A Convenient One-Pot Synthesis of Spirocyclic Pyrido[1,2-*a*]indole Derivatives from 3-(2-Bromoethyl)indole

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Abstract: A convenient one-pot approach for the synthesis of spirocyclic pyrido[1,2-*a*]indole derivatives is described. The method involves treatment of 1,3-diketones and 1,3-ketoesters with base to generate dianions, which react with 3-(2-bromoethyl)indole to construct a spirocyclopropyl ring and an N-heterocyclic ring sequentially in moderate to very good yields.

Key words: spirocyclic pyrido[1,2-*a*]indole derivatives, tandem reactions, heterocycles.

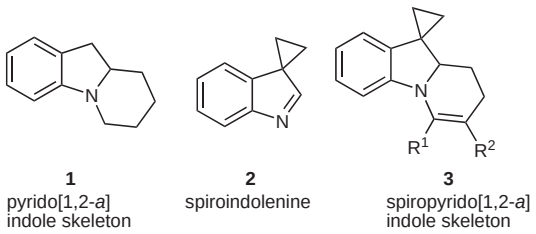
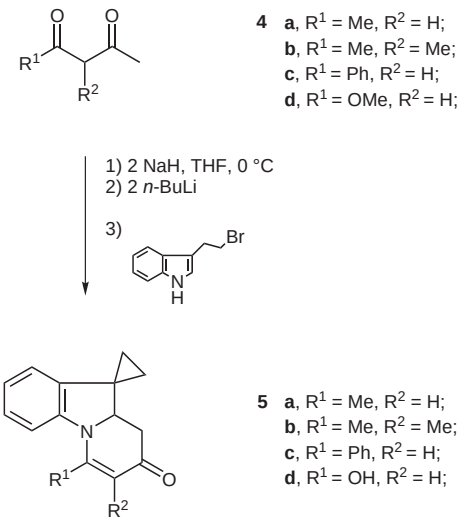


Figure 1

The indole unit represents a key structure among natural products and pharmaceutically important compounds.[1] The synthesis of pyrido[1,2-*a*]indole derivatives, a class of tricyclic compounds **1**, has drawn considerable attention due to their biological activity and synthetic interest.[2] Although a variety of strategies has been developed to generate these heterocyclic derivatives,[3,4] the popular methods mainly involve the cyclization catalyzed by metal compounds such as Pd(II),[3b,5] Sm(II),[3a] and Ni(II) complexes.[3d] Solid-phase synthesis has also been used to construct the pyrido[1,2-*a*]indole derivatives via radical cyclization.[6] Spiroindolenine (**2**) first synthesized by Closson also contains an indole subunit.[7] Compound **2** can be readily accessed from 3-(2-bromoethyl)indole[8] and was recently used as a electron-deficient adduct to synthesize pyrrole derivatives.[9]

While numerous approaches to **1** and **2** (Figure 1) are available, there are no reports describing easy access to the related spiropyrido[1,2-*a*]indole **3** (Figure 1), in spite of the fact that such a protocol would provide important approaches to a range of natural product precursors.[10] Inspired by the protocol originally described by Closson, we reasoned that the dianions generated from 1,3-diketones and 1,3-ketoesters[11] would be good candidates to undergo reaction with 3-(2-bromoethyl)indole to simultaneously construct the spiro ring in **2** and the N-heterocyclic six-membered ring in compound **1** to produce **3**. A convenient one-pot approach to spirocyclic pyrido[1,2-*a*]indole derivatives is reported herein.

To initially examine this approach, 2,4-pentadione (**4a**) was treated with two equivalents of sodium hydride in tetrahydrofuran at 0 °C and then two equivalents of *n*-butyllithium followed by the addition of 3-(2-bromoethyl)indole (Scheme 1).[12]



Scheme 1 One-pot transformation from 3-(2-bromoethyl)indole to spirocyclic pyrido[1,2-*a*]indole derivatives

The reaction worked well to afford a novel spirocyclic pyrido[1,2-*a*]indole compound **5a** in 85% isolated yield. The success of this reaction encouraged us to investigate its generality and scope. Two other 1,3-diketones (**4b**,**c**) and a 1,3-ketoester (**4d**) were reacted with 3-(2-bromoethyl)indole using the same procedure. The data for these reactions is summarized in Table 1. The data in Table 1 shows the reaction proceeds to produce spirocyclic pyrido[1,2-*a*]indole derivatives for all four 1,3-diketones and 1,3-ketoesters (**4a**–**d**). Moderate to good yields (66–85%) were achieved and all products were purified and characterized by NMR, GC–MS, and HRMS.[13]

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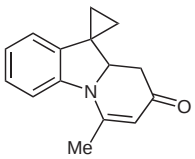
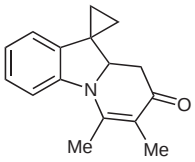
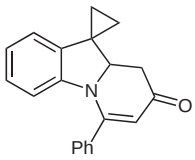
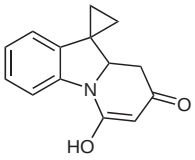
Table 1 Synthesis of Spirocyclic Pyrido[1,2-*a*]indole Derivatives from 3-(2-Bromoethyl)indole and 1,3-Diketones or 1,3-Ketoesters

Entry	Substrate	R^1	R^2	Product	Yield (%)[a]
1	**4a**	Me	H		**5a** (85%)
2	**4b**	Me	Me		**5b** (81%)
3	**4c**	Ph	H		**5c** (76%)
4	**4d**	OMe	H		**5d** (66%)[b]

[a] Isolated yield.
[b] Keto–enol mixture.

Although the bridgehead methine (CHN) proton in the products show a large coupling constant of approximately 16 Hz, this finding is consistent with other multicyclic ring systems where a bridgehead methine is adjacent to a methylene group (CH_2CO protons).[14] Nonetheless ^1H–^1H COSY and ^1H–^{13}C HMQC experiments were carried out on compound **5a** to confirm the structure derived from ^1H and ^{13}C NMR data. ^1H–^1H COSY cross peaks were observed between the following signals: 2.14 ppm × 2.42 ppm, 2.14 ppm × 4.41 ppm, and 2.42 ppm × 4.41 ppm. In a ^1H–^{13}C HMQC experiment, the proton corresponding to a dd at δ = 2.14 ppm and the proton corresponding to a triplet at δ = 2.42 ppm cross into the carbon resonance at δ = 38.4 ppm; the proton corresponding to a dd at δ = 4.41 ppm crosses into the carbon resonance at δ = 64.3 ppm. The additional data are consistent with the structure of compound **5a** and further support the structure derived from the ^1H and ^{13}C NMR data.

While the mechanism of the reaction was not studied in detail, exposure of **2** to **4a** in tetrahydrofuran containing two equivalents of sodium hydride and two equivalents of *n*-butyllithium produces product **5a** and unreacted starting material. As a result, it is likely that the presence of excess base leads to deprotonation of the NH group providing the spiroindolenine as shown by Closson.[7] Reaction of **2** with the dianion generated from the 1,3-diketones and 1,3-ketoesters furnishes the N-heterocyclic six-membered ring in the product. The loss of water produces compounds **5a**–**c** while the loss of methanol leads to compound **5d** (Scheme 2).

The convenience of the one-pot, two-component strategy generally provides a number of advantages and this initial contribution based on known chemistry shows that a fairly complex product can be produced from readily available starting materials. The extension of this reaction could potentially lead to the convenient synthesis of other spiropyrido[1,2-*a*]indole compounds when the bromoethyl group in 3-(2-bromoethyl)indole is replaced by other substituents containing a good leaving group. Such a protocol would provide spiro compounds that can possibly serve as platforms or intermediates for the synthesis of more complex natural products. Studies on the application of this reaction protocol are currently underway in our research group.

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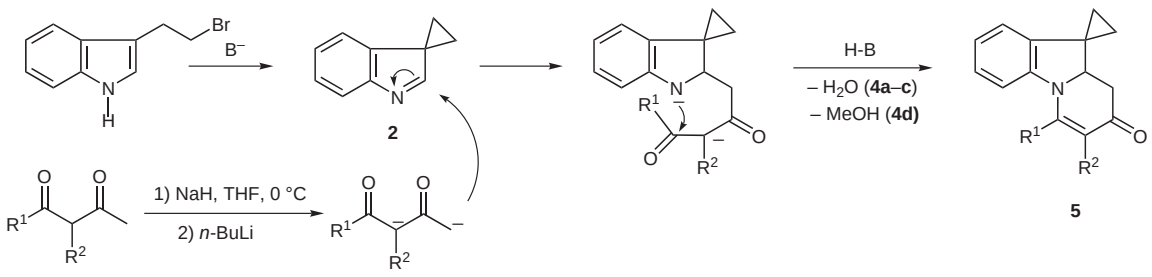

Scheme 2 Proposed mechanism for the reaction of the dianions of 1,3-diketones and 1,3-ketoesters with 3-(2-bromoethyl)indole

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(11) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(12) **General Procedure for Reaction Protocol**: NaH (12 mmol, 0.29 g) was weighed out with a flask in a dry box and then THF (40 mL) was added. The flask was placed in an ice bath. The mixture was stirred and 1,3-diketones or 1,3-ketoesters **4** (6 mmol) in THF (5 mL) was added dropwise into the flask. The mixture was further stirred for 10 min at 0 °C and then *n*-BuLi (12 mmol, 7.6 mL of 1.6 M *n*-BuLi solution in hexane) was added dropwise. After 20 min, 3-(2-bromo-ethyl) indole (5 mmol, 1.12 g) in THF (5 mL) was added dropwise with stirring. The reaction mixture was warmed to r.t. slowly and further stirred overnight. The reaction mixture was hydrolyzed with 1% HCl solution (30 mL) and extracted with Et_2O. The combined organic extracts were washed with H_2O and dried over $MgSO_4$. After filtration, the crude product was concentrated and purified with column chromatography. The obtained pure products **5** were characterized with 500 MHz NMR, GC–MS, and HRMS.
(13) The NMR spectra were recorded with 500 MHz NMR spectrometer. GC–MS method: initial temperature: 50 °C (hold for 3 min), rate: 15 °C/min, final temperature: 280 °C (hold for 7 min). Compound **5a**: The general procedure was followed with the use of substrate **4a** (0.6 g) and product **5a** (0.95g, 85%) was obtained as a brown solid after purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.2 Hz, 1 H), 7.12 (t, *J* = 7.3 Hz, 1 H), 6.94 (t, *J* = 7.4 Hz, 1 H), 6.72 (d, *J* = 7.2 Hz, 1 H), 5.19 (s, 1 H), 4.41 (dd, *J* = 4.1, 16.5 Hz, 1 H), 2.47 (s, 3 H), 2.42 (t, *J* = 16.2 Hz, 1 H), 2.14 (dd, *J* = 4.0, 15.8 Hz, 1 H), 1.22–1.29 (m, 2 H), 0.90–0.95 (m, 1 H), 0.71–0.76 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.5, 156.7, 143.1, 137.8, 127.2, 122.9, 119.5, 112.3, 104.4, 64.3, 38.4, 26.6, 22.5, 15.4, 12.1. GC–MS (t_R = 19.96 min): *m*/*z* = 225 (56) [M^+], 197 (100), 154 (48), 115 (13). HRMS (FAB): *m*/*z* [M + H^+] calcd for $C_{15}H_{16}ON$: 226.1232; found: 226.1216.
5b: The general procedure was followed with the use of substrate **4b** (0.68 g) and product **5b** (0.97 g, 81%) was obtained as a orange-brown solid after purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.2 Hz, 1 H), 7.10 (t, *J* = 7.5 Hz, 1 H), 6.88 (t, *J* = 7.4 Hz, 1 H), 6.69 (d, *J* = 7.4 Hz, 1 H), 4.30 (dd, *J* = 4.0, 16.4 Hz, 1 H), 2.50 (s, 3 H), 2.47 (t, *J* = 16.1 Hz, 1 H), 2.18 (dd, *J* = 3.9, 15.9 Hz, 1 H), 1.86 (s, 3 H), 1.21–1.27 (m, 2 H), 0.90–0.93 (m, 1 H), 0.73–0.76 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.7, 153.8, 143.8, 137.8, 127.1, 121.8, 119.3, 111.9, 111.1, 64.0, 39.2, 29.9, 18.7, 14.9, 13.4, 10.6. GC–MS (t_R = 20.02 min): *m*/*z* = 239 (100) [M^+], 211 (90), 196 (20), 182 (35), 168 (88), 129 (18), 115 (29). HRMS (FAB): *m*/*z* [M + H^+] calcd for $C_{16}H_{18}ON$: 240.1388; found: 240.1388.
5c: The general procedure was followed with the use of substrate **4c** (0.97 g) and product **5c** (1.09 g, 76%) was obtained as a brown-black solid after purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.52 (m, 5 H), 6.79 (td, *J* = 1.0, 7.4 Hz, 1 H), 6.73 (td, *J* = 1.4, 7.5 Hz, 1 H), 6.65 (dd, *J* = 1.0, 7.3 Hz, 1 H), 5.71 (d, *J* = 8.2 Hz, 1 H), 5.38 (s, 1 H), 4.65 (dd, *J* = 4.0, 15.9 Hz, 1 H), 2.75 (t, *J* = 16.1 Hz, 1 H), 2.24 (dd, *J* = 4.0, 16.3 Hz, 1 H), 1.19–1.22 (m, 2 H), 1.08–1.12 (m, 1 H), 0.88–0.91 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4, 157.8, 145.1, 139.5, 135.7, 131.1, 128.0, 127.1, 122.6, 118.5, 116.2, 114.9, 108.8, 66.3, 39.9, 27.0, 16.0, 13.8. GC–MS (t_R = 24.35 min): *m*/*z* = 287 (81) [M^+], 258 (100), 230 (85), 154 (26), 129 (45). HRMS (FAB): *m*/*z* [M + H^+] calcd for $C_{20}H_{18}ON$: 288.1388; found: 288.1390.
5d: The general procedure was followed with the use of substrate **4d** (0.70 g) and product **5d** (0.75 g, 66%) was obtained as a yellow solid after purification. ^{1}H NMR (500 MHz, $CDCl_3$; enol–keto mixture): δ = 8.15 (d, *J* = 8.0 Hz, 0.4 H), 7.20 (t, *J* = 7.5 Hz, 0.6 H), 7.06 (t, *J* = 7.4 Hz, 0.5 H), 6.97 (td, *J* = 1.0, 7.6 Hz, 0.9 H), 6.69 (d, *J* = 7.6 Hz, 0.6 H), 6.65 (t, *J* = 7.3 Hz, 0.8 H), 6.56 (t, *J* = 7.0 Hz, 1.6 H), 5.28 (s, 0.1 H), 4.67 (m, 0.5 H), 4.11 (m, 1 H), 3.73 (s, 3.5 H), 2.73 (m, 1 H), 2.51–2.59 (m, 2 H), 1.22–1.39 (m, 3 H), 0.79–1.03 (m, 6.5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.5, 167.3, 150.0, 133.3, 127.5, 127.0, 125.0, 118.8, 118.5, 116.0, 108.9, 59.8, 58.8, 52.5, 49.9, 49.5, 46.7, 42.3, 30.2, 28.0, 15.9, 15.5, 14.6, 12.2. GC–MS (t_R = 19.26 min): *m*/*z* = 227 (35) [M^+], 199 (82), 130 (100), 115 (48). HRMS (FAB): *m*/*z* [M + H^+] calcd for $C_{14}H_{14}O_2N$: 228.1025; found: 228.1013.
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