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An Entry to the Synthesis of Novel Nitrogen Macroheterocycles

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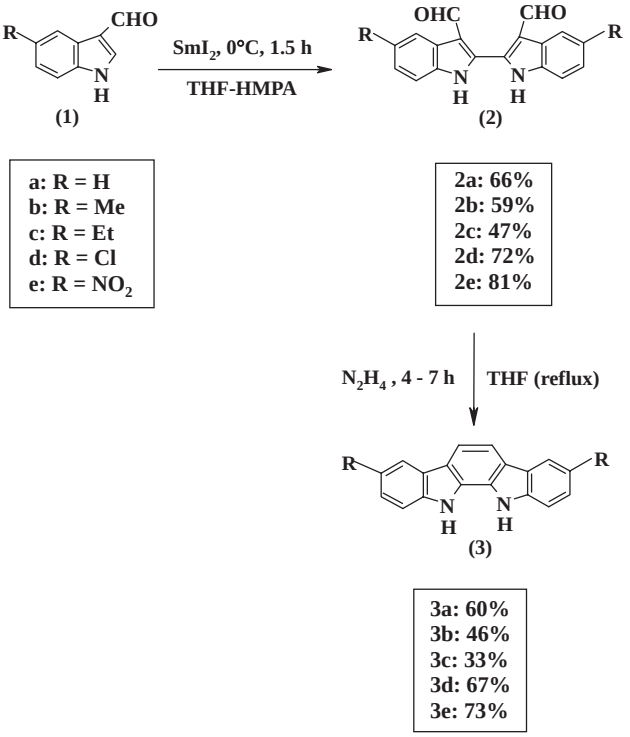
2,2′-Bi(1*H*-indolyl)-3,3′-dicarbaldehydes, prepared from 1*H*-indole-3-carbaldehydes by exploiting SET methodology, served as the key compound for synthesizing indolo[2,3-*a*]carbazoles as well as nitrogen macroheterocycles. Condensation of 2,2′-bi(1*H*-indolyl)-3,3′-dicarbaldehyde with aliphatic diamines produced Schiff's base type compounds possessing a 10–14-membered ring.

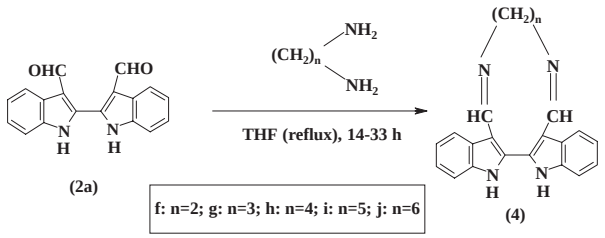
In recent years, organic reactions involving the single electron transfer (SET) mechanism have received increasing interest, as they serve as the key step in the overall synthetic strategy of a wide range of molecules.[1–11] However, SET reductions have scarcely been exploited in indole chemistry probably due to highly electron-rich system of the indole ring. The tendency to form indolyl radical anion by accepting an electron may be increased by introducing a strong electron-withdrawing group at C-3 of the indole ring. As a part of our investigation in SET reaction,[12–14] we have recently reported[15] a new route to the synthesis of indolo[2,3-*a*]carbazoles, which enjoys wide range of applications.[16] The process reported from this laboratory involves only two steps that is SET reduction of 1*H*-indole-3-carbaldehyde (**1a**) to form symmetrical 2,2′-bi(1*H*-indolyl)-3,3′-dicarbaldehyde (**2a**)[12] and then reductive cyclization[17] with hydrazine. A logical extension of this work has been carried out, which includes condensation of **2a** with aliphatic diamines. This short article is a detailed report of the synthesis of indolo[2,3-*a*]carbazoles along with dialdehyde–diamine condensation, which ultimately introduces a new entry to the synthesis of nitrogen macroheterocycles.

Results and Discussion

Treatment of 1*H*-indole-3-carbaldehydes (**1**) with sodium naphthalenide (NaNaph), a well-known SET reagent, resulted in the formation of 2,2′-bi(1*H*-indolyl)-3,3′-dicarbaldehydes (**2**)[12] in low yields. The yield of **2** was high when SmI_2 was used.[4–6] The most plausible mechanistic pathway may be the formation of a radical anion from **1** under the influence of SmI_2, which readily dimerizes to form a dianion of 2,2′-bi(1*H*-indolyl)-3,3′-dicarbaldehyde, which ultimately yields **2** by restoring aromaticity. Compound **2** was refluxed with hydrazine[17] in THF to yield indolo[2,3-*a*]carbazoles (**3**) as the sole product (Scheme 1). In the case of **1d** and **1e**, which have electron-withdrawing substituents, such as Cl and NO_2, formation of the corresponding dialdehydes **2d** and **2e** was smooth. On the other hand, electron-donating substituents (CH_3 and C_2H_5) increased the electron density of the aromatic nucleus, and as a result the SET process was not as facile as before, resulting in low yield. A plausible mechanism leading to the formation of indolo[2,3-*a*]carbazole moiety has been proposed involving the elimination of nitrogen possibly through a concerted mechanism.[15] Next, we tried to synthesize nitrogen macroheterocycles **4** by condensing **2a** with straight chain aliphatic diamines as shown in Scheme 2. It is pertinent to state that the design and synthesis of macroheterocycles[18] has received interest due to the remarkable role of "tirofiban" in acute coronary syndrome. Moreover, nitrogen- and sulfur-containing macroheterocycles are frequently used as a synthetic model of α-chymotripsin enzyme,[19] of which "synzyme"[20] is a striking example. The condensation reactions were carried out in very dilute solution; the concentration was ≈10 times less than



Scheme 1.



Scheme 2.

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Table 1. Reaction of Aliphatic Diamines with 2,2′-Bi(1*H*-indolyl)-3,3′-dicarbaldehyde (**2a**)

Entry	Substrate	Product	Time /h	Yield /%
1	1,2-Diaminoethane	**4f**	14	36
2	1,3-Diaminopropane	**4g**	17	47
3	1,4-Diaminobutane	**4h**	19	53
4	1,5-Diaminopentane	**4i**	26	32
5	1,6-Diaminohexane	**4j**	33	13
6	1,7-Diaminoheptane	No product	45	—

that used for the synthesis of indolo[2,3-*a*]carbazoles. The reaction proceeded satisfactorily for five aliphatic diamines, that is, 1,2-diaminoethane, 1,3-diaminopropane, 1,4-diaminobutane, 1,5-diaminopentane, and 1,6-diaminohexane, resulting moderate to good yield for first four diamines. However, the yield decreased sharply from 1,5-diaminopentane (Table 1). This may be due to the fact that the energy of the products decreases as ring size increases, and consequently, yield increased from **4f** to **4h**, although possibility of desired collision decreases with increase in ring size at a fixed dilution. No compound was isolated from the reaction between **2a** and 1,7-diaminoheptane even with a reaction period up to forty-five hours.

Conclusion

In conclusion, 1*H*-indole-3-carbaldehydes underwent SmI_2-promoted homocoupling, subsequent condensation with hydrazine and straight chain aliphatic diamines afforded indolo[2,3-*a*]carbazoles and nitrogen macroheterocycles, respectively. The method introduces (i) a simple procedure for the synthesis of indolo[2,3-*a*]carbazoles and (ii) a new entry for synthesizing novel nitrogen macrocycles of structural as well as biological interest.

Experimental

The melting points were recorded on an electrically heated Köfler Block apparatus and are uncorrected. IR were recorded as KBr discs on a Perkin-Elmer RX1 FT-IR spectrophotometer and MS spectra (EIMS) were recorded on a JEOL AX-500 mass spectrometer. NMR spectra (both one and two dimensional) were recorded on a Bruker AM-300L super conducting oxford magnet NMR spectrometer (7.5 Tesla) with 5 mm NMR sample tube at 27 °C temperature. The actual frequencies are 300.133 and 75.457 MHz for ^{1}H and ^{13}C NMR respectively. Elemental analysis (C, H, N) was conducted using the Perkin-Elmer 2400 Series II elemental analyzer. Column chromatography was performed using neutral alumina (Acme), whereas preparative TLC was performed using silica gel (Loba Chemié, 100–200 mesh). Typical experimental procedure is as follows.

Experimental Procedure for 2a. To a solution of (107.3 mg, 0.74 mmol) of **1a** in 20-mL dry THF and 1.5-mL dry hexamethylphosphoramide (HMPA) at 0 °C under argon, 15 mL of 0.1 M solution of SmI_2 in THF (≈0.61-g SmI_2) was added drop wise during 20 min. The reaction mixture was stirred for 30 min, followed by addition of 6 drops of Bu^{t}OH. It was then further stirred for 60 min and eventually quenched with saturated aqueous sodium hydrogencarbonate solution. It was then passed through a silica column to remove the samarium salt. The aqueous layer was extracted 3 times with 25 mL distilled $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine solution followed by distilled water and dried over anhydrous sodium sulfate. Finally, the solvent evaporated in a rotary evaporator under reduced pressure to leave a crude mass, which was chromatographed over neutral alumina to yield **2a** (145.9 mg, 66%).

Experimental Procedure for 3a. The dicarbaldehyde **2a** (288 mg, 1 mmol) was refluxed with 10.3-mL 1 M hydrazine in THF protecting atmospheric moisture and the reaction was monitored continuously with TLC. After the reaction was complete, the solvent was evaporated under reduced pressure, and the crude mass on repeated column chromatography yields the product **3a**, yield 60% (153.7 mg), mp > 250 °C, IR (KBr) 3390, 1592, 1451, 875, 811 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 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, DMSO-d_6) δ 110.42, 117.73, 118.97, 120.06, 127.23, 129.43, 133.67, 134.09, 139.79. EI-MS m/z 256 (M^+, 62), 254 (100); HR-MS Calc for $C_{18}H_{12}N_2$. m/z 256.3044. Found m/z 256.3036. Similar protocol was followed for the other four substrates viz. **1b**–**1e** to obtain **3b** to **3e** respectively. **3b**: yield 46% (130.6 mg), mp > 250 °C, IR (KBr) 3374, 2976, 1585, 1458, 872, 812, 732 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 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); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 22.31, 111.27, 122.13, 124.21, 128.52, 130.15, 131.67, 132.47, 136.26, 137.42. EI-MS m/z 284 (M^+, 37), 269 (100). Found: C, 84.33; H, 5.62; N, 9.74%. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85%. **3c**: yield 33% (102.9 mg), mp > 250 °C, IR (KBr) 3371, 1601, 1452, 839, 810 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.17 (2H, s), 7.91 (2H, d, J = 1.6 Hz), 7.86 (2H, s), 7.53 (2H, d, J = 8.8 Hz), 7.31 (2H, d, J = 7.7 Hz), 2.83 (4H, m), 2.02 (6H, m); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.42, 27.43, 111.37, 121.82, 122.54, 128.10, 129.87, 130.64, 131.43, 135.75, 139.29. EI-MS m/z 312 (M^+, 23), 283 (100). Found: C, 84.65; H, 6.36; N, 9.06%. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97%. **3d**: yield 67% (217.8 mg), mp > 250 °C, IR (KBr) 3401, 3080, 1572, 1488, 875, 812 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 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); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 111.41, 120.13, 122.64, 123.21, 128.03, 129.96, 131.98, 134.87, 137.37. EI-MS m/z 325 (M^+, 17), 324 (100). Found: C, 66.36; H, 2.94; N, 8.47%. Calcd for $C_{18}H_{10}N_2Cl_2$: C, 66.48; H, 3.08; N, 8.62%. **3e**: yield 73% (252.6 mg), mp > 250 °C, IR (KBr) 3401, 3080, 1543, 1362, 871, 812 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.36 (2H, s), 8.32 (2H, s), 8.11 (2H, s), 7.92 (2H, d, J = 8.6 Hz), 7.55 (2H, d, J = 8.7 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 110.96, 118.91, 121.02, 129.79, 131.48, 134.73, 134.27, 137.31, 148.64. Found: C, 62.37; H, 2.79; N, 16.25%. Calcd for $C_{18}H_{10}N_4O_4$: C, 62.43; H, 2.91; N, 16.18%.

Experimental Procedure for 4f. In a similar fashion, but at lower concentration (≈10 times) the reaction between 2,2′-bi(1*H*-indolyl)-3,3′-dicarbaldehyde (**2a**) and 1,2-diaminoethane was carried out. The dicarbaldehyde **2a** (288 mg, 1 mmol) was refluxed with 1,2-diaminoethane (60 mg, 1 mmol) in THF protecting atmospheric moisture (i.e. in a dry atmosphere) and the reaction was monitored continuously with TLC. After the reaction was complete, the solvent was evaporated under reduced pressure and the crude mass after column chromatography and preparative TLC yields the product.

2,3-Dihydrodiindolo[3,2-*f*:2,3-*h*]-1,4-diazecine (4f): Yield

36% (112.3 mg), gummy mass, IR (KBr) 3338, 1673, 1495, 1466, 810 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.06 (2H, s), 8.17 (2H, s), 7.91 (2H, d, $J = 1.8$ Hz), 7.82 (2H, m), 7.64 (2H, dd, $J = 8.8$, 2.2 Hz), 7.58 (2H, dd, $J = 7.2$, 1.8 Hz), 3.83 (4H, m); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 43.32, 111.14, 119.8, 121.35, 123.87, 128.52, 131.33, 134.46, 137.01, 139.26, 143.95. Found: C, 76.69; H, 5.22; N, 18.07%. Calcd for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16; N, 17.94%. Similar protocol was followed for the reactions between **2a** with straight chain aliphatic diamines, that is, 1,3-diaminopropane, 1,4-diaminobutane, 1,5-diaminopentane, and 1,6-diaminohexane to obtain **4g** to **4j**, respectively.

3,4-Dihydrodiindolo[3,2-*g*:2,3-*i*]-1,5-diaza-2*H*-cycloundecene (4g): Yield 47% (153.2 mg), gummy mass, IR (KBr) 3346, 1681, 1489, 1472, 811 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.14 (2H, s), 8.21 (2H, s), 7.86 (2H, d, $J = 1.8$ Hz), 7.84 (2H, m), 7.67 (2H, dd, $J = 8.7$, 2.2 Hz), 7.61 (2H, dd, $J = 7.1$, 1.8 Hz), 3.79 (4H, m), 2.63 (2H, m); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 43.02, 37.64, 111.19, 119.09, 121.93, 124.05, 128.58, 131.82, 134.19, 136.82, 143.18. Found: C, 77.21; H, 5.49; N, 17.28%. Calcd for $C_{21}H_{18}N_4$: C, 77.28; H, 5.56; N, 17.16%.

2,3,4,5-Tetrahydrodiindolo[3,2-*h*:2,3-*j*]-1,6-diazacyclododecene (4h): Yield 53% (180.2 mg), gummy mass, IR (KBr) 3352, 1671, 1487, 1472, 812 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.17 (2H, s), 8.13 (2H, s), 7.84 (2H, d, $J = 1.7$ Hz), 7.79 (2H, m), 7.59 (2H, dd, $J = 8.7$, 2.3 Hz), 7.52 (2H, dd, $J = 7.2$, 1.7 Hz), 3.77 (4H, m), 2.19 (4H, m); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 37.71, 42.04, 111.06, 118.94, 121.55, 124.17, 129.72, 131.62, 135.09, 139.41, 144.30. Found: C, 76.51; H, 5.87; N, 16.42%. Calcd for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46%.

3,4,5,6-Tetrahydrodiindolo[3,2-*i*:2,3-*h*]-1,7-diaza-2*H*-cyclotridecene (4i): Yield 32% (113.3 mg), gummy mass, IR (KBr) 3351, 1685, 1482, 1421, 812 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.01 (2H, s), 8.12 (2H, s), 7.89 (2H, d, $J = 1.9$ Hz), 7.78 (2H, m), 7.61 (2H, m), 7.53 (2H, dd, $J = 7.2$, 1.7 Hz), 3.80 (4H, m), 2.27 (4H, m), 1.91 (2H, m); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 27.19, 36.79, 42.94, 111.05, 118.41, 120.84, 124.51, 129.31, 132.06, 136.23, 138.52, 146.42. Found: C, 77.96; H, 6.23; N, 15.79%. Calcd for $C_{23}H_{22}N_4$: C, 77.94; H, 6.26; N, 15.81%.

2,3,4,5,6,7-Hexahydrodiindolo[3,2-*j*:2,3-*l*]-1,8-diazacyclotetradecene (4j): Yield 13% (49.7 mg), gummy mass, IR (KBr) 3316, 1679, 1489, 1470, 812 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.10 (2H, s), 8.22 (2H, s), 7.87 (2H, d, $J = 1.8$ Hz), 7.84 (2H, m), 7.65 (2H, dd, $J = 8.7$, 2.1 Hz), 7.63 (2H, dd, $J = 7.2$, 1.8 Hz), 3.79 (4H, m), 2.24 (4H, m), 1.87 (4H, m); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 24.47, 35.14, 42.13, 111.17, 119.23, 122.06, 124.62, 127.21, 130.52, 133.86, 136.52, 142.97. Found: C, 78.21; H, 6.61; N, 15.04%. Calcd for $C_{24}H_{24}N_4$: C, 78.23; H, 6.57; N, 15.20%.

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