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Molecular iodine-catalyzed efficient and highly rapid synthesis of bis(indolyl)methanes under mild conditions

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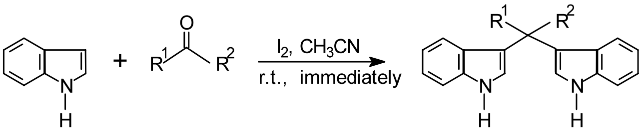
Abstract—Highly rapid and efficient electrophilic substitution reactions of indoles with various aldehydes and ketones were carried out using I_2 in CH_3CN to afford the corresponding bis(indolyl)methanes in excellent yields. © 2003 Elsevier Science Ltd. All rights reserved.

Indoles and their derivatives are used as antibiotics in the field of pharmaceuticals.[1] Bisindolylalkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin.[2] The acid-catalyzed reaction of electron rich heterocyclic compounds with *p*-dimethylaminobenzaldehyde is knows as the Ehrlich test[3] for π-electron rich heterocycles such as pyrroles and indoles. The analogous reaction of indoles with other aromatic or aliphatic aldehydes and ketones produces azafulvenium salts. The azafulvenium salts can undergo further addition with a second indole molecule to afford bis(indolyl)methanes.[4] Protic acids[5] as well as Lewis acids[6,7] are known to promote these reactions. Recently, montmorillonite clay K-10[8] and lanthanide triflates[9] were also found to catalyze these reactions. However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are required because the acids are trapped by nitrogen.[10] These problems can be somewhat circumvented by using expensive lithium perchlorate.[11] However, it requires longer reaction times for nitro-substituted aromatic aldehydes giving the corresponding bis(indolyl)methanes in moderate yields whereas reactions with aromatic ketones were very slow resulting in poor yields of the products.

In recent years, molecular iodine has received considerable attention as an inexpensive and easily available catalyst for effecting various organic transformations.[12] We now report here the synthesis of bis(indolyl)methanes by condensation of indoles with various carbonyl compounds using molecular iodine in acetonitrile as an efficient catalyst under mild conditions in a very short time, <1 min (Scheme 1).

Bis(indolyl)methanes are formed in almost quantitative yields when indole was treated with various aldehydes or ketones in the presence of a catalytic amount (20%) of I_2 in acetonitrile. The electrophilic substitution reactions of indoles with aldehydes as well as ketones proceeded smoothly at room temperature. The results summarized in Table 1, clearly indicate the scope and generality of the reaction as the reactions of aliphatic aldehydes (entries 3a–d), α,β-unsaturated aldehydes (entry 2), a variety of substituted aromatic aldehydes (entries 1a–i) as well as aliphatic, alicyclic and aromatic ketones (entries 4a–c) with indoles in the presence of I_2 (20%) in acetonitrile gave the corresponding bis(indolyl)methanes in excellent yields. It is reported that aromatic aldehydes with strong electron withdrawing substituents on the ring and both aliphatic and aromatic ketones required longer reaction times giving low to moderate yields of the corresponding bis(in-



Scheme 1.

Keywords: iodine; bis(indolyl)methanes; aldehydes and ketones; indoles; electrophilic substitution reactions.

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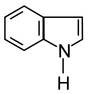
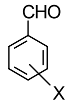
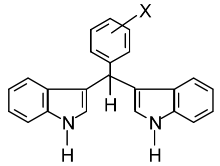
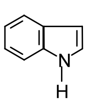
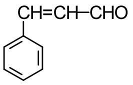
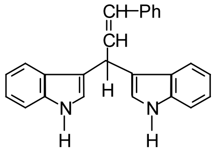
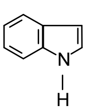
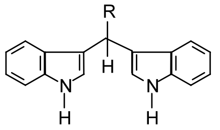
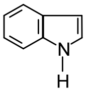
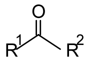
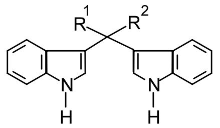
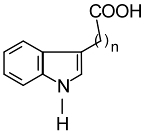
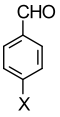
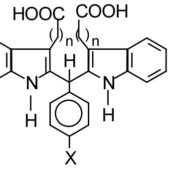
Table 1. I_2-catalyzed synthesis of bis(indolyl)methanes

Entry	Indole	Aldehyde/Ketone	Product	Yield^{a,b}
1				
		a. $X = H$		98
		b. $X = 4\text{-}OMe$		99
		c. $X = 4\text{-}Cl$		96
		d. $X = 2,4\text{-}Cl_2$		94
		e. $X = 4\text{-}OH$		100
		f. $X = 4\text{-}N(CH_3)_2$		98
		g. $X = 4\text{-}Br$		96
		h. $X = 4\text{-}CH_3$		99
		i. $X = 4\text{-}NO_2$		98
2				98
3		R–CHO		
		a. $R = CH_3(CH_2)_2$		87
		b. $R = CH_3(CH_2)_4$		91
		c. $R = CH_3(CH_2)_5$		93
		d. $R = CH_3(CH_2)_7$		81
4				
		a. $R^1 = R^2 =$ Me		81
		b. $R^1 =$ Me, $R^2 =$ Ph		92
		c. $R^1, R^2 = -(CH_2)_5-$		93
5				
		a. $X = NO_2$, $n = 1$		98
		b. $X = OMe$, $n = 1$		99
		c. $X = NO_2$, $n = 2$		98
		d. $X = OMe$, $n = 3$		97

a. Yield of isolated pure products b. Products were characterized by IR, ^{1}H NMR, elemental analysis and comparison with authentic samples.

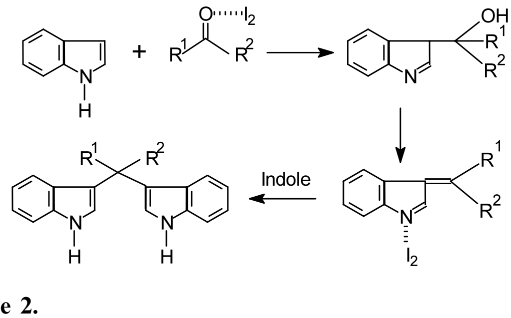
dolyl)methanes. In this context, the present protocol is noteworthy because even nitro substituted aromatic aldehydes and both aliphatic and aromatic ketones underwent smooth reactions with indoles giving excellent yields of products under mild and neutral conditions in a very short time (<1 min).

Furthermore, the reaction of indole with α,β-unsaturated aldehydes in the presence of I_2 (20%) furnished excellent yields of the corresponding bis(indolyl)methanes in <1 min. However, the reported catalysts require longer reaction times giving moderate yields of products for this conversion. The present procedure is superior in comparison with $BF_3 \cdot Et_2O$- or $AlCl_3$-catalyzed reactions of acetone with indole which generated several unexpected products[7a,13] whereas expensive lanthanide triflate-catalyzed reactions took a very long reaction time (24 h).[9] 3-Substituted indoles such as indole-3-acetic acid, indole-3-propionic acid and indole-3-butyric acid were examined for this reaction with aldehydes or ketones (entry 5). Since the more active site (C-3) was blocked in these cases electophilic substitution took place at C-2 giving the corresponding bis(indolyl)methanes (entry 5) in good to excellent yields. In comparison to the reported catalysts, I_2 in acetonitrile was found to be an excellent catalyst in terms of yields and reaction times. This is because of the mild Lewis acidity of iodine, which activates the carbonyl group as well as the indole moiety to promote the reaction (Scheme 2).

In conclusion, I_2 in acetonitrile was found to be mild and effective catalyst for the electophilic substitution reactions of indoles with aldehydes and ketones giving bis(indolyl)methanes in excellent yields. The use of this inexpensive and easily available catalyst under essentially neutral reaction and work-up conditions, the cleaner reaction and greater selectivity make this protocol practical and economically attractive. The procedure was found to be general as a variety of aldehydes and ketones react with indoles under mild reaction conditions in a very short time (<1 min)

Typical procedure: A mixuture of 4-methylbenzaldehyde (1 mmol), indole (2 mmol) and I_2 (0.2 mmol) in acetonitrile (10 ml) was stirred at room temperature for a few seconds. After completion of the reaction (TLC, <1 min), the mixture treated with aq. $Na_2S_2O_3$ solution (5%, 10 ml) and the product was extracted with ethyl acetate (3×5 ml). The combined organic layer was dried with anhydrous sodium sulphate, concentrated in vacuo and purified by column chromatography (ethyl acetate:petroleum ether = 1:9) to afford the pure product.

3,3′-Bis(indolyl)-4-methylphenylmethane: solid; mp 96–97°C; yield 99%; IR (KBr): ν 765, 1050, 1210, 1520, 1600, 2950, 3040, 3110, 3450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, Ar-CH_3), 5.85 (s, 1H, Ar-CH), 6.70 (d, 2H, $J = 2.5$ Hz), 7.02 (t, 2H, $J = 8.1$ Hz), 7.1 (d, 2H, $J = 8.1$ Hz), 7.2–7.3 (m, 6H), 7.4 (d, 2H, $J = 8.1$ Hz), 7.85 (br, s, 2H, NH); MS (70 eV, 130°C) m/z (%): 336 (M^+, 100). Anal. calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.75; H, 5.88; N, 8.28%.



Scheme 2.

References

1. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
2. (a) Porter, J. K.; Bacon, C. W.; Robins, J. D.; Himmelsbach, D. S.; Higman, H. C. *J. Agric. Food Chem.* **1977**, *25*, 88; (b) Osawa, T.; Namiki, M. *Tetrahedron Lett.* **1983**, *24*, 4719; (c) Fahy, E.; Potts, B. C. M.; Faulkner, D. J.; Smith, K. *J. Nat. Prod.* **1991**, *54*, 564; (d) Bifulco, G.; Bruno, I.; Riccio, R.; Lavayre, J.; Bourdy, G. *J. Nat. Prod.* **1995**, *58*, 1254; (e) Bell, R.; Carmell, S.; Sar, N. *J. Nat. Prod.* **1994**, *57*, 1587; (f) Garbe, T. R.; Kobayashi, M.; Shimizu, N.; Takesue, N.; Ozawa, M.; Yukawa, H. *J. Nat. Prod.* **2000**, *63*, 596.
3. (a) Ehrlich, P. *Med. Woche* **1901**, 151; (b) Morgan, L.; Schunior, R. *J. Org. Chem.* **1962**, *27*, 3696; (c) Dolphin, D. *J. Heterocyclic Chem.* **1979**, *7*, 275.
4. Remers, W. *Chem. Heterocyclic Compd.* **1972**, *25*, 1.
5. (a) Roomi, M.; MacDonald, S. *Can. J. Chem.* **1970**, *48*, 139; (b) Gregorovich, B.; Liang, K.; Clugston, D.; MacDonald, S. *Can. J. Chem.* **1968**, *46*, 3291.
6. (a) Woland, W.; Venkiteswaren, M.; Richards, C. *J. Org. Chem.* **1961**, *26*, 4241; (b) Banerji, J.; Chatterjee, A.; Manna, S.; Pascard, C.; Prange, T.; Shoolery, J. *Heterocycles* **1981**, *15*, 325.
7. (a) Chatterjee, A.; Manna, S.; Banerji, J.; Pascard, C.; Prange, T.; Shoolery, J. *J. Chem. Soc.*, *Perkin Trans. 1* **1980**, 553; (b) Babu, G.; Sridhar, N.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 1609.
8. Maiti, A. K.; Bhattacharyya, P. *J. Chem. Res. (S)* **1997**, 424.
9. Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467.
10. Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.
11. Yadav, J. S.; Subba Reddy, B. V.; Murthy, C. V. S. R.; Kumar, G. M.; Madan, C. *Synthesis* **2001**, *5*, 783.
12. (a) Banik, B. K.; Mukhopadhyay, C.; Venkatraman, M. S.; Becker, F. F. *Tetrahedron Lett.* **1998**, *39*, 7743; (b) Banik, B. K.; Zegrocka, O.; Banik, I.; Hackfeld, L.; Becker, F. F. *Tetrahedron Lett.* **1999**, *40*, 673; (c) Banik, B. K.; Zegrocka, O.; Becker, F. F. *J. Chem. Res.* (*S*) **2000**, *7*, 321; (d) Mukhopadhyay, C.; Becker, F. F.; Banik, B. K. *J. Chem. Res.* (*S*) **2001**, 28; (e) Basu, M. K.; Samajdar, S.; Becker, F. F.; Banik, B. K. *Synlett* **2002**, *2*, 319; (f) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527.
13. (a) Banerjee, J.; Chatterjee, A.; Manna, S.; Pascard, C.; Prange, T.; Shoolery, J. *Heterocycles* **1981**, *15*, 325; (b) Roder, E. *Arch. Pharm.* **1972**, *305*, 96; (c) Roder, E. *Arch. Pharm.* **1972**, *305*, 117; (d) Noland, W.; Venkiteswaren, M.; Richards, C. *J. Org. Chem.* **1961**, *37*, 2169.