Organic reactions in aqueous media: InF_3 catalysed synthesis of bis(indolyl)methanes in water under mild conditions

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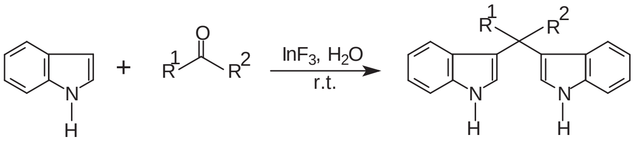
InF_3 catalysed electrophilic substitution reactions of indoles with aldehydes and ketones are carried out in water to furnish the corresponding bis(indolyl)methanes in high yield under mild conditions.

Keywords: bis(indolyl)methanes, indole, InF_3, organic reactions in aqueous media

In organic syntheses and reactions, increasing attention is being focused on green chemistry using environmental benign reagents and conditions and particularly, reactions in aqueous media.[1] Where a solvent must be used, water is without doubt the most acceptable in terms of cost and environmental impact. However, despite its large liquid range and extremely high specific heat capacity, it is frequently overlooked as a solvent for organic reactions.[1] Most catalysts and reagents are deactivated or decomposed in water and in general organic compounds are insoluble in water. Therefore, efforts to carry out organic reactions in water poses an important challenge in the area of reaction design.

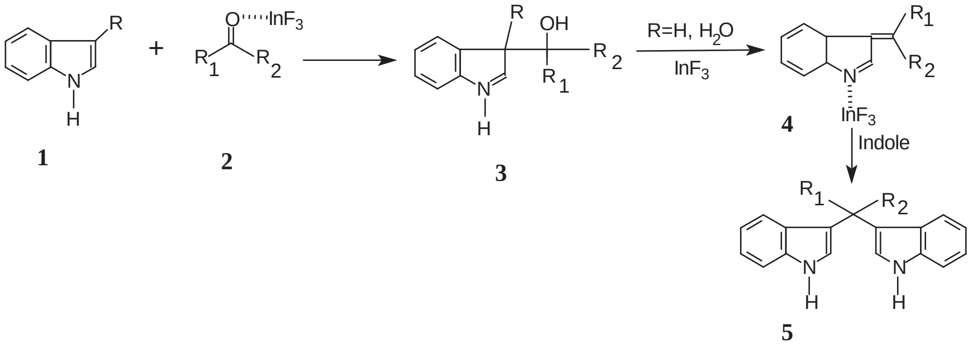
Indole and its derivatives are used as antibiotics.[2] Bisindolylalkanes and their derivatives constitute an important group of bioactive metabolites of terrestrial and marine origin.[3] The acid catalysed reaction of electron-rich heterocyclic compounds with *p*-dimethylaminobenzaldehyde is known as the Ehrlich test[4] for π-electron excessive heterocycles such as pyrroles and indoles. The analogous reaction of indoles with aliphatic and aromatic aldehydes and ketones produces azafulvenium salts. The azafulvenium salts can undergo addition of a second indole molecule to afford bis(indolyl)methanes.[5] Lewis acids[6,7] promote these reactions. Montmorillonite clay K-10[8] and lanthanide triflates[9] also catalyse these reactions. However, many Lewis acids are deactivated or sometimes decomposed by water or by nitrogen containing reactants. Even when the desired reactions proceed, more than a stoichiometric amount of Lewis acids are required because the acids are trapped by nitrogen bases.[10] These problems can be somewhat circumvented by using expensive lithium perchlorate[11] and lanthanide triflates[9] as catalysts. However, the longer reaction times for nitro-substituted aldehydes and ketones cause low to moderate yields. Lanthanide triflates are water tolerant[9] Lewis acids useful to catalyse reaction of indoles with aldehydes and ketones. However, lanthanide triflate catalysed reaction of indole-3-acetic acid with *p*-anisaldehyde did not proceed in an aqueous medium and even when the desired reactions proceed with other indole substrates and carbonyl compounds, ethanol is required as a co-solvent. Otherwise these reactions are very slow, giving low yields of products in water alone as a solvent.



Scheme 1

Even though indium belongs to the same group in the periodic table as boron and aluminium, $InCl_3$ and InF_3 as Lewis acids for organic reactions have not been exploited. But recently, it has been proven that $InCl_3$ is a mild, worthwhile Lewis acid; which is stable in aqueous media and effectively and selectively catalyses various important organic reactions.[12] We now report our results involving InF_3 catalysed synthesis of bis(indolyl)methanes by condensation of indoles with aldehydes and ketones in water, under mild conditions (Scheme 1).

When indole/substituted indole was treated with various aldehydes and ketones in the presence of a catalytic amount of InF_3 in water, the corresponding bis(indolyl)methanes are formed in high yields. It is truly catalytic method as the amount of catalyst, InF_3 used is 5%. The electophilic substitution reactions of indoles with aldehydes as well as ketones proceed smoothly at room temperature. The results, presented in Table 1, indicate the generality of the protocol as various aliphatic and aromatic aldehydes as well as both aliphatic and aromatic ketones reacted with indoles giving the corresponding bis(indolyl)methanes in excellent yields. It is reported that aromatic aldehydes with strong electron withdrawing substitutents on the ring and α,β-unsaturated aldehydes required longer reaction times giving moderate yields of the corresponding bis(indolyl)methanes as compared to their simple and electron rich counterparts. In this context, the present procedure is noteworthy because even nitro substituted aldehydes (Entry 6) and α,β-unsaturated aldehydes (Entry 4) underwent smooth reactions with indoles giving



Scheme 2

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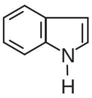
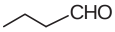
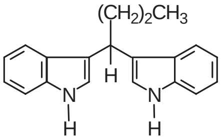
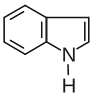
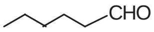
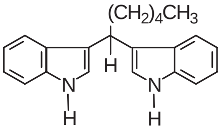
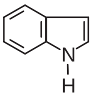
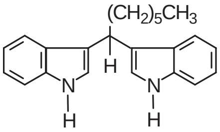
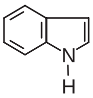
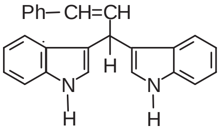
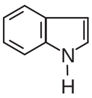
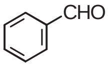
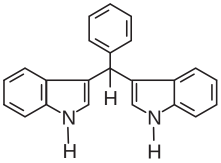
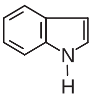
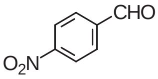
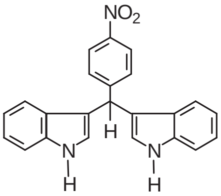
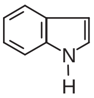
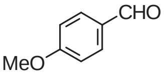
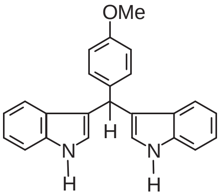
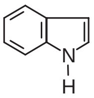
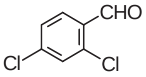
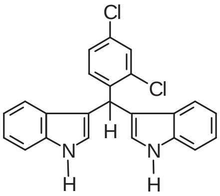
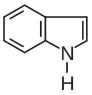
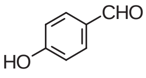
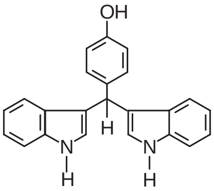
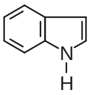
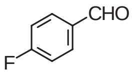
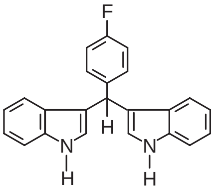
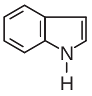
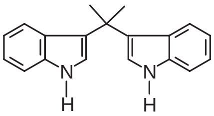
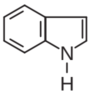
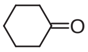
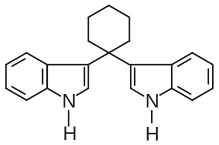
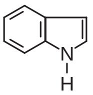
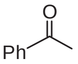
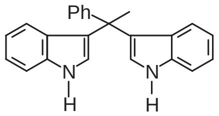
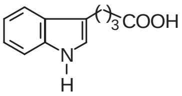
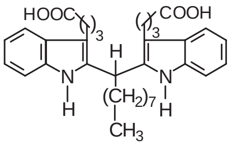
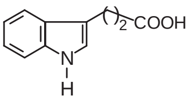
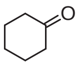
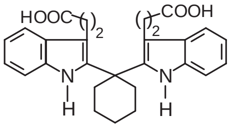
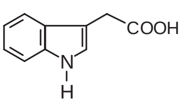
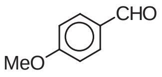
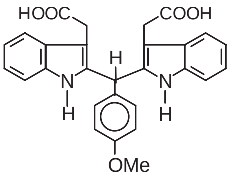
Table 1 InF_3 catalysed synthesis of bis(indolyl)methanes.

Entry	Indole	Aldehyde/ketone	Product	Time/h	Yield/%[a,b]
1				15	92
2				14	86
3				12	91
4		PhCH=CHCHO		15	90
5				12	95
6				13	99
7				10	95
8				13	99
9				10	99
10				14	92
11				15	81

Entry	Indole	Aldehyde/ketone	Product	Time/h	Yield[a,b]/%
12				16	79
13				17	77
14		$CH_3(CH_2)_7CHO$		14	81
15				14	70
16				10	98

[a] Yield of isolated pure product. [b] Products are characterised by IR, ^{1}H NMR elemental analysis and comparison with authentic samples.

excellent yield of products. $AlCl_3$ or $BF_3.Et_2O$ catalysed reactions of acetone with indole were reported to generate several unexpected products.[6a,13] However, it is important to note that InF_3 catalysed reactions of indole with acetone gave high yield of desired product without any side reaction. In comparison with dysprosium triflate,[9] InF_3 is found to be a superior catalyst in terms of reaction time and application in water without co-solvent, which is otherwise sometimes problematic due to side reactions.[11]

The possible mechanism is as follows: An aldehyde/ketone after activation by InF_3 undergoes electrophilic substitution at C-3 of an indole to yield **3**. After loss of water, an intermediate, **4**, is generated which is further activated by InF_3 and serves as an electrophile to attack a second molecule of indole to form the 2+1 adduct, **5.**

In conclusion, InF_3 is found to be effective, water tolerant catalyst for the electrophilic substitution reactions of indoles with aldehydes and ketones. The procedure is simple and efficient giving high yields of bis(indolyl)methanes as useful bioactive molecules. When the 3-position of indole is blocked, substitution takes place at the 2-position yielding the corresponding bis(indolyl)methanes.

Experimental

Typical procedure: A mixture of benzadehyde (1 mmol), indole (2 mmol), and indium trifluoride (0.05 mmol, 5%) in distilled water (25 ml) was stirred at room temperature for specified time (Table 1). After completion of the reaction (TIC), insoluble product was filtered, washed with water and dried under vacuum giving pure product in excellent yield 3,3'-Bis(indolyl)phenylmethane: Yield = 96%; Solid; m.p.= 88–90 ^{0}C; IR (KBr): ν = 750, 1050, 1210, 1500, 1600, 3030, 3460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : δ : 6.1 (s, 1H, CH), 6.5 (d, 2H, J = 2.5 Hz), 7.1 (t, 2H, J = 8.1 Hz), 7.2 (t, 2H, J = 8.1), 7.35 (m, 9H), 8.9 (br s, 2H, NH); ^{13}C NMR (75 MHz, $CDCl_3$, proton decoupled) : 41, 112, 121, 122, 122.5, 123.7, 124.1, 127, 127.7, 129, 130, 137, 145; Mass (70 eV, 150 ^{o}C) = *m/z* (%) = 322 (M^+, 100) Anal. Cacld. For $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69. Found : C, 85.58; H, 5.71; N, 8.61.

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