A New Route to the Synthesis of Indolo[2,3-*a*]carbazoles

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A straightforward, easy and smooth process of synthesizing indolo[2,3-*a*]carbazoles, which can frequently serve as a nucleus of several natural products is reported. The process involves only two steps viz. single electron transfer reaction and subsequent reductive cyclization with hydrazine.

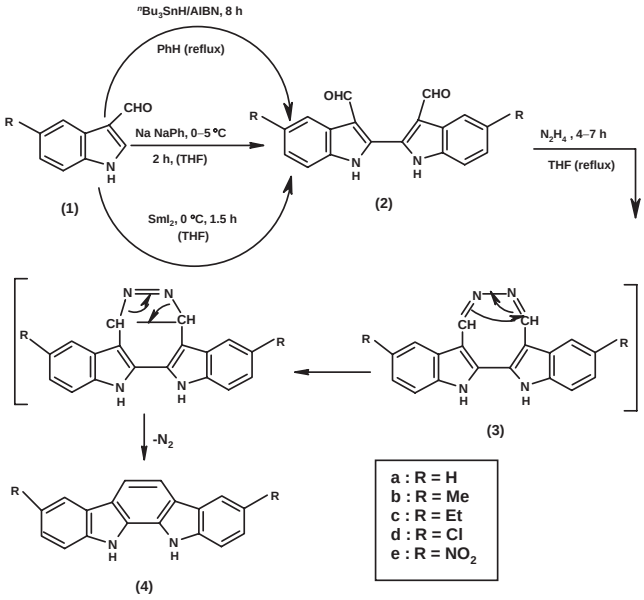
Indolocarbazole, a well-known biologically active family comprises five possible isomeric compounds among which indolo[2,3-*a*]carbazole is most commonly known owing to its wide range of applications.[1] It can serve as a nucleus of several medicinally important compounds e.g. staurosporine,[2] rebeccamycin,[3] K-252a;[4] alkaloids[5] e.g. arcyriaflavin A, AT2433-B aglycone, etc. Until now, three general methods viz., Fischer indolization,[4–7] Diels–Aider reaction,[8–10] and oxidative cyclization of bisindolylmaleimides[11–14] exist to prepare the [2,3-*a*] framework. This communication deals with a totally different pathway in order to synthesize indolo[2,3-*a*]carbazoles which initially involves single electron transfer reaction[15,16] of 3-formylindoles, followed by reductive cyclization with hydrazine.

The single electron transfer (SET) reactions are not exploited so much for synthesizing indole derivatives probably due to highly electron-rich system of the indole ring, which has little tendency to accept an electron. The tendency to form indolyl anion by accepting an electron may be increased by introducing a strong electron-withdrawing group at C-3 of the indole ring. Treatment of 3-formylindoles (**1**) with sodium naphthalenide (NaNaph), a well-known SET reagent, resulted in 3,3′-diformyl-2,2′-biindolyls (**2**)[15] by successful application of SET reaction, which is the key step of the synthesis. Unfortunately, the yield is hopelessly low (Table 1). In order to increase the yield of **2** and consequently that of the target compounds (**4**), an endeavor was taken by treating 3-formylindoles with two other SET reagents viz. tributyltin hydride using AIBN as initiator and Samarium(II) iodide.

It was observed that the yield of diformyl derivative (**2**) is sufficiently high when SmI_2 was used as SET reagent (Entry 3, Table 1). Compound (**2**) on reflux with hydrazine[17] in THF to yield the target compounds indolo[2,3-*a*]carbazoles (**4**) as the sole product[18] (Table 2) with elimination of N_2 possibly through concerted mechanism (Scheme 1).

Table 1. Reaction of 3-formylindole (**1a**) with different SET reagents (a comparative study)

Entry	SET regent	Reaction condition	Yield of **2**/%
1	Na Naph	0–5 °C, THF, 2 h, N_2	11
2	*n*-Bu_3SnH/AIBN	PhH (reflux), 8 h, N_2	34
3	SmI_2	0 °C, THF, 1.5 h, Ar	66



Scheme 1.

Table 2. Yield (%) of the products using Sm(II)I_2 as SET reagent and subsequent reflux with N_2H_4

Entry	Substrate	Intermediate product	Final product
1	**1a**	**2a** (66%)	**4a** (60%)
2	**1b**	**2b** (59%)	**4b** (46%)
3	**1c**	**2c** (47%)	**4c** (33%)
4	**1d**	**2d** (72%)	**4d** (67%)
5	**1e**	**2e** (81%)	**4e** (73%)

However, formation of diformyl derivatives of biindolyl system (**2**) was further increased with the presence of electron-withdrawing substituents (Cl and NO_2) on the aromatic nucleus (Entries 4 and 5, Table 2). On the other hand, the presence of substituents with electron-donating capacity (CH_3 and C_2H_5) increases the electron density of the aromatic nucleus and as a result SET process was not facilitated as before, resulting in low yield (Entries 2 and 3, Table 2).

In conclusion, a simple procedure has been developed for the synthesis of indolo[2,3-*a*]carbazoles which is not only new but also the first report of the synthesis of indolo[2,3-*a*]-carbazoles exploiting only two successive processes as well as involving lesser number of steps in comparison to most of the previously reported methodologies.[4–14]

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18 Typical experimental procedure is as follows: To a solution of (0.74 mmol) of **1a** in 20 mL dry THF and 1.5 mL dry hexamethylphosphoric triamide, at 0 °C under argon, 15 mL of Samarium(II) iodide was added drop wise for 20 min. The reaction mixture was stirred for 30 min followed by addition of 6 drops of *t*-BuOH. It was then further stirred for 60 min and eventually quenched with saturated aqueous sodium bicarbonate solution. It was then passed through silica column to remove samarium salt. The aqueous layer was extracted with 25 mL distilled $CHCl_3$ (3 times). The combined chloroform extracts were washed with brine solution followed by distilled water and dried over anhydrous sodium sulfate. Finally, it was evaporated in a rotary evaporator under reduced pressure to leave a crude mass which chromatographed over neutral alumina to yield **2a**. The dialdehyde **2a** was refluxed with hydrazine (1:1 mol) in THF protecting atmospheric moisture and the reaction was monitored continuously with TLC. After the reaction was over the solvent was evaporated under reduced pressure and the crude mass on repeated recrystallization yielded the product (**4a**), yield 60% (113.7 mg), mp >250 °C, IR (KBr) 3390, 1592, 1451, 875, 811 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 11.31 (2H, s), 8.04 (2H, d, $J = 1.8$ Hz), 7.95 (2H, s), 7.62 (2H, dd, $J = 8.7$ Hz, 2.2 Hz), 7.57 (2H, dd, $J = 7.2$ Hz, 1.9 Hz), 7.31 (2H, m); ^{13}C NMR (75.5 MHz, d_6-DMSO) δ 110.42, 117.73, 118.97, 120.06, 127.23, 129.43, 133.67, 134.09, 139.79. EIMS m/z 256 (M^+, 62), 254 (100); HRMS (m/z) calcd for $C_{18}H_{12}N_2$, 256.3044; found 256.3036. Similar protocol was followed for the rest four substrate viz. **1**(**b**–**e**) to obtain **4b** to **4e** respectively. (**4b**), yield 46% (96.6 mg), mp >250 °C, IR (KBr) 3374, 2976, 1585, 1458, 872, 812, 732 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 11.22 (2H, s), 7.98 (2H, d, $J = 1.7$ Hz), 7.92 (2H, s), 7.60 (2H, d, $J = 8.9$ Hz), 7.27 (2H, d, $J = 7.8$ Hz), 2.32 (6H, s). (**4d**), yield 67% (161.6 mg), mp >250 °C, IR (KBr) 3401, 3080, 1572, 1488, 875, 812 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 11.27 (2H, s), 8.26 (2H, d, $J = 1.7$ Hz), 7.96 (2H, s), 7.70 (2H, d, $J = 8.5$ Hz), 7.37 (2H, dd, $J = 8.3$ Hz, 1.9 Hz).

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