Efficient Friedel–Crafts alkylation of indoles and pyrrole with enones and nitroalkene in water†

Najmedin Azizi,*[b] Fezzeh Arynasab[a] and Mohammad R. Saidi*[a]

Received 18th July 2006, Accepted 6th October 2006
First published as an Advance Article on the web 17th October 2006
DOI: 10.1039/b610263h

An operationally simple and entirely green protocol for heteropoly acid (10 mg) catalyst conjugate addition of indoles and pyrrole to unsaturated carbonyl compounds and nitroalkene in water at ambient temperature in good to excellent yields has been developed.

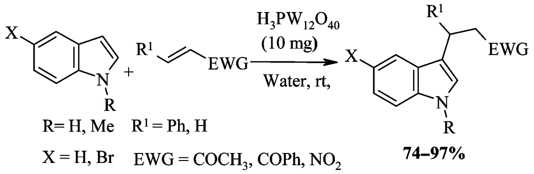
Heteropolyacids (HPAs) are environmentally-friendly and economically feasible solid acid catalysts

owing to their high catalytic activities and reactivating power, ease of handling, cleaner reactions in comparison to conventional catalysts (less waste production), non-toxicity and experimental simplicity. The catalytic application of solid acids as efficient heterogeneous catalysts has been demonstrated, both by successful large-scale applications in industry and by promising laboratory results.[1]

On the other hand, the development of water as a green media for organic synthesis has become an important research area. Other than the economical and environmental benefits of using water, it may exhibit unique reactivity and selectivity in comparison with conventional organic solvents. Thus, the development of novel reactivity, as well as selectivity, that cannot be attained in conventional organic solvents is one of the challenging goals of water chemistry.[2]

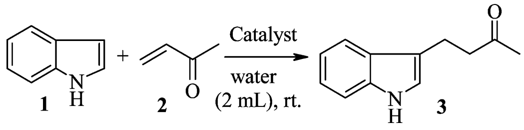
Indole and many of its derivatives are present in many substances commonly found in nature,[3] as well as in many compounds that show pharmacological and biological activities.[4] Thus, the development of a new, efficient, selective and green synthetic method for the preparation of 3-substituted indole derivatives has attracted much attention in recent years. A variety of methods have been explored for the Michael addition reaction of indoles and pyrroles with α,β-unsaturated ketones in the presence of protic or Lewis acids for the preparation of substituted indoles and pyrroles.[5] MacMillan was also reported the enantioselective Friedel–Crafts alkylation of pyrroles.[6] However, many of these procedures involved strong acidic conditions, expensive reagents, longer reaction times, low yields of products and uneasy handling. While most Michael addition reactions are performed in organic solvents, Michael additions in water are relatively scarce. Furthermore, to the best of our knowledge, few reports about conjugate indole addition with steric hindrance enones, such as chalcone, have been reported in the literature.[7]

In continuation of our research interest for developing green organic chemistry by using water as reaction media or by performing organic transformations under solvent-free conditions,[8] herein, we wish to report a novel catalytic system that is quite effective and entirely green procedure for the Michael-type addition of indol, *N*-methyl indol, and pyrrole to α,β-unsaturated compounds in water and in the presence of heteropoly acids (Scheme 1). First, we decided to focus on the catalytic activity-screening study of conjugate indole addition with methyl vinyl ketone in water at room temperature. Interestingly, the Michael addition between indole and methyl vinyl ketone in the presence of catalysts, such as $CeCle_3 \cdot 7H_2O$, $FeCl_3 \cdot 6H_2O$, $ZrCl_4$, WCl_6 and H_3PO_4, proceeded efficiently, furnishing moderate to excellent yields of the desired products in water (Table 1). Unlike the conventional Lewis acid-catalyzed reactions, heteropoly acids such as $H_3PMo_{12}O_{40}$ and



Scheme 1

Table 1 Reaction of indole and methyl vinyl ketone in water with various catalysts



Entry	Catalyst (mol%)	Time/h	Yield (%)
1	—	24	20
2	$CeCl_3 \cdot 7H_2O$ (3)	24	50
3	$CeCl_3 \cdot 7H_2O$ (30)	8	80
4	$MgClO_4 \cdot 5H_2O$ (6)	24	0
5	$ZrCl_4$ (10)	2	100
6	$FeCl_3 \cdot 7H_2O$ (7)	24	100
7	$CuCl_2.2H_2O$ (10)	24	68
8	$MnCl_2 \cdot 5H_2O$ (10)	10	70
9	$RuCl_3.7.H_2O$ (5)	8	78
10	VCl_3 (20)	8	80
11	WCl_6 (5)	2	96
12	H_3PO_4 (0.005)[b]	8	92
13	$H_3PMo_{12}O_{40}$ (1)	1	68[c]
14	$H_3PMo_{12}O_{40}$ (0.5)	0.2	100
15	$H_3PW_{12}O_{40}$ (0.4)	0.2	100
16	$LiClO_4.3H_2O$ (60)	24	0

[a] Conversion yields. [b] 2 ml H_3PO_4. [c] Solvent THF.

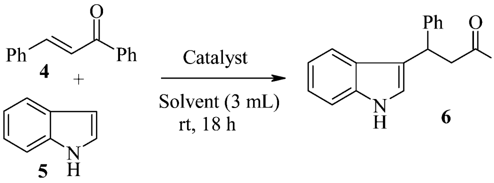
---

[a] *Department of Chemistry, Sharif University of Technology, P. O. Box 11465-9516, Tehran, 11365, Iran. E-mail: Saidi@sharif.edu; Fax: +98 (0)21 66005718*

[b] *Organic Chemistry Laboratory, Chemistry & Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, Iran*

† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b610263h

Table 2 Reaction of chalcone with indole at various conditions[a]



Entry	Solvent	Catalyst (10 mg)	Yield (%)[b]
1	Water	—	0
2	Water	$H_3PMo_{12}O_{40}$	90
3	Water	$H_3PW_{12}O_{40}$	85
4	EtOH	$H_3PMo_{12}O_{40}$	35
5	EtOH	$H_3PW_{12}O_{40}$	27
6	Toluene	$H_3PMo_{12}O_{40}$	20
7	Toluene	$H_3PW_{12}O_{40}$	12
8	CH_3CN	$H_3PMo_{12}O_{40}$	76
9	CH_3CN	$H_3PW_{12}O_{40}$	52
10	$ClCH_2CH_2Cl$	$H_3PMo_{12}O_{40}$	80
11	$ClCH_2CH_2Cl$	$H_3PW_{12}O_{40}$	58
12	Water	$ZrCl_4$	0
13	Water	$RuCl_3$	0
14	Water	H_2SO_4	30
15	Water	$HClO_4$	70
16	Water	$MeSO_3H$	0
17	Water	$p-MeC_6H_4SO_3H$	50

[a] Reaction conditions: indole (1 mmol), Chalcone (1 mmol), HPA (10 mg) and solvent (3 ml). [b] Isolated yield.

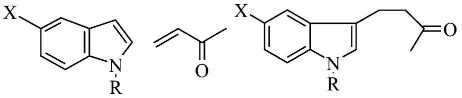
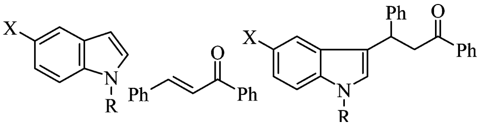
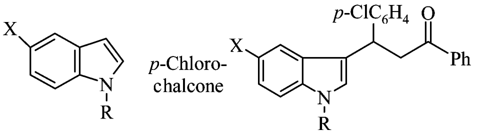
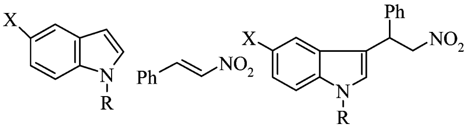
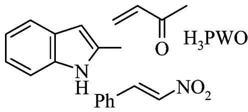
$H_3PW_{12}O_{40}$ in water were also effective in this reaction and showed high catalytic activity in a short reaction time.

A literature survey reveals that there are few reports on the reaction of chalcone with indoles in water. Therefore, we were particularly interested in the use of chalcone, which reacts sluggishly with indoles in the presence of common catalysts. So, we extended our studies by investigating the Friedel–Crafts alkylation between indole and chalcone in water and other organic solvents, using different catalysts (Table 2).

The reactions worked well in water, CH_3CN and $ClCH_2CH_2Cl$ at room temperature, whereas in THF, PhMe, EtOH very low yields of the product were obtained. When $MnCl_2$, $RuCl_3$, $ZrCl_4$, H_2SO_4 and $MeSO_3H$ were used as a catalyst in water, no Michael adducts were detected, but in the presence of $HClO_4$ and *p*-toluenesulfonic acid (TsOH) moderate yields were obtained in water. In addition, $H_3PMo_{12}O_{40}$ has been compared with $H_3PW_{12}O_{40}$ and we found the same results for both of these heteropoly acids for the above reaction in water.

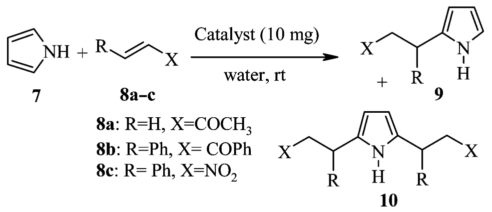
Encouraged by the remarkable results obtained with indole and chalcone, a variety of substituted indoles and electron deficient compounds were tested using this new Friedel–Crafts alkylation method. The results clearly demonstrate that HPA is an excellent catalyst for this reaction in water (Table 3). By using substituted indoles such as *N*-methylindole, 2-methylindole and 5-bromoindole, good to excellent yields were obtained. The substituents did not affect the reactivity of indoles significantly. The only significant difference in reactivity was observed for *N*-methylindole, which gives a higher yield in comparison with indole. With regard to Michael acceptors, the reactions proceeded smoothly with electron-deficient olefins such as methyl vinyl ketone, chalcone, chlorochalcone and β-nitrostyrene to afford the corresponding Michael adducts in good to excellent yields. In all cases the reactions proceeded at room temperature with high selectivity. It is important to note that products arising from 1,2-addition were not observed under these reaction conditions. In the case of sterically hindered and less reactive enone, such as chalcone, the reaction proceeds smoothly with good yield. (Table 3, entries 4 and 5). However, α,β-unsaturated esters are not suitable substrates for Michael addition reaction of indoles under these reaction conditions.

Table 3 HPA-Catalyzed Michael addition of various substrates in water

		Michael acceptor		Products
Entry	Indole	Catalysts	Time/h	Yields (%)[a]
				
1	X=H, R=H	$H_3PW_{12}O_{40}$	0.3	97[b]
2	X=H, R=H	$H_3PMo_{12}O_{40}$	0.3	97
3	X=Br, R=H	$H_3PW_{12}O_{40}$	1	97[b]
4	X=Br, R=H	$H_3PMo_{12}O_{40}$	1	97
5	X=H, R=CH_3	$H_3PW_{12}O_{40}$	0.2	97[b]
6	X=H, R=CH_3	$H_3PMo_{12}O_{40}$	0.2	97
				
7	X=H, R=H	$H_3PW_{12}O_{40}$	18	90
8	X=H, R=H	$H_3PMo_{12}O_{40}$	18	85
9	X=H, R=CH_3	$H_3PW_{12}O_{40}$	12	95
10	X=H, R=CH_3	$H_3PMo_{12}O_{40}$	12	93
11	X=Br, R=H	$H_3PW_{12}O_{40}$	18	78
12	X=Br, R=H	$H_3PMo_{12}O_{40}$	18	80
				
13	X=H, R=H	$H_3PW_{12}O_{40}$	18	76[c]
14	X=H, R=H	$H_3PMo_{12}O_{40}$	18	80[c]
15	X=H, R=CH_3	$H_3PW_{12}O_{40}$	18	83
16	X=H, R=CH_3	$H_3PMo_{12}O_{40}$	18	89
				
17	X=H, R=H	$H_3PW_{12}O_{40}$	18	82
18	X=H, R=H	$H_3PMo_{12}O_{40}$	18	86
19	X=H, R=CH_3	$H_3PW_{12}O_{40}$	14	90
20	X=H, R=CH_3	$H_3PMo_{12}O_{40}$	14	93
21	X=Br, R=H	$H_3PW_{12}O_{40}$	18	74
22	X=Br, R=H	$H_3PMo_{12}O_{40}$	18	76
23		H_3PWO_{40}	1	95
24		H_3PWO_{40}	18	74
25	Chalcone	H_3PWO_{40}	28	68

[a] Isolated yields. [b] Conversion 100%. [c] CH_3OH as solvent

Table 4 The HPA-catalyzed reaction of electron-deficient olefins with pyrrole in water[a]



					Yield (%)[a]	
Entry	Michael acceptor	Molar ratio of **7** : **8**	Catalyst	Time/h	**9**	**10**
1	**8a**	1 : 1	$H_3PW_{12}O_{40}$	2	36	28
2	**8a**	1 : 1	$H_3PMo_{12}O_{40}$	2	34	25
3	**8a**	1 : 2.5	$H_3PW_{12}O_{40}$	8	0	82
4	**8a**	1 : 2.5	$H_3PMo_{12}O_{40}$	8	0	86
5	**8b**	1 : 1	$H_3PW_{12}O_{40}$	18	20	30
6	**8b**	1 : 1	$H_3PMo_{12}O_{40}$	18	14	32
7	**8b**	1 : 2.5	$H_3PW_{12}O_{40}$	18	8	68[b]
8	**8b**	1 : 2.5	$H_3PW_{12}O_{40}$	18	12	66[b]
9	**8c**	1 : 1	$H_3PW_{12}O_{40}$	18	25	30
10	**8c**	1 : 1	$H_3PMo_{12}O_{40}$	18	20	32
11	**8c**	1 : 2.5	$H_3PMo_{12}O_{40}$	18	10	48[c]

[a] Yields refer to pure isolated compounds. [b] Methanol as solvent. [c] 0.05 gram SDS was added.

Pyrroles also readily underwent Michael addition at α-positions under the same reaction conditions. However, in this case, 2,5-disubstituted pyrroles were the major products using a 1 : 1 pyrrole–reactant ratio. Any excess of the Michael acceptor resulted in the formation of 2,5-disubstituted pyrroles in some cases (Table 4, entries 3 and 4).

In summary, we have demonstrated a novel, highly efficient and entirely green protocol for Friedel–Crafts alkylation of indole and pyrrole with several electron-deficient olefins in water at room temperature with good to excellent yields. Furthermore, this procedure offers several advantages including the use of green and low-loading catalyst, green solvent, improved yields, cleaner reactions and simple experimental procedures, which make it a useful and attractive strategy in multicomponent reactions and combinational chemistry. In addition, easy workup has been realized without the use of organic solvents when the products are solid or insoluble in water. In some cases the pure products were obtained after the evaporation of the solvent from the reaction mixture.

References

1 (*a*) I. V. Kozhevnikov, *Chem. Rev.*, 1998, **98**, 171–198; (*b*) L. E. Briand, G. T. Baronetti and H. J. Thomas, *Appl. Catal., A*, 2003, **256**, 37–50; (*c*) J. Kaur and I. V. Kozhevnikov, *Chem. Commun.*, 2002, 2508–2509.

2 (*a*) J. L. Chao, *Chem. Rev.*, 2005, **105**, 3095–3165; (*b*) C. J. Li and T. H. Chang, *Organic Reactions in Aqueous Media*, Wiley, New York, 1997; (*c*) Z. P. Demko and K. B. Sharpless, *J. Org. Chem.*, 2001, **66**, 7945–7950; (*d*) M. C. Pirrung and K. D. Sarma, *J. Am. Chem. Soc.*, 2004, **126**, 444–445.

3 (*a*) B. Jiang, C. G. Yang and J. Wang, *J. Org. Chem.*, 2002, **67**, 1396–1398 and references therein; (*b*) R. J. Sundberg, *The Chemistry of Indoles*, Academic, New York, 1970; (*c*) T. S. Kam, in *Alkaloids, Chemical and Biological Perspectives*, ed. S. W. Pelletier, Pergamon, Amsterdam, 1999, vol. 4, pp. 285.

4 (*a*) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2005, **22**, 73–103; (*b*) R. Reddy, J. B. Jaquith, V. R. Neelagiri, S. Saleh-Hanna and T. Durst, *Org. Lett.*, 2002, **4**, 695–697; (*c*) H. D. King, Z. Meng, D. Denhart, R. Mattson, R. Kimura, D. Wu, Q. Gao and J. E. Macor, *Org. Lett.*, 2005, **7**, 3437–3440; (*d*) P. S. Baran and J. M. Richter, *J. Am. Chem. Soc.*, 2004, **126**, 7450–7451; (*e*) R. J. Sundberg, *Indoles*, Academic Press, San Diego, 1996, pp. 175; (*f*) K. C. Nicolaou and S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, 2003, ch. 5, 8, 12, 18–20.

5 (*a*) D. A. Evans, K. A. Scheidt, K. R. Fandrik, H. V. Lam and J. Wu, *J. Am. Chem. Soc.*, 2003, **125**, 10780–10781; (*b*) G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri and E. Torregiani, *J. Org. Chem.*, 2003, **68**, 4594–4597; (*c*) S. Yamazaki and Y. Iwata, *J. Org. Chem.*, 2006, **71**, 739–743; (*d*) J. Moran, T. Suen and A. M. Beauchemin, *J. Org. Chem.*, 2006, **71**, 676–679; (*e*) H. Firouzabadi, N. Iranpoor and F. Nowrouzi, *Chem. Commun.*, 2005, 789–791; (*f*) M. Bandini, P. G. Cozzi, M. Giacomini, P. Melchiorre, S. Selva and A. Umani-Ronchi, *J. Org. Chem.*, 2002, **67**, 3700–3704; (*g*) B. K. Banik, M. Fernandez and C. Alvarez, *Tetrahedron Lett.*, 2005, **46**, 2479–2482; (*h*) Y.-X. Jia, S.-F. Zhu, Y. Yang and Q.-L. Zhou, *J. Org. Chem.*, 2006, **71**, 75–80.

6 (*a*) D.-P. Li, Y.-C. Guo, Y. Ding and W.-J. Xiao, *Chem. Commun.*, 2006, 799–801; (*b*) J. F. Austin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 1172–1173; (*c*) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370–4371.

7 (*a*) Z.-P. Zhan and K. Lang, *Synlett*, 2005, 1551–1554; (*b*) S.-Y. Wang, S.-J. Ji and T.-P. Loh, *Synlett*, 2003, 2377–2379; (*c*) M. Bandini, M. Fagioli and A. Umani-Ronchi, *Adv. Synth. Catal.*, 2004, **346**, 545–548; (*d*) K. Manabe, N. Aoyama and S. Kobayashi, *Adv. Synth. Catal.*, 2001, **343**, 174–176; (*e*) W. Zhuang, R. G. Hazell and K. A. Jørgensen, *Org. Biomol. Chem.*, 2005, **3**, 2566–2571.

8 (*a*) N. Azizi and M. R. Saidi, *Organometallics*, 2004, **23**, 1457–1458; (*b*) N. Azizi and M. R. Saidi, *Eur. J. Org. Chem.*, 2003, 4630–4633; (*c*) N. Azizi and M. R. Saidi, *Org. Lett.*, 2005, **7**, 3649–3651; (*d*) N. Azizi, R. Yousefi and M. R. Saidi, *J. Organomet. Chem.*, 2006, **691**, 817–820; (*e*) N. Azizi, F. Aryanasab, L. Torkiyan, A. Ziyaei and M. R. Saidi, *J. Org. Chem.*, 2006, **71**, 3634–3635; (*f*) N. Azizi, L. Torkiyan and M. R. Saidi, *Org. Lett.*, 2006, **8**, 2079–2082.