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Short communication

A highly selective and efficient acetylation of alcohols and amines with acetic anhydride using $NaHSO_4 \cdot SiO_2$ as a heterogeneous catalyst☆

Biswanath Das*, Ponnaboina Thirupathi

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

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Abstract

Treatment of alcohols and amines (aliphatic and aromatic) with acetic anhydride at room temperature using $NaHSO_4 \cdot SiO_2$ as a heterogeneous catalyst affords the corresponding acetates in excellent yields. The method is highly chemoselective—alcoholic hydroxyl group can be protected while phenolic hydroxyl group remains intact and the amine group can be acetylated in the presence of hydroxyl. Symmetrical diols produced only the monoacetates. The method has been applied for the preparation of venkatasin, a natural coumarino-lignan and of Baylis–Hillman acetates.

Keywords: Alcohols; Amines; Acetylation; $NaHSO_4 \cdot SiO_2$; Selectivity

Protection of functional groups is highly essential in organic synthesis. The alcohols and amines are frequently protected as acetates, which are generally prepared by reaction with Ac_2O in the presence of pyridine [1]. 4-(Dimethylamino)pyridine (DMAP) and 4-pyrrolidino pyridine (PPY) are known to catalyze the acetylation of alcohols [2]. Several Lewis acids, such as TMSCl [3a], $TaCl_5$ [3b], $CoCl_2$ [3c], as well as $Sn(OTf)_2$ [3d], $Cu(OTf)_2$ [3e], $In(OTf)_3$ [3f] and $Sc(OTf)_3$ [3g] are also used for preparation of acetates from alcohols. However, many of these methods are associated with one or more drawbacks such as unavailability of the reagents, harsh reaction conditions, long reaction times, unsatisfactory yields and disturbance to other functional groups. Moreover, selectivity of acetylation is also important in multistep syntheses. Thus a suitable efficient and selective method for acetylation of alcohols and amines is highly useful.

In recent years heterogeneous catalysts have gained importance for their interesting reactivity as well as economic and environmental benefits. In continuation of our work [4] with these catalysts, we have recently observed that silica supported $NaHSO_4$ ($NaHSO_4 \cdot SiO_2$) is highly effective to catalyze the acetylation of alcohols and amines with Ac_2O at room temperature. The catalyst can conveniently be prepared [5] from the readily available bench top reagents, $NaHSO_4$ and silica gel (finer than 200 mesh). Although previously this catalyst was used for transesterification using esters and alcohols [5,6] (or acids [7]) the present systematic studies on acetylation of alcohols and amines with Ac_2O generated some interesting valuable results (regarding reaction times, selectivities and applicabilities). A large number of alcohols (primary, secondary, allylic and benzylic) and amines (aliphatic, aromatic, primary and secondary) were converted into their corresponding acetates in excellent yields (Table 1). The conversion was complete within 15–20 min. The transestrification using $NaHSO_4 \cdot SiO_2$ generally requires high temperature and long reaction times [5,6]. In the present case the acetylation of alcohols was carried out keeping intact other hydroxyl and amine protecting groups, such as acetyl (Table 1, entry 11), benzyl (entry 8), TBDMS (entries 10 and 11), tosyl (entry 14), BOC (entry 9) and acetonide (entries 12–14). The isomerization of an unsaturated alcohol (entry 23) and epimerization of a chiral alcohol (entries 7 and 15) were not observed. The anilines containing both electron-withdrawing group (entry 36) and electron-donating group (entries 35 and 38) in the aromatic ring underwent acetylation smoothly. Acetylation of aliphatic amines (entries 29–33) was somewhat faster than that of anilines (entries 34–38).

The chemoselectivity of the present acetylation method is remarkable. An alcoholic hydroxyl group can conveniently be acetylated keeping intact the phenolic hydroxyl group in a

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* Corresponding author. Tel.: +91 40 7160512; fax: +91 40 7160512.
E-mail address: biswanathdas@yahoo.com (B. Das).

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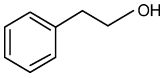
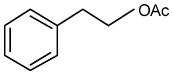
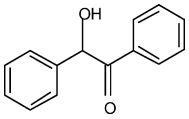
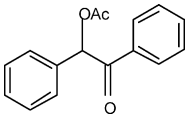
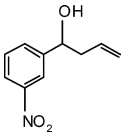
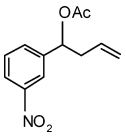
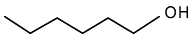
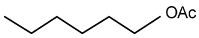
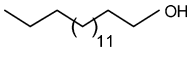
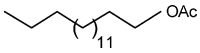
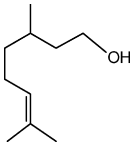
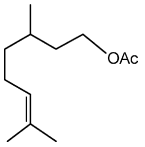
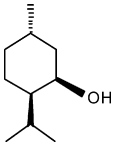
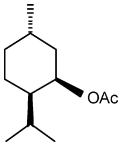
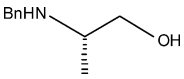
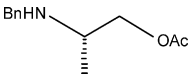
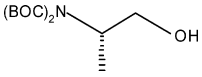
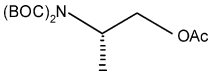
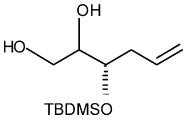
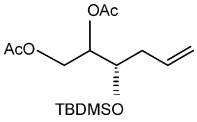
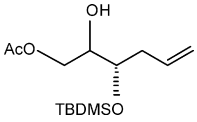
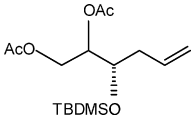
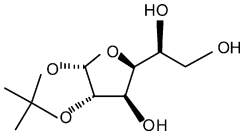
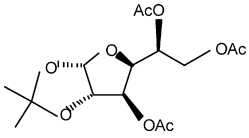
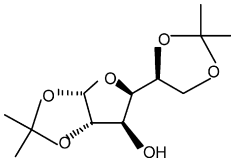
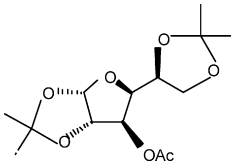
Table 1
Acetylation of alcohols and amines in the presence of $NaHSO_4 \cdot SiO_2$

Entry	Substrate	Product[a]	Time (min)	Yield[b] (%)
1			15	96
2			15	93
3			15	94
4			15	95
5			15	96
6			15	98
7			15	94
8			15	92
9			18	90
10			15	96
11			18	93
12			18	95
13			15	92

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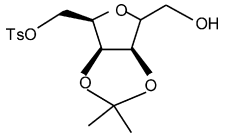
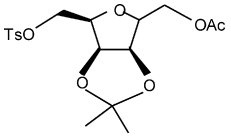
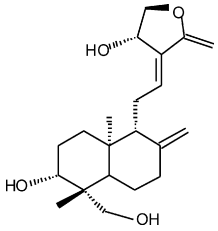
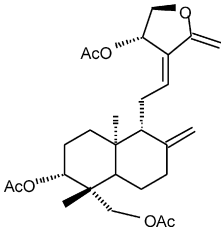
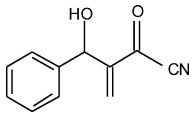
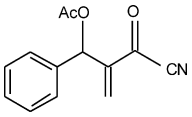
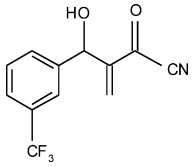
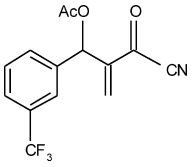
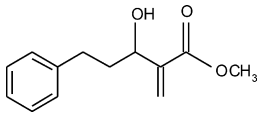
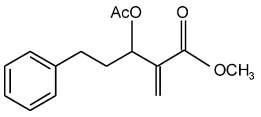
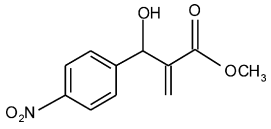
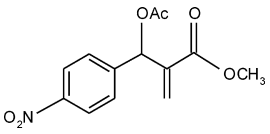
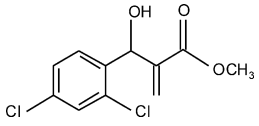
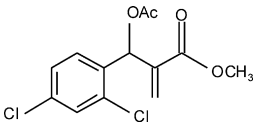
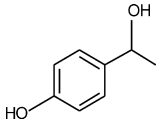
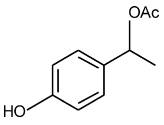
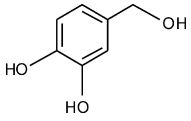
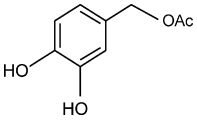
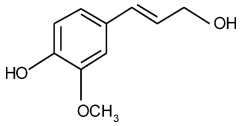
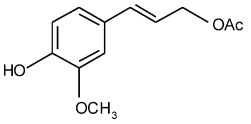
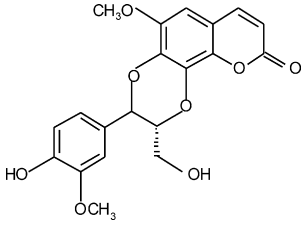
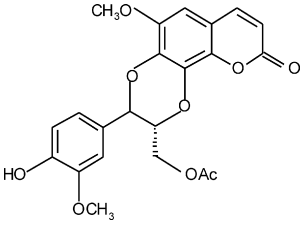
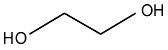
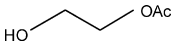
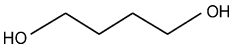
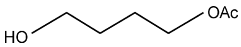
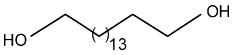
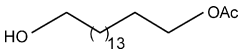
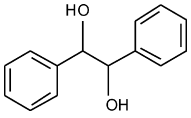
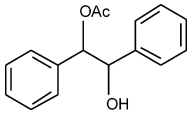
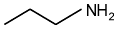
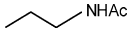
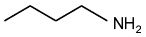
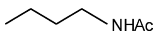
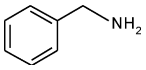
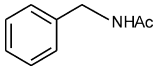
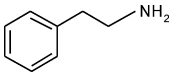
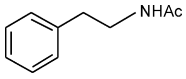
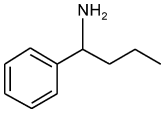
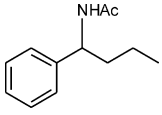
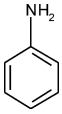
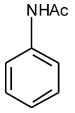
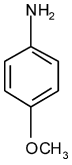
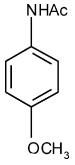
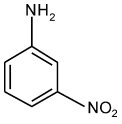
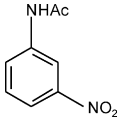
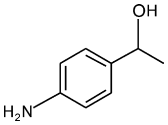
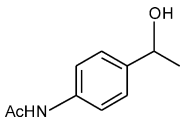
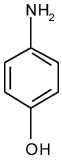
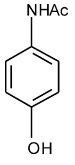
14			15	96
15			20	92
16			15	95
17			15	92
18			15	98
19			15	94
20			15	93
21			15	94
22			15	96
23			15	94
24			15	92

Table 1 (*Continued*)

Entry	Substrate	Product[a]	Time (min)	Yield[b] (%)
25			15	96
26			15	98
27			15	94
28			15	95
29			15	94
30			15	94
31			15	96
32			15	95
33			15	94
34			20	92
35			20	92
36			20	92
37			20	95
38			20	95

[a] All the compounds were characterized by ^{1}H NMR and mass spectral data.
[b] Isolated yields after column chromatography.

molecule (entries 21–24). If the reaction time was increased to 2 h only a minor amount (12–15%) of the diacetyled product was obtained. This selectivity is highly important to carry out modifications to two different types of hydroxyl groups at different stages of a reaction sequence. When in a molecule both hydroxyl and amine groups were present (entries 37 and 38) only the amine group was protected selectively. The interesting selectivity of the method can be utilized for the preparation

of bioactive natural products. Thus cleomiscosin A, a natural anticancer agent, was directly converted into another natural coumarino-lignan, venkatasin [8] (entry 24) by acetylation with Ac_2O in the presence of $NaHSO_4{\cdot}SiO_2$. Symmetrical diols on acetylation by the present method afforded only the monoacetates (entries 25–28).

The other application of the present method is the preparation of Baylis–Hillman acetates [9] from the corresponding adducts (entries 16–20). Baylis–Hillman acetates are useful for the synthesis of stereo-defined trisubstituted alkenes [9]. However, on acetylation with Ac_2O–pyridine Baylis–Hilaman adducts generally form isomeric acetates along with normal acetylation products [10]. The problem can be solved by acetylation of the adducts with Ac_2O catalyzed by $NaHSO_4{\cdot}SiO_2$.

In conclusion, we have developed a simple and efficient method for acetylation of alcohols and amines with Ac_2O using $NaHSO_4{\cdot}SiO_2$ as a heterogeneous catalyst. The notable advantages are (i) mild reaction conditions, (ii) short reaction times, (iii) excellent yields, (iv) application of an inexpensive heterogeneous catalyst, (v) compatibility with other hydroxyl and amine protecting groups, (vi) high chemoselectivity and (vii) monoprotection of symmetrical diols. The method is quite suitable for direct preparation of venkatasin, a natural coumarino-lignan from anticancer agent, cleomiscosin A and for the preparation of Baylis–Hilman acetates from corresponding adducts without affecting isomerization.

1. Experimental

1.1. General procedure for acetylation of alcohols and amines

To a mixture of an alcohol (or amine) (1 mmol) and Ac_2O (1.2 mmol) in CH_2Cl_2 (5 mL) $NaHSO_4{\cdot}SiO_2$ (100 mg) was added. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion of the reaction the mixture was filtered. The filterate was concentrated and the residue was subjected to column chromatography (silica gel, 20% EtOAc in hexane) to obtain pure acetate.

Acknowledgements

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References

[1] T.W. Greene, P.G.M. Wutts, Protecting Groups in Organic Synthesis, John Wiley and Sons, New York, 1991.
[2] (a) G. Hofle, V. Steglich, H. Vorbruggen, Angew. Chem. Int. Ed. Engl. 17 (1978) 569;
(b) E.F.V. Scriven, Chem. Soc. Rev. 12 (1983) 129.
[3] (a) R. Kumareswaran, A. Gupta, Y.D. Vankar, Synth. Commun. 27 (1997) 277;
(b) S. Chandrasekhar, T. Ramchander, M. Takhi, Tetrahedron Lett. 39 (1998) 3263;
(c) J. Iqbal, R.R. Srivastava, J. Org. Chem. 57 (1992) 2001;
(d) T. Mukaiyama, T. Shilina, M. Miyashita, Chem. Lett. (1992) 625;
(e) P. Sarvanaan, V. Singh, Tetrahedron Lett. 40 (1999) 2611;
(f) K.K. Chauhan, C.G. Frost, L. Love, D. Waite, Synlett (1999) 1743;
(g) K. Ishira, M. Kubota, H. Kurihara, H. Yamamoto, J. Org. Chem. 61 (1996) 4560.
[4] (a) B. Das, R. Ramu, B. Ravikanth, K.R. Reddy, Tetrahedron Lett. 47 (2006) 779;
(b) B. Das, P. Thirupathi, V.S. Reddy, Y.K. Rao, J. Mol. Catal. A: Chem. 247 (2006) 233;
(c) B. Das, A. Majhi, J. Benerjee, N. Chowdhury, K.H. Kishore, U.S.N. Murty, Chem. Pharm. Bull. 54 (2006) 403.
[5] G.W. Breton, J. Org. Chem. 62 (1997) 8952.
[6] (a) T. Nishiguchi, H. Taya, J. Chem. Soc., Perkin Trans. I (1990) 172;
(b) T. Nishiguchi, K. Kawamine, T. Ohtsuka, J. Org. Chem. 57 (1992) 312.
[7] B. Das, B. Venkataiah, Synthesis (2000) 1671.
[8] B. Das, B. Venkataiah, A. Kashinatham, Nat. Prod. Lett. 13 (1999) 293.
[9] (a) B. Das, J. Banrjee, G. Mahender, A. Majhi, Org. Lett. 6 (2004) 3349;
(b) B. Das, N. Chowdhury, J. Chowdhury, A. Majhi, G. Mahender, Chem. Lett. 35 (2006) 358.
[10] B. Das, J. Banrjee, A. Majhi, N. Chowdhury, K. Venkateswarlu, H. Holla, Indian J. Chem. 45B (2006) 1729.