



Research Journal of Pharmaceutical, Biological and Chemical Sciences

SnCl₂·2H₂O; a precious addition to catalyst range for synthesis of bis (indolyl) methanes

KA Shaikh ^{*}, ZA Mohammed^a, NT Patel^a, SA Syed^b, Vishal A Patil^b

^{*b}PG department of Organic Chemistry, Sir Sayyad College of Arts, Commerce and Science, Aurangabad (M.S.) India.

^{a,c}PG department of Organic Chemistry, Yeshwant Mahavidyalaya, Nanded (M.S.) India.

ABSTRACT

An efficient, fast and high yielding protocol for the solid -phase synthesis of bis (indolyl) methanes via electrophilic substitution of indoles with various carbonyl compounds catalyzed by stannous chloride dihydrate.

Keywords: Indoles; aldehydes; ketones; bis (indolyl) methanes; stannous chloride dihydrate.

****Corresponding author***

Email: shaikh_kabeerahmed@rediffmail.com,

INTRODUCTION

Presently the world is facing with the lot of issues related to the environment. So a good chemist should adopt the neat and ecofriendly protocols for the synthesis of molecules. Advantages of solid state reactions observed to be occurring efficiently and more selectively than the solution reaction [1] the reason might be the regular and tight arrangement of molecules in a crystal.

Indoles and their derivatives are known to exhibit applications in pharmaceuticals [6], material sciences [7] & agrochemicals [8]. 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 [9]. 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 [10]. Indoles promote estrogen metabolism both in men & women and also prevents the breast cancer [11].

In recent years, $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ is frequently used in organic synthesis [2] as a catalyst due to its properties such as nontoxic nature, easy availability, inexpensiveness and easiness for work up procedures. It played a great role for the synthesis of biologically active heterocycles such as benzimidazoles [3], Quinoxalines [4] & functionalization of 4, 5-diaminopyrazoles [5].

Common route for the synthesis of bis (indolyl) methanes are electrophilic substitution reaction of indoles with the aromatic or aliphatic aldehyde and ketones catalyzed by protic acids [12] or Lewis acids [13]. However, Lewis acids are required in excess because it is destroyed by the presence of even small amount of moisture or when trapped by nitrogen present in heterocycles [14].

To overcome these limitations various researchers developed novel methodologies for the synthesis of bis(indolyl)methanes such as use of $\text{InF}_3 \cdot \text{H}_2\text{O}$ [15], $\text{Ln}(\text{OTf})_3$ [16], $(\text{BMIM})\text{BF}_4$ [17], $\text{Zn}(\text{HSO}_4)_3$ [18], CAN [19], Amberlyst-15 [20], $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ [21], SSA [22] etc the detailed study about the catalytic systems utilized by different researchers for the synthesis of bis (indolyl) methanes are summarized in Table 1.

Despite of having these varieties of methodologies for the synthesis of bis (indolyl) methanes, still we find the problems of longer reaction time, use of hazardous solvents & expensive catalytic systems. Synthesis of bis (indolyl) methanes is also achieved in the absence of catalyst using protic solvents [23] but with great sacrifice of time. Longer reaction times, use of expensive catalytic systems, perilous solvents and formation of side products increases our curiosity for the development of extremely rapid and efficient synthesis of bis (indolyl) methanes.

In our previous studies, we have reported the use of inexpensive, non hazardous molecular iodine [34] as a catalyst for the synthesis of bis (indolyl) methanes in good to excellent yields. We have also introduced hydrate of indium trifluoride ($\text{InF}_3 \cdot \text{H}_2\text{O}$) [15] as a catalyst for the synthesis of bis (indolyl) methanes.

A green methodology for solid phase synthesis of bis (indolyl) methanes using $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ catalyst via electrophilic substitution reaction of indoles with various carbonyl compounds has been reported.

EXPERIMENTAL

All melting points were recorded using open capillary method and are uncorrected. The purity of the compound is checked by TLC on silica gel and purified by column chromatography.

General procedure

A mixture of indole (2 mmol) and benzaldehyde (1mmol) were crushed in a mortar with a pestle at room temperature, then $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (20 mol %) was added and crushed. Progress of the reaction was checked by TLC, the reaction was completed within one minute. The water was added to the reaction mixture and filtered. The crude product so obtained is purified by column chromatography (Ethyl acetate: Hexane, 1:9). Melting points of all the products were authenticated on comparison with those found in literature.

3,3'- Bis(indolyl) phenyl methane (**3a**): Solid, m.p.150-155 °C : IR (KBr) cm^{-1} : 3387, 3047, 2957, 2927, 1482, 1456, 1340, 1095, 736 ; ^1H 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 (**3f**): Solid, m.p. 216-218 °C; IR (KBr) cm^{-1} ; 3420, 3050, 1595, 1510, 1455, 1340.; ^1H 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 (**3k**): Solid, m.p. 94-96 °C; IR (KBr) cm^{-1} : 3410, 3040, 2930, 1600, 1510, 1215, 1050, 775.; ^1H NMR(CDCl_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).

RESULT AND DISCUSSION

In the present study we made the use of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ as an efficient catalyst for the synthesis of bis (indolyl) methanes by the condensation of indoles with various carbonyl compounds (Scheme 1).

The reaction is carried out in mortar via solid-phase and completed within 1 min providing us the excellent yields. The generality of the reaction is authenticated by the use of

aromatic aldehydes with electron withdrawing, electron releasing and alpha beta unsaturated substituents and also variety of ketones. Further we explored our studies for the acid derivatives of indoles (1^a and 1^b), as expected acid derivatives of indoles also found to possess smooth applicability over electrophilic substitution reaction to furnish bis (indolyl) methanes. The results are summarized in Table 2.

Table-1 Synthesis of bis (indolyl) methanes using various catalysts

Entry	Catalyst	Solvents	Temp. (°C)	Time (%)	Yield ^b	lit
1	InF ₃ .H ₂ O	Aqueous	R.T	10-15 hrs	99	15
2	Ln (OTf) ₃	EtoH/H ₂ O	R.T	12 hrs	98	16
3	NO	a) MeOH b) H ₂ O	R.T	4-20 hrs 75	23	
4	[BMIM] BF ₄	solvent free	100	4 hrs	trace	17
5	Zn (HSO ₄)	EtoH	R.T	3-6 hrs	92	18
6	CAN	EtoH	R.T	2-5 hrs	96	19
7	Amberlyst-15	DCM	R.T	3 hrs	89	20
8	ZrOCl ₂ .8H ₂ O/ Silica gel	--	50	20-180 min	94	21
9	SSA	solvent free	R.T	1-6 hrs	95	22
10	Montmorillonite K-10	solvent free	R.T	1-6 hrs	97	24
11	Sb ₂ (SO ₄) ₃	MeOH	R.T	1.3 hrs	90	25
12	Zeolite	DCM	R.T	1 hrs	85	26
13	ZnO	solvent free	80	45 min	98	27
14	NaBF ₄	solvent free	R.T	45 min	90	28
15	Sulfamic acid	solvent free	R.T	30 min	95	29
16	15-ZTPA	solvent free	60	30 min	90	30
17	Phosphated Zirconia	solvent free	80	20 min	95	31
18	Alum (K Al (SO ₄) ₂ 12H ₂ O)	solvent free	R.T	10 min	92	32
19	HBF ₄ -SiO ₂	solvent free	R.T	10 min	94	33
20	I ₂	CH ₃ CN	R.T	1 min	99	34

^bYield of isolated products

Previous studies shows that it requires longer reaction time for ketones and aromatic aldehydes with electron withdrawing substituents but on use of SnCl₂.2H₂O, We observed the rapid completion of reaction (< 1 min, TLC) with all substituents providing excellent yields except for ketones which consume somewhat longer reaction time and low yield as compare to others.

Table 2. SnCl₂·2H₂O catalyzed synthesis of bis (indolyl) methanes

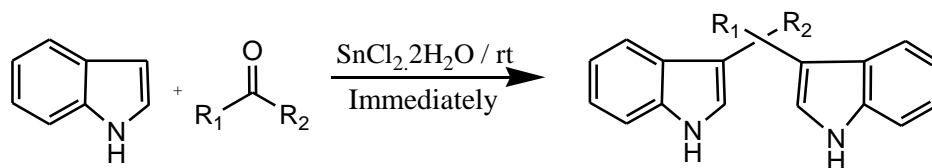
Entry	Indoles 1	Carbonyl compounds 2	Products 3	Yield (%) ^{a,b}
1	1	a. PhCHO	a	99
2		b. 4-OMePhCHO	b	98
3		c. 4-ClPhCHO	c	98
4		d. 2-ClPhCHO	d	95
5		e. 2, 4-Cl ₂ PhCHO	e	96
6		f. 4-NO ₂ PhCHO	f	99
7		g. 2-NO ₂ PhCHO	g	98
8		h. 4-OH PhCHO	h	99
9		i. 2-OH PhCHO	i	96
10		j. 4-Br PhCHO	j	98
11		k. 4-Me PhCHO	k	95
12		l. PhCH=CH-CHO	l	97
13		m. CH ₃ (CH ₂) ₄ -CHO	m	95
14		n. CH ₃ (CH ₂) ₅ -CHO	n	96
15		o. MeCOMe	o	87
16		p. MeCOPh	p	85
17		q. – (CH ₂) ₅ -CO	q	85
18	1a	a ¹ . 4-NO ₂ PhCHO	a ¹	99
19		b ¹ . 4-OMe PhCHO	b ¹	98
20	1b	a ² . 4-NO ₂ PhCHO	a ²	99
21		b ² . 4-OMe PhCHO	b ²	97

^aYield of the isolated pure product. ^bProducts were compared with authentic samples. ^{1a}Indole 3-acetic acid.
^{1b}Indole 3-propionic acid

Table 3. Catalytic evolution for the synthesis of 3a

Entry	SnCl ₂ ·2H ₂ O (Mol %)	Time (Min)	Yield ^a (%)
1	No catalyst	12 ^b	Trace
2	5	20	Trace
3	10	10	50
4	20	01	99
5	30	01	99
6	40	01	99

^b = time in hour, ^a = isolated yield of the product.



Scheme 1

Reactions were carried out using indole and benzaldehyde at different molar ratios of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ for the optimization of the catalyst. We come to know that only 20 mol % of catalyst is sufficient for the fruitful completion of reaction. The catalytic study is shown in Table 3.

However, we have carried this reaction without use of catalyst, we found it requires more than 12 hrs for the completion of reaction with the formation of by products, hence the poor yield of bis (indolyl) methanes (8-10%) is reported.

CONCLUSIONS

In conclusion, we have demonstrated the simplest and rapid method for the synthesis of bis (indolyl) methanes by using $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ as a novel catalyst. The smooth applicability of the catalyst for various carbonyl compounds, short reaction time and simple workup procedures with excellent yields are the promising features of this methodology.

ACKNOWLEDGMENT

The authors are thankful to **Prof. Mohammed Tilawat Ali** for providing facilities for the research work.

REFERENCES

- [1] Toda F. Springer New York 2002.
- [2] a. Rai G, Jeong JM, Lee YS, Kim HW, Lee DS, Chung JK, Lee MC. *Tetrahedron Lett* 2005, 463: 987.
 b. Raffy Q, Recoux R, Mahy J-P *Tetrahedron Lett* 2008; 49: 1865.
 c. Roy UK, Roy S. *Tetrahedron*, 2006; 62: 678.
 d. Gonzalo JR, Tejedor JL, Parra TL, Diaz C. *Tetrahedron* 2006; 62: 3355.
 e. Barros AIRNA and Silva AMS. *Tetrahedron Lett* 2003; 44: 5893.
 f. Chemburkar SR, Deming KC, Reddy RE. *Tetrahedron* 2010; 66: 1955.
- [3] Wu Z, Philip R and Wickham G. *Tetrahedron Lett* 2000; 41: 9871.
- [4] Shi DQ, Dou GL, Ni SN, Shi JW, Li XY. *J Heterocyclic Chem* 2008; 45: 1797.
- [5] Blass BE, Srivastava A, Coburn KR, Faulkner AL and Seibel WL. *Tetrahedron Lett* 2003; 44: 3009.
- [6] Sundberg RJ. Academic Press New York 1970.

- [7] a. Jayaraj MK, Antony A, Ramachandram M. 2000; 25: 227.
b. Minne SC, Manalis SR, Quate CF. Appl. Phys Lett 1995; 67: 3918.
- [8] Plimmer JR, Gammon DW, Ragsdale NN. Johan Wiley and Sons New York 2003; 3.
- [9] Morgan L, Schunior R. J Org Chem 1962; 27: 3693.
- [10] Jones R, Bean G. Academic press London 1977.
- [11] Karthik M, Tripathi AK, Gupta NM, Murugeson V. Catal Commun 2004; 5: 371 & cited papers.
- [12] a. Auria M. Tetrahedron 1991; 47:44: 9225.
b. Kamal A, Qureshi AA Tetrahedron 1963; 19: 513.
- [13] Babu G, Sridhar N, Perumal PT. Synth Commun 2000; 30: 1609.
- [14] Kobayashi S, Araki M, Yasuda M. Tetrahedron Lett 1995; 36:32: 5773.
- [15] Bandgar BP, Shaikh KA. J Chem Res 2004; 34.
- [16] Chen SD, Yu L and Wang PG. Tetrahedron Lett 1996; 37:26, 4467.
- [17] Kurosh RM and Masoumeh Sharifi-kiasaraaie. Tetrahedron 2009; 65: 8816.
- [18] Niknam K, Zolfigol MA, Sadabadi T, Nejati A. Journal of the Iranian Chemical Society 2006; 3:4, 318.
- [19] Zeng XF, Ji SJ, Wang SY. Tetrahedron 2005; 61: 10235.
- [20] Chimmani R, Banerjee J, Pal R, Das B. Adv Synth Catal 2003; 345: 557.
- [21] Firouzabadi H, Iranpoor, Jafarpour M, Ghaderi A. J Mol Catal A: Chem 2006; 253: 249.
- [22] Pore DM, Desai UV, Thopate TS and Wadgaonkar PP. Arkivoc 2006; 12: 75.
- [23] Deb ML, Bhuyan PJ. Tetrahedron Lett 2006; 47: 1441.
- [24] Chakrabarthy M, Ghosh, Basak R, Harigaye Yoshihiro. Tetrahedron Lett 2002; 43: 4075.
- [25] Srinivasa A, Varma PP, Hulikal VJ, Mahadevan KM. Monatshefte fur Chemie 2008; 139: 111.
- [26] Reddy AV, Ravinder K, Reddy VLN, Goud TV, Ravikanth V, Venkateswarlu Y. Synth Commun 2003; 33:21, 3687.
- [27] Mona Hosseini-Sravari. Synth Commun 2008; 38: 832.
- [28] Kamble VT, Bandgar BP, Bavikar SN Chin J Chem 2007; 25: 13.
- [29] Tao AL, Ding FQ, Zou JP, Lu XH, Zhang LL. Chin J Chem 2007; 822.
- [30] Satam JR, Parghi KD, Jayaram RV. Catal Commun 2008; 9: 1071.
- [31] Nadkarni SV, Gawande MB, Jayaram RV, Nagarkar JM. Catal Commun 2008; 9: 1728.
- [32] Sonar SS, Sadaphal SS, Kategaonkar AH, Pokalwar RU, Shingate BB, Shingare MS. Bull Korean Chem Soc 2009; 30:4, 825.
- [33] Bandgar BP, Patil AV, Kamble VT. Arkivoc 2007; 16: 252.
- [34] Bandgar BP, Shaikh KA. Tetrahedron Lett 2003; 44: 1959.