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A General Synthesis of Benzoazepinoindoles – A New Class of Heterocycles

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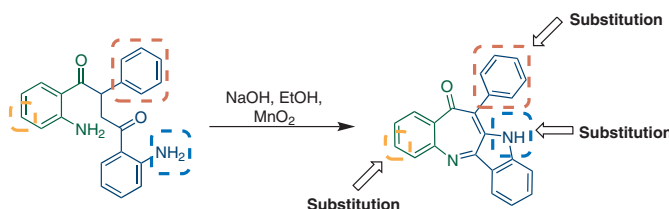
- New class of heterocycles
- Highly functionalisable structures
- Efficient two-step synthesis
- Inexpensive

43–68% Yield
16 Novel derivatives

Abstract A new class of heterocyclic compounds, namely the benzoazepinoindolones, has been synthesised through a base-catalysed cyclisation reaction of 1,4-bis(2-aminophenyl)-2-phenylbutane-1,4-dione derivatives and features the prominent seven-membered azepine ring moiety. This synthesis has considerable scope for the rapid generation of more complex structures and is inexpensive and generally applicable.

Key words dihydrobenzo[6,7]azepino[3,2-c]indolones, fused-ring systems, umpolung, condensation, heterocycles

Heterocyclic compounds, in particular those containing the indole moiety, are a core focus for medicinal chemists due to the inherent range of biological properties associated with them. The indole moiety can be found in many natural products and has the potential for the introduction of high degrees of functionality.[1] Various indole-containing compounds have found applications in the treatment of cancer,[2] bacterial infections,[2–4] and type-II diabetes.[5]

Similarly, compounds containing the benzazepine scaffold have attracted significant attention due to their broad applicability, most prominently as drugs for the treatment of heart conditions[6] and neuropsychiatric disorders[7] as well as in the treatment of various cancers.[8]

Fusion of the indole moiety with the benzazepine scaffold would generate an interesting collection of compounds with potentially diverse biological properties. Although various approaches have been used to generate indole and benzazepine derivatives, a suitable synthetic route to fused indole and benzazepine derivatives is required. To date, there are no reports of the synthesis of dihydroben-zo[6,7]azepino[3,2-c]indoles and only limited reports relating to the synthesis and functionalisation of the benzoazepine scaffold with other heterocycles.[9,10]

Previously, we described the generation of 1,4-bis(2-aminophenyl)-2-phenylbutane-1,4-diones through a base-catalysed addition, oxidation, and ring-cleavage process starting with 2-aminochalcones and 2-oxindole. We showed that the second amine functionality is crucial for the generation of the novel benzo[6,7]azepino[3,2-c]quinolinones.[9]

In this work we have developed a two-step synthesis of a new class of heterocycles, namely the benzo[6,7]azepino[3,2-c]indolones. The initial base-catalysed reaction of 2-aminochalcone with 2-oxindole using manganese dioxide and DMSO gives the intermediate 1,4-bis(2-aminophenyl)-2-phenylbutane-1,4-dione, and a subsequent base-catalysed reaction with manganese dioxide and ethanol gives the previously unreported benzo[6,7]azepino[3,2-b]indol-12(10H)-one ring system (Scheme 1).
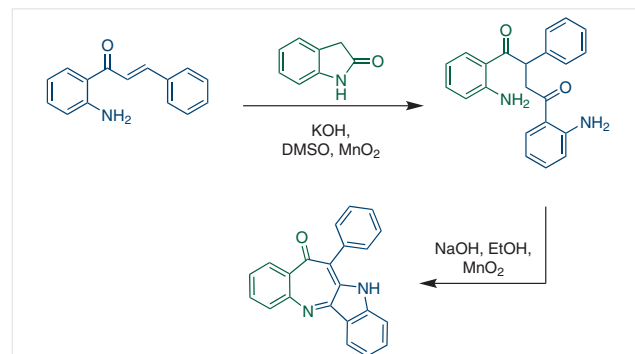
Scheme 1 Accessing a new class of heterocycles: benzo[6,7]azepino[3,2-c]indolones

The formation of the novel benzo[6,7]azepino[3,2-*c*]in-dolones is possible through an oxidative cyclisation of di-amino-1,4-diketones, which have been previously reported by our group.[9] However, these are now more readily available through an improved synthesis using potassium hydroxide and manganese dioxide in DMSO. In order to optimise the conditions for the condensation reaction, 1,4-bis(2-aminophenyl)-2-(4-iodophenyl)butane-1,4-dione (**1**) was used as a model substrate to generate 11-(4-iodophe-nyl)benzo[6,7]azepino[3,2-*b*]indol-12(10*H*)-one (**2**, Scheme 2, Table 1).
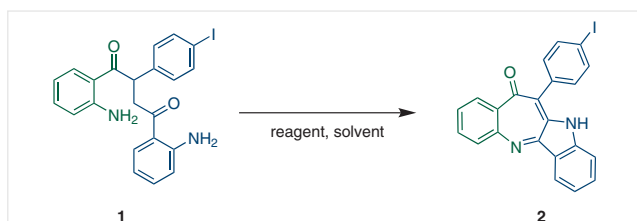
Scheme 2 Conversion of 1,4-bis(2-aminophenyl)-2-(4-iodophenyl)bu-tane-1,4-dione 1 into 11-(4-iodophenyl)benzo[6,7]azepino[3,2-*b*]indol-12(10*H*)-one (**2**)

Table 1 Optimisation of Condensation Reaction to Generate 11-(4-Io-dophenyl)benzo[6,7]azepino[3,2-*b*]indol-12(10*H*)-one (**2**)

Entry	Reagent	Solvent	Time (h)	Temp (°C)	Yield (%)
1	PTSA	EtOH	24	80	0
2	PTSA	2-PrOH	24	80	0
3	KOH	DMSO	48	80	0
4	NaOH	DMSO	48	80	0
5	NaOH	EtOH	48	80	49
6	NaOH	EtO Hair bubbled	48	80	49
7	NaOH/MnO$_2$	EtOH	48	80	60

Under acidic conditions several byproducts were generated, none of which were the desired compound (Table 1, entries 1 and 2). Strongly basic conditions in DMSO did not give the desired product (Table 1, entries 3 and 4); whereas use of sodium hydroxide in ethanol, either with or without bubbled air, gave a moderate yield of the desired product (Table 1, entries 5 and 6). The addition of manganese dioxide (1 equiv) improved the yield of 11-(4-iodophenyl)ben-

zo[6,7]azepino[3,2-*b*]indol-12(10*H*)-one (**2**) to 60% (Table 1, entry 7). Increasing the amount of manganese dioxide gave no further improvement.

The benzo[6,7]azepino[3,2-*c*]indolone moiety presumably arises through the initial imine formation between the primary amine featured in the (2-aminophenyl)(oxo)meth-anide and the 4-carbonyl group of the 1,4-bis(2-aminophe-nyl)-2-(4-iodophenyl)butane-1,4-dione (**1**) to give 2-(2-aminophenyl)-4-(4-iodophenyl)-3,4-dihydro-5*H*-benzo-[*b*]azepin-5-one (**3**). An oxidation step generates the α,β-unsaturated ketone **4** allowing for nucleophilic attack of the remaining free amine to form the 11-(4-iodophenyl)-10,10a-dihydrobenzo[6,7]azepino[3,2-*b*]indol-12-ol (**5**), with a final oxidation to give the desired 11-(4-iodophe-nyl)benzo[6,7]azepino[3,2-*b*]indol-12(10*H*)-one (**2**, Scheme 3).
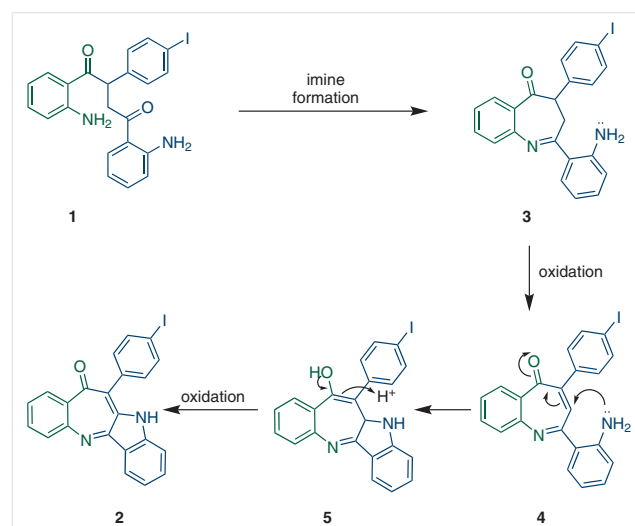
Scheme 3 Proposed mechanism for formation of **2**

Alternatively, oxidation of **1** to an ene-dione structure **6** would allow for the formation of a 3-indolinone **7**, which could undergo imine formation and subsequent oxidation to give the observed product **2** (Scheme 4).
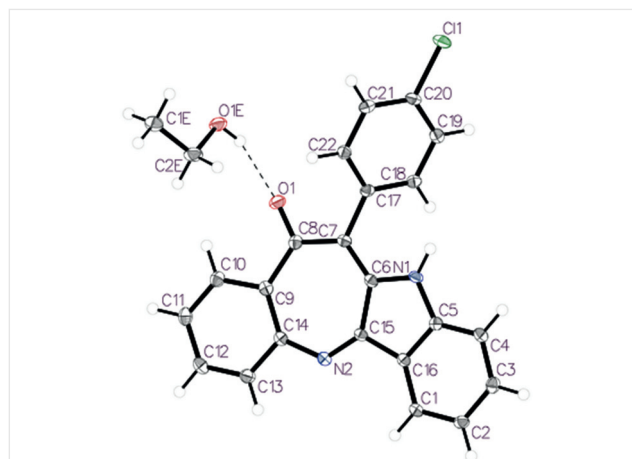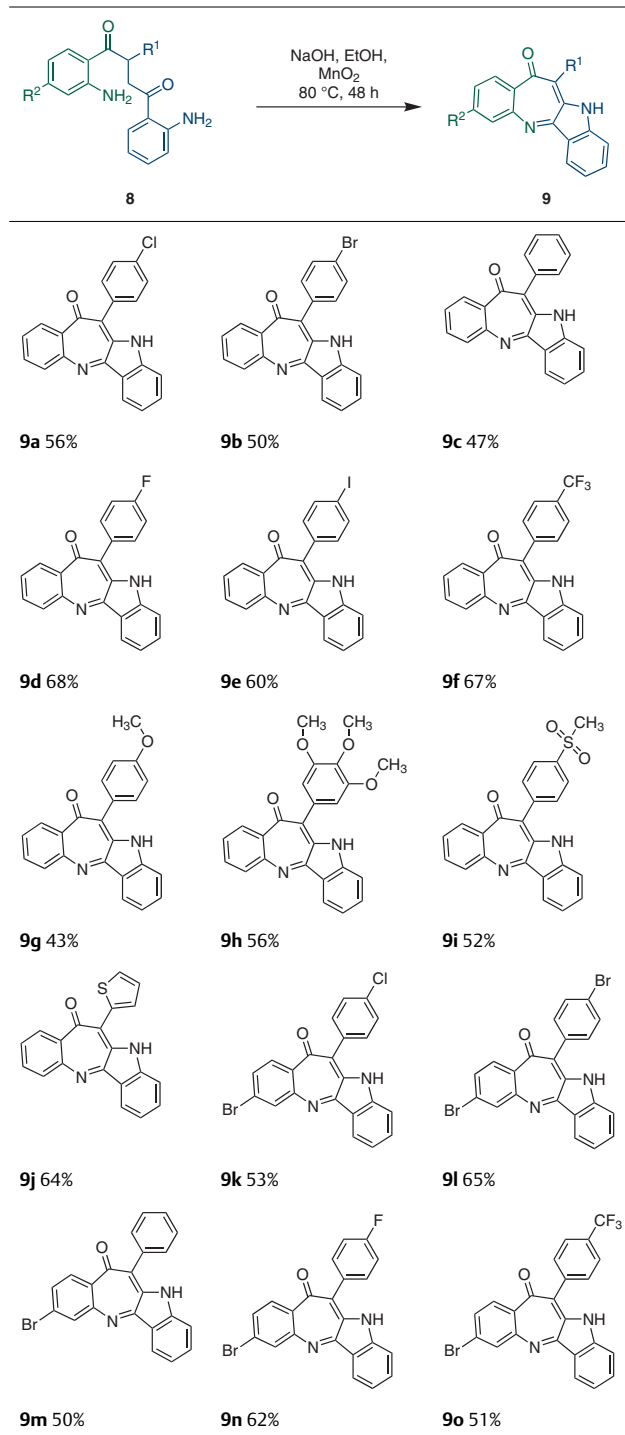
The reaction is general and tolerates both electron-withdrawing and electron-donating groups on the pendant phenyl ring. The structures of compounds **9a–o** (Table 2) were determined by spectroscopic analysis. For example, the ^{1}H NMR spectrum of compound **9a** showed a signal at δ = 10.10 ppm corresponding to the indole NH. The struc-
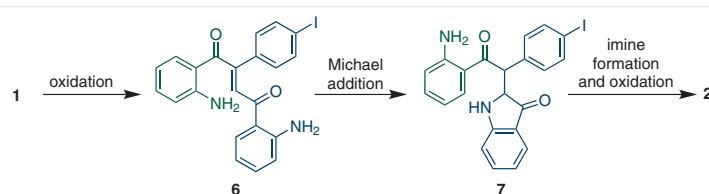
**Scheme 4** Alternative mechanism for formation of compound **2**

ture of **9a** matched the expected molecular mass of $m/z =$ 357.0788 and was further confirmed by X-ray crystallographic analysis (Figure 1).

Table 2 Synthesised Benzo[6,7]azepino[3,2-*b*]indolones **9**

9a 56%   **9b** 50%   **9c** 47%

9d 68%   **9e** 60%   **9f** 67%

9g 43%   **9h** 56%   **9i** 52%

9j 64%   **9k** 53%   **9l** 65%

9m 50%   **9n** 62%   **9o** 51%

Figure 1 ORTEP diagram of compound **9a**

It would be logical to assume that a direct one-pot synthesis of dihydrobenzo[6,7]azepino[3,2-*c*]indolones is possible, starting with 2-aminochalcones and oxindoles. To explore this possibility, we reacted (*E*)-1-(2-aminophenyl)-3-(4-chlorophenyl)prop-2-en-1-one (**10**) with 2-oxindole (**11**) under a range of conditions (Scheme 5).
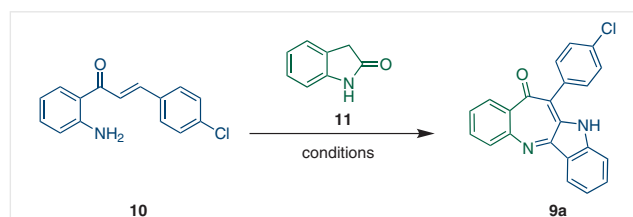
**Scheme 5** Attempted one-pot synthesis of **9a**

The conditions included a variety of organic and inorganic bases as well as solvents and temperatures, but the desired 11-(4-chlorophenyl)benzo[6,7]azepino[3,2-*b*]indol-12(10*H*)-one (**9a**) could only be generated in very limited yields. At best, only 11% of the desired final product was obtained when potassium carbonate and DMSO were used at 80 °C. Increasing the temperature further to 150 °C resulted in a large amount of byproducts, whereas conducting the reaction at room temperature gave only traces of product. Use of other solvents such as DMF or acetonitrile provided no improvement. Changing to a stronger base such as sodium hydroxide or potassium hydroxide resulted in no product formation and use of a range of organic or inorganic bases led to complex reaction mixtures and only trace amounts of product.

Improvements were made to the previously reported 1,4-diketone synthesis,[9] with the use of potassium hydroxide and manganese dioxide in DMSO significantly improving the yield and ease of purification of the 1,4-bis(2-aminophenyl)-2-phenylbutane-1,4-diones. Additionally, previ-

ously unreported 1,4-bis(2-aminophenyl)-2-phenylbutane-1,4-dione derivatives were successfully synthesised using the new method.

Given the improved method for the synthesis of the 1,4-bis(2-aminophenyl)-2-phenylbutane-1,4-diones and the subsequent base-catalysed oxidative cyclisation reaction to generate the desired benzo[6,7]azepino[3,2-b]indol-12-ones, the two-step synthesis is clearly preferred.
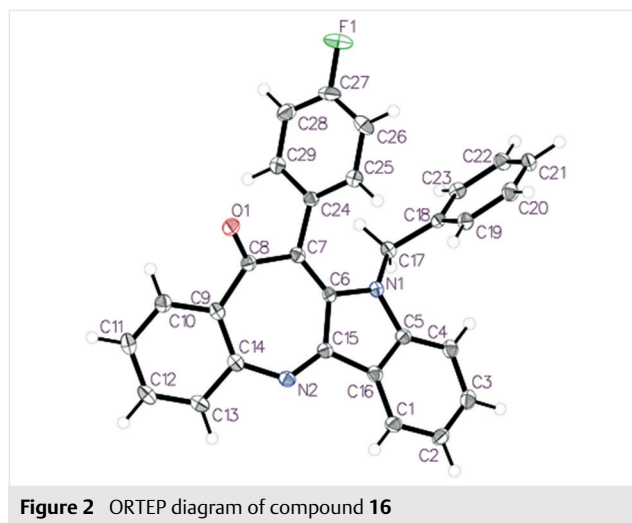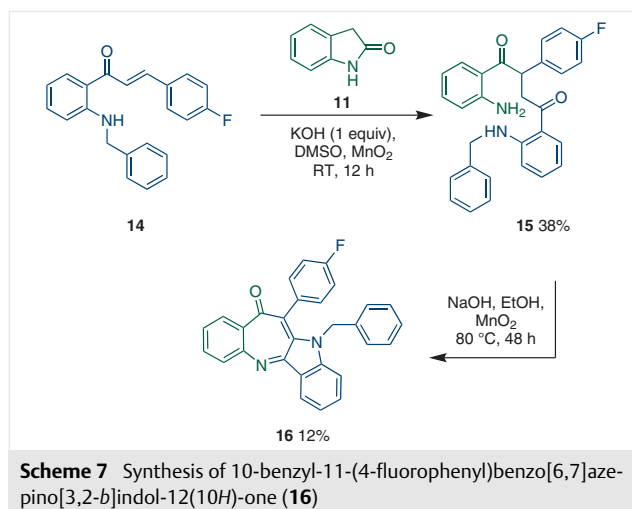
In an attempt to isolate the intermediate 2-(2-amino-phenyl)-4-(4-iodophenyl)-3,4-dihydro-5H-benzo[b]azepin-5-one 3, N-protected 1,4-bis(2-aminophenyl)-2-(4-io-dophenyl)butane-1,4-diones were used. However, when N-{2-[4-(2-aminophenyl)-3-(4-iodophenyl)-4-oxobutanoyl]phenyl}acetamide (12) or tert-butyl {2-[4-(2-amino-phenyl)-3-(4-iodophenyl)-4-oxobutanoyl]phenyl}carbamate (13) were used with sodium hydroxide and manganese dioxide in ethanol, both reactions gave the same isolated product, namely the final 11-(4-iodophenyl)benzo[6,7]aze-pino[3,2-b]indol-12(10H)-one (2, Scheme 6). This suggests that deprotection of the amide to a free amine takes place before formation of the 5-membered ring.

Scheme 6 Deprotection of the amide to generate 11-(4-iodophe-nyl)benzo[6,7]azepino[3,2-b]indol-12(10H)-one (2)
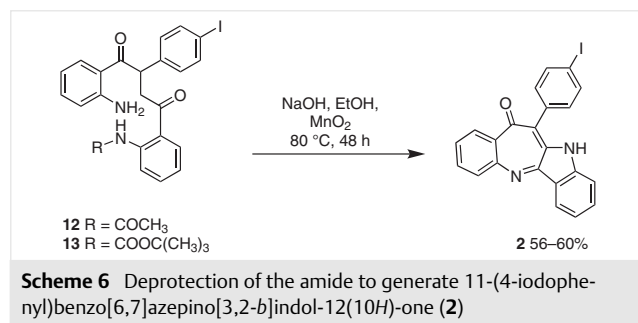
Alternatively, reaction of 1-[2-(benzylamino)phenyl]-3-(4-fluorophenyl)prop-2-en-1-one (14) with oxindole 11 gave the 1-(2-aminophenyl)-4-(2-(benzylamino)phenyl)-2-(4-fluorophenyl)butane-1,4-dione (15) and subsequent cy-clisation under the previously used conditions gave the N-substituted 10-benzyl-11-(4-fluorophenyl)benzo[6,7]aze-pino[3,2-b]indol-12(10H)-one (16, Scheme 7).

The structure of compound 16 was determined by spec-troscopic analysis with the ¹H NMR spectrum showing a singlet at δ = 4.64 ppm corresponding to the benzyl group. The structure of compound 16 matched the expected mo-lecular mass of m/z = 431.1554 and was further confirmed by X-ray crystallographic analysis (Figure 2).

An AlamarBlue assay was used to test the 11-phenyl-benzo[6,7]azepino[3,2-b]indol-12(10H)-one derivatives against breast cancer adenocarcinoma cells (MCF-7 cells). The novel analogues display inhibitory activity against the growth of MCF-7 cells. For example, compound 9a was found to have an IC₅₀ of 72.9 µM and compound 9f dis-played similar activity of 73.8 µM. Therefore, there is po-

Scheme 7 Synthesis of 10-benzyl-11-(4-fluorophenyl)benzo[6,7]aze-pino[3,2-b]indol-12(10H)-one (16)

Figure 2 ORTEP diagram of compound 16

tential to explore further and develop biologically active compounds based on this novel scaffold.

In summary, the rapid access to 11-phenylbenzo-[6,7]azepino[3,2-b]indol-12(10H)-one derivatives has been achieved through a robust synthetic pathway proceeding via an efficient two-step procedure with initial formation of the 1,4-bis(2-aminophenyl)-2-phenylbutane-1,4-dione in-termediates, followed by a base-catalysed oxidative cyclisa-tion reaction. The described synthesis has broad substrate scope and can be used to access a new class of heterocyclic compounds, namely the benzo[6,7]azepino[3,2-b]indol-12-ones, in moderate to high yields. This synthetic strategy is efficient and low cost and provides quick access to the de-sirable azepine moiety that can be seen in a range of drugs on the market today. These novel structures open the possi-bility of generating new biologically active compounds.

Synlett J. C. Dobrowolski et al. **Letter**

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690700.

References and Notes

(1) Singh, T. P.; Singh, O. M. *Mini-Rev. Med. Chem.* **2018**, *18*, 9.
(2) Lindsay, A. C.; Kim, S. H.; Sperry, J. *Nat. Prod. Rep.* **2018**, *35*, 1347.
(3) Melander, R. J.; Minvielle, M. J.; Melander, C. *Tetrahedron* **2014**, *70*, 6363.
(4) Mielczarek, M.; Thomas, R. V.; Ma, C.; Kandemir, H.; Yang, X.; Bhadbhade, M.; Black, D. S.; Griffith, R.; Lewis, P. J.; Kumar, N. *Bioorg. Med. Chem.* **2015**, *23*, 1763.
(5) Lamotte, Y.; Martres, P.; Faucher, N.; Laroze, A.; Grillot, D.; Ancellin, N.; Saintillan, Y.; Beneton, V.; Gampe, R. T. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1399.
(6) Fukuda, H.; Ito, S.; Watari, K.; Mogi, C.; Arisawa, M.; Okajima, F.; Kurose, H.; Shuto, S. *ACS Med. Chem. Lett.* **2016**, *7*, 493.
(7) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14048.
(8) Al-Qawasmeh, R. A.; Lee, Y.; Cao, M.-Y.; Gu, X.; Viau, S.; Lightfoot, J.; Wright, J. A.; Young, A. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 104.
(9) Dobrowolski, J. C.; Nguyen, D. H. T.; Fraser, B. H.; Bhadbhade, M.; Black, D. S.; Kumar, N. *Synlett* **2019**, *30*, 567.
(10) Miao, C.-B.; Zeng, Y.-M.; Shi, T.; Liu, R.; Wei, P.-F.; Sun, X.-Q.; Yang, H.-T. *J. Org. Chem.* **2016**, *81*, 43.