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Kewords: indoles, aldehydes, (indolyl) methanes, ionic liquids.

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CHEMISTRY RESEARCH ARTICLE

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ABSTRACT

Efficient electrophilic substitution reactions of indoles with various aromatic aldehydes were carried out using [bmim] BF_4 ionic liquids under solvent-free conditions to afford the corresponding bis(indolyl)methanes in excellent yields.

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1. INTRODUCTION

Indoles and their derivatives are important intermediates in organic synthesis and exhibit various physiological properties and pharmacological activities. Bis(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism and induce apoptosis in human cancer cells. Therefore, the preparation of indoles has received much attention from synthetic organic chemists and biologists . Synthetically, the reaction of 1H-indole with aldehydes or ketones produce azafulvenium salts that react further with a second 1H-indole molecule to form bis(indol-3-yl)methanes. In recent years, synthesis of this class of molecules under mild conditions have been reported with promoters, such as Montmorillonite clay K-10 , trichloro-1,3,5-triazine, $AlPW_{12}O_{40}$, sodium dodecyl sulfate (SDS), $ZrCl_4$, sulfated zirconia, $ZrOCl_2/SiO_2$, I_2, zeolites, bentonite, $CuBr_2$, $InCl_3$, metal hydrogen sulfates[37], tetrabutylammonium tribromide, NBS , Ph_3CCl and $LiClO_4$. However, most of the existing methods involve toxic metal ions and solvent and high cost work-up procedures that address these drawbacks are desirable.

An ionic liquid is a salt in which the ions are poorly coordinated, which results in these solvents being liquid below 100°C, or even at room temperature (room temperature ionic liquids, RTIL's). At least one ion has a delocalized charge and one component is organic, which prevents the formation of a stable crystal lattice. The absence of volatility is one of the most important benefits of ionic liquids, offering a much lower toxicity as compared to low-boiling-point solvents. The dipole characteristics of ionic liquids translate into rapid excitation by microwaves, and consequently faster reactions. Ionic liquids not only have the potential to increase chemical reactivity and thus lead to more efficient processes, but are also non-flammable and are less toxic.

In recent years ionic liquids are attracting increasing interest as green recyclable alternative to classical molecular solvents for synthetic organic chemistry. Motivated by these observations, we have accomplished synthesis of bis (indolyl) methanes mediated

by ionic liquid, [bmim] BF_4. The reaction is fairly general, facile and devoid of any side products. The process is environmentally benign. The experimental procedure is very simple.

The initial studies were focused on the optimization of the reaction conditions for the synthesis of bis(indolyl)methanes by choosing the reaction between 2-methylindole 20 and benzaldehyde 21 as a model reaction (Scheme 1). The model reaction was carried out by taking a 2:1 molar ratio of indole and benzaldehyde respectively in Lewis acidic ionic liquid, [bmim]BF_4 was stirred at room temperature for 5.0 hr. Work-up of the reaction mixture afforded phenyl-3′,3′-bis(indolyl)methane 22, in 92% yield. This reaction was also carried out without the catalyst and it was observed that there was no conversion of indole even after 6.0 hr of reaction time. These studies indicate that catalysts are highly active in this present protocol.

3. MATERIALS AND METHOD

In order to show the general applicability and efficiency of this method, different benzaldehydes **2b-j** are allowed to react with two equivalents of 2-methylindole **1** in the same conditions and found that the reaction proceeded smoothly and furnished the corresponding bis(indolyl)methanes **3b-j** in 90-95% yields within 5.0-6.0 hours and the results were recorded in **Table-1.** The influence of electron withdrawing and electron donating substituents on the aromatic ring of aldehydes upon results of the reaction was investigated. Interestingly, the results showed that both electron withdrawing and electron donating substituents had no significant effect on the reaction times and yields. After completion of the reaction (monitored by TLC), the reaction mixture was poured into cold water. The separated solid was filtered, washed with water and purified by silica gel column chromatography to produce pure bis(indolyl)methane derivatives as solids 90-95% yields.

4. CONCLUSION

The present investigation offers a convenient and alternate method for the synthesis of bis(3-methyl-1*H*-indolyl)methane derivatives where the reaction is rapid, the yields are very good, the purity is excellent , the procedure is simple and minimum environmental impact.

Spectral data of 3a-g (Entry Table 1)

Phenyl-3,3′-bis(indolyl)methane (3a): **IR (KBr):** 3451, 1661, 1597, 1445, 1423, 1037, 738 cm^{-1}; **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 5.85 (*s*, 1H, -CH), 6.50-6.60 (d,2H, J=2.4Hz), 7.30-7050 (m, 9H, Ar-H), 7.75 - 7.85 (brs, 2H, NH); **GC-MS:** *m*/*z* 322(M^+).

4-Methylphenyl-3,3′-bis(indolyl)methane (3b): **IR (KBr):** 3447, 1636, 1506, 1457, 1416, 1086, 736 cm^{-1}; **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 2.65 (*s*, 3H, CH_3), 5.65(s, 1H, -CH), 6.35-6.50 (t, 2H, J=7.8Hz), 7.00-7.10 (t, 2H, J=7.8 Hz), 7.10 - 7.20 (m, 4H, Ar-H), 7.20-7.35(m, 4H, Ar-H), 7.80-7.90(brs, 2H, NH); **GC-MS:** *m*/*z* 336(M^+).

4-Methoxyphenyl-3,3′-bis(indolyl)methane (3c): **IR (KBr):** 3396, 1610, 1508, 1454, 1417, 1336, 1244, 1172, 1092, 1024, 783, 742 cm^{-1}; **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 3.75 (*s*, 3H, OCH_3), 5.80 (s, 1H, -CH), 6.60-6.75 (d, 2H, J=2.4 Hz), 6.80-6.90 (t, 2H, J=8.1 Hz), 6.90-7.00 (t, 2H), 7.10-7.15(t, 2H), 7.20-7.40 (m, 6H), 7.80 (brs, 2H, NH); **GC-MS:** *m*/*z* 352(M^+).

4-Nitrophenyl-3,3′-bis(indolyl)methane (3d): **IR (KBr):** 3405, 1708, 1615, 1470, 1421, 1336, 1103, 744 cm^{-1}; **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 5.95 (*s*, 1H, -CH), 6.65-6.75 (d, 2H, J=2.4 Hz), 6.80-6.95 (t, 2H), 7.05-7.15 (t, 2H), 7.20-7.25 (d, 2H, J=8.1 Hz), 7.35-7.40 (d, 2H, J=8.1 Hz), 7.50-7.60 (d, 2H, J=8.0 Hz), 8.05-8.10 (d, 2H, J= 8.0 Hz), 10.45(s, br, 2H, NH); **GC-MS:** *m*/*z* 367 (M^+).

2-Chlorophenyl-3,3′-bis(indolyl)methane (3e): **IR (KBr):** 3412, 3056, 1616, 1093, 742 cm^{-1}; **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 6.35 (*s*, 1H, -CH), 6.60-6.70 (d, 2H, J=2.1 Hz), 6.95-7.05 (t, 2H, J=8.0 Hz), 7.10-7.25 (m, 6H, Ar-H), 7.35-7.45 (m, 4H, Ar-H), 7.95 (s, br, 2H, NH); **GC-MS:** *m*/*z* 356 (M^+).

4-Hydroxyphenyl-3,3′-bis(indolyl)methane (3f): **IR (KBr):** 3441, 1632, 1166, 746 cm^{-1}; **^{1}H-NMR (500 MHz, $CDCl_3$):** δ 4.85 (*s*, 1H, OH), 5.85(s, 1H, -CH) 6.65 (d, 2H), 6.85-6.90 (t, 2H, J=1.6 Hz), 7.00-7.95 (d, 2H, J=7.6 Hz), 7.05-7.15 (m, 3H, Ar-H), 7.20-7.25(d, 2H, J=7.6 Hz), 7.30-7.35(m, 3H, Ar-H), 10.15 (s, br, 2H, NH); **GC-MS:** *m*/*z* 338 (M^+).

2,4-Dimethoxyphenyl-3,3′-bis(indolyl)methane (3g): **IR (KBr):** 3450, 3060, 1620, 1490, 1230, 105, 750 cm^{-1}; **^{1}H-NMR (500 MHz, $CDCl_3$)**: δ 3.75 (*s*, 3H, OCH_3), 3.85 (*s*, 3H, OCH_3), 5.75 (s, 1H, -CH), 6.65-6.75 (d, 2H, J=2.4 Hz), 6.75-6.85 (d, 2H, J=8.0 Hz), 6.85 (s, 1H), 6.90-7.00 (d, 2H, J=8.0 Hz), 7.05-7.15 (t, 2H, J=8.0 Hz), 7.30-7.40 (t, 4H, J= 8.0 Hz), 7.90(s, br, 2H, NH); **GC-MS:** *m*/*z* 382(M^+).

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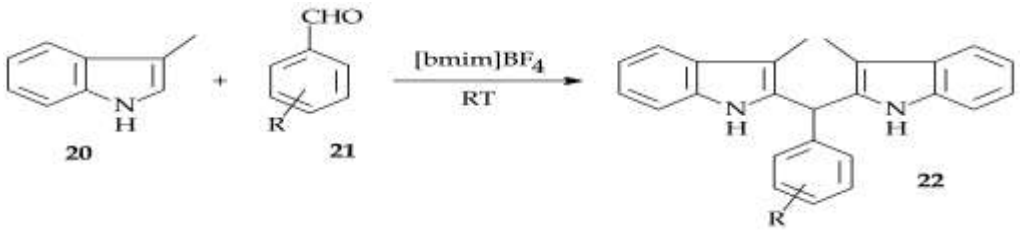
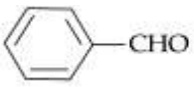
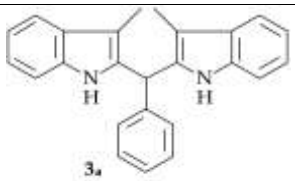
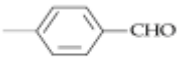
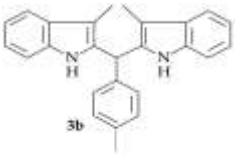
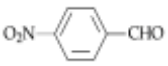
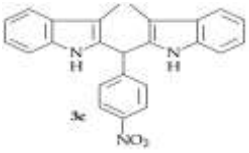
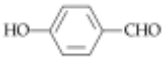
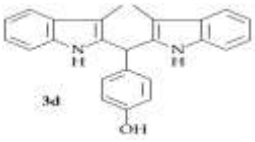
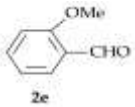
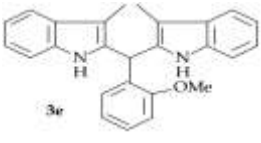


Scheme 1

Table-1: Condensation of 3-methylindole with various aldehydes

Entry	Aldehyde (**21**)	Product (**22**)	Time (hr)	Yield (%)
1	 **2a**	 **3a**	5.0	92
2	 **2b**	 **3b**	5.5	91
3	 **2c**	 **3c**	6.0	94
4	 **2d**	 **3d**	5.0	92
5	 **2e**	 **3e**	5.5	93

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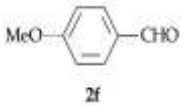
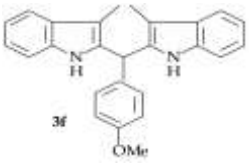
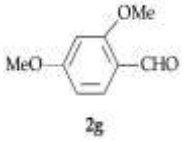
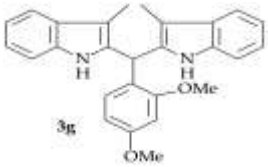
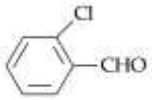
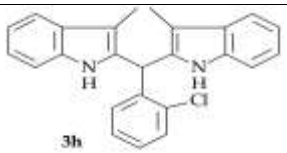
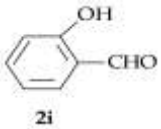
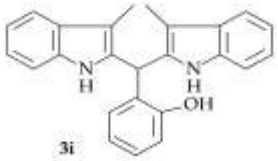
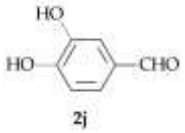
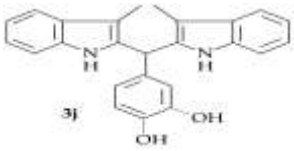
Entry	Aldehyde (**21**)	Product (**22**)	Time (hr)	Yield (%)
6	 2f	 3f	5.5	94
7	 2g	 3g	5.0	95
8	 2h	 3h	6.0	93
9	 2i	 3i	5.5	91
10	 2j	 3j	5.5	93