

Sml₂-Promoted Oxidation of Aldehydes in the Presence of Electron-Rich Heteroatoms

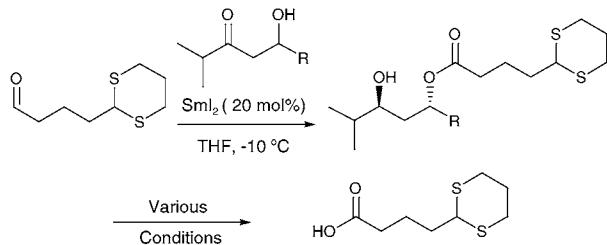
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Received October 12, 2002

ABSTRACT

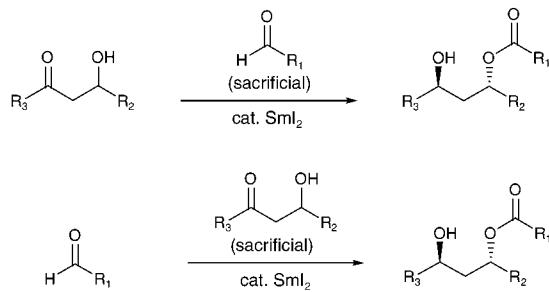


The Evans–Tishchenko reaction provides an efficient and practical solution for the oxidation of aldehydes possessing sensitive electron-rich heteroatoms to the corresponding esters. Careful selection of the sacrificial β -hydroxy ketone provides considerable subsequent flexibility to access the desired carboxylic acid.

The oxidation of aldehydes to carboxylic acids or related congeners is one of the most common reactions in synthetic organic chemistry.¹ Although a large variety of reagents have been developed, oxidations in the presence of electron-rich heteroatoms (i.e. S, Se, N, P) can prove to be challenging. Our long-term interest in the use of 1,3-dithianes as an effective linchpin for constructing architecturally complex natural and unnatural products² has revealed the critical need for a reliable method for oxidizing aldehydes in the presence of sulfur.³

In 1990, Evans and co-workers introduced the Sml₂-catalyzed Tishchenko reaction, a process involving *reduction* of β -hydroxy ketones via hydride transfer from a sacrificial aldehyde for the stereoselective elaboration of anti 1,3-diols (Scheme 1).⁴ Alternatively, this reaction can be viewed as an *oxidation* of an aldehyde via hydride transfer to a sacrificial hydroxy ketone. We reasoned that these mild

Scheme 1



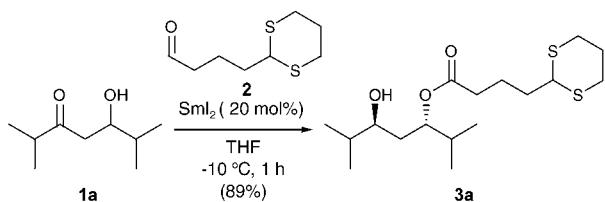
reaction conditions might prove to be useful for the oxidation of aldehydes in the presence of electron-rich heteroatoms.

Pleasingly, treatment of β -hydroxy ketone **1a**⁴ with 1 equiv of dithiane aldehyde **2⁵** and 20 mol % Sml₂ in THF at -10 °C results in the formation of ester **3a**⁶ in high yield (Scheme 2).

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Scheme 2



To make this tactic synthetically useful, we explored the use of a series of β -hydroxy ketones, each offering a different method for liberation of the required carboxylic acid. A number of racemic β -hydroxy ketones (**1a–f**) were prepared from inexpensive commercially available ketones and aldehydes via the aldol reaction.⁷ In each case, 1 equiv of β -hydroxy ketones (**1a–f**) reacted smoothly, and in good yield, with 1 equiv of dithiane aldehyde **2** to furnish the desired esters (Table 1).

Table 1. Oxidation of Aldehyde **2** with Various β -Hydroxy Ketones

entry	R	product	time (min)	yield (%)
1	<i>i</i> -Pr	3a	60	89
2	Et	3b	45	78
3	Me	3c	60	67
4	CH=CH ₂	3d	45	75
5	Ph	3e	60	85
6	<i>p</i> -MeOPh	3f	15	80

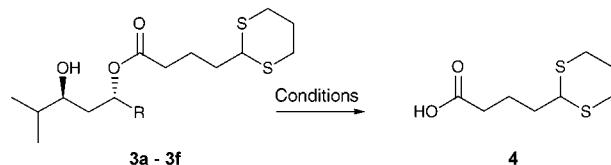
With the desired esters in hand, various means for liberation of the carboxylic acid were investigated (Table

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Table 2. Formation of Acid **4** from Esters **3a–f**

entry	ester	conditions	yield (%)
1	3a	LiOH, aqueous MeOH, rt, 5 h	95
2	3a	$\text{SO}_3\text{-Pyr}$, Et_3N , DMSO, then DBU	86
3	3b	LiOH, aqueous MeOH, rt, 4 h	96
4	3c	LiOH, aqueous MeOH, rt, 2.5 h	94
5	3d	$\text{Pd}(\text{PPh}_3)_4$, morpholine, THF, rt, 1 h	90
6	3d	$\text{Rh}(\text{PPh}_3)_3\text{Cl}$, aqueous EtOH, 80°C , 3–5 h	70
7	3d	LiOH, aqueous MeOH, rt, 2 h	89
8	3e	$\text{BF}_3\text{-Et}_2\text{O}$, 1,3-propanedithiol, rt	92
9	3e	LiOH, aqueous MeOH, rt, 2 h	95
10	3f	DDQ, aqueous DMSO, 80°C , 1 h	75
11	3f	LiOH, aqueous MeOH, 2.5 h	92

2). Treatment of **3a–f** with LiOH/aqueous MeOH afforded acid **4** in high yield (entries 1, 3, 4, 7, 9, 11, Table 2).

Alternatively, Parikh–Doering oxidation⁸ of the secondary hydroxyl in **3a**, followed by β -elimination using DBU, afforded the desired carboxylic acid **4** in one pot (entry 2, Table 2). Carboxylic acid **4** could also be liberated from allyl ester **3d** either via Rh-catalyzed isomerization of the allyl group, followed by heating at reflux in aqueous ethanol⁹ (entry 6, Table 2) or by a Pd-catalyzed⁹ allyl transfer to morpholine in THF at room temperature (entry 5, Table 2); both reactions are quite mild and proceed in good to excellent yield. Benzyl ester **3e** could also be converted to **4** in 92% yield via treatment with 1,3-propanedithiol in the presence of boron trifluoride etherate^{10,11} (entry 8, Table 2). Finally, oxidative-cleavage employing DDQ¹² in DMSO furnished carboxylic acid **4** from PMB ester **3f** in good yield (entry 10, Table 2).

We next turned our attention to aldehydes containing other electron-rich heteroatoms. Aldehydes (**5a–d**) were prepared⁷ and reacted in a similar fashion with 1 equiv of **1a** in the presence of 20 mol % SmI_2 (Table 3). In all cases, the reaction reliably furnished the desired ester in good yield. For phenylselenenyl aldehyde **5a** the reaction temperature was reduced to -15°C to prevent decomposition. Aldehyde **5c**,

(6) Stereochemical assignments of ester **3a** have been identified by comparison of the spectral data of its diol obtained by methanolysis (K_2CO_3 /MeOH) with those of both known anti-1,3 diol and syn-1,3 diol.

(7) Experimental procedures for the synthesis of all new compounds can be found in Supporting Information.

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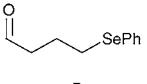
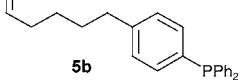
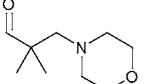
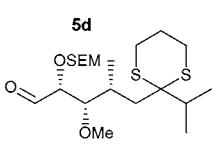
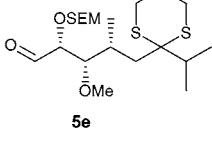
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Table 3. Oxidations in the Presence of S, Se, N, P, and Sn

aldehyde	1a	Sml ₂ (20 mol%)	THF	6a - 6e
aldehyde	temp. (°C)	time (h)	yield (%)	
	-15	1	86	
5a				
	-10	1	83	
5b				
	-10 to 0	1.5	80	
5c				
	-10	1	88	
5d				
	-10	1	70	
5e				

on the other hand, required longer reaction times and slightly higher temperature, presumably due to the steric bulk of the *gem*-dimethyl substitution α to the aldehyde group. Finally, aldehyde (+)-**5e** (Table 3), a model system used in our (+)-tedanolide^{13,14} and (+)-13-deoxytedanolide¹⁵ synthetic venture,³ was also successfully oxidized in 70% yield.

In summary, the Evans–Tishchenko reaction provides an efficient and practical solution for the oxidation of aldehydes possessing sensitive electron-rich heteroatoms to esters. Importantly, careful selection of the sacrificial β -hydroxy ketone provides considerable flexibility to liberate the desired carboxylic acid.

Acknowledgment. Support was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant GM-29028 and 3-Dimensional Pharmaceuticals, Inc., for a Graduate Fellowship (C.M.A.).

Supporting Information Available: Spectroscopic and analytical data, as well as experimental details for compounds **1b**, **1d**, **1f**, **3a–f**, **4**, **5b**, **5d**, **5e**, and **6a–f**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL027095P

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