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Efficient synthesis of bis(indolyl) methanes in aqueous medium catalyzed by molybdenyl acetylacetonate

B Banerjee, S K Mandal & S C Roy*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700 032, India

E-mail: ocscr@iacs.res.in

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A mild and efficient electrophilic substitution reaction of indoles with aldehydes and ketones has been carried out in water medium using a catalytic amount of $MoO_2(acac)_2$ to afford the corresponding bis(indolyl)methanes in excellent yields. Vibrindole A, a bacterial metabolite and biologically active 3,3'-diindolyl methane has been successfully synthesized in excellent yield using this methodology.

Keywords: Bis(indolyl)methanes, molybdenyl acetylacetonate, aqueous medium, carbonyl compounds, catalysis.

IPC: Int.Cl.[8] C07D

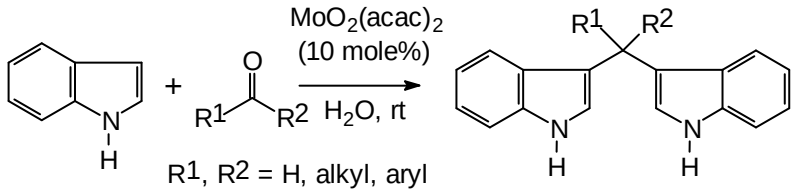
Organic transformations in aqueous medium have become a crucial and demanding research area in modern organic chemical research. In 1980, Breslow discovered that huge rate accelerations occurred when the Diels-Alder reaction was performed in water[1]. This observation increased the interest of synthetic organic chemists to analyze organic reactions in water medium. Soon it was discovered that other organic reactions, like the Claisen rearrangement[2], the aldol condensation[3], the benzoin condensation[4] and the Barbier-Grignard reaction[5] exhibit rate enhancement in water. To date, many more organic transformations have been carried out in water[5,6].

Indoles and their derivatives are used as antibiotics in the field of pharmaceuticals[7]. Due to such potent biological activity exhibited by various indole derivatives, there is a continuous demand for novel synthetic methods in this area. Bis(indolyl)methanes are gaining prominence in view of their occurrence in bioactive metabolites of terrestrial and marine origin[8]. The simple method for the synthesis of this class of compounds involves the electrophilic substitution of indoles with various aldehydes and ketones in the presence of either protic[9] or Lewis acids[10]. Recently, varieties of efficient reagents were also found to catalyze the reaction[11]. Most of these procedures are associated with certain limitations such as low yields, harsh reaction conditions, long reaction times, expensive or toxic catalysts, and the use of toxic organic solvents. So, an environmental friendly, more efficient and cost-effective alternative procedure is still desirable. In continuation to our study on $MoO_2(acac)_2$ catalyzed organic transformations[12], we wish to report herein an efficient synthesis of bis(indolyl)methanes in excellent yields by condensation of indoles with various carbonyl compounds in water.

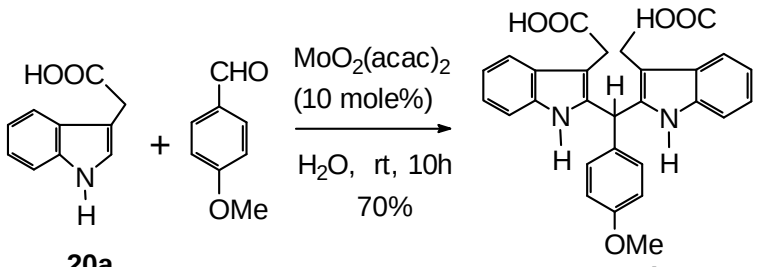
Results and Discussion

In a typical experiment, a heterogeneous mixture of the carbonyl compound (1 mmole) and indole (2 mmole) in water (4 mL) was stirred in the presence of $MoO_2(acac)_2$ (0.1 mmole) at room temperature to furnish bis(indolyl)methanes in excellent yields without using any organic solvent (**Scheme I**). Here, the catalyst, $MoO_2(acac)_2$, acts as a mild Lewis acid which activates the carbonyl group as well as the indole moiety to promote the reaction[13].

Thus, a series of aldehydes and ketones were subjected to the condensation with indole in water in the presence of a catalytic amount of $MoO_2(acac)_2$ and the results were summarized in **Table I**. The reaction did not proceed at all without the catalyst in water even on prolonged stirring at room temperature. The generality of the reaction was indicated by the reaction of a variety of substituted aromatic aldehydes **1-9a**, heteroaromatic aldehydes **10a** and **11a**, α,β-unsaturated aldehydes **12a** and **13a** and aliphatic



Scheme I



20a **20b**

Scheme II

aldehydes **14**-**16a** and ketones **17**-**19a** with indoles. It was found that the aldehydes reacted faster than the ketones and produced better yields of the products. Vibrindole A **15b**, a bacterial metabolite[8e], and the biologically active 3,3'-diindolyl methane **14b**, a potent anticarcinogenic agent[14] have been synthesized in excellent yield using this green methodology. Under the above reaction conditions, indole-3-acetic acid **20a** on reaction with *p*-methoxybenzaldehyde furnished the corresponding bis(indolyl)methane **20b**[11q] in good yield (**Scheme II**). Since the more active site (C-3) was blocked in this case, electrophilic substitution probably took place at C-2 (ref. 11g, q.) There is also a possibility of initial 3-substitution followed by 1,2-migration of the arylalkyl group leading to the desired bis(indolyl)methane[11d].

In conclusion, a general protocol for the synthesis of bis(indolyl)methanes has been deveoped through the electrophilic substitution reaction of indoles with various aldehydes and ketones in water medium catalyzed by $MoO_2(acac)_2$ in excellent yield. Vibrindole A, a bacterial metabolite and biologically active 3,3'-diindolyl methane have been successfully synthesized in excellent yield using this methodology.

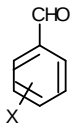
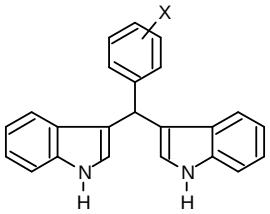
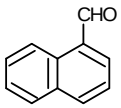
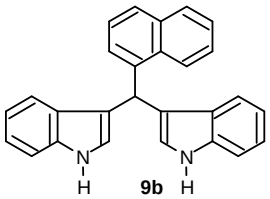
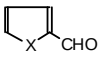
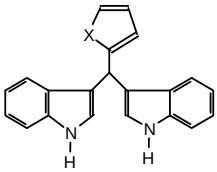
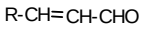
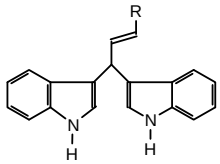
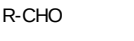
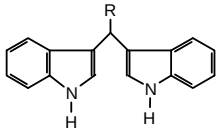
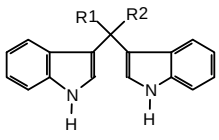
Experimental Section

To a stirred mixture of the carbonyl compound (1 mmole) and indole (2 mmole) in water (4 mL) was added $MoO_2(acac)_2$ (0.1 mmole) and the mixture was stirred at room temperature (progress of the reaction was monitored by TLC). The heterogeneous reaction mixture was diluted with diethyl ether and the ether layer was successively washed with water (20 mL), brine (20 mL) and finally dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography over silica gel (10% ethyl acetate in petroleum ether) to furnish pure bis(indolyl)methanes in excellent yields (**Table I**). The known compounds were identified by comparison of their spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR) with those reported in the literature. The spectral data and elemental analyses of the new compounds are provided below.

3-[1*H*-indol-3yl(4-methoxyphenyl)methyl]-1*H*-indole 4b: Crystalline solid, m.p. 187-88°C; IR (KBr): 3396, 3055, 2925, 2831, 1610, 1508, 1456, 1244, 1093, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H), 5.82 (s, 1H), 6.59 (s, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 6.99 (dd, *J* = 7.7, 7.3 Hz, 2H), 7.12-7.39 (m, 8H), 7.83 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 39.3, 55.2, 111.0, 113.6, 119.2, 119.9, 120.0, 121.9, 123.5, 127.1, 129.6, 136.3, 136.7, 157.9. Anal. Calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.71; H, 5.70; N, 7.90.

3-[1*H*-indol-3yl(2-hydroxyphenyl)methyl]-1*H*-indole 5b: Crystalline solid, m.p. 348-49°C; IR

Table I - $MoO_2(acac)_2$ catalyzed synthesis of bis(indolyl)methanes in water

Substrate	Product[a]	Time (min)	Yield[b]	Ref
				
1a, X = H	**1b**, X = H	15	97	11e
2a, X = 4-Me	**2b**, X = 4-Me	20	95	11e
3a, X = 4-Cl	**3b**, X = 4-Cl	18	94	11h
4a, X = 4-OMe	**4b**, X = 4-OMe	45	92	11s
5a, X = 2-OH	**5b**, X = 2-OH	40	93	11s
6a, X = 4-NO_2	**6b**, X = 4-NO_2	20	95	11s
7a, X = 3,4-methylenedioxy	**7b**, X = 3,4-methylenedioxy	30	91	11e
8a, X = 3,4-dimethoxy	**8b**, X = 3,4-dimethoxy	20	93	11e
 **9a**	 **9b**	20	92	11s
				
10a, X = O	**10b**, X = O	25	91	11s
11a, X = S	**11b**, X = S	30	92	11c
				
12a, R = Ph	**12b**, R = Ph	55	88	11s
13a, R = Me	**13b**, R = Me	45	83	11s
				
14a, R = H	**14b**, R = H	12	91	11s
15a, R = Me	**15b**, R = Me	20	90	11s
16a, R = C_5H_{11}	**16b**, R = C_5H_{11}	30	93	11e
				
17a, $R^1 = R^2$ = Me	**17b**, $R^1 = R^2$ = Me	180	82	11g
18a, R^1,R^2 = -$(CH_2)_5$-	**18b**, R^1,R^2 = -$(CH_2)_5$-	150	86	11e
19a, R^1 = Ph, R^2 = Me	**19b**, R^1 = Ph, R^2 = Me	480	71	11g

[a]All the products gave satisfactory spectral and analytical data.

[b]Yields refer to pure isolated products.

(KBr): 3417, 3305, 3057, 2976, 2875, 1593, 1454, 1095, 742 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.60 (brs, OH), 6.05 (s, 1H), 6.67 (s, 2H), 6.90 (d, *J* = 6.8 Hz, 2H), 7.07 (t, *J* = 6.5 Hz, 2H), 7.22-7.36 (m, 6H), 7.44 (d, *J* = 7.1 Hz, 2H), 7.90 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 35.7, 111.3, 116.6, 117.1, 119.5, 119.9, 120.8, 122.3, 123.7, 126.8, 128.0, 129.2, 130.0, 136.9, 154.4. Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.52; H, 5.32; N, 8.27.

3-[1*H*-indol-3yl(4-nitrophenyl)methyl]-1*H*-indole 6b: Crystalline solid, m.p. 223-24°C; IR (KBr): 3456, 3421, 3386, 1593, 1508, 1456, 1340, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.91 (S, 1H), 6.61 (d, *J* = 2.3 Hz, 2H), 6.95 (t, *J* = 7.9 Hz, 2H), 7.09-7.32 (m, 6H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.95 (brs, 2H, NH), 8.06 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 40.2, 111.2, 118.1, 119.5, 119.6, 122.3, 123.6, 126.6, 129.5, 136.7, 151.8. Anal. Calcd for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44. Found: C, 75.08; H, 4.60; N, 11.32.

3-[1*H*-indol-3yl(1-naphthyl)methyl]-1*H*-indole 9b: Crystalline solid, m.p. 252-53°C; IR (KBr): 3409, 3055, 2922, 2846, 1595, 1456, 1336, 1089, 742 cm^{-1}; ^1H NMR ($CDCl_3$): δ 6.58 (s, 1H), 6.66 (s, 1H), 6.99 (t, *J* = 7.3 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 2H), 7.24-7.46 (m, 9H), 7.24 (s, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.89 (brs, 2H, NH), 8.15 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 36.1, 111.3, 119.6, 119.7, 120.2, 122.3, 124.6, 125.6, 125.8, 126.1, 127.3, 127.4, 128.9, 134.3, 137.0. Anal. Calcd for $C_{27}H_{20}N_2$: C, 87.07; H, 5.41; N, 7.52. Found: C, 87.01; H, 5.34; N, 7.50.

3-[2-furyl(1*H*-indol-3-yl)methyl]-1*H*-indole 10b: Crystalline solid, m.p. 323-25°C; IR (KBr): 3411, 3305, 2976, 2871, 1620, 1456, 1338, 1008, 742 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.97 (s, 1H), 6.09 (d, *J* = 2.5 Hz, 1H), 6.33 (dd, *J* = 1.8, 2.9 Hz, 1H), 6.82 (s, 2H), 7.05-7.39 (m, 7H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.88 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 34.4, 106.9, 110.5, 111.5, 117.4, 119.7, 120.0, 122.3, 123.4, 127.1, 136.8, 141.6, 157.5. Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.70; H, 5.11; N, 8.91.

3-[(2*E*)-1-(1*H*-indol-3-yl)-3-phenylprop-2-enyl]-1*H*-indole 12b: Crystalline solid, m.p. 98-99°C; IR (KBr): 3411, 3057, 3010, 2873, 1620, 1456, 1217, 1095, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.39 (d, *J* = 7.0 Hz, 1H), 6.50-6.62 (m, 1H), 6.79 (dd, *J* = 7.0, 15.8 Hz, 1H), 6.86 (s, 2H), 6.90-7.45 (m, 12H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.90 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 37.4, 110.9, 111.0, 118.3, 119.1, 119.2, 119.9, 121.8, 122.5, 123.5, 126.1, 126.3, 126.9, 128.1, 128.3, 128.4, 128.6, 129.9, 132.3, 136.6, 137.7. Anal. Calcd for $C_{25}H_{20}N_2$: C, 86.17; H, 5.79; N, 8.04. Found: C, 86.10; H, 5.75; N, 7.99.

3-[(2*E*)-1-(1*H*-indol-3-yl)but-2-enyl]-1*H*-indole 13b: Crystalline solid, m.p. 130-31°C; IR (KBr): 3417, 3055, 2962, 1651, 1456, 1166, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.60 (d, *J* = 7.0 Hz, 3H), 3.94-3.98 (m, 1H), 6.46 (dd, *J* = 16.0, 6.8 Hz, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 7.05-7.21 (m, 6H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 8.00 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 14.2, 31.9, 111.0, 118.9, 119.0, 119.2, 119.7, 119.8, 120.3, 121.5, 121.7, 122.5, 126.8, 127.1, 136.5, 136.6. Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.77; H, 6.30; N, 9.75.

3-(1*H*-indol-3-ylmethyl)-1*H*-indole 14b: Crystalline solid, m.p. 163-64°C; IR (KBr): 3396, 2831, 1618, 1454, 1340, 1089, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.22 (s, 2H), 6.88 (s, 2H), 7.05-7.22 (m, 4H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.61 (d, *J* = 7.8 Hz, 2H), 7.82 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 21.0, 110.9, 115.5, 119.0, 119.1, 121.7, 122.0, 127.4, 136.3. Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.81; H, 5.70; N, 11.29.

3-[1-(1*H*-indol-3-yl)ethyl]-1*H*-indole 15b: Crystalline solid, m.p. 154-55°C; IR (KBr): 3411, 3057, 2966, 2869, 1618, 1456, 1338, 1095, 740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.78 (d, *J* = 7.0 Hz, 3H), 4.65 (q, *J* = 7.0 Hz, 1H), 6.86 (s, 2H), 7.00-7.22 (m, 4H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.56 (d, *J* = 7.9 Hz, 2H), 7.81 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 21.7, 28.2, 111.1, 119.0, 119.7, 121.2, 121.7, 121.8, 126.9, 136.6. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 82.97; H, 6.14; N, 10.70.

3-[1-(1*H*-indol-3yl)methyl]-1-methylethyl]-1*H*-indole 17b: Visous liquid; IR (neat): 3406, 2960, 1620, 1456, 1332, 1099, 744 cm^{-1}; ^1H NMR ($CDCl_3$): 1.89 (s, 6H), 6.87 (t, *J* = 7.1 Hz, 2H), 6.98 (d, *J* = 2.4 Hz, 2H), 7.06 (dd, *J* = 7.1, 8.0 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.77 (brs, 2H, NH); ^{13}C NMR ($CDCl_3$): δ 30.0, 34.9, 111.1, 118.7, 120.6, 121.3, 121.4, 125.5, 126.3, 137.1. Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.11; H, 6.58; N, 10.15.

3-[1-(1*H*-indol-3-yl)-1-phenylethyl]-1*H*-indole 19b: Viscous liquid; IR (neat): 3415, 3004, 2977, 1456, 1336, 1217, 1099, 744 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.35 (s, 3H), 6.60 (d, *J* = 2.4 Hz, 2H), 6.92 (t, *J* = 7.4 Hz, 2H), 7.05-7.40 (m, 11H), 7.86 (brs, 2H); ^{13}C NMR ($CDCl_3$): δ 28.7, 65.9, 111.1, 118.9, 121.5, 122.0, 123.4, 124.7, 125.8, 126.4, 127.8, 128.1, 137.1,

148.0. Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.61; H, 5.91; N, 8.28.

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