## Facile Synthesis of Bis(indolyl)alkanes Catalyzed by Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O Under Solvent Free Conditions

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Abstract: Copper perchlorate hexahydrate is found to be an efficient catalyst for the electrophilic substitution of indole with carbonyl compounds to prepare bis(indolyl)methane derivatives without solvent in excellent yield at room temperature.

Keywords: Bis(Indolyl)methanes, carbonyl compounds, Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O, indole,.

The importance of indole and its derivatives is well known in the field of medicinal chemistry and biology [1]. Bis(indolyl)alkanes are naturally occurring biologically useful class of compounds. Many of their biologically important derivatives were isolated from terrestrial and marine natural sources [2]. For example, vibrindole A (3,3'-diindolyl-ethane) possesses antibacterial properties and 3, 3'-diindolyllakanes therefore, is receiving significant interests in drug design. The electrophilic substitution reaction of indole with carbonyl compounds catalyzed by acid is one of the attractive methods for this synthesis. Many reagents such as acetic acid [4], InCl<sub>3</sub> [5], In(OTf)<sub>3</sub> [6], InF<sub>3</sub> [7], Dy(OTf)<sub>3</sub> [8], Ln(OTf)<sub>3</sub> [9], LiClO<sub>4</sub> [10], ZrCl<sub>4</sub> [11] TBATB [12], FeCl<sub>3</sub> [13], NBS [14], KHSO<sub>4</sub> [15], NaHSO<sub>4</sub> . SiO<sub>2</sub> [16],

Copper perchlorate hexahydrate is an inexpensive Lewis acid reported to catalyze many organic reactions for example *O*-, *N*-, and *S*- acetylation [33], hydrocyanation of aldehydes [34], addition of indole to alkylidene malonates [35], and so on [36]. However, this reagent has never been reported as a catalyst for the electrophilic substitution reaction of indole with carbonyl compounds. Herein we wish to report the use of copper perchlorate hexahydrate as a catalyst for this substitution reaction which was found very effective for clean and fast formation of corresponding bis(indolyl)methanes without any solvent (Scheme 1).

In the present typical reaction conditions [37], carbonyl compounds were mixed well with indole and catalytic amounts of  $Cu(ClO_4)_2.6H_2O$ . Reaction mixtures were then kept at room temperature for required time and the pro-



**Scheme 1.** Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O catalyzed synthesis of bisindolylmethanes.

PPh<sub>3</sub>.HClO<sub>4</sub> [17], CAN [18], zeolites [19], clay [20], H<sub>3</sub>PMo<sub>12</sub>O<sub>40</sub>.xH<sub>2</sub>O [21], CuBr<sub>2</sub> [22], Cu(BF<sub>4</sub>)<sub>2</sub>.SiO<sub>2</sub> [23], CuSO<sub>4</sub>.5H<sub>2</sub>O [24], trichloro-1,3,5-triazine [25], hexamethylenetetraamine-bromine [26], ion-exchange resin [27], ionic liquids in combination with In(OTf)<sub>3</sub> or FeCl<sub>3</sub> . 6H<sub>2</sub>O [28], Bi(NO<sub>3</sub>)<sub>3</sub>.5H<sub>2</sub>O [29], oxalic acid dehydrate [30], fluoroboric acid on silica [31], and boric acid [32] etc. have been used to carry out this transformation. However, some of the reported methods have some drawbacks like, use of expensive reagents, longer reaction times, low yields of products, and use of additional microwave energy. Therefore new reagents and mild conditions for this reaction are still interesting. gresses were monitored by TLC. Aldehydes were observed to be more reactive than ketones as acetone and cyclohexanone (Table 1) have shown formation of products in moderate yield with longer reaction times. 5 mole % amount of catalyst to the aldehydes was observed sufficient for this conversion in 5 to 20 minutes with high yield at room temperature. The effect of electron donating and electron withdrawing substituents on the aromatic ring of aldehydes did not show huge differences in the reactivity.

We also have studied the solvents effect on this catalyst by performing the reactions of p-Nitrobenzadehyde and anisaldehyde with indole in Methanol, THF, Dichloro-methane and acetonitrile (Table 2). Consequently it was observed that, in methanol no reactions occurred until 5hrs for both the cases. In THF and dichloromethane, the reactions were clean but the formation of products was very slow. Acetoni-

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Entry	Carbonyl compounds	Time (min)	Yield <sup>a</sup> (%)	Ref. <sup>b</sup>
a	СНО	5	94	[20]
b	МеО-СНО	8	98	[11]
с		10	95	[26]
d	СІ——СНО	10	95	[26]
e	F————————————————————————————————————	10	96	[31]
f	Br — CHO	10	95	[29(a)]
g	но — Сно	10	90	[12]
h		5h	57	[11]
i	0=	5h	55	[10]

 Table 1
 Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O-Catalyzed Synthesis of Bis(indolyl)methane Derivatives

<sup>a</sup>Isolated yields.

<sup>b</sup>All products were characterized by comparing their <sup>1</sup>H NMR data and melting points of solids with the literature reports.

## Table 2. Studied Solvents and Conditions

Entry	Solvent	Time	Yield (%)
1	Neat	5-30 minutes	50-97
2	MeCN	40 minutes	80
3	THF	4h	90
4	MeOH	5h	trace
5	$CH_2Cl_2$	4h	90

trile was proved to be the best choice since the reactions were at similar rate as neat but gave lower yields and trace amount of a side product was observed due to the reaction of nitrile and indole.

In conclusion, we have described a novel efficient method for the electrophilic substitution of indole with carbonyl compounds using copper perchlorate hexahydrate as a catalyst at room temperature without solvent. This method is rapid, clean, high yielding and possesses easy work up protocol. Solvent free conditions have established this procedure as nature friendly.

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## REFERENCES

- Sundberg, R.J. *The Chemistry of Indoles*, Academic press: New York, **1970**.
- [2] Bell, R.; Carmelli, S.; Sar, N. Vibrindole A, a Metabolite of the Marine Bacterium, Vibrio parahaemolyticus, Isolated from the Toxic Mucus of the Boxfish Ostracion cubicus. J. Nat. Prod., 1994, 57, 1587-1590.
- [3] Hong, C.; Firestone, G.L.; Bjelanes, L.F. Bcl-2 family-mediated apoptotic effects of 3,3'-diindolylmethane (DIM) in human breast cancer cells. *Biochem. Pharmacol.* 2002, 63(6), 1085-1097.
- [4] Kamal, A.; Qureshi, A.A. Synthesis of substituted diindolylmethanes in aqueous medium at room temperature. *Tetrahedron*, **1963**, *19*, 513-520.
- [5] Babu, G.; Sridhar, N.; Perumal, P.T. A convenient method of synthesis of bis-indolylmethanes: Indium trichloride-catalyzed reactions of indole with aldehydes and Sciff's bases. *Synth. Commun.*, 2000, 30, 1609-1614.
- [6] Nagarajan, R.; Perumal, P.T. InCl3- and In(OTf)<sub>3</sub>- catalyzed reactions: Synthesis of 3-acetyl indoles, bisindolylmethane and indolylquinoline derivatives. *Tetrahedron*, 2002, 58, 1229-1232.
- [7] Bandgar, B.P.; Shikh, K.A. Organic reactions in aqueous medium: InF3 catalyzed synthesis of bis(indolyl)methanes in water under mild conditions. J. Chem. Res. Synop., 2004, 1, 34-36.
- [8] Mi, X-L.; Luo, S-Z.; He, J-Q.; Cheng, J-P. Dy(OTf)<sub>3</sub> in ionic liquid: An efficient catalytic system for reaction of indole with aldehydes / ketones or imines. *Tetrahedron Lett.*, 2004, 45, 4567-4570.
- [9] Chen, D.; Yu, L.; Wang, P.G. Lewis acid-catalyzed reactions in protic media. Lanthanide catalyzed reactions of indoles or ketones. *Tetrahedron Lett.* **1996**, *37*, 4467-4470.
- [10] Yadav, J.S.; Subba Reddy, B.V.; Murthy, C.V.S.R.; Kumar, G.M.; Madan, Ch. Lithium perchlorate-catalyzed reactions of indoles: An expeditious synthesis of bis(indolyl)methanes. *Synthesis*, 2001, 5, 783-787.
- [11] Zhang, Z.H.; Yin, L.; Wang, Y.M. An Efficient and Practical Process for the Synthesis of Bis(indolyl)methanes Catalyzed by Zirconium Tetrachloride. *Synthesis*, 2005, 12, 1949-1954.
- [12] Lin, X.F.; Cui, S.-L.; Wang, Y.G. Mild and Efficient Synthesis of bis-Indolylmethanes Catalyzed by Tetrabutylammonium Tribromide. Synth. Commun., 2006, 36, 3153-3160.
- [13] Xia, M.; Wang, S-H.; Yuan, W-B. Lewis Acid Catalyzed Electrophilic Substitution of Indole with Aldehydes and Schiff's Bases Under Microwave Solvent-Free Irradiation. *Synth. Commun.*, 2004, 34(17), 3175-3182.
- [14] Koshima, H.; Matsuaka, W. N-Bromosuccinimide catalyzed condensations of indoles with carbonyl compounds under solvent free conditions. J. Heterocycl. Chem., 2002, 39, 1089-1091.
- [15] Nagarajan, R.; Perumal, P. T. Potassium hydrogen sulfatecatalyzed reactions of indoles: A mild expedient synthesis of bisindolylmethanes. *Chem. Lett.*, 2004, 33, 288-289.
- [16] Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. Silica supported sodium hydrogen sulfate and amberlyst-15: Two efficient heterogeneous catalysts for facile synthesis of bis- and tris(1H-indole-3yl)methanes from indoles and carbonyl compounds. *Adv. Synth. Catal.*, 2003, 345, 557-559.
- [17] Nagarajan, R.; Perumal, P.T. Electrophilic substitution of indoles catalyzed by triphenyl phophonium perchlorate: synthesis of 3acetyl indoles and bis-indolylmethane derivatives. *Synth. Commun.*, 2002, 32, 105-109.
- [18] Ramesh, C.; Rabindranath, N.; Das, B. Electrophilic substitution reactions of indoles with carbonyl compounds using ceric ammonium nitrate: A novel and efficient method for the synthesis of diand tri-indolylmethanes. J. Chem. Res. Synop., 2003, 1, 72-74.
- [19] Karthik, M.; Tripathi, A.K.; Gupta, N.M.; Palanichamy, M.; Murugesan, V. Zeolite-catalyzed electrophilic substitution reactions of indoles with aldehydes: Synthesis of bis(indolyl)methanes. *Catal. Commun.*, 2004, 5, 371-375.
- [20] Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. Dry reactions of indoles with carbonyl compounds on montmorilonite K10 clay: A mild expedient synthesis of diindolylalkanes and vibrindole A. *Tetrahedron Lett.*, 2002, 43, 4075-4078.

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- [21] Zolfigol, M. A.; Salehi, P.; Shiri, M. An efficient procedure for the preparation of mono- and di-bis-indolyl methanes catalyzed by molibdatophosphoric acid. *Phosphorus, Sulfur Silicon Relat. Elem.*, 2004, 179, 2273-2277.
- [22] Mo, L.P.; Ma, Z-C.; Zhang, Z-H. CuBr<sub>2</sub> catalyzed synthesis of Bis(indolyl)methanes. *Synth. Commun.*, 2005, 35, 1997-2004.
- [23] Meshram, G.A.; Patil, V.D. Simple and efficient method for synthesis of Bis(indolyl)methanes with Cu(BF<sub>4</sub>)<sub>2</sub>.SiO<sub>2</sub> under mild conditions. *Synth. Commun.*, 2010, 40, 29-38.
- [24] Suresh, D. K.; Sandhu, J.S. CuSO<sub>4</sub>.5H<sub>2</sub>O, A novel and efficient catalyst for the synthesis of Bisindolylmethanes. *J. Ind. Chem Soc.*, 2009, 86, 488-490.
- [25] Sharma, G.V.M.; Reddy, J.J.; Lakshmi, P.S.; Krishna, P.R. A versatile and practical synthesis of bis(indoyl)methanes/bis(indolyl)glycoconjugates catalyzed by trichloro-1,3,5-triazine. *Tetrahedron Lett.*, **2004**, *45*, 7729-7732.
- [26] Bandgar, B.P.; Bettigeri, S.V.; Joshi, N.S. Hexamethylenetetraamine-bromine-catalyzed rapid and efficient synthesis of bis(indolyl)methanes. *Monatsh. Chem.*, 2004, 135, 1265-1273.
- [27] Feng, X-L.; Guan, C-J.; Zhao, C-X. Ion exchange resin-catalyzed condensation of indole and carbonyl compounds-Synthesis of bisindolylmethanes. *Synth. Commun.*, 2004, 34, 487-492.
- [28] Ji, S-J.; Zhou, M-F.; Gu, D-G.; Wang, S-Y.; Loh, T-P. Efficient synthesis of bis(indolyl)methanes catalyzed by Lewis acids in ionic liquids. *Synlett*, **2003**, *13*, 2077-2079.
- [29] (a) Khodaei, M.M.; Mohammadpoor-Baltork, I.; Memarian, H.R.; Khosropour, R.; Nikofar, K.; Ghanbary, P. Synthesis of 3substituted indole promoted by activated method catalyzed by Bi(NO<sub>3</sub>)<sub>3</sub>: 5H<sub>2</sub>O. J Heterocyclic Chem., 2008, 45, 1-5.; (b) Deodhar, D.K.; Bhat, R.P.; Samant, S.D. Bismuth(III) nitrate pentahydrate: an efficient catalyst for the synthesis of bis(indolyl)methanes under mild condition. Ind. J Chem. Sec B: Org Chem including Med. Chem., 2007, 46B, 1455-1458.; (c) Iglesias, L.; Aguliar, C.; Bandyopadhyay, D.; Banik, B.K. A new Bismuth nitrate-catalyzed electrophilic substitution of indoles with carbonyl compounds under solvent free conditions. Synth. Commun., 2010, 40, 3678-3682.
- [30] Ghorbani-Vaghei, R.; Veisi, H.; Keypour, H.; Dehghani-Firouzabadi, A.A. A practical and efficient synthesis of bis(indolyl)methanes in water, and synthesis of di-, tri-, and tetra(bis-indolyl)methanes under thermal conditions catalyzed by oxalic acid dehydrate. *Mol. Divers.*, 2010, 14(1), 87-96.
- [31] Bandgar, B.P.; Patil, A.V.; Kamble, V.T. Fluoroboric acid absorbed on silica gel catalyzed synthesis of bisinolyl alkanes under mild and solvent-free conditions. *ARKIVOC*, 2007, *xvi*, 252-259.
- [32] Yadav, J.S.; Gupta, M.K.; Jain, R.; Yadav, N.N.; Reddy, B.V.S. A practical synthesis of bis(indolyl)methanes employing boric acid. *Monatsh Chem.*, 2010, 141, 1001-1004.
- [33] Jeyakumar, K.; Chand, D.K. Copper perchlorate: Efficient acetylation catalyst under solvent free conditions. *Journal of Molecular Catalysis A: Chemical*, 2006, 255, 275-282.
- [34] Majhi, A.; Kim, S.S.; Kim, H.S. Copper perchlorate hexahydrate: a highly efficient catalyst for the cyanosilylation of aldehydes. *Appl. Organometal. Chem.*, 2008, 22, 407-411.
- [35] Zhou, J.; Tang, Y. Sidearm effect: Improvement of the enantiomeric excess in the asymmetric Michael addition of indoles to alkylidene malonates. J. Am. Chem. Soc., 2002, 124, 9030-9031.
- [36] Dalpozzo, R.; Bartoli, G.; Sambri, L.; Melchiorre, P. Perchloric acid and its salts: very powerful catalysts in organic chemistry. *Chem. Rev.*, 2010, 110, 3501-3551.
- [37] General Procedure: In a small vial, Indole (1mmol), carbonyl compounds (0.5 mmol) and 10mg (5% to the carbonyl compounds) of Cu(ClO<sub>4</sub>)<sub>2</sub>.6H<sub>2</sub>O were placed and mixed well with a spatula. Within minutes, the reaction mixtures were turned to a dark colored oily paste which was then kept at room temperature for appropriate time. The progression was monitored by TLC by dissolving small amount in dichloromethane. After completion, dichloromethane (15mL) was added and the solution was washed with water (5mL).The separated organic part was dried over anhydrous sodium sulfate, concentrated in vacuo and purified by column chromatography over silica using ethyl acetate:hexane(4:6) as eluent. The yields for individual products are given in Table 1.