**), 129.0 (Ar **C**-H), 128.9 (Ar **C**-H), 125.3 (Ar **C**-H), 77.9 (Ph**C**H), 31.6 (**C**H_2). No C=N observed.

Spectroscopic data in agreement with literature.[70]

3.15 2-Diazomalonic acid diethyl ester



Methods investigating reaction conditions using resin 3.9

Variation of resin equivalents

For each reaction 1.3, 1.5, 1.8, 2 equivalents of resin **3.9** (69.4 mg, 80.1 mg, 96.1 mg, 106.7 mg respectively, based on the theoretical loading of 1.17 mmol/g) was swollen in CH_3CN (0.2 mL) for 10 min. To the respective resins was added diethyl malonate (9.48 μL, 62.4 μmol) and *i*-Pr_2EtN (10.9 μL, 62.4 μmol). The substrate and base were added using 0.5 mL of a premixed stock solution (18.9 μL/mL diethyl malonate, 21.7 μL/mL *i*-Pr_2EtN in CH_3CN) in order to give a total reaction mixture volume of 0.7 mL. The reactions were monitored by HPLC over time by taking 70 μL aliquots of the reaction mixture and diluting to 1 mL in CH_3CN:H_2O (1:1).

Variation of solvent (i-Pr_2EtN as base)

For each reaction 2 equivalents of resin **3.9** (106.7 mg, based on the theoretical loading of 1.17 mmol/g) was swollen in their respective solvents (0.8 mL of either CH_3CN, CH_2Cl_2, or CH_3CN:CH_2Cl_2 (1:1)). To the resins was added diethyl malonate (9.48 μL, 62.4 μmol) by adding 0.1 mL of a stock solution (94.8 μL/mL in CH_3CN or CH_2Cl_2 for reaction involving CH_2Cl_2 only). *i*-Pr_2EtN (10.9 μL, 62.4 μmol) was added by using 0.1 mL of a stock solution (109 μL/mL *i*-Pr_2EtN in CH_3CN, or CH_2Cl_2 for both reactions involving CH_2Cl_2) giving a total reaction volume of 1 mL. The reactions were monitored by HPLC over time by taking 50 μL aliquots of the reaction mixture and diluting to 0.5 mL with CH_3CN:H_2O (1:1).

Variation of solvent (Et_3N as base)

For each reaction 2 equivalents of resin **3.9** (106.7 mg, based on the theoretical loading of 1.17 mmol/g) was swollen in their respective solvents (0.8 mL of either CH_3CN, CH_2Cl_2, or CH_3CN: CH_2Cl_2 (1:1)). To the resins was added diethyl malonate (9.48 μL, 62.4 μmol) by adding 0.1 mL of a stock solution (94.8 μL/ mL in CH_3CN or CH_2Cl_2 for reaction involving CH_2Cl_2 only). Et_3N (8.7 μL, 62.4 μmol) was added by

using 0.1 mL of a stock solution (87 μL/mL Et_3N in CH_3CN, or CH_2Cl_2 for both reactions involving CH_2Cl_2) giving a total reaction volume of 1 mL. The reactions were monitored by HPLC over time by taking 50 μL aliquots of the reaction mixture and diluting to 0.5 mL with CH_3CN:H_2O (1:1).

Variation of base equivalents

For each reaction (A, B, C, D) 2 equivalents of resin **3.9** (106.7 mg respectively, based on the theoretical loading of 1.17 mmol/g) was swollen in CH_3CN (0.2 mL) for 10 min. To the respective resins was added diethyl malonate (9.48 μL, 62.4 μmol) by adding 0.1 mL of a stock solution (94.8 μL/ mL in CH_3CN). The base (*i*-Pr_2EtN) was added using a stock solution (109 μL/mL in CH_3CN) according to the table below. The reactions were all make up to the same volume (0.7 mL) by adding CH_3CN (see table below for amounts). The reactions were monitored by HPLC over time by taking 70 μL aliquots of the reaction mixture and diluting to 1 mL in CH_3CN:H_2O (1:1).

Reaction	**Equivalents of base**	**Amount base stock solution added / mL**	**CH_3CN to make up to 0.7 mL / mL**
A	1	0.1	0.3
B	1.5	0.15	0.25
C	2	1.2	0.2
D	3	0.3	0.1

Method for Diazo-transfer with resin 4.14

Sulfonyl azide resin **4.14** (463 mg, 421 μmol, 0.91 mmol/g) was swollen in CH_3CN (1 mL) for 10 min. To the resin suspension was added *i*Pr_2EtN (210 μL, 1.20 mmol) and diethyl malonate (48 mg, 301 μmol) and the resulting mixture shaken for 16 h. The resin was filtered off and washed CH_2Cl_2 (80 mL) and the combined filtrates concentrated *in vacuo* to give a crude yellow oil. Purification by flash chromatography eluting with Et_2O:hexane (1:99, 2:98, 5:95, 1:9) afforded the title compound as a yellow oil (40 mg, 217 μmol, 72 %).

CAS registry number [5256-74-6]

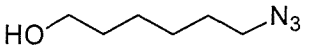
IR (cm^{-1}) 2990 (m), 2142 (s, C=N_2), 1761 (s), 1738 (s), 1692 (m), 1373 (m), 1323 (s), 1094 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 4.30 (2H, q, J = 7.1 Hz, O-C**H**$_2$ x 2), 1.32 (3H, t, J = 7.4 Hz, C**H**$_3$ x 2).

^{13}C-NMR ($CDCl_3$, δ ppm) 161.3 (**C**OO x 2), 61.8 (**C**H$_2$ x 2), 14.5 (**C**H$_3$ x 2). No C=N observed.

Mass Spec. (ES+) ***m/z*** **(relative intensity and ion)** 395.3 (80, $[2M + Na]^+$), 250.1 (100, $[M + Na + CH_3CN]^+$), 225.0 (5, $[M + K]^+$), 209.0 (17, $[M + Na]^+$).

3.18 6-Azido-1-hexanol



To a solution of 6-chlorohexanol (500mg, 3.66 mmol) in dry CH_3CN (3 mL) was added sodium azide (474 mg, 7.3 mmol) and 15-crown-5 (73 μL, 0.37 mmol) under a nitrogen atmosphere. The resulting mixture was heated to reflux and stirred for 16 h. The mixture was diluted with Et_2O (20 mL) and washed with water (3 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a colourless oil (504 mg, 3.52 mmol, 96 %).

CAS registry number [146292-90-2]

IR (cm^{-1}) 3302 (br, -OH), 2936 (m), 2861 (w), 2095 (s, C-N_3), 1460 (w), 1262 (m), 1056 (m).

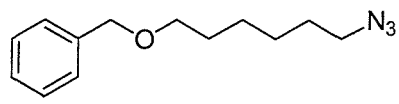
^{1}H-NMR ($CDCl_3$, δ ppm) 3.60 (2H, t, J = 6.6 Hz, C**H**$_2$OH), 3.25 (2H, t, J = 6.6 Hz, C**H**$_2$N$_3$), 2.16 (1H, broad s, -O**H**), 1.64-1.51 (4H, m, C**H**$_2$), 1.43-1.35 (4H, m, C**H**$_2$).

^{13}C-NMR ($CDCl_3$, δ ppm) 62.7 (CH_2OH), 51.5 (CH_2N_3), 32.6 (CH_2CH_2OH), 28.9 ($CH_2CH_2N_3$), 26.6 (**C**H$_2$), 25.5 (**C**H$_2$).

Mass Spec. ***m/z*** **(relative intensity and ion)** 144 (13 %, $[M + H]^+$), 116 (28 %, $[(M - N_2) + H]^+$), 98 (54 %, $[M - (N_2 + OH)]^+$), 70 (79 %, $[(CH_2)_5]^+$).

Spectroscopic data in agreement with literature.[231]

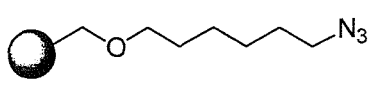
3.20 (6-Azidohexyloxymethyl) benzene



Potassium iodide (30 mg, 0.41 mmol) and potassium *t*-butoxide (80 mg, 0.14 mmol) were stirred in dry THF (1.5 mL) under a nitrogen atmosphere. Alcohol **3.18** (100 mg, 0.70 mmol) was added dropwise followed by a dropwise addition of benzyl chloride (79 μL, 0.69 mmol). The resulting mixture was heated to reflux and stirred for 24 h. The reaction was quenched with excess aqueous HCl (1 M) and diluted with Et_2O (20 mL). The organic layer was washed with aqueous 1 M HCl (1 x 20 mL), water (2 x 10 mL), brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a yellow oil (134 mg, 0.57 mmol, 83 %).

IR (cm^{-1}) 2941 (m), 2856 (m), 2090 (s, C-N_3), 1455 (w), 1356 (w) 1252 (m), 1101 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 7.40-7.28 (5H, m, Ar C-**H**), 4.53 (2H, s, Ph-C**H**$_2$-O), 3.50 (2H, t, J = 6.3 Hz, C**H**$_2$OBn), 3.27 (2H, t, J = 7.0 Hz, C**H**$_2$$N_3$), 1.68-1.59 (4H, m, C**H**$_2$), 1.46-1.41 (4H, m, C**H**$_2$).
^{13}C-NMR ($CDCl_3$, δ ppm) 138.8 (**C**CH$_2$O), 128.5 (Ar **C**-H), 127.8 (Ar **C**-H), 127.7 (Ar *p*-**C**-H), 73.1 (Ph-**C**H$_2$-O), 70.3 (**C**H$_2$OBn), 51.6 (**C**H$_2$$N_3$), 29.8 (**C**H$_2CH_2$OH), 29.0 (**C**H$_2CH_2$$N_3$), 26.7 (**C**H$_2$), 26.0 (**C**H$_2$).
Mass Spec. *m/z* (relative intensity and ion) 234 (5 %, $[M + H]^+$), 206 (58 %, $[(M - N_2) + H]^+$), 91 (100 %, $[C_6H_5CH_2]^+$).
High Res. Mass Spec. Calculated: $C_{13}H_{20}N_3O$ = 234.1606. Found: 234.1608 (31.15, $[M+H]^+$).

3.21 Poly (styryl-DVB) – ether linked 6-azido hexyl resin



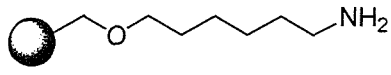
Merrifield resin (200 mg, 0.32 mmol, 1.6 mmol/g) was swollen in dry THF (3 mL) under a nitrogen atmosphere for 15 min. Potassium iodide (28 mg, 0.13 mmol) and

potassium *t*-butoxide (108 mg, 0.96 mmol) were added to the resin followed by alcohol **3.18** (224 mg, 0.96 mmol) dissolved in dry THF (0.5 mL). The reaction mixture was heated to reflux for 36 h without stirring. The resin was filtered off and washed with THF, aqueous HCl (1M), THF, water, THF, CH_2Cl_2, Et_2O (80 mL of each) and dried in a vacuum oven (40 C) to give the title resin with a theoretical loading of 1.37 mmol/g.

IR (cm^{-1}) 3062 (w), 3022 (w), 2924 (m), 2851 (m), 2094 (s, R-N_3), 1603 (m), 1491 (m), 1094 (s, R-O-R).

^{1}H-NMR (MAS, δ ppm) 4.5 (broad s, CH_2-O), 3.5 (broad s, CH_2), 3.2 (s, *J*-resolved 2-D spectrum shows: t, $J = 7$ Hz, CH_2N_3).

3.22 Poly (styryl-DVB) – ether linked 6-amino hexyl resin



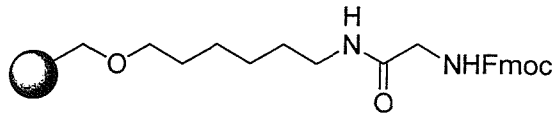
Azide resin **3.21** (150 mg, 0.21 mmol, based on the theoretical loading of 1.37 mmol/g) was swollen in dry THF (2.5 mL) for 15 min. PPh_3 (275 mg, 1.05 mmol) was added and the resulting mixture shaken under a nitrogen atmosphere in the absence of light for 18 h. Water (660 μL) was added to the mixture and warmed to 70 °C and very gently stirred for a further 8 h. The resin was filtered off and washed with THF, DMF, CH_2Cl_2, MeOH, Et_2O (50 mL of each) and dried in a vacuum oven (40 °C) to give the title resin with a theoretical loading of 1.42 mmol/g.

IR (cm^{-1}) 3023 (w), 2924 (w), 2851 (w), 1602 (m, R-NH_2), 1094 (s, R-O-R).

^{1}H-NMR (MAS, δ ppm) 2.7 (broad s, CH_2NH_2).

Elemental Analysis Calculated: N = 1.99 %. Found: N = 1.96 %.

3.25 Poly (styryl-DVB) – ether linked hexyl 6-amido-FmocGlycine resin



Amine resin **3.22** (100 mg, 0.14 mmol) was swollen in CH_2Cl_2 (1 mL) for 15 min. A solution of FmocGlycine (84 mg, 0.28 mmol) in the minimal amount of CH_2Cl_2:DMF (9:1) to dissolve, with DMAP (5 mg, 43 μmol) and DIC (89 μL, 0.57 mmol) was stirred for 10 min and added to the resin. The reaction was shaken for 2 h after which the resin was filtered off and washed with CH_2Cl_2, DMF, CH_2Cl_2, MeOH, CH_2Cl_2 (30 mL of each) and dried in a vacuum oven (40 C). Qualitative ninhydrin test on the product resin gave a positive result for free $-NH_2$ groups.[142] The reaction procedure was repeated a number of times to try to allow the complete reaction of all amine functionality, shown by a negative qualitative ninhydrin result. However, a negative ninhydrin test was not forthcoming.

Fmoc-cleavage test

Fmoc protected resin **3.25** (5 mg) was treated with piperidine:DMF (1:4, 1 mL) and shaken for 15 min. The solution was filtered off through glass wool and made up to 25 mL in a volumetric flask with piperidine:DMF (1:4). The absorbance at 302 nm of the piperidyl-fulvene adduct was measured and the following equation used to determine the loading of the resin:

$$\text{mmol/g} = \left[\frac{A_{302} \times V}{\varepsilon_{302} \times W}\right] \times 10^3$$

Where: A_{302} = Absorbance of piperidyl-fulvene adduct

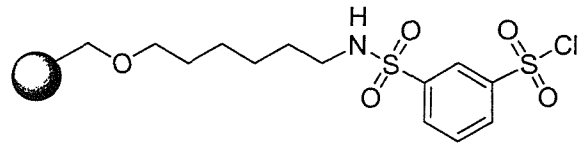
V = Total volume (mL)

e_{302} = extinction coefficient of adduct (7800 $M^{-1}cm^{-1}$)

W = weight of resin (mg)

The resin loading was determined by Fmoc test to be 0.72 mmol/g.

3.26 Poly (styryl-DVB) – ether linked *N*-hexyl sulfonamido phenyl *m*-sulfonyl chloride resin



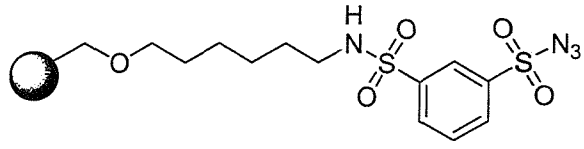
Aminohexyl resin **3.22** (50 mg, 71 μL, 1.42 mmol/g) was swollen in dry CH_2Cl_2 (1 mL). Et_3N (99 μL, 0.71 mmol) was added to the resin **3.22** and the mixture shaken for 15 min, followed by addition of 1,3-benzenedisulfonyl chloride (195 mg, 0.71 mmol). The resulting mixture was shaken under a nitrogen atmosphere for 18 h. The resin was filtered off and washed with CH_2Cl_2, Et_2O (80 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3062 (w), 3023 (w), 2924 (m), 2858 (w), 1602 (m, C-NR_2), 1382 (s, SO_2R), 1174 (s, SO_2R), 1090 (m, R-O-R).

^{1}H-NMR (MAS, δ ppm) 2.2 (broad s, CH_2NHSO_2).

Elemental Analysis Calculated: N = 1.48 %, S = 6.78 %. Found: N = 1.64 %, S = 6.5 %.

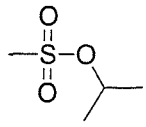
3.27 Poly (styryl-DVB) – ether linked *N*-hexyl sulfonamido phenyl *m*-sulfonyl azide resin



Sulfonyl chloride resin **3.26** (20 mg, 21 μmol, based on the theoretical loading of 1.06 mmol/g) was swollen in CH_2Cl_2 (0.2 mL) for 10 min. Sodium azide (5.5 mg, 85 μmol) was added followed by Bu_4NHSO_4 (720 μg, 2.12 μmol, 0.1 mL of a 7.2 mg/mL stock solution). The reaction was shaken for 16 h and the resin filtered off and washed with DMF, water, DMF, water, DMF, water, DMF, CH_2Cl_2, Et_2O (10 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3056 (w), 3023 (w), 2923 (m), 2859 (w), 2129 (m, R-N_3), 1602 (m, C-NR_2), 1381 (s, SO_2R), 1175 (s, SO_2R), 1082 (m, R-O-R).

3.28 Isopropyl methanesulfonate

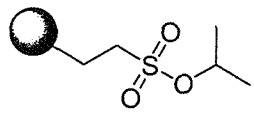


To a solution of *i*-propyl alcohol (668 μL, 8.73 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under a nitrogen atmosphere was added Et_3N (1.23 mL, 8.8 mmol) followed by dropwise addition of methanesulfonyl chloride (700 μL, 8.73 mmol) and the reaction stirred for 4 h. After dilution with CH_2Cl_2 (30 mL) the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), aqueous 1 M HCl (2 x 20 mL), water (5 x 20 mL), brine (1 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a colourless oil (947 mg, 6.85 mmol, 79 %).

CAS registry number [926-06-7]
IR (cm^{-1}) 2987 (w), 2941 (w), 1342 (s), 1326 (s), 1171 (s), 1096 (m), 972 (m), 909 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 4.89 (1H, qq, J = 6.3 Hz, C**H**$(CH_3)_2$), 2.95 (3H, s, **C**H_3-S), 1.37 (6 H, d, J = 5.9 Hz, CH(CH_3)$_2$).
^{13}C-NMR ($CDCl_3$, δ ppm) 77.0 (O-**C**H), 38.6 (**C**H_3-S), 23.2 (CH(**C**H_3)$_2$).
Mass Spec. *m/z* **(relative intensity and ion)** 156 (44, $[M + NH_4]^+$), 139 (5, $[M + H]^+$), 123 (21, $[M - CH_3]^+$), 43 (100).

Spectroscopic data in agreement with literature.[232]

3.29 Poly (styryl-DVB) – ethylene isopropyl sulfonate resin

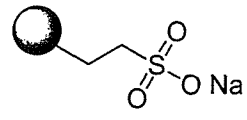


To a solution of isopropyl methanesulfonate **3.28** (815 mg, 5.89 mmol) in dry THF (2.8 mL) at – 78 °C under a nitrogen atmosphere was added n-BuLi (2.4 mL of a 2.5 M solution in hexane, 6.0 mmol) dropwise and the resulting solution stirred for 20 min. To Merrifield resin (230 mg, 0.37 mmol) swollen in dry THF (2.3 mL) and stirred very gently at – 78 °C under a nitrogen atmosphere was added the sulfonate anion solution dropwise *via* cannula. The resulting mixture was stirred for 5 min before warming the solution to – 20 °C and stirred for 16 h. The reaction was quenched at – 20 °C by the addition of MeOH (5 mL) after which the resin was filtered off and washed with MeOH, THF:H_2O (2:1), H_2O, THF:H_2O (2:1), THF, MeOH, CH_2Cl_2, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3024 (w), 2921 (w), 2847 (w), 1492 (m), 1470 (m), 1326 (m), 1168 (s), 909 (s).

Elemental Analysis Calculated: S = 4.38 %. Found: S = 3.66 %.

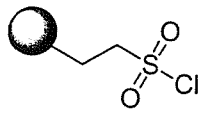
3.30 Poly (styryl-DVB) – ethylene sulfonate (sodium salt)



Isopropyl sulfonate resin **3.29** (150 mg, 0.21 mmol based on the theoretical loading of 1.37 mmol/g) was suspended in acetone (6 mL) and sodium iodide (1.34 g, 8.95 mmol) added. The resulting mixture was stirred slowly at 55 °C under nitrogen for 20 h. The resin was filtered off and suspended in ethanol (10 mL) and stirred for a further 30 min. The resin was filtered off and washed with acetone, ethanol, acetone:water (1:1), CH_2Cl_2, MeOH, CH_2Cl_2, Et_2O (50 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3027 (w), 2922 (w), 2852 (w), 1492 (m), 1450 (m), 1178 (s), 1045 (m).

3.31 Poly (styryl-DVB) – ethylene sulfonyl chloride

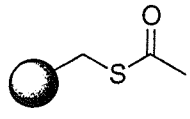


Sulfonate resin **3.30** (100 mg, 0.14 mmol based on the theoretical loading of 1.41 mmol/g) was swollen in dry CH_2Cl_2 (1 mL) for 15 min. To a separate solution of PPh_3 (164 mg, 0.63 mmol) in dry CH_2Cl_2 (0.5 mL) under a nitrogen atmosphere at 0 °C was added sulfuryl chloride (50 μL, 0.63 mmol) dropwise and stirred for 10 min. The sulfuryl chloride/PPh_3 mixture was added to the resin suspension at 0 °C under nitrogen and stirred for 15 min before warming to room temperature and stirring for 16 h. The resin was filtered off and washed with CH_2Cl_2, MeOH, DMF:water (1:1), water, DMF:water (1:1), DMF, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, Et_2O (30 mL of each) and dried in a vacuum over (40 °C).

IR (cm^{-1}) 3024 (w), 2920 (w), 2847 (w), 1595 (w), 1494 (m), 1450 (m), 1370 (m), 1165 (m), 1106 (w), 1024 (w).

Elemental Analysis Calculated: S = 4.54 %, Cl = 5.04 %. Found: S = 3.28 %, Cl = 3.89 % (indicates an approximate 72 % overall yield in 3 steps from Merrifield resin).

3.32 Poly (styryl-DVB) – *S*-methylene thioacetate resin



General Method

A mixture of Merrifield resin (3 g, 4 mmol, 1.6 mmol/g) and potassium thioacetate (1.37 g, 12 mmol) in DMF (20 mL) was agitated by shaking for 20 h at room temperature. The resin was filtered off and washed with DMF, CH_2Cl_2, DMF, CH_2Cl_2, Et_2O (300 mL of each) and dried in a vacuum oven (40 °C).

NB. The reaction was also carried out at 80 °C (with careful stirring) and swelling the resin with CH_2Cl_2 before suspension in DMF for the reaction.

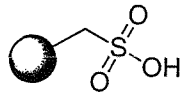
IR (cm^{-1}) 2925 (w), 1690 (s), 1450 (m), 1132 (m), 953 (m).

^{1}H-NMR (MAS, δ ppm) 4.06 (broad s, CH_2-S), 2.32 (broad s, CH_3).

^{13}C-NMR (MAS, δ ppm) 195.4 (**C**=O), 30.4 (**C**H_3).

Elemental analysis See section 3.5 (chapter 3) for individual analysis for Cl.

3.33 Poly (styryl-DVB) – methylenesulfonic acid resin

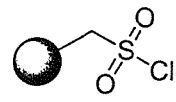


Formic acid (9 mL) and hydrogen peroxide (0.9 mL, 27 % aqueous solution) were premixed and stirred for 15 min. Meanwhile, thioacetate resin **3.32** (1 g, 1.5 mmol) was swollen in CH_2Cl_2 (11 mL) for 15 min after which the pre-formed performic acid solution was added carefully in three portions and the resulting mixture shaken for 5 h (DMF as solvent can be used as solvent instead of CH_2Cl_2, but with longer reactions times). The resin was filtered off and washed with CH_2Cl_2, DMF, DMF:water (1:1), water, DMF:water (1:1), DMF, CH_2Cl_2, Et_2O (100 mL) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3025 (w), 2920 (w), 2851 (w), 1492 (m), 1451 (m), 1373 (m), 1166 (s), 1030 (m).

Elemental analysis Calculated: S = 4.77 %. Found: S = 4.99 %.

3.34 Poly (styryl-DVB) – methylenesulfonyl chloride resin



Method 1 (Phosphorus pentachloride /DMF or CH_2Cl_2)

Sulfonic acid resin **3.33** (300 mg, 447 μmol) was swollen in dry solvent (2.5 mL) for 10 min under a nitrogen atmosphere. PCl_5 (466 mg, 2.24 mmol) was added to the resin and the mixture shaken for 16 h. The resin was filtered off and washed with DMF, CH_2Cl_2, Et_2O (150 mL of each) and dried in a vacuum oven (40 °C).

Method 2 (sulfuryl chloride/PPh_3)

Sulfonic acid resin **3.33** (300 mg, 447 μmol) was swollen in dry CH_2Cl_2 (2 mL) for 10 min under a nitrogen atmosphere. Meanwhile, a solution of PPh_3 (577 mg, 2.2 mmol) in CH_2Cl_2 (1 mL) was stirred under a nitrogen atmosphere at 0 °C and SO_2Cl_2 (177 μL, 2.2 mmol) added dropwise. The resulting mixture was transferred to the resin suspension dropwise and the resulting mixture shaken for 16 h. The resin was filtered off and washed with DMF, CH_2Cl_2, Et_2O (150 mL of each) and dried in a vacuum oven (40 °C).

Method 3 (triphosgene)

Sulfonic acid resin **3.33** (300 mg, 447 μmol) was swollen in dry CH_2Cl_2 (2 mL) and dry DMF (0.4 mL) for 10 min under a nitrogen atmosphere. Triphosgene (133 mg, 448 μmol) was added very carefully in small portions to the resin suspension and the mixture shaken overnight. The resin was filtered off (the filtrate dropped into an ammonia solution to destroy remaining phosgene) and washed with CH_2Cl_2, DMF, CH_2Cl_2, Et_2O (150 mL of each) and dried in a vacuum oven (40 °C).

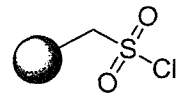
Method 4 (thionyl chloride)

Sulfonic acid resin **3.33** (300 mg, 447 μmol) was swollen in dry CH_2Cl_2 (2 mL) and dry DMF (1.5 mL) for 10 min under a nitrogen atmosphere. $SOCl_2$ (5 mL) was added dropwise to the resin suspension and the resulting mixture warmed to reeflux and

gently stirred for 16 h. The resin was filtered off and washed with CH_2Cl_2 (400 mL) and Et_2O (50 mL) and dried in a vacuum oven (40 °C).

Typical IR (cm^{-1}) 3025 (w), 2920 (w), 2852 (w), 1492 (m), 1451 (m), 1371 (variable strength), 1165 (variable strength), 1112 (w), 1020 (w).
See section 3.5 (chapter 3) for specific IR spectra

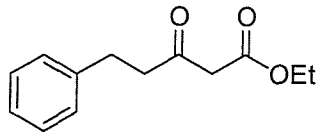
3.34(M) Macroporous poly (styryl-DVB) – methylenesulfonyl chloride resin



To a suspension of macroporous thioacetate resin **3.32(M)** (1.5 g, 3.8 mmol, 2.52 mmol/g, synthesised from macroporous Merrifield resin using the optimised procedure for the synthesis of thioacetate resin **3.32**) in acetic acid (12 mL) and H_2O (4.8 mL) was added *N*-chlorosuccinimide (1.50 g, 11.25 mmol) and the resulting mixture agitated by shaking for 16 h. The resin was filtered off and washed with warm solvents: H_2O, DMF, H_2O, DMF and after with CH_2Cl_2, H_2O, DMF, CH_2Cl_2, Et_2O (150 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3024 (w), 2923 (w), 2857 (w), 1701 (w), 1604 (w), 1445 (m), 1371 (s, SO_2Cl), 1262 (w), 1227 (w), 1167 (s, SO_2Cl), 1033 (w), 797 (m), 704 (s).
Elemental analysis Calculated: S = 7.60 %, Cl = 8.4 %. Found: S = 4.66 %, Cl = 11.77 % (showing the undesired chlorination side-reaction).

3.39 Ethyl 5-phenyl-3-oxopentanoate



To a stirred suspension of sodium hydride (307 mg of a 60 % dispersion in mineral oil, 7.68 mmol) in dry THF (8 mL) under a nitrogen atmosphere at 0 °C, ethyl acetoacetate (0.98 mL, 7.68 mmol) was added dropwise. After stirring for 10 min, *n*-BuLi (3.07 mL of a 2.5 M solution in hexane, 7.68 mmol) was added and the mixture stirred for a further 10 min, after which a solution of benzyl chloride (0.88 mL, 7.65 mmol) in dry THF (2 mL) was added dropwise and the resulting mixture allowed to warm to room temperature. After 2 h, the reaction was quenched with excess aqueous HCl (1 M) and diluted with Et_2O (30 mL). The organic layer was washed with aqueous 1 M HCl (1 x 20 mL) and water until pH neutral, dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography eluting with Et_2O:hexane (5:95) afforded the title compound as a pale yellow oil (0.996 g, 4.52 mmol, 59 %).

CAS registry number [17071-29-3]

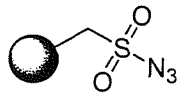
IR (cm^{-1}) 2983 (w), 2936 (w), 1743 (s), 1716 (s), 1497 (m), 1454 (m), 1409 (m), 1367 (m), 1318 (s), 1244 (s), 1183 (s), 1030 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.32-7.18 (5H, m, Ar C-**H**), 4.18 (2H, q, J = 7.1 Hz, OCH_2), 3.43 (2H, s, $COCH_2CO$), 2.97-2.85 (4H, m, $PhCH_2CH_2$), 1.27 (3H, t, J = 7.0 Hz, O-CH_2CH_3).

^{13}C-NMR ($CDCl_3$, δ ppm) 202.1 (**C**=O), 167.3 (**C**OOEt), 140.7 (Ar **C**), 128.7 (Ar **C**-H), 128.5 (Ar **C**-H), 126.4 (Ar C-H), 61.6 (O-**C**H_2), 49.6 ($COCH_2CO$), 44.7 ($PhCH_2CH_2$), 29.6 ($PhCH_2$), 14.2 (O-CH_2CH_3).

Spectroscopic data in agreement with literature.[233]

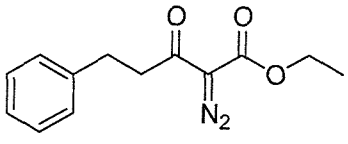
3.40 Poly (styryl-DVB) – methylenesulfonyl azide resin



Sulfonyl chloride resin **3.34** (500 mg, 0.72 mmol, based on the theoretical loading of 1.45 mmol/g) was swollen in CH_2Cl_2 (5 mL) for 15 min. Bu_4NHSO_4 (124 mg, 0.36 mmol) and sodium azide (236 mg, 3.63 mmol) were added and the resulting mixture shaken for 16 h. The resin was filtered off and washed with CH_2Cl_2, DMF, DMF:water (1:1), water, DMF:water (1:1), DMF, CH_2Cl_2, DMF, DMF:water (1:1), water, DMF:water (1:1), DMF, CH_2Cl_2, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3025 (w), 2920 (w), 2131 (m, N_3), 1492 (m), 1451 (m), 1369 (m, SO_2), 1161 (m, SO_2), 1027 (w).

3.41 Ethyl 2-diazo-5-phenyl-3-oxopentanoate



Method using resin 3.40

Sulfonyl azide resin **3.40** (378 mg, 0.54 mmol based on the theoretical loading of 1.44 mmol/g) was swollen in CH_3CN (2 mL) for 10 min. To the resin suspension was added *i*Pr_2EtN (47 μL, 0.27 mmol) and β-ketoester **3.39** (60 mg, 0.27 mmol) and the resulting mixture shaken for 16 h. The resin was filtered off and washed with CH_3CN (10 mL) and CH_2Cl_2 (80 mL) and the combined filtrates concentrated *in vacuo* to give a crude yellow oil (68 mg). Purification by flash chromatography eluting with CH_2Cl_2 afforded the title compound as a yellow oil (37 mg, 0.15 mmol, 56 %).

Method optimised using resin 4.14

Sulfonyl azide resin **4.14** (218 mg, 197 μmol, 0.91 mmol/g) was swollen in CH_3CN (1 mL) for 10 min. To the resin suspension was added *i*Pr_2EtN (99 μL, 568 μmol) and β-ketoester **3.39** (31 mg, 142 μmol) and the resulting mixture shaken for 16 h. The resin was filtered off and washed CH_2Cl_2 (80 mL) and the combined filtrates concentrated *in vacuo* to give a crude yellow oil (37 mg). The crude mixture was dissolved in CH_2Cl_2 (3 mL) and the mixture passed through a silica plug, which afforded the title compound as a yellow oil (34 mg, 0.14 mmol, 98 %).

CAS registry number [402567-85-5]

IR (cm^{-1}) 3027 (w), 2987 (w), 2932 (w), 2131 (s), 1711 (s), 1654 (s), 1453 (w), 1371 (m), 1299 (s), 1209 (m), 1124 (m), 1050 (s).

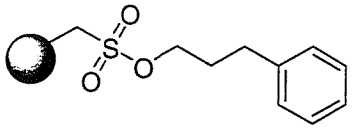
^{1}H-NMR ($CDCl_3$, δ ppm) 7.32-7.18 (5H, m, Ar C-**H**), 4.30 (2H, q, J = 7.1 Hz, OCH_2), 3.20 (2H, t, J = 7.4 Hz, $PhCH_2$), 2.98 (2H, t, J = 7.7 Hz, CH_2CO), 1.33 (3H, t, J = 7.0 Hz, CH_3).

^{13}C-NMR ($CDCl_3$, δ ppm) 192.1 (**C**=O), 161.5 (**C**OOEt), 141.0 (Ar **C**), 128.7 (Ar **C**-H), 128.6 (Ar **C**-H), 126.3 (Ar **C**-H), 61.6 (O-CH_2), 42.0 (CH_2CO), 30.4 (Ph-CH_2), 14.5 (O-CH_2CH_3). No C=N observed.

Mass Spec. (ES+) ***m/z*** **(relative intensity and ion)** 269.1 (23, $[M + Na]^+$), 310.1 (54, $[M + Na + CH_3CN]^+$).

Spectroscopic data in agreement with literature.[234]

3.42 Poly (styryl-DVB) – dihydrocinnamyl sulfonate resins



General method to give results in Table 3.2 (Chapter 3)

Sulfonyl chloride resins **3.34** (110 mg, 160 μmol, based on the theoretical loading of 1.45 mmol/g), were swollen in dry CH_2Cl_2:pyridine (1:1, 1 mL) for 15 min. To the resins were added 3-phenylpropanol (152 μL, 1.12 mmol) and the reaction mixtures

shaken at room temperature under nitrogen for 5 h (or 20 h). All resins were filtered off and washed with CH_2Cl_2 (200 mL), Et_2O (50 mL) and dried in a vacuum oven (40 C).

General method to give results in Table 3.3 (Chapter 3)

Sulfonyl chloride resins **3.34** (110 mg, 160 μmol, based on the theoretical loading of 1.45 mmol/g) or commercial Aldrich resin (110 mg, ≈ 193 μmol, 1.5-2 mmol/g) were swollen in dry CH_2Cl_2 (1.1 mL) for 15 min. To the resins were added 3-phenylpropanol (for amounts see table below) and Et_3N (for amounts see table below) and the reaction mixtures shaken at room temperature under nitrogen for 40 h. The respective resins were filtered off and washed with CH_2Cl_2, Et_2O and dried in a vacuum oven (40 °C).

Sulfonyl chloride resin	**Amount of 3-phenylpropanol**	**Amount of Et_3N**
Resin **3.34**	109 μL, 0.8 mmol	112 μL, 0.8 mmol
Commercial Aldrich resin	131 μL, 0.96 mmol	134 μL, 0.96 mmol

Method using Mitsunobu chemistry at room temperature

Sulfonic acid resin **3.33** (300 mg, 0.45 mmol, 1.49 mmol/g) was swollen in dry THF (5 mL) under a nitrogen atmosphere for 15 min. To the resin suspension was added 3-phenylpropanol (370 μL, 2.7 mmol), PPh_3 (734 mg, 2.8 mmol). DIAD (550 μL, 2.8 mmol) was added dropwise with gentle swirling of the reaction vessel by hand. The mixture was agitated by shaking overnight. The resin was filtered off and washed thoroughly with CH_2Cl_2, DMF, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, DMF, CH_2Cl_2, Et_2O (50 mL of each) and dried in a vacuum oven (40 °C).

General method using Mitunobu chemistry with microwave assistance

Sulfonic acid resin **3.33** (150 mg, 0.22 mmol, 1.49 mmol/g) was swollen in dry THF (2 mL) under a nitrogen atmosphere for 15 min in an oven-dried microwave reaction vessel. To the resin mixtures was added 3-phenylpropanol (for amounts, see table below) and PPh_3 (for amounts, see table below). DIAD (for amounts, see table below) was added dropwise with gentle stirring of the reaction. The resulting reaction mixture

was placed in the microwave reactor (Smith Synthesiser from personal chemistry[170]) for the appropriate time and temperature (see Table 3.4, Chapter 3). The resin was filtered off and washed thoroughly with CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, Et_2O and dried in a vacuum oven (40 °C).

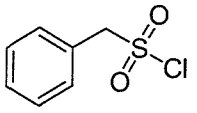
Rxn	**Amounts of reagents:**		
	3-Phenylpropanol	**PPh_3**	**DIAD**
1	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
2	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
3	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
4	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
5	31 μL, 0.22 mmol	59 mg, 0.23 mmol	44 μL, 0.23 mmol
6	31 μL, 0.22 mmol	59 mg, 0.23 mmol	44 μL, 0.23 mmol
7	31 μL, 0.22 mmol	59 mg, 0.23 mmol	44 μL, 0.23 mmol
8	31 μL, 0.22 mmol	59 mg, 0.23 mmol	44 μL, 0.23 mmol
9	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
10	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
11	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
12	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
13	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
14	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
15	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol
16	183 μL, 1.34 mmol	354 mg, 1.35 mmol	266 μL, 1.35 mmol

IR (cm^{-1}) 3026 (w), 2922 (w), 2850 (w), 1493 (m), 1452 (m), 1355 (s, SO_2R), 1167 (SO_2R), 923 (s), 835 (m), 747 (s).

^{1}H-NMR (MAS, δ ppm) 4.19 (broad s, CH_2SO_2O), 3.98 (broad s, $CH_2SO_2OCH_2$), 2.60 (broad s, CH_2CH_2Ph), 1.88 (broad s, $CH_2CH_2CH_2$).

^{13}C-NMR (MAS, δ ppm) 140.4 (Ar **C**), 70.1 ($CH_2SO_2OCH_2$), 31.3 ($CH_2CH_2CH_2$), 30.9 (CH_2CH_2Ph).

3.43 Phenylmethanesulfonyl chloride

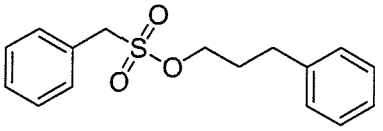


To a stirred mixture of benzyl thioacetate **3.45** (200 mg, 1.2 mmol) in acetic acid (4 mL) and water (1.4 mL) at 0 °C was added *N*-chloro succinimide (529 mg, 3.96 mmol) in one portion and and resulting mixture stirred for 1 hour. The reaction was diluted with CH_2Cl_2 (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers washed with water (3 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a cream coloured solid (225 mg). Purification by recrystallisation from CH_2Cl_2/Hexane gave the title compound as a white crystalline solid (185 mg, 0.972 mmol, 81 %).

CAS registry number [1939-99-7]
IR (cm^{-1}) 2994 (w), 2922 (w), 1494 (m), 1458 (m), 1362 (s, SO_2Cl), 1258 (m), 1202 (m), 1157 (s, SO_2Cl), 1137 (m), 1078 (m).
^{1}H-NMR ($CDCl_3$, δ ppm) 7.56-7.44 (5H, m, Ar C-**H**), 4.88 (2H, s, Ph-C**H**$_2$).
^{13}C-NMR ($CDCl_3$, δ ppm) 131.5 (Ar **C**-H), 130.5 (Ar **C**-H), 129.3 (Ar **C**-H), 126.3 (Ar **C**), 71.1 Ph**C**H$_2$).

Spectroscopic data in agreement with literature.[235]

3.44 3-Phenylpropyl phenylmethanesulfonate



To a stirred solution of benzylsulfonyl chloride **3.43** (200 mg, 1.05 mmol) in dry CH_2Cl_2 (8 mL) at 0 °C under a nitrogen atmosphere was added dry pyridine (85 μL, 1.05 mmol) and 3-phenylpropanol (143 μL, 1.05 mmol). After stirring and allowing to

warm to room temperature for 16 h the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1N HCl (aq. 2 x 20 mL), H_2O (3 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a colourless oil. Purification by column chromatography eluting with CH_2Cl_2:Hexane (1:9, 3:7, 1:1) afforded the title product as a white crystalline solid (228 mg, 0.79 mmol, 75 %).

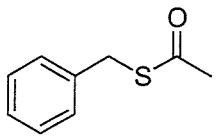
IR (cm^{-1}) 3035 (w), 2941 (w), 2905 (w), 1498 (m), 1454 (m), 1349 (s, -SO_2O), 1278 (m), 1171 (s, SO_2O), 1144 (s), 960 (s), 1072 (w), 852 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.45-7.40 (4H, m, Ar C-**H**), 7.34-7.20 (4H, m, Ar C-**H**), 7.15 (2H, d, J = 8.1 Hz, C-**H**), 4.37 (2H, s, Ph-C**H**$_2$-S), 4.07 (2H, t, J = 6.3 Hz, Bn-SO_2OC**H**$_2$), 2.66 (2H, t, J = 7.7 Hz, PhC**H**$_2$$CH_2$), 1.97 (2H, quin, J = 7.0 Hz, CH_2C**H**$_2$$CH_2$).

^{13}C-NMR ($CDCl_3$, δ ppm) 140.6 (**C**-CH_2S), 130.8 (Ar C-**H**), 129.3 (Ar C-**H**), 129.1 (Ar C-**H**), 128.7 (Ar C-**H**), 128.6 (Ar C-**H**), 128.1 (Ar **C**), 126.4 (Ar C-**H**), 70.4 ($CH_2SO_2OCH_2$), 57.0 (Ph**C**H_2SO_2O), 31.6 (Ph**C**H_2CH_2), 31.0 (SO_2OCH_2**C**H_2).

Mass Spec. *m/z* **(relative intensity and ion)** 308 (30, $[M + NH_4]^+$), 118 (61), 91 (100, $[PhCH_2]^+$).

3.45 *S*-Phenylmethane thioacetate



To a stirred solution of benzyl chloride (909 μL, 7.9 mmol) in dry DMF (40 mL) was added potassium thioacetate (902 mg, 7.9 mmol) and the resulting mixture stirred overnight. The mixture was diluted with CH_2Cl_2 (60 mL) and the organic layer was washed with water (5 x 20 mL), brine (4 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a brown oil (1.161 g, 6.95 mmol, 88 %).

CAS registry number [32362-99-5]

IR (cm^{-1}) 1690 (s), 1495 (w), 1454 (w), 1354 (w), 1132 (s), 1105 (m), 956 (m).

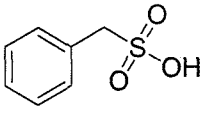
^{1}H-NMR ($CDCl_3$, δ ppm) 7.33-7.29 (5H, m, -C_6H_5), 4.14 (2H, s, CH_2-S), 2.36 ($COCH_3$).

^{13}C-NMR ($CDCl_3$, δ ppm) 195.3 (C=O), 137.7 (CCH_2S), 129.0 (Ar C-H), 128.8 (Ar C-H), 127.4 (Ar C-H), 33.6 (CH_2S), 30.5 ($COCH_3$).

Mass Spec. *m/z* **(relative intensity and ion)** 184 (55, $[M+NH_4]^+$), 167 (18, $[M+H]^+$), 91 (100, $[C_6H_5CH_2]^+$).

Spectroscopic data in agreement with literature.[236]

3.46 Phenylmethanesulfonic acid



A mixture of formic acid (54 mL, 98 %) and hydrogen peroxide (5.4 mL, 30 % solution in H_2O) were stirred for 10 min and cooled to 0 C. Benzyl thioacetate **3.45** (1.5 g, 9.03 mmol) was added to the mixture dropwise and stirred for 2 h before allowing to warm to room temperature and stirring for 20 h. The mixture was cooled to 0 C and Pd/C (10 %) was added to the mixture to decompose excess peroxide (effervescence observed). The solids were filtered off through celite and the filtrate concentrated *in vacuo* to give a dark brown solid (1.54 g, 8.94 mmol, 99 %).

CAS registry number [100-87-8]

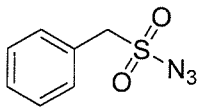
IR (cm^{-1}) 1212 (m), 1149 (m), 1084 (s), 1083 (s), 1037 (s), 1026 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.35-7.24 (5H, m, Ar C-H), 4.88 (2H, s, Ph-CH_2).

^{13}C-NMR ($CDCl_3$, δ ppm) 130.7 (Ar C-H), 129.5 (Ar C-H), 128.8 (Ar C), 128.7 (Ar C-H), 57.4 $PhCH_2$).

Spectroscopic data in agreement with literature.[237]

3.47 Phenylmethanesulfonyl azide



Method 1

To a stirred solution of commercially available α-Toluenesulfonyl chloride (60 mg, 315 μmol) in CH_2Cl_2 (2 mL) was added Bu_4NHSO_4 (214 mg, 230 μmol) and NaN_3 (102 mg, 1.6 mmol) and the resulting reaction monitored by TLC. After completion, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (3 x 10 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo* to give a white crystalline solid (59 mg, 0.30 mmol, 94 %).

Method 2

NaN_3 (102 mg, 1.6 mmol) was dissolved in the minimum amount of H_2O and the resulting solution added to a stirred solution of commercially available α-Toluenesulfonyl chloride (60 mg, 315 μmol) in DMF (2 mL). The resulting reaction mixture was monitored by TLC and after completion, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (3 x 10 mL), brine (3 x 10 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo* to give a white crystalline solid (57 mg, 0.29 mmol, 91 %).

Method 3

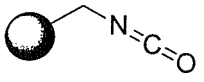
NaN_3 (102 mg, 1.6 mmol) was dissolved in the minimum amount of H_2O and the resulting solution added to a stirred solution of commercially available α-Toluenesulfonyl chloride (60 mg, 315 μmol) in CH_2Cl_2 (2 mL). The resulting reaction mixture was monitored by TLC and after completion, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (3 x 10 mL) and the organic layer dried ($MgSO_4$) and concentrated *in vacuo* to give a white crystalline solid (56 mg, 0.28 mmol, 89 %).

CAS registry number [20474-37-7]

IR (cm^{-1}) 3072 (w), 2985 (w), 2930 (w), 2132 (s, N_3), 1455 (w), 1406 (w), 1354 (s, SO_2), 1153 (s, SO_2), 1134 (s), 1073 (m), 884 (s), 788 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.54-7.42 (5H, m, Ar C-**H**), 4.55 (2H, s, $PhCH_2$).

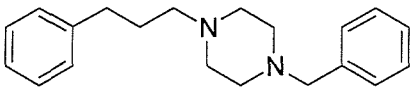
3.48 Poly (styryl-DVD)-methyl isocyanate



Aminomethyl resin **3.3** (1.5 g, 2.48 mmol, 1.65 mmol/g) was swollen in CH_2Cl_2 (15 mL) for 15 min under a nitrogen atmosphere. To the resin suspension was added Et_3N (1.16 mL, 8.3 mmol) and triphosgene (488 mg, 1.65 mmol) and the resulting mixture was shaken for 5 h. The resin was filtered off and washed with CH_2Cl_2, Et_2O, THF, Et_2O, THF, Et_2O (200 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3057 (w), 2922 (m), 2260 (s, N=C=O), 1493 (m), 1491 (m), 1346(w).

3.49 1-(Phenylmethyl)-4-(3-phenylpropyl)piperazine



Sulfonate resin **3.42** (120 mg, 152 μmol, based on theoretical loading of 1.27 mmol/g) was swollen in dry CH_3CN (1.5 mL) under a nitrogen atmosphere for 15 min. *N*-Benzyl piperazine (79 μL, 456 μmol) and iPr_2EtN (159 μL, 910 μmol) were added to the resin and the resulting mixture stirred gently for 16 h at 60 °C. The resin was filtered off and washed with CH_2Cl_2 (30 mL) and concentrated *in vacuo* to give a yellow oil. The crude material was dissolved in CH_2Cl_2 (3 mL) and isocyanate resin added (289 mg, 457 μmol, 1.58 mmol/g) which was the title compound with some impurity. Purification by flash chromatography, to determine an isolated yield, eluting

with CH_2Cl_2, CH_2Cl_2:EtOAc (9:1, 7:3, 1:1) and CH_2Cl_2:MeOH (95:5) afforded the title compound as a pale yellow oil (27 mg, 93 μmol, 61 %).

CAS registry number [76087-52-0]

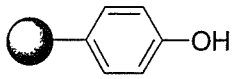
^{1}H-NMR ($CDCl_3$, δ ppm) 7.24-7.17 (8H, m, Ar C-**H**), 7.10 (2H, d, J = 6.5 Hz, Ar C-**H**), 3.44 (2H, s, PhC**H**$_2$N), 2.55 (2H, t, J = 7.8 Hz, PhC**H**$_2$CH$_2$), 2.49-2.34 (8H, m, piperazine C**H**$_2$ x 4), 2.30 (2H, t, J = 7.8 Hz, CH$_2$C**H**$_2$N), 1.74 (2H, quin, J = 7.7 Hz, CH$_2$C**H**$_2$CH$_2$).

^{13}C-NMR ($CDCl_3$, δ ppm) 142.2 (Ar **C**), 138.1 (Ar **C**), 129.2 (Ar **C**-H), 128.4 (Ar **C**-H), 128.3 (Ar **C**-H), 128.2 (Ar **C**-H), 127.0 (Ar **C**-H), 125.7 (Ar **C**-H), 63.1 (N**C**H$_2$Ph), 58.0 (**C**H$_2$N), 53.2 (piperazine **C**H$_2$ x 2), 53.1 (piperazine **C**H$_2$ x 2), 33.8 Ph**C**H$_2$CH$_2$), 28.6 (CH$_2$**C**H$_2$CH$_2$).

Mass Spec. (ES+) ***m/z*** **(relative intensity and ion)** 295.3 (100, $[M + H]^+$).

Spectroscopic data in agreement with literature.[238]

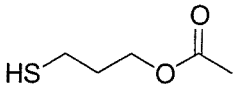
4.2 Poly (styryl-DVD)-phenol



To a suspension of polystyrene acetate resin (10g) in CH_2Cl_2 (89 mL) and MeOH (33 mL) was added TMSOK (7.13 g, 55.56 mmol) and the resulting mixture shaken overnight. The resin was filtered off and washed with CH_2Cl_2, MeOH, water, aqueous HCl (2 M), water, MeOH, CH_2Cl_2, (100 mL) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3320 (br, OH), 2924 (w), 1612 (m), 1511 (s), 1447 (m), 1365 (m), 1228 (s, C-O).

4.5 3-(Mercaptopropyl) acetate



To a solution of 3-chloropropanol (442 μL, 5.29 mmol) in DMF (5 mL) was added potassium thioacetate (763 mg, 5.29 mmol) and the resulting mixture warmed to 80 C and stirred overnight. After dilution with CH_2Cl_2 (20 mL) the organic layer was washed with water (4 x 10 mL), brine (4 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the brown oil. Purification by flash chromatography eluting with hexane:Et_2O (99:1, 98:2, 95:5) afforded the title compound as a pale brown oil (244 mg, 1.83 mmol, 35 %).

CAS registry number [26473-61-0]

IR (cm^{-1}) 2956 (w), 1733 (s, C=O), 1431 (w), 1386 (w), 1365 (m), 1231 (s, C-O), 1038 (m).

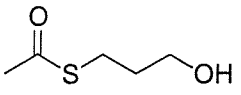
^{1}H-NMR ($CDCl_3$, δ ppm) 4.06 (2H, t, J = 6.3 Hz, CH_2OCO), 2.49 (2H, q, J = 7.4 Hz, CH_2SH), 1.94 (3H, s, CH_3), 1.83 (2H, quin, J = 6.6 Hz, $CH_2CH_2CH_2$), 1.33 (1H, t, J = 8.1 Hz, SH).

^{13}C-NMR ($CDCl_3$, δ ppm) 171.0 (C=O), 62.5 (CH_2-O), 32.8 ($SHCH_2CH_2$), 21.2 ($SHCH_2$), 21.0 (CH_3).

Mass Spec. (EI) ***m/z*** **(relative intensity and ion)** 134 (95, $[M]^{\bullet+}$), 117 (76), 73 (100).

Spectroscopic data in agreement with literature.[239]

4.6 *S*-(3-Hydroxypropyl) thioacetate



To a stirred suspension of potassium thioacetate (27.12 g, 237.3 mmol) in acetone (1350 mL) was added 3-bromopropanol (19.51 mL, 215.7 mmol) dropwise with stirring. The resulting mixture was stirred for 4.5 h and the mixture concentrated *in vacuo* in order to give a grey slurry. The mixture was partitioned between water (500

mL) and CH_2Cl_2 (300 mL) and the aqueous layer extracted further with CH_2Cl_2 (3 x 200 mL) and the combined organic layers concentrated *in vacuo* in order to give the title compound as a pale yellow oil (27.92 g, 208.4 mmol, 96 %).

CAS registry number [115051-66-6]

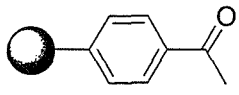
IR (cm^{-1}) 3390 (Br, OH), 2939 (w), 2877 (w), 1687 (s, C=O), 1424 (m), 1354 (m), 1131 (s), 1049 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 3.56 (2H, dd, J = 11.0, 5.9 Hz, CH_2OH), 3.04 (1H, br s, OH), 2.90 (2H, t, J = 7.0 Hz, CH_2-S), 2.27 (3H, s, CH_3), 1.74 (2H, quin, J = 6.8 Hz, $CH_2CH_2CH_2$).

^{13}C-NMR ($CDCl_3$, δ ppm) 197.3 (C=O), 60.5 (CH_2OH), 32.4 (CH_2CH_2OH), 30.7 (CH_3), 25.6 (S-CH_2).

Mass Spec. *m/z* (relative intensity and ion) 152 (25, $[M + NH_4]^+$), 135 (4, $[M + H]^+$), 74 (43), 60 (100, $[C_3H_6OH + H]^+$).

4.8 Poly (styryl-DVD)-acetyl resin



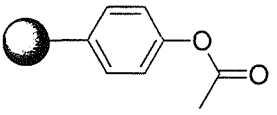
To a suspension of unfunctionalised polystyrene resin (10g, 1% DVB cross-linking) in carbon disulfide (97 mL) was added anhydrous $AlCl_3$ (10.36 g, 77.67 mmol) followed by dropwise addition of acetyl chloride (5.52 mL, 77.57 mmol) at 0 °C under a nitrogen atmosphere. The resulting mixture was warmed to reflux and stirred gently for 5.5 h. The resin was filtered off and washed with CH_2Cl_2, aqueous HCl (2M, CARE! Effervescence occurs due to residual $AlCl_3$ remaining), water, DMF, MeOH, CH_2Cl_2 (250 mL of each solvent) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 2924 (w), 1676 (s, C=O), 1604 (s), 1415 (m), 1386 (m), 1267 (s), 1183 (m).

^{1}H-NMR (MAS, δ ppm) 7.58 (broad s, Ar C-CO), 2.53 (broad s, $COCH_3$).

^{13}C-NMR (MAS, δ ppm) 198.2 (CO), 27.0 (CH_3).

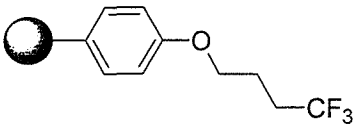
4.9 Poly (styryl-DVD)-acetate



To a suspension of acetylated polystyrene resin (10.59 g) in CH_2Cl_2 (100 mL) was added mCPBA (35 g of an approximate 77 % mixture, 156 mmol) and the resulting mixture was shaken at room temperature for 50 h. The resin was filtered off and washed with CH_2Cl_2, MeOH, water, MeOH, CH_2Cl_2 and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 2927 (w), 1753 (s, C=O), 1504 (m), 1367 (m), 1204 (s), 1166 (m), 1015 (m).
^{1}H-NMR (MAS, δ ppm) 2.13 (broad s, CH_3).
^{13}C-NMR (MAS, δ ppm) 169.7 (COO), 21.6 (CH_3).

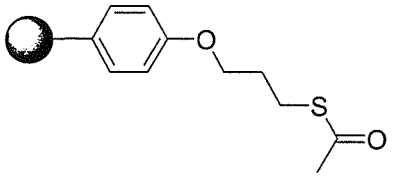
4.10 Poly (styryl-DVD)-4,4,4-trifluorobutyl ether



To a mixture of phenolic resin (150 mg, 0.3 mmol based on an estimated loading of 2 mmol/g) and PPh_3 (341 mg, 1.3 mmol) under a nitrogen atmosphere was added THF (1 mL) and after 15 min to allow swelling of the resin, 4,4,4-trifluorobutanol (154 mg, 1.2 mmol) added under a nitrogen atmosphere. DIAD (256 μL, 1.3 mmol) was added dropwise and the resulting mixture shaken overnight. The resin was filtered off and washed with CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and Et_2O and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 2922 (w), 1510 (m), 1385 (w), 1238 (s, R-O-R), 1149 (s, C-F), 1023 (s, R-O-R), 827 (m).
^{19}F-NMR (gel-phase, $CDCl_3$, δ ppm ref to $CFCl_3$) –66.7 (s).

4.11 Poly (styryl-DVD)-3-oxypropyl thioacetate



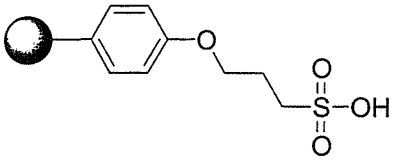
To a mixture of phenolic resin **4.2** (16 g, 34.4 mmol, 2.15 mmol/g) and PPh_3 (36.19 g, 138 mmol) under a nitrogen atmosphere was added THF (106 mL) and after 15 min to allow swelling of the resin, thioacetate **4.6** (18.47 g, 137.6 mmol) added under a nitrogen atmosphere. DIAD (27.17 mL, 138 mmol) was added dropwise and the resulting mixture shaken overnight. The resin was filtered off and washed with CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and Et_2O and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 2925 (w), 1686 (s, C=O), 1610 (m), 1509 (m), 1238 (s), 1177 (m), 1133 (m), 1109 (m), 1036 (m).

^{1}H-NMR (MAS, δ ppm) 3.91 (broad s, O-CH_2), 3.05 (broad s, CH_2-S), 2.32 (broad s, CH_3), 2.04 (broad s, $CH_2CH_2CH_2$)

^{13}C-NMR (MAS, δ ppm) 195.7 (C=O), 157.0 (Ar C-O), 69.9 (O-CH_2), 30.9 ($CH_2CH_2CH_2$), 29.7 (CH2-S), 26.2 (CH_3).

4.12 Poly (styryl-DVD)-3-oxypropanesulfonic acid



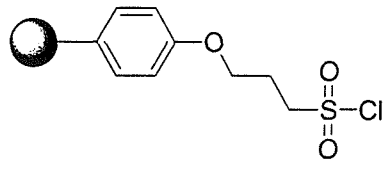
Formic acid (230.4 mL) and hydrogen peroxide (23 mL, 27 % aqueous solution) were premixed and stirred gently for 15 min. Meanwhile, thioacetate resin **4.11** (18 g, 30.6 mmol, based on the theoretical loading of 1.72 mmol/g) was swollen in CH_2Cl_2 (11 mL) for 15 min after which the pre-formed performic acid solution was added carefully in three portions and the resulting mixture shaken for 5 h. The resin was

filtered off and washed with CH_2Cl_2, DMF, DMF:water (1:1), water, DMF:water (1:1), DMF, CH_2Cl_2, Et_2O and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 2927 (w), 1708 (w), 1608 (w), 1509 (m), 1238 (s), 1175 (m), 1107 (m), 1027 (s).

Elemental analysis Calculated: S = 5.4 % (calculated from the theoretical loading based on the 100 % yield of all subsequent reactions from phenol resin **4.2**, having a loading of 2.15 mmol/g). Found: S = 2.84 % (determines that loading is 0.89 mmol/g).

4.13 Poly (styryl-DVD)-3-oxypropanesulfonyl chloride



Method 1 (sulfuryl chloride/triphenyl phosphine)

Sulfonic acid resin **4.12** (300 mg, 0.27 mmol, 0.89 mmol/g) was swollen in dry CH_2Cl_2 (2 mL) for 10 min under a nitrogen atmosphere. Meanwhile, a solution of PPh_3 (339 mg, 1.34 mmol) in CH_2Cl_2 (1 mL) was stirred under a nitrogen atmosphere at 0 °C and SO_2Cl_2 (177 µL, 1.34 mmol) added dropwise. The resulting mixture was transferred to the resin suspension dropwise and the resulting mixture shaken for 16 h. The resin was filtered off and washed with DMF, CH_2Cl_2, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C).

Method 2 (thionyl chloride)

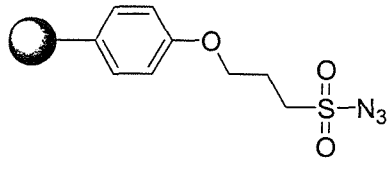
Sulfonic acid resin **4.12** (300 mg, 0.27 mmol, 0.89 mmol/g) was swollen in dry chloroform (3 mL) and DMF (0.3 mL) for 10 min under a nitrogen atmosphere. $SOCl_2$ (1.5 mL) was added dropwise to the resin and the resulting mixture warmed to reflux and gently stirred for 16 h. The resin was filtered off and washed with CH_2Cl_2, MeOH, CH_2Cl_2, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C).

Method 3 (triphosgene)

Sulfonic acid resin **4.12** (300 mg, 0.27 mmol, 0.89 mmol/g) was swollen in dry CH_2Cl_2 (2 mL) and dry DMF (0.4 mL) for 10 min under a nitrogen atmosphere. Triphosgene (160 mg, 0.54 μmol) was added very carefully in small portions to the resin suspension and the mixture shaken overnight. The resin was filtered off (the filtrate dropped into an ammonia solution to destroy remaining phosgene) and washed with CH_2Cl_2, DMF, CH_2Cl_2, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 2927 (w), 1608 (m), 1509 (s), 1370 (s, SO_2Cl), 1239 (s), 1161 (s, SO_2Cl), 1107 (m), 1035 (m).

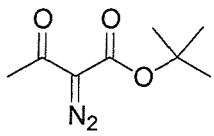
4.14 Poly (styryl-DVD)-3-oxypropanesulfonyl azide



Sulfonyl chloride resin **4.13** (5 g, 4.4 mmol, 0.88 mmol/g) was swollen in CH_2Cl_2 (50 mL) for 10 min. Sodium azide (2.86 g, 44 mmol) and Bu_4NHSO_4 (12 mg, 35 μmol) were added to the resin suspension and the resulting mixture was shaken for 16 h. The resin was filtered off and washed with CH_2Cl_2, DMF, H_2O, DMF, H_2O, DMF, CH_2Cl_2, Et_2O (200 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 2930 (w), 2138 (s, N_3), 1609 (m), 1509 (m), 1354 (m, SO_2), 1239 (s), 1176 (s), 1153 s), 1041 (s).

4.16 *tert*-Butyl 2-diazo-3-oxobutanoate

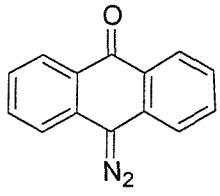


Sulfonyl azide resin **4.14** (306 mg, 279 μmol, 0.91 mmol/g) was swollen in CH_3CN (1 mL) for 10 min. To the resin suspension was added *i*Pr_2EtN (139 μL, 0.76 mmol) and *t*-butylacetoacetate (32 mg, 199 μmol) and the resulting mixture shaken for 16 h. The resin was filtered off and washed CH_2Cl_2 (80 mL) and the combined filtrates concentrated *in vacuo* to give a crude yellow oil. The crude mixture was dissolved in CH_2Cl_2 (3 mL) and the mixture passed through a silica plug, which afforded the title compound as a yellow oil (32 mg, 0.17 mmol, 87 %).

CAS registry number [13298-76-5]
IR (cm^{-1}) 2978 (w), 2965 (w), 2935 (w), 2135 (s, C=N_2), 1715 (s), 1660 (s), 1369 (m), 1324 (s), 1261 (s), 1148 (m), 1069 (s), 1019 (m).
^{1}H-NMR ($CDCl_3$, δ ppm) 2.45 (2H, s, CH_3CO), 1.53 (9H, s, $C(CH_3)$).
^{13}C-NMR ($CDCl_3$, δ ppm) 190.8 (**C**=O), 160.8 (**C**OO), 83.3 (O-**C**), 28.4 ($C(CH_3)_3$), 20.7 (CH_3CO). No C=N observed.
Mass Spec. *m/z* **(relative intensity and ion)** No ionisation possible.

Spectroscopic data in agreement with literature.[58]

4.18 10-Diazoanthracen-9-one



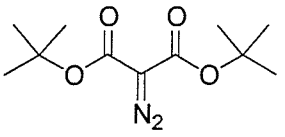
Sulfonyl azide resin **4.14** (373 mg, 340 μmol, 0.91 mmol/g) was swollen in CH_3CN (1 mL) for 10 min. To the resin suspension was added *i*Pr_2EtN (169 μL, 0.97 mmol) and

Anthrone (48 mg, 301 μmol). CH_2Cl_2 (0.5 mL) was added to the mixture to aid the solubilisation of Anthrone in the reaction mixture and the resulting mixture shaken for 16 h. The resin was filtered off and washed CH_2Cl_2 (80 mL) and the combined filtrates concentrated *in vacuo* to give a crude orange slurry. Purification by flash chromatography eluting with Et_2O:hexane (1:99, 2:98, 5:95, 1:9) afforded the title compound as an orange solid (55 mg, 250 μmol, 83 %).

CAS registry number [1705-82-4]
IR (cm^{-1}) 2051 (s, CN_2), 1633 (s), 1590 (s), 1480 (s), 1295 (s), 1267 (m), 1163 (m).
^{1}H-NMR ($CDCl_3$, δ ppm) 8.55 (2H, d, J = 8.8 Hz, Ar C-**H**), 7.71 (2H, m , Ar C-**H**), 7.42 (2H, t, J = 7.0 Hz, Ar C-**H**), 7.33 (2H, t J = 8.1 Hz, Ar C-**H**).
^{13}C-NMR ($CDCl_3$, δ ppm) 180.2 (**C**=O), 133.1 (Ar **C**-H), 129.9 (**C**CO), 129.1 (Ar **C**-H), 128.5 (**C**CN_2), 125.4 (Ar **C**-H), 120.8 (Ar **C**-H). No C=N observed.
Mass Spec. (EI) ***m/z*** **(relative intensity and ion)** 220 (12, $[M]^{\bullet+}$), 192 (78, $[M - N_2]^{\bullet+}$), 164 (100, $[M - (CN_2 + O)]^{\bullet+}$).

Spectroscopic data in agreement with literature.[58]

4.20 2-Diazomalonic acid di-*tert*-butyl ester



Sulfonyl azide resin **4.14** (218 mg, 198 μmol, 0.91 mmol/g) was swollen in CH_3CN (1 mL) for 10 min. To the resin suspension was added DBU (85 μL, 0.57 mmol) and di-*t*-butyl malonate (31 mg, 143 μmol) and the resulting mixture shaken for 16 h. The resin was filtered off and washed CH_2Cl_2 (80 mL) and the combined filtrates concentrated *in vacuo* to give a crude yellow oil. Purification by flash chromatography eluting with Et_2O:hexane (1:99, 2:98, 5:95, 1:9) afforded the title compound as a yellow oil (17 mg, 715 μmol, 50 %).

CAS registry number [35207-75-1]

IR (cm^{-1}) 2979 (m), 2935 (w), 2130 (s, C=N_2), 1747 (s), 1728 (s), 1682 (m), 1368 (m), 1327 (s), 1165 (s), 1095 (s), 1073 (s).

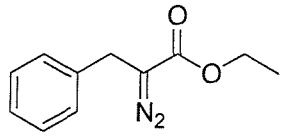
^{1}H-NMR ($CDCl_3$, δ ppm) 1.51 (18 H, s, C(CH_3)$_3$ x 2).

^{13}C-NMR ($CDCl_3$, δ ppm) 82.9 (**C**-O x 2), 28.4 (C(**C**H_3)$_3$ x 2). No C=N observed.

Mass Spec. (ES+) ***m/z*** **(relative intensity and ion)** 749.4 (8, $[3M + Na]^+$), 507.4 (100, $[2M + Na]^+$).

Spectroscopic data in agreement with literature.[240]

4.22 2-Diazo-3-phenylpropionic acid ethyl ester



Sulfonyl azide resin **4.14** (186 mg, 170 μmol, 0.91 mmol/g) was swollen in CH_3CN (1 mL) for 10 min. To the resin suspension was added *i*Pr_2EtN (86 μL, 0.49 mmol) and acetoacetate **4.21** (27 mg, 121. μmol) and the resulting mixture shaken for 16 h. The resin was filtered off and washed CH_2Cl_2 (80 mL) and the combined filtrates concentrated *in vacuo* to give a crude yellow oil. The crude mixture was dissolved in CH_2Cl_2 (3 mL) and the mixture passed through a silica plug, which afforded the title compound as a yellow oil (2 mg, 5 μmol, 4 %).

CAS registry number [15626-54-7]

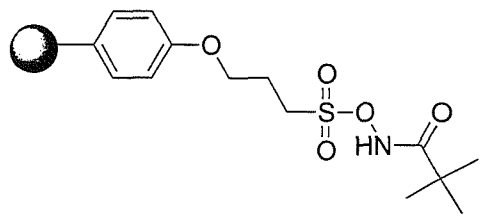
IR (cm^{-1}) 2970 (w), 2930 (w), 2083 (s, C=N_2), 1738 (s), 1691 (s), 1370 (s), 1228 (m), 1216 (m), 1204 (m), 1105 (w).

^{1}H-NMR ($CDCl_3$, δ ppm) 7.39-7.24 (5H, m, Ar C-**H**), 4.25 (2H, q, J = 7.2 Hz, O-CH_2), 3.64 (2H, s, Ph CH_2), 1.29 (3H, t, J = 7.0 Hz, CH_3).

^{13}C-NMR ($CDCl_3$, δ ppm) 167.3 (**C**=O), 137.3 (Ar **C**), 128.8 (Ar **C**-H), 128.4 (Ar **C**-H), 127.1 (Ar **C**-H), 60.9 (O-CH_2), 29.4 (PhCH_2), 14.5 (CH_3). No C=N observed.

Spectroscopic data in agreement with literature.[241]

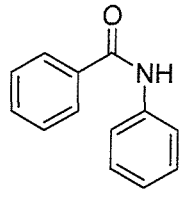
4.27 Poly (styryl-DVD)-3-oxypropane-*O*-sulfonyl-*N*-Boc-hydroxylamine



Sulfonyl chloride resin (300mg, 264 μmol, 0.88 mmol/g) was swollen in CH_2Cl_2 (3 mL) for 15 min. *N*-Boc-hydroxylamine (346 mg, 2.6 mmol) and pyridine (210 μL, 2.6 mmol) were added to the resin suspension and the resulting mixture shaken for 16 h. The resin was filtered off and washed with CH_2Cl_2, DMF, water, DMF, CH_2Cl_2, Et_2O (80 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 2979 (w), 2931 (w), 1738 (m), 1610 (m), 1509 (m), 1370 (m, SO_2O), 1242 (s), 1153 (s, SO_2O), 1032 (s).

4.26 *N*-Phenylbenzamide



Method 1

Commercially available sulfonyl chloride resin (1.18 g, 3.03mmol, 2.56 mmol/g) was swollen in dry CH_2Cl_2:pyridine (1:1, 10 mL) for 15 min. Benzophenone oxime (200 mg, 1.01 mmol) was added and the resulting mixture shaken overnight. The resin was filtered off and washed with CH_2Cl_2 (50 mL) and the combined organic layers were concentrated to give a dark yellow slurry. Purification by flash chromatography eluting with CH_2Cl_2 and CH_2Cl_2:EtOAc (8:2) afforded the title compound as a pale yellow solid (194 mg, 0.98 mmol, 97 %).

Method 2

Commercially available sulfonyl chloride resin (297 mg, 2.56 mmol/g) was swollen in CH_2Cl_2 (3 mL) for 15 min. Benzophenone oxime (100 mg, 0.51 mmol) and Et_3N (106 μL, 0.76 mmol) were subsequently added and the resulting mixture shaken overnight. The resin was filtered off and washed with CH_2Cl_2 (50 mL) and the combined organic layers were combined and washed with water (4 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound as a pale yellow solid (81 mg, 0.42 mmol, 81 %).

Method 3

N-Boc-*O*-sulfonyl hydroxylamine resin **4.27** (146 mg, 123 μmol, 0.84 mmol/g) was swollen in CH_2Cl_2 (0.8 mL) for 10 min, after which TFA (0.2 mL) and benzophenone (16 mg, 88 μmol) and the resulting mixture shaken for 16 h. after analysis of the reaction mixture by GC against authentic samples of starting material and title product, conversion to the title compound of 10 % was determined.

CAS registry number [93-98-1]

IR (cm^{-1}) 3342 (w), 1654 (s, C=O), 1598 (m), 1528 (s), 1438 (m), 1324 (m), 1261 (m).

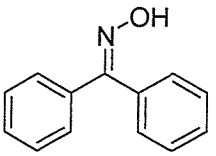
^{1}H-NMR ($CDCl_3$, δ ppm) 7.90-7.87 (2H, m, Ar C-**H**), 7.66 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.54-7.47 (3H, m, Ar C-**H**), 7.37 (2H, t, J = 7.0 Hz, Ar C-**H**), 7.17 (1H, t, J = 7.4 Hz, Ar C-**H**).

^{13}C-NMR ($CDCl_3$, δ ppm) 137.9 (Ar **C**), 135.1 (Ar **C**), 132.0 (Ar **C**-H), 129.3 (Ar **C**-H), 129.0 (Ar **C**-H), 127.2 (Ar **C**-H), 124.7 (Ar **C**-H), 120.3 (Ar **C**-H).

Mass Spec. ***m/z*** **(relative intensity and ion)** 198, (100, $[M + H]^+$), 105 (35, $[C_6H_5CO]^+$), 77 (10, $[C_6H_5]^+$).

Spectroscopic data in agreement with literature.[242]

5.3 Benzophenone oxime



To a stirred solution of benzophenone (2.5 g, 13.7 mmol) in ethanol (5 mL) and water (1 mL), hydroxylamine hydrochloride (1.5 g, 22.6 mmol) was added followed by NaOH pellets (2.8 g, 70 mmol), which were added in portions with shaking (cooling the flask with water if the reaction becomes too vigorous). After complete addition of NaOH, the mixture was heated and stirred at reflux for 5 min. The mixture was allowed to cool and poured over a mixture of conc. HCl (7.5 mL) in water (50 mL). The resulting precipitate was filtered off, washed thoroughly with cold water and dried in a vacuum oven (40 C) to afford the title compound as a white solid (2.60 g, 13.2 mmol, 96 %).

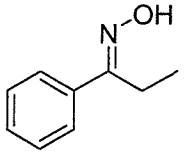
CAS registry number [574-66-3]

IR (cm^{-1}) 3209 (br), 3057 (w), 3022 (w), 2887 (w), 1492 (w), 1444 (m), 1329 (m), 1160 (w), 993 (s), 919 (s).

^{1}H-NMR ($CDCl_3$, δ ppm) 8.71 (1H, s, =N-**OH**), 7.50-7.32 (10H, m, $(C_6\mathbf{H}_5)_2C$).

^{13}C-NMR ($CDCl_3$, δ ppm) 158.1 (**C**=N), 136.2 (**C**-C=N), 132.6 (**C**-C=N), 129.5 (Ar **C**-H), 129.2 (Ar **C**-H), 129.1 (Ar **C**-H), 128.3 (Ar **C**-H), 128.2 (Ar **C**-H), 127.9 (Ar **C**-H).

5.4 Propiophenone oxime



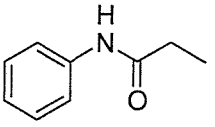
To a stirred solution of propiophenone (665 μL, 5 mmol) in ethanol (5 mL) and water (0.6 mL) was added sodium acetate (738 mg, 9 mmol) and hydroxylamine hydrochloride (521 mg, 7.5 mmol) under a nitrogen atmosphere. The resulting mixture

was heated to reflux and stirred for 5 h and after cooling was stirred overnight. The reaction mixture was concentrated *in vacuo* and the residue partitioned between EtOAc (30 mL) and water (15 mL). The organic layer was washed with brine (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound as a white solid (647 mg, 4.35 mmol, 87 %).

CAS registry number [2157-50-8]
IR (cm^{-1}) 3197 (br), 2973 (w), 2941 (w), 1465 (m), 1454 (m), 1440 (m), 1335 (m), 1291 (m), 970 (s), 912 (s).
^{1}H-NMR ($CDCl_3$, δ ppm) 9.57 (1H, br s, O**H**), 7.66-7.63 (2H, m, Ar C-**H**), 7.43-7.39 (3H, m, Ar C-**H**), 2.87 (2H, q, J = 7.8 Hz, COC**H**$_2$), 1.21 (3H, t, J = 7.7 Hz, C**H**$_3$).
^{13}C-NMR ($CDCl_3$, δ ppm) 160.9 (**C**=N), 135.7 (**C**C=N), 129.4 (Ar **C**-H), 128.8 (Ar **C**-H), 126.4 (Ar **C**-H), 19.9 (**C**H$_2$), 11.1 (**C**H$_3$).
Mass Spec. *m/z* **(relative intensity and ion)** 150 (6, $[M + H]^+$), 134 (100, $[M + H (-O)]^+$).

Spectroscopic data in agreement with literature.[243]

5.5 *N*-Phenyl propanamide



Commercially available sulfonyl chloride resin (447 mg, 1.5-2 mmol/g from Aldrich) was swollen in CH_2Cl_2 (2.2 mL) and pyridine (2.2 mL) for 10 min under nitrogen. Propiophenone oxime (50 mg, 0.36 mmol) was added and the mixture placed in the Smith synthesiser and treated with microwave radiation, heating to 120 °C for 10 min. The resin was filtered off and washed with CH_2Cl_2 (80 mL) and the filtrate concentrated *in vacuo* to give a brown crude slurry. Purification by flash chromatography eluting with CH_2Cl_2 and CH_2Cl_2:EtOAc (95:5) gave the title compound as a cream solid (21 mg, 0.15 mmol, 42 %).

CAS registry number [670-71-5]

IR (cm^{-1}) 3254 (m), 3195 (m), 3136 (m), 3082 (w), 2976 (m), 1664 (s), 1600 (s), 1545 (s), 1496 (s), 1440 (s), 1370 (m), 1299 (s), 1244 (m), 1203 (m).

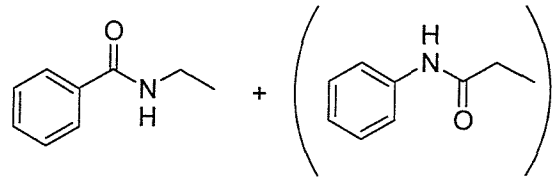
^{1}H-NMR ($CDCl_3$, δ ppm) 7.53 (2H, d, J = 7.4 Hz, Ar C-**H**), 7.45 (1H, broad s, N-**H**), 7.30 (2H, t, J = 7.7 Hz, Ar C-**H**), 7.10 (1H, t, J = 7.4 Hz, Ar C-**H**), 2.40 (2H, q, J = 7.6 Hz, CH_2CO), 1.25 (3H, t, J = 7.7 Hz, CH_3CH_2).

^{13}C-NMR ($CDCl_3$, δ ppm) 172.3 (**C**=O), 138.2 (Ar **C**), 129.1 (Ar **C**-H), 124.3 (Ar **C**-H), 120.0 (Ar **C**-H), 30.9 (CH_2CO), 9.9 (CH_2CH_3).

Mass Spec. (ES+) *m/z* **(relative intensity and ion)** 150 (5, $[M + H]^+$).

Spectroscopic data in agreement with literature.[244]

5.6 *N*-Ethyl benzamide (+ 5.5 *N*-phenyl propanamide)



Sulfonyl chloride resin (447 mg, 1.5-2 mmol/g from Aldrich) was swollen in CH_2Cl_2 (4.6 mL) for 10 min after which pyridine (81.7 μL, 1.01 mmol), propiophenone oxime (50 mg, 0.36 mmol) and water (18.2 μL, 1.01 mmol) added. The mixture was placed in the smith synthesiser and treated with microwave radiation, heating to 120 °C over 1 minute and reacted for 20 min. The resin was filtered off and washed with CH_2Cl_2 (80 mL) and concentrated *in vacuo* to give a brown crude slurry. Purification by flash chromatography eluting with CH_2Cl_2 and CH_2Cl_2:EtOAc (95:5) afforded compound *N*-phenyl propanamide as a cream solid (20 mg, 0.14 mmol, 40 %) and afforded the title compound *N*-ethyl benzamide (**5.6**) as a white solid (2.5 mg, 17 μmol, 5 %).

CAS registry number [614-17-5]

^{1}H-NMR ($CDCl_3$, δ ppm) 7.79-7.76 (2H, m, Ar C-**H**), 7.53-7.41 (3H, m, Ar C-**H**), 6.10 (1H, broad s, N-**H**), 3.57-3.48 (2H, m, $NHCH_2$), 1.28 (3H, t, J = 7.0 Hz, CH_2CH_3).

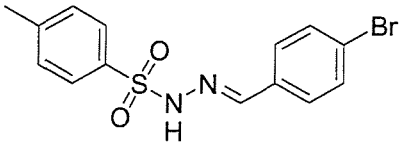
^{13}C-NMR ($CDCl_3$, δ ppm) 167.8 (**C**=O), 135.3 (Ar **C**), 131.7 (Ar **C**-H), 128.9 (Ar **C**-H), 127.2(Ar **C**-H), 35.3 ($NH\mathbf{C}H_2$), 15.3 ($CH_2\mathbf{C}H_3$).

Mass Spec. (ES+) *m/z* **(relative intensity and ion)** 150 (3, $[M + H]^+$).

Spectroscopic data in agreement with literature.[245]

(5.5 *N*-phenyl propanamide) Spectroscopic data as above.

5.20 *N*-1-[-1-(4-Bromophenyl) methylidene]-4-methyl-1-benzenesulfonyl hydrazone



To a stirred solution of bromobenzaldehyde (500 mg, 2.70 mmol) in dry THF (12 mL) under a nitrogen atmosphere was added *p*-toluenesulfonyl hydrazide (503 mg, 2.70 mmol) and the resulting mixture stirred at room temperature for 48 h. The mixture was the concentrated *in vacuo* and the resulting residue purified by recrystallisation (THF/hexane) in order to afford the title compound as a white solid (754 mg, 2.16 mmol, 80 %).

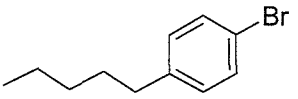
IR (cm^{-1}) 3181 (m, N-H), 2916 (w), 1595 (m, N=C), 1467 (m), 1330 (s, SO_2N), 1164 (s, SO_2N), 1066 (s), 958 (m), 807 (s).

^{1}H-NMR (d_6-DMSO, δ ppm) 11.57 (1H, br s, N**H**), 7.89 (1H, s, N=C**H**), 7.76 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.59 (2H, d, J = 8.8 Hz, Ar C-**H**), 7.50 (2H, d, J = 8.1 Hz, Ar C-**H**), 7.40 (2H, d, J = 8.1 Hz, Ar C-**H**), 2.35 (3H, s, $C\mathbf{H}_3$).

^{13}C-NMR (d_6-DMSO, δ ppm) 145.8 (**C**H=N), 143.6 (**C**-CH_3), 136.1 (**C**-SO_2), 133.0 (**C**-C=N), 131.9 (Ar **C**-H), 129.8 (Ar **C**-H), 128.7 (Ar **C**-H), 127.3 (Ar **C**-H), 123.4 (**C**-Br), 21.1 ($\mathbf{C}H_3$).

Spectroscopic data in accordance with literature.[208]

5.21 1-(4-Bromophenyl)pentane



Method 1

Tosyl hydrazone **5.20** (200 mg, 566 μmol) was dissolved in dry THF (4 mL) under a nitrogen atmosphere. Tributyl borane (570 μL of a 1 M solution in THF, 570 μmol) was added dropwise followed by Bu_4NOH (570 μL of a 1 M solution in MeOH, 570 μmol) and the resulting mixture warmed gently to reflux. After 2.5 h, water (2.5 mL) was added and the mixture allowed to cool to room temperature and extracted with Et_2O (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography eluting with CH_2Cl_2 afforded the title compound as a colourless oil (65 mg, 289 μmol, 51 %).

Method 2

To a suspension of sulfonyl hydrazide resin **5.22** (150 mg, 264 μmol, 1.76 mmol/g) swollen in THF (1.5 mL) was added 4-bromobenzaldehyde (488 mg, 2.64 mmol) and the resulting mixture shaken for 60 h. The resin was filtered off and washed with THF, CH_2Cl_2, THF, CH_2Cl_2, Et_2O (50 mL of each) and dried in a vacuum oven (40 °C). The resin was swollen in THF (0.5 mL) under a nitrogen atmosphere and tributyl borane (1.32 mL of a 1 M solution in THF, 1.32 mmol) was added dropwise followed by Bu_4NOH (790 μL of a 1 M solution in MeOH, 0.79 mmol) and the resulting mixture warmed to reflux and stirred gently for 16 h. The resin was filtered off and washed with CH_2Cl_2 (50 mL) and the combined filtrate concentrated *in vacuo* and purification by flash chromatography eluting with CH_2Cl_2 afforded the title compound as a colourless oil (8 mg, 34 μmol, 13 %).

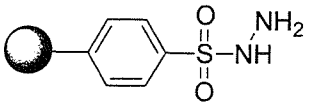
^{1}H-NMR ($CDCl_3$, δ ppm) 7.35 (2H, dt, J = 8.8, 2.2 Hz, Ar C-**H**), 7.07 (2H, d, J = 8.1 Hz, Ar C-**H**), 2.57 (2H, t, J = 7.7 Hz, Ph-C**H**$_2$), 1.66-1.56 (2H, m, Ph-CH$_2$C**H**$_2$), 1.37-1.28 (4H, m, C**H**$_2$), 0.91 (3H, t, J = 6.6 Hz, C**H**$_3$).

^{13}C-NMR ($CDCl_3$, δ ppm) 142.0 (Ar **C**-CH$_2$), 131.4 (Ar **C**-H), 130.3 (Ar **C**-H), 119.4 (**C**-Br), 35.5 (Ph-**C**H$_2$), 31.5 (**C**H$_2$), 31.2 (**C**H$_2$), 22.7 (**C**H$_2$CH$_3$), 14.2 (CH$_2$**C**H$_3$).

Mass Spec. (EI) *m/z* **(relative intensity and ion)** 228 (19, $[M]^{\bullet+}$, ^{81}Br isotope), 226 (21, $[M]^{\bullet+}$, ^{79}Br isotope), 171 (49, $[M - (CH_2)_3CH_3]^{\bullet+}$, ^{81}Br isotope), 169 (48, $[M - (CH_2)_3CH_3]^{\bullet+}$, ^{79}Br isotope), 57 (56 $[(CH_2)_3CH_3]^{\bullet+}$), 28 (100, $[CH_2CH_2]^{\bullet+}$).

Spectroscopic data in agreement with literature.[246]

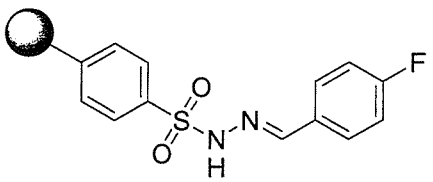
5.22 Poly (styryl-DVB) – sulfonyl hydrazide



Commercial sulfonyl chloride resin (800 mg, 1.4 mmol, 1.5 –2 mmol/g) was swollen in THF (7 mL) for 15 min. Hydrazine monohydrate (679 μL, 14 mmol) was added to the resin and the resulting mixture was shaken for 24 h. The resin was filtered off and washed with THF, CH_2Cl_2, DMF, DMF:H_2O (1:1), H_2O, DMF:H_2O, DMF, CH_2Cl_2, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C).

IR (cm^{-1}) 3349 (w, N-H), 2920 (w), 2857 (w), 1596 (m, N-H), 1492 (m), 1450 (m), 1411 (m), 1322 (s, SO_2N), 1156 (s, SO_2N), 1093 (m), 1008 (m), 950 (m).

5.23 Poly (styryl-DVB) – sulfonyl (4-fluorobenzyl) hydrazone



Sulfonyl hydrazide resin **5.22** (500 mg, 0.88 mmol) was swollen in dry THF (4 mL) for 15 min after which 4-fluorobenzaldehyde (944 μL, 8.8 mmol) and the resulting mixture shaken for 60 h. The resin was filtered off and washed with THF, CH_2Cl_2, THF, CH_2Cl_2, Et_2O (100 mL of each) and dried in a vacuum oven (40 °C) to give a pale yellow resin (633 mg).

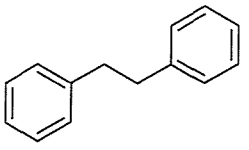
IR (cm^{-1}) 3191 (w), 2923 (w), 2850 (w), 1600 (m, C=N), 1510 (m, N-H), 1322 (m, SO_2N), 1230 (s), 1154 (s, SO_2N), 1054 (m), 935 (m), 832 (m).

^{1}H-NMR (MAS, δ ppm) 7.49 (broad s, C**H**=N)

^{13}C-NMR (MAS, δ ppm) 145.3 (**C**H=N).

^{19}F-NMR (gel-phase, $CDCl_3$, δ ppm ref to $CFCl_3$) -109.28 (br s).

5.27 1,2-Diphenylethane



Sulfonyl hydrazide resin **5.22** (630 mg, 1.11 mmol, based on a theoretical loading of 1.75 mmol/g) was swollen in dry DMF (5 mL) for 15 min under a nitrogen atmosphere. To the resin was added *trans*-stilbene (40 mg, 222 μmol) and the mixture stirred gently and warmed to 100 °C for 18 h. The resin was filtered off and washed with CH_2Cl_2 (40 mL) and the combined filtrates concentrated *in vacuo* to give a white crystalline solid crude (78 mg). Resolvation in CH_2Cl_2 showed a precipitate that was filtered off through glass wool and the filtrate concentrated *in vacuo* to give a white crystalline solid (43 mg). Purification by flash chromatography eluting with hexane, CH_2Cl_2 afforded the title compound as a white solid (28 mg, 155 μmol, 70 %)

CAS registry number [103-29-7]

^{1}H-NMR ($CDCl_3$, δ ppm) 7.23-7.11 (10 H, m, Ph x 2), 2.85 (4H, s, CH_2 x 2).

^{13}C-NMR ($CDCl_3$, δ ppm) 140.8 (Ar **C** x 2), 127.4 (Ar **C**-H x 2), 127.3 (Ar **C**-H x 2), 124.9 (Ar **C**-H x 2), 36.9 (**C**H_2 x 2).

Mass Spec. (EI) *m/z* (relative intensity and ion) 182 (3, $[M]^{\bullet+}$), 91 (14, $[M - PhCH_2]^{\bullet+}$), 28 (100).

Spectroscopic data in agreement with literature.[247]

Experimental appendix

Crytallographic data for Neopentyl (*E*)-2(4-formylphenyl)-1-ethene-1-sulfonate (2.14)

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{14}H_{18}O_4S$
Formula weight	282.34
Temperature	150(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	$a = 8.441(5)$ Å
	$b = 10.408(5)$ Å $\quad \beta = 96.724(5)°$
	$c = 16.976(5)$ Å
Volume	1481.1(12) Å^3
Z	4
Density (calculated)	1.266 Mg / m^3
Absorption coefficient	0.225 mm^{-1}
F(000)	600
Crystal	Block
Crystal size	0.35 × 0.35 × 0.35 mm^3
θ range for data collection	3.11 – 23.25°
Index ranges	$-9 \le h \le 9, -10 \le k \le 11, -18 \le l \le 18$
Reflections collected	7287
Independent reflections	2111 [$R_{int} = 0.0494$]
Completeness to $\theta = 23.25°$	99.5 %
Max. and min. transmission	0.9253 and 0.9253
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2111 / 0 / 245
Goodness-of-fit on F^2	1.053
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0373$, $wR2 = 0.1021$
R indices (all data)	$R1 = 0.0473$, $wR2 = 0.1096$
Extinction coefficient	0.009(4)
Largest diff. peak and hole	0.191 and –0.367 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were located from the difference map and fully refined.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	671(1)	5562(1)	−1344(1)	36(1)	1
C1	3164(3)	−1715(2)	393(2)	48(1)	1
C2	2761(2)	−473(2)	−3(1)	38(1)	1
C3	1937(3)	459(2)	373(1)	47(1)	1
C4	1578(3)	1622(2)	20(1)	44(1)	1
C5	2045(2)	1896(2)	−727(1)	32(1)	1
C6	2870(3)	960(2)	−1096(1)	39(1)	1
C7	3226(3)	−211(2)	−741(1)	41(1)	1
C8	1687(2)	3127(2)	−1124(1)	34(1)	1
C9	947(3)	4104(2)	−850(1)	39(1)	1
C10	−2225(2)	4967(2)	−1924(1)	40(1)	1
C11	−3949(2)	5347(2)	−1855(1)	38(1)	1
C12	−4954(3)	4383(3)	−2383(2)	50(1)	1
C13	−4269(3)	6705(3)	−2153(2)	57(1)	1
C14	−4309(3)	5229(3)	−1002(1)	46(1)	1
O1	2781(2)	−2016(2)	1029(1)	68(1)	1
O2	1131(2)	5432(2)	−2119(1)	44(1)	1
O3	1345(2)	6558(2)	−833(1)	49(1)	1
O4	−1167(2)	5799(1)	−1390(1)	37(1)	1

Table 3. Bond lengths [Å] and angles [°].

O2–S1	1.4214(15)	C5–C8	1.463(3)
O3–S1	1.4270(16)	C6–C7	1.377(3)
O4–S1	1.5638(17)	C8–C9	1.308(3)
C1–O1	1.204(3)	C9–S1	1.737(2)
C1–C2	1.478(3)	C10–O4	1.477(3)
C2–C7	1.384(3)	C10–C11	1.526(3)
C2–C3	1.391(3)	C11–C13	1.515(3)
C3–C4	1.369(3)	C11–C14	1.520(3)
C4–C5	1.401(3)	C11–C12	1.533(3)
C5–C6	1.388(3)		

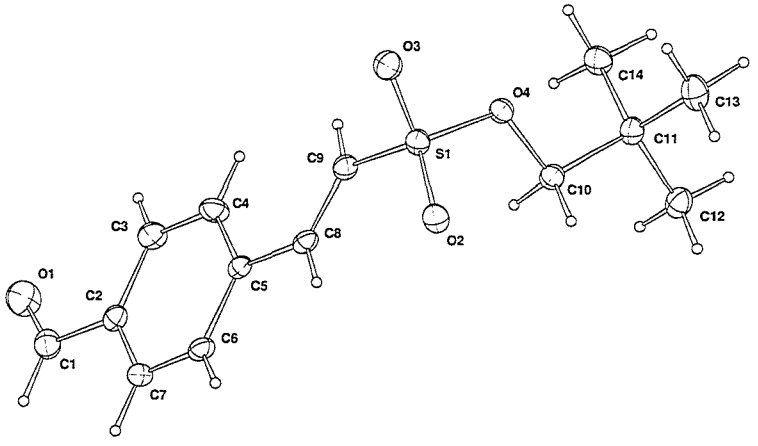
O2–S1–O3	119.97(10)	C4–C5–C8	122.04(18)
O2–S1–O4	110.25(8)	C7–C6–C5	121.2(2)
O3–S1–O4	103.77(9)	C6–C7–C2	120.0(2)
O2–S1–C9	109.17(10)	C9–C8–C5	126.8(2)
O3–S1–C9	108.63(10)	C8–C9–S1	123.39(18)
O4–S1–C9	103.78(9)	O4–C10–C11	108.29(17)
O1–C1–C2	124.3(2)	C13–C11–C14	110.2(2)
C7–C2–C3	119.2(2)	C13–C11–C10	110.53(19)
C7–C2–C1	120.6(2)	C14–C11–C10	110.60(17)
C3–C2–C1	120.2(2)	C13–C11–C12	110.5(2)
C4–C3–C2	120.8(2)	C14–C11–C12	110.24(19)
C3–C4–C5	120.3(2)	C10–C11–C12	104.63(19)
C6–C5–C4	118.4(2)	C10–O4–S1	117.55(12)
C6–C5–C8	119.56(18)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	46(1)	43(1)	53(2)	1(1)	−1(1)	1(1)
C2	34(1)	42(1)	37(1)	−2(1)	−2(1)	−3(1)
C3	54(2)	54(2)	34(1)	6(1)	15(1)	3(1)
C4	52(1)	46(1)	37(1)	0(1)	18(1)	8(1)
C5	29(1)	40(1)	27(1)	−3(1)	2(1)	−5(1)
C6	41(1)	51(1)	26(1)	−4(1)	7(1)	−1(1)
C7	41(1)	43(1)	39(1)	−10(1)	4(1)	5(1)
C8	31(1)	47(1)	25(1)	−3(1)	5(1)	−6(1)
C9	38(1)	53(1)	26(1)	3(1)	8(1)	5(1)
C10	32(1)	54(2)	34(1)	−3(1)	6(1)	1(1)
C11	31(1)	49(1)	34(1)	8(1)	5(1)	3(1)
C12	34(1)	74(2)	43(2)	2(1)	4(1)	−1(1)
C13	49(2)	64(2)	59(2)	21(1)	7(1)	10(1)
C14	39(1)	61(2)	40(1)	6(1)	13(1)	7(1)
O1	87(1)	60(1)	60(1)	19(1)	16(1)	8(1)
O2	40(1)	59(1)	36(1)	12(1)	17(1)	8(1)
O3	40(1)	50(1)	57(1)	−7(1)	2(1)	−4(1)
O4	30(1)	48(1)	36(1)	−2(1)	7(1)	2(1)
S1	30(1)	46(1)	34(1)	4(1)	8(1)	2(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	3770(20)	−2280(20)	99(12)	38(6)	1
H3	1590(30)	290(20)	858(15)	51(6)	1
H4	1010(20)	2230(20)	263(12)	42(6)	1
H6	3200(20)	1150(20)	−1542(13)	36(6)	1
H7	3760(30)	−850(20)	−994(14)	48(6)	1
H8	2060(20)	3215(19)	−1595(13)	39(6)	1
H9	560(30)	4090(20)	−392(15)	53(7)	1
H10A	−2020(20)	4060(20)	−1763(12)	45(6)	1
H10B	−1920(20)	5090(20)	−2471(13)	41(6)	1
H12A	−4770(30)	3520(30)	−2195(16)	66(8)	1
H12B	−6040(30)	4580(20)	−2363(12)	44(6)	1
H12C	−4710(30)	4410(20)	−2914(16)	51(7)	1
H13A	−3590(30)	7360(30)	−1853(15)	61(8)	1
H13B	−4030(30)	6770(30)	−2677(17)	66(8)	1
H13C	−5340(40)	6940(30)	−2091(16)	81(9)	1
H14A	−3700(30)	5850(20)	−623(14)	53(7)	1
H14B	−5450(30)	5400(20)	−973(14)	60(7)	1
H14C	−4010(30)	4380(20)	−792(15)	58(7)	1



Crytallographic data for Neopentyl 2-[4-(hydroxymethyl) phenyl]-1-ethene-1-sulfonate (2.15)

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{14}H_{20}O_4S$
Formula weight	284.36
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	*P2/c*
Unit cell dimensions	$a = 20.6875(5)$ Å
	$b = 5.65210(10)$ Å $\quad \beta = 110.463(3)°$
	$c = 26.8958(5)$ Å
Volume	2946.42(10) Å^3
Z	8
Density (calculated)	1.282 Mg / m^3
Absorption coefficient	0.227 mm^{-1}
F(000)	1216
Crystal	Colourless Plate
Crystal size	0.07 × 0.07 × 0.02 mm^3
θ range for data collection	3.00 – 20.81°
Index ranges	$-20 \le h \le 20, -5 \le k \le 5, -26 \le l \le 26$
Reflections collected	16095
Independent reflections	3093 [$R_{int} = 0.2370$]
Completeness to $\theta = 20.81°$	99.8 %
Max. and min. transmission	0.9955 and 0.9843
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3093 / 46 / 346
Goodness-of-fit on F^2	0.979
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.1048, *wR2* = 0.2905
R indices (all data)	*R1* = 0.1812, *wR2* = 0.3483
Extinction coefficient	0.0010(11)
Largest diff. peak and hole	0.602 and –0.485 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	–200(7)	–3820(40)	–1719(8)	240(20)	1
C2	51(6)	–2288(19)	–1168(4)	65(3)	1
C3	723(6)	–2650(20)	–841(5)	79(4)	1
C4	1034(6)	–1120(20)	–424(4)	73(4)	1
C5	690(4)	817(17)	–319(4)	53(3)	1
C6	4(5)	1100(20)	–639(4)	67(4)	1
C7	–304(6)	–500(20)	–1045(4)	70(4)	1
C8	1036(4)	2438(18)	118(4)	61(3)	1
C9	1684(4)	2725(17)	382(4)	63(3)	1
C10	2914(5)	2000(20)	1447(4)	85(4)	1
C11	3204(5)	1049(16)	2012(3)	64(3)	1
C12	3479(5)	3093(18)	2391(4)	72(4)	1
C13	3802(5)	–553(19)	2017(4)	91(5)	1
C14	2675(5)	–346(19)	2162(4)	79(4)	1
O1	2490(3)	6252(12)	749(3)	73(2)	1
O2	1414(3)	6085(12)	936(3)	73(3)	1
O3	2313(3)	3454(13)	1395(2)	79(3)	1
O4	–810(11)	–4220(40)	–1745(7)	335(17)	1
S1	1982(2)	4899(5)	862(1)	65(1)	1
C15	1142(7)	–9110(30)	–2290(8)	152(9)	1
C16	1608(6)	–7310(20)	–1828(5)	102(5)	1
C17	1929(7)	–5510(30)	–1998(4)	104(6)	1
C18	2363(6)	–3950(20)	–1638(4)	88(5)	1
C19	2511(5)	–4170(20)	–1095(3)	77(4)	1
C20	2213(6)	–6070(20)	–927(4)	83(4)	1
C21	1773(7)	–7600(20)	–1297(5)	94(5)	1
C22	2955(5)	–2454(19)	–723(3)	69(4)	1
C23	3091(4)	–2210(17)	–219(3)	74(4)	1
C24	4624(5)	–2935(18)	537(3)	59(3)	1
C25	5093(4)	–3937(15)	1066(3)	56(3)	1
C26	5523(5)	–1955(18)	1398(4)	73(4)	1
C27	5563(5)	–5679(16)	919(4)	57(3)	1
C28	4693(5)	–5198(19)	1362(4)	71(4)	1
O5	3968(3)	1068(12)	–173(2)	70(2)	1
O6	3238(3)	1528(12)	369(2)	75(3)	1
O7	4142(3)	–1284(12)	638(2)	63(2)	1
O8	565(10)	–8700(80)	–2247(11)	450(30)	1
S2	3617(1)	38(6)	141(1)	66(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O4	1.259(18)	C9–S1	1.732(9)
C1–C2	1.636(18)	C10–O3	1.457(9)
C2–C7	1.356(12)	C10–C11	1.523(11)
C2–C3	1.377(13)	C11–C14	1.514(11)
C3–C4	1.381(13)	C11–C12	1.513(11)
C4–C5	1.389(11)	C11–C13	1.530(10)
C5–C6	1.388(11)	O1–S1	1.417(6)
C5–C8	1.465(12)	O2–S1	1.427(5)
C6–C7	1.389(13)	O3–S1	1.584(6)
C8–C9	1.290(10)		
C15–O8	1.259(18)	C23–S2	1.732(9)
C15–C16	1.635(18)	C24–O7	1.458(9)
C16–C21	1.356(12)	C24–C25	1.523(11)
C16–C17	1.377(13)	C25–C28	1.514(11)
C17–C18	1.381(13)	C25–C26	1.513(11)
C18–C19	1.389(11)	C25–C27	1.530(10)
C19–C20	1.388(12)	O5–S2	1.417(6)
C19–C22	1.465(12)	O6–S2	1.426(5)
C20–C21	1.389(13)	O7–S2	1.584(6)
C22–C23	1.290(10)		
O4–C1–C2	98.0(14)	C14–C11–C12	110.8(7)
C7–C2–C3	117.7(10)	C14–C11–C10	112.3(7)
C7–C2–C1	126.0(11)	C12–C11–C10	109.1(7)
C3–C2–C1	115.6(10)	C14–C11–C13	110.3(7)

C2–C3–C4	120.5(9)	C12–C11–C13	109.5(7)
C3–C4–C5	122.0(10)	C10–C11–C13	104.6(6)
C6–C5–C4	116.8(9)	C10–O3–S1	117.5(5)
C6–C5–C8	122.2(6)	O1–S1–O2	119.1(4)
C4–C5–C8	121.0(7)	O1–S1–O3	110.8(3)
C5–C6–C7	120.0(9)	O2–S1–O3	103.4(3)
C2–C7–C6	122.6(10)	O1–S1–C9	108.7(3)
C9–C8–C5	130.0(6)	O2–S1–C9	110.0(3)
C8–C9–S1	122.0(6)	O3–S1–C9	103.7(4)
O3–C10–C11	108.6(6)		

O8–C15–C16	98.3(14)	C20–C19–C22	122.2(6)
C21–C16–C17	117.8(10)	C18–C19–C22	121.0(7)
C21–C16–C15	126.1(11)	C19–C20–C21	120.1(9)
C17–C16–C15	115.6(10)	C16–C21–C20	122.6(10)
C16–C17–C18	120.5(9)	C23–C22–C19	130.0(6)
C17–C18–C19	122.0(10)	C22–C23–S2	122.0(6)
C20–C19–C18	116.8(9)	O7–C24–C25	108.6(6)
C28–C25–C26	110.8(7)	O5–S2–O6	119.1(4)
C28–C25–C24	112.3(7)	O5–S2–O7	110.6(3)
C26–C25–C24	109.1(7)	O6–S2–O7	103.5(3)
C28–C25–C27	110.3(7)	O5–S2–C23	108.7(3)
C26–C25–C27	109.5(7)	O6–S2–C23	110.0(3)
C24–C25–C27	104.7(6)	O7–S2–C23	103.7(4)
C24–O7–S2	117.2(5)		

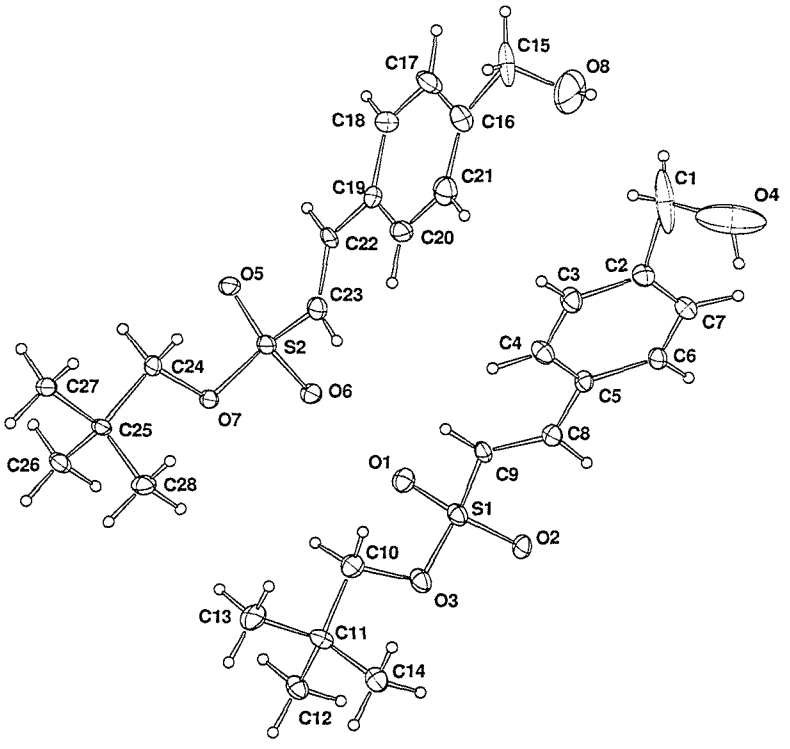
Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	43(11)	83(14)	490(50)	0(20)	−23(18)	−39(10)
C2	69(10)	56(9)	64(9)	−19(7)	16(8)	−7(8)
C3	69(10)	75(10)	84(10)	−6(8)	15(8)	20(8)
C4	77(9)	63(8)	61(9)	−5(7)	1(8)	17(8)
C5	49(8)	47(8)	61(8)	−1(6)	16(7)	11(6)
C6	51(8)	84(9)	60(8)	0(8)	13(7)	26(7)
C7	69(9)	70(10)	60(9)	5(7)	9(7)	4(8)
C8	61(9)	57(8)	60(8)	−4(7)	15(7)	25(7)
C9	44(8)	83(9)	51(8)	1(7)	1(6)	17(7)
C10	77(10)	101(11)	78(10)	−12(9)	30(8)	24(9)
C11	77(9)	61(8)	43(8)	5(6)	10(7)	−6(8)
C12	68(9)	68(9)	66(8)	−14(7)	7(7)	−1(7)
C13	97(11)	87(11)	99(11)	−9(8)	46(9)	29(9)
C14	74(9)	78(10)	75(9)	−8(8)	14(8)	7(8)
O1	68(6)	71(6)	81(6)	−3(5)	28(5)	−6(5)
O2	53(5)	85(6)	79(6)	−8(5)	20(5)	30(5)
O3	65(6)	86(6)	71(6)	−17(5)	5(5)	24(5)
O4	660(50)	210(20)	141(16)	−64(15)	160(20)	−70(30)
S1	59(2)	68(2)	58(2)	−5(2)	6(2)	18(2)
C15	36(9)	145(17)	230(20)	−2(16)	−5(12)	8(10)
C16	75(12)	133(16)	84(13)	14(12)	10(10)	25(11)
C17	91(12)	146(17)	52(10)	−19(10)	−4(9)	20(12)
C18	76(10)	129(13)	60(10)	−3(9)	25(8)	8(10)
C19	52(9)	116(13)	68(11)	9(9)	25(8)	24(9)
C20	77(10)	110(12)	57(9)	8(9)	17(8)	38(10)
C21	77(11)	92(12)	112(14)	17(11)	30(10)	14(9)
C22	48(8)	99(10)	45(8)	12(7)	−3(7)	32(7)
C23	58(9)	92(10)	67(10)	−1(8)	16(7)	25(8)
C24	44(7)	74(8)	56(8)	−8(6)	13(6)	19(6)
C25	59(8)	70(8)	32(7)	3(6)	8(6)	25(7)
C26	68(9)	91(10)	45(8)	−8(7)	1(7)	5(8)
C27	66(8)	58(8)	47(7)	4(6)	20(6)	19(6)
C28	84(9)	76(9)	57(8)	−4(7)	31(7)	17(8)
O5	72(6)	93(6)	48(5)	12(5)	24(5)	29(5)
O6	68(6)	101(7)	55(5)	−7(5)	21(4)	47(5)
O7	55(5)	86(6)	45(5)	3(4)	14(4)	40(5)
O8	115(14)	960(90)	270(20)	−290(40)	64(15)	−180(30)
S2	57(2)	88(2)	48(2)	6(2)	14(2)	32(2)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H15A	1149	−8677	−2645	182	1
H15B	1285	−10777	−2210	182	1
H17	1850	−5335	−2366	125	1
H18	2567	−2697	−1766	106	1
H20	2311	−6324	−559	100	1
H21	1579	−8893	−1174	113	1
H22	3176	−1347	−876	83	1
H23	2898	−3297	−41	89	1
H24A	4903	−2109	357	71	1
H24B	4367	−4233	304	71	1
H26A	5785	−1184	1202	109	1
H26B	5844	−2603	1731	109	1
H26C	5220	−794	1476	109	1
H27A	5284	−6960	703	85	1
H27B	5900	−6340	1243	85	1
H27C	5806	−4852	716	85	1
H28A	4420	−6479	1142	106	1
H28B	4384	−4073	1444	106	1
H28C	5015	−5858	1693	106	1
H8	345	−9976	−2277	676	1
H1A	−183	−2886	−2025	283	1
H1B	69	−5297	−1687	283	1
H3	975	−3951	−902	95	1
H4	1498	−1411	−202	88	1
H6	−256	2388	−581	80	1
H7	−782	−339	−1244	84	1
H8A	736	3430	224	73	1

H9	2008	1713	311	76	1
H10A	3268	2952	1368	102	1
H10B	2781	666	1192	102	1
H12A	3810	3999	2281	108	1
H12B	3709	2481	2750	108	1
H12C	3096	4123	2386	108	1
H13A	3624	−1883	1774	137	1
H13B	4036	−1156	2377	137	1
H13C	4130	353	1903	137	1
H14A	2500	−1648	1910	119	1
H14B	2292	695	2152	119	1
H14C	2890	−988	2521	119	1
H4A	−862	−3752	−1464	502	1



Crytallographic data for Neopentyl (*E*)-2(4-benzaldehyde dimethylacetal)-1-ethene-1-sulfonate (2.18)

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{16}H_{24}O_5S$	
Formula weight	328.41	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 5.4697(2) Å	α = 71.2200(13)°
	b = 10.9770(3) Å	β = 81.7810(13)°
	c = 14.9675(7) Å	γ = 77.902(3)°
Volume	829.15(5) Å^3	
Z	2	
Density (calculated)	1.315 Mg / m^3	
Absorption coefficient	0.216 mm^{-1}	
F(000)	352	
Crystal	Pale Yellow Prism	
Crystal size	0.30 × 0.20 × 0.07 mm^3	
θ range for data collection	2.97 – 25.03°	
Index ranges	$-6 \le h \le 6, -13 \le k \le 13, -17 \le l \le 17$	
Reflections collected	11330	
Independent reflections	2918 [R_{int} = 0.0758]	
Completeness to θ = 25.03°	99.1 %	
Max. and min. transmission	0.9851 and 0.9382	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2918 / 0 / 205	
Goodness-of-fit on F^2	1.053	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0463, *wR2* = 0.1175	
R indices (all data)	*R1* = 0.0594, *wR2* = 0.1257	
Extinction coefficient	0.011(4)	
Largest diff. peak and hole	0.383 and –0.627 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution:** *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C(1)	12199(4)	5744(2)	9174(2)	33(1)	1
C(2)	15590(4)	8215(2)	8812(2)	34(1)	1
C(3)	14348(4)	7136(2)	7870(1)	22(1)	1
C(4)	12491(4)	7321(2)	7155(1)	20(1)	1
C(5)	12312(4)	6260(2)	6866(1)	22(1)	1
C(6)	10683(4)	6389(2)	6200(1)	21(1)	1
C(7)	9201(4)	7597(2)	5799(1)	20(1)	1
C(8)	9413(4)	8654(2)	6080(1)	24(1)	1
C(9)	11035(4)	8516(2)	6756(1)	24(1)	1
C(10)	7454(4)	7790(2)	5085(1)	22(1)	1
C(11)	6878(4)	6867(2)	4801(1)	20(1)	1
C(12)	8202(4)	8125(2)	2591(1)	20(1)	1
C(13)	9657(3)	7920(2)	1690(1)	19(1)	1
C(14)	11429(4)	6616(2)	1888(2)	25(1)	1
C(15)	7856(4)	8000(2)	967(1)	24(1)	1
C(16)	11134(4)	9052(2)	1297(1)	26(1)	1
O(1)	14478(2)	5921(1)	8591(1)	26(1)	1
O(2)	13740(3)	8193(1)	8237(1)	26(1)	1
O(3)	3448(2)	6205(1)	4111(1)	24(1)	1
O(4)	3575(2)	8544(1)	3732(1)	24(1)	1
O(5)	6701(2)	7095(1)	3024(1)	19(1)	1
S(1)	4857(1)	7227(1)	3919(1)	19(1)	1

Table 3. Bond lengths [Å] and angles [°].

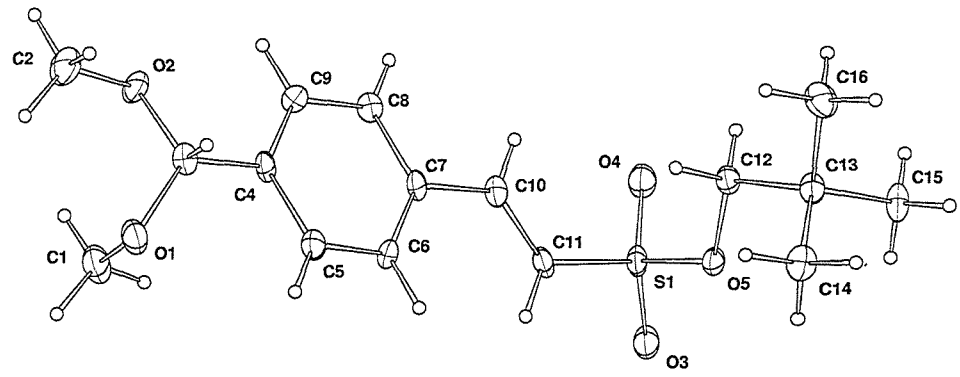
C1–O(1)	1.426(2)	C8–C(9)	1.391(3)
C2–O(2)	1.427(2)	C10–C(11)	1.325(3)
C3–O(2)	1.399(2)	C11–S(1)	1.7369(19)
C3–O(1)	1.416(2)	C12–O(5)	1.463(2)
C3–C(4)	1.517(3)	C12–C(13)	1.522(3)
C4–C(9)	1.380(3)	C13–C(14)	1.518(3)
C4–C(5)	1.392(3)	C13–C(15)	1.534(3)
C5–C(6)	1.385(3)	C13–C(16)	1.536(2)
C6–C(7)	1.396(3)	O3–S(1)	1.4240(13)
C7–C(8)	1.387(3)	O4–S(1)	1.4250(15)
C7–C(10)	1.470(3)	O5–S(1)	1.5844(13)
O2–C3–O(1)	112.14(16)	C14–C13–C(12)	111.74(16)
O2–C3–C(4)	108.38(16)	C14–C13–C(15)	109.38(16)
O1–C3–C(4)	113.28(16)	C12–C13–C(15)	110.64(15)
C9–C4–C(5)	118.77(19)	C14–C13–C(16)	110.55(16)
C9–C4–C(3)	122.30(17)	C12–C13–C(16)	105.03(15)
C5–C4–C(3)	118.89(18)	C15–C13–C(16)	109.43(16)
C6–C5–C(4)	120.95(19)	C3–O1–C(1)	114.32(15)
C5–C6–C(7)	120.30(18)	C3–O2–C(2)	112.79(16)
C8–C7–C(6)	118.49(19)	C12–O5–S(1)	116.65(11)
C8–C7–C(10)	118.97(19)	O3–S1–O(4)	119.32(8)
C6–C7–C(10)	122.54(18)	O3–S1–O(5)	104.18(7)
C7–C8–C(9)	121.0(2)	O4–S1–O(5)	108.91(8)
C4–C9–C(8)	120.53(18)	O3–S1–C(11)	109.89(9)
C11–C10–C(7)	126.4(2)	O4–S1–C(11)	110.05(9)
C10–C11–S(1)	122.06(17)	O5–S1–C(11)	103.13(8)
O5–C12–C(13)	109.63(15)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	44(1)	39(1)	17(1)	−4(1)	−1(1)	−15(1)
C(2)	39(1)	37(1)	31(1)	−14(1)	−16(1)	−7(1)
C(3)	26(1)	25(1)	15(1)	−6(1)	−2(1)	−5(1)
C(4)	25(1)	24(1)	9(1)	−5(1)	1(1)	−6(1)
C(5)	29(1)	22(1)	14(1)	−6(1)	−1(1)	−3(1)
C(6)	32(1)	22(1)	13(1)	−9(1)	−1(1)	−7(1)
C(7)	28(1)	24(1)	8(1)	−4(1)	2(1)	−7(1)
C(8)	36(1)	21(1)	16(1)	−5(1)	−6(1)	−4(1)
C(9)	36(1)	21(1)	18(1)	−7(1)	−3(1)	−10(1)
C(10)	29(1)	23(1)	12(1)	−5(1)	−1(1)	−4(1)
C(11)	26(1)	23(1)	10(1)	−1(1)	−3(1)	−6(1)
C(12)	25(1)	22(1)	14(1)	−4(1)	−1(1)	−10(1)
C(13)	19(1)	25(1)	12(1)	−6(1)	−1(1)	−7(1)
C(14)	24(1)	31(1)	21(1)	−10(1)	−4(1)	−5(1)
C(15)	24(1)	38(1)	14(1)	−9(1)	−2(1)	−7(1)
C(16)	23(1)	32(1)	20(1)	−4(1)	0(1)	−9(1)
O(1)	31(1)	27(1)	16(1)	−4(1)	−6(1)	−1(1)
O(2)	35(1)	25(1)	23(1)	−11(1)	−12(1)	−4(1)
O(3)	29(1)	32(1)	16(1)	−6(1)	0(1)	−15(1)
O(4)	27(1)	26(1)	19(1)	−8(1)	−3(1)	−1(1)
O(5)	24(1)	22(1)	12(1)	−7(1)	1(1)	−9(1)
S(1)	22(1)	24(1)	10(1)	−6(1)	−1(1)	−6(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H(1A)	11604	6492	9418	49	1
H(1B)	12497	4942	9705	49	1
H(1C)	10929	5678	8799	49	1
H(2A)	15714	7427	9361	50	1
H(2B)	15109	8991	9029	50	1
H(2C)	17216	8241	8441	50	1
H(3)	16046	7167	7521	26	1
H(5)	13322	5436	7129	26	1
H(6)	10574	5653	6014	25	1
H(8)	8436	9485	5807	29	1
H(9)	11141	9250	6945	28	1
H(10)	6660	8661	4800	26	1
H(11)	7593	5982	5088	24	1
H(12A)	9385	8107	3039	24	1
H(12B)	7090	8989	2439	24	1
H(14A)	12532	6548	2370	37	1
H(14B)	12444	6553	1305	37	1
H(14C)	10454	5905	2118	37	1
H(15A)	6846	7307	1232	37	1
H(15B)	8824	7890	386	37	1
H(15C)	6749	8853	822	37	1
H(16A)	9964	9886	1176	39	1
H(16B)	12101	8990	704	39	1
H(16C)	12281	9004	1759	39	1



Crystallographic data for Phenyl (*E*)-2(4-formylphenyl)-1-ethene-1-sulfonate (2.24)

Table 1. Crystal data and structure refinement.

Empirical formula	$C_{15}H_{12}O_4S$
Formula weight	288.31
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	$a = 5.4721(5)$ Å
	$b = 17.0243(14)$ Å $\quad \beta = 99.320(7)°$
	$c = 14.3226(12)$ Å
Volume	1316.7(2) Å^3
Z	4
Density (calculated)	1.454 Mg / m^3
Absorption coefficient	0.256 mm^{-1}
F(000)	600
Crystal	Orange Block
Crystal size	0.20 × 0.10 × 0.10 mm^3
θ range for data collection	3.12 – 25.03°
Index ranges	$-6 \le h \le 6, -20 \le k \le 19, -17 \le l \le 16$
Reflections collected	12916
Independent reflections	2320 [$R_{int} = 0.0778$]
Completeness to $\theta = 25.03°$	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9749 and 0.9506
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2320 / 0 / 182
Goodness-of-fit on F^2	1.067
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1 = 0.0352$, $wR2 = 0.0884$
R indices (all data)	$R1 = 0.0487$, $wR2 = 0.0951$
Extinction coefficient	0.0072(19)
Largest diff. peak and hole	0.204 and –0.369 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	−1808(4)	10860(1)	6351(2)	34(1)	1
C2	−574(3)	10094(1)	6354(1)	28(1)	1
C3	−1683(3)	9473(1)	5820(1)	29(1)	1
C4	−463(3)	8765(1)	5823(1)	28(1)	1
C5	1887(3)	8671(1)	6352(1)	26(1)	1
C6	2992(3)	9302(1)	6878(1)	30(1)	1
C7	1745(4)	10005(1)	6882(1)	31(1)	1
C8	3274(3)	7936(1)	6373(1)	27(1)	1
C9	2366(3)	7242(1)	6094(1)	29(1)	1
C10	5739(3)	6411(1)	4580(1)	26(1)	1
C11	7501(3)	5907(1)	4347(1)	32(1)	1
C12	9026(4)	6173(1)	3731(2)	38(1)	1
C13	8799(4)	6925(1)	3382(2)	39(1)	1
C14	7016(4)	7417(1)	3633(1)	34(1)	1
C15	5449(3)	7160(1)	4231(1)	29(1)	1
O1	−3768(3)	11022(1)	5879(1)	45(1)	1
O2	6749(2)	6645(1)	6554(1)	33(1)	1
O3	3115(3)	5823(1)	6668(1)	39(1)	1
O4	4105(2)	6106(1)	5160(1)	29(1)	1
S1	4267(1)	6423(1)	6211(1)	28(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–O1	1.203(2)	C10–C15	1.368(3)
C1–C2	1.468(3)	C10–C11	1.373(3)
C2–C7	1.377(3)	C10–O4	1.415(2)
C2–C3	1.387(3)	C11–C12	1.386(3)
C3–C4	1.377(3)	C12–C13	1.372(3)
C4–C5	1.392(3)	C13–C14	1.377(3)
C5–C6	1.393(3)	C14–C15	1.378(3)
C5–C8	1.461(3)	O2–S1	1.4188(14)
C6–C7	1.377(3)	O3–S1	1.4152(14)
C8–C9	1.319(3)	O4–S1	1.5875(13)
C9–S1	1.7320(18)		

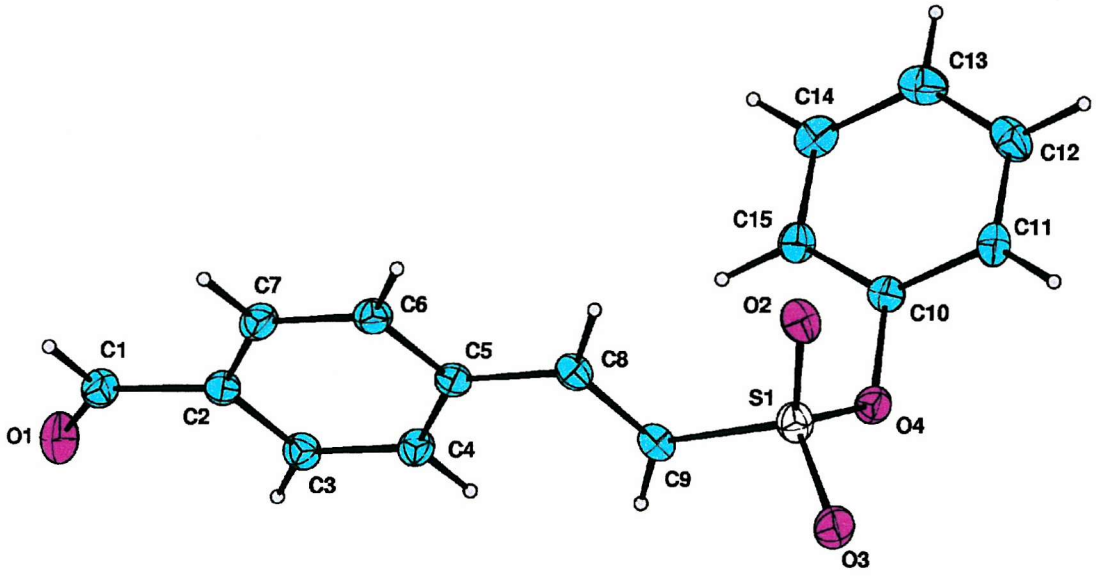
O1–C1–C2	124.98(19)	C15–C10–O4	120.66(16)
C7–C2–C3	120.05(17)	C11–C10–O4	116.61(16)
C7–C2–C1	118.86(18)	C10–C11–C12	117.95(18)
C3–C2–C1	121.08(18)	C13–C12–C11	120.62(18)
C4–C3–C2	119.84(18)	C12–C13–C14	119.89(18)
C3–C4–C5	120.40(17)	C13–C14–C15	120.51(19)
C6–C5–C4	119.24(17)	C10–C15–C14	118.40(18)
C6–C5–C8	118.06(16)	C10–O4–S1	119.23(11)
C4–C5–C8	122.69(17)	O3–S1–O2	120.33(9)
C7–C6–C5	119.99(17)	O3–S1–O4	103.48(8)
C2–C7–C6	120.46(17)	O2–S1–O4	108.83(7)
C9–C8–C5	126.29(17)	O3–S1–C9	108.66(9)
C8–C9–S1	120.08(15)	O2–S1–C9	110.19(9)
C15–C10–C11	122.62(18)	O4–S1–C9	103.98(8)

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	41(1)	28(1)	37(1)	1(1)	15(1)	−1(1)
C2	32(1)	25(1)	28(1)	2(1)	13(1)	0(1)
C3	29(1)	30(1)	28(1)	1(1)	7(1)	1(1)
C4	30(1)	27(1)	27(1)	−3(1)	4(1)	−2(1)
C5	29(1)	27(1)	23(1)	1(1)	9(1)	−1(1)
C6	28(1)	32(1)	30(1)	−3(1)	6(1)	−4(1)
C7	36(1)	28(1)	31(1)	−4(1)	9(1)	−6(1)
C8	26(1)	32(1)	24(1)	−1(1)	5(1)	2(1)
C9	25(1)	33(1)	30(1)	0(1)	7(1)	4(1)
C10	26(1)	30(1)	21(1)	−3(1)	3(1)	−2(1)
C11	36(1)	26(1)	33(1)	−5(1)	1(1)	5(1)
C12	31(1)	50(1)	33(1)	−12(1)	5(1)	5(1)
C13	36(1)	53(1)	28(1)	−6(1)	8(1)	−9(1)
C14	42(1)	34(1)	27(1)	1(1)	4(1)	−5(1)
C15	33(1)	27(1)	26(1)	−1(1)	4(1)	2(1)
O1	51(1)	34(1)	49(1)	1(1)	7(1)	11(1)
O2	32(1)	38(1)	28(1)	−2(1)	1(1)	7(1)
O3	49(1)	31(1)	39(1)	7(1)	18(1)	3(1)
O4	33(1)	26(1)	28(1)	−1(1)	7(1)	−1(1)
S1	33(1)	27(1)	26(1)	2(1)	6(1)	5(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	–997	11258	6751	41	1
H3	–3280	9535	5453	34	1
H4	–1230	8338	5461	34	1
H6	4605	9248	7235	36	1
H7	2490	10430	7252	38	1
H8	4997	7961	6612	33	1
H9	666	7192	5828	35	1
H11	7670	5390	4601	39	1
H12	10240	5832	3549	46	1
H13	9870	7105	2968	46	1
H14	6865	7937	3391	41	1
H15	4197	7494	4397	35	1



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