Communication

Highly Efficient Method for Synthesis of Bis(indolyl)methanes Catalyzed by $FeCl_3$-based Ionic Liquid

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A simple and highly efficient green protocol for synthesis of bis(indolyl)methanes was carried out by the reaction of indole with aldehydes and ketones in the presence of $FeCl_3$-based ionic liquid. These liquids serve as efficient media as well as Lewis acid catalysts.

Keywords: Bisindole; Carbonyl compounds; Ionic liquid; Lewis acid.

INTRODUCTION

Bis(indolyl)methanes, indole and their derivatives are known as important intermediates in organic synthesis and pharmaceutical chemistry and exhibit various physiological properties.[1] Bis(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism[2] and induce apoptosis in human cancer cells. Therefore, there is great interest in the synthesis of these compounds.[3-5] Synthetically the reaction of indole with aldehydes or ketones produces azafulvenium salts that react further with a second indole molecule to form bis(indol-3-yl)methanes.[6] In recent years, synthesis of this class of molecules under mild conditions have been reported, with promoters such as Montmorillonite clay K-10,[7] trichloro-1,3,5-triazine,[8] $AlPW_{12}O_{40}$,[9] sodium dodecyl sulfate (SDS),[10] $ZrCl_4$,[11] I_2,[12] $In(OTf)_3$/ionic liquid,[13] $CuBr_2$,[14] MW/Lewis acids ($FeCl_3$, $BiCl_3$, $InCl_3$, $ZnCl_2$, $CoCl_2$),[15] $NaHSO_4$ and Amberlyst-15,[16] silica sulfuric acid (SSA),[17] metal hydrogen sulfates,[18] $NaHSO_4$/ionic liquid,[19] CAN,[20] NBS,[21] and Ph_3CCl.[22] However, most of the existing methods involve toxic metal ions and solvents, have high costs, use corrosive reagents and have cumbersome work-up procedures. Consequently, new procedures that that address these drawbacks are desirable.

The design of solvent-free reactions and the use of ionic liquids in organic synthesis have gained significant interest.[23] Some of the unique physical and chemical properties of ionic liquids, such as thermal stability, negligible vapour pressure, ability to dissolve a large range of organic and inorganic compounds, increased reaction rate, selectivity and tendency to immobilize starting materials and catalysts, make them an attractive substitute for various volatile organic solvents.

RESULTS AND DISCUSSION

Herein, we report the use of benzyl tributylammonium chloride (BTBAC) at 60 °C as catalyst in the electrophilic substitutions of indole with a variety of aldehydes and ketones to afford bis(indolyl)methanes. The best result based on yield and time of the reaction was obtained with [BTBAC]Cl-$FeCl_3$,[24] $N = 0.5$ (Scheme I).

To investigate the scope and the generality of this new protocol for various aldehydes and ketones under optimized conditions, as shown in Table 1, a series of aromatic, aliphatic aldehydes smoothly underwent electrophilic substitution reaction with indole to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields. The electron deficiency and nature of the substituents on the aromatic ring affect the conversion rate; aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table 1, entries 3, 4, 9) react faster than electron-donating groups (Table 1, entries 2, 8). Furthermore, unsaturated aldehydes, such as cinamaldehyde, give the corresponding bis(indolyl)methanes without polymerization under the above reaction conditions. Ketones required longer reaction times, which is most probably due to the electron-

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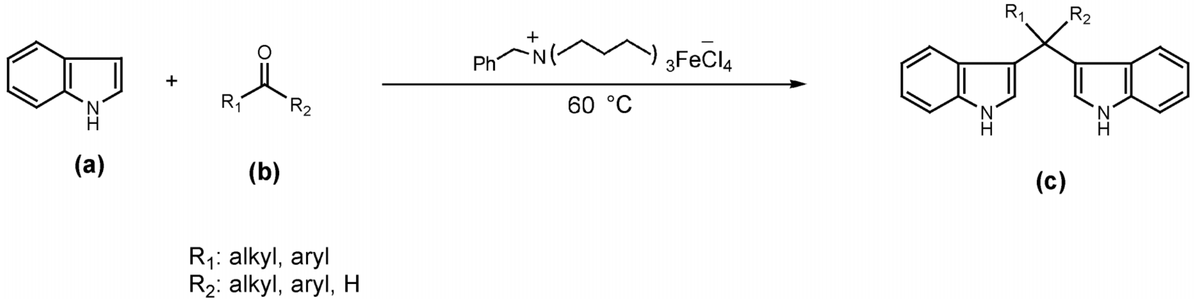
Scheme I



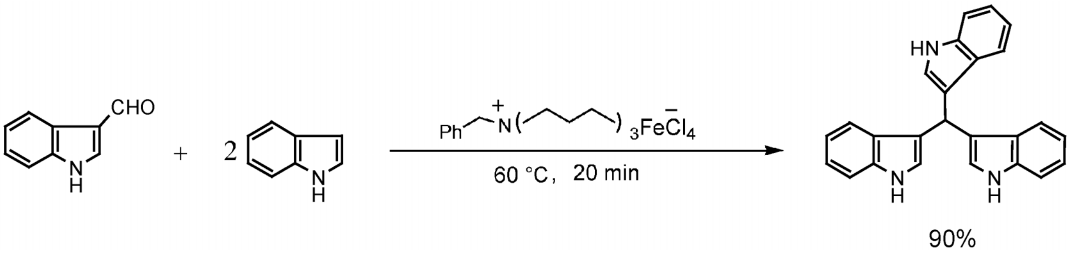
donating and steric effects of the methyl group.

This reaction was further explored for the synthesis of tri-indolylmethane by the condensation of indol-3-carbaldehyde with two equivalents of indole under similar conditions in high yields (Scheme II).

This reaction was further explored for the synthesis of tri(bis-indolyl)methane **e** by the condensation of aldehyde **d** with 6 equivalents indole under similar conditions in high yield (Scheme III).

This method is also highly chemoselective for arylaldehydes in the presence of aliphatic aldehydes and ketones. For example, when a 1:1 mixture of benzaldehyde and acetophenone was allowed to react with indole in the presence of [BTBAC]Cl-$FeCl_3$, it was found that only phenyl-3,3-bis(indolyl)methane was obtained, while acetophenone did not give the corresponding product under these reaction

Scheme II



Scheme III

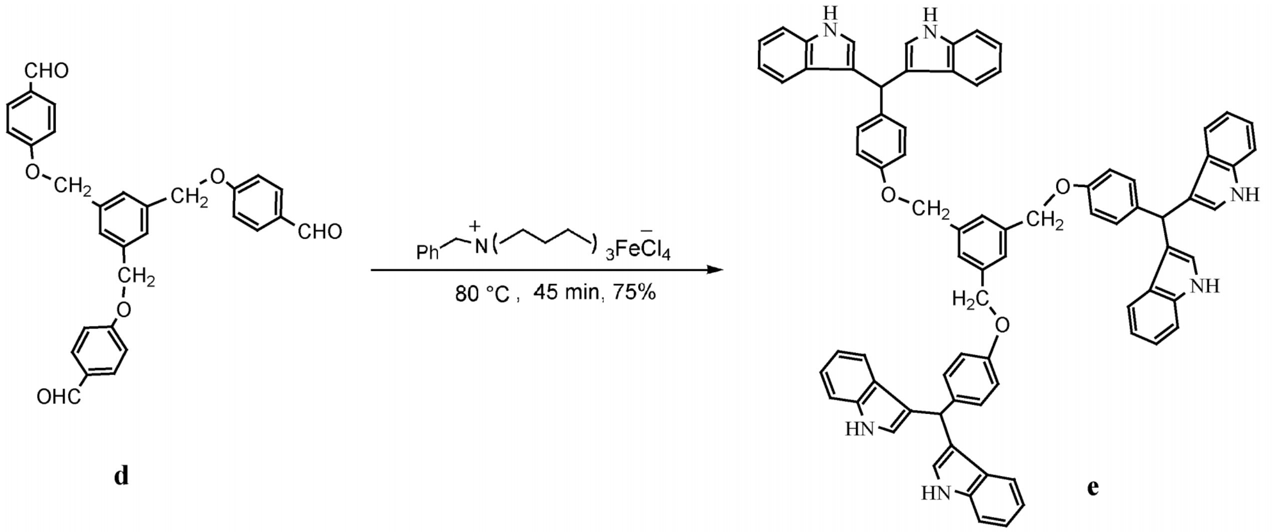
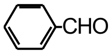
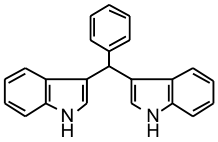
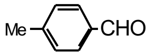
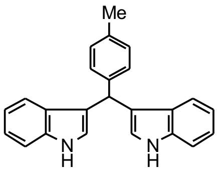
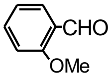
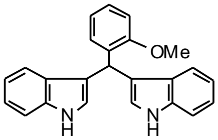
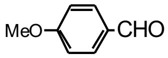
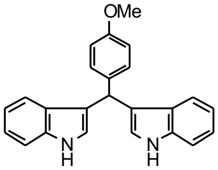
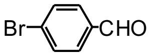
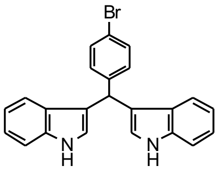
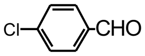
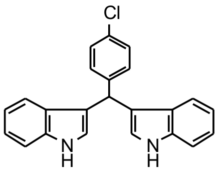
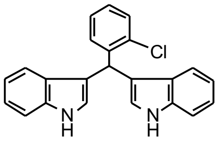
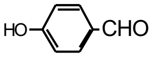
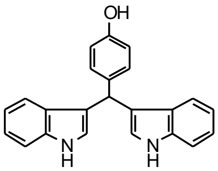
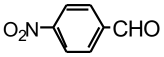
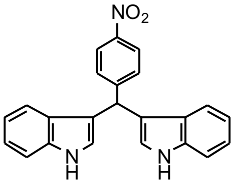
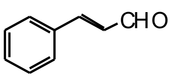
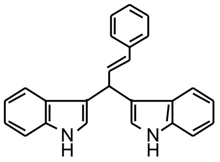
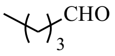
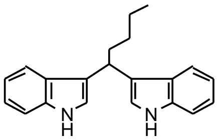
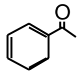
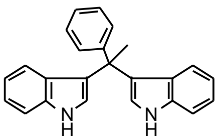
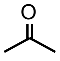
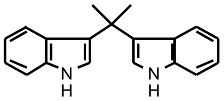
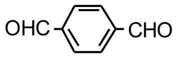
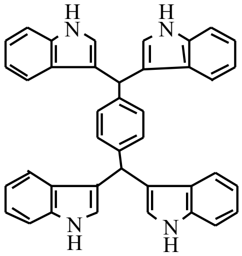


Table 1. Synthesis of bis(indolyl)methanes by the reaction of indole with aldehydes and ketones in the presence of $FeCl_3$-based ionic liquid ($N = 0.5$)

Entry	Substrate	Product	Time (min)	Yield (%)[a]	Refs.
1			10	98	11
2			15	92	11
3			10	98	11
4			15	96	11
5			20	90	25
6			15	95	11
7			8	92	11
8			25	85	11
9			25	95	11

10			15	90	11
11			20	70	11
12			30	85	11
13			30	80	11
14			10	90	11

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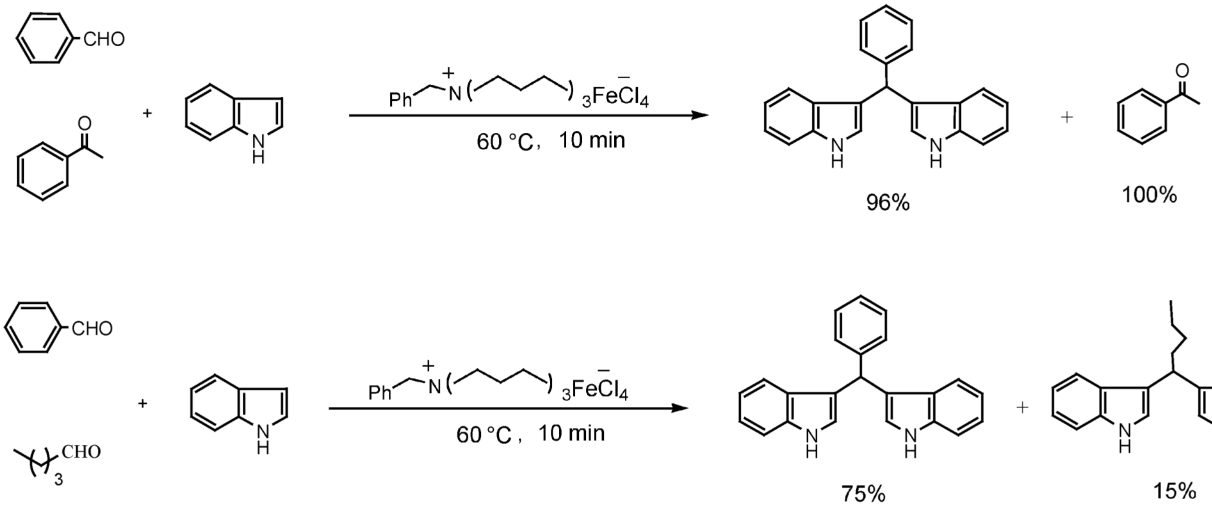
[a] The products were characterized by comparison of their spectroscopic and physical data with those of samples synthesized by reported procedures.

Scheme IV



conditions (Scheme IV). Also, in an equimolar mixture of arylaldehyde and aliphatic aldehyde, it was found that the arylaldehydes were chemoselectively converted to the corresponding bis(indolyl)methane but the aliphatic ones converted only slightly (Scheme IV). The reaction was clean and the products were obtained in high yields without the formation of any side products.

In conclusion, the best results are realized and the utility of the $FeCl_3$-based ionic liquid both as solvent and catalyst is satisfactorily justified. The advantages of this method using $FeCl_3$-based ionic liquid are mild reaction conditions, good to high yield, short reaction time, simple work-up procedure, easy preparation of the catalyst and chemoselectivity. This protocol provides a low cost procedure for the synthesis of these compounds.

EXPERIMENTAL

All commercially available chemicals were obtained from Merck and Fluka companies, and used without further purification unless otherwise stated. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 300 MHz and Jeol 90 MHz FT NMR spectrometer. Infrared (IR) measurements were conducted on a Perkin Elmer GX FT-IR spectrometer.

Preparation of ionic liquid

The [BTBAC]Cl-$FeCl_3$ ionic liquid was prepared by the grinding of benzyl tributyl ammonium chloride (311.94 mg, 1 mmol) with $FeCl_3$ (162.2 mg, 1 mmol) for 2 min; mp = 57-59 °C.

Synthesis of bis(indolyl)methanes catalyzed by [BTBAC]Cl-$FeCl_3$

To [BTBAC]Cl-$FeCl_3$ ($N = 0.5$, 1 mmol), indole (2.0 mmol), aldehyde or ketone (1.0 mmol) were added. The reaction mixture was stirred magnetically, at 60 °C. After complete conversion, as indicated by TLC (hexane/acetone 4:1), the reaction mixture was quenched by adding water (10 mL), extracting with CH_2Cl_2 (3×10 mL), and then the extract was dried with anhydrous $MgSO_4$. The filtrate was evaporated and the corresponding bis(indolyl)methanes were obtained in excellent yields and then recrystallized from ethanol-water to afford pure products (Table 1).

Analytical data for compound 14c

Red solid, mp: 196-197 °C. IR (KBr): 3405, 3049, 2957, 2919, 2851, 2852, 1604, 1455, 1415, 1334, 1218, 1084, 1010, 740 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 5.83 (s, 2H), 6.97 (m, 8H), 7.05 (t, $J = 7.4$ Hz, 4H), 7.28-7.38 (m, 8H), 10.81 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c (ppm) 31.13, 111.90, 118.60, 118.79, 119.63, 121.29, 123.94, 127.18, 128.49, 137.06, 142.82. Ms: *m/z*: 566. Anal. Calcd for $C_{40}H_{36}N_4$: C, 84.80; H, 6.36; N, 9.89. Found: C, 84.46; H, 6.22; N, 6.28.

Analytical data for compound e

Light red solid, mp: 208-210 °C. IR (KBr): 3421, 2950, 2900, 1635, 1506, 1457, 1377, 1216, 1173, 1082, 742 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ_H (ppm) 5.01 (s, CH_2 benzylic, 6H), 5.72 (s, CH, 3H), 6.74-7.50 (m, CH aromatic, 46H), 10.71 (s, NH, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_c (ppm) 40.08, 69.48, 111.85, 114.67, 115.24, 118.54, 118.82, 119.58, 121.25, 123.87, 127.05, 129.66, 137.03, 137.73, 138.15, 156.91. Anal. Calcd for $C_{78}H_{60}N_6O_3$: C, 82.97; H, 5.32; N, 7.44. Found: C, 83.23; H, 4.86; N, 7.02.

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