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Synthesis of benz[5,6]azepino[4,3-*b*]indoles by 1,7-electrocyclisation of azomethine ylides

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Abstract—A new, general route to the benz[5,6]azepino[4,3-*b*]indole ring system has been developed via the 1,7-dipolar electrocyclisation reactions of azomethine ylides derived from easily available 3-formyl indole derivatives. The intermediacy of azomethine ylides was shown by the trapping of the proposed α,β:γ,δ-conjugated dipole with *N*-phenylmaleimide.

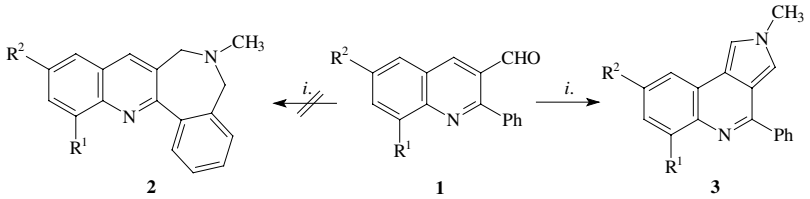
The 1,3-dipolar cycloaddition of dipoles to an olefin or an acetylene derivative is one of the most useful approaches for the construction of five-membered heterocyclic rings.[1] There are, however, many other synthetically useful reactions of these dipoles, including the 1,5- and 1,7-electrocyclic[2,3] ring closure of appropriately substituted unsaturated dipolar systems. Recently, we[4] and others[5] published the first examples of the 1,7-electrocyclisation of nonstabilised azomethine ylides with α,β:γ,δ-unsaturation, followed by some examples of 1,7-electrocyclisation of electron-withdrawing group stabilised azomethine ylides.[6]

As a continuation of these studies our aim was to show the generality of this method as a tool for the annelation of a benzazepine ring to different heterocycles in one step. Our previous experiments with 2-phenyl-3-formylquinolines **1** resulted in the formation 1*H*-pyrrolo[3,4-*c*]quinolines **3** as products via a 1,5-electrocyclisations (Scheme 1).[7]

In this letter we describe the reactions of the analogous azomethine ylides formed from 2-aryl-indol-3-carbaldehydes **7a**–**h** and **8a**,**b**. In these conjugated dipoles the 1,5-electrocyclisation pathway is not accessible.

The starting materials were prepared via the appropriate 2-arylindoles **6a**–**h** by the treatment with small excess of Vilsmeier reagent.[8] In the case of 2-phenylindole-3-carbaldehyde (**7a**) the protection of the indole nitrogen was achieved (Scheme 2).

The nonstabilised azomethine ylides **9** R = H, CH_3, Bn, $R^1 = CH_3$, Bn, E = H (Table 1, entries 1–6) were



Scheme 1. Reagents and conditions: (i) sarcosine, xylene, reflux.

Keywords: Azomethine ylide; Cycloaddition; Electrocyclisation; Indole.
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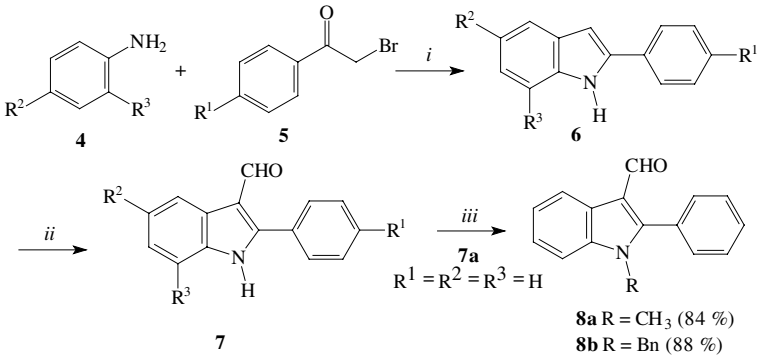


Scheme 2. Reagents and conditions: (i) *N*,*N*-dimethylaniline, 170 °C (45–62%); (ii) $POCl_3$, DMF, 80 °C (73–91%); (ii) KOBu^t, MeI, ^{t}BuOH; or BnBr, NaH, DMF.

Table 1. Benz[5,6]azepino[4,3-*b*]indoles produced via Scheme 3

Entry	Starting aldehyde	*R*	R^1	R^2	R^3	R^4	*E*	Reaction time (h)	Product	Yield %
1	**7a**	H	H	H	H	CH_3	H	6	**11a**	54
2	**7a**	H	H	H	H	Bn	H	10	**11b**	46
3	**8a**	CH_3	H	H	H	CH_3	H	18	**11c**	46
4	**8a**	CH_3	H	H	H	Bn	H	16	**11d**	38
5	**8b**	Bn	H	H	H	CH_3	H	18	**11e**	40
6	**8b**	Bn	H	H	H	Bn	H	96	**11f**	41[a]
7	**7a**	H	H	H	H	CH_3	CO_2CH_3	15	**11g**	15
8	**8a**	CH_3	H	H	H	CH_3	CO_2CH_3	20	**11h**	18
9	**8b**	Bn	H	H	H	CH_3	CO_2CH_3	60	**11i**	—
10	**7b**	H	CH_3	H	H	CH_3	H	6	**11j**	52
11	**7c**	H	Cl	H	H	CH_3	H	8	**11k**	58
12	**7d**	H	CH_3O	H	H	CH_3	H	6	**11l**	55
13	**7e**	H	H	CH_3O	H	CH_3	H	6	**11m**	59
14	**7f**	H	Br	CH_3O	H	CH_3	H	8	**11n**	55
15	**7g**	H	H	H	CH_3	CH_3	H	6	**11o**	54
16	**7h**	H	Br	H	CH_3	CH_3	H	6	**11p**	61

[a] ≈20% Starting material recovered.

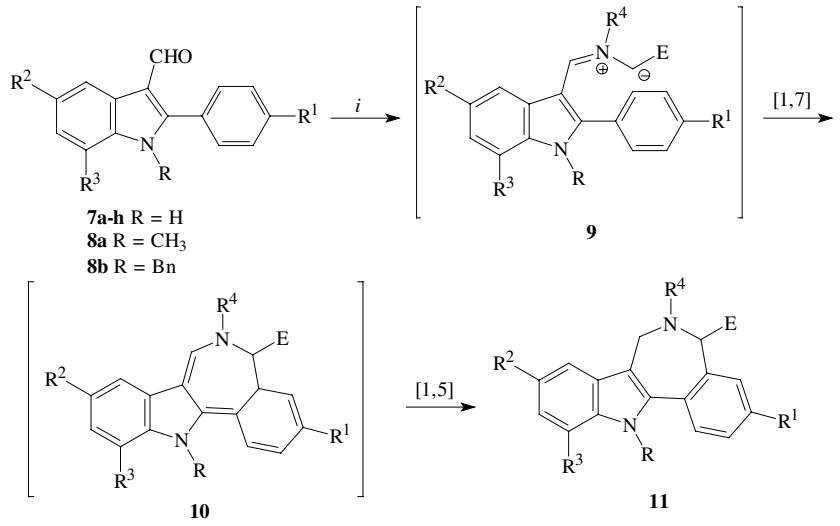
generated from the aldehydes in refluxing xylene using the method of decarboxylative condensation with sarcosine or *N*-benzyl-glycine.[9] The azomethine ylide intermediates reacted via the expected 1,7-electrocyclisation reaction to the azepines **10** and finally by a 1,5-hydrogen shift to give the products **11a**–**f** (Scheme 3). The products were isolated in acceptable yields after column chromatography. As can be seen from the table beside the very similar yields, the reaction times depended on the *N* substituent of the indole and the glycine. The fastest reaction was observed in the case of unprotected indole aldehyde **7a** with sarcosine, while the reaction of **8b** with *N*-benzyl-glycine was not complete after four days boiling in xylene.

In our early studies we found significant differences between the reactivity of α,β:γ,δ-unsaturated, nonstabilised and α,β:γ,δ-unsaturated, ester-stabilised azomethine ylides. The former dipoles react via a 1,7-electrocyclisation to yield dihydrobenzazepines,[10] whilst the latter give other products via novel rearrangements.[11,12] We have also investigated the reactions of **7a** and **8a**,**b** aldehydes with methyl sarcosinate. The ester-stabilised azomethine ylides **9** (R = H, CH_3, R_1 = CH_3, E = CO_2CH_3) in this case reacted again via 1,7-electrocyclisation to give benzazepines **11g**,**h**, however in low yields. In the reaction of **8b** and *N*-benzyl glycine there was no product observed by TLC after refluxing for 60 h in xylene.

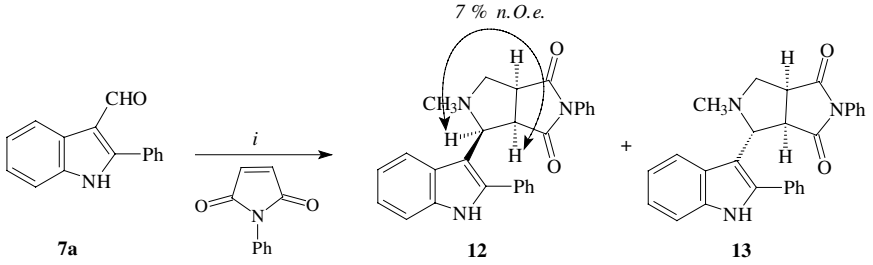
In a few examples, we investigated the effect of the additional substituents on the indole nucleus and/or 2-aryl ring on the course of the electrocyclisation process. In the reactions of the unprotected indoles **7b**–**h** and sarcosine, azepines **11j**–**p** were again isolated in acceptable yields, with no visible effects of the substituents of the starting materials on the yield, or the reaction times.

The intermediacy of azomethine ylides was shown in one case by trapping the dipole **9** (R = CH_3, E = H) with *N*-phenylmaleimide to give the two isomeric cycloadducts **12** and **13** (ratio ≈ 5:1) in good yield. The stereochemistry of the major isomer (**12**) was proved by NOE experiments (Scheme 4).

In summary we have explored a convenient reaction sequence which provides a useful route to the benzo[*c*]-indolo[2,3-*e*]azepine ring system[13] via the 1,7-dipolar electrocyclisation reactions of azomethine ylides derived from easily available 3-formylindole derivatives.[14]



Scheme 3. Reagents and conditions: (i) E = H: sarcosine or *N*-benzyl glycine, xylene, reflux; E = CO_2CH_3:$CH_3NCH_2CO_2CH_3$·HCl, Et_3N, xylene, reflux.



Scheme 4. Reagents and conditions: (i) sarcosine, toluene, reflux (92%).

Acknowledgements

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13. *General procedure for the preparation of compounds* **11a–f**: the corresponding indole aldehyde (1 mmol) was dissolved in hot xylene (50 ml) and sarcosine (0.27 g, 3.0 mmol) or sarcosine methyl ester (0.3 g, 3.0 mmol) was added. The reaction mixture was refluxed and further portions of sarcosine (0.09 g, 1.0 mmol) or sarcosine methyl ester (0.10 g, 1 mmol) were added every 2 h until the starting aldehyde completely disappeared (6–18 h, judged by TLC except for **11f**). All the solvent was removed in vacuo and the residue was purified by column chromatography (eluent: chloroform–methanol 8:1).
14. *All new compounds afforded correct elemental analyses and spectroscopic data. Selected examples*: *6-benzyl-5,6,7,12-tetrahydro-benz[c]azepino[4,3-b]indole* (**11b**): ^{1}H NMR (250 MHz, $CDCl_3$): 10.68 (s, 1H), 7.84 (d, 2H, J = 7.6 Hz), 7.44–6.94 (m, 11H), 4.26 (s, 2H), 3.89 (s, 2H), 3.76 (s, 2H); ^{13}C NMR (62.5 MHz, $CDCl_3$): 138.3 (q), 136.8 (q), 135.8

(q), 131.7 (q), 131.2 (q), 129.0 (CH), 127.9 (CH), 127.5 (q), 127.2 (2 × CH), 126.4 (CH), 126.0 (2 × CH), 124.4 (CH), 121.5 (CH), 118.0 (CH), 117.1 (CH), 111.7 (q), 110.3 (CH), 58.6 (CH_2), 57.8 (CH_2), 52.4 (CH_2); IR (KBr, cm^{-1}): 3401, 3029, 2945, 2917, 2780, 1451, 1340, 1314, 1248, 1116, 1065. *6,12-Dimethyl-5,6,7,12-tetrahydrobenz[c]azepino[4,3-b]indole* (**11c**): ^1H NMR (250 MHz, $CDCl_3$): 7.73 (d, 1H, J = 7.8 Hz), 7.55 (m, 2H), 7.51 (t, 1H, J = 7.3 Hz), 7.46 (d, 1H, J = 8.2 Hz), 7.43 (t, 1H, J = 7.4 Hz), 7.34 (t, 1H, J = 7.7 Hz), 7.25 (t, 1H, J = 7.4 Hz), 3.93 (s, 3H), 3.66 (s, 2H), 3.48 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): 137.9 (q), 137.8 (q), 137.7 (q), 132.6 (q), 131.0 (CH), 127.5 (CH), 127.3 (CH), 127.2 (CH) 127.1 (q), 121.9 (CH), 119.7 (CH), 118.1 (CH), 111.6 (q), 109.5 (CH), 58.3 (CH_2), 48.4 (CH_2), 43.8 (CH_3), 31.1 (CH_3); IR (KBr, cm^{-1}): 3446, 3044, 2933, 2777, 1930, 1681, 1600, 1488, 1467, 1352, 1258, 1241, 1200, 1130, 1090, 1034, 1008. *Methyl, 6,12-dimethyl-5,6,7,12-tetrahydrobenz[c]azepino[4,3-b]indole-5-carboxylate* (**11g**): ^1H NMR (250 MHz, $CDCl_3$): 7.68 (d, 1H, J = 7.7 Hz), 7.58 (d, 1H, J = 7.4 Hz), 7.52–7.18 (m, 6H); 3.89 (s, 3H), 3.78 (s, 2H), 3.60 (s, 1H), 3.56 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): 177.5 (q), 137.9 (q), 135.6 (q), 132.4 (q), 131.7 (CH), 130.7 (q), 128.5 (q), 128.1 (CH), 127.8 (CH), 127.7 (CH), 122.4 (CH), 120.2 (CH), 117.9 (CH), 109.7 (CH), 109.4 (q), 57.3 (CH_2), 47.7 (CH_3), 43.9 (CH_2); 42.6 (CH_3); 31.2 (CH_3); IR (KBr, cm^{-1}): 3404, 2963, 2515, 2361, 1708, 1635, 1542, 1497, 1468, 1388, 1355, 1262, 1096, 1030. *Methyl, 3-bromo-9-methoxy-6-methyl-5,6,7,12-tetrahydro-benz[c]azepino[4,3-b]indole* (**11l**): ^1H NMR (300 MHz, DMSO-d_6): 11.11 (s, 1H), 7.75 (d, 1H, J = 8.3 Hz), 7.56 (d, 1H, J = 8.3 Hz), 7.48 (s, 1H), 7.30 (d, 1H, J = 8.7 Hz), 6.93 (s, 1H), 6.82 (d, 1H, J = 8.7 Hz), 4.08 (s, 2H), 3.78 (s, 3H), 3.45 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): 153.5 (q), 140.1 (q), 132.3 (CH), 131.8 (q), 131.3 (q), 130.1 (CH), 127.9 (q), 127.1 (CH), 119.5 (q), 113.1 (CH), 112.9 (q), 112.1 (CH), 99.9 (CH), 60.1 (CH_2), 55.5 (CH_3), 43.9 (CH_3), 40.0(CH_2); IR (KBr, cm^{-1}): 3222, 3054, 2968, 2791, 1489, 1353, 1327, 1304, 1280, 1259, 1233, 1110, 1050. *Cycloadduct* **12**: ^1H NMR (250 MHz, $CDCl_3$): 8.59 (s, 1H), 7.79 (d, 1H, J = 7.5 Hz), 7.57–7.08 (m, 13 H), 3.88 (dd, 1H, J = 6.9 and 13.8 Hz), 3.77 (d, 1H, J = 7.7 Hz), 3.64 (m, 3H), 2.06 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): 176.7 (q), 173.3 (q), 161.8 (q), 138.2 (q), 133.5 (2 × CH), 132.1 (q), 130.8 (q), 129.1 (CH), 128.6 (2 × CH), 128.0 (CH), 126.1 (2 × CH), 125.6 (q), 125.6 (2 × CH), 121.6 (CH), 119.6 (CH), 111.1 (CH), 108.0 (CH), 65.3 (CH), 57.3 (CH_2), 50.7 (CH), 43.9 (CH), 38.4 (CH_3); IR (KBr, cm^{-1}): 2944, 2843, 1708, 1593, 1492, 1481, 1389, 1320, 1188, 1144, 1089, 1024.