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Efficient Method for Inversion of Secondary Alcohols by Reaction of Chloromethanesulfonates with Cesium Acetate

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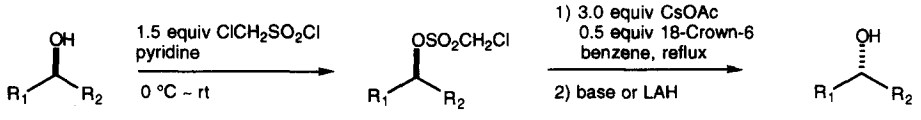
Abstract : Inversion of a variety of secondary alcohols using the (chloromethylsulfonyl)oxy group as a favorable leaving group with cesium acetate in the presence of 18-crown-6 has been performed to give the inverted acetates in high yields. Copyright © 1996 Elsevier Science Ltd

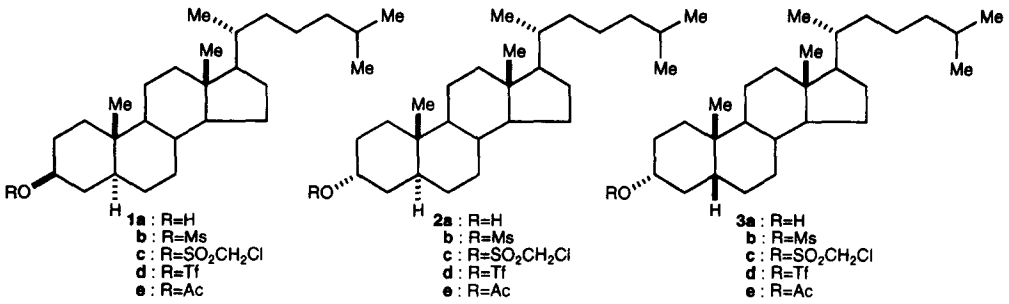
Inversion of configuration of a secondary alcohol is one of the most fundamental tasks in synthetic organic chemistry. Among the numerous methods developed for the inversion,[1a-l] the reaction of the sulfonates, mesylate[1a,b] or triflate[1c], with cesium acetate in the presence of 18-crown-6 is in certain cases superior to the other methods in terms of mildness of the reaction conditions and the suppressed formation of cyclic ether or eliminated products. However, during our synthetic studies of natural products, the method using mesylates or triflates gave unsatisfactory results in some cases. The mesylates resulted in slow reaction or recovery of the starting material in the case of sterically hindered alcohols, while the triflates were labile giving the elimination products or the original alcohols. After several attempts, we have found that the chloromethanesulfonate in place of a mesylate or a triflate afforded the inverted acetate in excellent yield.[2] In this paper, we describe an efficient method for inversion of a variety of secondary alcohols using the (chloromethylsulfonyl)oxy group as a favorable leaving group with cesium acetate in the presence of 18-crown-6, in comparison with the reactions of the corresponding mesylates and triflates.



The sulfonates as the substrates for the inversion were prepared from the corresponding alcohols using 1.5 equiv of sulfonyl chloride (MsCl or $ClCH_2SO_2Cl$[3]) or Tf_2O in pyridine. Chloromethanesulfonylation proceeded smoothly at a comparable rate to triflation and was faster than mesylation to give the corresponding sulfonates quantitatively in most cases. Then, the mesylates, chloromethanesulfonates, and triflates were treated with 3.0 equiv of cesium acetate in the presence of 0.5 equiv of 18-crown-6 in benzene under reflux to afford the inverted acetates. The results are shown in Table 1. The mesylate **1b** of dihydrocholesterol (**1a**) reacted slowly with cesium acetate to afford the inverted acetate **2e** in 90% yield after

4 d. On the other hand, treatment of the chlomomethanesulfonate **1c** with cesium acetate afforded **2e** in 91% yield after 9 h; the reaction proceeded about 11 times faster than that of **1b**. The chloromethanesulfonates (**2c-7c**) prepared from a variety of secondary alcohols were converted into the inverted acetates (**1e**, **4e**, **3e**, **5e-7e**) by treatment with cesium acetate in 69-94% yields. Each reaction rate accelerated and was 3-19 times faster than that of the corresponding mesylates **2b-7b**. The reaction of the chloromethanesulfoates **2c** and **4c** having an axial hydroxyl group afforded the acetates **1e** and **3e** in 71% and 69%, respectively, along with undesirable olefinic compounds as by-products in 19-21% yields. The chloromethanesulfonates **2c** and **4c** are unstable and decompose to the olefinic compounds gradually even at room temperature. On the other hand, in every case of the triflates **1d-7d**, the same treatment with cesium acetate produced the original alcohols **1a-7a** in high yields via selective cleavage of the S-O single bond.

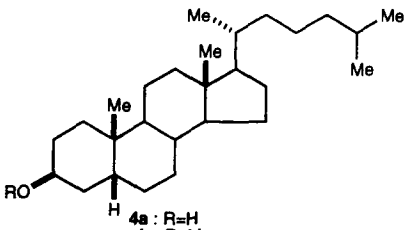
The sulfonates of R-(-)-pantolactone (**8a**) having an α-carbonyl group showed different reactivities under the present reaction conditions. Although the mesylate **8b** gave the complete racemic alcohol (0% ee), the inverted S-(+)-pantolactone (**8f**) ([α]$_D$ +15.9, 97% ee) was obtained from the triflate **8d** via hydrolysis of the acetate **8e** with K_2CO_3 or NaOMe. [α]$_D$ of the alcohol prepared from the chloromethanesulfoate **8c** via



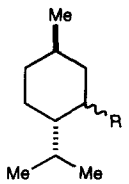
1a : R=H
b : R=Ms
c : R=SO_2CH_2Cl
d : R=Tf
e : R=Ac

2a : R=H
b : R=Ms
c : R=SO_2CH_2Cl
d : R=Tf
e : R=Ac

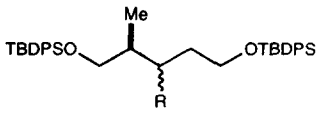
3a : R=H
b : R=Ms
c : R=SO_2CH_2Cl
d : R=Tf
e : R=Ac



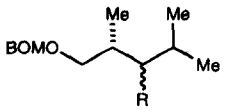
4a : R=H
b : R=Ms
c : R=SO_2CH_2Cl
d : R=Tf
e : R=Ac



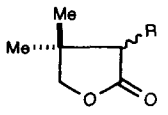
5a : R=β-OH
b : R=β-OMs
c : R=β-OSO_2CH_2Cl
d : R=β-OTf
e : R=α-OAc
f : R=α-OH



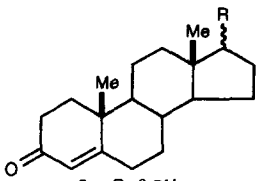
6a : R=α-OH
b : R=α-OMs
c : R=α-OSO_2CH_2Cl
d : R=α-OTf
e : R=β-OAc
f : R=β-OH



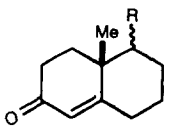
7a : R=β-OH
b : R=β-OMs
c : R=β-OSO_2CH_2Cl
d : R=β-OTf
e : R=α-OAc
f : R=α-OH



8a : R=β-OH
b : R=β-OMs
c : R=β-OSO_2CH_2Cl
d : R=β-OTf
e : R=α-OAc
f : R=α-OH



9a : R=β-OH
b : R=β-OMs
c : R=β-OSO_2CH_2Cl
d : R=β-OTf
e : R=α-OAc
f : R=α-OH



10a : R=β-OH
b : R=β-OMs
c : R=β-OSO_2CH_2Cl
d : R=β-OTf
e : R=α-OAc
f : R=α-OH

Table 1. Inversion of Secondary Alcohols by Reaction of the Sulfonates with CsOAc/18-Crown-6[a]

Alcohol	Reaction Time (Sulfonylation)	Sulfonate (Crude Yield, %)	Reaction Time (with CsOAc)	Yield from Alcohol (%) Acetate[b]	Olefins	Alcohol
1a	15 m	**1b** (100)	4 d	**2e** 90	4	
1a	5 m	**1c** (100)	9 h	**2e** 91	7	
1a	5 m	**1d** (93)	7 d	**2e** 0	0	**1a** 90
2a	3 h	**2b** (100)	1 d	**1e** 82	10	
2a	45 m	**2c** (100)	2 h	**1e** 71[c]	19	
2a	5 m	**2d** (93)	4 d	**1e** 0	0	**2a** 89
3a	15 m	**3b** (100)	4 d	**4e** 82	6	
3a	10 m	**3c** (100)	5 h	**4e** 93	4	
3a	10 m	**3d** (93)	1 d	**4e** 0	0	**3a** 62
4a	1.5 h	**4b** (100)	1 d	**3e** 82	12	
4a	1 h	**4c** (100)	9 h	**3e** 69	21	
4a	10 m	**4d** (63)	1 d	**3e** 0	0	**4a** 84
5a	3 h	**5b** (96)	5 d	**5e** 88	4	
5a	25 m	**5c** (93)	15 h	**5e** 91	7	
5a	15 m	**5d** (83)	3 d	**5e** 0	0	**5a** 80
6a	9 h	**6b** (92)	2 d	**6e** 91	0	
6a	30 m	**6c** (98)	5 h	**6e** 94	0	
6a	5 m	**6d** (94)	5 d	**6e** 0	0	**6a** 88
7a	2 d	**7b** (75)	2 d	**7e** 65	5	
7a	10 m	**7c** (100)	4 h	**7e** 76	16	
7a	10 m	**7d** (100)	7 d	**7e** 0	0	**7a** 95
8a	10 m	**8b** (88)	2 d	**8e** 38[d]	0	
8a	10 m	**8c** (98)	3 h	**8e** 94[d]	0	
8a	10 m	**8d** (93)	1.5 h	**8e** 91[d]	0	
9a	1 h	**9b** (98)	5 d	**9e** 0	0	
9a	15 m	**9c** (100)	3 d	**9e** 76	10	
9a	15 m	**9d** (94)	2 d	**9e** 0	0	**9a** 92
10a	2 h	**10b** (70)	4 d	**10e** 0	0	
10a	20 m	**10c** (100)	8 d	**10e** 53[c]	31	
10a	20 m	**10d** (15)	2 h	**10e** 0	0	**10a** 12

a) The crude sulfonate, prepared from an alcohol with 1.5 equiv of MsCl, $ClCH_2SO_2Cl$ or Tf_2O in pyridine at 0°C to room temperature, was treated with 3.0 equiv of CsOAc and 0.5 equiv of 18-crown-6 in benzene under reflux.

b) The acetates **1e-9e** were hydrolyzed with 5% aqueous KOH in MeOH under reflux, K_2CO_3 or NaOMe in MeOH at room temperature to afford the alcohols **1a-4a** and **5f-9f**, respectively, in nearly quantitative yield. The acetate **10e** was converted into the 9α-alcohol **10f** by reduction with $LiAlH_4$ in THF at room temperature followed by oxidation with MnO_2 in EtOAc at room temperature.

c) 5.0 equiv of CsOAc and 1.0 equiv of 18-crown-6 were used.

d) $[\alpha]_D$ of R-(-)-pantolactone **8a** is -16.4 (c 1.0, $CHCl_3$). On the other hand, $[\alpha]_D$ of the alcohols derived from **8b**, **8c** and **8d** were 0, +2.0 and +15.9 (c 1.0, $CHCl_3$), respectively.

the acetate was +2.0 (12% ee). This low value is due to the cesium acetate-catalyzed epimerization of **8c**, because the recovered **8c** has low optical purity and the acetate **8e** is not epimerized under hydrolysis conditions.[4]

Finally, the sterically hindered alcohol, which did not react under the original Mitsunobu conditions,[5] was investigated. Reaction of the mesylate **9b**, prepared from testosterone (**9a**), with cesium acetate recovered the unchanged starting material **9b**. However, the chloromethanelfonate **9c** produced the inverted acetate **9e** in 76% yield along with a small amount of an olefinic compound. The sulfonates **10b** and **10c** of bicyclic alcohol **10a** having an α-trisubstituted carbon showed similar reactivities to **9b** and **9c**. Although the mesylate **10b** was completely recovered even after 4 d, the inverted acetate **10e** was obtained from the chloromethanesullfonate **10c** in 53% yield. The triflates **9d** and **10d** also converted into the original alcohols **9a** and **10a** as **1d-7d**, respectively.

The inverted acetates **1e-9e** were hydrolyzed with 5% KOH in MeOH under reflux or NaOMe in MeOH at room temperature to afford the corresponding alcohols **1a-4a** and **5f-9f** in nearly quantitative yields.[6] The acetate **10e** was also converted into the 9α-alcohol **10f** by $LiAlH_4$ reduction followed by MnO_2 oxidation.[6]

We have developed an efficient method for the inversion of a variety of secondary alcohols by reaction of the corresponding chloromethanesulfonates with cesium acetate. The chloromethanesulfonates reacted with CsOAc much faster than that of the corresponding mesylates, and were more stable than the corresponding triflates. Application of this method to natural product synthesis and development of useful reactions using the (chloromethylsulfonyl)oxy group as a leaving group are being further investigated in this laboratory.

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