

Highly efficient synthesis of bis(indolyl)methanes in water

Najmodin Azizi^b, Lalleh Torkian^a, Mohammad R. Saidi^{a,*}

^a Department of Chemistry, Sharif University of Technology, P.O. Box 11465-9516, Tehran, Iran

^b Chemistry and Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, Iran

Received 16 April 2007; received in revised form 16 May 2007; accepted 17 May 2007

Available online 21 May 2007

Abstract

A simple, atom economy and highly efficient green protocol have been developed for synthesis of bis(indolyl)alkane by the reaction of indole derivatives with aldehydes and ketones in the presence of small amount of the heteropoly acids in water.

© 2007 Elsevier B.V. All rights reserved.

Keywords: Bisindole; Environmental friendly; Heteropoly acid; Indole; Water

1. Introduction

There has been tremendous interest to develop highly efficient transformations for the preparation of organic compounds, as well as, biologically active materials, with potential application in the pharmaceutical or agrochemical industries, from the commercially available compounds. There is also a need for synthetic chemists to find new, efficient, and strategically important processes, which are environmentally benign and lead to the greater structural variation in a short period of time with high yields and simple work up procedure. For this reasons, over the last few year's enormous advances have been made to chemical processes to achieve the ultimate goal of hazard-free, waste-free, and energy-efficient synthesis [1]. In this context, organic reaction in water has played an important role in these processes and several organic reactions have been shown that are accelerate in water [2–6].

Indole framework is present in many substances commonly found in nature [7,8], as well as in many compounds that show pharmacological and biological activities [9–12]. The bis(indolyl)alkane moiety is also present in various natural products possessing important biological activity [13–18]. Therefore, a number of synthetic methods for preparation of bis(indolyl)alkane derivatives have been reported in the literature by reaction of indole with various aldehydes and ketones in the presence of either a Lewis acid [19,20] or a protic acid [21–30].

In fact, the acids commonly used are generally toxic catalysts, difficult to handle, stoichiometric amount maybe needed, and require tedious aqueous work-up, along with the use of environmentally harmful organic solvents. In view of the importance of bis(indolyl)alkane derivatives, these problems were overcome to some extent by recently reported green methods under solvent-free conditions or using ionic liquids as reaction medium [31–41]. However, to the best of our knowledge, only few reports have been published for the synthesis of indole derivatives in water [37,42–45].

2. Experimental section

2.1. General procedure for preparation of bis(indolyl)methanes

To the mixture of indole (2 mmol), an aldehyde or a ketone (1 mmol), water (4 mL), $H_3PW_{12}O_{40}$ (10 mg) or $H_3PMo_{12}O_{40}$ (10 mg) was added and stirred vigorously at room temperature until the disappearance of the starting indole (1–8 h). When the reaction was complete, the reaction mixture was filtrate and washed with water. The crude product was analyzed by NMR and purified by recrystallization or column chromatography (EtOAc–petroleum ether) to afford the pure bisindole.

2.2. General procedure for preparation of di(1H-indol-3-yl)acetic acid (6)

To the mixture of indole (2 mmol), glyoxylic acid (50% solution in water, 3 mmol), $H_3PMo_{12}O_{40}$ (10 mg, 0.14 mol%) was

* Corresponding author. Fax: +98 21 6601 2983.
E-mail address: saidi@sharif.edu (M.R. Saidi).

added and stirred at room temperature for 4 h. After the completion of the reaction, the mixture was diluted with ethyl acetate and purified by flash column chromatography (Et₂O–hexanes) to give the desired product.

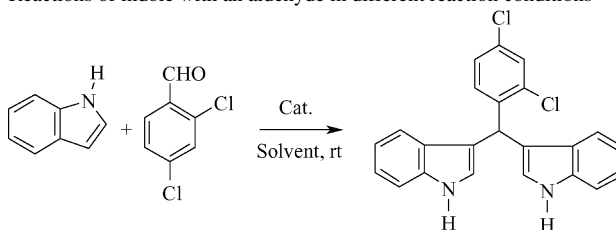
3. Results and discussion

Due to the commercial availability, ease of handling, remarkably low toxicity, environmentally friendly, and economically feasible solid catalyst, organic reactions using heteropoly acids, HPAs, received more attention in recent years [46–49]. In continuation of our ongoing interest in using water as reaction medium [50–56], we herein report the use of HPAs as catalysts in the electrophilic substitutions of indole and substituted indole with a variety of aldehydes and ketones in water to afford bis(indolyl)methanes at room temperature with excellent yields (Scheme 1).

At first, the reaction of indole with 2,4-dichlorobenzaldehyde catalyzed by heteropoly acids in water and other solvents was investigated, and the results are presented in Table 1. Initial screening studies identified water as the optimal solvent for this reaction. Organic solvents, such as CH₃CN, CH₂Cl₂, CH₂ClCH₂Cl and THF, were also proved effective with longer reaction time, although, the reaction in ethanol was carried out with 5 mol% of catalyst [27].

Furthermore, we also tested the catalytic activity of different catalysts such as HClO₄ and *p*-toluenesulfonic acid (TsOH), RuCl₃, WCl₆ and ZnCl₂, and we obtained only moderate yields in water. One of the most interesting point in this work is the difference of the catalytic activity between simple mineral acids (HClO₄ and H₂SO₄, Table 1, entries 14, 15) and heteropoly acids in water. The reaction rate at the low conversion of substrate shows the high catalytic activity of heteropoly acids more clearly. In addition, H₃PMo₁₂O₄₀ has been compared with H₃PW₁₂O₄₀ and we found out the same results for both of these heteropoly acids in this reaction in water and other solvents

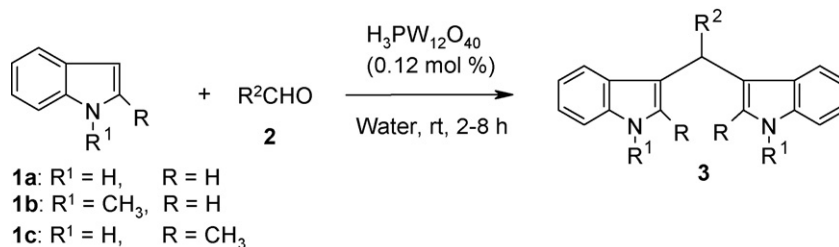
Table 1
Reactions of indole with an aldehyde in different reaction conditions



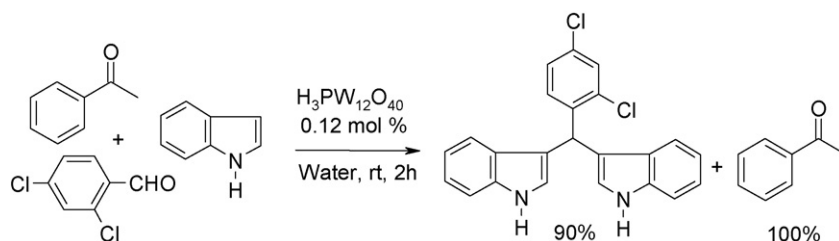
Entry	Solvent (2 mL)	Catalyst (mol%)	Yield (%)	Time (h)
1	Water	–	5	1
2	Water	H ₃ PMo ₁₂ O ₄₀ (0.12)	86	1
3	Water	H ₃ PW ₁₂ O ₄₀ (0.12)	90	1
4	THF	H ₃ PMo ₁₂ O ₄₀ (0.12)	90	6
5	THF	H ₃ PW ₁₂ O ₄₀ (0.12)	90	6
6	CH ₃ CN	H ₃ PMo ₁₂ O ₄₀ (0.12)	85	3
7	CH ₃ CN	H ₃ PW ₁₂ O ₄₀ (0.12)	90	3
8	CH ₂ Cl ₂	H ₃ PMo ₁₂ O ₄₀ (0.12)	88	2
9	CH ₂ Cl ₂	H ₃ PW ₁₂ O ₄₀ (0.12)	90	2
10	ClCH ₂ CH ₂ Cl	H ₃ PMo ₁₂ O ₄₀ (0.12)	86	2
11	ClCH ₂ CH ₂ Cl	H ₃ PW ₁₂ O ₄₀ (0.12)	88	2
12	Water	ZnCl ₂ (5)	45	1
13	Water	RuCl ₃ (1)	48	1
14	Water	H ₂ SO ₄ (1)	55	1
15	Water	HClO ₄ (1)	74	1
16	Water	CeCl ₃ ·7H ₂ O (5)	58	1
17	Water	WCl ₆ (1)	60	1

(Table 1). The reactions were carried out in the simplest manner, only by stirring the mixture of indole, an aldehyde and catalytic amount of commercially available heteropoly acids in water at room temperature in a test tube.

These results prompted us to investigate the scope and the generality of this new protocol for various aldehydes and ketones under optimized conditions (Table 2). A series of aromatic aldehydes and simple ketones underwent electrophilic substitution reaction with indole, 1-methyl indole, and 2-

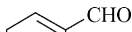
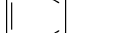

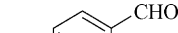

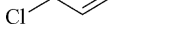
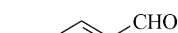
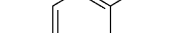
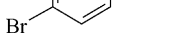

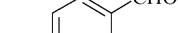
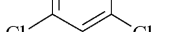

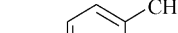
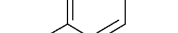


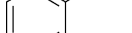

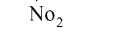



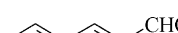

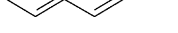
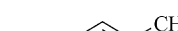

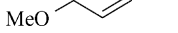


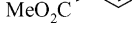
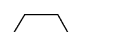


Scheme 1. Reaction of indole with aldehyde in the presence of a heteropoly acid.

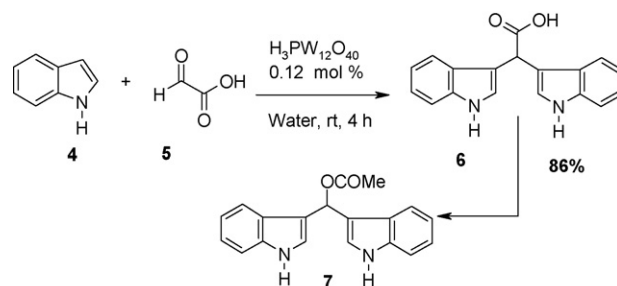


Scheme 2. Chemoselectivity of aldehyde in reaction with indole in the presence of a ketone.

Table 2
Synthesis of bis(1*H*-indol-3-yl) methanes in water

Entry	Aldehydes	Indole	Time (h)	Yield (%)
1		1a	2	84
2		1b	1	92
3		1c	2	80
4		1a	3	88
5		1b	1	95
6		1c	2	84
7		1a	2	80
8		1b	2	93
9		1c	2	84
10		1a	1	88
11		1b	1	90
12		1c	1	80
13		1a	4	84
14		1b	4	88
15		1c	4	78
16		1a	2	80
17		1b	2	86
18		1c	2	80
19		1a	2	92
20		1b	2	94
21		1c	2	86
22		1a	6	80
23		1b	4	84
24		1c	6	76
25		1a	8	78
26		1b	8	82
27		1c	8	74
28		1a	5	86
29		1b	5	90
30		1a	8	84
31		1b	8	90
32		1b	8	76
33		1a	6	00

methyl indole smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields. This method is equally effective for aldehydes bearing electron withdrawing or donating substituents in the aromatic rings. Furthermore, acid sensitive aldehydes worked well without any decomposition or polymerization under these reaction conditions. As it is expected, 1-methyl indole provided better yields of prod-



Scheme 3. Preparation of di(1*H*-indol-3-yl)acetic acid from indole and glyoxylic acid.

ucts in compare with indole and 2-methylindole under the same reaction conditions. Furthermore, simple ketones like cyclohexanone and 2-butanone reacted at the same reaction condition albeit with longer reaction time. However, hindered ketones did not participate in this reaction.

This method is also highly chemoselective for aldehydes. For example, when a 1:1 mixture of 2,4-dichlorobenzaldehyde and acetophenone was allowed to react with indole in the presence of $H_3PW_{12}O_{40}$ in water, it was found that only 2,4-dichlorophenyl-3,3-bis(indolyl)methane (**3a**) was obtained, while acetophenone did not give the corresponding product under this reaction conditions (Scheme 2). The reactions were clean and the products were obtained in high yields without the formation of any side products such as *N*-alkylated product.

Finally, the high yield, simple reaction protocol, and originality of this novel process is further demonstrated in the synthesis of biologically active bis(indole), such as streptindole (**7**), with pharmacological activity (Scheme 3) [57]. Thus, the electrophilic reaction of indole was carried out with glyoxylic acid (50% solution in water), and the expected product was obtained in good yields under these reaction conditions.

4. Conclusion

In conclusion, we have described a simple, convenient and efficient protocol for the synthesis of wide range of bis(1*H*-indol-3-yl)alkane in water. The simplicity, efficiency, mild reaction condition, high yields of products, easy work up procedure, and using very small amount of heteropoly acids make it the preferred procedure for the preparation of different kind of bis(1*H*-indol-3-yl)alkane. Another important feature of this methodology is the use of heteropoly acids as catalyst, water as reaction medium, and avoidance of hazardous organic solvent.

Acknowledgment

We are grateful to the Research Council of Sharif University of Technology for financial support.

References

- [1] D.J. Adams, P.J. Dyson, S.J. Tavener, Chemistry in Alternative Reaction Media, Wiley-VCH Verlag GmbH & Co., Weinheim, 2004.
- [2] J.L. Chao, Chem. Rev. 105 (2005) 3095.

- [3] C.J. Li, T.H. Chang, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997.
- [4] M.C. Pirrung, K.D. Sarma, *J. Am. Chem. Soc.* 126 (2004) 444.
- [5] K. Manabe, S. Limura, X.-M. Sun, S. Kobayashi, *J. Am. Chem. Soc.* 124 (2002) 11971.
- [6] H. Firouzabadi, N. Iranpoor, A. Garzan, *Adv. Synth. Catal.* 347 (2005) 1925.
- [7] A.L. Smith, G.I. Stevenson, S. Lewis, S. Patel, J.L. Castro, *Biorg. Med. Chem. Lett.* 10 (2000) 2693.
- [8] Y. Liu, G.W. Gribble, *Tetrahedron Lett.* 41 (2000) 8717.
- [9] R.A. Glennon, *J. Med. Chem.* 40 (1997) 1.
- [10] T. Walsh, R.B. Toupenca, F. Ujjainwalla, J.R. Young, M.T. Goulet, *Tetrahedron* 57 (2001) 5233.
- [11] M.G.N. Russell, R.J. Baker, L. Barden, M.S. Beer, L. Bristow, H.B. Howard, B. Broughton, M. Knowles, G. McAllister, S. Patel, J.L. Castro, *J. Med. Chem.* 44 (2001) 3881.
- [12] H.-C. Zhang, H. Ye, A.F. Moretto, K.K. Brumfield, B.E. Maryanoff, *Org. Lett.* 2 (2000) 89.
- [13] *The Alkaloids; Specialist Periodical Reports; the Chemical Society: London, 1971.*
- [14] G.A. Cordell, *Introduction to Alkaloids: A Biogenetic Approach*, Wiley, New York, 1981.
- [15] A.R. Pindur, *J. Heterocycl. Chem.* 25 (1988) 1.
- [16] J.D. Rainier, A.B. Smith, *Tetrahedron Lett.* 41 (2000) 9419.
- [17] M.-L. Bennesar, B. Vidal, J. Bosch, *J. Org. Chem.* 62 (1997) 3597.
- [18] M. Amat, S. Hadida, G. Pshenichnyi, J. Bosch, *J. Org. Chem.* 62 (1997) 3158.
- [19] B.V. Gregorovich, K. Liang, M. Clugston, S. Macdonald, *Can. J. Chem.* 46 (1968) 3291.
- [20] M. Roomi, S. Macdonald, *Can. J. Chem.* 48 (1970) 139.
- [21] A. Chatterjee, S. Manna, J. Benerji, C. Pascard, T. Prange, *J. Shoolery, J. Chem. Soc., Perkin Trans. 1* (1980) 553.
- [22] W.E. Noland, M.R. Venkiteswaran, C.G. Richards, *J. Org. Chem.* 26 (1961) 4241.
- [23] G. Babu, N. Sridhar, P.T. Perumal, *Synth. Commun.* 30 (2000) 1609.
- [24] Y.M. Wang, Z. Wen, X.M. Chen, D.M. Du, T. Matsuura, J.B. Meng, *J. Heterocycl. Chem.* 35 (1998) 313.
- [25] J.S. Yadav, B.V.S. Reddy, C.V.S.R. Mueth, G.M. Kumar, C. Madan, *Synthesis* (2001) 783.
- [26] H. Firouzabadi, N. Iranpoor, A.A. Jafari, *J. Mol. Catal. A* 244 (2005) 168.
- [27] M.A. Zolfigol, P. Salehi, M. Shiria, *Phosphorus Sulfur Silicon* 179 (2004) 2273.
- [28] P. Srinivasan, J. Amalraj, *J. Mole. Catal. A: chemical* 242 (2005) 168.
- [29] M. Chakrabarty, A. Mukherji, S. Karmakar, S. Arima, Y. Harigaya, *Heterocycles* 68 (2006) 331.
- [30] H. Firouzabadi, N. Iranpoor, A.A. Jafari, *J. of Mole. Catal. A* 244 (2006) 168.
- [31] C. Ramesh, J. Banerjee, R. Pal, B. Das, *Adv. Synth. Catal.* 345 (2003) 557.
- [32] J.S. Yadav, B.V.S. Reddy, S. Sunitha, *Adv. Synth. Catal.* 345 (2003) 349.
- [33] S.J. Ji, M.F. Zhou, D.G. Gu, Z.Q. Jiang, T.P. Loh, *Eur. J. Org. Chem.* 69 (2004) 1584.
- [34] B.P. Bandgar, K.A. Shaikh, *Tetrahedron Lett.* 44 (2003) 1959.
- [35] M. Chakrabarty, N. Ghosh, R. Basak, Y. Harigaya, *Tetrahedron Lett.* 43 (2002) 4075.
- [36] G. Bartoli, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambria, *Synlett* (2004) 895.
- [37] D.P. Chen, L.B. Yu, P.G. Wang, *Tetrahedron Lett.* 37 (1996) 4467.
- [38] R. Nagarajan, P.T. Perumal, *Tetrahedron* 58 (2002) 1229.
- [39] X.L. Mi, S.Z. Luo, J.Q. He, J.P. Chen, *Tetrahedron Lett.* 45 (2004) 4567.
- [40] S. Mehrzama, N. Azizi, M.R. Saidi, *Lett. Org. Chem.* 3 (2006) 161.
- [41] L. Wang, J. Han, H. Tian, J. Sheng, Z. Fan, X. Tang, *Synlett* (2005) 337.
- [42] W.H. Xie, K.M. Bloomfield, Y.F. Jin, N.Y. Dolney, P.G. Wang, *Synlett* (1999) 498.
- [43] M.L. Deb, P.J. Bhuyan, *Tetrahedron Lett.* 47 (2006) 1441.
- [44] M.B. Teimouri, H. Mivehchi, *Synth. Commun.* 35 (2005) 1835.
- [45] B.P. Bandgar, K.A. Shaikh, *J. Chem. Res.* (2004) 34.
- [46] I.V. Kozhevnikov, *Chem. Rev.* 98 (1998) 171.
- [47] L.E. Briand, G.T. Baronetti, H. Thomas, *J. Appl. Catal. A* 256 (2003) 37.
- [48] M.N. Timofeeva, *Appl. Catal. A.* 256 (2003) 19.
- [49] H. Firouzabadi, N. Iranpoor, F. Nowrouzi, K. Amani, *Chem. Commun.* (2003) 764.
- [50] N. Azizi, M.R. Saidi, *Organometallics* 23 (2004) 1457.
- [51] N. Azizi, M.R. Saidi, *Eur. J. Org. Chem.* (2003) 4630.
- [52] N. Azizi, M.R. Saidi, *Org. Lett.* 7 (2005) 3649.
- [53] B. Mirmashhori, N. Azizi, M.R. Saidi, *J. Mol. Catal. A* 247 (2006) 159.
- [54] N. Azizi, R. Yousefi, M.R. Saidi, *J. Organometallic Chem.* 691 (2006) 817.
- [55] N. Azizi, M.R. Saidi, *Catalysis Commun.* 7 (2006) 224.
- [56] N. Azizi, F. Aryanasab, L. Torkiyan, A. Ziyaei, M.R. Saidi, *J. Org. Chem.* 71 (2006) 3634.
- [57] T. Osawa, M. Namiki, K. Suzuki, T. Mitsuoka, *Mutat. Res.* 122 (1983) 299.