Available online at www.sciencedirect.com
ScienceDirect
Journal of Molecular Catalysis A: Chemical 280 (2008) 219–223
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
www.elsevier.com/locate/molcata

Phosphomolybdic acid-supported silica gel as efficient and cost-effective solid acid for the benzylation of indoles with benzylic alcohols

J.S. Yadav *, B.V. Subba Reddy, A. Srinivas Reddy

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India

Received 16 August 2007; received in revised form 1 October 2007; accepted 3 October 2007
Available online 9 October 2007

Abstract

Indoles undergo smooth alkylation with benzylic alcohols on the surface of 10 mol% of phosphomolybdic acid supported on silica gel under mild conditions to produce C-3 benzylated-indoles in high yields and with high selectivity. This method offers significant advantages such as high conversions, short reaction times, mild reaction conditions, cleaner reaction profiles, high selectivity and low cost of the heterogeneous catalyst.

Keywords: Heteropolyacid; Solid-supported catalysts; Benzylic alcohols; Indoles

1. Introduction

Indole nucleus is frequently found in natural products, pharmaceuticals, functional materials and agrochemicals [1–3]. Substituted indoles are capable of binding to many receptors with high affinity. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years [4–10]. Nucleophilic substitution of the hydroxy group in alcohols by nucleophiles generally requires preactivation of the alcohols because of the poor leaving ability of the hydroxyl group [11–13]. As a result, hydroxyl groups are generally transformed into the corresponding halides, carboxylates, carbonates, phosphonates, or related compounds [14–16]. However, such process inevitably produces a stoichiometric amount of salt waste and also the substitution of the halides requires a stoichiometric amount of a base which limits their use in large-scale synthesis. In most cases, either a high reaction temperature or a promoter is required to enhance the leaving ability of the hydroxyl group. Therefore, the direct catalytic substitution of alcohols with indoles using an efficient, cost-effective and recyclable catalyst is highly desirable.

Recently, the use of heteropolyacids, HPAs, as environmentally friendly and economically viable solid acids, is increasing continuously owing to their ease of handling, high catalytic activities and reactivities [17]. These compounds possess unique properties, such as well-defined structure, Bronsted acidity, possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility, etc. [18]. In view of green chemistry, the substitution of harmful liquid acids by reusable solid HPAs as catalysts in organic synthesis is the most promising application of these acids [19–23]. Among them, phosphomolybdic acid (PMA, $H_3PMo_{12}O_{40}$) is one of the less expensive and commercially available catalysts [24–27]. However, there have been no reports on the use of phosphomolybdic acid for the direct alkylation of indoles with benzylic alcohols.

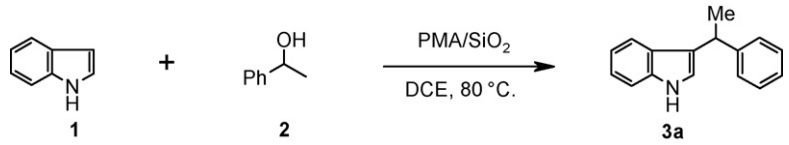
2. Results and discussion

In continuation of our efforts to explore the synthetic utility of phosphomolybdic acid supported on silica gel (PMA–SiO_2) [28,29], we herein report for the first time, a direct and efficient method for the alkylation of indoles with benzylic alcohols using 10 mol% of phosphomolybdic acid supported on silica gel, PMA–SiO_2 as the novel catalytic system. Initially, we attempted the alkylation of indole (1) with 1-phenylethanol (2) in dichloroethane in the presence of 10 mol% of PMA/SiO_2. The

Abbreviations: HPA, heteropolyacid; PMA, phosphomolybdic acid; SiO_2, silica gel; TLC, thin layer chromatography; $HClO_4$, perchloric acid; H_2SO_4, sulfuric acid; $NaHSO_4$, sodium bisulfate.

* Corresponding author. Fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

1381-1169/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.molcata.2007.10.004



Scheme 1. Alkylation of indole with benzylic alcohols.

Scheme 2. Alkylation of indoles with allylic alcohols.

reaction completed within 1.5 h and the product **3a** was obtained in 85% yield (Scheme 1).

Similarly, various benzyl alcohols such as 1-(4-bromophenyl) ethanol, 1-(4-aminophenyl) ethanol, tertrahydronaphthalen-1-ol, 2-phenylchroman-4-ol and 1-(6-bromobenzo[*d*][1,3]dioxol-5-yl)but-3-yn-1-ol reacted efficiently with indole to produce the corresponding 3-benzylated indoles (entries b–f, Table 1). Interestingly, substituted indoles such as 2-methyl-, 5-nitro-, 5-cyano-, 5-bromo-, 5-methoxy-, 7-ethyl-, and methyl 2-carboxy derivatives reacted well with a range of benzylic alcohols to furnish the respective 3-benzylated indoles in high yields (entries g–m, Table 1). Furthermore, *N*-ethyl- and *N*-benzyl-indoles also participated effectively in this reaction (entries n and p, Table 1). Interestingly, doubly activated allylic alcohols reacted rapidly with indoles at room temperature to furnish the corresponding C-3 allylated indoles (entries o and p, Scheme 2 and Table 1).

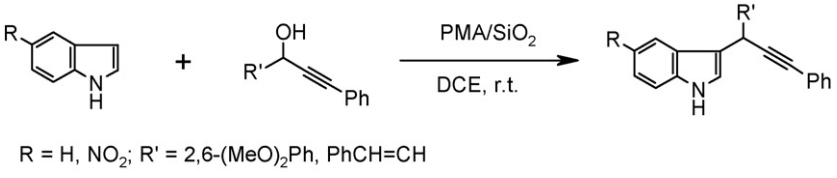
As no stoichiometric hydroxy-group activator is utilized, the products are produced with water as the only waste. No *N*-alkylation was observed under these conditions. Interestingly, electron-deficient indoles such as 5-nitro-, 5-cyano-indoles and ethyl 1*H*-indole-2-carboxylate also underwent smooth alkylation with benzylic alcohols under the reaction conditions to give the respective 3-benzylated indoles (entries h, i and m, Table 1). Furthermore, secondary propargylic alcohols also reacted well with indoles at room temperature to produce C-3 propargylated indoles (entries q and r, Table 1 and Scheme 3).

In all cases, the reactions proceeded efficiently with high selectivity and completed within 10–240 min. However, in the absence of catalyst, no reaction was observed between indoles and benzylic alcohols. In case of homopropargylic and homoallylic alcohols, no addition or rearranged products were observed (entries f, j, k and n, Table 1). The hydroxyl group was simply replaced by the indole in an S_N2 manner. It is noteworthy to mention that various functionalities such as halide, amine, amide, ether, ester, alkene, alkyne, nitro- and cyano-groups are well tolerated under the reaction conditions (Table 1). Primary benzylic alcohols failed to react with indoles under similar reaction conditions. This method was successful with secondary benzylic and allylic alcohols. As solvent, dichloroethane appeared to give the best results. All the products were characterized by ^1H, ^{13}C NMR, IR and mass spectroscopy. Among various solid acids such as $HClO_4/SiO_2$, H_2SO_4/SiO_2, Montmorillonite clay, and Amberlyst-15 tested, PMA/SiO_2 was found to give the best results in terms of conversion. There are several advantages of the use of PMA–SiO_2 as catalyst for this transformation, which include high conversions, low cost and reusability of the catalyst. In addition, the use of supported catalyst under heterogeneous conditions facilitates ease of separation and recovery of the catalyst. And also the supported PMA is more effective than the bulk PMA. The scope and generality of this process was illustrated with respect to various indoles and benzylic alcohols and the results are presented in Table 1.

To know the effect of PMA–SiO_2, we have carried out the comparative experiments with some silica gel supported Bronsted acids and the comparative results are summarized in Table 2.

The catalyst was recovered by simple filtration and washed with dichloromethane. The recovered catalyst was dried at 80 °C under reduced pressure (2 h) and reused in three to four successive runs with only a gradual decrease in activity and the results are presented in Table 3.

To determine the quantity of the catalyst leaching out from silica gel in solution, we have carried out ICP mass analysis. Only trace amount of PMA (0.001%) was leached out from silica, which has not affected on reaction rates considerably.



Scheme 3. Alkylation of indoles with propargyl alcohols.

Table 1
PMA/SiO_2-catalyzed benzylation of indoles with benzylic alcohols

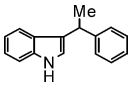
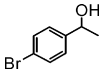
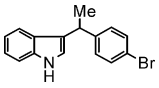
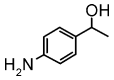
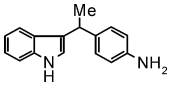
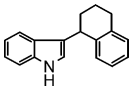
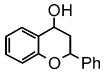
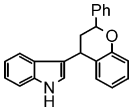
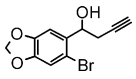
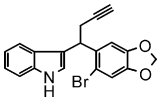
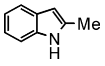
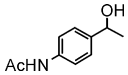
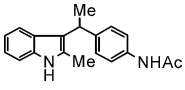
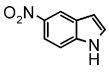
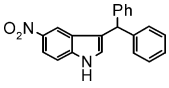
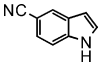
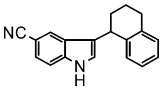
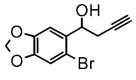
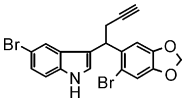
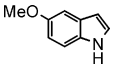
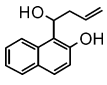
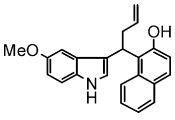
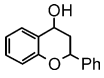
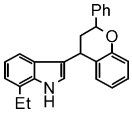
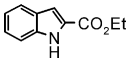
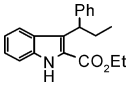
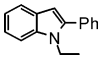
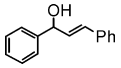
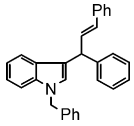
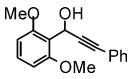
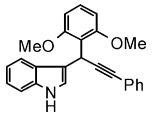
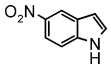
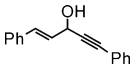
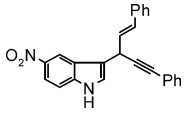
Entry	Indole (1)	Alcohols (2)	Product (3)[a]	Time (min)	Yield (%)[b]
a				90	85
b				60	80
c				60	95
d				90	75
e				90	82
f				120	80
g				150	89
h				45	90
i				90	86
j				180	85
k				60	96
l				240	70
m				45	90
n				60	94
o				10	95

Table 1 (*Continued*)

Entry	Indole (1)	Alcohols (2)	Product (3)[a]	Time (min)	Yield (%)[b]
p				15	93
q				40	98
r				30	70

[a] All products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

Table 2
A comparative study of various heterogeneous catalysts for the preparation of **3k** at 80 °C

S. no.	Catalyst	Time (h)	Yield (%)
a	$HClO_4$–SiO_2	2.5	85
b	H_2SO_4–SiO_2	3.5	82
c	PMA–SiO_2	1.0	96
d	$NaHSO_4$–SiO_2	4.0	80

3. Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. TLC was monitored on 0.25 mm pre-coated silica gel plates (60F-254).

3.1. General procedure for the benzylation of indoles

PMA/SiO_2 catalyst was prepared following the published procedure [10]. A mixture of indole (1.0 mmol), benzylic alcohol (1.0 mmol), PMA/SiO_2 (0.1 mmol%) in dichloroethane (5 mL) was stirred at 80 °C for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (2 mL) and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (Merck, 100–200 mesh, ethyl acetate–hexane, and 2:8) to afford pure 3-benzylated indole. The products thus obtained were characterized by comparison of their NMR, IR, mass, TLC, mixed TLC analysis and physical data with authentic samples.

Table 3
Reusability of the catalyst in the preparation of **3o**

S. no.	Number of cycles	Time (min)	Yield (%)
a	1st cycle	10	95
b	2nd cycle	25	92
c	3rd cycle	30	89
d	4th cycle	60	80

3.1.1. Spectroscopic data for selected compounds

3.1.1.1. 3c: 4-[1-(1H-3-indolyl)ethyl]phenylamine. Light yellow solid, mp 107–109 °C; IR (KBr): υ 3406, 3335, 3051, 2953, 2917, 2860, 1619, 1513, 1436, 1337, 1258, 1107, 840, 739, 542 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (d, 3H, J = 7.0 Hz), 3.52–3.14 (brs, 2H), 4.22 (q, 1H, J = 7.0 Hz), 6.51 (d, J = 8.5 Hz, 2H), 7.13–6.82 (m, 5H), 7.36–7.16 (m, 2H), 7.85–7.71 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 36.1, 111.0, 115.3, 119.1, 119.8, 122.0, 126.9, 128.2, 136.7, 137.2, 144.1; EIMS: 237 (M + H).

3.1.1.2. 3f: 3-[1-(6-bromo-1,3-benzodioxol-5-yl)-3-butynyl]-1H-indole. Brownish solid, mp 134–136 °C; IR (KBr): υ 3422, 3256, 2903, 2833, 2360, 1599, 1475, 1384, 1255, 1102, 1038, 935, 841, 745, 649 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.90 (t, 1H, J = 3.0 Hz), 2.88–2.82 (m, 2H), 4.90 (t, 1H, J = 6.7 Hz), 5.85 (s, 1H), 5.89 (s, 1H), 6.56 (s, 1H), 6.96 (t, 1H, J = 6.7 Hz), 7.02 (s, 1H), 7.10 (t, 1H, J = 6.7 Hz), 7.33–7.18 (m, 3H), 8.01–7.85 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.6, 29.5, 40.2, 70.1, 82.3, 101.6, 109.3, 111.1, 112.2, 114.4, 117.5, 119.4, 121.8, 122.4, 126.8, 135.7, 136.4, 146.9, 147.3; EIMS: 369.1 (M + H).

3.1.1.3. 3k: 1-[1-(5-methoxy-1H-3-indolyl)-3-butenyl]-2-naphthol. Colourless liquid, IR (KBr): 3441, 3067, 2926, 2852, 1621, 1583, 1484, 1259, 1210, 1172, 918, 811, 748 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.25–2.90 (m, 2H), 3.87 (s, 3H), 5.26–4.89 (m, 3H), 5.96–5.73 (m, 1H), 6.05 (s, 1H), 6.25 (d, 1H, J = 2.4 Hz), 6.79–6.69 (m, 1H), 6.93 (d, 1H, J = 8.3 Hz), 7.40–7.13 (m, 3H), 7.67–7.47 (m, 2H), 7.79 (d, 1H, J = 7.4 Hz), 8.02–7.99 (brs, 1H), 8.26 (d, 1H, J = 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 36.4, 55.4, 101.5, 111.9, 113.3, 116.4, 116.6, 119.3, 120.0, 122.0, 122.4, 122.8, 126.6, 127.3,

128.2, 128.4, 129.5, 132.0, 133.0, 136.7, 153.1, 153.8; EIMS: 344.3 ($M+H$).

3.1.1.4. 3p: 1-benzyl-3-[(E)-1,3-diphenyl-2-propenyl]-1H-indole. Colourless solid, mp 121–123 °C; IR (KBr): υ 3060, 3025, 2925, 2853, 1598, 1455, 1386, 1355, 1175, 1072, 964, 740, 965 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 5.09 (d, 1H, $J = 7.4$ Hz), 5.20 (s, 2H), 6.38 (d, 1H, $J = 15.7$ Hz), 6.75–6.61 (m, 1H), 6.81 (s, 1H), 7.38–6.89 (m, 19H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 46.3, 50.0, 109.8, 117.8, 119.2, 120.1, 121.9, 126.4, 126.6, 126.9, 127.2, 127.5, 128.5, 128.8, 130.5, 132.7, 143.5; EIMS: 400.4 ($M+H$).

4. Conclusion

In summary, we have described a simple, convenient and efficient protocol for the alkylation of indoles with benzylic alcohols using PMA/SiO_2 as the novel catalytic system. In addition to its efficiency, simplicity and mild reaction conditions, this method provides high yields of C-3 benzylated indoles in short reaction times with high selectivity. The use of inexpensive and recyclable PMA/SiO_2 catalytic system makes this process quite simple, more convenient, cost-effective and environmentally friendly.

Acknowledgement

ASR thanks CSIR, New Delhi for the award of fellowships.

References

[1] R.J. Sundberg, Indoles, Academic Press, San Diego, 1996.
[2] D.J. Faulkner, Nat. Prod. Rep. 18 (2001) 1.
[3] I. Ninomiya, J. Nat. Prod. 55 (1992) 541.
[4] M. Bandini, A. Melloni, A. Umani-Ronchi, Angew. Chem. Int. Ed. 43 (2004) 550.
[5] J.F. Austin, D.W.C. MacMillan, J. Am. Chem. Soc. 124 (2002) 1172.
[6] K.B. Jensen, J. Thorhange, R.G. Hazel, K.A. Jorgensen, Angew. Chem. Int. Ed. 40 (2001) 160.
[7] N. Srivastava, B.K. Banik, J. Org. Chem. 68 (2003) 2109.
[8] G. Bartoli, M. Bartolacci, M. Bosco, G. Foglia, A. Giuliani, E. Marcantoni, L. Sambri, E. Torregiani, J. Org. Chem. 68 (2003) 4594.
[9] N. Yoshiaki, Y. Masato, I. Youichi, H. Masnobu, U. Sakae, J. Am. Chem. Soc. 124 (2002) 11846.
[10] E. Wenkert, E.C. Angell, V.F. Ferreira, E.L. Michelotti, S.R. Piettre, J.H. Sheu, C.S. Swindell, J. Org. Chem. 51 (1986) 2343.
[11] B.M. Trost, M.L. Crawley, Chem. Rev. (2003) 2921.
[12] S. Ma, S. Yu, Z. Peng, H. Guo, J. Org. Chem. 71 (2006) 9865.
[13] J.S. Yadav, B.V.S. Reddy, A.K. Basak, A.V. Narsaiah, A. Prabhakar, B. Jagadeesh, Tetrahedron Lett. 46 (2005) 639.
[14] M. Westermaier, H. Mayr, Org. Lett. 8 (2006) 4791.
[15] M. Bandini, A. Melloni, A. Umani-Ronchi, Org. Lett. 6 (2004) 3199.
[16] G. De la Herrán, A. Segura, A.G. Csáky, Org. Lett. 9 (2007) 961.
[17] M. Misono, I. Ono, G. Koyano, A. Aoshima, Pure Appl. Chem. 72 (2000) 1305.
[18] I.V. Kozhevnikov, Chem. Rev. 98 (1998) 171.
[19] M.R. Saidi, L. Torkiyan, N. Azizi, Org. Lett. 8 (2006) 2079.
[20] S. Baskaran, G.D.K. Kumar, Chem. Commun. (2004) 1026.
[21] Y. Kita, H. Tohma, G.A. Kumar, H. Yamamoto, Chem. Eur. J. 8 (2002) 5377.
[22] E. Rafiee, H. Jafari, Bioorg. Med. Chem. Lett. 16 (2006) 2463.
[23] K. Okumura, K. Yamashita, M. Hirano, M. Niva, Chem. Lett. 34 (2005) 716.
[24] G.D. Kishore Kumar, S. Baskaran, Synlett (2004) 1719.
[25] G.D. Kishore Kumar, S. Baskaran, J. Org. Chem. 70 (2005) 4520.
[26] E.F. Kozhevnikova, E.G. Derouane, I.V. Kozhevnikov, Chem. Commun. (2002) 1178.
[27] H. Firouzabadi, N. Iranpoor, K. Amani, Synthesis (2003) 408.
[28] J.S. Yadav, S. Raghavendra, M. Satyanarayana, E. Balanarsaiah, Synlett (2005) 2461.
[29] J.S. Yadav, M. Satyanarayana, E. Balanarsaiah, S. Raghavendra, Tetrahedron Lett. 47 (2006) 6095.