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An Efficient and Simple Method for Synthesis of bis(indolyl) Methane Catalyzed by Imidazolium Ionic Liquids

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ABSTRACT
A mild and simple procedure is described for the synthesis of bis(indolyl)methane derivatives using ([Cmim]CF3COO) ionic liquid (20 mol%) as an efficient, cheap, and reusable catalyst under mild conditions.

Keywords : 3-carboxymethyl-1-methyl imidazolium trifluoroacetate, Indole, benzaldehyde, Bis(indolyl)methane

Introduction

Indole and its natural and synthetic derivatives are significant heterocyclic compounds due to their wide-ranging biological and pharmaceutical activities.[1 3] Among the different indole derivatives, aryl/alkylbis(indolyl)methanes are well-known as an old but advantaged class of bioactive metabolites,[4 6] due to their representation in natural products[7] and extensive applications in pharmaceuticals.[8] Over the past few years, a variety of bis (indolyl)methanes have been isolated from earthly and marine natural sources such as parasitic bacteria, tunicates, and sponges,[3,9]and these have exhibited antibacterial activity against *Staphylococcus aureus*, *S. albus* and *Bacillus subtilis*,[10] in addition to anti-inflammatory and antibacterial activity.[11]Bis(indolyl)methanes are the most active cruciferous substances for indorsing useful estrogen metabolism.[12] These can be effective in the prevention of cancer and moreover may normalize the abnormal cell growth associated with cervical dysplasia.[13] Therefore, the synthesis of this class of compounds is of considerable interest for synthetic organic chemists (towards the development of new protocols) and biologists. To seek efficient and convenient synthetic routes of bis(indolyl)methanes, great efforts have been made.

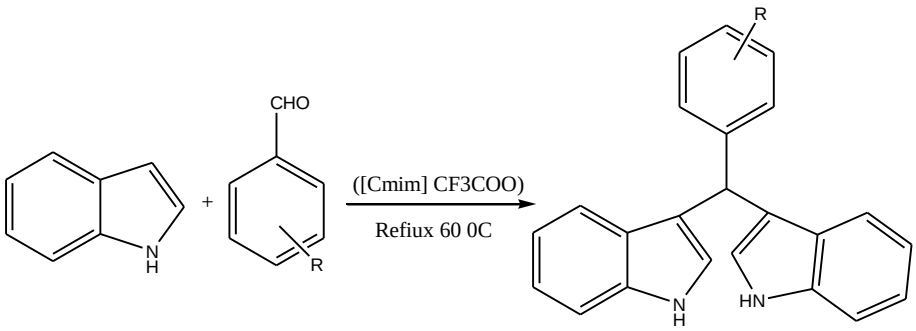
Traditionally, bis(indolyl)methanes have been synthesized by electrophilic substitution reaction of indoleswith carbonyl compounds, catalyzed by either protic or Lewis acids[14,15] such as montmorillonite clay,[16 , 17] oxone,[18] NH_4Cl,[19] cellulose sulfuric acid,[20] ionic liquid,[21] oxalic acid,[22] $La(OTf)_3$,[23] $In(OTf)_3$,[24] zirconium tetrakis(dodecyl sulfate),[25] $H_6P_2W_{18}O_{62}$,[26] phosphated zirconia,[27] 12-tungstophosphoric acid supported on zirconia,[28] $GaCl_3$,[29] ZnO,[30] $FeCl_3.6H_2O$,[31] Al_2O_3,[32]zirconyldodecylsulfate,[33] I_2,[34] silica gel,[35] pyridinium tribromide,[36] $SiO_2/AlCl_3$,[37] Iron(III)

dodecyl sulfate,[38] PPA-SiO_2,[39,40] ammonium niobium oxalate and tetrabutylammonium hydrogen sulfate.[41] The reported methods indicate that the catalysts commonly used for such a transformation, are generally associated with one or more of the following disadvantages such as high toxicity, high cost, difficulty of handling, low thermal stability and un-recyclability. In addition to these drawbacks, tedious methods required for the separation of the products, along with using the environmentally harmful organic solvents in some of these approaches, are definitely far from the concept of "Green Chemistry".

Keeping in view the increasing importance of bis(indolyl)methane derivatives in pharmaceutical and industrial chemistry, there is still much demand to develop a better catalytic process, that would abate the environmental impact of the pollution resulting from the above mentioned methods reported for the synthesis of such significant scaffolds.

Experimental

A mixture of indole (5 mmol) and aromatic aldehydes (5 mmol) and 3- carboxymethyl-1-methyl imidazolium trifluoroacetate ([Cmim]CF3COO) ionic liquid (20 mol%) in 3 ml water solvent was heated under reflux condition for appropriate time. The progress of the reaction was monitored by TLC after completion of the reaction the reaction mixture was cooled and solid formed was filter and recrystallized with ethanol to afford the desired compound in pure form. All the compounds are known compounds and were characterized by spectral data and comparison of their physical data with literature data



Scheme 1 ([Cmim]CF_3COO) ionic liquid synthesis of bis(indolyl)methane

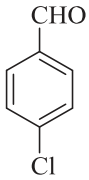
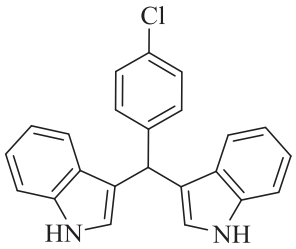
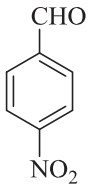
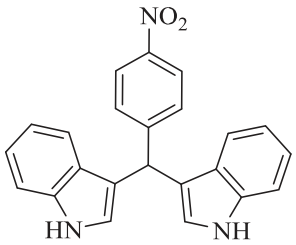
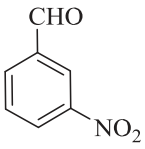
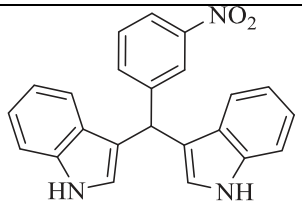
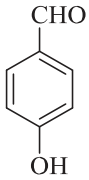
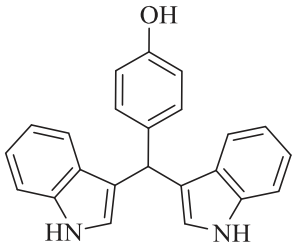
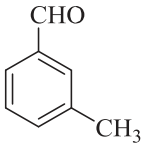
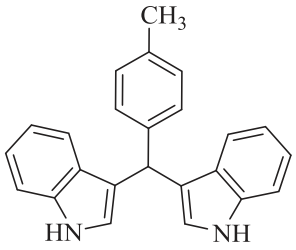
Characterization of selected compounds

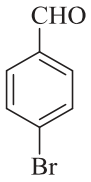
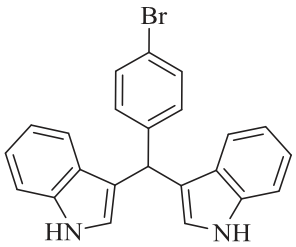
3,3'-(Phenylmethylene)bis(1H-indole) Colorless solid; M. F. C23H18N2; M. p. 128 130 C; IR (KBr): 3412, 3026, 1616, 1598, 850 cm^{-1}.1 H NMR (CDCl3, 400 MHz): dH 10.81 (brs, 2H, NH), 7.36 7.14 (9H, m, ArH), 7.02 (t, 2H, CH), 6.87 6.82 (m, 4H, ArH), 5.82 (s, 1H, CH); 13C NMR (CDCl3, 75 MHz): 143, 136, 128, 126, 126, 123, 121, 119, 110, 40.

3,3'-((4-Chlorophenyl)methylene)bis(1H-indole) (3a) Reddish brown solid; M. F. C23H17ClN2; M. p. 231 233 C; IR (KBr): 3415, 3055, 1490, 1450, 1090 cm^{-1}.1 H NMR (CDCl3, 400 MHz): dH 7.87 (brs, 2H, NH), 7.31 7.24 (m, 8H, Ar-H), 7.11 (d, J ¼ 7.9 Hz, 2H), 7.02 (d, J 8.3 Hz, 2H), 6.72 (s, 2H), 5.84 (s, 1H, Ar-CH); 13C NMR (CDCl3, 75 MHz); 143, 135, 132, 130, 128, 127, 119, 118, 117, 111, 110, 39, 11.

3,3'-((4-Nitrophenyl)methylene)bis(1H-indole) (3b) Red solid; M. F. C23H17N3O2; M. p. 218 220 C; IR (KBr): 3455, 1637, 1506, 1456, 1414, 1341, 1101, 744 cm^{-1}.1 H NMR (CDCl3, 400 MHz): dH 10.95 (brs, 2H, NH), 8.16 (s, 1H, ArH) , 8.08 (d, 1H, ArH) , 7.85 (d, 1H, ArH), 7.58 (t, 1H, ArH), 7.34 (m, 4H, ArH), 7.06 (t, 2H, CH), 6.89 (m, 4H, ArH), 6.07 (s, 1H, CH); 13C NMR (CDCl3, 75 MHz): 153, 146, 137, 129, 124, 123, 121, 119, 118, 112, 40, 39;

Table 1 Synthesis of bis(indolyl)methane in the presence of 1 ([Cmim]CF_3COO) ionic liquid.

Entry	Aldehyde	Product	Time	Yield
a		 3a	20 min	85
b		 3b	27	72
c		 3c	30	68
d		 3d	22	81
e		 3e	26	78

f		 3f	21	82

[a]*Reaction conditions: Aromatic aldehyde(1 mmol), Indole (2 mmol),* ([Cmim]CF_3COO) *(20 mol%) at 60 [0]C under reflux.* [b]*Isolated yield.*

Result and Discussion

Using indole and benzaldehyde as test substrates,the reaction parameters were optimized to determine the optimal condition for the synthesis of bis(indolyl)methanes (Table 1). When Indole (2 mmol) was treated with benzaldehyde (1 mmol) and water (3 ml) for 20 min. in ([Cmim] CF_3COO) (20 mol%) as a catalyst under the reflux corresponding bis(indolyl)methane (3a) was obtained in 85 % yield.

To gauge the scope of this methodology, a variety of substituted aldehydes (2a–j) were reacted with indole 1 in the presence of 20 mol% of ([Cmim] CF_3COO) under reflux to produce the corresponding bis(indolyl)methanes (3a–f, Table 1). The nature of substitution on the aromatic ring showed some effect on product yields and reactions times. Aromatic aldehydes with electron-withdrawing groups at m- and p- positions, provided products in excellent yields with shorter reactions time (Table 1). However, in the case of 3-nitrobenzaldehyde, a low yield of the corresponding product was obtained in longer reaction time (Table 1, entry c). Substrates with electron donating groups took a longer time with moderate yields (Table1)

Conclusion

3- carboxymethyl-1-methyl imidazolium trifluoroacetate ([Cmim]CF3COO) ionic liquid (an inexpensive and eco-friendly catalyst) was found to be an efficient catalyst for the electrophilic substitution reaction of indole with various carbonyl compounds to afford aryl/alkylbis(indolyl) methane derivatives in good to excellent yields. In addition, product isolation is easily accomplished by simple filtration, as the product is insoluble in the solvent. The ionic liquid is easily recovered by the distillation process and further reused three times without change in the yield of the product

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