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Alcohol Inversion Using Cesium Carboxylates and DMAP in Toluene

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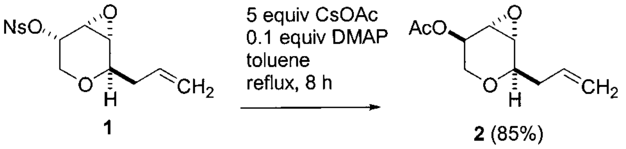
Inversion of secondary alcohols by the S_N2 reaction of a cesium carboxylate with a secondary sulfonate in DMF has been widely used in synthesis.[1,2] Because removal of DMF can be difficult, alternate procedures using benzene or toluene as the solvent with 0.5 equiv of 18-crown-6 to solubilize potassium and cesium carboxylates have also been extensively used.[3] During our synthesis of dysiherbaine,[4] we found that that the S_N2 reaction of CsOAc (5 equiv) with crude nitrobenzenesulfonate **1** proceeded cleanly in toluene at reflux for 12 h to give 75−85% of **2** without the use of 18-crown-6.[4] Surprisingly, no reaction occurred under the same conditions with pure **1**. Since **1** was prepared from the alcohol with nitrobenzenesulfonyl chloride, Et_3N, and DMAP in CH_2Cl_2, we suspected that residual DMAP present in crude **1** was necessary for the S_N2 reaction with CsOAc in toluene at reflux. This was confirmed by heating a suspension of CsOAc (5 equiv) in a toluene solution of pure nosylate **1** (0.13 M) and DMAP (0.1 equiv) at reflux for 8 h to give 85% of acetate **2**.

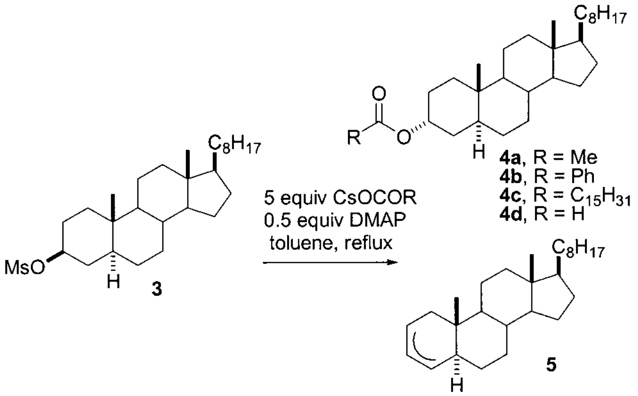


We decided to explore the generality of DMAP as an alternative to 18-crown-6 for the S_N2 reactions of cesium carboxylates in toluene at reflux since DMAP is less expensive than 18-crown-6 and is easy to remove and recycle by extraction into dilute acid. The inversion of 3*β*-cholestanyl mesylate (**3**) was chosen for initial studies since the starting material is readily available and both substitution and elimination products can be easily characterized. Mesylate **3** and 5 equiv of CsOAc were heated in toluene at reflux for 4 d with 18-crown-6, DMAP, or other amine additives as shown in Table 1. Use of 0.5 equiv of 18-crown-6 afforded 92% of 3-α-cholestanyl acetate (**4a**) and 8% of a mixture of 2- and 3-cholestenes (**5**) (entry 1).[3j] Use of 0.5 equiv of DMAP afforded 76% of 3-α-acetate **4a**, 8% of alkenes **5**, and 13% of recovered mesylate **3** (entry 4). Similar results were obtained with 0.25 and 0.75 equiv of DMAP (entries 3 and 5), while reaction was very slow with only 0.1 equiv of DMAP (entry 2). Heating mesylate **3** and 0.5 equiv of DMAP without CsOAc gave 2% of alkenes **5**, 5% of 3-α-cholestanyl mesylate (**6**), 93% of recovered **3**, and none of the known DMAP alkylation product.[5] Other 4-(dialkylamino)pyridines such as 4-pyrrolidino- and 4-(4-methylpiperidino)pyridine are as effective as DMAP at facilitating the S_N2 reaction (entries 6, 7).

Table 1. Reaction of 3*β*-Cholestanyl Mesylate (3) with 5 Equiv of CsOAc in Toluene at Reflux for 4 Days and Amine Catalysts

entry	amine	equiv	% acetate **4**	% alkenes **5**	% mesylate **3**
1	18-crown-6	0.5	92[a]	8[a]	0
2	DMAP	0.1	15	7	78
3	DMAP	0.25	76	10	13
4	DMAP	0.5	75[a]	8[a]	14[a]
5	DMAP	0.75	76	10	13
6	4-pyrrolidino-pyridine	0.5	83	13	4
7	4-(4-methyl-piperidino)-pyridine	0.5	85	11	4
8	TMEDA	0.5	0	0	99
9	pyridine	0.5	0	0	99
10	bipyridine	0.5	0	0	99
11	DABCO	0.5	0	0	95

[a] Isolated yield. Other yields were determined by analysis of NMR spectra.



We hypothesized that DMAP forms a toluene-soluble complex with CsOAc leading to a DMAP-complexed cesium cation and a reactive, uncomplexed acetate anion. We therefore investigated TMEDA since it could solubilize the cesium cation by chelation. No reaction occurred with TMEDA (entry 8); pyridine, bipyridine, and DABCO were equally ineffective (entries 9−11). These results suggest that only the strongly basic but unhindered pyridine nitrogen of 4-(dialkylamino)pyridines forms a

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Table 2. Reaction of Secondary Mesylates with 5 Equiv of CsOAc or CsOBz and 0.5 Equiv of DMAP in Toluene at Reflux

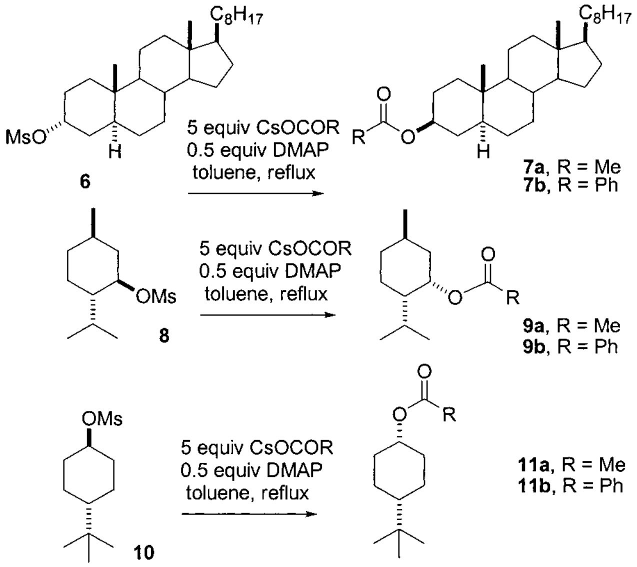
entry	substrate	CsOCOR, R =	time, d	ester (%)[a]	alkene (%)[a]	mesylate (%)[a]
1	**3**	Me	4	**4a** (75)	**5** (8)	14
2	**3**	Ph	1	**4b** (91)	**5** (9)	0
3	**6**	Me	1	**7a** (68)	**5** (32)	0
4	**6**	Ph	1	**7b** (68)	**5** (30)	0
5	**8**	Me	8	**9a** (20)	*b*	20
6	**8**	Ph	6	**9b** (63)	*b*	20
7	**10**	Me	2	**11a** (36)	*b*	0
8	**10**	Ph	2	**11b** (79)	*b*	0

[a] Isolated yield. [b] The unaccounted for material is the volatile alkene.

soluble complex with CsOAc in toluene at reflux, as does 18-crown-6, permitting the S_N2 reaction to occur in excellent yield. We examined the use of DME as a polar solvent that could chelate to CsOAc. Unfortunately, heating **3** with 5 equiv of CsOAc in DME at reflux for 4 d afforded a complex mixture of products, presumably resulting from S_N1 reaction.

As expected, more hydrophobic carboxylates are more reactive than acetate. Use of 5 equiv of CsOBz[1] and 0.5 equiv of DMAP in toluene at reflux for 20 h afforded 91% of 3-α-benzoate **4b** and 9% of alkenes **5**. No reaction occurred without DMAP after 4 d. Use of cesium palmitate[1] with 0.5 equiv of DMAP for 20 h or without DMAP for 4 d afforded 90% of 3-α-palmitate **4c** and 9% of alkenes **5**. However, the palmitate forms intractable soapy emulsions on workup. As expected, cesium formate was less reactive, providing only 13% of 3-α-formate **4d**, 7% of alkenes **5**, and 80% of recovered **3** after reflux for 4 d with DMAP.

The DMAP-catalyzed reaction of CsOAc and CsOBz with other mesylates was investigated to determine the scope of the reaction as shown in Table 2. 3-α-Cholestanyl mesylate (**6**) was more reactive than the *β*-isomer **3** requiring only 1 d for complete reaction, even with the less reactive CsOAc (entries 3 and 4), but giving more alkenes **5** as expected for an axial mesylate, as was also observed with 18-crown-6, which gave 82% of acetate **7** and 10% of alkenes **5**.[3i] Hindered menthyl mesylate (**8**) afforded only 20% of acetate **9a** after 8 d at reflux (entry 5). CsOBz is much more effective giving 63% of benzoate **9b** after 6 d at reflux (entry 6). Similarly, *trans-tert*-butylcyclohexyl mesylate **10** afforded 36% of acetate **11a** (entry 7) and 79% of benzoate **11b** (entry 8). CsOBz is not only more reactive than CsOAc, but also more selective for substitution rather than elimination with mesylates **3**, **8**, and **10**, since the mass not accounted for in entries 5−8 is volatile alkene that was lost on workup.



In conclusion, we have shown that DMAP catalyzes the displacement of secondary sulfonates by cesium carboxylates in toluene at reflux offering a practical and inexpensive alternative to 18-crown-6. The novel use of DMAP to solubilize a metal carboxylate in toluene may be of general utility in organic synthesis.

Experimental Section

General Procedure for Inversion of Mesylates. A 0.3 M solution of mesylate (1 equiv), cesium carboxylate (5 equiv), and DMAP (0.5 equiv) in dry toluene was heated at reflux for the indicated time. The mixture was concentrated and diluted with EtOAc. The EtOAc solution was washed with water, 1 M HCl, and brine, dried (Na_2SO_4), and concentrated to give crude ester. Purification by flash chromatography on silica gel using gradient elution with 10:1 hexane/EtOAc to 6:1 hexane/EtOAc gave alkene, followed by ester and unreacted mesylate in the yields indicated in Tables 1 and 2. The data for **1**,[4] **2**,[4] **3**,[3i] **4a**,[3i] **4b**,[6] **4d**,[7] **5**,[6] **6**,[3i] **7a**,[3i] **7b**,[6] **8**,[3i] **9a**,[3i] **9b**,[6] **10**,[1b] **11a**,[1b] and **11b**[6] are identical to those of authentic samples.

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