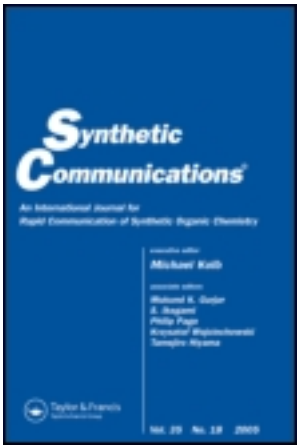

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Efficient Hexamethylenetetramine-Bromine (HMTAB)-Catalyzed Synthesis of Bis(indolyl)methanes in Water

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Efficient Hexamethylenetetramine-Bromine (HMTAB)-Catalyzed Synthesis of Bis(indolyl)methanes in Water

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Abstract: An efficient, facile, and environmentally friendly electrophilic substitution reaction of indoles with various aldehydes and ketones proceeded smoothly in water using the hexamethylenetetramine–bromine complex to afford the corresponding bis(indolyl)methanes in excellent yields. This method provides several advantages such as being environmentally friendly, giving high yields, and having simple workup procedure. Water was chosen as a cheap, nontoxic, green solvent.

Keywords: Carbonyl compounds, electrophilic substitution, hexamethylenetetramine–bromine, indole, water

INTRODUCTION

Bisindoles constitute important class of compounds because of their existence in bioactive metabolites.[1] In recent years the biological activity of bisindoles has been intensively studied. For example, diindolylmethane (DIM) has been gaining increasing importance because of its potent anticarcinogenic properties.[2] Bis(indolyl)methane derivatives affect the central nervous system

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and so are used as tranquilizers. The wide-ranging biological activities associated with bisindole derivatives, both naturally occurring and synthetic, ensure that the synthesis of these compounds remains a topic of current interest.[3] Generally, bis(indolyl)methanes are prepared by the condensation of indoles with various carbonyl compounds in the presence of either protic or Lewis acids.[4–6] Most of the previously reported methods suffer from several drawbacks such as low yields, expensive and highly toxic solvents and catalysts, long reaction times, complex reaction mixtures, and deactivation or decomposition of many Lewis acids by nitrogen-containing reactants. However, these problems were overcome to some extent by recently reported methods employing molecular iodine [7] and *N*-bromosuccinimide.[8] Hence, a more efficient and practical alternative using an inexpensive and environmentally friendly reagent is still warranted.

In the past decade, the use of aqueous media in organic synthesis has attracted much attention for environmental, economical, and safety reasons, and has shown unique reactivities and selectivities that are not observed for reactions in organic media.[9] The role of water was explained by introducing the concept of hydrophobic effects in organic reactions.[10] So far, various efficient catalytic reactions in water have been developed such as the Diels–Alder reaction, aldol condensation, the Claisen rearrangement, the Michael addition, the Mannich reaction, radical addition reaction and Grignard-type additions, allylation reactions, and the benzoin condensation.[11] This article shows that electrophilic substitutions of indoles with substituted benzaldehydes in the presence of catalytic amount of hexamethylenetetramine–bromine complex can successfully take place in water as a cheap, nontoxic, green solvent.

RESULTS AND DISCUSSION

Hexamethylenetetramine–bromine complex is readily prepared by adding bromine to a chloroform solution of hexamethylenetetramine. This yellow-orange, nonhygroscopic, homogeneous solid, stable at room temperature, is not affected by exposure to light, air, or water and has no offensive odor of bromine or amine. This complex is transformed during reaction into easily removable products and presents a convenient alternative to other *N*-bromo reagents such as *N*-bromosuccinimide.

In an earlier work, the HMTAB has been used for oxidation of primary and secondary alcohols to aldehydes and ketones, respectively.[12] Also, mechanistic aspects of the oxidation of diols[13] by HMTAB have been described. Furthermore, this complex has recently been used for selective regeneration of carbonyl compounds from oximes and toslylhydrazones.[14]

As part of our research to develop a green chemistry by synthesis of target molecules in an aqueous medium,[15] and in continuation of our interest on chemistry of hexamethylenetetramine–bromine,[16] we now report the

HMTAB-catalyzed condensation reaction of indoles and various carbonyl compounds (Scheme 1).

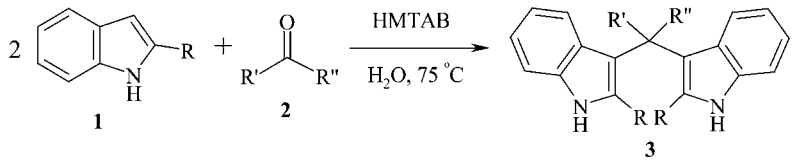
The condensation reaction of indoles with aromatic or aliphatic aldehydes or ketones in the presence of HMTAB in water proceeds well, giving bis(indolyl)methanes in good yield at 75°C. The results are summarized in Table 1, which shows the scope and generality of the present method with respect to various carbonyl compounds and indole derivatives.

CONCLUSION

In summary, the paper describes a facile and highly efficient procedure for the preparation of bis(indolyl)methanes through the hexamethylenetetramine-bromine-catalyzed electrophilic substitution reactions of indoles with aldehydes and ketones in water. The notable features of this procedure are neutral and mild reaction conditions, improved yields, easy workup, environmentally friendliness, and use of water as an ideal reaction medium.

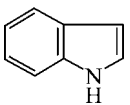
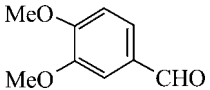
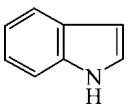
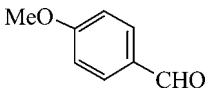
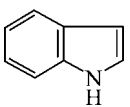
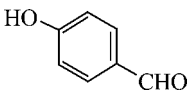
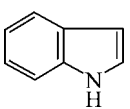
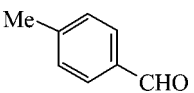
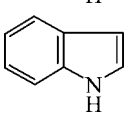
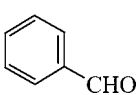
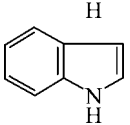
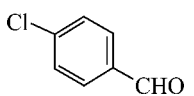
EXPERIMENTAL

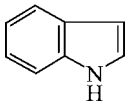
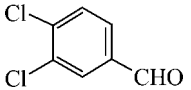
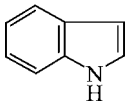
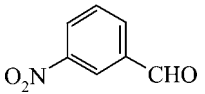
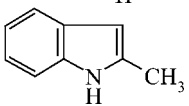
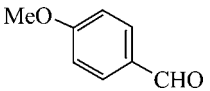
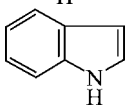
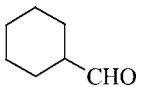
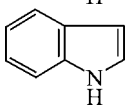
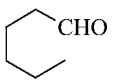
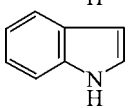
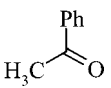
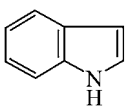
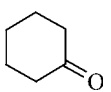
All products are known compounds and were identified by comparison of their physical, spectral (IR, ^{1}H NMR, and mass spectra), and elemental analysis data with those of authentic samples.[5–7] Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 MHz with $CDCl_3$ as solvent. All reagents and solvents used in this work are commercial materials and were purchased from Fluka (Buchs, Switzerland) or Merck and were used without further purification. Hexamethylenetetramine–bromine complex was prepared according to published procedure.[16a]



Scheme 1.

Table 1. Hexamethylenetetramine-bromine-catalyzed synthesis of bis(indolyl)methanes

Entry	Indole	Carbonyl compound	Time (h)	Yield[a] (%)	Mp/°C (reported)
a			1.5	92	199–200 (198–200)[5]
b			1.5	93	188–190 (187–189)[7]
c			1.5	93	121–123 (122–124)[6]
d			2.0	90	95–97 (95–97)[5]
e			2.5	86	90–92 (88–90)[5]
f			2.5	85	76–77 (76–77)[7]

g			2.5	88	153–155 (154–156)[5]
h			2.5	85	217–219 (218–220)[5]
i			1.5	89	99–101 (98–100)[5]
j			1.5	92	137–139 (138–140)[5]
k			1.5	87	67–69 (68–70)[5]
l			2.5	85	188–190 (190–192)[6]
m			2.5	88	117–119 (118–120)[5]

[a]Yield refers to pure isolated products.

General Procedure for Synthesis of Bis(indolyl)methanes

A mixture of aldehyde or ketone (1.0 mmol), indole (2.0 mmol), and HMTAB (0.1 g) in water (20 mL) was heated at 75°C for the appropriate time (Table 1). After completion of the reaction (monitored by TLC) and cooling to room temperature, the mixture treated with aq. $Na_2S_2O_3$ solution (5%, 10 mL) and the product was filtered off and washed with water (3 × 10 mL). The crude products were dried and crystallized from ethyl acetate–hexane (1 : 3) to give **3**.

3-[(3,4-Dimethoxyphenyl)(1*H*-indol-3-yl)methyl]-1*H*-indole (3a): Mp 199–200°C; IR (KBr) (ν_{max}, cm^{-1}): 3450, 1625, 1479, 1221, 760; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 3.70$ and 3.81 (6 H, 2 s, 2 OMe), 5.75 (1 H, s, Ar-CH), 6.71 (2 H, d, $J = 2.5$ Hz), 6.80 (2 H, d, $J = 8.0$ Hz), 6.86 (1 H, s), 6.89 (2 H, d, $J = 8.0$ Hz), 7.07 (2 H, t, $J = 8.0$ Hz), 7.31 (4 H, t, $J = 8.0$ Hz), 10.43 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 382 (M^+, 100), 265 (17), 244 (41), 69 (32); anal. calcd. for $C_{25}H_{22}N_2O_2$ (382.46): C, 78.51; H, 5.80; N, 7.32%. Found: C, 78.60; H, 5.84; N, 7.31%.

3-[1*H*-Indol-3-yl(4-methoxyphenyl)methyl]-1*H*-indole (3b): Mp 188–190°C; IR (KBr) (ν_{max}, cm^{-1}): 3427, 1609, 1512, 1451, 1234, 733; ^1H NMR ($CDCl_3$, 400 MHz) $\delta_H = 3.77$ (3 H, s, OMe), 5.84 (1 H, s, Ar-CH), 6.65 (2 H, s), 6.81 (2 H, d, $J = 8.2$ Hz,), 7.03 (2 H, t, $J = 7.3$ Hz), 7.18 (2 H, t, $J = 7.3$ Hz), 7.20 (2 H, s), 7.34–7.42 (4 H, m), 7.91 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 352 (M^+, 100), 338 (42), 238 (35), 207 (18), 131 (55); anal. calcd. for $C_{24}H_{20}N_2O$ (352.43): C, 81.79; H, 5.72; N, 7.95%. Found: C, 81.85; H, 5.78; N, 8.01%.

3-[1*H*-Indol-3-yl(4-hydroxyphenyl)methyl]-1*H*-indole (3c): Mp 121–123°C; IR (KBr) (ν_{max}, cm^{-1}): 3466, 3371, 1644, 1579, 1375, 761; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 5.53$ (1 H, s, Ar-CH), 6.72 (2 H, s), 7.19–7.29 (8 H, m), 7.45 (2 H, d, $J = 8.2$ Hz), 7.56 (2 H, d, $J = 8.2$ Hz), 7.64 (1 H, s, OH), 7.93 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 338 (M^+, 100), 321 (22), 246 (32), 131 (55), 77 (25); anal. calcd. for $C_{23}H_{18}N_2O$ (338.40): C, 81.63; H, 5.36; N, 8.28%. Found: C, 81.70; H, 5.41; N, 8.30%.

3-[1*H*-Indol-3-yl(4-methylphenyl)methyl]-1*H*-indole (3d): Mp 95–97°C; IR (KBr) (ν_{max}, cm^{-1}): 3419, 1607, 1504, 1221, 778; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 2.34$ (3 H, s, CH_3), 5.82 (1 H, s, Ar-CH), 6.66 (2 H, d, $J = 2.5$ Hz), 6.97 (2 H, t, $J = 7.6$ Hz), 7.08 (2 H, d, $J = 7.6$ Hz), 7.20–7.30 (6 H, m), 7.37 (2 H, d, $J = 7.6$ Hz), 7.90 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 336 (M^+, 100), 245 (51), 219 (40), 144 (18), 119 (9), 69 (27); anal. calcd. for $C_{24}H_{20}N_2$ (336.43): C, 85.68; H, 5.99; N, 8.33%. Found C, 85.56; H, 5.93; N, 8.26%.

3-[1*H*-Indol-3-yl(phenyl)methyl]-1*H*-indole (3e): Mp 90–92°C; IR (KBr) (ν_{max}, cm^{-1}): 3422, 3051, 1622, 1588, 1103, 751; ^1H NMR ($CDCl_3$,

400 MHz): $\delta_H = 5.90$ (1 H, s, Ar-CH), 6.63 (2 H, d, $J = 2.2$ Hz), 7.03 (2 H, t, $J = 7.2$ Hz), 7.19–7.35 (11 H, m), 7.94 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 322 (M^+, 100), 245 (66), 205 (34), 122 (40), 105 (12), 77 (19); anal. calcd. for $C_{23}H_{18}N_2$ (322.40): C, 85.68; H, 5.63; N, 8.69%. Found: C, 85.75; H, 5.70; N, 8.74%.

3-[(4-Chlorophenyl)(1*H*-indol-3-yl)methyl]-1*H*-indole (3f): Mp 76–77°C; IR (KBr) (ν_{max}, cm^{-1}): 3421, 3046, 1481, 1443, 1079, 1009, 742; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 5.86$ (1 H, s, Ar-CH), 6.83 (2 H, s), 7.02 (2 H, t, $J = 8.2$ Hz), 7.19 (2 H, t, $J = 8.2$ Hz), 7.23–7.37 (8 H, m), 8.01 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 356 (M^+, 100), 322 (11), 246 (55), 241 (38), 126 (31), 111 (23), 77 (15); anal. calcd. for $C_{23}H_{17}ClN_2$ (356.85): C, 77.41; H, 4.80; N, 7.85%. Found: C, 77.44; H, 4.76; N, 7.80%.

3-[(3,4-Chlorophenyl)(1*H*-indol-3-yl)methyl]-1*H*-indole (3g): Mp 153–155°C; IR (KBr) (ν_{max}, cm^{-1}): 3477, 1611, 1466, 1245, 1017, 766; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 5.84$ (1H, s), 6.75 (2H, d, $J = 2.2$ Hz), 6.84 (1H, m,), 6.89 (2 H, m), 6.93–7.09 (4 H, m), 7.18 (1H, s), 7.26 (2 H, t, $J = 8.2$ Hz), 7.36 (1H, s), 7.80 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 390 (M^+, 100), 274 (67), 245 (54), 204 (14), 176 (10), 117 (17), 77 (9); anal. calcd. for $C_{23}H_{16}Cl_2N_2$ (391.29): C, 70.60; H, 4.12; N, 7.16%. Found: C, 70.66; H, 4.17; N, 7.74%.

3-[1*H*-Indol-3-yl(3-nitrophenyl)methyl]-1*H*-indole (3h): Mp 217–219°C; IR (KBr) (ν_{max}, cm^{-1}): 3462, 3036, 1601, 1548, 1233, 1010, 762; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 5.96$ (1H, s, Ar-CH), 6.64 (2 H, d, $J = 2.4$ Hz), 6.86 (2 H, t, $J = 8.2$ Hz), 7.06 (2 H, t, $J = 8.2$ Hz), 7.26 (2 H, d, $J = 8.2$ Hz), 7.31 (2 H, d, $J = 8.2$ Hz), 7.45 (2 H, m), 8.07 (2 H, d, $J = 8.2$ Hz), 10.08 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 367 (M^+, 100), 245 (36), 204 (7), 160 (8), 122 (24), 97 (33), 69 (51); anal. calcd. for $C_{23}H_{17}N_3O_2$ (367.40): C, 75.19; H, 4.66; N, 11.44%. Found: C, 75.30; H, 4.70; N, 11.51%.

3-[(4-Methoxyphenyl)(2-methyl-1*H*-indol-3-yl)methyl]-2-methyl]-1*H*-indole (3i): Mp 99–101°C; IR (KBr) (ν_{max}, cm^{-1}): 3374, 1556, 1326, 1289, 748; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 2.05$ (6 H, s, CH_3), 3.72 (3 H, s, OCH_3), 5.85 (1 H, s, Ar-CH), 6.69 (2 H, t, $J = 7.3$ Hz), 6.83 (4 H, m), 6.90 (2 H, t, $J = 7.1$ Hz), 7.09 (2 H, d, $J = 8.0$ Hz), 7.21 (2 H, d, $J = 7.9$ Hz), 10.71 (2 H, s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 380 (M^+, 100), 365 (77), 273 (21), 247 (76), 217 (51), 162 (83), 147 (96), 122 (26), 69 (68); anal. calcd. for $C_{26}H_{24}N_2O$ (380.48): C, 82.08; H, 6.36; N, 7.36%. Found: C, 82.22; H, 6.42; N, 7.29%.

3-[Cyclohexyl(1*H*-indol-3-yl)methyl]-1*H*-indole (3j): Mp 137–139°C; IR (KBr) (ν_{max}, cm^{-1}): 3441, 3043, 1614, 1276, 1045, 768; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 1.21–1.88$ (10 H, m), 2.25 (1 H, m), 4.46 (1 H, m), 6.95 (2 H, d, $J = 2.5$ Hz), 7.04 (2 H, m), 7.15 (2 H, m), 7.26 (2 H, d, $J = 8.2$ Hz),

7.45 (2 H, d, $J = 8.2$ Hz), 7.88 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 328 (M^+, 51), 245 (72), 130 (14), 83 (75), 43 (21); anal. calcd. for $C_{23}H_{24}N_2$ (328.45): C, 84.11; H, 7.36; N, 8.53%. Found: C, 84.20; H, 7.39; N, 8.61%.

3-[1-(1*H*-Indol-3-yl)hexyl]-1*H*-indole (3k): Mp 67–69°C; IR (KBr) (ν_{max}, cm^{-1}): 3426, 3041, 1611, 1441, 1346, 1105, 776; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 0.83$ (3 H, t, $J = 7.1$ Hz), 1.24–1.33 (6 H, m), 2.26 (2 H, m), 4.62 (1 H, t, $J = 7.1$ Hz), 6.86 (2 H, d, $J = 2.3$ Hz), 7.03 (2 H, t, $J = 8.1$ Hz), 7.17 (2 H, t, $J = 8.1$ Hz), 7.36 (2 H, d, $J = 8.1$ Hz), 7.51 (2 H, d, $J = 8.1$ Hz), 7.85 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 316 (M^+, 82), 245 (100), 206 (14), 199 (54), 156 (72), 149 (46), 118 (26), 43 (22); anal. calcd. for $C_{22}H_{24}N_2$ (316.44): C, 83.50; H, 7.64; N, 8.85%. Found: C, 83.55; H, 7.68; N, 8.87%.

3-[1-(1*H*-Indol-3-yl)-1-phenylethyl]-1*H*-indole (3l): Mp 188–190°C; IR (KBr) (ν_{max}, cm^{-1}): 3426, 3023, 1628, 1437, 721; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 2.22$ (3 H, s, CH_3), 6.57 (1 H, s, Ar-CH), 7.37–7.48 (13 H, m), 7.80 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 336 (M^+, 80), 260 (100), 246 (27), 159 (15), 77 (43); anal. calcd. for $C_{24}H_{20}N_2$ (336.42): C, 85.68; H, 5.99; N, 8.33%. Found: C, 85.76; H, 6.04; N, 8.35%.

3-[1-(1*H*-Indol-3-yl)cyclohexyl]-1*H*-indole (3m): Mp 117–119°C; IR (KBr) (ν_{max}, cm^{-1}): 3426, 3044, 1603, 1442, 1345, 1104, 733; ^1H NMR ($CDCl_3$, 400 MHz): $\delta_H = 1.48–1.52$ (6 H, m), 1.84 (4 H, m), 2.26 (1 H, m), 4.27 (1 H, d, $J = 9.4$ Hz), 7.01–7.21 (6 H, m), 7.34 (2 H, d, $J = 5.9$ Hz), 7.55 (2 H, d, $J = 7.2$ Hz), 7.95 (2 H, br s, 2 NH) ppm; MS (EI, 70 eV) (m/z, %): 314 (M^+, 75), 286 (100), 246 (16), 207 (29), 199 (34), 83 (22), 43 (32); anal. calcd. for $C_{22}H_{22}N_2$ (314.42): C, 84.04; H, 7.05; N, 8.91%. Found: C, 83.96; H, 6.98; N, 9.00%.

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