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A simple, efficient and green procedure for the synthesis of bis-indolyl methanes in 1,1,1,3,3,3-hexafluoro-2-propanol

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ABSTRACT

A simple, inexpensive, environmentally friendly and efficient route for the synthesis of bis-indolyl methanes derivatives by the reaction of indole or *N*-methyl indole with aldehydes using hexafluoroisopropanol as a solvent is described. The solvent (HFIP) can be readily separated from reaction products and recovered in excellent purity for direct reuse.

1. Introduction

Indole and their derivatives have become increasingly useful and important in the field of pharmaceuticals [1–4]. Among various indole analogs, bis(indolyl)methanes derivatives (BIMs) display versatile biological and pharmacological activities [5,6]. Recent medicinal chemistry applications of BIMs include the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome [7,8], and as dietary supplements for promoting healthy estrogen metabolism in humans [9], and also effective in the prevention of cancer [10,11]. As a result of their biological and synthetic importance, a number of synthetic methods for preparation of bis(indolyl)alkane derivatives have been reported in the literature by reaction of indole with various carbonyl compounds in the presence of catalyst [12–23]. In fact, the acids commonly used are generally toxic catalysts, difficult to handle, stoichiometric amount maybe needed, and require tedious aqueous work-up, along with the use of environmentally harmful organic solvents. Keeping in view the disadvantages associated with reported protocols as well as increasing importance of bis(indolyl)methanes derivatives in pharmaceutical and industrial chemistry, there still remains a high demand for the development of more general, efficient, and eco-friendly protocol to assemble such scaffolds. 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP), an alcohol bearing two CF_3 groups, has withdrawn much attention of synthetic chemists in the past decade [24–39]. HFIP serves as a powerful hydrogen-bond donor, as was demonstrated not only by the spectral studies and calorimetric measurements [40,41], but also by the isolation of extremely stable complexes with a number of nucleophilic species [42]. Compared to other solvents, TFE (bp = 73 °C) and HFIP (bp = 58 °C) are unique due to their high ionizing powers, strong hydrogen bond donor abilities, mild acidic characters (pK_a = 12.4 and pK_a = 9.3, respectively), and low nucleophilicity [43–45]. Due to the current challenges for developing environmentally benign synthetic processes and in continuation of our interest in the application of fluorinated solvents for various organic transformations [46–51] we report a new, convenient, mild and efficient procedure for the synthesis of BIMs derivatives by the reaction of indole or *N*-methyl indole with aldehydes under mild reaction conditions in hexafluoroisopropanol (HFIP) (Scheme 1).

2. Results and discussion

To initiate our study, the reaction of indole with benzaldehyde was chosen as a model reaction in HFIP at room temperature. The corresponding bis(indolyl)methanes **3f** was obtained in high yield (90%) after 60 min (Table 1, entry 6). These results prompted us to investigate the scope and the generality of this new protocol for various aldehydes under optimized conditions (Table 1).

A series of aromatic, heterocyclic and aliphatic aldehydes underwent electrophilic substitution reaction with indole and *N*-methyl indole smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields (Table 1). This method is equally effective for aldehydes bearing electron

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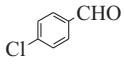
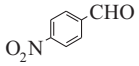
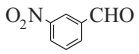
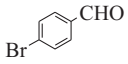
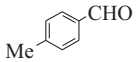
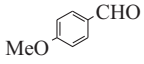
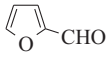
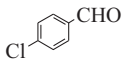
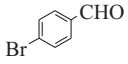
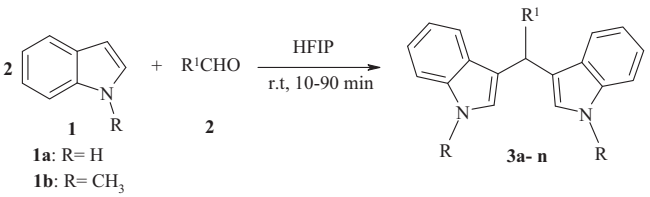
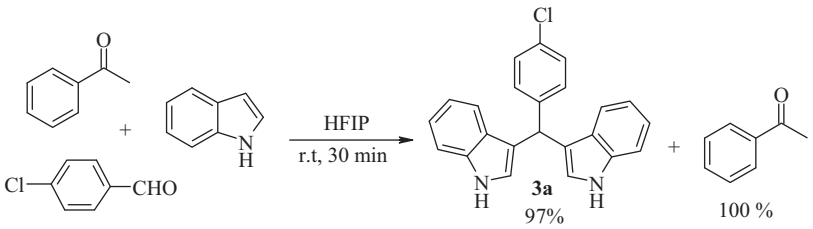
Table 1
Synthesis of BIMs in HFIP.

Entry	Aldehyde/ketone	Indole	Time (min)	Product	Yield %ref
1			30	**3a**	97[23]
2			45	**3b**	90[23]
3			30	**3c**	90[20]
4			45	**3d**	92[20]
5			30	**3e**	95[20]
6			60	**3f**	90[20]
7			60	**3g**	90[23]
8			60	**3h**	92[20]
9			45	**3i**	85[20]
10			50	**3j**	92[22]
11			90	**3k**	80[20]
12			90	**3l**	85[20]
13			90	**3k**	80[20]
14			10	**3m**	90[21]
15			10	**3n**	90[21]

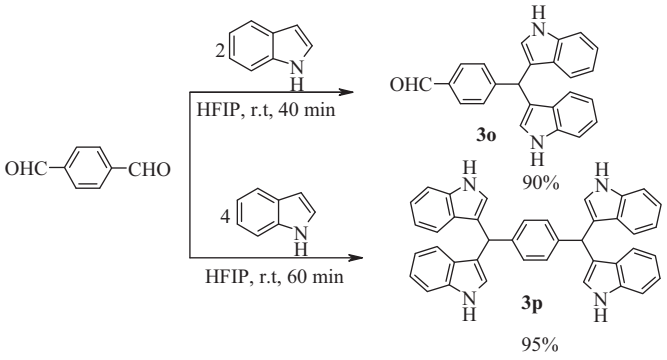


Scheme 1. Condensation of indole with aldehydes in HFIP.

withdrawing or donating substituents in the aromatic rings. Furthermore, acid sensitive aldehydes worked well without any decomposition or polymerization under these reaction conditions (Table 1, entry 9). Also tris-indolyl methane was produced in excellent yield (Table 1, entry 10). As it is expected, *N*-methyl indole provided better yields of products by comparing with indole under the same reaction conditions. This method is even effective with aliphatic aldehydes, which normally produce low yields due to their intrinsic lower reactivity (Table 1, entries 11–13). This



Scheme 2. Chemoselectivity of aldehyde in reaction with indole in the presence of a ketone.



Scheme 3. Selective condensation of a dialdehyde with indole.

present method is also highly chemoselective for aldehydes. For example, when a 1:1 mixture of 4-chlorobenzaldehyde and acetophenone was allowed to react with indole in HFIP, it was found that only 4-chlorophenyl-3,3-bis(indolyl)methane (**3a**) was obtained, while acetophenone did not give the corresponding product under this reaction conditions (Scheme 2).

The reactions were clean and the products were obtained in high yields without the formation of any side products such as *N*-alkylated product. Selective condensation of a dialdehyde, i.e. terephthaldialdehyde to the corresponding bis-indolyl methane was achieved by controlling the molar ratio of indole (Scheme 3). The results showed that addition of 2 equivalents of indole to terephthaldialdehyde, gives **3o** in 90% yield (Scheme 3). Treatment of 4 equivalents of indole with terephthaldialdehyde gave the corresponding di(bis-indolyl methanes), **3p**, respectively in high yields at room temperature in HFIP (Scheme 3).

After the reaction, HFIP can be easily separated (by distillation) and reused without decrease in its activity. For example, the reaction of indole with 4-chlorobenzaldehyde afforded the corresponding bis-indolyl methane derivative in 97%, 95%, and 95% isolated yield over three cycles. When we carried out the reaction in TFE at room temperature, the reaction proceeded very slowly to give moderate yields.

3. Conclusions

In conclusion, a simple and highly efficient method for the synthesis of bis-indolyl methanes derivatives has been developed via condensation of indole with aldehydes in HFIP at room temperature. In contrast to the existing methods using potentially hazardous catalysts/additives, this new method offers the following competitive advantages: (i) avoiding the use of any base, metal, or Lewis acid catalysts and reaction at room temperature (~25–30 °C), (ii) short reaction times, (iii) ease of product isolation/nonaqueous workup, (iv) high chemoselectivity, (v) no side reaction, and (vi) simplicity in process and handling. The recovered HFIP is ready for reuse. Further studies and efforts to extend the scope of this method for other useful reactions are currently underway.

4. Experimental

Typical experimental procedure: To a solution containing aldehyde (1 mmol), in HFIP (0.5 mL) was added the indole (2 mmol) and the mixture was vigorously stirred at r.t. for appropriate reaction time. After completion of the reaction as indicated by TLC, the products were isolated by filtration (for solid products) or after selective evaporation of the HFIP (for liquid products) to yield the highly pure bis-indolyl methane derivatives. The physical data (mp, IR, NMR) of known compounds were found to be identical with those reported in the literature. Spectroscopic data for selected examples are shown below.

Bis(3-indolyl)-tolylmethane (Table 1, *entry 7*): Pale-red solid, m.p. 96–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3H), 5.84 (s, 1H), 6.65 (s, 2H), 6.99 (t, 2H, J = 7.2 Hz), 7.07 (d, 2H, J = 8.0 Hz), 7.15 (t, 2H, J = 7.6 Hz), 7.21 (d, 2H, J = 8.0 Hz), 7.33 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.0 Hz), 7.86 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 39.8, 110.9, 119.2, 119.9, 120.0, 121.8, 123.5, 127.1, 128.5, 128.9, 135.4, 136.7, 141.0.

Tris (3-indolyl)methane (Table 1, *entry 10*): Pale yellow solid; m.p. 160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07 (s, 1 H), 6.87 (s, 3H), 6.85 (t, 3H, J = 7.4 Hz), 7.03 (t, 3H, J = 7.2 Hz), 7.43 (d, 3H, J = 7.8 Hz), 7.55 (d, 3H, J = 7.8 Hz), 10.72 (s, 3H, –NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8, 111.2, 117.8, 118.2, 119.4, 120.5, 123.1, 126.5, 136.4.

3,3′,3″,3‴-Tetraindolyl(terephthalyl)dimethane (Scheme 3, **3p**): Pink solid; m.p. 194 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (s, 2 H), 6.29 (s, 4H), 7.05 (t, 4H, J = 7.6 Hz), 7.16 (t, 4H, J = 7.6 Hz), 7.24–7.40 (m, 12H), 7.31 (br s, 4H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.2, 111.6, 118.2, 118.4, 119.3, 120.8, 123.4, 126.8, 128.2, 136.7, 142.5.

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