Ytterbium Triflate Mediated Selective Deprotection of Acetates#

G. V. M. Sharma,* A. Ilangovan

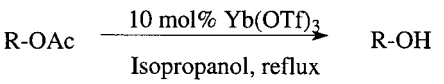
Discovery Laboratory, Organic Chemistry Division III, Indian Institute of Chemical Technology, Hyderabad-500 007, India
Fax +91-040-7173387/7173757; E-mail: esmvee@iict.ap.nic.in

Received 29 September 1999

Abstract: Ytterbium triflate mediated selective deprotection of acetates in isopropyl alcohol at reflux temperature is reported. Unlike hafnium triflate, under the present reaction conditions aryl acetates also undergo deacetylation instead of Fries migration.

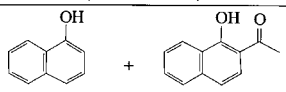
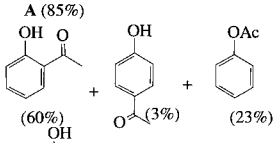
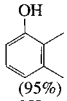
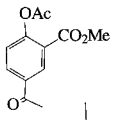
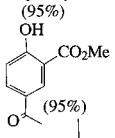
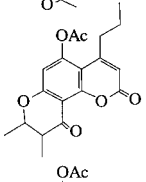
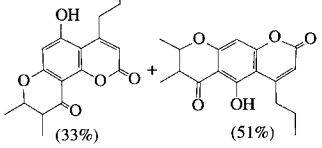
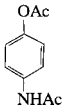
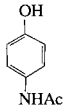
Key words: ytterbium triflate, deacetylation, alcohols, Fries migration

The protection of alcohols as *O*-acyl derivatives has long played a key role in organic synthesis, because of the ease with which they are formed and cleaved. A wide variety of ester groups[1] such as acetate, benzoate, substituted benzoates etc. came into practice for the multistep synthesis of complex natural products, which also resulted in the development of several reagents and reaction conditions for the selective unmasking[2] of a particular acyl group at an appropriate time. In spite of several efforts, the methods available for discriminative removal of same type of esters at two different carbon centers (for example, primary and secondary acetates) are very few and not general.[2] In continuation of our interest on the use of ytterbium triflate in the protection/deprotection[3] chemistry, herein we describe our findings on selective and differentiative deacetylation of alcohols.



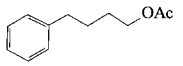
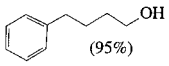
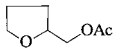
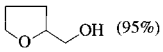
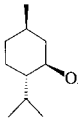
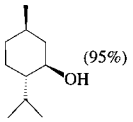
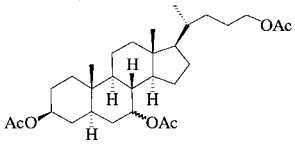
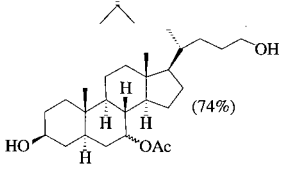
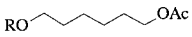
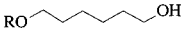
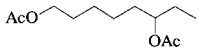
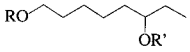
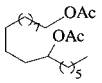
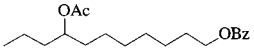
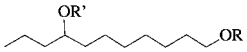
R = aryl, alkyl, steroid and terpenoid units

Table 1

Entry No.	Starting Materials	Solvent	Temp.(°C), Time(h)	Products[c] (Isolated Yields)
1		CH_3NO_2	rt, 64	 **A** (70%) + **B** (9%)
2		CH_3NO_2	reflux, 5	**A** (45%) + **B** (29%)
3		THF	reflux, 16	**A** (80%)
4		IPA	reflux, 9	**A** (85%)
5		CH_3NO_2	rt, 50	 (60%) + (3%) + (23%)
6		IPA	reflux, 12	 (96%)
7		IPA	reflux, 7	 (95%)
8		IPA	reflux, 20	 (95%)
9		IPA	reflux, 7	 (33%) (51%)
10		IPA	reflux, 15	 (96%)

a) IPA = Isopropyl alcohol. b) rt = Room temperature,c)charecterised by ^{1}H NMR, Mass and IR spectral data.

Table 2

Entry No.	Starting Materials	Time(h)	Products (Isolated Yields)
1		12	 (95%)
2		8	 (95%)
3		74	 (95%)
4		48	 (74%)
5	Cholesteryl Acetate	20	Cholesterol (45%)
6	 R = C_6H_5CO	15	 (58%)
7	R = 3,5-$MeOC_6H_3CO$	11	(51%)
8	R = 4-$NO_2C_6H_4CO$	60	(74%)
9	R = t-BuCO	26	(97%)
10		26	 **A**) R = H, R' = Ac (68%) **B**) R = R' = H (28%)
11		30	 **A**) R = H, R' = Ac (69%) **B**) R = R' = H (23%)
12		78	 **A**) R = Bz, R' = H (45%) **B**) R = R' = H (9%) **C**) R = Bz, R' = Ac (16%)

Rare earth triflates[4] are increasingly utilized as mild and selective reagents in several synthetic transformations. Ytterbium triflate in MeOH was utilized for selective removal of methoxy acetates over acetate,[5] while hafnium triflate[6] was used for Fries migration of aryl acetates.

The study was first carried out on aromatic acetates (Table 1). In the present study, unlike hafnium triflate, alpha-naphthyl acetate (entry 1) on reaction with 10 mol% of ytterbium triflate in nitromethane at reflux for 5h, gave deacetylated product (**A**) in 45% yield, while giving 29% of hydroxy ketone (**B**). However, the same reaction at room temperature for 64 h gave the desired product (**A**) in 70% yield with 9% of ketone (**B**). To evaluate the reaction conditions for deacetylation vs Fries migration the reaction was carried out in different solvents such as THF and isopropyl alcohol (IPA) and the latter at reflux temperature was found to be the best condition to give exclusive deacetylation (85%) with no trace of migration product. Similarly in the case of entry 5, the reaction in nitromethane gave both the ortho (60%) and para (3%) migration products with the recovery of starting material (23%), while in IPA at reflux, phenol was the exclusive product (96%). As seen in entry 8, deacetylation was quantitative (95%) with no trace of *trans* esterification, while in entry 10, deacetylation of phenolic acetate was exclusive (96%) leaving acetamide untouched. Attempted deacetylation of coumarin (entry 9), gave 33% of phenol and 51% of migrated phenol, thus effecting the total deprotection.

Having arrived at standard reaction conditions for the deacetylation of aryl acetates, the study was extended to a wide variety of aliphatic acetates (Table 2). Successful deacetylation of primary acetates (entries 1 and 2; 95%), terpenoid secondary acetate (entry 3; 95%) and steroidal acetates (entries 4 and 5; 74% and 45%) was demonstrated as is seen from Table 2. Further study revealed rapid cleavage of acetates over other esters such as dimethoxy benzoate (entry 7), benzoate (entry 6), *p*-nitro benzoate (entry 8) and pivaloate (entry 9), and highest selectivity being observed for the pivaloate. Discriminative deacetylation of primary vs. secondary acetates (entries 10 and 11) gave satisfactory yields (68% and 69% respectively) of alcohols, while entry 12 indicated a moderate (45%) selectivity for the secondary deacetylation over the primary benzoate.

Thus, the present study, amply indicated the utility of ytterbium triflate in IPA at reflux as an effective and highly selective system for a) selectivity between deacetylation vs. Fries migration of aryl acetates, b) deacetylation of a wide variety of acetates, c) differentiating primary acetate over secondary acetate, benzoate and pivaloate; secondary acetate over primary benzoate and phenolic acetate over acetamide. Thus the order of selectivity is: primary acetate > secondary acetate and primary benzoate > pivaloate. Thus the present method of deacetylation with good selectivity would find use in organic synthesis.

References and Notes

[#]IICT Communication No. 4295.

(1) Greene, T. W.; Wuts, P.G.M. *Protective Groups In Organic Synthesis;* 2nd ed.: John Wiley & sons Inc.: New York **1991**.

(2) Baptistella, L.H.B.; dos Santos, J.F.; Ballabio, K.C.; Marsaioli, A.J. *Synthesis* **1989**, 436 and references cited therein.

(3) Sharma, G.V.M.; Ilangovan, A.; Mahalingam, A.K. *J. Org. Chem*. **1998,** *63*, 9103.

(4) Marshman, R.W. *Aldrichimica Acta* **1995,** *28*, 77.

(5) Hanamoto, T.; Sugimoto Y.; Yokoyama Y.; Inanaga J. *J. Org. Chem.* **1996**,*61*, 4491.

(6) Kobayashi. S.; Moriwaki. M.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 2053.

(7) Typical experimental procedure: A solution of 6-acetyloxyhexyl pivaloate (0.5g, 2.04mmol) in isopropyl alcohol (5ml) was treated with $Yb(TOf)_3$ (0.127g, 0.204 mmol) at reflux temperature for 26h. After completion of reaction (Tlc analysis, silica gel, 4:1 hexane/ethyl acetate) the reaction mixture was allowed to cool to room temperature and solvent was evaporated under reduced pressure to get an oily residue. The residue was diluted with ethyl acetate (10 ml), washed with water (2 x 5 ml), dried (Na_2SO_4) and evaporated to get 6-hydroxyhexyl pivaloate (0.481g) in 97% yield as an oily liquid.
Spectral data for selected compounds (200MHz, $CDCl_3$, TMS, in ppm):6-hydroxyhexyl pivaloate:^{1}H NMR: δ 1.22 (s, 9H, $3CH_3$) 1.4-1.52 (m, 4H, 2 x -CH_2), 1.55-1.75 (m, 4H, 2 x -CH_2), 2.15 (br.s, 1H, OH), 3.65 (t, 2H, J 9Hz, CH_2OH), 4.04 (t, 2H, J 9Hz, CH_2); IR (neat): 3480(m), 2950(s), 1725, 1480, 1150. MSEI (m/z,%): 103(13), 85(10), 83(17), 82(41), 67(9). 6-hydroxyhexyl 3,5-dimethoxybenzoate:^{1}H NMR: δ 1.45-1.85 (m, 8H, 4 x CH_2), 3.65 (t, 2H, J 9Hz, CH_2), 3.85 (s, 6H, 2 x -OCH_3), 4.3 (t, 2H, J 9Hz, CH_2), 6.6 (t, 1H, J 3.5Hz, ArH), 7.13 (s, 1H, ArH), 7.15 (s, 1H, ArH); IR (neat): 3425(m), 2905(s), 1725, 1600, 1465, 1150; MSEI (m/z,%): 282 (M^+, 6), 183 (43), 165 (18), 139 (9). 5-hydroxy-7,8-dimethyl-4-propyl-7,8-dihydro-*2H*,6*H*-pyrano [3,2 -f] chromene-2,6-dione: m.p.: 133-134 °C; ^{1}H NMR: 1.03(t, 3H, J 9Hz, CH_3), 1.2-1.38 (m, 3H, CH_3), 1.45-1.6 (m, 3H, CH_3), 1.62-1.8 (m, 2H, CH_2), 2.6-2.75 (m, 1H, CH), 2.92 (t, 2H, J 9Hz, CH_2), 4.2-4.36 (m, 0.7H, CH), 4.6-4.75 (m, 0.3H, CH), 5.98 (s, 1H, ArH), 6.38 (s, 1H, COCH), 13.7 (s, 0.3H, OH), 14.0 (s, 0.7H, OH). IR (KBr): 2940(w), 1720(s), 1705, 1625, 1385, 1275. MSEI: 302(M^+,100), 287(13), 274(58), 259(59), 246(25), 218(10), 203(10).5-hydroxy-8,9-dimethyl-4-propyl-9,10-dihydro-*2H*,*8H* -pyrano[2,3-f]chromene-2,10-dione: m.p -210-213°C; ^{1}H NMR:1.01(t, 3H, J 9Hz, CH_3), 1.1-1.26 (m, 3H, CH_3), 1.35-1.5 (m, 3H, CH3), 1.56-1.76 (m, 2H, CH_2), 2.44 -2.6 (m, 1H, CH), 2.92 (t, 2H, J 9Hz, CH_2), 4.14-4.28 (m, 0.7H, CH), 4.58-4.68 (m, 0.3H, CH), 5.98 (s, 1H, ArH), 6.36 (s, 1H, COCH), 10.8 (br.s, 1H, OH). IR (KBr): 3430(w), 2960(w), 1750(s), 1725, 1605, 1375. MSEI:302(M^+, 82), 287(10), 274(37), 259(33), 246(100), 218(32).

Article Identifier:
1437-2096,E;1999,0,12,1963,1965,ftx,en;L11599ST.pdf