Tetrahedron Letters 57 (2016) 5395–5398

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Selective acetylation of primary alcohols by ethyl acetate

Raju Singha [a,b], Jayanta K. Ray [a,*]

[a] Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, India
[b] Department of Chemistry, Panskura Banamali College, Panskura R.S. 721152, India

ARTICLE INFO

Article history:
Received 30 September 2016
Revised 21 October 2016
Accepted 22 October 2016
Available online 24 October 2016

Keywords:
Acetylation
Alcohol
Ethyl acetate
KO^{t}Bu

ABSTRACT

A KO^{t}Bu and ethyl acetate mediated efficient methodology has been developed for the acetylation of primary and secondary alcohols where ethyl acetate is the source of acetyl group. The reaction is fast, mild, efficient, and highly selective towards the primary alcohols.

Introduction

Acetylation of alcohols is one of the most commonly employed transformations in organic chemistry for the synthesis of different fine chemicals, drugs, food preservatives, perfumes, plasticizers, pharmaceuticals etc. [1]. Acetylation of a drug molecule increases its activity and therefore various drug molecules contains acetyl group in their structure such as aspirin (1a), acetylcarnitine (1b), heroin (1c) [2] (see Fig. 1).

Depending upon their tremendous applications in organic synthesis, so many synthetic procedures for the acylations of alcohols have been developed in recent years. Acetyl chloride and acetic anhydride are most commonly employed for the acetylation of alcohols in presence of either acid [3] or base catalysts [4]. Recently differently metal triflates [5] and other metal salts [6] have been used as the efficient catalysts for the acetylation of structurally diverse alcohols with acetic anhydride. Although, most of these methods have successfully perform the desired transformation, however they suffers from some disadvantages such as toxicity, long reaction time, drastic reaction conditions, thermal stability, explosiveness of reagents and most importantly the selectivity problems. Thus in spite of the recent advances, the development of a simple, mild and time efficient procedure with high level of selectivity is still of critical importance.

Herein, we are reporting a short, mild and efficient methodology for the acetylation at room temperature with excellent yields and selectivity towards primary alcohols. There are few reports for the esterification of alcohols by ethyl acetate in presence of different transition metal catalysts [7] under refluxing reaction conditions and herein we are wishing to develop a simple methodology for acetylation under ambient reaction conditions using ethyl acetate as the source of acetyl group. We envisioned that if we reacts any alkoxide (1, Scheme 1) with excess amount of ethyl acetate then the equilibrium (1) (Scheme 1) will lie exclusively towards

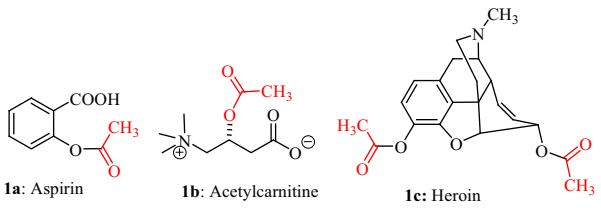
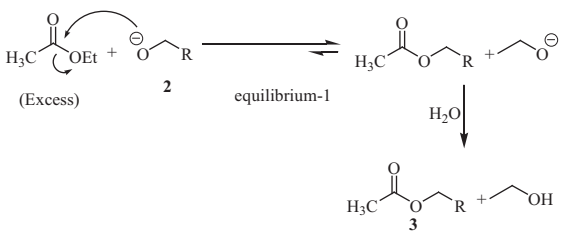


Fig. 1. Drug molecules containing acetyl group.



Scheme 1. Proposed reaction pathway.

* Corresponding author.
E-mail addresses: author@university.edu, jkray@chem.iitkgp.ernet.in (J.K. Ray).

http://dx.doi.org/10.1016/j.tetlet.2016.10.088
0040-4039/

right side. Thus, after workup with water, we will get the O-acetylated product **3**.

Results and discussion

At first we had chosen naphthalen-2-ylmethanol as the model substrate and treated it with different bases in various solvents for 10 min and then we added excess amount of ethyl acetate to the reaction mixture and stirred for the required times. The results are given in Table 1.

At first we stirred the substrate **2a** with KO^{t}Bu (1.0 equiv.) in DMSO (2 mL) at room temperature for 10 min and then 1.0 mL of ethyl acetate was added and the progress of the reaction were monitored by TLC. After 10 min, we observed that the substrate was vanished and then we isolated the acetylated product **3a** in 81% yield. Then we increased the amount of base and found that it gave 92% of acetylated product with two equivalents of KO^{t}Bu and on further increase of equivalent of base did not affect the yield of product. Then we varied the solvents and we found that DMF, DMA and MeCN gave the product in poor yields (Table 1, entries 4–6). The hydrocarbon solvents benzene and toluene also resulted the acetylated product in moderate yields (entry 7, 9). Then we employed different bases and observed that NaOAc, Na_2CO_3 and K_2CO_3 were failed to carry out the reaction. We also employed NaO^{t}Bu and it afforded 2a in 77% of yield. In absence of KO^{t}Bu the starting material remained unreacted. Thus the optimized reaction conditions were: substrate (0.5 mmol), KO^{t}Bu (1.0 mmol), DMSO (2 mL) and stirred at room temperature under argon atmosphere for 10 min. Then 1.0 mL of EtOAc was added and stirred for an additional 10 min. Then the reaction mixture was diluted with water.

After getting the standard reaction conditions we employed different substrates to examine the versatility of the methodology. At first different aryl-2-ylmethanols were used for the reaction and the corresponding acetylated products were obtained in moderate to good yields (Table 2). It was found that the electron rich substrates (Table 2, entries **3b**, **3d**, **3e**, **3g**, **3o**, **3p**) gave slightly higher yields than the electron poor substrates (entries **3c** and **3f**). The halogen containing substrates (entries **3i**-**3l**) gave the products in moderate yields. The thiophene-2-ylmethanol and furan-2-ylmethanol afforded the product in lower yields probably due to the decomposition of the substrates under strong basic conditions. The biphenyl-2-ylmethanols gave the product in good yields whereas the (4-nitrophenyl)methanol did not give any acetylated product due to the decomposition of the substrates as no starting material was recovered. The propargyl acetate (**3w**) was formed in moderate yield where as the cinnamyl alcohol got acetylated in good yield (**3x**). The saturated long chain alcohols got acetylated in quantitative yield (**3y** and **3z**).

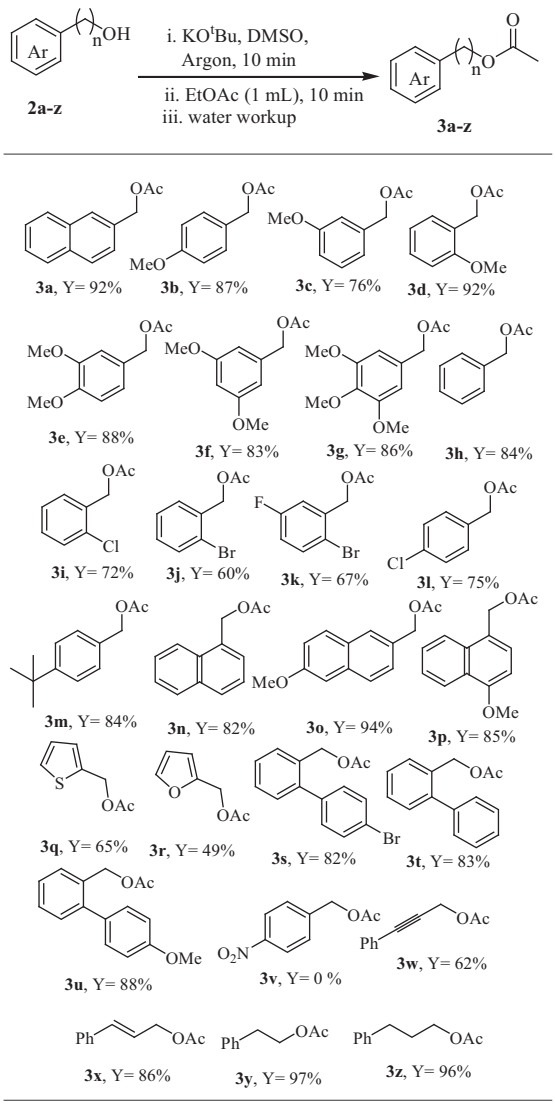
After successful acetylation of primary alcohols, we wished to employ the screened reaction condition on different substituted secondary alcohols to examine the scope of the reaction. When we applied the standard reaction condition on 1-phenylethanol (**4a**), we got the acetylated product only in 34% of yield. Then we increased the reaction time both in step I and step II and we observed the increase of yield to 51%. Then this modified reaction condition was applied on various 2° alcohols and we got the corresponding acetylated products in lower to moderate yields (Table 3). The electron rich substrates (Table 3, entries **5b**, **5c** and **5h**) gave the products in slight higher yields than the analogous electron poor substrates. The 1,2-dihydroacenaphthylen-1-ol afforded higher yield than the other secondary alcohols.

Table 1
Screening of the reaction conditions.[a]

Entry	Solvent	Base	Time (min)	Yield[b]
1	DMSO	KO^{t}Bu(1)	10	81
2	DMSO	KO^{t}Bu(2)	10	92
3	DMSO	KO^{t}Bu(3)	10	92
4	DMF	KO^{t}Bu(2)	30	24
5	DMA	KO^{t}Bu(2)	30	18
6	MeCN	KO^{t}Bu(2)	30	32
7	Benzene	KO^{t}Bu(2)	30	66
8	Cy-hexane	KO^{t}Bu(2)	30	37
9	Toluene	KO^{t}Bu(2)	30	71
10	DMSO	NaOAc(2)	120	00
11	DMSO	Na_2CO_3(2)	120	00
12	DMSO	K_2CO_3(2)	120	00
13	DMSO	NaO^{t}Bu(2)	30	77
14	DMSO	–	120	00

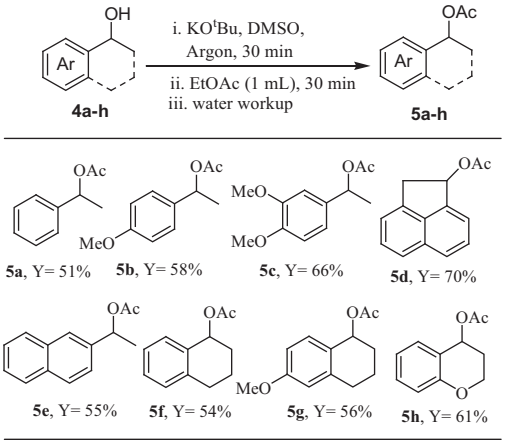
[a] Reaction conditions: (i) substrate 79 mg (0.5 mmol), base (equivalent), solvent 2 mL, r.t., 10 min; (ii) EtOAc (1 mL), r.t., 10 min, (iii) diluted with water.
[b] Isolated yield.

Table 2
Acetylation of different arylmethanols.[a,b]



[a] Isolate yields.
[b] Reaction conditions: substrate (0.5 mmol), KO^{t}Bu (1.0 mmol), DMSO (2 mL) and stirred at room temperature under argon atmosphere for 10 min. Then 1.0 mL of EtOAc was added and stirred for an additional 10 min. Then the reaction mixture was diluted with water.

Table 3
Acetylation of secondary alcohols.[a,b]

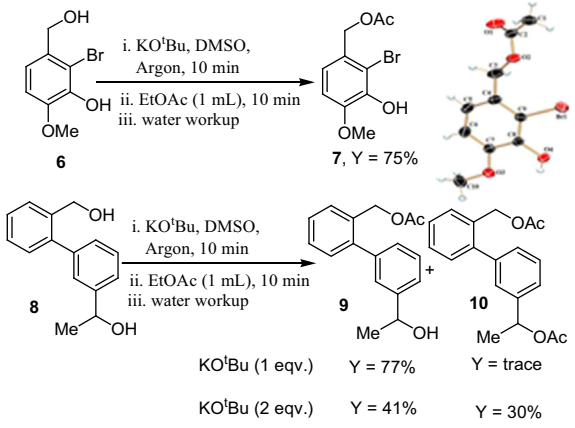


[a] Isolate yields.
[b] Reaction conditions: substrate (0.5 mmol), KO^{t}Bu (1.0 mmol), DMSO (2 mL) and stirred at room temperature under argon atmosphere for 30 min. Then 1.0 mL of EtOAc was added and stirred for an additional 30 min. Then the reaction mixture was diluted with water.

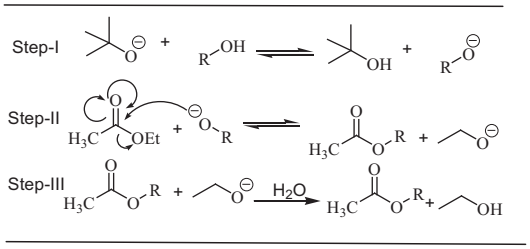
After getting success in the acetylation of primary and secondary alcohols, we employed our methodology on other systems and we found that phenol and aniline remained intact under the standard reaction conditions. Then we wanted to check the selectivity of the methodology and for that we examined the reaction on a substrate **6** (Scheme 2) containing both phenolic and alcoholic OH groups and we observed that only the alcoholic OH group got acetylated and afforded the product **7** in 75% yield. The structure of compound **7** was confirmed from the X-ray crystal structure (CCDC No. 1403960). Then we performed the reaction with a substrate **8** having both primary and secondary hydroxyl group and we found that the mono acetylation occurred selectively to the primary hydroxyl group with one equivalent Of KO^{t}Bu while the two equivalent Of KO^{t}Bu gave both mono- and di-acetylated product in 41% and 30% of yields respectively (Scheme 2).

From the experimental results we observed that primary alcohols are the most suitable substrate and phenols, anilines are the worst substrate for acetylation under the reaction condition. The order of reactivity of alcohols are 1° > 2° > 3°. All the results can be explained using the following three step reaction mechanism (Scheme 3).

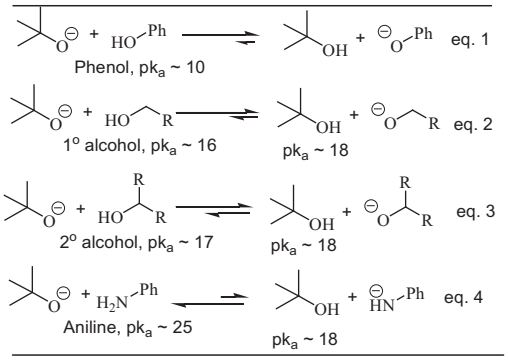
The step-I is a typical acid base reaction and hence there will be an equilibrium between *tert*-butoxide and the alkoxide as formed. The step-II is a transesterification reaction [8] and the equilibrium



Scheme 2. Selectivity study.



Scheme 3. Reaction mechanism.



Scheme 4. Mode of equilibrium at step-I.

depends upon stability of the alkoxide and ethoxide. The step-III is basically quenching of alkoxide. Phenol is much more acidic ($pk_a \sim 10$) than *tert*-butanol ($pk_a \sim 18$) as well as ethanol ($pk_a \sim 16$). Thus the equilibrium at step-I remains exclusively towards right (Scheme 4, Eq. (1)) but the step-II remains towards left as the phenoxide is much more stable than ethoxide. For aniline ($pk_a \sim 25$) the equilibrium at step-I remains solely towards left (Scheme 4, Eq. (4)). Thus phenol and aniline remain intact under the reaction condition. For the primary alcohols, both the step-I and step-II lies towards right side and hence the acetylation occurs with high yield. In case of secondary alcohols the equilibrium at step-I lies slightly on right side but due to increase of steric crowding the rate at step-II becomes slow. Thus for secondary alcohol the rate of reaction is slower and gave lower yields.

Conclusions

In conclusion, we have developed a KO^{t}Bu mediated mild, short and efficient methodology for the acetylation of alcohols at room temperature where EtOAc serves as the source of acetyl group [9]. The versatility and generality of the method was examined using different aliphatic, benzylic, allylic and propargylic alcohols. We hope that our methodology will be very much useful in organic synthesis because of its short reaction time, cheap reagent, and good selectivity with excellent yield and finally easily manageable reaction conditions at room temperature.

Acknowledgement

We would like to thank DST, Government of India for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.10.088.

References

[1] (a) L. Mrozek, L. Dvorakova, Z. Mandelova, L. Rarova, A. Rezacova, L. Placek, R. Opatrilova, J. Dohnal, O. Paleta, V. Kral, P. Drasar, J. Jampilek, Steroids 76 (2011) 1082;
(b) B. Schilter, G. Scholz, W. Seefelder, Eur. J. Lipid Sci. Technol. 113 (2011) 309;
(c) R. Nagase, N. Matsumoto, K. Hosomi, T. Higashi, S. Funakoshi, T. Misaki, Y. Tanabe, Org. Biomol. Chem. 5 (2007) 151;
(d) A. Zoller, A. Marcilla, J. Appl. Polym. Sci. 121 (2011) 1495;
(e) T. Verdelet, G. Mercey, N. Correa, L. Jean, P.Y. Renard, Tetrahedron 67 (2011) 8757.

[2] Alan Jones, Chemistry: An Introduction for Medical and Health Sciences, John Wiley & Sons, 2015, pp. 5–6.

[3] (a) A. Orita, C. Tanahashi, A. Kakuda, J. Otera, Angew. Chem. Int. Ed. 39 (2000) 2877;
(b) R. Alleti, M. Perambuduru, S. Samanha, V.P. Reddy, J. Mol. Catal. A Chem. 226 (2005) 57;
(c) B. Karimi, J. Maleki, J. Org. Chem. 68 (2003) 4951;
(d) N. Ahmed, J.E. Van Lier, Tetrahedron Lett. 47 (2006) 5345;
(e) R.H. Tale, R.N. Adude, Tetrahedron Lett. 47 (2006) 7263;
(f) T.S. Reddy, M. Narasimhulu, N. Suryakiran, K.C. Mahesh, K.Y. Ashalatha, Tetrahedron Lett. 47 (2006) 6825;
(g) P. Phukan, Tetrahdron Lett. 45 (2004) 4785;
(h) R. Dalpozzo, A. De Nino, L. Maiuolo, A. Procopio, M. Nardi, G. Bartoli, R. Romeo, Tetrahedron Lett. 44 (2003) 5621;
(i) A. Kamal, M.N.A. Khan, K.S. Reddy, Y.V.V. Srikanth, T. Krishnaji, Tetrahedron Lett. 48 (2007) 3813;
(j) S. Velusamy, S. Borpuzari, T. Punniyamurthy, Tetrahedron Lett. 2005 (2011) 61;
(k) G. Bartoli, M. Bosco, R. Dalpozzo, E. Marcantoni, M. Massaccesi, L. Sambri, Eur. J. Org. Chem. (2003) 4611;
(l) N. Ghaffari Khaligh, J. Mol. Catal. A Chem. 363–364 (2012) 90;
(m) F. Rajabi, Tetrahedron Lett. 50 (2009) 395;
(n) L. Osiglio, A.G. Sathicq, G.P. Romanelli, M.N. Blanco, J. Mol. Catal. A Chem. (2012) 359;
(o) I. Lopez, J.L. Bravo, M. Caraballo, J.L. Barneto, G. Silvero, Tetrahedron Lett. 52 (2011) 3339.

[4] (a) W. Steglich, G. Hofle, Angew. Chem. Int. Ed. 8 (1969) 981;
(b) E. Vedejs, T.S. Diver, J. Am. Chem. Soc. 115 (1993) 3358;
(c) E.F.V. Scriven, Chem. Soc. Rev. 12 (1983) 129;
(d) S. Tomohumi, O. Kousaburo, O. Takashi, Synthesis (1991) 1141.

[5] (a) K.K. Chauhan, C.G. Frost, I. Love, D. Waite, Synlett (1999) 1743;
(b) A. Orita, C. Tanahashi, A. Kakuda, J. Otera, Angrew. Chem. Int. Ed. 39 (2000) 2877;
(c) M. Moghadam, S. Tangestaninejad, V. Mirkhani, I.M. Baltork, M. Babghanbari, L. Zarea, J. Iran. Chem. Soc. 6 (2009) 523;
(d) N. Iranpoor, M. Shekarrize, Bull. Chem. Soc. Jpn. 72 (1999) 455;
(e) R. Alleti, M. Perambuduru, S. Samantha, V. Prakash, V.P. Reddy, J. Mol. Catal. A Chem. 226 (2005) 57;
(f) K. Ishihara, M. Kubota, H. Kurihara, H. Yamamoto, J. Am. Chem. Soc. 117 (1995) 6639;
(g) K. Ishihara, M. Kubota, H. Kurihara, H. Yamamoto, J. Org. Chem. 61 (1996) 4560;
(h) K. Ishihara, M. Kubota, H. Yamamoto, Synlett (1996) 265;
(i) A.G.M. Barrett, D.C. Braddock, Chem. Commun. (1997) 351;
(j) H. Zhao, A. Pendri, R.B. Greenwald, J. Org. Chem. 63 (1998) 7559;
(k) P.A. Procopiou, S.P.D. Baugh, S.S. Flack, G.G.A. Inglis, J. Org. Chem. 63 (1998) 2342;
(l) P.A. Procopiou, S.P.D. Baugh, S.S. Flack, G.G.A. Inglis, J. Chem. Soc. Chem. Commun. (1996) 2625.

[6] (a) M. Miyashita, I. Shiina, S. Miyoshi, T. Mukaiyama, Bull. Chem. Soc. Jpn. 66 (1993) 1516;
(b) Y. Nakae, I. Kusaki, T. Sato, Synlett (2001) 1584;
(c) G. Bartoli, M. Bosco, R. Dalpozzo, E. Marcantoni, M. Massaccesi, S. Rinaldi, L. Sambri, Synlett (2003) 39;
(d) T. Nishiguchi, H.J. Taya, Chem Soc. Perkin Trans. 1 (1990) 172.

[7] (a) T. Iwasaki, Y. Maegawa, Y. Hayashi, T. Ohshima, K. Mashima, Synlett (2009) 1659;
(b) M.M. Heravi, K. Bakhtiari, N.M. Javadi, H.A. Oskooie1, F.F. Bamoharram, Monatshefte fur Chemie 138 (2007) 445.

[8] (a) J. Otera, Chem. Rev. 93 (1993) 1449;
(b) H.E. Hydonckx, D.E. De Vos, S.A. Chavan, P.A. Jacobs, Top. Catal. 27 (2004) 83;
(c) G.A. Grasa, R. Singh, S.P. Nolan, Synthesis (2004) 971.

[9] General procedure for the acetylation of alcohols: The alcohol (0.5 mmol) and KO^{t}Bu (1.0 mmol) were taken in a two-neck round bottomed flask and then purged with nitrogen gas. Then 2 mL of dimethylsulphoxide (DMSO) was added to it and the reaction mixture was stirred at room temperature for 10 min. Then 1.0 mL of EtOAc was added to it and the stirring was continued for an additional 10 min. After completion of the reaction, the reaction mixture was diluted with water and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, evaporated under reduced pressure. Then the crude product was purified by column chromatography using silica gel (60–120 mesh) and hexane/EtOAc as eluent.