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### Ammonium trifluoroacetate mediated efficient synthesis of *bis (indolyl) methanes*

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#### ABSTRACT

An efficient rapid synthesis of pharmaceutically valued bis (indolyl) methanes were synthesized utilizing Ammonium Trifluoroacetate as an efficient catalyst by the reaction of aromatic aldehydes with indole in acetonitrile as a solvent, giving excellent yield of products within a short period of time at reflux temperature.

**Keywords:** Indole, Aldehydes, Bis (indolyl) methane, Ammonium Trifluoroacetate, Acetonitrile

#### INTRODUCTION

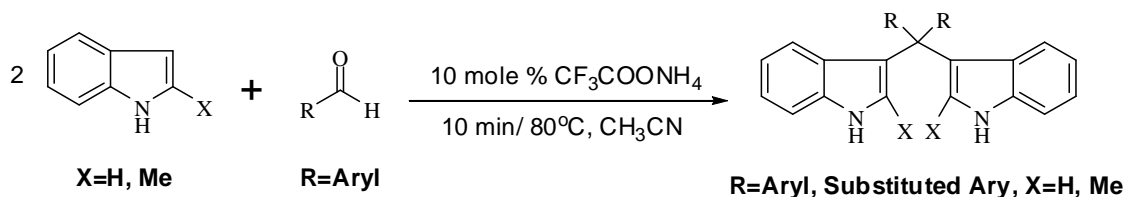
It is noteworthy to mention that, along with various heterocyclic ring systems [1] discovered over the period of time, the indole ring system has dominated its presence in many pharmaceuticals, natural bioactive products and agrochemicals [2]. In addition to this, Bis(indolyl) methane [3] compounds possess a wide range of pharmaceutical as well as novel therapeutic properties. Among the various activities that they possess, includes cytotoxic, insecticidal, anti-bacterial, antioxidative and activities. Further numerous bioactive metabolites that are isolated from natural sources contain bis- and tetra (indolyl) methanes, like bis (3-indolyl) methane (BIM), *i.e.* indole-3-carbinol, was found to be effective in cancer chemotherapy. Thus owing to such a wide pharmaceutical and potent biological applicability, we have witnessed a large number of synthetic reports from all over the world. Majority of methods reported in the literature so for the synthesis of BIM derivatives contain use of different Bronsted and Lewis acid catalyst[4].

These reported synthetic methods are considered to be highly atom-efficient, but it has some major demerits like the use of toxic reagents and solvents, longer reaction time, tedious workup procedure, elevated reaction temperature, poor yield of products etc., are drawbacks that limit the scale-up of most of these procedures.

#### MATERIALS AND METHODS

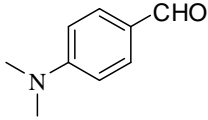
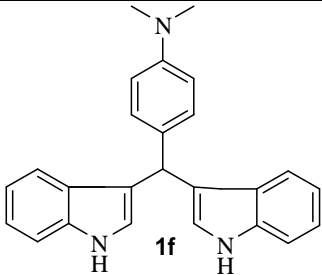
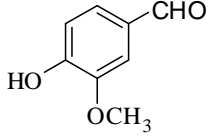
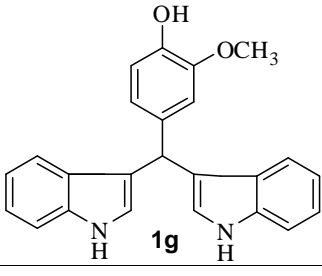
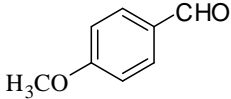
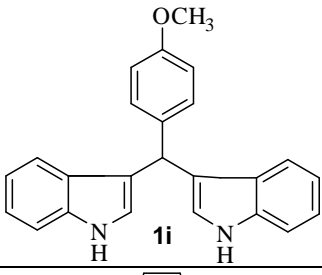
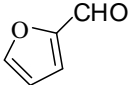
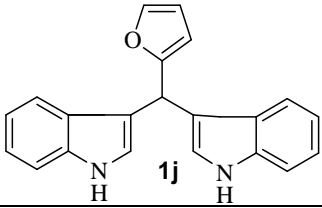
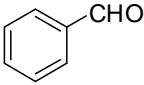
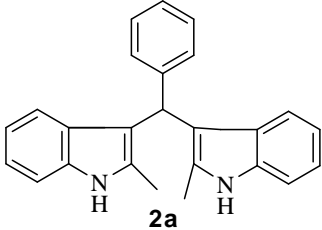
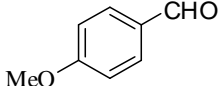
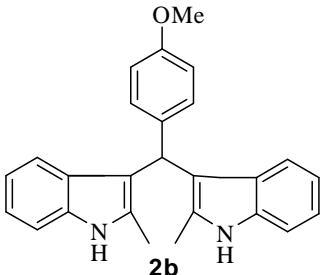
In short to think not only from environmental point of view but also from various point of view including economy, comfortable handling, easy separation and re-cyclability in most cases, there is earnest need to develop a method that can overcome all these drawbacks and leads successfully with more applicability and feasibility. In continuation of our research[5] towards developing novel synthetic methodologies for biologically valued molecules, herein we put forward a simple synthetic protocol, for the synthesis of the bis (indolyl) methanes in excellent yield, utilizing ammonium trifluoroacetate as an efficient catalyst. Although it is important to note that, catalytic activity of ammonium trifluoroacetate is less explored in the organic synthesis. Recently it was utilized for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones [6] giving excellent yields of products. So in this present report, we have developed a

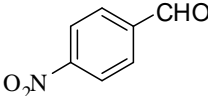
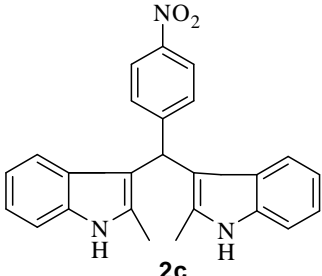
new synthetic protocol for the facile synthesis of *bis* (indolyl)methanes from the corresponding aromatic aldehydes and indoles *via* the electrophilic substitution of indoles with different aromatic aldehydes using ammonium trifluoroacetate as a novel, ecofriendly, catalyst at reflux temperature in acetonitrile.



**Table 1:** Yield and reaction time of Ammonium Trifluoroacetate catalyzed various bis(indolyl)methanes

S. No.	X	Aromatic Aldehyde	Product	Time (min.)	Yield	M. P. (°C)
1.	H			10	91	97-99 [7]
2.	H			10	92	77-79 [7]
3.	H			10	92	223-225 [7]
4.	H			10	88	122-124 [7]
5.	H			10	90	109-111 [8]

6.	H			10	89	179-181 [9]
7.	H			10	88	111-113 [7]
8.	H			10	92	189-191 [7]
9.	H			10	83	320-322 [7]
10.	Me			10	88	247-249 [10]
11.	Me			10	90	209-211 [8]

12.	Me			10	92	241-243 [9]
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## RESULTS AND DISCUSSION

The electrophilic substitution of indole with aromatic aldehyde is catalyzed by ammonium trifluoroacetate affording the product in excellent yield at reflux temperature in acetonitrile. The reaction conditions for the reaction between indole and aldehydes are summarized in (Table 1).

### 1.1. Experimental Part

All the chemicals (AR grade) were purchased from SD fine chemicals and used without further purification. Melting points of the products were recorded using capillaries open at one end and were uncorrected.  $^1\text{H}$  was recorded on 400 MHz Varian spectrophotometer in  $\text{CDCl}_3$  solvent with TMS as an internal standard. IR was recorded on Bruker Vector 22 FTIR spectrophotometer using KBr discs. Exact mass of the samples were recorded on Shimadzu mass analyzer. The progress of the reaction was monitored by Thin Layer Chromatography in 20 % ethyl acetate: hexane.

### 1.2. Typical procedure bis (indolyl) methane synthesis

In a typical model condensation reaction ammonium trifluoroacetate catalyst (10 mole %) was added to a preheated mixture of aromatic aldehyde (10 mmol) and indole (20 mmol) dissolved in acetonitrile. At the moment the catalyst is added, the reaction starts instantly, with change in color from colorless to colored viscous mass, with sudden rise in the reaction temperature by few degrees. Further the resulting mixture was allowed to stir at this temperature for around 10 minutes to complete the reaction. After completion of the reaction as indicated by TLC (20 % ethyl acetate: hexane) the reaction mass was diluted with cold water and after stirring for 5 minutes, the reaction mixture was poured onto the crushed ice. The reaction mixture was filtered and the separated mass was washed around 3-4 times with cold water and the pure product thus obtained was purified by recrystallization from ethanol. All the products reported are known compounds and were identified by comparison with physical and spectral data of authentic samples from literature.

The spectral data of selected compounds is described below:

**Compound (2b):** Brown solid, m.p. 209-211°C, IR (KBr)  $\text{cm}^{-1}$  3396, 3047, 2958, 2995, 1608, 1510, 1458, 1340, 1218, 1033; NMR (400 MHz  $\text{CDCl}_3$ )  $\delta$  ppm 2.05(s, 6H), 3.8 (s, 3H), 5.95 (s, 1H), 6.8 (dd, 2H), 6.9 (dd, 2H), 7.0 (m, 6H), 7.2(d, 2H), 7.73 (2H, br's, NH); ESMS 409( $\text{M}^+$ ); Elemental analysis Cal. C=82.07, H=6.36, N=7.36, found C=81.9, H=6.089, N=7.02.

**Compound (2c):** Yellow solid, m.p. 241-243°C, IR (KBr)  $\text{cm}^{-1}$  3385, 3056, 2913, 2844, 1618, 1593, 1515, 1461, 1424, 1385, 1341, 1223, 852;  $^1\text{H}$  NMR (400 MHz  $\text{CDCl}_3$ )  $\delta$  ppm 2.09(s, 6H), 6.059 (s, 1H), 6.85-6.92 (m, 4H), 7.05 (d, 2H), 7.25 (d, 2H), 7.4(d, 2H), 7.83 (s, 2H), 8.1 (s, 2H) ESMS 395 ( $\text{M}^+$ ); Elemental analysis Cal. C=75.93, H=5.35, N=10.63; found C=73.77, H=5.31, N=10.64.

## CONCLUSION

In short, an efficient synthesis of biologically valued bis(indolyl) methanes is achieved utilizing ammonium trifluoroacetate catalyst at reflux temperature in quantitative yield, having unique features like short reaction time, simple experimental process, cleaner reaction protocol and easy isolation of products with no side products and utilization of inexpensive catalyst, easily available, air stable, water-tolerant are the most promising and attractive features of this reaction protocol/methodology which makes this method superior to existing synthetic route.

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