N1-Arylation of 1,4-Benzodiazepine-2-ones with Diaryliodonium Salts

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Received: 13.07.2017
Accepted after revision: 06.09.2017
Published online: 25.09.2017
DOI: 10.1055/s-0036-1590920; Art ID: st-2017-d0556-l

Abstract A library of N1-arylated 5-phenyl-1,3-dihydro-2H-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.

Keywords 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 antagonist19 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 benzodiazepines26,27 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 N1-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 NH3 (25% w/w) and NaOH (sat. aq.) gave similar and the best results (Table 2, entries 1, 2).

Hence, optimal conditions appeared to use NH3 (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-
drawing groups is preferable. 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.

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

| Entry | Solvent | Conversion (%)<sup>a</sup> |
|-------|---------|---------------------------|
| 1     | toluene | 95                        |
| 2     | DCE     | 99                        |
| 3     | PEG     | –                         |
| 4     | AcOH    | –                         |
| 5     | CHCl₃   | 85                        |

<sup>a</sup> LC–MS conversion.

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

| Entry | Base          | Conversion (%)<sup>a</sup> |
|-------|---------------|-----------------------------|
| 1     | NaOH (sat. aq.) | 99                          |
| 2     | NH₃ (25% w/w)  | 99                          |
| 3     | K₂CO₃         | 80                          |
| 4     | NaH           | –                           |

<sup>a</sup> LC–MS conversion.

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 diaryiodonium 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 triflate gave, at best, traces of products.

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.

Table 3 Further N-Arylation of 1,4-Benzodiazepines

| Salt | Product (major) | Product (minor) |
|------|----------------|-----------------|
| OTf– | 3i; 51%        | 3j; 8%          |
| CF3  | 3k; 42%        | 3l; 9%          |

Table 4 Diaryl Ether Formation

| Substrate | Expected product | Observed product |
|-----------|------------------|------------------|
|           | 8                | 9: 0%            |
|           | 10               | 43%              |
|           | 11               | 10: 45%          |
|           | 12               | 0%               |

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).

Funding Information
R.K. is funded by an EPSRC/AZ funded PhD studentship [EP/M507568/1] with additional support from AstraZeneca [14550001 (SME)] and Tocris Biosciences. The EPSRC is also thanked for funding the UK National Crystallography Service

Acknowledgment
We thank Dr. Alaa Abdul-Sada (Sussex) and the EPSRC UK National Mass Spectrometry Facility at Swansea University for HRMS measurements.
Supporting Information

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

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The product was obtained as white solid (0.00 mmol scale, 170 mg, 96%). 1H NMR (500 MHz, CDCl3): δ = 8.27–8.22 (m, ArH, 2 H), 7.62 (dd, JHH = 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, JHH = 8.0 Hz, ArH, 1 H), 4.70 (d, JHH = 10.5 Hz, COCH3, 1 H), 3.83 (d, JHH = 10.5 Hz, COCH3, 1 H), 2.62 (s, CH3, 3 H). 13C NMR (126 MHz, CDCl3): δ = 170.1 (C=O), 168.1 (C=O), 146.7 (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 (COCH3), 25.5 (CH3). ESI-HRMS: m/z calc. for C16H13N3O3 [+H]+: 296.1030; found: 296.1033. LC-MS purity (UV) = 100%, tR = 8.10 min.

1-(4-Nitrophenyl)-5-(propan-2-yl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one (3b)
The product was obtained as a white solid (0.52 mmol scale, 166 mg, 95%). 1H NMR (500 MHz, CDCl3): δ = 8.27–8.20 (m, ArH, 2 H), 7.59 (dd, JHH = 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, JHH = 8.0, 1.5 Hz, ArH, 1 H), 4.72 (d, JHH = 10.5 Hz, COCH3, 1 H), 3.82 (d, JHH = 10.5 Hz, COCH3, 1 H), 3.34–3.25 (m, 1 H), 1.35 (d, JHH = 7.0 Hz, CNHC3H3, 1 H), 1.11 (d, JHH = 7.0 Hz, CNHC3H3, 1 H). 13C NMR (126 MHz, CDCl3): δ = 176.9 (C=O), 168.0 (C=O), 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 (COCH3), 35.6 (CNHC3H1), 22.0 (CNHC3H2), 19.2 (CNHC3H2). ESI-HRMS: m/z calc. for C16H13N3O3 [+H]+: 296.1030; found: 296.1281. LC-MS purity (UV) = 96%, tR = 18.73 min.

1-(4-Nitrophenyl)-3-(propan-2-yl)-5-(propan-2-yl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one (3c)
The product was obtained as white solid (0.025 mmol scale, 91 mg, 99%). 1H NMR (500 MHz, CDCl3): δ = 8.25–8.18 (m, ArH, 2 H), 7.61 (dd, JHH = 8.0, 1.5 Hz, ArH, 1 H), 7.39–7.24 (m, ArH, 4 H), 6.85 (dd, JHH = 7.0, 1.5 Hz, ArH, 1 H), 3.27 (hept, JHH = 7.0 Hz, COCH2CH2, 1 H), 3.12 (d, JHH = 9.5 Hz, COCH2CH2, 1 H), 2.72–2.61 (m, COCH2CH2, 1 H), 1.33 (d, JHH = 7.0 Hz, CNHC3H3, 1 H), 1.07 (t, JHH = 7.0 Hz, CNHC3H3, 3 H), 1.05–1.02 (m, COCH2CH2, 6 H). 13C NMR (126 MHz, CDCl3): δ = 173.9 (C=O), 168.3 (C=O), 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 (COCH2CH2), 35.5 (CNHC3H1), 22.2 (COCH2CH2), 21.9 (CNHC3H1), 20.1 (CNHC3H1), 19.3 (CNHC3H1), 18.7 (CNHC3H1). ESI-HRMS: m/z calc. for C21H23N3O3 [+H]+: 366.1812; found: 366.1816. LC-MS purity (UV) = 96%, tR = 23.47 min.

1-(4-Nitrophenyl)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (3d)
The product was obtained as white solid (0.60 mmol scale, 176 mg, 82%). 1H NMR (500 MHz, CDCl3): 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, JHH = 8.0 Hz, ArH, 1 H), 6.94 (d, JHH = 8.0 Hz, ArH, 1 H), 4.96 (d, JHH = 10.5 Hz, COCH3, 1 H), 4.03 (d, JHH = 10.5 Hz, COCH3, 1 H). 13C NMR (126 MHz, CDCl3): δ = 170.3 (C=O), 168.3 (C=O), 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), 124.3 (ArC × 2), 57.4 (COCH3). ESI-HRMS: m/z calc. for C21H18N3O3 [+H]+: 358.1186; found: 358.1187. LC-MS purity (UV) = 95%, tR = 18.35 min.
The reaction was run for 8 h. The product was obtained as white solid (0.50 mmol scale, 14 mg, 9%). 1H NMR (500 MHz, CDCl3): δ = 7.72 (d, JHH = 7.5 Hz, ArH, 2 H), 7.54–7.49 (m, ArH, 1 H), 7.47 (d, JHH = 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, JHH = 8.5 Hz, ArH, 1 H), 4.96 (d, JHH = 10.5 Hz, ArH, COCH2, 1 H), 4.01 (d, JHH = 10.5 Hz, COCH2, 1 H). 13C NMR (126 MHz, CDCl3): δ = 170.9 (CO), 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), 126.0 (ArC), 127.4 (ArC), 124.2 (ArC), 124.7 (ArC). ESI-HRMS: m/z calcd for C12H10F3N2O [+H+] = 247.1026; found: 247.1025. LC–MS purity (UV) = 96%, tR = 21.35 min.

1-Phenyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (3i)

The product was obtained as white solid (0.60 mmol scale, 2 equiv of diaryliodonium triflate, 146 mg, 51%). 1H NMR (500 MHz, CDCl3): δ = 7.72 (d, JHH = 7.5 Hz, ArH, 2 H), 7.58–7.48 (m, ArH, 2 H), 7.43–7.38 (m, ArH, 2 H), 7.37–7.30 (m, ArH, 2 H), 7.20–7.14 (m, ArH, 4 H), 7.19–7.14 (m, ArH, 2 H), 7.07–7.02 (m, ArH, 1 H). 13C NMR (126 MHz, CDCl3): δ = 170.7 (CO), 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), 126.0 (ArC), 127.4 (ArC), 124.2 (ArC), 124.7 (ArC). ESI-HRMS: m/z calcd for C12H10F3N2O [+H+] = 381.1214; found: 381.1209. LC–MS purity (UV) = 90%, tR = 16.10 min.

1-(4-Nitrophenyl)-3-(4-nitrophenyl)-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepine-2-one (3j)

The product was obtained as white solid (0.60 mmol scale, 2 equiv of diaryliodonium triflate, 146 mg, 51%). 1H NMR (500 MHz, CDCl3): 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). 13C NMR (126 MHz, CDCl3): δ = 166.0 (CO), 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), 124.3 (ArC × 2), 124.3 (ArC × 2), 123.1 (ArC × 2). ESI-HRMS: m/z calcd for C12H10F3N2O2 [+H+] = 490.1280; found: 480.1245. LC–MS purity (UV) = 95%, tR = 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 (MgSO4) and concentrated under reduced pressure to afford the product as a white powder (7 mg, 43%). 1H NMR (500 MHz, CDCl3): δ = 8.33–8.27 (m, ArH, 4 H), 7.19–7.14 (m, ArH, 4 H), 13C NMR (126 MHz, CDCl3): δ = 166.0 (ArC × 2), 144.2 (ArC × 2), 126.2 (ArC × 4), 119.3 (ArC × 4). ESI-HRMS: m/z calcd for C12H10F3N2O2 [+H+] = 261.0511; found: 261.0513.

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