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*N*1-Arylation of 1,4-Benzodiazepine-2-ones with Diaryliodonium Salts

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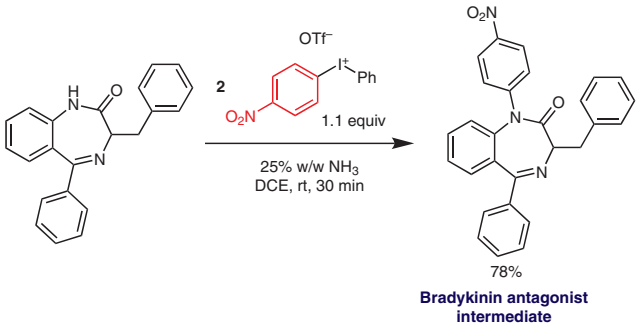

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Abstract A library of *N*1-arylated 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones has been synthesized starting with unsymmetrical diaryliodonium salts using aqueous ammonia as a base. This can also be applied to a similar 1,3,4-benzotriazepin-2-one derivative.

Key words benzodiazepines, N-arylation, iodonium salt, privileged scaffold, benzotriazepine

Compounds containing a 1,4-benzodiazepine scaffold are often termed as 'privileged structures' and are of significant interest to organic and medicinal chemists.[1–18] Many bioactive 1,4- benzodiazepines include *N*-arylated benzodiazepines; for example, the benzodiazepine derivative **A** (Figure 1) is a bradykinin antagonist[19] and the related benzotriazepine **B** is an antagonist at the parathyroid hormone (PTH)-1 receptor.[20] Typically *N*-arylated benzodiazepines can be prepared by transition-metal- catalysed couplings, often with copper, with various arylating agents. Generally, the reaction scope is limited with these routes and often requires high temperatures and strong bases. [19,21–23]

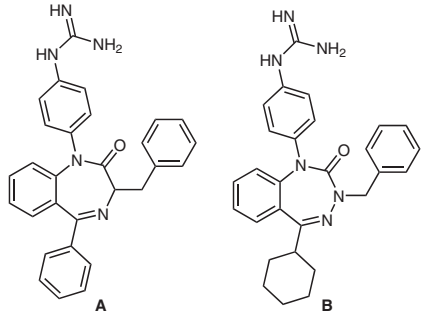


Figure 1 Bioactive *N*-arylated Benzodiazepine and Benzotriazepine

Being able to generate libraries of diverse analogues, in this case by adding *N*-functionality to a privileged core unit, using mild and efficient methodologies, can substantially improve SAR studies (structure–activity relationship) and optimise the drug development process potentially repurposing privileged scaffolds for new biological targets.[24,25]

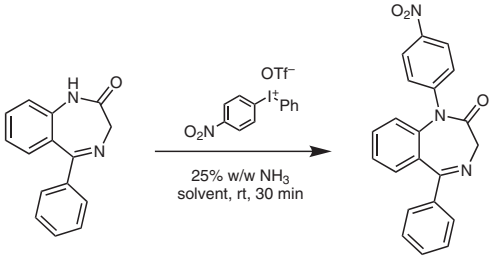
We have an active interest in benzodiazepines [26,27] and recently reported a method to functionalise 5-phenyl-1,3-dihydro-*2H*-1,4-benzodiazepin-2-ones via a late-stage palladacycle assisted *ortho* C–H activation protocol.[28,29] Herein we present our approach to generate a series of *N*1-arylated 1,4-benzodiazepines using diaryliodonium salts. The latter react with nucleophiles in the absence of transition-metal catalysts and are commonly used in organic synthesis as electrophilic reagents.[30–35]

Novak et al. recently reported a protocol for the *N*-arylation of pyrazoles.[36] A quick screen of conditions, adapting this protocol using diaryliodonium salts with weak bases under mild conditions, showed that it was indeed possible to perform similar arylations on the 1,4-benzodiazepine system. Upon initial screening of a number of solvents, 1,2-dichloroethane (DCE) was found to give the best results (Table 1, entry 2). Solvents such as polypropylene glycol (PEG) and acetic acid (AcOH) gave poor yields. Similar results were observed on pyrazoles by Novak et al. where aprotic solvents, immiscible in water, produced the best results.

A number of bases were tested subsequently and both NH_3 (25% w/w) and NaOH (sat. aq.) gave similar and the best results (Table 2, entries 1, 2).

Hence, optimal conditions appeared to use NH_3 (aq.), DCE at room temperature for 30 min. Next, a series of functionalized 1,4-benzodiazepines was *N*-arylated using (4-nitrophenyl)phenyliodonium triflate in good to excellent yields (Scheme 1). Generally, in transition-metal-free processes unsymmetrical diaryliodonium salts give a mixture of products where both groups are transferred and the transfer of more sterically hindered and electron-with-

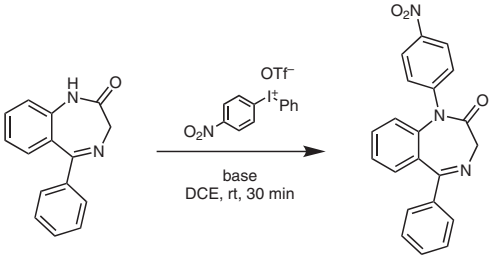
Table 1 Optimization of *N*-Arylation of 1,4-Benzodiazepines – Solvent Effects



Entry	Solvent	Conversion (%)[a]
1	toluene	95
2	DCE	99
3	PEG	–
4	AcOH	–
5	$CHCl_3$	85

[a] LC–MS conversion.

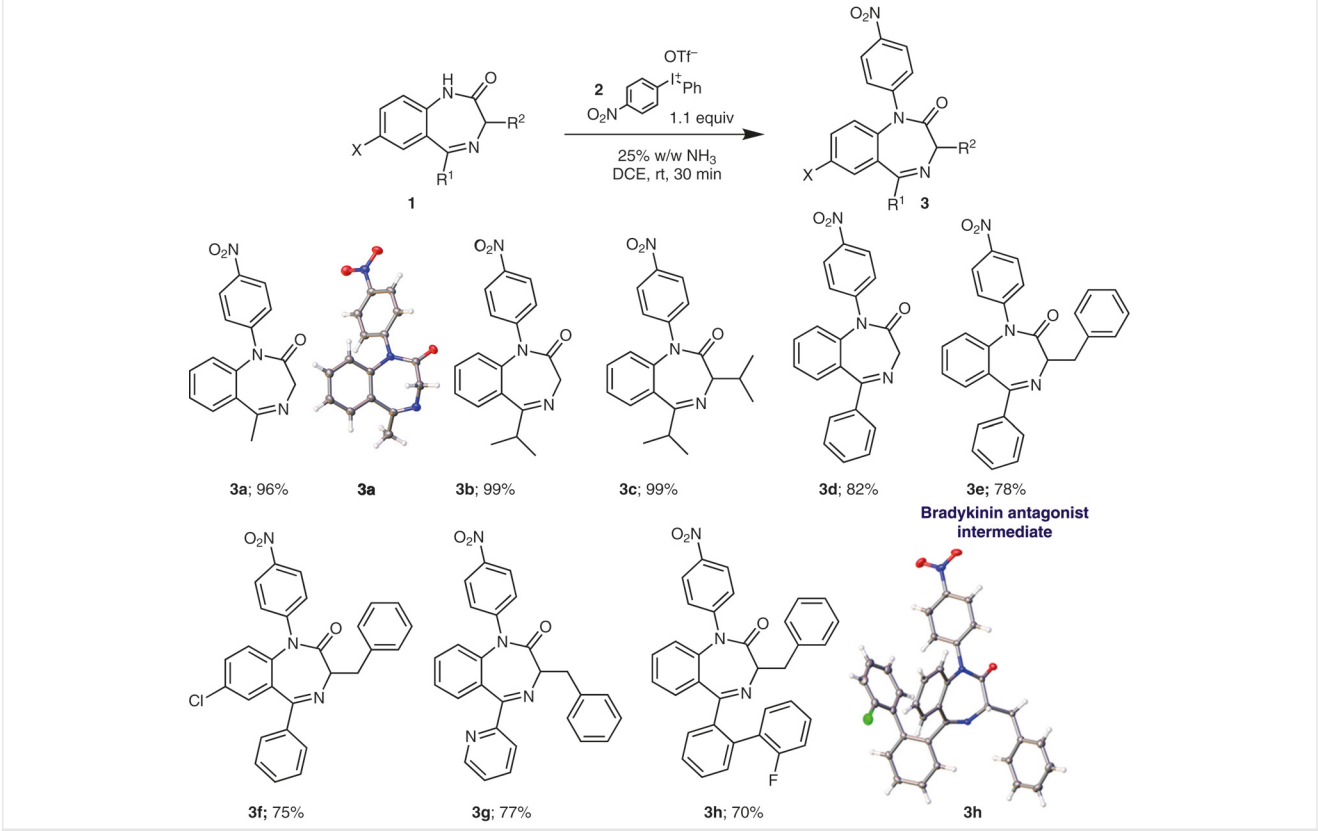
Table 2 Optimization of *N*-Arylation of 1,4-Benzodiazepines – Base Effects



Entry	Base	Conversion (%)[a]
1	NaOH (sat. aq.)	99
2	NH_3 (25% w/w)	99
3	K_2CO_3	80
4	NaH	-

[a] LC–MS conversion.

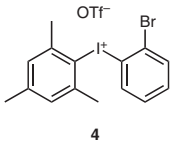
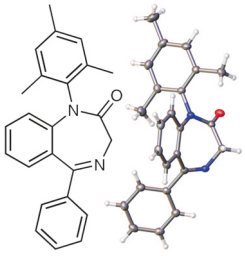
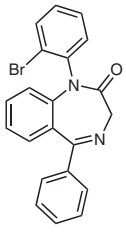
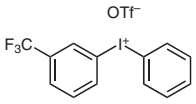
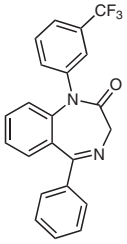
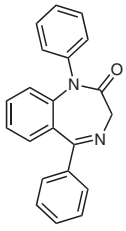
drawing groups is preferable.[34] However, in this case (Scheme 1) only the nitrophenyl group was transferred. We were able to *N*-arylate quite sterically hindered benzodiazepines such as **3e**, **3f**, and **3g**. Of note, **3e** is a key intermediate towards **A**. We were also pleased to be able to conduct *N*-arylation on a previously *ortho*-arylated hindered benzodiazepine, **3h**, in good yield, whose structure was also confirmed by X-ray crystallography. Such molecules may be useful precursors to, e.g., α-helical mimetics in medicinal chemistry.[37,38]



Scheme 1 *N*-Arylated 1,4-Benzodiazepines

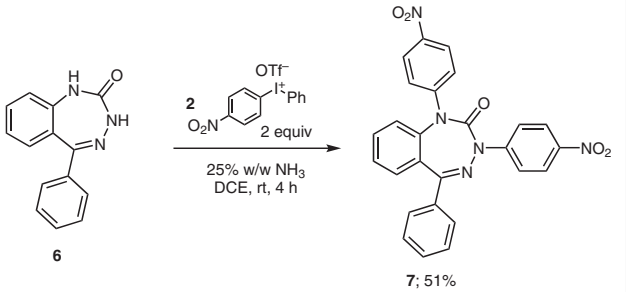
The use of other unsymmetrical diaryliodonium triflates was also explored (Table 3), which required longer reaction time and led to both aryl groups being transferred to obtain **3i–l**. As expected, the transfer of more sterically hindered or less electron-rich groups was preferred. Further attempts to use unsymmetrical diaryliodonium salts such as phenyl(3-methylphenyl)iodonium triflate, phenyl(4-methylphenyl)iodonium triflate, and (2-methylphenyl)(2,4,6-trimethylphenyl)iodonium triflate gave little or no products. Additionally, attempted *N*-arylation with symmetrical diaryliodonium triflates or tetrafluoroborates such as bis(2-fluorophenyl)iodonium tetrafluoroborate and bis(4-bromophenyl)iodonium triftlate gave, at best, traces of products.

Table 3 Further *N*-Arylation of 1,4-Benzodiazepines[a]

Salt	Product (major)	Product (minor)
 **4**	 **3i**; 51%	 **3j**; 8%
 **5**	 **3k**; 42%	 **3l**; 9%

[a] Reaction time = 8 h.

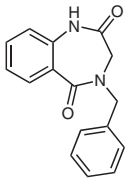
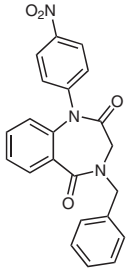
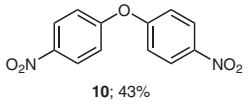
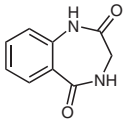
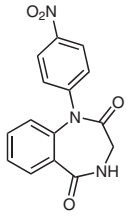
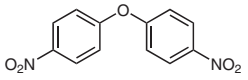
We have briefly explored the *N*-arylation on a 1,3,4-benzotriazepine **6**, which resulted in diarylation and yielded **7** (Scheme 2).



Scheme 2 *N*-Arylation on a 1,3,4-Benzotriazepine

Interestingly, the iodonium salts were observed to undergo reaction with water present in the reaction to give diarylether products. The ether product is only observed in substantial amounts when the benzodiazepine substrates react poorly with the diaryliodonium salts (Table 4). The ether product **10** was also obtained merely by stirring the iodonium salt with water in DCE with a mild base for 20 min at room temperature with a yield of 43%. Olofsson et al. have reported the synthesis of related diarylethers by reacting diaryliodonium salts with phenols in the presence of mild bases.[39]

Table 4 Diaryl Ether Formation

Substrate	Expected product	Observed product
 **8**	 **9**; 0%	 **10**; 43%
 **11**	 **12**; 0%	 **10**; 45%

In summary we have presented a mild metal-free route to *N*-arylated benzodiazepines, three of which were structurally characterized in the solid state (**3a**, **3h**, **3i**).[40,41]

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590920.

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(41) All reactions were conducted under an inert atmosphere unless specified otherwise. All commercially purchased materials and solvents were used without further purification unless specified otherwise. NMR spectra were recorded on a Varian VNMRS 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) spectrometer and prepared in deuterated solvents such as $CDCl_3$ and DMSO-d_6. ^{1}H and ^{13}C chemical shifts were recorded in parts per million (ppm). Multiplicity of ^{1}H NMR peaks are indicated by s – singlet, d – doublet, dd – doublets of doublets, t – triplet, pt – pseudo triplet, q – quartet, m – multiplet, and coupling constants are given in Hertz (Hz). Electrospray ionisation–high resolution mass spectra (ESI-HRMS) were obtained using a Bruker Daltonics Apex III where Apollo ESI was used as the ESI source. The molecular ion peaks $[M]^+$ were recorded as mass to charge m/z ratio.
(42) LC–MS spectra were acquired using a Shimadzu LC-MS 2020, on a Gemini 5 µm C18 110 Å column and percentage purities were run over 30 min in water/acetonitrile with 0.1% formic acid (5 min at 5%, 5–95% over 20 min, 5 min at 95%) with the UV detector at 254 nm. Purifications were performed by flash chromatography on silica gel columns or C18 columns using a Combi flash RF 75 PSI, ISCO unit.

General Procedure

To a stirred solution of the appropriate 1,4-benzodiazepine or 1,3,4-benzotriazepine (0.030–1.00 mmol, 1 equiv) and diaryliodonium salt (0.033–1.10 mmol, 1.1 equiv) in DCE (5–10 mL) was added 25% w/w NH_3 solution (aq. 5–10 mL), and the reaction mixture was stirred for 30 min (unless stated other-

wise). Upon completion, the reaction mixture was diluted with dichloromethane (3 × 15 mL), and the layers were separated. Combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and purified by column chromatography, hexane/ethyl acetate (80:20 to 30:70).

1-(4-Nitrophenyl)-5-methyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3a)

The product was obtained as white solid (0.60 mmol scale, 170 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27–8.21 (m, ArH, 2 H), 7.62 (dd, $^3J_{HH}$ = 7.5, 1.5 Hz, ArH, 1 H), 7.40–7.35 (m, ArH, 3 H), 7.34–7.29 (m, ArH, 1 H), 6.82 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1 H), 4.70 (d, $^2J_{HH}$ = 10.5 Hz, $COCH_2$, 1 H), 3.83 (d, $^2J_{HH}$ = 10.5 Hz, $COCH_2$, 1 H), 2.62 (s, CH_3, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.1 (C=O), 168.1 (C=N), 146.7 (ArC), 146.0 (ArC), 140.8 (ArC), 131.4 (ArC), 131.3 (ArC), 128.7 (ArC × 2), 127.8 (ArC), 125.9 (ArC), 125.1 (ArC), 124.5 (ArC × 2), 56.6 ($COCH_2$), 25.5 (CH_3). ESI-HRMS: *m/z* calcd for $C_{16}H_{13}N_3O_3$ $[+H]^+$: 296.1030; found: 296.1033. LC–MS purity (UV) = 100%, t_R = 8.10 min.

1-(4-Nitrophenyl)-5-(propan-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3b)

The product was obtained as a white solid (0.52 mmol scale, 166 mg, 99%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27–8.20 (m, ArH, 2 H), 7.59 (dd, $^3J_{HH}$ = 7.5, 2.0 Hz, ArH, 1 H), 7.39–7.35 (m, ArH, 3 H), 7.34–7.30 (m, ArH, 1 H), 6.83 (dd, $^3J_{HH}$ = 8.0, 1.5 Hz, ArH, 1 H), 4.72 (d, $^2J_{HH}$ = 10.5 Hz, $COCH_2$, 1 H), 3.82 (d, $^2J_{HH}$ = 10.5 Hz, $COCH_2$, 1 H), 3.34–3.25 (m, 1 H), 1.35 (d, $^3J_{HH}$ = 7.0 Hz, $CNCHC_2CH_6$, 3 H), 1.11 (d, $^3J_{HH}$ = 7.0 Hz, $CNCHC_2CH_6$, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 176.9 (C=O), 168.7 (C=N), 146.7 (ArC), 145.9 (ArC), 141.5 (ArC), 131.6 (ArC), 130.9 (ArC), 128.3 (ArC × 2), 127.0 (ArC), 126.0 (ArC), 125.0 (ArC), 124.5 (ArC × 2), 56.5 ($COCH_2$), 35.6 ($CNCHC_2H_6$), 22.0 ($CNCHC_2H_6$), 19.2 ($CNCHC_2H_6$). ESI-HRMS: *m/z* calcd for $C_{18}H_{17}N_3O_3$ $[+H]^+$: 324.1270; found: 324.1281. LC–MS purity (UV) = 96 %, t_R = 18.73 min.

1-(4-Nitrophenyl)-3-(propan-2-yl)-5-(propan-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3c)

The product was obtained as white solid (0.25 mmol scale, 91 mg, 99%). ^{1}H NMR (500 MHz) $CDCl_3$: δ = 8.25–8.18 (m, ArH, 2 H), 7.61 (dd, $^3J_{HH}$ = 8.0, 1.5 Hz, ArH, 1H), 7.39–7.24 (m, ArH, 4 H), 6.85 (dd, *J* = 8.0, 1.5 Hz, ArH, 1 H), 3.27 (hept, $^3J_{HH}$ = 7.0 Hz, $CNCHCH_3CH_3$, 1 H), 3.12 (d, $^3J_{HH}$ = 9.5 Hz, $COCHCHC_2H_6$, 1 H), 2.72–2.61 (m, $COCHCHC_2H_6$, 1 H), 1.33 (d, $^3J_{HH}$ = 7.0 Hz, $CNCHC_2H_6$, 3 H), 1.07 (d, $^3J_{HH}$ = 7.0 Hz, $CNCHC_2CH_6$, 3 H), 1.05–1.02 (m, $COCHCHC_2H_6$, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 173.9 (C=O), 168.3 (C=N), 147.4 (ArC), 145.7 (ArC), 141.1 (ArC), 131.9 (ArC), 130.6 (ArC), 128.4 (ArC × 2), 126.8 (ArC), 125.7 (ArC), 125.1 (ArC), 124.4 (ArC × 2), 69.3 ($COCHCHC_2H_6$), 35.5 ($CNCHCH_3CH_3$), 22.2 ($COCHCHC_2H_6$), 21.9 ($CNCHC_2H_6$), 20.1, ($CNCHC_2H_6$) 19.3 ($COCHCHC_2H_6$), 18.7 ($COCHCHC_2H_6$). ESI-HRMS: *m/z* calcd for $C_{21}H_{23}N_3O_3$ $[+H]^+$: 366.1812; found: 366.1816. LC–MS purity (UV) = 95%, t_R = 23.47 min.

1-(4-Nitrophenyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3d)

The product was obtained as white solid (0.60 mmol scale, 176 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30–8.23 (m, ArH, 2 H), 7.77–7.71 (m, ArH, 2 H), 7.55–7.51 (m, ArH, 1 H), 7.49–7.45 (m, ArH, 3 H), 7.45–7.41 (m, ArH, 3 H), 7.29 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1 H), 6.94 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1 H), 4.96 (d, $^2J_{HH}$ = 10.5 Hz, $COCH_2$, 1 H), 4.03 (d, $^2J_{HH}$ = 10.5 Hz, $COCH_2$, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.3 (C=O), 168.3 (C=N), 146.7 (ArC), 146.0 (ArC), 142.7 (ArC), 138.4 (ArC), 131.4 (ArC), 130.8 (ArC), 130.4 (ArC), 130.3 (ArC), 129.4 (ArC × 2), 128.5 (ArC × 2), 128.4 (ArC × 2), 125.4 (ArC), 125.0 (ArC), 124.5 (ArC × 2), 57.4 ($COCH_2$). ESI-HRMS: *m/z* calcd for $C_{21}H_{15}N_3O_3$ $[+H]^+$: 358.1186; found: 358.1187. LC–MS purity (UV) = 95%, t_R = 18.35 min.

1-(4-Nitrophenyl)-3-benzyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3e)

The product was obtained as white solid (0.40 mmol scale, 140 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27–8.21 (m, ArH, 2 H), 7.67 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 2 H), 7.52–7.48 (m, 1 H), 7.47–7.43 (m, ArH, 2 H), 7.41–7.37 (m, ArH, 5 H), 7.36–7.30 (m, ArH, 3 H), 7.25–7.21 (m, ArH, 2 H), 6.90 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1 H), 4.01 (dd, *J* = 7.5, 6.0 Hz, $COCHCH_2$, 1 H), 3.68 (dd, $^{2,3}J_{HH}$ = 14.0, 6.0 Hz, $COCHCH_2$, 1 H), 3.62 (dd, $^{2,3}J_{HH}$ = 14.0, 7.5 Hz, $COCHCH_2$, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.8 (C=O), 168.5 (C=N), 147.1 (ArC), 145.9 (ArC), 142.1 (ArC), 138.9 (ArC), 138.4 (ArC), 131.5 (ArC), 130.8 (ArC), 130.5 (ArC), 130.3 (ArC), 130.0 (ArC × 2), 129.5 (ArC × 2), 128.6 (ArC × 2), 128.5 (ArC × 2), 128.3 (ArC × 2), 126.3 (ArC), 125.3 (ArC), 125.1 (ArC), 124.5 (ArC × 2), 65.6 ($COCHCH_2$), 37.9 ($COCHCH_2$). ESI-HRMS: *m/z* calcd for $C_{28}H_{21}N_3O_3$ $[+H]^+$: 448.1656; found: 448.1669. LC–MS purity (UV) = 99 %, t_R = 20.81 min.

7-Chloro-1-(4-nitrophenyl)-3-benzyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (3f)

The product was obtained as white solid (0.15 mmol scale, 54 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, $^3J_{HH}$ = 8.5 Hz, ArH, 2 H), 7.66 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 2 H), 7.57–7.50 (m, ArH, 1 H), 7.51–7.44 (m, ArH, 2 H), 7.42–7.36 (m, ArH, 3 H), 7.34–7.30 (m, ArH, 2 H), 7.26 (s, ArH, 3 H), 7.17 (d, *J* = 8.7 Hz, ArH, 1 H), 6.85 (d, $^3J_{HH}$ = 8.5 Hz, ArH, 1 H), 3.99 (dd, *J* = 7.5, 6.0 Hz, $COCHCH_2$, 1 H), 3.70–3.57 (m, $COCHCH_2$, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.4, (C=O), 167.2 (C=N), 146.6 (ArC), 146.1 (ArC), 140.6 (ArC), 138.6 (ArC), 137.7 (ArC), 131.7 (ArC), 131.1 (ArC), 129.9 (ArC × 2), 129.8 (ArC), 129.5 (ArC × 2), 128.7 (ArC × 2), 128.6 (ArC × 2), 128.3 (ArC × 2), 126.5 (ArC), 126.4 (ArC), 126.2 (ArC), 124.6 (ArC × 2), 119.3 (ArC) 65.8 ($COCHCH_2$), 37.9 ($COCHCH_2$). ESI-HRMS: *m/z* calcd for $C_{28}H_{20}ClN_3O_3$ $[+H]^+$: 482.1266; found: 482.1286. LC–MS purity (UV) = 95%, t_R = 19.71 min.

1-(4-Nitrophenyl)-3-benzyl-5-(pyridine-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3g)

The product was obtained as white solid (0.11 mmol scale, 38 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.67–8.62 (m, ArH, 1 H), 8.15 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 2 H), 8.18–8.12 (m, ArH, 1 H), 7.88–7.81 (m, ArH, 1 H), 7.44–7.42 (m, ArH, 2 H), 7.42–7.37 (m, ArH, 4 H), 7.35–7.26 (m, ArH, 3 H), 7.25–7.21 (m, ArH, 2 H), 6.89 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1 H), 4.10 (dd, $^3J_{HH}$ = 8.0, 6.0 Hz, $COCHCH_2$, 1 H), 3.70 (dd, $^{2,3}J_{HH}$ = 14.0, 7.0 Hz, $COCHCH_2$, 1 H), 3.62 (dd, $^{2,3}J_{HH}$ = 14.0, 7.5 Hz, $COCHCH_2$, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 168.6 (C=O), 167.6 (C=N), 155.9 (ArC), 148.7 (ArC), 147.1 (ArC), 145.9 (ArC), 141.9 (ArC), 138.9 (ArC), 136.8 (ArC), 131.4 (ArC), 130.8 (ArC), 129.9 (ArC × 2), 128.8 (ArC × 2), 128.3 (ArC × 2), 126.3 (ArC), 125.2 (ArC), 125.1 (ArC), 124.8 (ArC × 2), 124.4 (ArC × 2), 123.8 (ArC), 65.8 ($COCHCH_2$), 37.8 ($COCHCH_2$). ESI-HRMS: *m/z* calcd for $C_{27}H_{20}N_4O_3$ $[+H]^+$: 449.1608; found: 449.1617. LC–MS purity (UV) = 99%, t_R = 20.81 min.

1-(4-Nitrophenyl)-3-benzyl-5-(2′-fluorobiphenyl-2-yl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3h)

The product was obtained as white solid (0.03 mmol scale, 11 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.14 (d, $^3J_{HH}$ = 8.5 Hz, ArH, 2 H), 7.57–7.52 (m, ArH, 1 H), 7.51–7.45 (m, ArH, 1 H), 7.42 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 1 H), 7.38 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 1 H), 7.32–7.27 (m, ArH, 7 H), 7.26–7.19 (m, ArH, 2 H), 7.15–7.09 (m, ArH, 1 H), 7.06 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 1 H), 7.00–6.93 (m, ArH, 3 H), 6.65 (d, $^3J_{HH}$ = 8.5 Hz, ArH, 1 H), 3.80 (dd, $^3J_{HH}$ = 8.0, 5.5 Hz, $COCHCH_2$, 1 H), 3.69 (d, $^3J_{HH}$ = 8.0 Hz, $COCHCH_2$, 1 H), 3.66 (d, $^3J_{HH}$ = 8.0 Hz,

COCHCH_2, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.5 (C=O), 167.9 (C=N), 159.2 (d, $^1J_{FC}$ = 247.5 Hz, ArC) 147.1 (ArC), 145.7 (ArC), 141.5 (ArC), 138.8 (ArC), 138.7 (ArC), 135.7 (ArC), 132.0 (d, $^3J_{FC}$ = 3.5 Hz, ArC), 131.6 (ArC), 131.4 (ArC), 130.8 (ArC), 130.3 (ArC), 129.9 (ArC x 2), 129.8 (ArC), 129.5 (ArC), 129.2 (ArC), 128.9 (d, $^3J_{FC}$ = 8.0 Hz, ArC), 128.5 (ArC × 2), 128.3 (ArC × 2), 128.1 (ArC), 126.3 (ArC), 125.2 (ArC), 124.8 (ArC), 124.5 (d, $^4J_{FC}$ = 3.5 Hz, ArC), 124.2 (ArC x 2), 115.4 5 (d, $^2J_{FC}$ = 22.0 Hz, ArC) 66.0 (COCHCH$_2$), 37.8 (COCHCH$_2$). ESI-HRMS: *m/z* calcd for $C_{34}H_{24}N_3O_3$ [+H]$^+$: 542.1874; found: 542.1881. LC–MS purity (UV) = 93%, t_R = 23.27 min.

1-(2,4,6-Trimethylphenyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3i)

The reaction was run for 8 h. The product was obtained as white solid (1.00 mmol scale, 181 mg, 51%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.60–7.57 (m, ArH, 2 H), 7.54–7.46 (m, ArH, 4 H), 7.32 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1 H), 7.27–7.23 (m, ArH, 1 H), 7.10–7.07 (m, ArH, 1 H), 6.88 (s, ArH, 1 H), 6.78 (d, $^3J_{HH}$ = 8.0, 1.1 Hz, ArH, 1 H), 4.70 (d, $^2J_{HH}$ = 10.0 Hz, COCH_2,1 H), 4.04 (d, $^2J_{HH}$ = 10.0 Hz, COCH_2, 1 H), 2.26 (s, CH_3, 3 H), 2.24 (s, CH_3, 3 H), 1.61 (s, CH_3, 3 H). ^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.3 (C=O), 167.5 (C=N), 142.2 (ArC), 138.9 (ArC), 137.9 (ArC), 137.0 (ArC), 136.2 (ArC), 134.7 (ArC), 132.3 (ArC), 130.9 (ArC), 130.0 (ArC × 2), 129.6 (ArC × 2), 129.5 (ArC), 128.9 (ArC × 2), 128.7 (ArC), 124.4 (ArC), 122.1 (ArC), 57.3 (COCH_2), 21.0 (CH_3), 18.5(CH_3), 17.5 (CH_3). ESI-HRMS: *m/z* calcd for $C_{24}H_{22}N_2O$ [+H]$^+$: 355.1805; found: 355.1804. LC–MS purity (UV) = 97%, t_R = 21.13 min.

1-(2-Bromophenyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3j)

The reaction was run for 8 h. The product was obtained as white solid (1.00 mmol scale, 31 mg, 8%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.84 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1 H), 7.70 (d, $^3J_{HH}$ = 8.0 Hz, ArH, 1 H), 7.66–7.59 (m, ArH, 4 H), 7.52–7.46 (m, ArH, 3 H), 7.41–7.37 (m, ArH, 1 H), 7.32 (dd, *J* = 7.8, 1.7 Hz, ArH, 1 H), 7.27 (d, $^3J_{HH}$ = 7.0 Hz, ArH, 1 H), 6.92–6.83 (m, ArH, 1 H), 4.69 (d, $^2J_{HH}$ = 10.5 Hz, COCH_2, 1 H), 4.01 (d, $^2J_{HH}$ = 10.5 Hz, COCH_2, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.7 (C=O), 168.9 (C=N), 142.0 (ArC), 138.9 (ArC), 138.6 (ArC), 134.3 (ArC), 133.7 (ArC), 132.0 (ArC), 131.0 (ArC), 130.9 (ArC), 130.8 (ArC), 129.9 (ArC × 2), 129.8 (ArC), 129.1 (ArC), 128.8 (ArC × 2), 124.7 (ArC), 123.0 (ArC), 121.5 (ArC), 57.0 (COCH$_2$). ESI-HRMS: *m/z* calcd for $C_{21}H_{15}BrN_2O$ [+H]$^+$: 391.0441; found: 391.0457. LC–MS purity (UV) = 93%, t_R = 15.23 min.

1-(3′-Trifluoromethylphenyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3k)

The reaction was run for 8 h. The product was obtained as white solid (0.50 mmol scale, 80 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 2 H), 7.60–7.55 (m, ArH, 2 H), 7.53 (d, $^3J_{HH}$ = 8.5 Hz, ArH, 2 H), 7.49–7.45 (m, ArH, 2 H), 7.44–7.38 (m, ArH, 3 H), 7.25–7.20 (m, ArH, 1 H), 6.92 (d,$^3J_{HH}$ = 8.5 Hz, ArH, 1 H), 4.95 (d, $^2J_{HH}$ = 10.5 Hz, COCH_2, 1 H), 4.02 (d, $^2J_{HH}$ = 10.5 Hz, COCH_2, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.3 (C=O), 168.3 (C=N), 143.1 (ArC), 141.3 (ArC), 138.6 (ArC), 132.0 (q, $^2J_{FC}$ = 29.9 Hz, ArC), 131.9 (ArC), 131.6 (ArC), 131.4 (ArC), 130.7 (ArC), 130.4 (ArC), 129.8 (ArC × 2), 129.5 (ArC), 128.5 (ArC × 2), 125.2 (q, $^3J_{FC}$ = 3.5 Hz, ArC), 124.8 (ArC), 124.8 (ArC), 123.5 (q, $^1J_{FC}$ = 273.0 Hz, ArC), 124.2 (q, $^3J_{FC}$ = 3.5 Hz, ArC), 57.3 (COCH$_2$). ESI-HRMS: *m/z* calcd for $C_{22}H_{15}F_3N_2O$ [+H]$^+$: 381.1209; found: 381.1208. LC–MS purity (UV) = 96%, t_R = 21.35 min.

1-Phenyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3l)

The reaction was run for 8 h. The product was obtained as white solid (0.50 mmol scale, 14 mg, 9%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 2 H), 7.54–7.49 (m, ArH, 1 H), 7.47 (d, $^3J_{HH}$ = 7.5 Hz, ArH, 2 H), 7.43–7.38 (m, ArH, 2 H), 7.37–7.30 (m, ArH, 2 H), 7.24–7.21 (m, ArH, 3 H), 7.20–7.16 (m, ArH, 1 H), 6.97 (d, $^3J_{HH}$ = 8.5 Hz, ArH, 1 H), 4.96 (d, $^2J_{HH}$ = 10.5 Hz, ArH, COCH_2, 1 H), 4.01 (d, $^2J_{HH}$ = 10.5 Hz, COCH_2, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.7 (C=O), 168.3 (C=N), 146.5 (ArC), 143.3 (ArC), 140.7 (ArC), 138.6 (ArC), 131.3 (ArC), 130.7 (ArC), 130.3 (ArC), 129.6 (ArC × 2), 129.3 (ArC × 2), 128.4 (ArC × 2), 128.3 (ArC × 2), 127.5 (ArC), 124.7 (ArC), 124.2 (ArC), 57.2 (COCH_2). ESI-HRMS: *m/z* calcd for $C_{21}H_{16}N_2O$ [+H]$^+$: 313.1335; found: 313.1338. LC–MS purity (UV) = 90%, t_R = 16.10 min.

1-(4-Nitrophenyl)-3-(4-nitrophenyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (7)

The product was obtained as white solid (0.60 mmol scale, 2 equiv of diaryliodonium triflate, 146 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34–8.22 (m, ArH, 4 H), 7.85–7.79 (m, ArH, 2 H), 7.77–7.71 (m, ArH, 2 H), 7.74–7.57 (m, ArH, 3 H), 7.59–7.50 (m, ArH, 3 H), 7.41–7.32 (m, ArH, 2 H), 7.07–7.02 (m, ArH, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.0 (C=O), 158.3 (C=N), 149.1 (ArC), 146.7 (ArC), 145.6 (ArC), 144.1 (ArC), 143.3 (ArC), 135.0 (ArC), 132.6 (ArC), 131.5 (ArC), 129.9 (ArC), 129.6 (ArC), 129.5 (ArC × 2), 128.9 (ArC × 2), 126.8 (ArC × 2), 126.3 (ArC), 125.4 (ArC) 124.5 (ArC × 2), 124.3 (ArC × 2), 121.3 (ArC × 2). ESI-HRMS: *m/z* calcd for $C_{26}H_{17}N_5O_5$ [+H]$^+$: 480.1230; found: 480.1245. LC–MS purity (UV) = 95%, t_R = 18.35 min.

1,1′-Oxybis(4-nitrobenzene)

To a solution of (4-nitrophenyl)phenyliodonium triflate (30 mg, 0.06 mmol) in DCE (1 mL) was added sodium hydroxide (aq., 1 mL) and stirred for 20 min at room temperature. Upon completion, the reaction was diluted with dichloromethane (5 mL × 3) and the layers were separated. Combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford the product as a white powder (7 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33–8.27 (m, ArH, 4 H), 7.19–7.14 (m, ArH, 4 H).^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.6 (ArC × 2), 144.2 (ArC × 2), 126.2 (ArC × 4), 119.3 (ArC × 4). ESI-HRMS: *m/z* calcd for $C_{12}H_8N_2O_5$ [+H]$^+$: 261.0511; found: 261.0513.

(43) CCDC numbers 1560492–1560494 contain the supplementary crystallographic data for compounds **3a**, **3h**, **3i**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.