

A practical synthesis of bis(indolyl)methanes employing boric acid

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Abstract A variety of aldehydes and ketones react rapidly with indoles in the presence of boric acid under solvent-free conditions to afford the corresponding bis(indolyl)methanes. Excellent yields and short reaction times together with the environmentally friendly nature of boric acid make this procedure useful and attractive to produce a variety of bis(indolyl)methanes. The use of boric acid makes it quite simple, more convenient, and practical. This new method offers several advantages such as high conversions, cleaner reaction profiles, short reaction times, and the use of inexpensive and readily available boric acid.

Keywords Coupling reactions · Boric acid · Indoles · Aldehydes · Ketones

Introduction

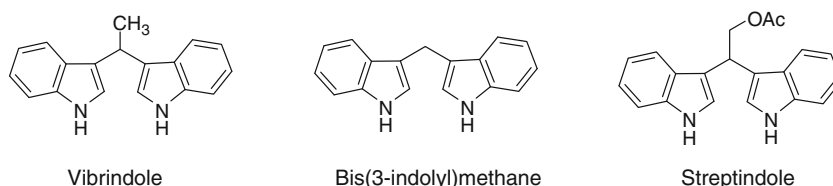
Bis(indolyl)methanes are present in various natural products possessing important biological activity [1–7]. Interestingly, a variety of bis(indolyl)methanes have been isolated from terrestrial and marine natural sources, viz. parasitic bacteria, tunicates, and sponge [8, 9], and many of them possess significant biological activity: e.g., vibrindole A [10] exhibits antibacterial activity against *Staphylococcus aureus*, *S. albus*, and *Bacillus subtilis*; bis(3-indolyl)methane [10] exhibits significant anticarcinogenic

activity; and streptindole is the first bacterial metabolite possessing genotoxicity and DNA-damaging activities, which are replicable in *B. subtilis* cells [11] (Fig. 1).

Furthermore, indole derivatives are used as antibiotics [12]. Consequently, several methods for the preparation of bis(indolyl)alkanes have been reported in the literature by reacting indoles with various aldehydes and ketones in the presence of either a Lewis acid [13–21] or a protic acid [22–26]. Recently, Dy(OTf)₃/ionic liquid [27], molecular iodine [28], KHSO₄ [29], and NaBF₄ [30] have also been employed for the synthesis of bis(indolyl)alkanes. Recently, we reported a novel synthesis of bis(indolyl)phenylethane by reacting indole with phenylacetylene in the presence of gallium(III) halide [31]. In spite of a large number of methods reported for this conversion [32–35], there is always considerable interest in exploring more mild, practical, and benign reagents for the synthesis of bis(indolyl)-alkane derivatives. Therefore, the development of simple and convenient procedures for the synthesis of bis(indolyl)-alkanes continues to be a challenging endeavor in synthetic organic chemistry.

Recently, great attention has been focused on the use of water-soluble boric acid as environmentally friendly reagents in organic synthesis. In addition to its abundance and for economical and safety reasons, boric acid has naturally become a substitute and an alternative environmentally benign reagent in organic synthesis [36–38]. The boric acid employed in the proposed reaction is an inexpensive, commercially available, and green catalyst. By virtue of the simplicity of the process, the operation is easy to conduct. Therefore, it is amenable for large-scale preparations. There have been no reports on the coupling of indoles with aldehydes and ketones to produce bis(indolyl)alkanes using this environmentally friendly catalyst under solvent-free conditions.

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Fig. 1 Bis(indolyl)methanes exhibiting biological activity

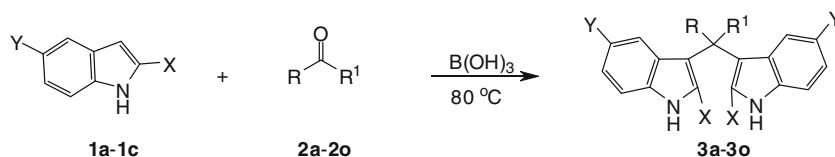
Boric acid, also called boracic acid, orthoboric acid, or acidum boricum, is a mild acid often used as an antiseptic, insecticide, flame retardant, in nuclear power plants to control the fission rate of uranium, and as a precursor of other chemical compounds. It exists in the form of colorless crystals or a white powder and dissolves in water.

Results and discussion

In this article, we describe our results on boric acid-mediated synthesis of bis(indolyl)alkanes via the coupling of indoles with aldehydes and ketones under solvent-free conditions. Initially, the reaction was attempted by coupling of indole (**1a**, 2 equiv.) with benzaldehyde (**2a**, 1.2 equiv.) in the presence of 20 mol% of boric acid under solvent-free conditions at room temperature. The reaction went to completion in 4 h and the product **3a** was isolated

in 60% yield. Consequently, we changed our strategy to achieve complete conversion. Subsequently, indole (**1a**) was treated with benzaldehyde (**2a**) in the presence of 20 mol% of boric acid under solvent-free conditions at 80 °C. The reaction went to completion within 1 h and the desired product **3a** was obtained in 94% yield (Scheme 1, Table 1).

Encouraged by the above result, we turned our attention toward various aromatic aldehydes. *p*-Fluoro-, *p*-chloro-, *p*-cyano-, *p*-nitro-, *p*-methyl-, and *m*-phenoxybenzaldehyde (entries b–g, Table 1) underwent smooth coupling with indole to afford the corresponding bis(indolyl)methanes in good yields. Aliphatic aldehydes such as cyclohexanecarboxaldehyde and propanaldehyde also gave the desired product (entries h–i, Table 1). Like indole, 5-nitroindole and 2-methylindole also coupled with aromatic and aliphatic aldehydes (entries j–l, Table 1) to afford the corresponding bis(indolyl)alkanes in good yields. Furthermore,

Scheme 1**Table 1** Boric acid-catalyzed synthesis of bis(indolyl)methanes

Entry	Indoles	Aldehydes/ketones	Product ^a	Time (min)	Yield ^b (%)	Ref.
a	1a : X = Y = H	2a : R = H; R ¹ = C ₆ H ₅	3a	60	94	[13, 14]
b	1a : X = Y = H	2b : R = H; R ¹ = 4-FC ₆ H ₄	3b	30	95	[32]
c	1a : X = Y = H	2c : R = H; R ¹ = 4-ClC ₆ H ₄	3c	20	92	[14, 15]
d	1a : X = Y = H	2d : R = H; R ¹ = 4-NCC ₆ H ₄	3d	35	88	[32]
e	1a : X = Y = H	2e : R = H; R ¹ = 4-NO ₂ C ₆ H ₄	3e	22	92	[13, 14]
f	1a : X = Y = H	2f : R = H; R ¹ = 4-MeC ₆ H ₄	3f	75	85	[13, 15]
g	1a : X = Y = H	2g : R = H; R ¹ = 3-PhOC ₆ H ₄	3g	25	92	–
h	1a : X = Y = H	2h : R = H; R ¹ = cyclohexyl	3h	150	87	[33]
i	1a : X = Y = H	2i : R = H; R ¹ = C ₂ H ₅	3i	85	83	[34]
j	1b : X = H; Y = NO ₂	2j : R = H; R ¹ = C ₆ H ₅	3j	125	88	[33]
k	1b : X = H; Y = NO ₂	2k : R = H; R ¹ = C ₂ H ₅	3k	155	78	–
l	1c : X = Me; Y = H	2l : R = H; R ¹ = 4-FC ₆ H ₄	3l	10	95	[35]
m	1a : X = Y = H	2m : R = R ¹ = Me	3m	190	70	[33]
n	1a : X = Y = H	2n : R = R ¹ = cyclopentyl	3n	180	72	[14]
o	1a : X = Y = H	2o : R = R ¹ = cyclohexyl	3o	150	75	[14]

^a All products were characterized by IR, ¹H NMR, and mass spectra

^b Isolated and unoptimized yields after column chromatography

Scheme 2

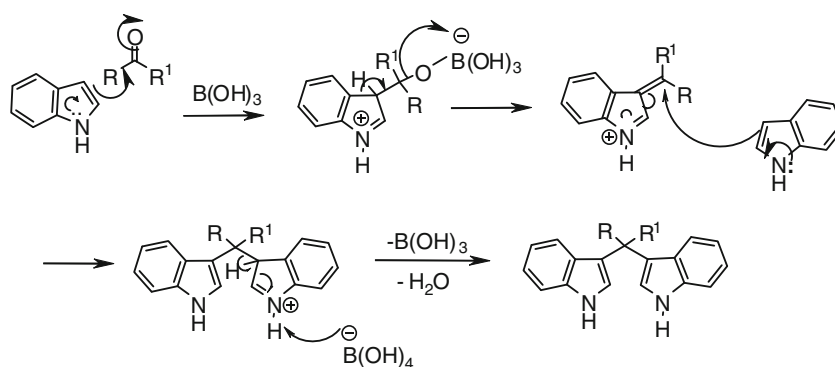


Table 2 A comparative study of the synthesis of **3a** from indole and benzaldehyde using other catalysts

Entry	Catalyst	Conversion (%)	Time (h)	Yield (%)	Ref.
1	Boric acid (20 mol%)	98	1.0	94 ^a	– ^b
2	Sulphamic acid	96	3.0	94	[27]
3	5% TBAT	93	4.0	91	– ^b
4	I ₂ (2 mol%)/CH ₃ CN	95	0.5	90	[28]
5	In(OTf) ₃ /Dy(OTf) ₃	96	12.0	95	[17]
6	Ln(OTf) ₃ (0.05 equiv)	77	0.5	71	[20]
7	Dy(OTf) ₃ in ionic liquid (2 mol%)	96	1.0	90	[26]
8	HY-zeolite	88	1.0	85	[22]
9	PPh ₃ .HClO ₄ (20 mol%)	66	0.5	61	– ^b

TBAT tetrabutylammonium tribromide

^a 80 °C

^b This study

the coupling of indole with ketones such as acetone, cyclopentanone, and cyclohexanone (entries m–o, Table 1) in the presence 20 mol% boric acid produced the desired product in satisfactory yield.

Finally we attempted the coupling of indole with phenylacetylene. Phenylacetylene did not couple with indole under the reaction conditions and no desired product was obtained. A plausible catalytic pathway is depicted in Scheme 2.

To investigate the efficacy of the boric acid catalysis, we compared the reaction of indole with benzaldehyde using other reported catalysts and the results are summarized in Table 2. Boric acid is highly selective and affords the bis-adduct without formation of any side products such as mono-adduct or self-condensation products.

Furthermore the scope and generality of this process is illustrated with respect to various indoles and the results are presented in Table 1.

Experimental

Boric acid (99.999%) and all other chemicals were purchased from Aldrich Chemical Company. Melting points were recorded on a Buchi R-535 apparatus. IR spectra were

recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ¹H NMR spectra were recorded on a Varian Unity 300 spectrometer in CDCl₃ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure for the synthesis of bis(indolyl)methanes

A mixture of indole (2 mmol), aldehyde/ketone (1.2 mmol), and B(OH)₃ (20 mol%) was heated at 80 °C (see Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with 10 cm³ H₂O and extracted with EtOAc (2 × 10 cm³). The combined organic layers were dried (Na₂SO₄), concentrated in vacuo, and purified by column chromatography (Merck, 60–120 mesh, EtOAc/hexane, 2:8) to afford pure bis(indolyl)methane in high yield as summarized in Table 1.

Experiments 3 and 9 shown in Table 2 were carried out in the same manner but boric acid was replaced by the given amount of other catalysts.

All products were characterized by IR, NMR spectroscopy, and their physical constants. The characterization data were found to be consistent with authentic samples. All products **3a–3o** were prepared by the same procedure.

Analytical data of compounds **3a–3f**, **3h–3j**, and **3l–3o** were identical to those described in Refs. [13–15, 32–35].

3,3'-[[3-(Phenylloxy)phenyl]methyl]bis[1H-indol]

(**3g**, C₂₉H₂₂N₂O)

Solid, m.p.: 84–86 °C; IR (KBr): $\bar{\nu}$ = 3,454, 2,956, 2,848, 1,429, 1,354, 1,252, 1,161, 1,078, 1,019, 889, 780, 695, 527 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 7.70 (brs, 2H, NH), 7.34 (d, *J* = 7.4 Hz, 2H), 7.25–7.17 (m, 5H), 7.13–7.06 (m, 3H), 6.99–6.95 (m, 4H), 6.88–6.81 (m, 3H), 6.51 (s, 2H), 5.80 (s, 1H) ppm; EIMS: *m/z* (%) = 414 (M⁺, 30), 298 (5), 245 (7), 198 (5), 70 (10), 43 (100).

3,3'-(Propan-1,1-diyl)bis[5-nitro-1H-indol]

(**3k**, C₁₉H₁₆N₄O₄)

Colourless liquid; IR (KBr): $\bar{\nu}$ = 3,484, 2,866, 2,853, 2,737, 1,448, 1,565, 1,376, 1,341, 1,254, 1,209, 1,185, 1,145, 1,084, 1,021, 960, 893, 868, 808, 717, 563 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ = 11.23 (brs, 2H, NH), 8.31 (s, 2H), 7.90 (d, *J* = 9.5 Hz, 2H), 7.38–7.31 (m, 4H), 4.39–4.36 (m, 1H), 2.31–2.25 (m, 2H), 1.00 (t, *J* = 7.3 Hz, 3H) ppm; FAB MS: *m/z* (%) = 365 (M + 1, 5), 335 (8), 290 (5), 261 (55), 238 (5), 203 (8), 137 (20), 109 (20), 95 (40), 81 (45), 69 (68), 55 (82).

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