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Protecting Group for Carboxyl Function. Cleavage of 2-Tosylethyl Esters with Fluoride Ion in Non-aqueous Media

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2-Tosylethyl carboxylates reacted with tetrabutylammonium fluoride in tetrahydrofuran at 0 °C for 1 h to give the corresponding free acids in nearly quantitative yields. Under the same conditions, t-butyldimethylsilyl protecting group of secondary alcohols remained intact.

The selection of the proper combination of protecting groups is crucial for the successful synthesis of multifunctional complex molecules.[1] Although a variety of hydroxyl protecting groups have been devised and successfully utilized in organic synthesis, there are only a limited number of carboxyl protecting groups which can be used in the elaboration of complex or polyfunctional organic structures. In most cases, a free carboxyl group can be protected as the corresponding ester. Regeneration of free carboxyl functions can generally be achieved by acidic or basic treatment in aqueous media. However these conditions may sometimes be precluded by the stability or sensitivity of a given substrate.

Since 2-tosylethyl carboxylates can be cleaved to the corresponding free acids and tosylethene by treatment with a strong base such as DBU in non-aqueous media, 2-tosylethyl (TSE) group has been successfully utilized in the total synthesis of natural products such as (±)-pyrenophorin and colletodiol.[2-5] In this paper, we wish to report that TSE group can be removed by fluoride ion.[6] Although fluoride ion is a strong base in an aprotic solvent,[7] it can be safely utilized for the removal of silyl functionarity used for the protection of hydroxyl groups in a variety of labile compounds.[8]

At the outset, 2-tosylethyl 3-phenyl-2-propenoate (1a) was treated with an equivalent amount of tetrabutylammonium fluoride (TBAF)[9] in tetrahydrofuran (THF) at 0 °C for 1 h, 3-phenyl-2-propenoic acid (2a) and tosylethene (3) being obtained in 52% and 57% yields, respectively, along with 35% recovery of 1a (Table 1, Entry 1). The use of 5 equiv. of TBAF, however, resulted in a complex mixture of products. The reaction of 1a with 3 equiv. of TBAF at 0 °C proceeded smoothly to afford 2a and 3 in 93% and 92% yields, respectively. Under the same conditions, 2-tosylethyl 3-phenylpropanoate (1b) gave 3-phenylpropanoic acid in nearly quantitative yield (Table 1, Entries 2, 4).

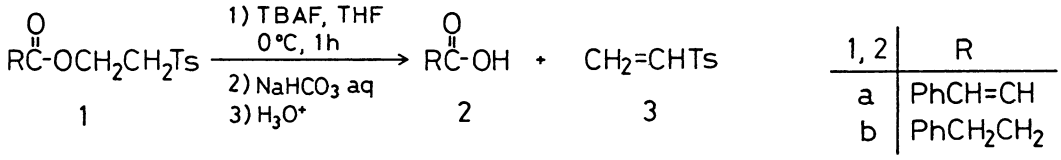
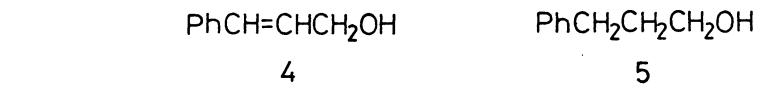


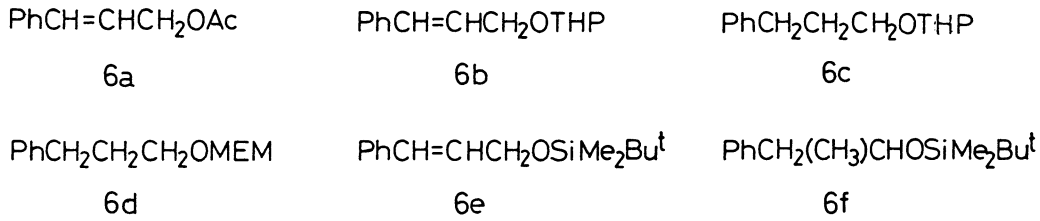
Table 1. Reaction of 1a or 1b with TBAF in THF at 0 °C for 1 h

Entry	2-Tosylethyl ester	TBAF equiv.	Products/% 2	3	Recovery of 1a or 1b/%
1	1a	1	52	57	1a: 35
2	1a	3	93	92	1a: -
3	1a	5	a)	a)	1a: -
4	1b	3	95	97	1b: -

a) A complex mixture of products was formed.

As expected, selective cleavage of 2-tosylethyl carboxylate is possible in the presence of acetates, tetrahydropyranyl (THP) ethers and methoxyethoxymethyl (MEM) ethers. Thus, 3-phenyl-2-propen-1-ol (4) or 3-phenyl-1-propanol (5) were protected by acetyl, THP, and/or MEM groups (6a, b, c, d) and subjected to competitive reaction with 1a under the above conditions, where the protected alcohols remained intact (Table 2, Entries 1-4).





When an equimolar mixture of 1a and 1-t-butyldimethylsiloxy-3-phenyl-2-propene (6e) was treated with TBAF in THF at 0 °C for 1 h, both t-butyldimethylsilyl (TBDMS) and TSE groups were removed to give 2a and 4 in 83% and 80% yields, respectively (Table 2, Entry 5). Under similar competitive conditions, however, a secondary alcohol protected by TBDMS group (6f) remained unchanged and the corresponding free carboxylic acid was selectively obtained (Table 2, Entries 6, 7).[8)]

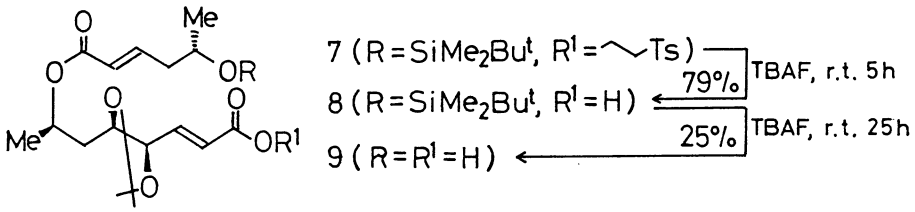
Table 2. Competitive Reaction of 1a or 1b and Protected Alcohols with TBAF[a)]

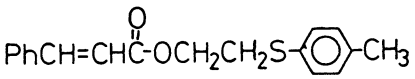
Entry	Ester	Protected alcohol No.	Structure	Products and isolated yields/% 2a or 2b	3	4 or 5	Recovery/% No.
1	1a	6a	Ph⟋⟍OAc	2a: 87	94	-	6a: 98
2	1a	6b	Ph⟋⟍OTHP	2a: 90	92	-	6b: 94
3	1a	6c	Ph⟋⟍OTHP	2a: 92	88	-	6c: 92
4	1a	6d	Ph⟋⟍OMEM	2a:100	79[b)]	-	6d: 86[b)]
5	1a	6e	Ph⟋⟍OTBDMS	2a: 83	80	4: 80	6e: 9
6	1a	6f	Ph⟋OTBDMS	2a: 79	75	-	6f: 94
7	1b	6f	Ph⟋OTBDMS	2b: 89	79	-	6f: 95

a) Molar ratio, 1a or 1b : protected alcohol : TBAF = 1 : 1 : 3. The reaction was carried out in THF at 0 °C for 1 h.

b) Yields were determined by ^{1}H NMR-spectrum of a mixture of 3 and 6d.

The reaction of the fully protected seco acid (7)[10)] of colletodiol with 2.9 molar amounts of TBAF in THF at room temperature for 5 h afforded free acid (8) in 79% yield. On further treatment with TBAF (2.5 molar amounts) at room temperature for 25 h, 8 was converted into the seco acid (9) in 25% yield.[11)]





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Contrary to the 2-tosylethyl esters, 2-(p-tolylthio)ethyl 3-phenyl-2-propenoate (10) was found to be stable under the above conditions where 89% of 10 was recovered.[12)]

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8) For a review of the organosilicon reagents as protective groups in organic synthesis, see, M. Lalonde and T. H. Chan, Synthesis, 1985, 817.

9) The commercial TBAF (1.0 M solution in THF containing < 5 wt% of water) was used (Aldrich Chemical Co.).

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11) The reaction has not been optimized.

12) The oxidation of 2-arylthioethyl carboxylates to the corresponding 2-arylsulfonylethyl esters has been reported, see Ref.1.

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