Exploration and development of a C-H activated route to access the [1,2]dithiolo[4,3-*b*]indole-3(4*H*)-thione core and related derivatives

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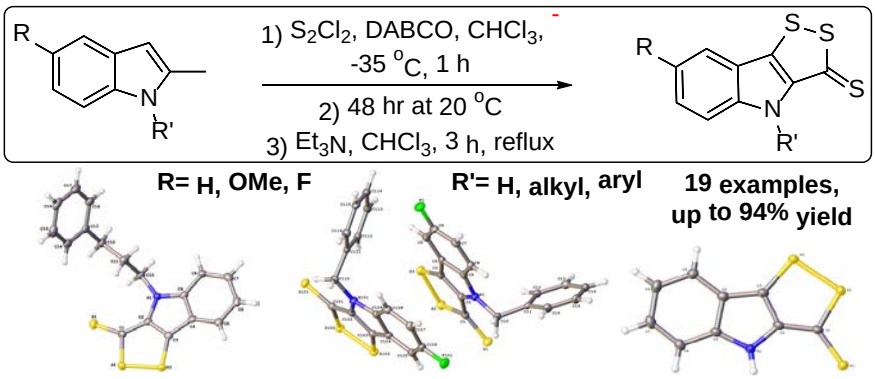


Received:
Accepted:
Published online:
DOI:

Abstract A robust procedure for the production of [1,2]dithiolo[4,3-b]indole-3(4H)-thione analogues using a DABCO/S_2Cl_2 complex as a sulfur source *via* a C-H activated approach.

Key words Indole, Indole sulfides, Sulfur-nitrogen heterocycles, Fused 3*H*-1,2-dithiole-3-thiones, C-H activation, Disulfur dichloride

The privileged indole structure has been shown to be a favorable biological scaffold, and despite a plethora of examples of known drugs containing indole only limited indole polysulfide research has been carried out.[1] This is despite the fact that examples of sulfur containing indoles such as **1**-**4** show various biological activities including tyrosine kinase inhibition,[2] anti-inflammation,[3] cytoprotectant activity,[4] anti-fungal activity,[5] anti-viral properties,[6] cannabinoid receptor binding,[7] and ion channel modulation.[8] (fig 1). As part of a wider research program within our group, we became interested in the electronics of the ring system attached to a thione functionality[5] and its potential biological applications, along with development of a robust mild synthetic route to access them.

There are a several examples in the literature of synthetic methodologies towards indole polysulfides. Initial work by Snyder *et al.* and Wawzonek *et al.* involved heating elemental sulfur with indole and cyclic amines, respectively, producing a number of sulfides, with little control of the products produced.[9-10] Several methods have since been employed to control the sulfur addition and improve the yields including use of thioureas,[11] sulfur,[12] thiols,[13] sulfenyl chlorides,[14] disulfides,[15] and more recently sulfonyl hydrazides[16] and carbon disulfide/iodine.[17] Despite a number of methods and sulfur sources, the chemistry described has limited scope and suffers from a lack of full exploration. Broad, general methods have yet to be developed.

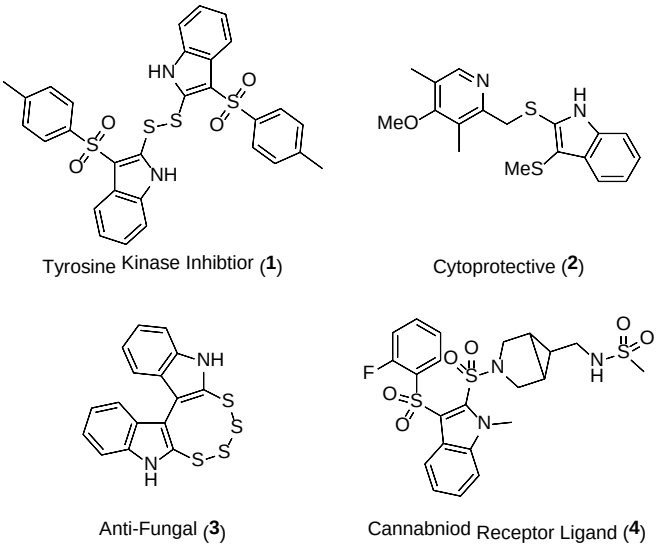
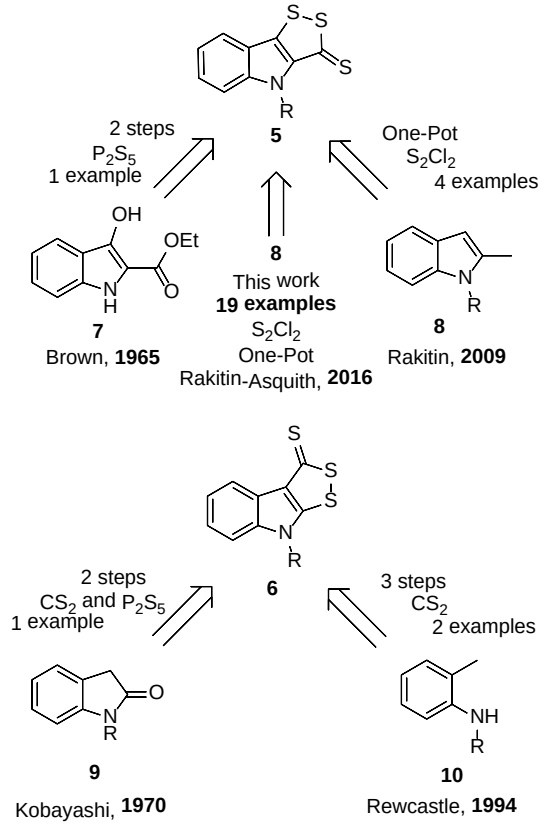


Figure 1 Examples of biologically active indole sulfides

This trend continues when looking into the indole attached to a cyclized ring systems such as the pentathiepin[18,5,6] and the 3*H*-1,2-dithiole-3-thione. The latter caught our interest due in part to its unusual electronic properties which provide a potentially mutually beneficial stabilizing electronic effect for both the indole and thione parts of the molecule. We sought to develop a robust synthetic pathway to access these molecules in order to open this class of compound up to the wider medicinal chemistry applications.

There are limited examples of [1,2]dithiolo[4,3-*b*]indole-3(4*H*)-thione in the literature with synthesis tending to lack substrate

scope, likely due in part to the complex mechanistic pathways required for these reactions to proceed. There are two potential isomers of the indole thione, the *alpha* (**5**) and *Pri* (**6**). Previous routes to access these compounds proceed using phosphorous sulfide to form **5** from **7**, and have limited scope.[19] Other examples include a two-step phosphorous sulfide, carbon disulfide combination to produce **6** from **9**,[20] and a method using carbon disulfide produces compounds **6** from **10** in a three step protocol.[21] These methods produce **5** and **6** in low yields, consistent with more recent reports on analogous ring systems.[18] However utilizing the disulfur dichloride/DABCO complex[22] enabled the 3*H*-1,2-dithiole-3-thione to be accessed in a respectable yield in one step.[23]

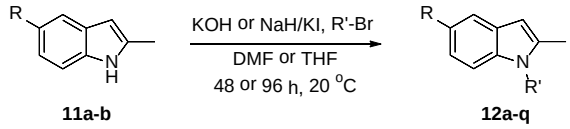


Scheme 1 Previously reported routes to fused 3*H*-1,2-dithiole-3-thiones **6** and **9**.

To date there has been little exploration to produce a route that can reliably and reproducible generate a library of compounds under mild conditions in high yield. We now present a robust one-pot route to synthesize a broad range of cyclized indole sulfide derivatives. We confirm their structures with x-ray crystallography.[24] We first treated 2-methyl indoles **11a-b** with a series of alkyl halides using mild conditions (method A: powdered potassium hydroxide in DMF at room temperature, 48 h). In some cases (**12 a-p**) that were sluggish or proceeded in low yields we utilized Finkelstein type conditions (condition B) utilizing sodium hydride and potassium iodide (sch. 2, tab. 1). A head to head comparison of the two methods showed that method B can increase the yield by a factor of three in certain cases. The yields tended to be higher with the *meta*-substituted derivative (**12F** & **12K**), which also corresponded to a milder reaction requirement.

11a was also treated with corresponding aryl bromides using standard Ullman conditions at 180°C for 45 minutes in the microwave to afford **13a-b** in good yield (sch 3, tab 2). This allowed for testing the versatility of the incorporation of sulfur on indole *N*-aryl systems.[25]

Table 1 Results of coupling reactions on 2-methyl-Indoles



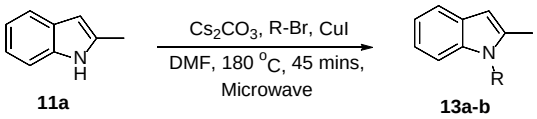
11a-b **12a-q**

Scheme 2 Formation of substituted indole.

Name	-R	-R`	Method	Yield[a]
12a	H	-methyl	A	81
12b	H	-ethyl	A	74
12c	H	-*iso*-propyl	A	51
12d	H	-(2-methyl)propyl	A	52
12e	H	2-fluoro-benzyl	B	63
12f	H	3-fluoro-benzyl	A	72
12g	H	4-fluoro-benzyl	B	81
12h	H	3,4-difluoro-benzyl	A	56
12i	H	-propylbenzene	A	91
12j	H	2-cyano-benzyl	B	52
12k	H	3-cyano-benzyl	A	74
12l	H	4-cyano-benzyl	A	25
12l	H	4-cyano-benzyl	B	64
12m	H	-benzyl	A	65
12n	5-F	-benzyl	A	67
12o	H	2-methoxy-benzyl	A	83
12p	H	3-methoxy-benzyl	A	56

[a] Yield of isolated product (%)

Table 2 Ullman coupling reactions on 2-methyl-Indole **11a**



11a **13a-b**

Scheme 3 Formation of Ullman products

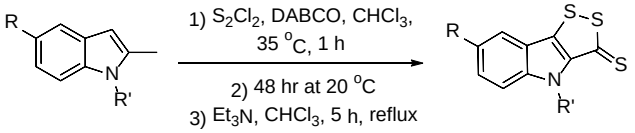
Name	-R	Method	Yield[a]
13a	3,4-dimethoxybenzene	C	82
13b	3-fluoro-4-methoxybenzene	C	81

[a] Yield of isolated product (%)

With the substituted indoles (**11a**, **12a-q** & **13a-b**) in-hand we treated them with the disulfur dichloride/DABCO complex in an operationally simple three step, one pot protocol.[23] The reaction can be followed through a series of visual transitions between a set of previous proposed intermediates.[23] We were able to access the [1,2]dithiolo[4,3-*b*]indole-3(4*H*)-thione products **14a-s** in moderate to excellent yields (sch. 4, tab. 3). In keeping with our previous observation the *meta*-substituted indoles (**12F** & **12K**) had the highest yields. We did however notice a drop off in yield in the production of **14r-s**; this is likely due to the potential steric and electronic interference of the directly bound phenyl ring system. Overall this method is operationally simple, robust and amenable to scale up and array synthesis.

The disulfide bridges contained within these compounds have never been investigated and we wondered if the stabilizing effect of the indole would lengthen or shorten the thio carbonyl or the disulfide bridge head. The typical bond length for a S-S bond is 2.07 Å and C=S is 1.63 Å.[25] We observed a slight lengthening of the C=S bond by 0.01-0.04 Å in all structures except **14q** and the minor disorder component of **14h**. The only significant deviation from the typical S-S bond length was observed in the minor disorder component of **14h** (fig. 2, tab. 4).

Table 3 [1,2]dithiolo[4,3-*b*]indole-3(4*H*)-thione results



Scheme 4 Synthesis of of [1,2]dithiolo[4,3-*b*]indole-3(4*H*)-thione products

Name	R	R`	Yield[a]
14a	H	*N*-H	27
14b	H	*N*-methyl	94[b]
14c	H	*N*-ethyl	56[b]
14d	H	*N*-*iso*-propyl	66[b]
14e	H	*N*-(2-methyl)propyl	52
14f	H	2-fluoro-*N*-benzyl	64
14g	H	3-fluoro-*N*-benzyl	79
14h	H	4-fluoro-*N*-benzyl	71
14i	H	3,4-difluoro-*N*-benzyl	39
14j	H	*N*-propylbenzene	62
14k	H	2-cyano-*N*-benzyl	74
14l	H	3-cyano-*N*-benzyl	82
14m	H	4-cyano-*N*-benzyl	73
14n	H	*N*-benzyl	70[b]
14o	5-F	*N*-benzyl	63
14p	H	2-methoxy-*N*-benzyl	58
14q	H	3-methoxy-*N*-benzyl	86
14r	H	3,4-dimethoxy-*N*-benzene	34
14s	H	3-fluoro-4-methoxy-*N*-benzene	24

[a] Yield of isolated product (%)
[b] consistent with previous report[23]

There are no hydrogen bond donors or acceptors present in these compounds (aside from the indole N-H in **14a**) so the crystal structures arise from simple close-packing. The only exception to this is the higher symmetry trigonal structure of **14f** which is solvent mediated (tab. 4). The smaller R' residues of **14a** and **14b** result in structures comprising of simple stacks of alternately orientated molecules whilst the larger R' residues of **14e-s** give rise to more complex stacking arrangements of molecules (tab. 4).

The observed lengthening of S-S bonds in x-ray structures led us to study how well commonly used electronic structure calculations are able to reproduce these x-ray results. We used crystal form conformation for the compound **14l** and calculated standard geometry optimizations using standard DFT geometry optimization (B3LYP/6-31G*) using Gaussian09 software.[26] Results reveal that this level of theory, which usually produces reliable molecular geometries, is actually overestimating the S-S bond lengths of [1,2]dithiolo system; giving a 2.13 Å length for S-S bond in the case of **14l**, which has an actual length of 2.08 by x-ray. Whereas with a length of 1.67 Å for C=S bond, this is more consistent with our experimental data. Optimization using higher level basis sets B3LYP/6-311+G** and B3LYP/cc-PVTZ didn't improve the performance of DFT while both unconstrained optimizations resulted in a calculated 2.14 Å bond length for the S-S bond in question.

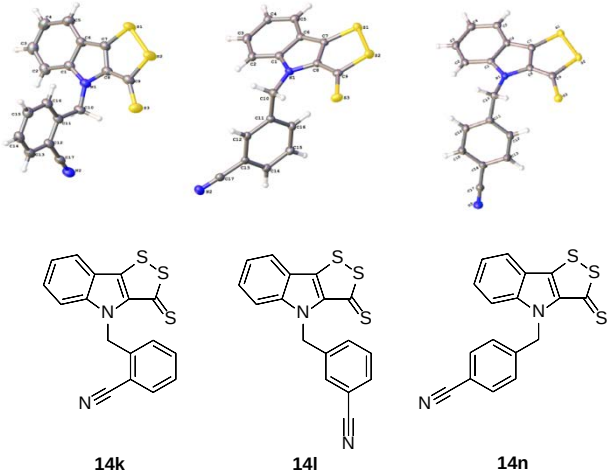


Figure 2 *Ortho*-Cyano(**14k**)/*Meta*-Cyano(**14L**)/*Para*-Cyano(**14n**) crystal structures showing orthogonal ring system.

Table 4 [1,2]dithiolo[4,3-*b*]indole-3(4*H*)-thione **14a-t** crystal structure results showing S-S and S-C bonds.

Name	S-S	S-C	Crystal Structure	
14a	2.073(2)	1.664(4)	Triclinic	plate
14b	2.0755(9)	1.670(3)	Monoclinic	block
14c	-	-	-	-
14d	-	-	-	-
14e	2.0668(13)	1.653(3)	Monoclinic	block
14f	2.0717(10)	1.651(3)	Trigonal	block
14g	2.0734(6)	1.6700(17)	Monoclinic	block
14h	2.0745(17) 2.001(16)	1.655(4) 1.604(16)	Monoclinic	plate
14i	2.065(2) 2.067(2)	1.669(6) 1.669(5)	Triclinic	plate
14j	2.0772(13)	1.656(3)	Orthorhombic	blade
14k	2.0701(12)	1.647(3)	Orthorhombic	block
14l	2.0751(7)	1.6620(19)	Monoclinic	block
14m	2.0752(7)	1.6612(19)	Monoclinic	block
14n	-	-	-	-
14o	2.0710(6) 2.0746(6)	1.6549(18) 1.6532(18)	Monoclinic	rod
14p	2.0669(19)	1.554(5)	Triclinic	plate
14q	2.0766(6)	1.6643(16)	Monoclinic	block
14r	2.0634(9)	1.657(3)	Monoclinic	block
14s	2.0799(19) 2.079(2)	1.664(6) 1.663(6)	Orthorhombic	needle

This C-H activation to produce the 3*H*-1,2-dithiole-3-thiones has been observed as a thermodynamic product of a reaction of methyl indole with elemental sulfur.[28] To our knowledge this is the first report of crystallisation, full crystallographic structural determination, and characterisation of the [1,2]dithiolo[4,3-*b*]indole-3(4*H*)-thione core functionality. This work has demonstrated an efficient synthetic route to 3*H*-1,2-dithiole-3-thiones with broad substrate scope which we hope to utilise in

further investigation of the potential of disulfide bridge networks in medicinal and organic chemistry.

Acknowledgment

The authors are grateful to Bloomsbury Colleges - University of London; University College London; Russian Science Foundation (grant no. 15-13-10022) and the Biocenter Finland/DDCB for financial support towards the goals of our work. We would also like to thank the EPSRC UK National Mass Spectrometry Facility at the Swansea University for spectroscopic services and the EPSRC UK National Crystallography Service at the University of Southampton for the collection of the crystallographic data. In addition we thank CSC - IT Center for Science Ltd. for software licenses and computational resources and Prof. David H. Drewry and Prof. Timothy M. Wilson (University of North Carolina - Chapel Hill, NC, USA) for their insights in preparation of this manuscript.

Supporting Information

NO (this text will be deleted prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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General Procedures

Method A: 2-Methylindole (1.31 g, 10.0 mmol) in dry DMF (15 mL) was treated with powdered KOH (0.67 g, 12.0 mmol) and the mixture stirred for 30 min, where upon 3-(bromomethyl)benzonitrile (1.99 g, 10.0 mmol) was added in one portion. The reaction became exothermic and was cooled in an ice bath and after stirring for 96 h at r.t., the mixture was concentrated under vacuum and the residue taken up in ethyl acetate. The solution was washed with water, brine, dried ($MgSO_4$) and concentrated to dryness *in vacuo*. Purification *via* flash column chromatography on silica gel (hexanes/EtOAc, 1:1) to afford 3-((2-methyl-1H-indol-1-yl)methyl)benzonitrile (**12k**) (1.95 g, 7.4 mmol, 74% yield) as colourless crystals; MP - 120-121°C; HMRS: found m/z 247.1231; calcd for $C_{17}H_{14}N_2$ $[M+H]^+$ 247.1235; IR (film): υ_{max} = 3019 m (C-H), 2945 m (C-H), 2915 m (C-H), 2224 s (C≡N), 1552 m (C=C), 1457 m, 1426 w, 1395 w, 1136 w, 783 m 744 s, 686 m cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.60-7.57 (1H, m, CH^{Ar}), 7.54 (1H, d, *J*= 8.1 Hz, CH^{Ar}), 7.38 (1H, t, *J*= 7.8 Hz, CH^{Ar}), 7.28 (1H, s, CH^{Ar}), 7.17 (1H, dq, *J*= 1.0, 8.1 Hz, CH^{Ar}), 7.14-7.11 (3H, m, CH^{Ar}), 6.38 (1H, s, CH^{Ar}), 5.43 (2H, s, CH_2), 2.37 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$). 139.6 (C^{Ar}), 136.9 (C^{Ar}), 136.1 (C^{Ar}), 131.2 (CH^{Ar}), 130.4 (CH^{Ar}), 129.7 (CH^{Ar}), 129.5 (CH^{Ar}), 128.3 (C^{Ar}), 121.2 (CH^{Ar}), 120.1 (CH^{Ar}), 120.0 (CH^{Ar}), 118.5 (C^{Ar}), 113.1 (C≡N), 108.8 (CH^{Ar}), 101.3 (CH^{Ar}), 45.7 (CH_2), 12.7 (CH_3).

Method B: Sodium hydride (0.5 g of a 60% dispersion in mineral oil, 12.5 mmol) was added portionwise to a solution of 2-methylindole (1.31 g, 10.0 mmol) in dry THF (20 mL). The mixture was stirred for 30 min, and then 2-(bromomethyl)benzonitrile (1.96 g, 10.0 mmol) was added in one portion, in addition to NaI

(1.50 g, 10.0 mmol). The reaction became exothermic and was cooled in an ice bath and after stirring for 48 h at r.t., it was concentrated *in vacuo* and the residue taken up in ethyl acetate. The solution was washed with water, brine, dried ($MgSO_4$) and concentrated to dryness *in vacuo*. Purification *via* flash column chromatography on silica gel (hexanes/EtOAc, 1:1) to afford 2-((2-methyl-1*H*-indol-1-yl)methyl)benzonitrile (**12j**) (1.28 g, 5.2 mmol, 52% yield) as colourless crystals; MP - 124-125 °C; HMRS: found m/z 247.1233; calcd for $C_{17}H_{15}N_2$ $[M+H]^+$ 247.1235; IR (film): υ_{max} = 3055 m (C-H), 2920 m (C-H), 2851 m (C-H), 2220 s (C≡N), 1460 m (C=C), 1396 w, 747 s, 703 s cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.74 (1H, dd, *J*=1.2, 7.0 Hz, CH^{Ar}), 7.62-7.59 (1H, m, CH^{Ar}), 7.40-7.34 (2H, m, CH^{Ar}), 7.16-7.12 (3H, m, CH^{Ar}), 6.52 (1H, d, *J*= 6.3, CH^{Ar}), 6.41 (1H, s, CH^{Ar}), 5.55 (2H, s, CH_2), 2.39 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.7 (C^{Ar}), 137.0 (C^{Ar}), 136.4 (C^{Ar}), 133.5 (CH^{Ar}), 132.9 (CH^{Ar}), 128.3 (C^{Ar}), 127.8 (CH^{Ar}), 126.5 (CH^{Ar}), 121.2 (CH^{Ar}), 120.0 (CH^{Ar}), 117.1 (C^{Ar}), 110.1 (C≡N), 108.9 (CH^{Ar}), 101.2 (CH^{Ar}), 44.7(CH_2), 12.6 (CH_3).

Method C: Disulfur dichloride (0.4 mL, 5 mmol) was added dropwise at – 35 °C to a stirred solution of DABCO (1.12 g, 10 mmol) in chloroform (25 mL) under nitrogen. The mixture was stirred at room temperature for 1 h.

3-((2-methyl-1*H*-indol-1-yl)methyl)benzonitrile (**12j**) (0.239 g, 1 mmol) in chloroform (5 mL) was added and the mixture was stirred at room temperature for 48 h under nitrogen. Triethylamine (1.4 mL, 10 mmol) was then added to the resultant mixture at 0 °C, the mixture stirred at room temperature for 2 h, heated at reflux for 3 h, filtered, and solvents evaporated. Purification *via* flash column chromatography on silica gel (hexanes/CH_2Cl_2) to afford 3-((3-thioxo-[1,2]dithiolo[4,3-*b*]indol-4(3*H*)-yl)methyl)benzonitrile (**14l**) (0.277 g, 0.82 mmol, 82% yield) as orange crystals; MP - 190-191 °C; HMRS: found m/z 339.0077; calcd for $C_{17}H_{11}N_2S_3$ $[M+H]^+$ 339.0079; IR (film): υ_{max} = 3054 m (C-H), 2952 m (C-H), 2921 m (C-H), 2872 w (C-H), 2851 w (C-H), 2226 s (C≡N), 1472 s (C=C), 1330 s, 1258 w, 1122 w, 1060 s, 685 m cm^{-1}; (400 MHz, $CDCl_3$) δ: 7.77 (1H, dt, *J*= 1.0, 8.0 Hz, CH^{Ar}), 7.46 (2H, ddd, *J*= 1.0, 4.8, 5.9 Hz, CH^{Ar}), 7.40-7.32 (3H, m, CH^{Ar}), 7.24-7.19 (2H, m, CH^{Ar}), 6.15 (2H, s, CH^{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$) δ:195.9 (C=S), 146.9 (C^{Ar}), 142.2 (C^{Ar}), 149.4 (C^{Ar}), 139.0 (C^{Ar}), 131.4 (CH^{Ar}), 131.3 (C^{Ar}), 130.3 (CH^{Ar}), 129.6 (CH^{Ar}), 125.5 (C^{Ar}), 121.9 (CH^{Ar}), 121.7 (CH^{Ar}), 120.6 (CH^{Ar}), 114.3 (CH^{Ar}),113.0 (C≡N), 111.8 (CH^{Ar}), 44.0 (CH_2).

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