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An expeditious and efficient synthesis of symmetrical tris(indolyl)methanes under catalyst-free conditions in fluorinated alcohols

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ABSTRACT

Hexafluoro-2-propanol (HFIP) is explored as an effective medium for the synthesis of symmetrical tris(indolyl)methanes through the reaction of indole derivatives with orthoesters at room temperature. The solvent (HFIP) can be readily separated from reaction products and recovered in excellent purity for direct reuse.

1. Introduction

Recently, indole derivatives have attracted much attention due to the broad scope of their biological activity [1–6]. Among various indole analogs, tris(indolyl)methane derivatives (TIMs) display versatile biological and pharmacological activities [7]. TIMs show an affinity for hydride ions [8] and dye materials [9,10] and can potentially be utilized as acceptors for these substances. They are also effective frameworks for the construction of very bulky π-acidic phosphine ligands [11]. Moreover, the TIMs motifs is present in many products isolated from bacteria [12] serve as bacterial metabolic [13] and cytotoxic agents [14]. As a result of their biological and synthetic importance, a number of synthetic methods for preparation of tris(indolyl)methane derivatives have been reported in the literature by reaction of indole derivatives with various orthoesters in the presence of catalysts [15–20]. TIMs are also obtained from the reaction of indoles and acetic–formic anhydride [21] or diethoxycarbenium salts [22] and *N*,*N*-dimethylformamide dimethyl acetal [23]. These protocols often suffer from disadvantages, however, such as the high toxicity or corrosiveness of the promoters employed, or the requirement to use expensive reagents. Furthermore, on completion of the reaction, the Lewis acid is often destroyed in an aqueous work-up, liberating quantities of waste that must be disposed of. Keeping in view the disadvantages associated with reported protocols as well as increasing importance of tris(indolyl)methane 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. The development of cost-effective and environmentally benign catalytic systems is one of the main themes of contemporary organic synthesis. From the viewpoint of green chemistry, the fluorinated alcohols are attracting growing interest as alternative reaction media for various organic transformations [24–39]. Fluorinated alcohols are solvents with peculiar properties [40] such as low nucleophilicity, high polarity, strong hydrogen bond donating ability and ability to solvate water. Reactions in fluorinated solvents are generally selective and without effluents, allowing thus a facile isolation of the product and a recovery of the solvent by distillation. As part of our ongoing programme to develop highly efficient and environmentally benign synthetic processes [41–49], we have developed a mild and expedient synthesis of symmetrical tris(indolyl)methanes (TIMs) under mild reaction conditions in hexafluoro-2-propanol (HFIP) (Scheme 1).

2. Results and discussion

In preliminary experiments, indole (3 mmol) in 1 mL of trifluoroethanol (TFE) was allowed to stir at room temperature with trimethylorthoformate. After 10 h, only 50% of expected tris(indol-3-yl)methane **3a** was obtained. Our efforts were then focused on HFIP. As a strong H-bond donor (α = 1.96, pK_a = 9.3), with high ionizing power (Y_{OTs} = 3.79), and polarity (P_s = 11.08), it could activate the orthoesters towards the nucleophilic attack [45].

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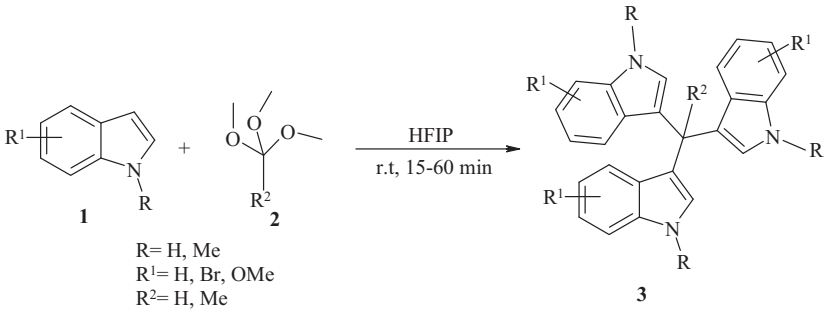


Scheme 1. Synthesis of tris(indolyl)methanes 3 in HFIP.

The reaction was then investigated in HFIP: where a solution of indole (3 mmol), trimethylorthoformate (1 mmol) in HFIP (Table 1, entry 1) was stirred at room temperature. The reaction was remarkably fast (20 min) and, after distilling off the HFIP, the tris(indol-3-yl)methane **3a** was isolated in 95% yield. Further experiments revealed that a similar procedure is applicable for the preparation of a wide range of compounds analogous to adduct **3** (Table 1). As shown in Table 1, for both reactive and unreactive substituted indoles, the condensation proceeded smoothly in HFIP to provide the desired products in excellent yields (88–98%) at room temperature. For all the substrates, the reaction time was reduced drastically even under ambient conditions in contrast to reported methods [15–20], and better yields were obtained. As it is expected, *N*-methyl indole provided better yields of products in comparison with indole under the same reaction conditions. When trimethylorthoacetate was used, the reaction time would get longer and the yield was lower, which was presumably due to the fact that trimethylorthoacetate was more sterically hindered than the trimethylorthoformate. The reactions were clean and the products were obtained in high yields without the formation of any side products such as N-alkylated product. To further expand the scope of the reaction, we next examined the reactions using different molar ratio of both substrates. Surprisingly, in all cases the symmetrical tris(indolyl)methanes were the main product. The possible mechanism is shown in Scheme 2.

In this process, HFIP act as Brønsted acid [50] and play a significant role in increasing the electrophilic character of the orthoester. Interestingly, the reaction did not proceed to completion when either ethanol or water alone was used as solvent, even at higher temperatures.

Table 1
Synthesis of symmetrical tris(indolyl)methanes in HFIP.

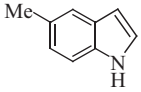
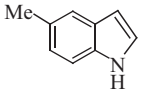
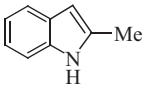
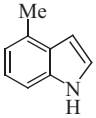
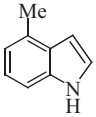
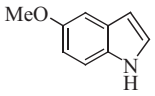
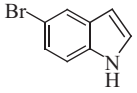
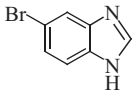
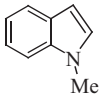
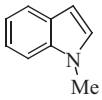
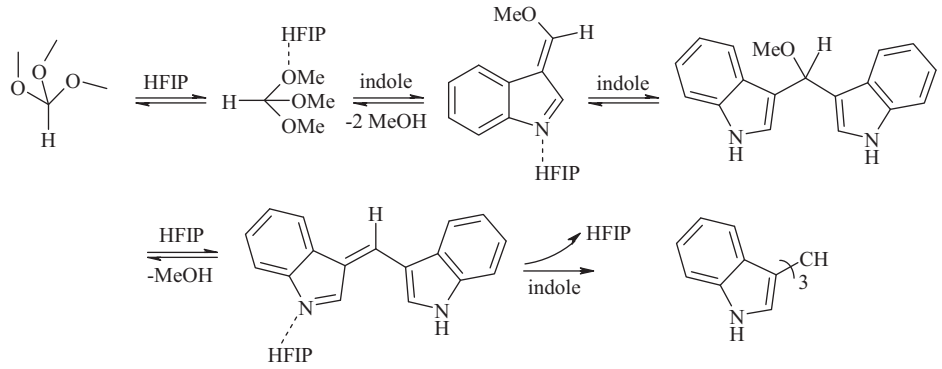
Entry	Indole	Ortho-ester	Time (min)	Product	Yield %[ref]
1		$CH(OMe)_3$	20	**3a**	95[20]
2		$CH(OEt)_3$	20	**3b**	92[20]
3		$CH_3CH(OMe)_3$	60	**3c**	90[20]
4		$CH(OMe)_3$	25	**3d**	92[20]
5		$CH(OEt)_3$	20	**3e**	94[15]
6		3 $CH(OMe)_3$	40	**3f**	94[15]
7		$CH(OMe)_3$	30	**3g**	90[20]
8		$CH(OEt)_3$	30	**3g**	90[15]

Table 1 (*Continued*)

Entry	Indole	Ortho-ester	Time (min)	Product	Yield %[ref]
9		$CH(OEt)_3$	20	**3h**	96[20]
10		$CH(OMe)_3$	30	**3i**	90[20]
11		$CH(OEt)_3$	30	**3j**	88[20]
12		$CH(OMe)_3$	15	**3k**	98[16]
13		$CH_3CH(OMe)_3$	30	**3l**	95[16]



Scheme 2. Proposed mechanism for the synthesis of tris(indolyl)methanes.

After the reaction, HFIP can be easily separated (by distillation) and reused without decrease in its activity. For example, the reaction of indole and trimethylorthoformate afforded the corresponding tris(indol-3-yl)methane derivative in 95%, 95%, 93%, 92% and 92% isolated yield over five cycles. The notable advantages of this method are the operational simplicity, direct use of indoles and inexpensive, reusable and non-toxic HFIP medium which render this method an important alternative to previously reported methods.

3. Conclusions

In conclusion, we have developed an efficient methodology for the symmetrical tris(indolyl)methanes through the reaction of indole derivatives with orthoesters at room temperature. The reaction is performed in HFIP as solvent and requires no use of any acid or metal promoter.

4. Experimental

4.1. Typical experimental procedure

To a solution containing trimethylorthoformate (1 mmol), in HFIP (0.5 mL) was added the indole (3 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 tris-indolyl methane derivatives. The physical data (mp, IR, and NMR) of known compounds were found to be identical with those reported in the literature. Spectroscopic data for selected examples are shown below.

4.1.1. Tri(1H-indol-3-yl)methane (3a)

mp = 238–240 °C, IR (KBr): 3395, 3048, 1484, 1455, 1418, 1336, 1216, 1009, 801 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.19 (s, 1H), 6.88 (t, J = 7.8 Hz, 3H), 6.92 (s, 3H), 7.03 (t, J = 7.8 Hz, 3H), 7.37 (d, J = 7.8 Hz, 3H), 7.47 (d, J = 7.8 Hz, 3H), 7.92 (br s, 3H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.5, 111.4, 118.4, 119.2, 119.7, 121.1, 123.5, 127.5, 137.4.

4.1.2. Tris(2-methyl-1H-indol-3-yl)methane (3f)

mp = 333–335 °C, IR (neat): 3393, 3051, 2908, 1618, 1461, 1427, 1340, 1297, 1218, 1010, 816, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.91 (s, 9H), 6.08 (s, 1H), 6.61 (t, J = 8.1 Hz, 3H), 6.78 (d, J = 8.1 Hz, 3H), 6.85 (t, J = 8.1 Hz, 3H), 7.18 (d, J = 8.1 Hz, 3H), 7.93 (br s, 3H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 10.5, 28.6, 101.1, 111.2, 113.0, 117.8, 124.2, 127.8, 132.4, 152.4.

4.1.3. Tris(5-methoxy-1H-indol-3-yl)methane (3h)

mp = 221–223 °C, IR (KBr): 3413, 2932, 1620, 1579, 1483, 1450, 1290, 1212, 1172, 1039, 842 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 3.61 (s, 9H), 6.04 (s, 1H), 6.70 (dd, J = 8.7, 2.4 Hz, 3H), 6.94 (d,

J = 1.2 Hz, 3H), 6.97 (d, J = 2.4 Hz, 3H), 7.27 (d, J = 8.7 Hz, 3H), 7.92 (br s, 3H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 31.7, 55.1, 102.1, 111.0, 112.0, 118.8, 124.2, 127.9, 132.5, 153.4.

*4.1.4. Tris(5-bromo-1H-indol-3-yl)methane (**3i**)*

mp = 260–262 °C, IR (KBr): 3428, 2924, 1562, 1457, 1417, 1213, 1090, 868 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.06 (s, 1H), 6.98 (s, 3H), 7.13 (d, J = 8.4 Hz, 3H), 7.32 (d, J = 8.4 Hz, 3H), 7.50 (s, 3H), 7.90 (br s, 3H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 30.9, 111.4, 114.2, 118.1, 122.0, 123.9, 125.6, 129.0, 135.9.

*4.1.5. Tri(1-methyl-1H-indole-3-yl)methane (**3l**)*

mp = 264–266 °C, IR (KBr): 3048, 1484, 1455, 1418, 1336, 1216, 1009, 801 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.51 (s, 3H), 3.71 (s, 9H), 6.88 (s, 3H), 6.93 (t, J = 7.8 Hz, 3H), 7.17 (t, J = 7.8 Hz, 3H), 7.37 (d, J = 7.8 Hz, 3H), 7.47 (d, J = 7.8 Hz, 3H), 7.92 (br s, 3H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 26.7, 34.1, 42.2, 112.4, 117.4, 119.2, 119.8, 122.1, 123.5, 128.5, 137.2.

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