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Facile synthesis of bis(indolyl)methanes using catalytic amount of iodine at room temperature under solvent-free conditions

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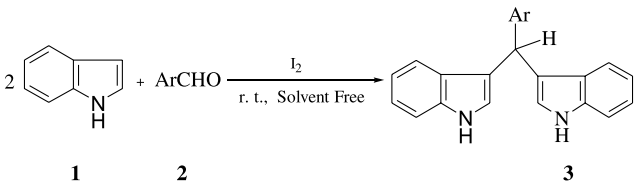
Abstract—Efficient electrophilic substitution reactions of indoles with various aromatic aldehydes were carried out using a catalytic amount of I_2 under solvent-free conditions to afford the corresponding bis(indolyl)methanes in excellent yields.

1. Introduction

Indole fragment is featured widely in a wide variety of pharmacologically and biologically active compounds.[1] For example, bisindolylalkanes and their derivatives are found in bioactive metabolites of terrestrial and marine origin.[2] Therefore, there is a great deal of interest in the synthesis of this class of compounds. Among the many methods, the synthesis of this class of compounds in the presence of Lewis acids, Brønsted acids or montmorillonite clay K-10 to promote the reaction of indoles with other aromatic or aliphatic aldehydes and ketones have been widely studied.[3–9] More recently, bis(indolyl)methanes were found to be formed in acetonitrile in the presence of other catalysts such as $InCl_3$, $PPh_3{\cdot}HClO_4$ and so on.[10] However, many of these Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required.[11] These problems can be somewhat circumvented by using expensive lithium perchlorate.[12] However, it requires longer reaction times for nitro-substituted aromatic aldehydes, giving the corresponding bis(indolyl)methanes in moderate yields. In this report, we wish to introduce molecular iodine as a mild and highly efficient catalyst for the preparation of bis(indolyl)methanes under solvent-free conditions at room temperature (Scheme 1).



1 2 3

Scheme 1. I_2-catalyzed synthesis of bis(indolyl)methanes in free solvent.

In recent years, molecular iodine has received considerable attention as an inexpensive and easily available catalyst for various organic transformations.[13] Given the large number of similar condensation reactions that have been reported to proceed readily under solvent-free conditions,[14] we proceed to examine the synthesis of bis(indolyl)methanes under solvent-free conditions. The results are shown in Table 1.

2. Results and discussion

In comparison to the reported methods, I_2 in solvent-free conditions was found to be an efficient catalyst in terms of handling, temperature, yields and reaction times. The grinding of solid reagents yields viscous liquid melt phase, which may contain dispersed solid material corresponding to one of the reagents. After the corresponding time, the desired crude product was obtained in very good yields.

As shown in Table 1, this method works with a wide variety of substrates. It is also found that the reaction of **2k** (1 mmol) with **1** (4 mmol) proceeded rapidly in the presence of I_2 at room temperature (by grinding) to give **3k** and **3k′** in 62 and 19%, respectively. The structures of **3a**[15] and **3k** were further confirmed by single crystal X-ray crystallography.[16]

Keywords: Solvent-free; Iodine; Indoles; Aldehydes; Bis(indolyl)methanes.
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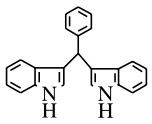
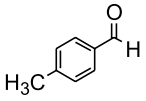
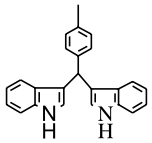
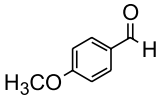
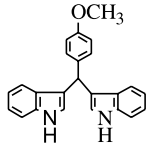
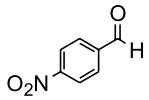
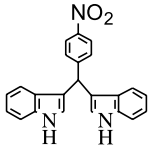
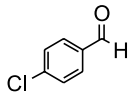
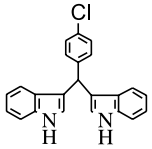
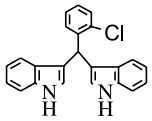
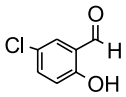
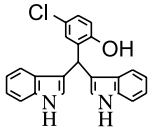
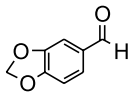
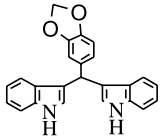
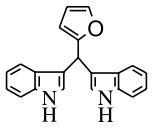
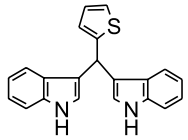
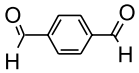
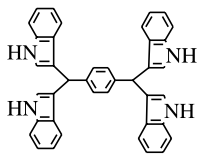
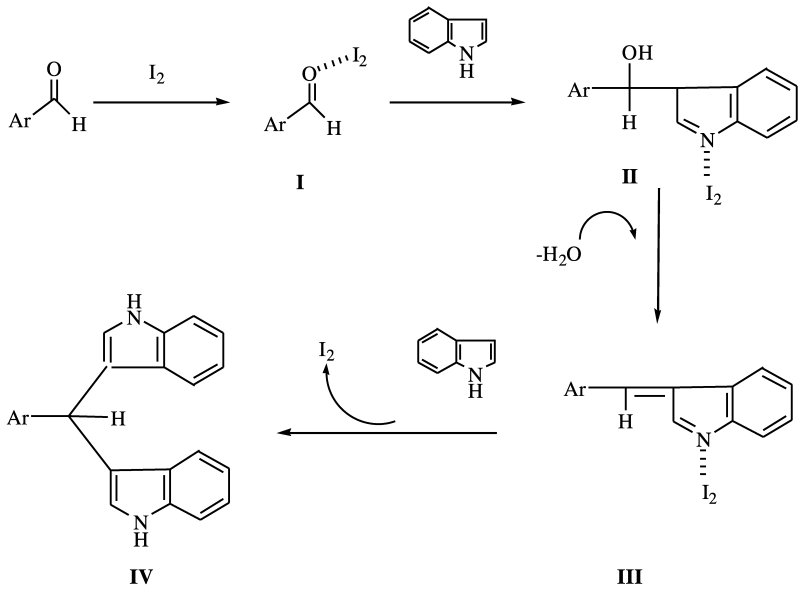
Table 1. The reaction of aromatic aldehyde with indole under solvent-free condition at room temperature[a]

Compdound	Ar–CHO	Products	Time (min)	Yield (%)[b]
2a		**3a** 	10	72
2b		**3b** 	10	83
2c		**3c** 	7	85
2d		**3d** 	7	86
2e		**3e** 	8	91
2f		**3f** 	7	82
2g		**3g** 	9	82
2h		**3h** 	9	90
2i		**3i** 	5	89
2j		**3j** 	9	82
2k		**3k** 	7	62/19[c]

[a] All reactants were ground at room temperature.
[b] Isolation yields.
[c] **3k** and 4-[Bis-(1*H*-indol-3-yl)-methyl]-benzaldehyde (**3k′**) were obtained in 62 and 19%, respectively.



Scheme 2. The probably mechanism for reactions of indoles with various aromatic aldehydes.

According to the literatures,[10a,c,12] we think that iodine catalyzes the reaction as a mild Lewis acid even under solvent-free conditions. As shown in Scheme 2, we give the likely mechanism for the reaction. First, molecular iodine activates the carbonyl group of the aromatic aldehyde to give intermediate **I**, and is followed by indole attack to **I** to give **II** and loss of H_2O from **II** to afford **III** which is activated by iodine. The other indole is added to **III** in the following step to give the TM (**IV**) and molecular iodine, which can catalyze the reaction in a catalytic manner.

3. Conclusions

In summary, we have developed a simple, convenient and efficient synthetic protocol for **3** using a catalytic amount of I_2 under solvent-free conditions at room temperature. The short reaction time coupled with the simplicity of the reaction procedure make this method one of the most efficient methods for the synthesis of this class of compounds (Figs. 1 and 2).

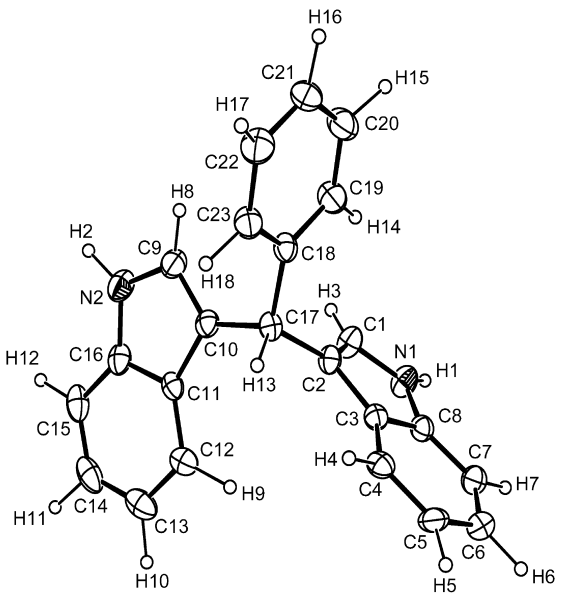


Figure 1. X-ray crystal structure of **3a**.

4. Experimental

4.1. General

Melting points were recorded on an Electrothermal digital melting point apparatus and were uncorrected. ^{1}H NMR (400 MHz) spectra were recorded on a Varian Mercury MHz spectrometer in $CDCl_3$. IR Spectra were obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. Elemental analyses were performed by a Carlo-Erba EA1110 CNNO-S analyzer. High resolution Mass spectra were obtained using GCT-TOF instrument. X-ray diffraction data were made on a Rigaku Mercury CCD area detector with graphite monochromated Mo Kα radiation.

4.2. Typical experimental procedure

A mixture of benzaldehyde (1 mmol), indole (2 mmol) and I_2 (0.2 mmol) were ground together in a mortar with a pestle at room temperature for several minutes. After completion of the reaction as monitored by TLC, the mixture was treated with $Na_2S_2O_3$ to yield solid **3a**, which was purified by column chromatography (ethyl acetate:petroleum ether=1:9) to afford the pure product (yield: 72%).

4.2.1. 1*H*,1′*H*-3,3′-Phenylmethanediyl-bis-indole, 3a. Colorless needles; mp 150–152 °C (lit,[17] 150–152 °C); IR (KBr): ν 744, 1093, 455, 1600, 1618, 3055, 3412 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (s, 1H, Ar–CH), 6.67 (s, 2H), 7.00 (t, 2H, J=6.8 Hz), 7.15–7.23 (m, 3H), 7.28–7.30 (m, 2H), 7.34–7.40 (m, 6H), 7.94 (br, s, 2H, NH); Anal. calcd for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found: C, 85.75; H, 5.56; N, 8.56.

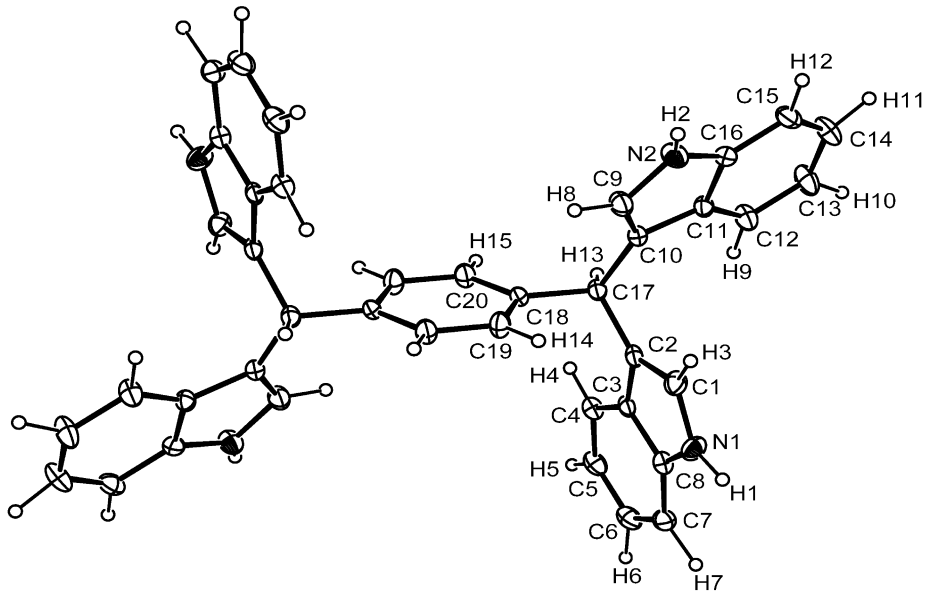


Figure 2. X-ray crystal structure of **3k**.

4.2.2. 3,3′-Bis(indolyl)-4-methylphenylmethane, 3b. Pink solid; mp 94–96 °C (lit,[10] 95–97 °C); IR (KBr): ν 775, 1050, 1215, 1510, 1600, 2930, 3040, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, Ar–CH_3), 5.86 (s, 1H, Ar–CH), 6.68 (s, 2H), 7.02 (t, 2H, J=7.2 Hz), 7.1 (d, 2H, J=7.2 Hz), 7.23–7.27 (m, 6H), 7.4 (d, 2H, J=7.2 Hz), 7.93 (br, s, 2H, NH); Anal. calcd for $C_{24}H_{20}ON_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.37; H, 5.95; N, 8.04.

4.2.3. 1*H*,1′*H*-3,3′-(4-Methoxy-phenylmethanediyl)-bis-indole, 3c. Brown needles; mp 187–189 °C (lit,[10a] 189 °C); IR (KBr): ν 1220, 1244, 1455, 1508, 1609, 2928, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 3H, CH_3), 5.84 (s, 1H, Ar–CH), 6.66 (s, 2H), 6.82 (d, 2H, J=8.3 Hz), 7.00 (t, 2H, J=7.3 Hz), 7.17 (t, 2H, J=7.3 Hz), 7.19 (s, 2H), 7.35–7.40 (m, 4H), 7.94 (br, s, 2H, NH); Anal. calcd for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95. Found: C, 81.72; H, 5.82; N, 7.98.

4.2.4. 1*H*,1′*H*-3,3′-(4-Nitro-phenylmethanediyl)-bis-indole, 3d. Yellow needles; mp 217–219 °C (lit,[10a] 220–222 °C); IR (KBr): ν 1340, 1456, 1507, 1592, 3052, 3422 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.00 (s, 1H, Ar–CH), 6.70 (s, 2H), 7.00–7.05 (m, 3H), 7.35 (d, 3H, J=8.0 Hz), 7.40 (d, 2H, J=8.0 Hz), 7.52 (d, 2H, J=8.8 Hz), 8.04 (br, s, 2H, NH), 8.15 (d, 2H, J=8.8 Hz); Anal. calcd for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44. Found: C, 75.28; H, 4.51; N, 11.60.

4.2.5. (4-Chloro-phenyl)-(1*H*-indol-3-yl)-methyl]-phenyl-amine, 3e. Pink solid; mp 76–77 °C; IR (KBr): ν 1089, 1455, 1487, 3054, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (s, 1H, Ar–CH), 6.66 (s, 2H), 7.02 (t, 2H, J=8.3 Hz), 7.18 (t, 2H, J=7.9 Hz), 7.26–7.38 (m, 8H), 7.98 (br, s, 2H, NH); HRMS [Found: m/z 356.1069(M^+), calcd for $C_{23}H_{17}ClN_2$: M, 356.1080].

4.2.6. (2-Chloro-phenyl)-(1*H*-indol-3-yl)-methyl]-phenyl-amine, 3f. Pink solid; mp 72–74 °C; IR (KBr): ν 1010, 1037, 1093, 1337, 1417, 1455, 1616, 3052, 3412 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.34 (s, 1H, Ar–CH), 6.66 (s, 2H), 7.02 (t, 2H, J=8.0 Hz), 7.11–7.23 (m, 6H), 7.36–7.43 (m, 4H), 7.96 (br, s, 2H, NH); HRMS [Found: m/z 356.1071(M^+), calcd for $C_{23}H_{17}ClN_2$: M, 356.1080].

4.2.7. 2-[Bis-(1*H*-indol-3-yl)-methyl]-4-chloro-phenol, 3g. Yellow needles; mp 78–80 °C; IR (KBr): ν 1039, 1095, 1338, 1416, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.40 (br, s, 1H, OH), 5.96 (s, 1H, Ar–CH), 6.90 (s, 3H), 7.05 (t, 2H, J=7.2 Hz), 7.12–7.14 (m, 2H), 7.23 (t, 2H, J=7.2 Hz), 7.39 (d, 4H, J=8.8 Hz), 8.05 (br, s, 2H, NH); HRMS [Found: m/z 372.1023(M^+), calcd for $C_{23}H_{17}ClN_2O$: M, 372.1029].

4.2.8. Benzo[1,3]dioxol-5-yl-di-indol-3-yl-methane, 3h. Yellow solid; mp 89–91 °C (lit,[10a] 89**–91 °C); IR (KBr): ν 1260, 1450, 1715, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.82 (s, 1H, Ar–CH), 5.92 (s, 2H, CH_2), 6.70 (s, 2H), 6.74 (d, 1H, J=8.2 Hz), 6.84 (d, 2H, J=8.2 Hz), 7.02 (t, 2H, J=7.3 Hz), 7.18 (t, 2H, J=7.3 Hz), 7.36–7.42 (m, 4H), 7.95 (br, s, 2H, NH); HRMS [Found: m/z 366.1355(M^+), calcd for $C_{24}H_{18}N_2O_2$: M, 366.1368].

4.2.9. 3,3′-Bis(indolyl)-4-methylphenylmethane, 3i. Brown solid; mp 322–325 °C (lit,[10a] 325 °C); IR (KBr): ν 1260, 1450, 1715, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.95 (s, 1H, Ar–CH), 6.90 (s, 2H), 7.03–7.50 (m, 11H), 8.00 (br, s, 2H, NH); HRMS [Found: m/z 312.1255(M^+), calcd for $C_{21}H_{16}N_2O$: M, 312.1263].

4.2.10. Diindol-3-yl-[2]thienyl-methane, 3j. Brown solid; mp 151–153 °C (lit,[10a] 149–156 °C); IR (KBr): ν 1260, 1450, 1715, 3410 (NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 1H, Ar–CH), 6.87 (s, 2H), 6.92–7.48 (m, 11H), 7.98 (br, s, 2H, NH); Anal. calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 76.62; H, 5.04; N, 8.54.

4.2.11. 3k·2AcOEt. Colorless solid; mp 121–123 °C (lit,[10a] 138–140 °C); IR (KBr): ν 1260, 1450, 1715, 3410

(NH) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 6H, CH_3, J=6.4 Hz), 2.05 (s, 6H, CH_3), 4.09–4.15 (m, 4H, CH_2), 5.84 (s, 2H, Ar–CH), 6.58 (s, 4H), 7.00 (t, 4H, J=7.6 Hz), 7.16 (t, 4H, J=7.6 Hz), 7.32–7.40 (m, 12H), 7.80 (br, s, 4H, NH); Anal. calcd for $C_{48}H_{46}N_4O_4$: C, 77.60; H, 6.24; N, 7.54. Found: C, 77.60; H, 6.42; N, 7.44.

Acknowledgements

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16. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 215713-215714 for compounds **3a** and **3k**·2AcOEt. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (E-mail: linstead@ccdc.cam.ac.uk or deposit@ccdc.cam.ac.uk; Fax:+44 1223 336033). Structural parameters for **3k**·2AcOEt: data collection: Rigaku Mercury CCD area detector; radiation: Mo Kα wavelength: λ=0.71070 Å; crystal size: 0.20×0.40×0.05 mm^3; crystal system: triclinic; space group: *P*-1 (#2); unit cell: a=7.1255(9) Å, b=12.1249(5) Å, c=12.5865(5) Å, α=68.89(2)°, β=82.29(2)°, γ=84.44(2)°.
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