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A Domino Green Synthesis of Bis(indolyl)methanes Catalyzed by Ionic Liquid $[Et_3NH][HSO_4]$

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Abstract: Indole is one of the privileged molecules of organic chemistry and most of its derivatives are established pharmaceuticals. Because of the interesting biological activities, development of selective protocols for the synthesis of bis(indolyl)methanes is of current interest. In the present work, various electrophilic substitution reactions of indoles with several aldehydes were carried out using an inexpensive and reusable ionic liquid $[Et_3NH][HSO_4]$ as catalyst to afford bis(indolyl)methanes in excellent yields. The optimal reaction conditions were fixed and the products were characterized by FT-IR, ^{1}H-NMR and ^{13}C-NMR studies. The catalytic behavior of Ionic Liquid $[Et_3NH][HSO_4]$ compared with that of conventional catalyst. The ionic liquid was recovered and reused for more than five times without the potential loss in its activity. There is also the possibility of avoiding the use of any reaction medium as solvent less reaction, which is the main theme of this article. The present scope and potential economic impact of the reaction are demonstrated by the synthesis of bis (indolyl) methanes. Remaining challenges and future perspectives of the new transformation are discussed.

Keywords: Domino synthesis**,** green synthesis, ionic liquid, bis (indolyl) methanes, spectral analysis.

Introduction and Experimental

The importance of indoles and their derivatives are well recognized by synthetic as well as biological chemists[1]. Indoles have been widely identified as a privileged structure or pharmacophore with representation in over 3000 natural isolates[2] and are known to possess broad spectrum of biological and pharmaceutical activities[3]. In the past one decade or so several bis(indolyl)methanes have been isolated from natural sources[4]. A few members from this class like vibrindole A have shown promising biological activity[5]. Particularly bis(indolyl)methanes are known to enhance estrogen metabolism in humans and is likely to be drug of choice for breast cancer preventive[6] and antibacterial agent. Bis (indolyl) methanes are the most active cruciferous substances for promoting beneficial estrogen metabolism in women and men[7]. Because of these interesting biological activities and other uses, development of protocols for the synthesis of bis (indolyl)methanes is of current interest.

To achieve facile and efficient production of this group of indoles several Bronsted acids (e.g., HCl, H_2SO_4)[8] or Lewis acids like $AlCl_3$, $BF_3.Et_2O$)[9] and others[10,11,12] have been used. Generally, traditional Lewis acids catalysts are moisture sensitive and are easily decomposed or deactivated in presence of water while in some cases more than stoichiometric amounts of Lewis acids are necessitated because these acids are trapped by nitrogen containing reactants. Therefore to provide efficient synthesis, recently $NaHSO_4$-SiO_2, I_2, NBS, montmorillonite K-10, and rare earth thiflate have also been used in this reaction[13, 14]. Even though various procedures are reported, disadvantages including low yield, prolonged reaction times, use of an excess of reagent/catalyst and formation of hazardous by products during aqueous work-up and at the top of everything majority of them are expensive rare chemicals or needs special preparation, this necessitate further development of an environment benign, economical alternative for the synthesis of bis (indolyl) methanes.

Ionic liquids have attracted extensive research interest in recent years as environmentally benign solvents due to their favorable properties like non-inflammability negligible vapor pressure, reusability and high thermal stability[15].They have also been referred to as designer solvents as their physical and chemical properties could be adjusted by a careful choice of cation and anion. Apart from this they exhibit acidic properties of ionic liquids they are emerging as a 'green reaction media' (catalyst + solvent). The use of ionic liquids as reaction medium may offer a convenient solution to both the solvent emission and catalytic recycling problem [16, 17.]

Our recent interest has been in the development of new synthetic methods on using ionic liquids as reaction media[18, 19, 20, 21, 22]. Following our interest to develop new simple, ecoefficient and environmentally friendly procedures for the synthesis of biologically and pharmaceutically relevant molecules including indole heterocycles, we explored, $[Et_3NH][HSO_4]$ catalyzed electrophilic substitution reactions of indoles with various carbonyl compounds for the one pot efficient synthesis of bis(indolyl)methanes (Scheme 1).

Materials and reagents

All the chemicals were of AR grade and used without further purification unless otherwise stated. All the aromatic aldehydes were obtained from S.D. fine chemicals, Mumbai. Ionic liquid was obtained from Lancaster (UK) and used as received.

Analytical and spectral methods

^{1}H-NMR spectra were recorded in Varian Gemini 300 spectrometer (300MH$_Z$) using tetramethylsilane (TMS) as internal standard. IR spectra were obtained by using Perkin-Elmer 237B infrared spectrometer in KBr discs. Melting points were determined in open capillary and compared with those of authentic samples.

Typical experimental procedure for the synthesis of 3, 3'-bis(indolyl) phenylmethane:

To a solution of ionic liquid $[Et_3NH][HSO_4]$ (142mg, 0.3 mmol) was added indole (234 mg, 2 mmol) and benzaldehyde (106 mg, 1 mmol). The reaction mixture was stirred at 80°C for 20 minutes. After the completion of reaction (TLC, hexane: ethyl acetate, 3:1 v/v), reaction mixture was cooled to RT and solid thus obtained was filtered and washed thoroughly with cold water. Recrystallized with ethanol to afford pure bis(indolyl)phenylmethane, 3a in 95% yield, m.p.147-150°C. [m.p.149-150°C (Sullivan, 1972)].

Scheme 1

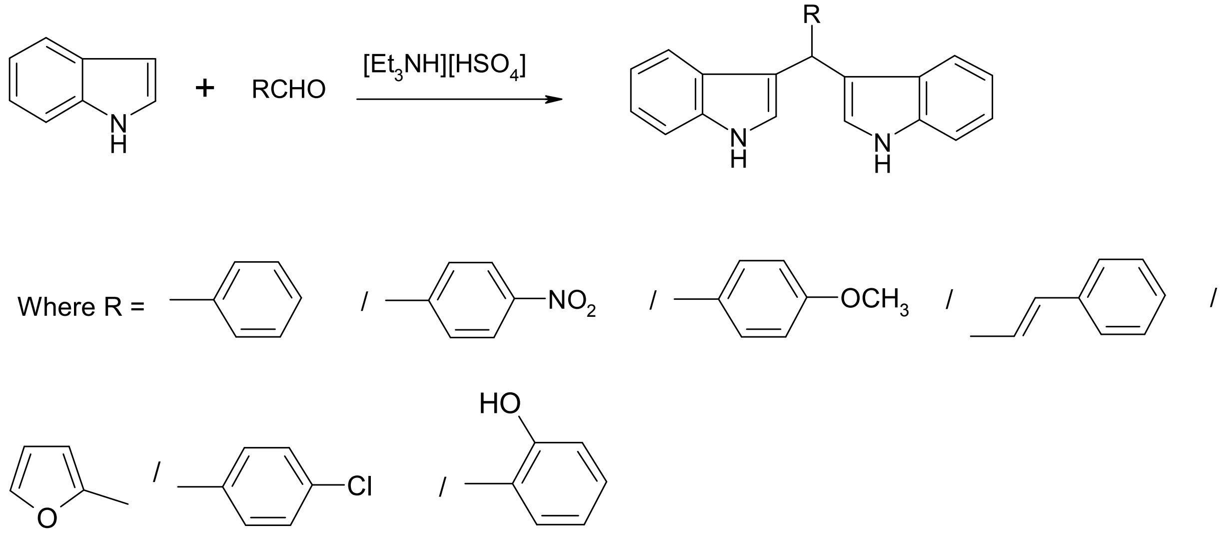


Table 1.Effect of temperature for the synthesis of bis(indolyl)phenyl methanes

S.No.	Temperature °C	Yields (%)
1	RT	62
2	40	67
3	50	77
4	80	95
5	100	92

Table 2. Synthesis of 3a with varied amount of catalyst

S.No.	Catalyst (equiv.)	Time (min)	Yield (%)
1	0.1	50	74
2	0.2	35	81
3	0.3	25	94
4	0.5	20	95
5	1.0	20	95

Table 3. Catalyst recyclables

Run	R	Time (min)	Yield (%)[a]
1st	Ph	25	94
2nd	Ph	25	91
3rd	Ph	25	89
4th	Ph	25	87
5th	Ph	25	83

[a] Yield refers to pure isolated products

Table 4. [Et$_3$NH][HSO$_4$] catalyzed synthesis of bis(indolyl)methanes

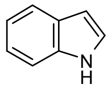
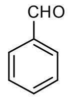
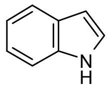
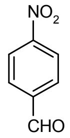
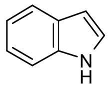
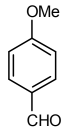
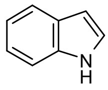
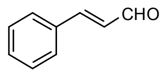
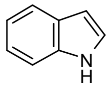
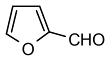
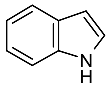
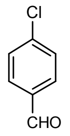
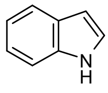
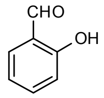
Entry	Product	Indole	Aldehyde	Time (min)	Yield (%)	m.p(°C)
1	3a			25	95	149-150
2	3b			35	93	217-220
3	3c			40	91	185-187
4	3d			40	90	98-99
5	3e			40	87	>300
6	3f			35	86	76-77
7	3g			35	83	122-123

Table 5. Spectral and elemental analyses of the products

Entry	Product	Name	IR (KBr) cm^{-1}	^{1}H NMR (CDCl$_3$) ppm	^{13}C NMR (CDCl$_3$) ppm	EIMS m/z	Anal.	
							Calcd%	Found %
1	3a	3,3’-Bis(indolyl)phenylmethane	3482,3012,1598,1532,1465,1465,1427,1218,1091	δ 5.89(1H,s),6.67(2H,s),7.09-7.58 (13H,m),7.94 (2H,br,s NH)	δ 143.7, 136.4,128.1,126.9,123.4,122.1,120.1,119.1,118.8,110.9,39.8	322(M+)	$C_{23}H_{18}N_2$ C,85.68;H,5.62;N,8.68	C,85.71;H,5.59;N,8.63
2	3b	3,3’-Bis(indolyl)-4-nitrophenylmethane	3481,3023,2917,1612,1533,1461,1425,1231,1206	δ 5.89(1H,s),6.67(2H,d,J=8.2Hz),7.11-7.85(12H,m),7.91 (2H,b,NH)	δ 136.7,130.3,128.4,126.5,123.9,122.2,120.1,119.5,119.5,119.2,111.2,39.7	367(M$^+$)	$C_{23}H_{17}N_3O_2$ C,75.2;H,4.6;N,11.44%	C,75.07;H,4.55;N,11.33%
3	3c	3,3’-Bis(indolyl)-4-methoxyphenylmethane	3485,3021,2848,1616,1517,1465,1411,1326,1221,1094	δ3.79 (3H,s),5.83(1H,s),6.67(2H,d),6.81(2H,d),7.01(2H,t,J=7.2Hz);7.28-7.46(6H,m),7.92(2H,br,sNH)	δ 136.9, 135.8,127.0,123.2,122.1,119.7119.4,119.2,118.7,113.2,111.1,55.3,38.6	352(M+)	$C_{24}H_{20}N_2O$ C,81.79;H,5.72;N,7.95	C,81.67;H,5.62;N,7.82
4	3d	3,3’-Bis(indolyl)styrylmethane	3482,3012,1598,1532,1465,1465,1427,1218,1091	δ4.45 (1H,t,J=13.5),4.5 (2H,d,J=13.5) 6.67(2H,s),7.09-7.58 (13H,m),7.94 (2H,br,s NH)	δ 143.7, 136.4,128.1,126.9,123.4,122.1,120.1,119.1,118.8,110.9,39.8	348(M+)	$C_{25}H_{20}N_2$ C,86.21;H,5.75;N,8.04	C,85.92;H,5.60;N,8.01
5	3e	3,3’-Bis(indolyl)-2-furfurylmethane	3481,3014,2387,1064,1466,1421,1218,1097	δ 5.95(1H,s),6.03(1H,d,J=7.3Hz),6.31(1H,d,J=7.2Hz),6.86(1H,d),7.09(2H,t),7.31-7.52(5H,m),7.96(2H,b,NH).	----	264 (M+)	$C_{17}H_{16}N_2O$ C,77.24,H,6.10,N,10.59,	C,77.31;H,6.16;N,10.53
6	3f	3,3’-Bis(indolyl)-4-chlorophenylmethane	3481,3023,2917,1612,1533,1461,1425,1231,1206	δ 5.89(1H,s),6.67(2H,d,J=8.2Hz),7.11-7.85(12H,m),7.91 (2H,b,NH)	δ 136.7,130.3,128.4,126.5,123.9,122.2,120.1,119.5,119.5,119.2,111.2,39.7	356 (M$^+$)	$C_{23}H_{17}ClN_2$ C,77.41;H,4.80;N,7.85%	C,77.36;H,4.69;N,7.78%
7	3g	3,3’-Bis(indolyl)-2-hydroxyphenylmethane	3485,3021,2848,1616,1517,1465,1411,1326,1221,1094	δ3.79 (1H,s),5.83(1H,s),6.67(2H,d),6.81(2H,d),7.01(2H,t,J=7.2Hz);7.28-7.46(6H,m),7.92(2H,br,sNH)	δ 136.9, 135.8,127.0,123.2,122.1,119.7119.4,119.2,118.7,113.2,111.1,55.3,38.6	338(M$^+$)	$C_{23}H_{18}N_2O$ C,81.66;H,5.32;N,8.25%	C,81.66;H,5.34;N,8.20%

Results and Discussion

In course of optimization of reaction conditions Benzaldehyde (1mmol), indole (2mmol) and [Et_3NH][HSO_4] (0.5mmol) in water were stirred at RT and afforded the 3,3’-bis (1H-indolyl) phenylmethane 3a in 62% yield even after 24 hr. The optimum temperature was found to be 80°C for efficient conversion indicated in (Table 1) which afforded the desired product in 95% yield in 20 minutes.

Further it was investigated that the efficacy of the catalyst and 0.3 eq of catalysts were enough to obtain the optimum yield of bis(indolyl)methanes. Decrease in amount of catalyst affected the reaction time inversely both in terms of yields as well as reaction time (Table 2). Increase in amount of catalyst did not provide any fruitful result (Table 2).

The catalyst efficacy is fairly general and catalyst can be recycled without any considerable loss of reactivity to afford the desired products (Table 3). Products are obtained by simple filtration of the reaction mixture in almost pure form. After removal of the reaction product by filtration, water was removed under reduced pressure to recover the catalyst and the recovered catalyst is used without any further purification.

Table 4 shows the generality of the present protocol for various substituted indoles and a variety of aldehydes to produce bis(indolyl)methanes. Under these conditions the yields were significantly good to excellent (83-95%). Several aromatic aldehydes carrying either electron releasing or electron withdrawing substituent as well as heterocyclic and aliphatic aldehydes afforded the desired product without any side product. The reaction however was highly chemo selective and applicable only to aldehydes and not to ketones. Table 5 displays the spectral (FT-IR, ^{1}H-NMR, ^{13}C-NMR and EIMS and elemental (C, H, N) analysis of the various products obtained. The domino syntheses of different bis (indolyl)methanes were investigated for their efficiency with $[Et_3NH][HSO_4]$ as ionic liquid. The results indicated that $[Et_3NH][HSO_4]$ exhibited excellent catalytic activity for these electrophilic substitution reactions of indoles and better yield (with high degree of purity) under mild reaction conditions than those conventional reactions. After the reaction was over, the ionic liquid was regenerated and reused with no appreciable change in activity.

Conclusion

In conclusion this present domino protocol affords bis(indolyl)methanes in excellent yields employing mild, efficient, environmentally benign, reusable and inexpensive ionic liquid $[Et_3NH][HSO_4]$ as catalyst. In contrast several of the earlier used catalyst are expensive, moisture sensitive, time consuming and are not environmental friendly which is the present day concern. Furthermore this process is wider in scope and is devoid of formation of any by product.

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