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RESEARCH ARTICLE

Synthesis of Bis(indolyl)methanes: A Natural Approach

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Abstract: An efficient and greener synthesis of bis(indoly)methanes was investigated via electrophilic substitution reaction of indole with carbonyl compounds in the presence of lemon juice as natural acid catalyst. The demonstrated environmentally benign protocol provided bis(indoly)methanes under mild reaction conditions, shorter reaction time and in excellent yield with simple work up procedure.

Keywords: Aldehydes, Ketones, Bis(indolyl)methanes, Natural catalyst

Introduction

The scaffolds with indole structures have been found to reflect the various applications in pharmaceuticals[1], material sciences[2] & agrochemicals[3]. The properties include cytotoxic, insecticidal, antibacterial *etc*. Acid catalyzed reactions of electron rich heterocycles such as pyrroles and indoles with *p*-dimethylaminobenzaldehyde is known as Ehrlich test[4]. And azafulvenium salts are produced by the analogous reaction of indoles with aromatic or aliphatic aldehydes and ketones. Further addition of second molecule of indole to azafulvenium salts gives bis(indolyl)methanes[5]. Indoles promote estrogen metabolism both in men & women and also prevents the breast cancer[6]. Literature data reveals that various catalytic systems were employed for the synthesis of bis(indolyl)methanes such as protic acids[7] or Lewis acids[8] via electrophilic substitution reaction of indoles with substituted aromatic or aliphatic aldehydes or ketones. However, lewis acids are required in excess because it is destroyed by the presence of even small mount of moisture or when trapped by nitrogen present in heterocycles[9]. With the aim to find out neat methodology for the synthesis of bis(indolyl)methanes various chemists employed different catalysts[10-30] summarized in Table 1. Though the synthesis of bis(indolyl)methanes achieved by various protocols but still we realize the need of an efficient method which avoid the use perilous solvents, expensive catalytic systems and longer reaction time. Synthesis of bis(indolyl)methanes is also achieved in the absence of catalyst using protic solvents[12] but with great sacrifice of time.

In continuation of our studies to develop neat methodologies in synthetic chemistry[10,29-31], we have investigated here an efficient and environmentally benign protocol for the condensation reaction of indole with various carbonyl compounds to synthesize bis(indolyl)methanes using lemon juice as natural acid catalyst.

Experimental

The required chemicals were purchased from S.D. fine chemicals (India). Melting points were determined by an open capillary method and are uncorrected. The IR spectra were recorded on Shimadzu FT-IR 157 spectrophotometer. ^{1}H NMR spectra were recorded using $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard either on Brucker 300 MHz or 400 MHz NMR spectrophotometer. The chemical shift values are expressed in part per million (ppm). The mass spectra were recorded on EI-Shimadzu-GC-MS spectrometer. The purity of the synthesized compounds was checked by thin layer chromatography (TLC) technique on silica gel plate using hexane and ethyl acetate (9:1).

General procedure for the synthesis of bis(indolyl)methanes ***(3a-q)***

To a mixture of indole (2 mmol) and 4-chloro benzaldehyde (1 mmol) taken in round bottom flask was added 5 mL of lemon juice and the reaction mixture was stirred at room temperature for 20 min. The progress of reaction was checked by TLC. After consumption of reactants, water was added to the reaction mixture and filtered. The crude product so obtained was purified by column chromatography (Ethyl acetate: Hexane, 1:9). All the synthesized compounds were confirmed by comparing their physical and spectral analysis data found in the literature.

*3,3'- Bis(indolyl)phenyl methane (**Entry 1, 3a**)*

Solid, M.P.: 150-155 ^{0}C; IR (KBr)cm^{-1}: 3387, 3047, 2957, 2927, 1482, 1456, 1340, 1095, 736 ; ^{1}H NMR($CDCl_3$, 300 MHz): 5.90(s, 1H), 6.65(s, 2H), 7.00(t, 2H), 7.20-7.24(m, 3H), 7.29-7.31(m, 2H), 7.33-7.37(m, 6H), 7.95(brs, 2H).

*3,3´-Bis(indolyl)-4-nitrophenyl methane (**Entry 6, 3e**)*

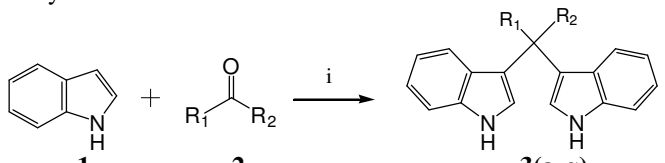
Solid, M.P.: 216-218 ^{0}C; IR (KBr)cm^{-1}: 3420, 3050, 1595, 1510, 1455, 1340.; ^{1}H NMR ($CDCl_3$, 300 MHz): 5.98(s, 1H), 6.70(s, 2H), 7.00-7.05(m, 3H), 7.35(d, 3H), 7.40(d, 2H), 7.50(d, 2H), 8.05(brs, 2H), 8.15(d, 2H).

*3,3'-Bis(indolyl)-4-methyl phenyl methane (**Entry 11, 3k**)*

Solid, M.P.: 94-96 ^{0}C; IR (KBr)cm^{-1}: 3410, 3040, 2930, 1600, 1510, 1215, 1050, 775.; ^{1}H NMR(CDl_3, 300 MHz): 2.35(s, 3H), 5.85(s, 1H), 6.70(s, 2H), 7.05(t, 2H), 7.1(d, 2H), 7.25-7.29(m, 6H), 7.5(d, 2H), 7.98(brs, 2H).

Results and Discussion

We have demonstrated the condensation of indole with various carbonyl compounds via electrophilic substitution reaction affording bis(indolyl)methanes by employing lemon juice as natural acid catalyst.



1 **2** **3(a-q)**

Scheme 1. Reaction Conditions: i) Lemon juice, (*Const.stir, rt, 20 min*)

Lemon juice extract is not only worked as a catalyst but also as solvent media. The reaction was carried out at room temperature via stirring. The completion of the reaction was realized within 20 min (progress of the reaction was monitored by TLC) affording moderate to good yield of bis(indolyl)methanes. We made a successful attempt to explore the efficiency of the methodology towards various aromatic aldehydes with electron withdrawing, releasing and alpha beta unsaturated substituents and ketones. The results are summarized in Table 2.

Various catalytic systems under different reaction conditions were reported[10-30] with an intention to develop efficient methodology for the synthesis of bis(indolyl)methanes (Table 1). But, the literature data acknowledged us about the poor reactivity of ketones and aromatic aldehydes with electron withdrawing substituents towards the condensation reaction with indole in presence of various catalytic systems.

In our investigation, we observed the smooth applicability of the protocol with various substituted aromatic aldehydes. However, ketones required longer reaction times when compared with substituted aromatic aldehydes. The same behavior of ketones towards this reaction is observed regarding various catalytic systems. However, in our previous report[30] we have performed this reaction without use of any catalyst via grinding technique, it required more than 12 h for the completion of reaction with the formation of by products, hence the poor yield of bis(indolyl)methanes (8-10%) was reported.

Table 1. Condensation reaction of indole with various carbonyl compounds to synthesize bis(indolyl)methanes using various catalytic systems and reaction conditions

Entry	Catalysts	Solvents	Temp., ^{0}C	Time, h/ min	Yield[b] %	Ref
1	$InF_3 \cdot H_2O$	Aqueous	r.t	10-15 h	99	[10]
2	Ln $(OTf)_3$	EtOH/H_2O	r.t	12 h	98	[11]
3	NO	a) MeOH	r.t	4-20 h	75	[12]
		b) H_2O	r.t	1-5 h	90	
4	[BMIM] BF_4	Solvent free	100	4 h	trace	[13]
5	Zn (HSO_4)	EtOH	r.t	3-6 h	92	[14]
6	CAN	EtOH	r.t	2-5 h	96	[15]
7	Amberlyst-15	DCM	r.t	3 h	89	[16]
8	$ZrOCl_2 \cdot 8H_2O$/Silica gel	--	50	20-180 min	94	[17]
9	SSA	Solvent free	r.t	1-6 h	95	[18]
10	MontmorilloniteK-10	Solvent free	r.t	1-6 h	97	[19]
11	$Sb_2 (SO_4)_3$	MeOH	r.t	1.3 h	90	[20]
12	Zeolite	DCM	r.t	1 h	85	[21]
13	ZnO	Solvent free	80	45 min	98	[22]
14	$NaBF_4$	Solvent free	r.t	45 min	90	[23]
15	Sulfamic acid	Solvent free	r.t	30 min	95	[24]
16	15-ZTPA	Solvent free	60	30 min	90	[25]
17	Phosphated zirconia	Solvent free	80	20 min	95	[26]
18	alum (K Al $(SO_4)_2$ $12H_2O$)	Solvent free	r.t	10 min	92	[27]
19	HBF_4-SiO_2	Solvent free	r.t	10 min	94	[28]
20	I_2	CH_3CN	r.t	1 min	99	[29]
21	$SnCl_2 \cdot 2H_2O$	Solvent free	r.t	1 min	99	[30]

[b]*Yield of isolated products; r.t= Room temperature*

Table 2. Lemon juice catalyzed condensation reaction of indole with various carbonyl compounds to synthesize the corresponding bis(indolyl)methanes

Entry	Indole 1	Carbonyl compounds 2	BIM **3(a-q)**	Yield, % [a,b]
1	1	PhCHO	**3a**	77
2	1	4-OMePhCHO	**3b**	75
3	1	4-ClPhCHO	**3c**	80
4	1	2-ClPhCHO	**3e**	76
5	1	2, 4-Cl_2PhCHO	**3d**	74
6	1	4-NO_2PhCHO	**3f**	75
7	1	2-NO_2 PhCHO	**3g**	78
8	1	4-OH PhCHO	**3h**	70
9	1	2-OH PhCHO	**3i**	76
10	1	4-Br PhCHO	**3j**	72
11	1	4-Me PhCHO	**3k**	74
12	1	PhCH=CH-CHO	**3l**	69
13	1	CH_3 $(CH_2)_4$-CHO	**3m**	71
14	1	CH_3 $(CH_2)_5$-CHO	**3n**	70
15	1	MeCOMe	**3o**	69
16	1	MeCOPh	**3p**	70
17	1	– $(CH_2)_5$-CO	**3q**	68

BIM- Bis (indolyl) methanes, [a]Yield of the isolated pure product, [b]Products were compared with authentic samples

Conclusion

In the present investigation, we put forth here an efficient and environmentally benign synthesis of bis(indolyl)methanes at room temperature by employing lemon juice as a natural acid catalyst. The efficiency of the methodology towards various carbonyl compounds with ease of work up procedure, fast reaction rate and the excellent yield are of ample evidence to draw the attention of the chemists.

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