An Efficient Method for the Synthesis of Indolo[3,2-*b*]carbazoles from 3,3′-Bis(indolyl)methanes Catalyzed by Molecular Iodine

Mohit L. Deb, Pulak J. Bhuyan*

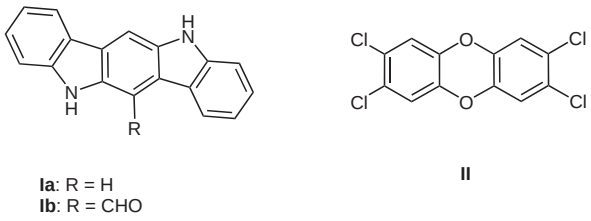
Medicinal Chemistry Division, North East Institute of Science & Technology, Jorhat 785006, Assam, India
Fax +91(376)2370011; E-mail: pulak_jyoti@yahoo.com

Received 24 August 2007

Abstract: The reaction of 3,3′-bis(indolyl)methanes in the presence of molecular iodine as catalyst in refluxing acetonitrile affords indolo[3,2-*b*]carbazoles in good yields.

Key words: indolo[3,2-*b*]carbazoles, 3,3′-bis(indolyl)methanes, iodine, indole

Indolo[3,2-*b*]carbazole (ICZ, **I**, Figure 1) which is formed in vivo after consumption of cruciferous vegetables such as cabbage and brussels sprouts, is a molecule of considerable biological significance.[1] Indolo[3,2-*b*]carbazole shares the biological activity with TCDD (2,3,7,8-tetrachloro-dibenzo-*p*-dioxin, **II**) receptor (Ah-receptor). Recently it has been demonstrated that 6-formyl-indolo[3,2-*b*]carbazole[2] (**Ib**) has an extremely strong affinity to the TCDD receptor, in fact even stronger than the highly toxic dioxin TCDD itself.[3] The TCDD receptor is very important in the primary detoxification of unpolar substances, as this receptor triggers the expression of many enzymes (including cytochrome P-4501A1 or CYP1A1) involved in this process. Furthermore, in certain animals, the development of a proper liver and immune system are dependent on a working receptor.[4] Moreover, 5,11-disubstituted indolo[3,2-*b*]carbazoles are a new class of high-performance organic semiconductors suitable for organic thin film transistor (OTFT) applications.[5]



Ia: R = H
Ib: R = CHO

II

Figure 1

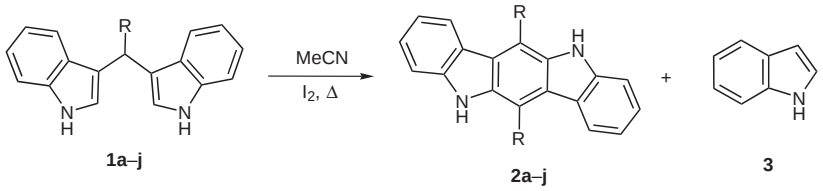
Considering the significant biological and synthetic importance of these compounds, a variety of methods have been reported for the preparation of indolo[3,2-*b*]carbazoles; for example: (1) Pt-mediated cyclodehydrogenation of *N*,*N*-diphenyl-*p*-phenyl-enediamine,[6] (2) double Fischer indolization of cyclohexane-1,4-dione bis(phenylhydrazone),[7] (3) condensation of indole and formaldehyde in the presence of strong acid, air, and sensitizers,[8] (4) Lewis acid catalyzed dimerization of 1-(1-benzotriazol-1-yl-alkyl)indoles,[9] (5) intramolecular cyclization of 2-(1*H*-indol-3-yl-methyl)-1*H*-indolecarbaldehyde,[10] (6) condensation of indole with aliphatic aldehydes under acidic conditions,[11] (7) cyclization of 3,3′-bis(indolyl)methanes[12] or 2,3′-bis(indolyl)methanes[13] via acid-catalyzed reaction in the presence of triethyl orthoformate. However, all these methods have their own limitations and a number of drawbacks, e.g. long reaction time, drastic conditions, tedious workup procedure, poor yield of the desired product, lack of selectivity, and formation of byproducts.

The use of molecular iodine in organic synthesis has been known for a long time and presently it is receiving considerable attention as an inexpensive, nontoxic, readily available, and mild Lewis acid catalyst for various organic reactions under convenient conditions to afford the desired product in excellent yields.[14] Moreover, it has high solubility in organic solvents and is easily removable from the reaction mixture.

In a recent study it was reported that the reaction of two equivalents of indole and one equivalent of carbonyl compound in the presence of iodine at room temperature in a very short time affords 3,3′-bis(indolyl)methanes.[14a] On the other hand when the same reaction was allowed to continue for a long time (14 h) at room temperature the 3,3′-bis(indolyl)methane initially formed was isomerized to 2,3′-bis(indolyl)methane.[15] To investigate these observations[14a,15] we studied the iodine-catalyzed reaction of indole and aromatic aldehyde[14a] under thermal conditions. In the reaction, however, we obtained a mixture of many compounds that could not be separated. We then studied the reaction of 3,3′-bis(indolyl)methanes in the presence of molecular iodine as catalyst under thermal conditions. As a result of this study and our continued work[16] on indoles and synthesis of diverse heterocyclic compounds of biological importance we report herein a very simple and efficient method for the synthesis of indolo[3,2-*b*]carbazoles.

In our reaction strategy, utilizing 3,3′-bis(indolyl)methanes **1** with catalytic amount of molecular iodine in refluxing acetonitrile for 20–35 minutes afforded after workup indolo[3,2-*b*]carbazoles **2** in good yields (Scheme 1). The 3,3′-bis(indolyl)methanes were prepared by our own reported method.[16b] In a simple experimental procedure[17] when 3,3′-bis(indolyl)methane **1a** was heated

SYNLETT 2008, No. 3, pp 0325–0328
Advanced online publication: 16.01.2008
DOI: 10.1055/s-2008-1032052; Art ID: D26407ST



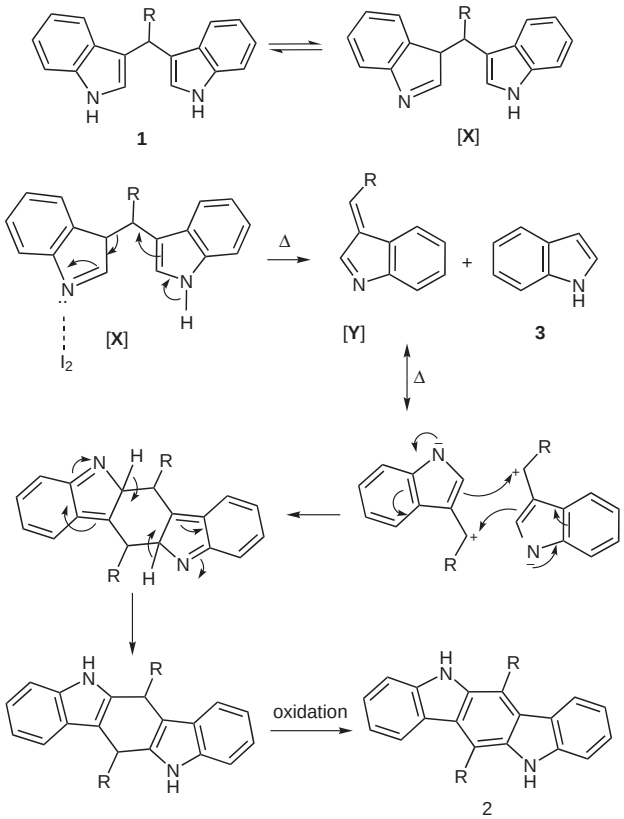
Scheme 1

in the presence of catalytic amount of molecular iodine (2 mol%), in refluxing acetonitrile for 20 minutes, afforded indolo[3,2-*b*]carbazole **2a** in 80% yield (Table 1). The product was isolated simply by filtration and recrystallized from a mixture of DMF and $CHCl_3$. The structure of the compound was determined from spectroscopic data and elemental analysis. The indole molecule **3**, which was eliminated during the reaction was isolated from the filtrate and characterized. Following the same reaction procedure we synthesized and characterized a series of compounds **2b**–**j**. Our observations are recorded in Table 1. The 3,3′-bis(indolyl)methanes prepared by using aliphatic aldehydes and aromatic aldehydes having strong electron-withdrawing substituents did not react under these reaction conditions to give the desired product.

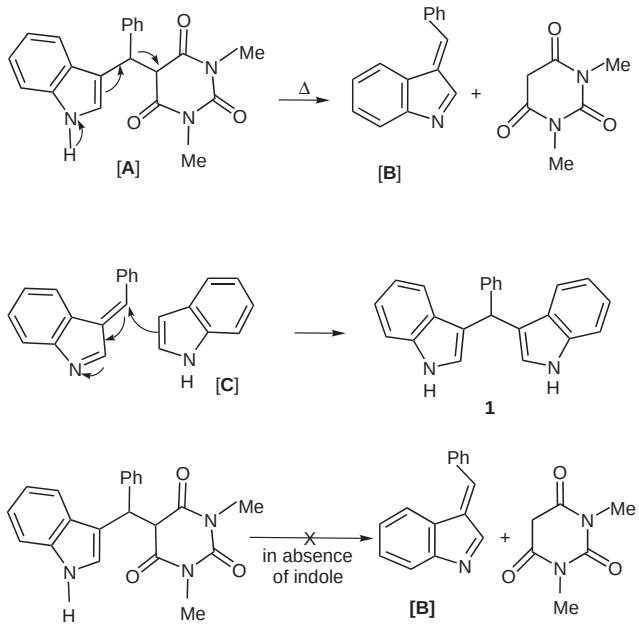
Although the yield of products in the reaction is not very high in some cases, there is selective formation of the indolo[3,2-*b*]carbazole. In many reported methods, both the indolo[3,2-*b*]carbazoles and indolo[2,3-*b*]carbazoles were formed which were difficult to separate due to their insolubility.[18] In the present case there is no possibility of formation of the indolo[2,3-*b*]carbazole isomer.

A plausible mechanism for the reaction is outlined in Scheme 2. The 3,3′-bis(indolyl)methanes which can be considered as 3-alkylated indoles, undergo 1,3-tautomerization[19] and thus can exist in the indolenine form as **[X]** (Scheme 2). In the presence of iodine under thermal conditions this gives the intermediate **[Y]** and indole **3**. Under the reaction conditions, two molecules of the intermediate **[Y]** then react and finally are oxidized to give the indolo[3,2-*b*]carbazoles **2**. The isolation of the indole molecule **3** eliminated during the reaction supports this mechanism. Although at room temperature the intermediate **[Y]** and indole **3** may react in presence of iodine to give 3,3′-bis(indolyl)methanes,[14a] the thermal conditions favor the forward reaction to give the indolo[3,2-*b*]carbazole **2**. The 3,3′-bis(indolyl)methanes prepared by using aromatic aldehydes having electron-withdrawing substituents do not give the product, as they cannot stabilize the intermediate. Similarly, the reaction is not applicable to aliphatic aldehydes due to instability of the intermediate **[Y]**.[16g]

Recently, we reported the preparation of some novel 3-alkylated indoles **[A]** (Scheme 3) via a three-component reaction of indole, aldehyde, and barbituric acids.[16g] In this reaction we observed the formation of a small amount

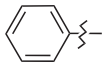
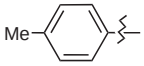
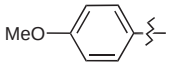
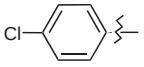
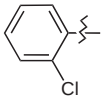
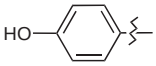
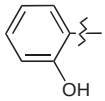
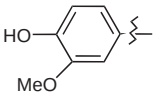
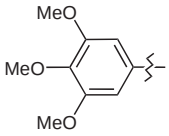
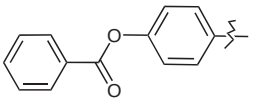


Scheme 2



Scheme 3

Table 1 Synthesis of Indolo[3,2-*b*]carbazoles **2** from the 3,3′-Bis(indolyl)methanes **1** Catalyzed by Iodine

Product[a]	R	Time (min)	Yield (%)[b]	Mp (°C)
2a		20	80	350
2b		20	80	>400
2c		20	84	384
2d		35	55	365
2e		35	50	340
2f		22	75	>400
2g		20	75	358
2h		20	75	392
2i		20	85	>400
2j		35	68	373

[a] All reactions were performed at 1 mmol scale using 2 mol% of I_2.
[b] Isolated yields.

of 3,3′-bis(indolyl)methane. As we expected that decomposition of **[A]** would lead to formation of **[B]** avoiding the presence of indole **[C]** we performed the reaction of 3-alkylated indoles **[A]** under thermal conditions using a catalytic amount of iodine in an attempt to form indolo[3,2-*b*]carbazoles. Unfortunately, we did not obtain the desired product. Hence it was concluded that the intermediate **[B]** does not form in the absence of indole under these reaction conditions. However, these observations further support our proposed mechanism shown in Scheme 2.

We then studied the reaction using different Lewis acid catalysts such as $InCl_3$, CAN, $ZnCl_2$, but only $InCl_3$ gave the desired product (15%) after refluxing for two hours. Hence iodine is the optimal catalyst for the purpose of the reaction. Further study of the reaction is in progress.

In summary, we have reported a very simple, mild, and highly efficient method for the synthesis of indolo[3,2-*b*]carbazoles from 3,3′-bis(indolyl)methanes of aromatic aldehydes in the presence of molecular iodine as catalyst. This very simple, mild, and cost-effective procedure for the synthesis of various indolo[3,2-*b*]carbazoles is a valuable addition to the chemistry of indolocarbazoles.

Acknowledgment

The authors thank Dr. P. G. Rao, the Director, NEIST, Jorhat for providing the facilities to perform the work. M.L.D. thanks CSIR (India) for the award of a Senior Research Fellowship.

References and Notes

(1) Bradfield, C. A.; Bjeldanes, L. F. *J. Agric. Food Chem.* **1987**, *35*, 46.
(2) Rannug, U.; Rannug, A.; Sjoberg, U.; Li, H.; Westerholm, R.; Bergman, J. *Chem. Biol.* **1995**, *2*, 841.
(3) Wei, Y.; Helleberg, H.; Rannug, U.; Rannug, A. *Chem. Biol. Interact.* **1998**, *110*, 39.
(4) Gonzalez, F. J.; Fernandez-Salguero, P.; Ward, J. M. *J. Toxicol. Sci.* **1996**, *21*, 273.
(5) Wu, Y. L.; Li, Y.; Gardner, S.; Ong, B. S. *J. Am. Chem. Soc.* **2005**, *127*, 614.
(6) Grotta, H. M.; Riggle, C. J.; Bearse, A. E. *J. Org. Chem.* **1961**, *26*, 1509.
(7) Robinson, B. *J. Chem. Soc.* **1963**, 3097.
(8) Bergman, J. *Tetrahedron* **1970**, *26*, 3353.
(9) Katritzky, A. R.; Li, J. Q.; Stevens, C. V. *J. Org. Chem.* **1995**, *60*, 3401.
(10) Wille, G.; Mayser, P.; Thoma, W.; Monsees, T.; Baumgart, A.; Schmitz, H.-J.; Schrenk, D.; Polborn, K.; Steglich, W. *Bioorg. Med. Chem.* **2001**, *9*, 955.
(11) Tholander, J.; Bergman, J. *Tetrahedron* **1999**, *55*, 12577.
(12) Pindur, U.; Muller, J. *Arch. Pharm. (Weinheim, Ger.)* **1987**, *320*, 280.
(13) Wahlstrom, N.; Stensland, B.; Bergman, J. *Synthesis* **2004**, 1187.
(14) (a) Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, *44*, 1959. (b) Wu, J.; Xia Guang, H.; Gao, K. *Org. Biomol. Chem.* **2006**, *4*, 126. (c) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932.
(15) Gu, R.; Hameurlaine, A.; Dehaen, W. *Synlett* **2006**, 1535.
(16) (a) Bhuyan, P. J.; Boruah, R. C.; Sandhu, J. S. *Tetrahedron Lett.* **1989**, *30*, 1421. (b) Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2006**, *47*, 1441. (c) Devi, I.; Bhuyan, P. J. *Synlett* **2004**, 283. (d) Devi, I.; Borah, H. N.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 2405. (e) Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 8625. (f) Devi, I.; Baruah, B.; Bhuyan, P. J. *Synlett* **2006**, 2593. (g) Deb, M. L.; Bhuyan, P. J. *Tetrahedron Lett.* **2007**, *48*, 2159. (h) Kalita, P.; Baruah, B.; Bhuyan, P. J. *Tetrahedron Lett.* **2006**, *47*, 7779.
(17) **Experimental Procedure:** 3,3′-Bis(indolyl)phenylmethane (**1a**, 1 mmol, 322 mg) was taken up in a round-bottom flask containing MeCN (5 mL). I_2 (2 mol%) was added and the mixture refluxed for 20 min. The obtained solid was filtered, dried, and recrystallized from a mixture of DMF–$CHCl_3$. The structure of the compound obtained was identified from spectroscopic data and elemental analysis.
6,12-Diphenyl-5,11-dihydroindolo[3,2-*b*]carbazole (2a) White solid, mp 350 °C. Yield 80% (326 mg). R_f = 0.84 [EtOAc (7%)–PE]. IR (KBr): 3394 (NH stretch), 3062 (w),

3019 (w), 1492 (w), 1456 (s), 745 (s), 702 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 6.72–6.77 (t, 2 H, *J* = 7.41 Hz), 6.87–6.92 (t, 2 H, *J* = 7.32 Hz), 6.98–7.0 (d, 4 H, *J* = 7.71 Hz), 7.05–7.08 (d, 2 H, *J* = 7.83 Hz), 7.14–7.19 (t, 6 H, *J* = 7.14 Hz), 7.58 (s, 2 H), 9.93 (s, 2 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 140.0, 136.51, 134.29, 133.31, 132.44, 130.18, 128.11, 126.93, 124.61, 122.33, 117.64, 114.81, 111.47. MS: *m/z* = 409.8 $[M + H]^+$. Anal. Calcd for $C_{30}H_{20}N_2$; C, 88.23; H, 4.90; N, 6.86. Found: C, 88.26; H, 4.93; N, 6.82.

(18) Black, D. StC; Ivory, A. J.; Kumar, N. *Tetrahedron* **1995**, *51*, 11801.

(19) Julian, P. L.; Meyer, E. W.; Printy, H. C. In *Heterocyclic Compounds*, Vol. 3; Elderfield, R. C., Ed.; John Wiley & Sons, Inc.: New York, **1960**, 1–274.