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An Efficient and Eco-Friendly Synthesis of Bis (Indolyl) Methanes in Aqueous Medium

Azhar A.R. Antule, Shoyab Hamid Kazi, Abrar Shaikh and Mohammed Zamir Ahmed*

Organic Chemistry Research Laboratory, Poona College of Arts, Science & Commerce, Pune-411001, Maharashtra, India.

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ABSTRACT

An electrophilic substitution reaction of indole with variety of carbonyl compounds catalyzed by stannous chloride dihydrate in presence of aqueous medium has been investigated. The offered green method provided the target molecules in better yields and less reaction time at room temperature.

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Introduction

In recent years, Indole moieties engrossed the chemists and biologists due to their applications in pharmaceuticals, material sciences & agrochemicals [1-3]. Acid catalyzed reactions of electron rich heterocycles such as pyrroles and indoles with *para*-dimethylaminobenzaldehyde is known as Ehrlich test [4] and the analogous reaction of indoles with aromatic or aliphatic aldehydes and ketones produces azafulvenium salts. Further addition of second molecule of indole to azafulvenium salts gives bis (indolyl) methanes [5]. Literature data reveals that various catalytic systems were employed for the synthesis of bis (indolyl) methanes such as protic acids [6] or lewis acids [7] via electrophilic substitution reaction of indoles with substituted aromatic or aliphatic aldehydes or ketones [8-28]. 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. 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 of 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 [10] but with great sacrifice of time.

Organic reactions in aqueous media attracted the attention of the chemists due to able properties of water as a solvent media in synthetic chemistry [29]. Many reagents, catalysts & organic substrates are either sensitive towards water or decomposed or deactivated in it's presence, but still it is realized that the extensive use of water as a cheap, safe non-toxic solvent is greatly appreciated in organic processes to reduce the cost and to develop the environmentally benign and green protocols [30]. In addition to this, the ease in work up procedure by utilizing the water soluble catalysts & water insoluble products encouraged the chemists to step up with water promoted reactions in organic synthesis.

Exploring our efforts to develop neat methodologies in the field of synthetic chemistry [31], we have investigated here an efficient and environmentally benign protocol for the synthesis of bis (indolyl) methanes in aqueous medium in presence of stannous chloride dihyrate.

Experimental

The chemicals required to carry out this research work 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).

Typical procedure for the synthesis of bis (indolyl) methanes (3a-m)

To a mixture of indole (2 mmol) and 4-Nitro benzaldehyde (1 mmol) taken in round bottom flask was added 5 ml of water and catalytic amount of stannous chloride dihydrate. The reaction mixture was stirred at room temperature for 90 min. The progress of reaction was checked by TLC. After completion of the reaction, the solid product was extracted with ethyl acetate and the solvent was removed under vacuum. The crude product so obtained is purified by column chromatography (Ethyl acetate: Hexane, 1:9). The synthesized compounds were authentified 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); MS (m/z): 322.40

3,3'-Bis(indolyl)-4-Chloro phenyl methane (Entry 3, 3c)

Solid, M.P.: 94-96 ^{0}C; IR (KBr) cm^{-1}: 3410, 3040, 2930, 1600, 1510, 1215, 1050, 775.; ^{1}H NMR ($CDCl_3$, 300 MHz): 5.83(s,

Tele:

E-mail: mohammedzameer_chem@rediffmail.com

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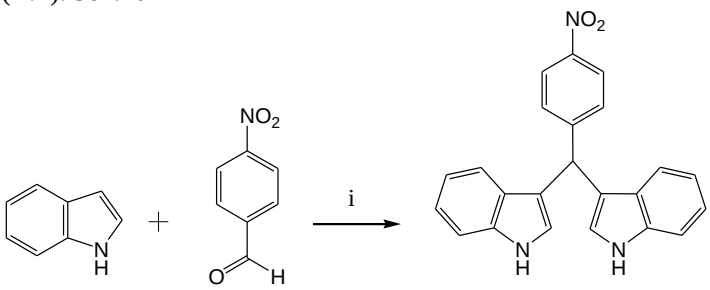
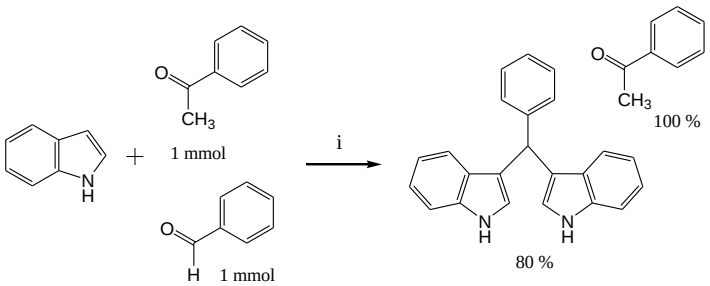
1H), 6.50(s, 2H), 7.05(t, 2H), 7.1(d, 2H), 7.25-7.29(m, 6H), 7.5(d, 2H), 7.98(br, s, 2H, -NH); MS (m/z): 355.1

3,3'-Bis(indolyl)-4-nitrophenyl methane (Entry 6, 3f)

Solid, M.P.: 216-218 ^{0}C; IR (KBr) cm^{-1}: 3420, 3050, 1595, 1510, 1455, 1340.; ^{1}H NMR ($CDCl_3$, 300 MHz): 5.99 (s, 1H), 6.82 (s, 2H), 6.87-7.59 (m, 12H), 8.11 (br, s, 2H, -NH); MS (m/z): 367.20



Scheme 1. Reaction Conditions: i) $SnCl_2{\cdot}2H_2O$, water, stir, rt, 90 min, 80 %



Reaction Conditions: i) $SnCl_2{\cdot}2H_2O$, water, stir, rt, 90 min, 80 %

Scheme 2. Chemoselectivity of indole in reaction with benzaldehyde in presence of acetophenone

Table 1. Synthesis of bis (indolyl) methanes in aqueous medium

Entry	Indole 1	Carbonyl compounds 2	BIM 3 (a-m)	Yield (%) [a,b]
1	1	PhCHO	**3a**	80
2	1	4-OMePhCHO	**3b**	74
3	1	4-ClPhCHO	**3c**	80
4	1	2-ClPhCHO	**3d**	79
5	1	2, 4-Cl_2PhCHO	**3e**	76
6	1	4-NO_2PhCHO	**3f**	80
7	1	2-NO_2 PhCHO	**3g**	78
8	1	4-OH PhCHO	**3h**	68
9	1	2-OH PhCHO	**3i**	65
10	1	Thiophene-2-aldehyde	**3j**	75
11	1	Pyridine-2-aldehyde	**3k**	78
12	1	CH_3COCH_3	**3l**	60
13	1	$C_6H_5COCH_3$	**3m**	55

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

Results and Discussion

While carrying out the reactions of indole with carbonyl compounds we come to know that, this electrophilic substitution reaction can be made to occur more efficiently by using water as solvent medium in presence of catalytic amount of stannous chloride **(Scheme 1,** as a model reaction**)**.

The reaction was performed at room temperature via stirring. The consumption of the reactants was observed since 30 min but the complete reaction or disappearance of the reactants was observed after 90 min as evidenced by thin layer chromatography. We utilized various carbonyl compounds to check the applicability of this methodology and the results are in agreement to declare the presented method as a fruitful approach for the development of environmentally benign and eco-friendly protocols in organic synthesis. The results are summarized in **Table 1.**

We have mentioned few of the distinguished reports out of the box, available in the literature regarding the synthesis of bis (indolyl) methanes which includes the use of hazardous solvents, expensive catalytic systems and tedious work up procedures [8-28]. Herein, we observed the similar trend i.e. smooth reactions for aromatic aldehydes than ketones. However, in our previous report [31c], we have performed this reaction by using lemon extract as a natural catalyst. We have also investigated the synthesis of these molecules without use of any catalyst via grinding technique but it required 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%) was reported.

In addition to this, we have also investigated the chemoselectivity of the present protocol by the competitive reaction of aldehyde in presence of acetophenone **(Scheme 2)**.

Conclusion

In this research article, we introduced water as a solvent medium for the reaction between indole and various substituted carbonyl compounds in presence of stannous chloride dihydrate. Water promoted reactions, now a day's creating the diversion for the chemists towards green chemistry and could be a fertile approach for the development of environmentally benign and eco-friendly protocols in organic synthesis.

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References

[1] R. J. Sundberg. Academic Press; New York (1970).

[2] (a) M. K. Jayaraj, A. Antony, M. Ramachandram. See the special issues on transparent conducting oxides. MRS bulletin August issue, 25 (2000) 227-235.

(b) S. C. Minne, S. R. Manalis, C. F. Quate, "Parallel atomic force microscopy using cantilevers with integrated piezoresistive sensors and integrated piezoelectric actuators," Appl. Phys. Lett**.,** 67 (1995) 3918-3920.

[3] J.R. Plimmer, D.W. Gammon, N.N. Ragsdale, "Encyclopedia of agrochemicals," John Wiley and Sons, New York. 3 (2003).

[4] L. Morgan, R. Schunior, "The Chemistry of Neuraminic Acids. I. The Ehrlich Reaction," J. Org. Chem., 27 (1962) 693.

[5] R. Jones, G. Bean, "The chemistry of pyrroles," Academic press, London (1977).

[6] (a) M. Auria, "Photochemical synthesis of diindolylmethanes," Tetrahedron, 47(44) (1991) 9225-9230.

(b) A. Kamal, A.A. Qureshi, "Synthesis of some substituted di-indolyl methanes in aqueous medium at room temperature," Tetrahedron, 19 (1963) 513-520.

[7] G. Babu, N. Sridhar, P.T. Perumal, "A Convenient Method of Synthesis of bisindolylmethanes: Indium trichloride catalyzed reactions of indoles with Aldehydes and Schiff's bases," Synth. Commun**.,** 30 (2000) 1609.

[8] B.P. Bandgar, K.A. Shaikh, "Organic reaction in aqueous media: InF_3 catalyzed synthesis of bis (indolyl) methanes in water under mild conditions," J. Chem. Res., (2004) 34-36.

[9] S. Depu. Chen, Libing Yu and P.G. Wang, "Lewis Acid-Catalyzed Reactions in protic media. Lanthanide-Catalyzed Reactions of Indoles with Aldehydes & Ketones," Tetrahedron Lett., 37(26) (1996) 4467-4470.

[10] M.L. Deb, P.J. Bhuyan, "An efficient and clean synthesis of bis (indolyl) methanes in a protic solvent at room temperature," Tetrahedron Lett., 47 (2006) 1441-1443.
[11] R.M. Kurosh and Masoumeh Sharifi-kiasaraaie, "Indole 3-alkylaton/vinylation under catalysis of guanidium ionic liquids," Tetrahedron, 65 (2009) 8816-8820.
[12] K. Niknam, M.A. Zolfigol, T. Sadabadi, A. Nejati, "Preparation of Indolylmethanes catalyzed by Metal hydrogen Sulfates," Journal of the Iranian Chemical Society, 3(4) (2006) 318-322.
[13] X.F. Zeng, S.J. Ji, S.Y. Wang, "Novel method for synthesis of unsymmetrical bis (indolyl) alkanes catalyzed by Ceric ammonium nitrate (CAN) under ultrasonic radiation," Tetrahedron, 61 (2005) 10235-10241.
[14] R. Chimmani, J. Banerjee, R. Pal, B. Das, "Silica supported sodium hydrogen sulfate and amberlyst-15: Two efficient heterogeneous catalysts for the synthesis of Bis and Tris (1*H*-indole-3-yl) methanes from indoles and carbonyl compounds," Adv. Synth. Catal., 345 (2003) 557-559.
[15] H. Firouzabadi, N. Iranpoor, M. Jafarpoor, A. Ghaderi, "$ZrOCl_2.8H_2O$/silica gel as a new efficient and highly water-tolerant catalyst system for facile condensation of indoles with carbonyl compounds under solvent free conditions," J. Mol. Catal. A: Chem., 253 (2006) 249-251.
[16] D.M. Pore, U.V. Desai, T.S. Thopate and P.P. Wadgaonkar, "A mild expedient, solvent less synthesis of bis (indolyl) alkanes using silica sulfuric acid as a reusable catalyst," Arkivoc, 12 (2006) 75-80.
[17] M. Chakrabarthy, N. Ghosh, R. Basak, Harigaye Yoshihiro, "Dry reaction of indoles with carbonyl compounds on montmorillonite K-10 clay: a mild, expedient synthesis of diindolylalkanes and Vibriindole A," Tetrahedron Lett., 43 (2002) 4075-4078.
[18] A. Srinivasa, P.P. Varma, V.J. Hulikal, K.M. Mahadevan, "Antimony (III) sulfate catalyzed condensation reaction of indoles with carbonyl compounds," Monatshefte fur Chemie, 139 (2008) 111-115.
[19] A.V. Reddy, K. Ravinder, V.L.N. Reddy, T.V. Goud, V. Ravikanth, Y. Venkateswarlu, "Zeolite catalyzed synthesis of bis (indolyl) methanes," Synth. Commun., 33(21) (2003) 3687-3694.
[20] Mona Hosseini-Sravari, "Synthesis of Bis (indolyl) methanes using a catalytic amount of ZnO under solvent free conditions," Synth. Commun., 38 (2008) 832-840.
[21] V.T. Kamble, B.P. Bandgar, S.N. Bavikar, "Highly efficient synthesis of Bis (indolyl) methanes catalyzed by Sodium Tetraflouroborate," Chin. J. Chem., 25 (2007) 13-15.
[22] A.L. Tao, F.Q. Ding, J.P. Zou, X.H. Lu, L.L. Zhang, "An efficient and solvent free reaction for synthesis of Bis (indol-3-yl) methanes catalyzed by Sulfamic acid," Chin. J. Chem., (2007) 822-827.
[23] J.R. Satam, K.D. Parghi, R.V. Jayaram, "12-Tungstophosphoric acid supported on zirconia as an efficient and heterogeneous catalyst for the synthesis of bis (indolyl) methanes and tris (indolyl) methanes," Catal. Commun., 9 (2008) 1071-1078.
[24] S.V. Nadkarni, M.B. Gawande, R.V. Jayaram, J.M. Nagarkar, "Synthesis of bis (indolyl) methanes catalyzed by surface modified Zirconia," Catal. Commun., 9 (2008) 1728-1733.
[25] S.S. Sonar, S.S. Sadaphal, A.H. Kategaonkar, R.U. Pokalwar, B.B. Shingate, M.S. Shingare, "Alum Catalyzed Simple and Efficient Synthesis of Bis (indolyl) methanes by Ultrasound Approach," Bull. Korean Chem. Soc., 30(4) (2009) 825.
[26] B.P. Bandgar, A.V. Patil, V.T. Kamble, "Flouroboric acid adsorbed on silica gel catalyzed synthesis of bisindolyl alkanes under mild and solvent free conditions," Arkivoc, 16 (2007) 252-259.
[27] B.P. Bandgar, K.A. Shaikh, "Molecular iodine –catalyzed efficient and highly rapid synthesis of bis (indolyl) methanes under mild conditions," Tetrahedron Lett., 44 (2003) 1959-1961.
[28] K.A. Shaikh, Z.A. Mohammed, N.T. Patel, S.A. Syed, Vishal A. Patil, "$SnCl_2{\cdot}2H_2O$; a precious addition to catalyst range for synthesis of bis (indolyl) methanes," RJPBCS, 1(4) (2010) 730.
[29] (a) C.J. Li, T.H. Chan, "Organic Reactions in Aqueous Media," John Wiley and Sons, New York, (1997).
(b) P.A. Grieco, "Organic Synthesis in Water," Blackie Academic and Professional, London, (1998).
[30] Seyed Mohammad Vahdat, Samad Khaksar and Saeed Baghery, "An Efficient One-Pot Synthesis of Bis (Indolyl) methanes Catalyzed by Ionic Liquid with Multi-SO_3H Groups under Ambient Temperature in Water," World Applied Sciences Journal, 15(6) (2011) 877-884.
[31] (a) Mohammed Zamir Ahmed, N.T. Patel, K.A. Shaikh, M.A. Baseer, Shaikh Shahid, Vishal A. Patil, "Atom efficient grinding technique for the synthesis of hydrazones catalyzed by citric acid," Elixir Org. Chem., 43, (2012) 6583-6585.
(b) Mohammed Zameer Ahmed, N.T. Patel, K.A. Shaikh, M.M. Kendre, Shaikh Shahid, M.A. Baseer, "Green Protocols for the Synthesis of Hydrazones," J. Chem. & Cheml. Sci., 2(1), (2012) 13-19.
(c) Mohammed Zamir Ahmed, C.B. Khillare, Shaikh Kabeer Ahmed, "Synthesis of Bis(indolyl)methanes: A Natural Approach," Chemical Science Transactions, 2(4) (2013) 1513-1517.