A Simple and Efficient Method for the Synthesis of Indolo[3,2-*b*]carbazoles

Mohit L. Deb, Swarup Mazumder, Biswajita Baruah, Pulak J. Bhuyan*

North East Institute of Science & Technology, Jorhat 785006, Assam, India
Fax +91(376)2370011; E-mail: pulak_jyoti@yahoo.com

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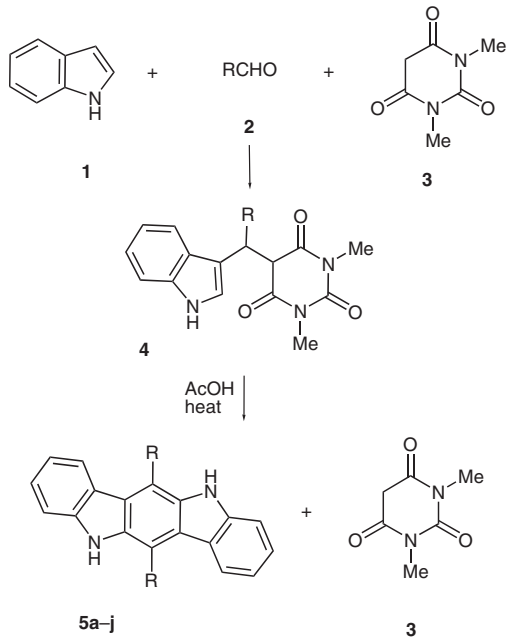
Abstract: 3-Alkylated indoles, obtained by three-component reactions of indole, aldehydes, and *N*,*N*-dimethylbarbituric acid, afford indolo[3,2-*b*]carbazoles in excellent yields under thermal conditions in acetic acid.

Key words: heterocycles, indoles, aldehydes, indolo[3,2-*b*]carbazole, *N*,*N*-dimethylbarbituric acid

Recently we synthesized a novel class of 3-alkylated indoles **4** by a three-component reaction of indole (**1**), aldehydes **2**, and *N*,*N*-dimethylbarbituric acid (**3**) (Scheme 1).[1] The 3-alkylated indoles thus obtained were then utilized for the synthesis of unsymmetrical bis(indolyl)methanes, which also demonstrated the good leaving nature of *N*,*N*-dimethylbarbituric acid.[2] As a part of our continued work in the area[3] and synthesis of diverse heterocyclic compounds of biological importance, we now report here a very simple and efficient method for the synthesis of indolo[3,2-*b*]carbazoles from 3-alkylated indole **4** (Scheme 1).



Scheme 1

The 3-alkylated indoles **4** were prepared from the reactions of indole (**1**), aldehydes **2**, and *N*,*N*-dimethylbarbituric acid (**3**) (Scheme 1) according to our own reported method.[1] In our reaction strategy, treatment of 3-alkylated indoles **4** in acetic acid under refluxing conditions afforded, after workup, the indolo[3,2-*b*]carbazoles **5** in 45–87% yield. Thus, in a simple experimental procedure, compound **4a**, for example, was refluxed in acetic acid for 15 minutes; after workup, this afforded indolo[3,2-*b*]carbazole **5a** in 80% yield (Scheme 1). The product was isolated simply by filtration followed by recrystallization from a mixture of *N*,*N*-dimethylformamide and chloroform. The structure of the compound was determined from spectroscopic data and elemental analysis. The *N*,*N*-dimethylbarbituric acid (**3**) that was eliminated during the reaction was isolated from the filtrate and characterized. Following the same reaction procedure, we synthesized and characterized a series of indolo[3,2-*b*]carbazoles **5b**–**j**. Our observations are recorded in Table 1.

Table 1 Synthesis of Indolo[3,2-*b*]carbazoles **5** from 3-Alkylated Indoles **4** Catalyzed by Acetic Acid[a]

4	R	Time (min)	Product **5**	Yield (%)[b]	Mp (°C)
4a	Ph	15	**5a**	80	350–352
4b	4-MeOC$_6$H$_4$	15	**5b**	82	383–385
4c	4-MeC$_6$H$_4$	15	**5c**	80	>400
4d	3,4,5-(MeO)$_3$C$_6$H$_2$	15	**5d**	87	>400
4e	4-HOC$_6$H$_4$	20	**5e**	72	>400
4f	2-HOC$_6$H$_4$	20	**5f**	70	357–359
4g	3-MeO-4-HOC$_6$H$_3$	20	**5g**	75	392–393
4h	4-ClC$_6$H$_4$	40	**5h**	48	364–366
4i	2-ClC$_6$H$_4$	40	**5i**	45	341–343
4j	4-BzOC$_6$H$_4$	40	**5j**	62	375–377

[a] Reaction conditions: **4** (2 mmol), AcOH (5 mL), heat.
[b] Isolated yields.

The reaction was also studied by utilizing the 3-alkylated indoles **4** with various Lewis acids, e.g., iodine, indium(III) chloride, cerium(IV) ammonium nitrate, and indium(III) trifluoromethanesulfonate, in solvents such as acetonitrile and tetrahydrofuran. Unfortunately, we could not get the desired products in any of these attempts. Next,

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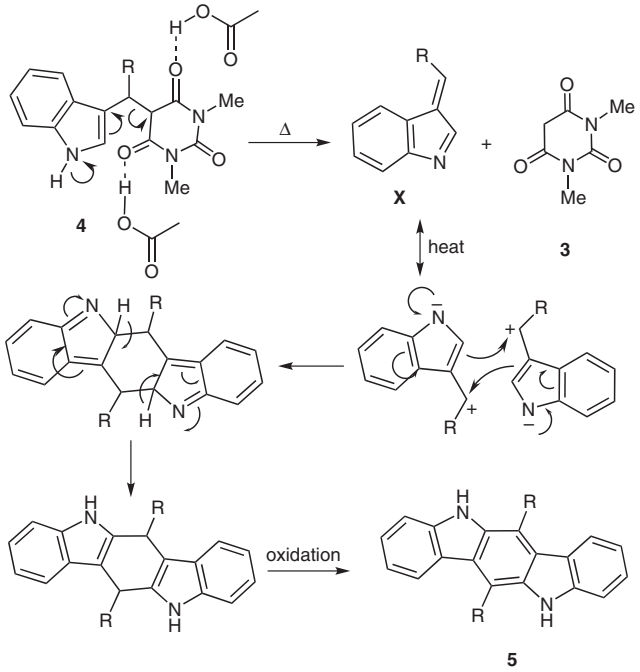
we studied the reaction in refluxing acetonitrile and using hydrogen chloride as catalyst. Initially the reaction was found to proceed, but some blackish compound appeared quickly during the reaction process; this might be due to decomposition of the product, and we were not able to isolate the desired compounds.

In many earlier reported methods for the synthesis of indolo[3,2-*b*]carbazoles, it was observed that indolo[2,3-*b*]carbazoles were also formed during the reaction process, but were difficult to separate due to their insolubility.[4] In the present case, it is not possible for the indolo[2,3-*b*]carbazole isomer to form, and that makes the method more suitable for the preparation of indolo[3,2-*b*]carbazoles.

A plausible mechanism for the reaction is outlined in Scheme 2. The 3-alkylated indoles **4** first give the intermediate **X** and *N*,*N*-dimethylbarbituric acid (**3**) in the presence of acetic acid under thermal conditions. Then two molecules of the intermediate **X** react; finally, oxidation affords the indolo[3,2-*b*]carbazoles **5**. The isolation of the *N*,*N*-dimethylbarbituric acid (**3**) eliminated during the reaction further supports this mechanism.



Scheme 2

3-Alkylated indoles **4** prepared from aromatic aldehydes that have electron-withdrawing substituents do not give the products, as they cannot stabilize the intermediate. Similarly, the reaction is not applicable to aliphatic aldehydes, due to the instability of the corresponding intermediates **X**.

In summary, we have developed a very simple and highly efficient method for the synthesis of indolo[3,2-*b*]carbazoles from 3-alkylated indoles that are available from a three-component reaction of indole, aldehydes, and *N*,*N*-dimethylbarbituric acid. In addition, the *N*,*N*-dimethylbarbituric acid that can be isolated in almost quantitative yield can be used again in the three-component reaction that leads to the formation of 3-alkylated indoles **4**. This very simple, efficient, and cost-effective procedure for the synthesis of various indolo[3,2-*b*]-carbazoles is a valuable addition to the chemistry of indolocarbazoles (ICZ).

All chemicals including the solvents were used without prior drying. All reagents and solvents were of reagent grade. All IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra (at 300 MHz and 75 MHz, respectively) were recorded on a Bruker Avance DPX FT spectrometer; DMSO-d_6 was used as solvent, and TMS as an internal standard. Mass spectra were recorded on a Bruker Daltonics ESQUIRE 3000 LC ESI ion-trap mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 instrument. Analytical TLC was performed on aluminum-backed silica gel plates coated with silica gel (0.2 mm thick layer) (E. Merck). Melting points (uncorrected) were determined on a Buchi B-540 apparatus. Indole, the aldehydes, and barbituric acid were purchased from Aldrich Chemical Co., and other commercially available reagents were used without further purification.

6,12-Diphenyl-5,11-dihydroindolo[3,2-*b*]carbazole (5a); Typical Procedure

Indole **4a** (722 mg, 2 mmol) in AcOH (5 mL) was refluxed for 15 min. The solvent was removed under reduced pressure and the residue was poured into EtOH (5 mL). The solid that had appeared was collected by filtration, dried, and recrystallized from a DMF–$CHCl_3$ mixture. The structure of the compound was determined to be that of **5a** on the basis of spectroscopic data and elemental analysis. The filtrate was distilled under reduced pressure and the eliminated *N*,*N*-dimethylbarbituric acid (**3**) was isolated from the residue by column chromatography (silica gel, EtOAc–hexane,1:3). The structure of **3** was ascertained from spectroscopic data and by comparison with an authentic sample.[5] Compounds **5b–j** were synthesized and characterized similarly.

Compound 5a

Yield: 326 mg (80%); white solid; mp 350–352 °C; R_f = 0.84 (EtOAc–PE, 7:93).

IR (KBr): 3394 (NH stretch), 3062 (w), 3019 (w), 1492 (w), 1456 (s), 744 (s), 702 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.74 (t, *J* = 7.41 Hz, 2 H), 6.89 (t, *J* = 7.32 Hz, 2 H), 7.0 (d, *J* = 7.71 Hz, 4 H), 7.07 (d, *J* = 7.83 Hz, 2 H), 7.17 (t, *J* = 7.14 Hz, 6 H), 7.58 (s, 2 H), 9.93 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 140.02, 136.57, 134.29, 133.28, 132.44, 130.18, 128.11, 126.96, 124.61, 122.33, 117.64, 114.77, 111.47.

ESI-MS: *m*/*z* = 409.3 $[M + H]^+$.

Anal. Calcd for $C_{30}H_{20}N_2$: C, 88.23; H, 4.90; N, 6.86. Found: C, 88.07; H, 4.99; N, 6.81.

6,12-Bis(4-methoxyphenyl)-5,11-dihydroindolo[3,2-*b*]carbazole (5b)

Yield: 196.5 mg (82%); white solid; mp 383–385 °C.

IR (KBr): 3394 (NH stretch), 3062 (w), 2977 (w), 1456 (s), 744 (s), 702 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.40 (s, 6 H), 6.76 (d, *J* = 7.88 Hz, 2 H), 6.85–6.97 (m, 4 H), 7.0 (d, *J* = 7.43 Hz, 2 H), 7.08–7.17 (m, 3 H), 7.26 (t, *J* = 7.42 Hz, 4 H), 7.72 (s, 1 H), 9.98 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 159.13, 140.08, 138.26, 136.45, 133.33, 130.93, 128.41, 127.11, 124.87, 122.41, 118.49, 113.93, 111.47, 55.19.

ESI-MS: *m*/*z* = 469.3 [M + H]$^+$.

6,12-Bis(4-methylphenyl)-5,11-dihydroindolo[3,2-*b*]carbazole (5c)
Yield: 174.5 mg (80%); white powder; mp >400 °C.

IR (KBr): 3397 (NH stretch), 3062 (w), 2951 (w), 1456 (s), 744 (s), 699 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.29 (s, 6 H), 6.78 (t, *J* = 7.44 Hz, 2 H), 6.86–6.97 (m, 2 H), 7.01 (d, *J* = 7.83 Hz, 3 H), 7.08 (d, *J* = 7.55 Hz, 2 H), 7.12–7.21 (m, 6 H), 7.61 (s, 1 H), 10.10 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 141.13, 136.59, 136.31, 134.62, 133.39, 130.23, 128.17, 127.82, 124.68, 121.69, 118.72, 114.91, 111.47, 21.23.

ESI-MS: *m*/*z* = 437.4 [M + H]$^+$.

6,12-Bis(3,4,5-trimethoxyphenyl)-5,11-dihydroindolo[3,2-*b*]carbazole (5d)
Yield: 250 mg (87%); white powder; mp >400 °C.

IR (KBr): 3402 (NH stretch), 3061 (w), 1456 (s), 1233 (s), 745 (s), 702 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.76–3.78 (m, 18 H), 6.83 (t, *J* = 7.48 Hz, 2 H), 6.92 (t, *J* = 7.18 Hz, 3 H), 7.0 (d, *J* = 7.56 Hz, 2 H), 7.09–7.17 (m, 2 H), 7.27 (t, *J* = 7.14 Hz, 2 H), 7.58 (s, 1 H), 10.02 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.0, 157.79, 141.33, 136.34, 134.42, 133.72, 131.57, 128.42, 127.91, 124.08, 122.80, 118.44, 114.63, 111.13, 55.47, 55.26.

ESI-MS: *m*/*z* = 589.8 [M + H]$^+$.

6,12-Bis(4-hydroxyphenyl)--5,11-dihydroindolo[3,2-*b*]carbazole (5e)
Yield: 165 mg (72%); white cotton-like solid; mp >400 °C.

IR (KBr): 3414 (br, s), 3019 (w), 1456 (s), 1233 (s), 744 (s), 699 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 5.67 (s, 2 H), 6.75 (t, *J* = 7.53 Hz, 2 H), 6.87 (t, *J* = 8.16 Hz, 2 H), 7.0–7.09 (m, 5 H), 7.15 (d, *J* = 7.31 Hz, 3 H), 7.18–7.29 (m, 3 H), 7.61 (s, 1 H), 9.98 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.08, 140.14, 136.53, 134.29, 133.69, 131.89, 130.11, 128.64, 126.90, 124.69, 121.37, 118.06, 111.43.

ESI-MS: *m*/*z* = 441.2 [M + H]$^+$.

6,12-Bis(2-hydroxyphenyl)--5,11-dihydroindolo[3,2-*b*]carbazole (5f)
Yield: 165.5 mg (70%); white solid; mp 357–359 °C.

IR (KBr): 3418 (br, s), 3019 (w), 1456 (s), 1233 (s), 744 (s), 699 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.78 (s, 2 H), 6.74 (t, *J* = 7.59 Hz, 2 H), 6.87 (t, *J* = 7.47 Hz, 2 H), 7.02–7.10 (m, 4 H), 7.20 (d, *J* = 7.74 Hz, 3 H), 7.23–7.29 (m, 3 H), 7.71 (s, 2 H), 10.64 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.34, 140.21, 136.53, 134.29, 133.13, 132.22, 130.17, 128.64, 127.17, 124.94, 122.08, 118.06, 111.44.

ESI-MS: *m*/*z* = 441.5 [M + H]$^+$.

6,12-Bis(4-hydroxy-3-methoxyphenyl)-5,11-dihydroindolo[3,2-*b*]carbazole (5g)
Yield: 188 mg (75%); yellowish powder; mp 392–393 °C.

IR (KBr): 3418 (br, s), 3062 (w), 1492 (w), 1456 (s), 1224, 744 (s), 702 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 3.41 (s, 6 H), 5.44 (s, 2 H), 6.75 (t, *J* = 7.44 Hz, 2 H), 6.87 (q, *J* = 7.56 Hz, 2 H), 7.0 (t, *J* = 7.93 Hz, 4 H), 7.10 (d, *J* = 7.43 Hz, 2 H), 7.14–7.27 (m, 3 H), 7.58 (s, 1 H), 9.93 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 158.08, 155.20, 140.06, 138.58, 136.44, 133.98, 132.02, 131.42, 128.56, 126.94, 124.61, 122.31, 118.51, 114.81, 111.53, 55.47.

ESI-MS: *m*/*z* = 501.3 [M + H]$^+$.

6,12-Bis(4-chlorophenyl)-5,11-dihydroindolo[3,2-*b*]carbazole (5h)
Yield: 131 mg (48%); white solid; mp 364–366 °C.

IR (KBr): 3399 (NH stretch), 3062 (w), 1456 (s), 1137 (m), 744 (s), 702 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.80 (t, *J* = 8.32 Hz, 2 H), 6.90 (d, *J* = 7.74 Hz, 2 H), 7.02–7.14 (m, 5 H), 7.20 (d, *J* = 7.19 Hz, 2 H), 7.34 (t, *J* = 7.47 Hz, 4 H), 7.71 (s, 1 H), 10.02 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 139.47, 136.50, 134.31, 133.88, 132.49, 130.76, 128.01, 127.46, 124.79, 121.93, 117.13, 111.47, 109.91.

ESI-MS: *m*/*z* (%) = 477.6 [M + H (2 × ^{35}Cl)]$^+$ (100), 479.6 [M + H (^{35}Cl + ^{37}Cl)]$^+$ (63), 481.6 [M + H (2 × ^{37}Cl)]$^+$ (10).

6,12-Bis(2-chlorophenyl)-5,11-dihydroindolo[3,2-*b*]carbazole (5i)
Yield: 119 mg (45%); yellowish powder; mp 341–343 °C.

IR (KBr): 3397 (NH stretch), 3062 (w), 1456 (s), 1137 (m), 745 (s), 702 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.73–6.87 (m, 3 H), 6.91 (t, *J* = 7.49 Hz, 2 H), 7.02 (d, *J* = 7.31 Hz, 3 H), 7.15 (d, *J* = 7.41 Hz, 2 H), 7.34 (t, *J* = 7.47 Hz, 4 H), 7.72 (s, 2 H), 10.02 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 139.49, 136.63, 134.80, 133.81, 132.49, 130.70, 128.0, 127.33, 124.61, 121.88, 117.22, 111.47, 109.93.

ESI-MS: *m*/*z* = 477.4 [M + H (2 × ^{35}Cl)]$^+$ (100), 479.4 [M + H (^{35}Cl + ^{37}Cl)]$^+$ (63), 481.4 [M + H (2 × ^{37}Cl)]$^+$ (10).

6,12-Bis[4-(benzoyloxy)phenyl]-5,11-dihydroindolo[3,2-*b*]carbazole (5j)
Yield: 220 mg (62%); white solid; mp 375–377 °C.

IR (KBr): 3394 (NH stretch), 3062 (w), 1737 (s), 1456 (s), 1271 (m), 744 (s), 702 (m) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 6.73–6.85 (m, 4 H), 6.89 (t, *J* = 7.43 Hz, 2 H), 7.05 (t, *J* = 7.71 Hz, 6 H), 7.14–7.23 (m, 8 H), 7.28 (d, *J* = 7.17 Hz, 4 H), 7.70 (s, 2 H), 10.03 (s, 2 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 166.32, 153.08, 141.21, 138.47, 136.07, 134.29, 133.77, 131.49, 130.27, 128.39, 126.93, 124.45, 122.0, 118.13, 113.41, 111.47, 109.46.

ESI-MS: *m*/*z* = 649.4 [M + H]$^+$.

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