Boric acid promoted convenient synthesis of bis (indolyl) methane in aqueous medium

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An efficient reaction of indole with various aldehydes using catalytic amount of boric acid in aqueous medium to afford the corresponding bis(indolyl) methane is reported. The products are obtained in excellent yields. The aqueous medium provides safety as well as economic and environmental benefits. When compared to other reported methods, decreased reaction time leads to a novel and particularly attractive avenue for the rapid generation of structurally diverse libraries. Simple reaction conditions, easy isolation and high yields of the products and environmentally benign medium are the attractive features of this method.

Keywords: Indole, aldehyde, bis(indolyl) methane, boric acid

Indole moiety is found in many bioactive natural products as well as in pharmaceutically active compounds. Particularly, bis(indolyl)methane compounds show broad spectrum of biological activities. For example bis(indolyl)methane promote estrogen metabolism both in men and women whereas bis(indolyl) derivatives bridged by heterocyclic ring exhibits cytotoxic activity against a wide range of human tumor cell lines.

Classical methods for the synthesis of bis(indolyl) methanes are based on the electrophilic substitution of indole with carbonyl compounds, which are catalyzed, by protic acids as well as Lewis acids. But Lewis acids encounter the problem of decomposition in the presence of nitrogen containing reactants and require stoichiometric amount or excess of Lewis acid. In addition to this, synthesis of bis(indolyl)-methane has been reported using expensive reagents like lithium perchlorate, lanthanide triflates, cyanoic chloride and sodium tetrafluoroborate. In recent times, bis(indolyl)methane was reportedly synthesised using water in presence of surfactant.

Results and Discussion

Most of the procedures for the synthesis of bis (indolyl) methane require organic solvents and also the reagents are expensive or moisture sensitive and generate unacceptable waste. There is a growing interest in boric acid catalyzed reactions because of inexpensiveness, easy availability and friendly nature of reagent. Moreover, boric acid if taken, internally or inhaled, is generally not considered to be much more toxic than table salt (based on its mammal LD50 rating of 2660 mg/kg body mass).

Very recently aqueous medium reactions are gaining more popularity due to its non-toxic nature, abundance, economy and safety. Quite recently, J. S. Yadav et al. reported boric acid catalyzed bis (indolyl) methane synthesis with boric acid under heating conditions (80°C) (Ref 13). The method deals only with simple indoles, N-substituted indoles are not reported and also under heating condition bis(indolyl) methane derivative may possibly degrade. The drawbacks associated with some of the procedures reported in literature are the use of hazardous catalysts, tedious workup procedures, and difficulties in product isolation. In continuation of our work in the development of greener methodologies, herein we wish to report the synthesis of bis (indolyl) methane catalyzed by boric acid in aqueous medium. The present method works at room temperature and also for N-substituted indoles under the standard reaction condition.

Reaction of indole with benzaldehyde was carried out in aqueous medium using equivalent amount of boric acid at room temperature (Scheme I). After workup the bis(indolyl) methanes was isolated in high yield. Later the experiments were planned with less than stoichiometric amount of boric acid (0.5 mmol, 1 mmol, 1.85 mmol, 2 mmol) and it was found that 1.85 mmol is suitable for optimum conversion. Increasing the mole ratio also did not improve the condition and yield of the reaction.

Further, the electronic effect of substituents in standard reaction condition was studied. It was observed that benzaldehyde having electron withdrawing substituent (Table I, entry-3d, 3e, 3h, 3i and 3j) undergoes very fast reaction and leads to expected product in good yield. However, the
Experimental Section

All reactions were carried out without any special precautions in an atmosphere of air. Chemicals were purchased from Aldrich, Fluka and S. D. Fine Chemicals. TLC: precoated silica gel plates (60 F254 purchased from Aldrich, Fluka and S. D. Fine Chemicals). The present protocol in aqueous medium has merits over earlier methods in terms of safety and economy. Moreover, the method is very efficient and avoids the use of organic solvent and generation of unacceptable waste.

General Procedure

To a mixture of indole (117 mg, 2 mmol) and the appropriate aldehyde (1 mmol) in water (5 mL), boric acid (115 mg, 1.85 mmol) was added and the reaction mixture was stirred at RT for 20-40 min. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The solvent was concentrated in vacuo and product purified by column chromatography (ethyl acetate/petroleum ether, 1:9) to afford the pure compounds.

The products were characterized by IR, NMR and mass spectroscopy. The characteristic data of some representative compounds are given below.

3-((1H-Indol-3-yl)(4-methoxyphenyl)methyl)-1H-indole, 3a. Brown solid m.p. 185-86°C. 1H NMR (300 MHz, CDCl3): δ 7.97 (s, 2H), 7.41-7.32 (m, 4H), 7.21 (s, 2H), 7.19 (t, 2H, J = 7.4), 7.02 (t, 2H, J = 7.4), 6.84 (d, 2H, J = 8.3), 6.67 (s, 2H), 5.82 (s, 1H), 3.76 (s, 3H); IR (KBr): 3413, 3050, 2928, 1608, 1555, 1506, 1339, 1242, 1096, 1030, 744 cm⁻¹; ESI-MS: m/z 353 ([M+1]+).

3-((1H-Indol-3-yl)(p-tolyl)methyl)-1H-indole, 3b. Pink solid. m.p. 95-96°C. 1H NMR (300 MHz, CDCl3): δ 7.93 (s, 2H), 7.40 (d, 2H, J = 7.0), 7.30 (d, 2H, J = 7.0), 7.28-7.20 (m, 6H), 6.99 (t, 2H, J = 7.0), 6.60 (s, 2H), 5.88 (s, 1H); IR (KBr): 3415, 3035, 2935, 1605, 1515, 1225, 1090, 744 cm⁻¹; ESI-MS: m/z 359 ([M+Na]+).

3-((1H-Indol-3-yl)(phenyl)methyl)-1H-indole, 3c. Red solid. m.p. 148-52°C. 1H NMR (300 MHz, CDCl3): δ 7.89 (s, 2H), 7.45-7.33 (m, 6H), 7.31-7.28 (m, 2H), 7.26-7.15 (m, 3H), 7.04 (t, 2H, J = 6.9), 6.58 (s, 2H), 5.82 (s, 1H); IR (KBr): 3415, 3023, 1605, 1520, 1455, 1405, 1225, 1090, 1020, 668 cm⁻¹; ESI-MS: m/z 345 ([M+Na]+).

3-((1H-Indol-3-yl)(4-nitrophenyl)methyl)-1H-indole, 3d. Yellow solid. m.p. 218-21°C. 1H NMR (300 MHz, CDCl3): δ 8.04 (s, 2H), 7.54 (d, 2H, J = 8.9), 7.42 (d, 2H, J = 8.0), 7.38 (d, 2H, J = 8.0), 7.08-7.00 (m, 3H), 6.73 (s, 2H), 5.98 (s, 1H); IR (KBr): 3415, 3050, 2925, 1598, 1505, 1452, 1350, 1240, 1080, 1020, 744 cm⁻¹; ESI-MS: m/z 368 ([M+Na]+).

3-((5-Bromobenzo[d][1,3]dioxol-6-yl)(1H-indol-3-yl)methyl)-1H-indole, 3e. Reddish solid. m.p. 173-76°C. 1H NMR (300 MHz, CDCl3): δ 8.01 (s, 2H), 7.32 (t, 4H, J = 7.3), 7.12 (d, 1H, J = 7.3), 7.05 (s, 1H), 7.01 (d, 1H), 6.92 (t, 2H, J = 6.6), 6.72 (s, 1H), 6.64 (d, 2H), 6.12 (s, 1H), 5.91 (s, 2H); IR (KBr): 3415, 3350, 3040, 2925, 1545, 1470, 1345, 1230, 1100, 1035, 738 cm⁻¹; ESI-MS: m/z 477 ([M+2]+), 445 ([M]+).
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*Reaction conditions: aldehyde (1 mmol), indole (2 mmol), boric acid (1.85 mmol), water (5 mL), RT.*

*All products were characterized by IR, NMR and mass spectroscopy.*
6.25-6.19 (m, 1H), 6.01 (d, 1H J = 7.0); 5.85 (s, 1H); IR (KBr): 3412, 3051, 2925, 1615, 1452, 1335, 1090, 1000, 735 cm⁻¹; ESI-MS: m/z 313 ([M+H]+).

3-(1H-Indol-3-yl)(thiophen-2-yl)methyl)-1H-indole, 3g. White solid. m.p. 150-53°C. ¹H NMR (300 MHz, CDCl₃): δ 10.21 (s, 2H), 7.36 (t, 4H J = 8.5), 7.16-7.10 (m, 1H), 7.06 (d, 2H, J = 7.8 Hz), 6.96-6.85 (m, 6H), 6.12 (s, 1H); IR (KBr): 3413, 3061, 2928, 1615, 1450, 1333, 1210, 1080, 744 cm⁻¹; ESI-MS: m/z 408 ([M+Na]+).

5-Chloro-3-((5-chloro-1H-indol-3-yl)(2-fluoro-5-nitrophenyl)(1-methyl-1H-indole, 3i. Light Yellow solid. m.p. 172-73°C. ¹H NMR (300 MHz, CDCl₃): δ 8.62 (dd, 2H J = 3.0, J = 6.0); 8.10 (m, 2H), 7.57 (d, 2H, J = 8.3); IR (KBr): 2924, 1585, 1523, 1473, 1343, 1241, 1073, 1034, 830, 742 cm⁻¹; ESI-MS: m/z 414 ([M+H]+).

5-Chloro-3-((5-chloro-1H-indol-3-yl)(2-fluoro-5-nitrophenyl)methyl)-1H-indole, 3j. Red solid. m.p. 103.4-103.9°C. ¹H NMR (300 MHz, CDCl₃): δ 8.19-8.14 (m, 2H), 8.10 (s, 2H), 8.10-7.97 (m, 1H), 7.28-7.24 (m, 6H), 7.15-7.12 (m, 2H), 6.67 (d, 2H J = 2.0), 6.13 (s, 1H); IR (KBr): 3454, 3078, 1581, 1479, 1454, 1345, 1238, 1092, 836, 742 cm⁻¹; ESI-MS: m/z 454 ([M+H]+).

Conclusion

In conclusion, a highly efficient and convenient synthesis of bis(indolyl) methane using inexpensive and environment friendly boric acid as a catalyst in aqueous medium has demonstrated. The method is applicable for aromatic as well as hetero aromatic aldehydes with good yields. Clean reaction conditions, simple workup procedure, easy isolation and environmentally acceptable medium are the best features in this process.

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References