Selective Acylation of Alcohols in the Presence of Phenols

MUHAMMAD RAZA SHAH*, QAMAR ALI, ZAHID HUSSAIN AND ITRAT ANIS
International Centre of Chemical and Biological Sciences, H.E.J. Research Institute of Chemistry, University of Karachi, Karachi-75270, Pakistan.
raza_shahm@yahoo.com*

(Received on 5th July 2010, accepted in revised form 10th December 2010)

Summary: A versatile method of chemoselective acylation of alcohol has been developed by way of Mitsunobu based strategy. The reaction works under mild conditions and can be selectively employed in presence of phenolic groups and acid sensitive functionalities.

Introduction

Selective acylation of alcohol has enjoyed great attraction of chemists due to its significance in synthetic organic chemistry especially in protecting group chemistry as reflected by the number of methods that have been developed to effect this transformation. To meet the challenging task of chemoselective transformation of aliphatic alcohols in the presence of phenolic alcohol mainly acidic catalyst ($Sc(OTf)_3/Ac_2O$ [1], $TMSOTf/Ac_2O$ [2], $CH_3(OMe)_3/TMSCl$ [3] have been developed. Beside acidic catalysts somewhat neutral distannoxane [4] and silica gel supported sodium hydrogen sulphate [5] are also reported for selective acylation.

Although the aforementioned catalysts are effective but have some limitations like the acidic conditions in lewis acid catalysed acylation leads to the cleavage of acid sensitive functionalities such as TBDMS, diene, oxazoline and epoxide.

The chemical transformation of methanol and cyclohexanol are most frequently employed in natural product synthesis while somewhat neutral distannoxane [4] is inert towards these. Similarly silica gel supported sodium hydrogen sulphate [5] is not useful for sterically bulky hydroxyl group because hydroxyl with bulky groups experience steric hindrance from the surface of silica gel.

Mitsunobu [6] reaction is quite frequently employed for esterification in organic synthesis. The reaction conditions of Mitsunobu are extremely mild due to which a wide range of functional groups are compatible to it like acetals [7], epoxides [8], TBDMS [9], oxazoline [10], nitro [11], lactames [12], esters [9].

In view of its mechanism [13] we realised that chemoselective transformation of alcohols is limited to alcohols in the presence of phenols.

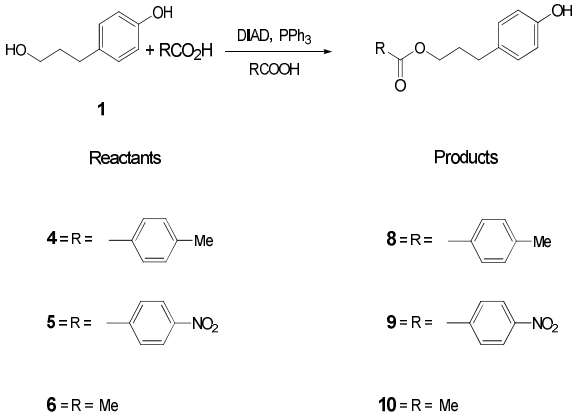
Results and Discussion

To test the selectivity of Mitsunobu reaction for acylation compound **1** (Scheme 1) was examined as a model substrate, treating with carboxylic acids **4, 5** and **6** (Scheme 1) in THF in the presence of PPh_3 and di-isopropyl azodicarboxylate (DIAD). After 17-19 hours of stirring at room temperature corresponding esters of aliphatic hydroxyl group were formed in good yield and high selectivity without affecting the aromatic hydroxyl group (Table-1).

Table-1: Selectivity and %yields of the Mitsunobu reaction.

Substrate	Product	% Yields of isolated products	Selectivity	Time(h)/ rt
1 + 4	8	80	Excellent	17
1 + 5	9	82	Excellent	18
1 + 6	10	79	Excellent	19
2 + 7	11	81	Excellent	19

The scope and generality of the reaction for selective acylation were explored by reaction of compound **1** (Scheme 1) with aromatic carboxylic acid (*i.e;* **4** and **5**) (Scheme 1) having either electron donating or electron withdrawing group. In both cases the reaction was excellent in selectivity and as well as reactivity. To further asses the wide applicability of the reaction, aliphatic carboxylic acid were employed. Thus when compound **1** was treated with **6** (CH_3COOH) the corresponding acetate was obtained in excellent yield. This acylation cannot be achieved by using Cp^*_2Smthf [14], since it is known that acetic acid destroy the samarium catalyst.



Scheme 1: Acylation of aliphatic alcohol in the presence of aromatic alcohols via Mitsunobu.

*To whom all correspondence should be addressed.

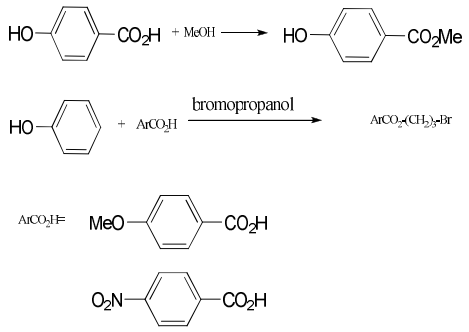
Literature reveals that a wide range of functionalities are compatible with Mitsunobu reaction.

When benzyl alcohol was treated with acetic acid, benzyl acetate was obtained in excellent yield. Moreover the work of Ganguly *et al*.. [15] shows that allylic and propargylic alcohols are also stable under Mitsunobu condition without accompanying any rearrangement. On the other hand Sabitha *et al.* [3] has reported that when benzyl alcohol was subjected to $CH_3(OMe)_3$/TMSCl, a dimerized product was obtained and similarly cinnamyl alcohol resulted in rearranged product, clearly demonstrating the versatility of Mitsunobu reaction. TMSOTf/Ac_2O [2] system was also used for the selective acylation of aliphatic hydroxyl group of 4-hydroxyphenyl ethanol. In this case due to thermodynamic equilibrium, the desired aliphatic ester was obtained after 3.5 days in 93% yield however accompanied by 7% of aromatic ester. In addition it is reported [16] that acetonide group is not stable under TMSOTf/Ac_2O conditions, contrary the Mitsunobu reaction was shown to be compatible with acetonide [21]. $Sc(OTf)_3/Ac_2O$ [1] is also an important catalyst for selective acylation, but the use of corrosive reagent (i.e.,Ac_2O) and extremely low temperature for fruitful reactivity of acid sensitive group decrease its appreciability in literature. Furthermore Orita *et al.* [18] reported that when geraniol was subjected to $Sc(OTf)_3/Ac_2O$ conditions, multiple products were obtained while Marriott *et al.* [19] has reported the tolerance of geraniol functionality under Mitsunobu conditions.

Silica gel supported sodium hydrogen sulphate [5] is also a very good catalyst for selective acylation of aliphatic alcohol in the presence of phenols, but the catalyst is commercially not available and it is useful for only small sized sterically free hydroxyl group as hydroxyl with bulky group experience steric hindrance from the surface of silica gel. On the other hand literature [20] shows that Mitsunobu does not encounter with such difficulties.

The importance of amide in selective acylation has been discovered by Yamada *et al.* [21] by the use of twisted amide for acylation. However the catalyst is commercially not available, the reaction conditions are also a little vigorous (high temp, *i.e.,* 80°C) and the yield of monoester recorded by GLC is rather low.

Mitsunobu reaction is also used for etherification in organic synthesis. We carried out a reaction between *p*-hydroxybenzoic acid and methanol to check the competition reaction of phenolic hydroxyl and carboxylic acid towards methanol, which afforded *p*-hydroxy methyl benzoate in quantitative yield and good selectivity. In order to explore the competition of esterification over etherification competitive reactions were carried out, a 1:1 mixture of *p*-nitrobenzoic acid and phenol was treated with 1eq of bromopropanol in the presence of DIAD and PPh_3 (Scheme 2) which resulted in *p*-nitrobenzoate exclusively, no traces of phenolic ether were observed in the ^{1}H NMR spectra of the crude product. Similarly 1eq of bromopropanol was reacted with 1:1 mixture of anisic acid and phenol under Mitsunobu condition which afforded anisic ester without subsequent formation of phenolic ether.

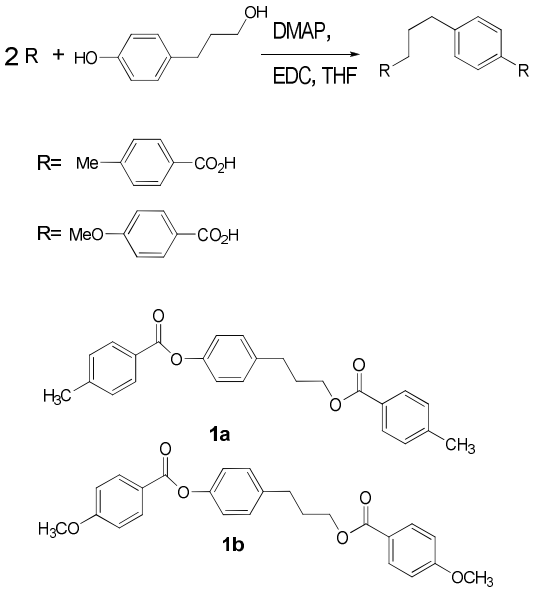


Scheme 2**:** Selectivity between esterification and etherification Mitsunobu (DIAD, PPh_3, THF, rt).

The above competitive experiments of phenol with either electron withdrawing (i.e., *p*-nitrobenzoic acid) or electron donating moieties (*p*-anisic acid) showed that selective acylation of alcohol can be carried out in the presence of phenolic hydroxyl group without subsequent etherification (Scheme 2).

In case of the Mitsunobu all reagents are commercially available; reaction is carried out at room temperature and the yield of monoester is also high.

To investigate the selectivity of the reaction and having authentic compounds for comparison, we synthesized compound **1a** and **1b** by treating **1** with 3 equiv. of tolulic acid and *p*-anisic acid respectively in the presence of DMAP and EDC in THF (Scheme 3). ^{1}H NMR of compound **1a** and **1b** showed that phenolic protons next to hydroxyl group shifted 0.5 ppm upon acylation. The crude product spectra of all synthesized compounds were compared with spectra of **1a** and **1b**, no peaks were found in the expected region.



Scheme 3: Synthesis of diacylated product by alternate method for comparison

Furthermore the integration of protons near to phenolic hydroxyl group was found to be exactly matching with the rest of protons in the spectra of crude products. These evidences show that the reaction is highly selective.

Purification of product from reaction mixture is also a problem in organic synthesis. Mitsunobu reaction has also by-products such as triphenylphosphine oxide and reduced azodicarboxylate which sometimes gives problems in purification we also faced problems in this regard because upon acylation, protons next to phenolic hydroxyl group were expected at 7 - 7.5 ppm as shown by the spectra of compound **1a**, **1b** and the increment taken from literature[21b], but this region was occupied by phosphine oxide protons, to solve this problem we carried out parallel experiments by using the standard reagents (i.e.; PPh_3/DIAD) and the reagent reported by Kiankarimi et al[22]. He replaced triphenylphosphine by biphenyl 2-pyridylphosphine and diisopropyl azodicarboxylate by di-*tert*-butylazodicarboxylate, which are having the same flexibility and high yields but make the purification of the product easy.

These new reagents can easily be extracted to aqueous phase on acidic work up. No difference in term of selectivity and reactivity were found except that we got considerably clean product with Kiankarimi a reagent, due to which now the region from 7 - 7.5 ppm was reasonably clean and the detection of protons next to phenolic hydroxyl group resulted from acylation was possible, subsequently no peaks were found for these protons. Beside this the acylation of phenolic hydroxyl should result an additional set of peak at 8 - 8.5 ppm as shown by the ^{1}H NMR spectra of compound **1a** and **1b** but no additional peak were observe in this region.

The introduction of these new reagents which are commercially available increased the utility of the Mitsunobu reaction because with just acidic work up reasonably pure product can be obtained which in most cases don't need further purification.

Experimental

All chemicals were obtained from commercial suppliers. For flash chromatography *Merck* silica gel (mesh 230-400) was used. TLC was carried out on silica gel coated aluminium foils (*Merck* alumina foils 60 F254). Compounds were detected using UV light. NMR spectra were recorded in $CDCl_3$ as solvent and internal standard on *Bruker AMX-300 MHz* at room temperature. The melting points were determined by using *Reicher Thermovar* melting table microscope. THF was distilled from Na / benzophenone.

Typical procedure for acylation of alcohols with acid.

To a mixture of alcohol (1 equiv.) and triphenyl phosphine (1.2 equiv.) in THF was added carboxylic acid (1.05 equiv.). Then the mixture was cooled in an ice bath and diisopropylazodicarboxylate (1.2 equiv.) was added. After stirring for 18h the solvent was removed under reduced pressure and the compound was isolated by column chromatography (acetone : petroleum ether 2:8 v/v).

3-(4-Hydroxyphenyl) toluene propionate (**8**)

Colourless crystals; m.p. 124-125 ºC, Elemental analysis (calcd. $CH_{17}H_{18}O_3$, C=75.53 %, H=6.71 % O=17.76%; Found C=75.21% H=7.01% O=18.02%). HR-EI-MS: Found *m/z* 270.351 (calcd for $C_{17}H_{18}O_3$, 270.1312). ^{1}H NMR δ = 2.08 (m, 2H), 2.69 (*t*, 2H), 4.3 (*t*, 2H), 6.75, 7.14 (A´A X´X, 2H each, H-Ar), 7.25, 7.91 (A´A X´X 2H each, ArH).

3-(4-Hydroxyphenyl) *p*-nitrophenyl propionate (**9**)

Colourless crystals; m.p. 120-121 ºC, Elemental analysis (calcd. $C_{16}H_{15}NO_5$, C=63.78 %, H=5.02 % O=26.55% N=4.65; Found C=63.88% H=5.12% O=26.81%). HR-EI-MS: Found *m/z* 301.1312 (calcd for $C_{16}H_{15}NO_5$, 301.29).^{1}H-NMR δ = 2.08 (m, 2H), 2.69 (*t*, 2H), 4.3 (*t*, 2H), 6.75, 7.14

(A´A X´X 2 H each, H-OPh), 8.27, 8.15 (A´A X´X 2H each, -$C_6H_4NO_2$)

3-(4-Hydroxyphenyl) propanacetate (**10**)

Colourless crystals; m.p. 119-121 ºC, Elemental analysis (calcd. $C_{11}H_{14}O_3$, C=68.02%, H=7.27% O=24.71%; Found C=68.41% H=7.42% O=24.82%). HR-EI-MS: Found *m/z* 194.251 (calcd for $C_{11}H_{14}O_3$, 194.23).^{1}H-NMR δ = 1.89 (m, 2H), 2.04 (s, 3H) 2.61 (*t*, 2H), 4.06 (*t*, 2H), 6.74, 7.01 (A´A X´X 2H each, H-Ar)

3-(4-Hydroxy 3, 5-diiodophenyl)-*p*-anisic propionate (**11**)

Amorphous powder; m.p. 98-101 ºC, Elemental analysis (calcd. $C_{17}H_{16}I_2O_4$, C=37.94%, H=3%, I=47.17%, O=11.89%; Found C=37.81%, H=3.31%, I=47.47%, O=11.97%). HR-EIMS: Found *m/z* 538.35 (calcd for $C_{17}H_{16}I_2O_4$ 538.12)

^{1}H NMR δ = 2.02 (m, 2H), 2.60 (*t*, 2H), 4.27 (*t*, 2H), 6.89, 7.93 (A´A X´X 2H each, H-Ar), 7.50 (*s*, 2H).

Methyl 4-hydroxybenzoate (**12**)

Colourless crystals; m.p. 89-91 ºC, Elemental analysis (calcd. $C_8H_8O_3$, C=63.15%, H=5.31% O=31.55%; Found C=63.25% H=5.25% O=32.01%). HR-EI-MS: Found *m/z* 152.05 (calcd for $C_8H_8O_3$, 152.26).^{1}H NMR δ = 7.91 (d, *J* = 8.5 Hz, 2H, ArH-2 and 6), 6.89 (d, *J* = 8.5 Hz, 2H, H-3 and 5), 3.90 (s, 3H, COO**Me**).

3-Bromo-propane 4-methoxybenzoate (**13**)

Colourless crystals; m.p. 118-121 ºC, Elemental analysis (calcd. $C_{20}H_{31}BrO_3$, C=65.15%, H=7.82%, Br=20.01%, O=12.02%; Found C=65.05% H=7.42%, Br=20.35%, O=12.42%). HR-EI-MS: Found *m/z* 398.251 (calcd for $C_{11}H_{14}O_3$, 398.15). ^{1}H NMR δ = 7.93, 6.98 (d, *J* = 8.5 Hz, 2H each, Ar-H-2, 6, 3 and 5), 4.33 (t, *J* = 6.7 Hz, 2H, COOC**H**$_2$), 3.83 (s, 3H, OCH_3), 3.36 (t, 2H, C**H**$_2$Br), 1.83 (m, C**H**$_2$CH$_2$Br), 1.78(m, 2H, OCH_2C**H**$_2$), 1.59-1.23 (m, 2H, CH_2).

3-Bromo-propane 4-nitrobenzoate (**14**)

Colourless crystals; m.p. 123-121 ºC, Elemental analysis (calcd. $C_{19}H_{28}BrNO_4$, C= 55.08%; H= 6.81%; Br= 19.28%; N= 3.38%; O= 15.45% ; Found C= 55.28%; H= 7.01%; Br= 19.08%; N= 3.28%; O= 15.65%). HR-EI-MS: Found *m/z* 414.251 (calcd for $C_{19}H_{28}BrNO_4$, 413.12). ^{1}H NMR δ = 8.25, 8.15 (d, *J* = 8.4 Hz, 2H each, Ar-H-2, 6, 3 and 5), 4.32 (t, *J* = 6.6 Hz, 2H, COOC**H**$_2$), 3.84 (s, 3H, OCH_3), 3.37 (t, 2H, C**H**$_2$Br), 1.82 (m, C**H**$_2$CH$_2$Br), 1.76 (m, 2H, OCH_2C**H**$_2$), 1.58-1.25 (m, 2H, CH_2).

3-{4-[(4-methylbenzoyl)oxy]phenyl}propyl 4-methylbenzoate (**1a**)

Colourless crystals; m.p. 134-136 ºC, Elemental analysis (calcd. $C_{25}H_{24}O_4$, C=77.30%, H=6.23%, O=16.47%; Found C=77.50%, H=6.43%, O=16.77%). HR-EI-MS: Found *m/z* 388.171 (calcd for $C_{25}H_{24}O_4$, 398.15). ^{1}H NMR δ = 8.15 (A´A X´X, 2H, Ar$_\gamma$-H-2, 6), 8.11 (A´A X´X, 2H, Ar$_\alpha$-H-2, 6), 7.99 (A´A X´X, 2H, Ar$_\beta$-H-2, 6), 7.31 (A´A X´X, 2H, Ar$_\gamma$-H-3, 5), 7.28 (A´A X´X, 2H, Ar$_\alpha$-H-3, 5), 7.15 (A´A X´X, 2H, Ar$_\beta$-H-3, 5), 4.31 (t, 6.0 Hz, 2H, OCH_2), 2.41 (s, 3H, Ar$_\gamma$CH$_3$), 2.42 (s, 3H, Ar$_\beta$CH$_3$), 2.69 (apparent triplet, *J* ~ 7Hz, ArC**H**$_2$CH$_2$), 2.08 (m, 2H, Ar CH_2C**H**$_2$CH$_2$).

3-{4-[(4-methoxybenzoyl)oxy]phenyl}propyl 4-methoxybenzoate (**1b**)

Colourless crystals; m.p. 141-139 ºC, Elemental analysis (calcd. $C_{25}H_{24}O_6$, C=71.41%, H=5.75%, O=22.83%; Found C=72.61%, H=6.05%, O=22.93%). HR-EI-MS: Found *m/z* 420.45 (calcd for $C_{25}H_{24}O_6$, 420.16). ^{1}H NMR δ = 8.20 (A´A X´X, 2H, Ar$_\gamma$-H-2, 6), 8.15 (A´A X´X, 2H, Ar$_\alpha$-H-2, 6), 7.95 (A´A X´X, 2H, Ar$_\beta$-H-2, 6), 6.99 (A´A X´X, 2H, Ar$_\gamma$-H-3, 5), 6.95 (A´A X´X, 2H, Ar$_\alpha$-H-3, 5), 6.91 (A´A X´X, 2H, Ar$_\beta$-H-3, 5), 4.32 (t, 6.0 Hz, 2H, OCH_2), 3.88 (s, 3H, Ar$_\gamma$$OCH_3$), 3.84 (s, 3H, Ar$_\beta$$OCH_3$), 2.70 (apparent triplet, *J* ~ 7 Hz, ArC**H**$_2$CH$_2$), 2.07 (m, 2H, Ar CH_2C**H**$_2$CH$_2$).

Conclusion

In conclusion we have shown that highly selective acylation of aliphatic hydroxyl group in the presence of phenolic hydroxyl group has been achieved in excellent yield with a variety of carboxylic acid groups. It is also found that a wide range of functional groups are compatible with Mitsunobu reaction conditions. The purification problems were solved by the use of new reagents.

References

1. K. Ishihara, M. Kuboto, H. Kurihara and H. Yamamoto, *Journal of the Organic Chemistry*, **61**, 4560 (1996).
2. P. A. Procopiou, S. P. D. Baugh, S. S. Flack and G. G. A. Inglis, *Journal of the Organic Chemistry*, **63**, 2342 (1998).

3. G. Sabitha, S. V. B. Reddy, K. S. G. Reddy and S. J. Yadav, *New Journal of Chemistry*, **24**, 63 (1998).
4. A. Orita, K. Sakamoto, Y. Hamada, A. Mitsutome and J. Otera, *Tetrahedron*, **55**, 2899 (1999).
5. W. G. Breton, *Journal of the Organic Chemistry*, **62**, 8952 (1997).
6. O. Mitsunobu, M. Wada and T. Sano, *Journal of the American Chemical Society*, **94**, 679 (1972).
7. J. Wang, J. Morral, C. Hendrix, P. Herdewijn, *Journal of the Organic Chemistry*, **66**, 8478 (2001).
8. D. C. Martyn, D. A. Hoult and A. D. Abell, *Australian Journal of Chemistry*, **54**, 391 (2001).
9. M. Diaz, F. Miguel, F. Susana and V. Gotor, *Journal of the Organic Chemistry*, **65**, 5647 (2000).
10. P. Wipf and C.P. Fritch, *Journal of the American Chemical Society*, **118**, 12358 (1996).
11. J. J. Turner, D. V. Filippov, M. Overhand, G. A. V. Marel and J. H. V. Boom, *Tetrahedron Letters*, **42**, 5763 (2001).
12. G. R. Kinder, S. Wattanasin, R. W. Versace, K. W. Bair, J. Bontempo, M. A. Green, Y. S. J. Lu, H. R. Marepalli, P. E. Phillips, D. Roche, L. D. Tran, R. M. Wang, L. Waykole, D. D. Xu and S. Zabludoff, *Journal of the Organic Chemistry*, **66**, 2118 (2001).
13. O. Mitsunobu and M. Yamada, *Bulletin of the Chemical Society of Japan*, **40**, 2380 (1967).
14. Y. Ishii, M. Takeno, Y. Kawasaki, A. Muromachi, Y. Nishiyama and S. Sakaguchi, *Journal of the Organic Chemistry*, **61**, 3088 (1996).
15. N. Ganguly, A. K. Sukai, S. Dutta, P. De, *Journal of the Indian Chemical Society*, **78**, 380 (2001).
16. P. A. Procopiou, S. P. D. Baugh, S. S. Flack and G. G. A. Inglis, *Journal of the Organic Chemistry*, **63**, 2342 (1998).
17. A. J. Marshall and S. Beaudoin, *Journal of the Organic Chemistry*, **61**, 581 (1996).
18. A. Orita, A. Mitsutome and J. Otera, *Journal of the Organic Chemistry*, **63**, 2420 (1998).
19. H. J. Marriott, M. M. A. Barber, R. I. Hardcastle, G. M. Rowlands, M. R. Grimshaw, S. Neidle and M. Jarman, *Journal of the Chemical Society, Perkin Transactions* 1, **24**, 4265 (2000).
20. N. Millot, A. Cox, C. C. Santini, Y. Molard and J. M. Basset, *Chemistry: A European Journal*, **8**, 1438 (2002).
21. S. Yamada, T. Sugaki and K. Matsuzaki, *Journal of the Organic Chemistry*, **61**, 5932 (1996).
22. M. Kiankarimi, R. Lowe, R. J. McCarthy and P. J. Whitten, *Tetrahedron Letters*, **40**, 4497 (1999).