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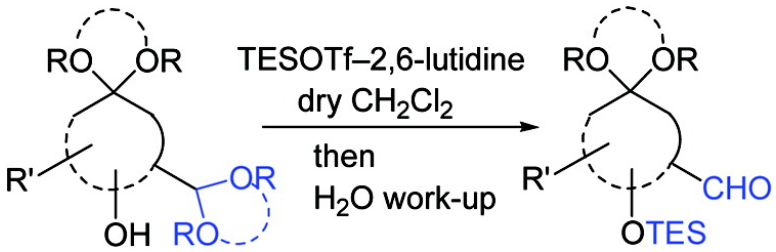

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Unexpected Highly Chemoselective Deprotection of the Acetals from Aldehydes and Not Ketones: TESOTf−2,6-Lutidine Combination

Hiromichi Fujioka,* Yoshinari Sawama, Nobutaka Murata, Takashi Okitsu, Ozora Kubo, Satoshi Matsuda, and Yasuyuki Kita*

Graduate School of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565-0871, Japan

Received July 1, 2004; E-mail: fujioka@phs.osaka-u.ac.jp; kita@phs.osaka-u.ac.jp

Acetal functions are recognized as good protecting groups of carbonyl functions and are widely used in synthetic organic chemistry. They are tolerant under neutral and basic conditions. Acidic conditions are usually used for their deprotection, and under these conditions, acetals from ketone functions are usually deprotected more easily than the acetals from aldehyde functions due to the stability of the cation intermediates.[1] On the other hand, an example of selective deprotection of the acetals from aldehyde functions in the presence of ketals from ketones is unprecedented, to the best of our knowledge, although many methods for the deprotection of acetals from aldehydes and ketones under neutral or mild conditions have been recently developed.[2] We present here a new method, which can selectively deprotect acetals, not ketals.

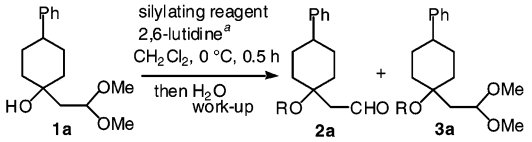
The method is the use of combinations of trimethylsilyltriflate (TMSOTf)−2,6-lutidine or triethylsilyltriflate (TESOTf)−2,6-lutidine. Trialkylsilyltriflates are more often recognized as one of the most powerful reagents for the trialkylsilylation of hindered hydroxyl functions such as *tert*-alcohols.[3] When we treated the acetal **1a** with TMSOTf−2,6-lutidine for producing compound **3a** (R = TMS), to our surprise, even the use of 1.2 equiv of TMSOTf afforded a small amount of the aldehyde **2a** (R = TMS), and the use of 2.0 equiv of TMSOTf gave **2a** in a quantitative yield (Table 1, runs 1, 2). This was an unexpected result. **2a** (R = TMS) must be obtained by the deprotection of an acetal in addition to the usual silylation of the *tert*-alcohol. TESOTf is also effective for the deprotection of the acetal to give **2a** (R = TES) in an excellent yield (run 3),[4] whereas TMSCl gave the only silyl acetal **3a** (R = TMS) and TESCl did not work at all (runs 4, 5). The use of TfOH resulted in no reaction, and no deprotection of the acetal occurred, which showed that the TfOH formed in the reaction mixture by silylation of the hydroxyl group could not deprotect the acetal (run 6).

This deprotection of the acetal was applied to the simple acetal **1b**, which has only the acetal function without the hydroxyl group (see Table 2). A non-basic condition proved that a base is necessary. Among the bases examined here (2,6-lutidine, Et_3N, $^iPr_2NEt$, pyridine, 2-picoline, 4-DMAP, 2,6-di-*tert*-butylpyridine), 2,6-lutidine proved to be the base of choice to give aldehyde **2b**. The reaction using $^iPr_2NEt$ afforded the enol ether, nonpolar spot.[5] On the other hand, the reaction using 2,6-lutidine first gave the polar compound. TLC can monitor the progress of the reaction. Compound **1b** first afforded a very polar spot (R_f value 0.0) even using EtOAc as the developing solvent within 0.5 h, and then the H_2O workup afforded compound **2b** (R_f value 0.65 by hexane−CH_2Cl_2 (1/1)). ^1H NMR also monitored the progress of the reaction (Supporting Information).

Other kinds of acetals were next examined (Table 2). For acyclic acetal and dioxolane (**1b** and **1c**), both TMSOTf and TESOTf were effective for producing the aldehyde **2b**, respectively, within 0.5 h (runs 1−4). The behaviors of the reaction mixtures were the same as above (first formation of polar spot and then H_2O treatment affording **2b**). On the other hand, for dioxane **1d**, TMSOTf was effective for the deprotection to give the aldehyde **2b** although it needed a longer reaction time (3.0 h) (run 5), whereas TESOTf afforded the enol ether **4**, which was less polar on TLC (R_f value 0.95 by hexane−CH_2Cl_2 (1/1)) and isolated after workup in place of aldehyde **2b** (run 6). The methoxyl and acetoxy group tolerated the conditions (runs 7, 8).

The most characteristic feature of our method, the high chemoselectivity, is shown in Scheme 1. The 1-to-1 mixture of **1g** and **1h** afforded the deprotected aldehyde **2e** from **1g** with intact **1h**. This result confirmed the deprotection of the acetal from the aldehyde faster than that of the ketal from the ketone. This result is very interesting, since ketals are usually deprotected faster than acetals

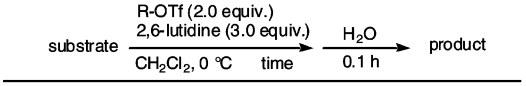
Table 1. Study on Silylating Reagents for Deprotection of Acetal **1a**

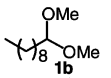
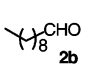
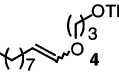
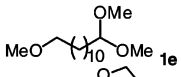
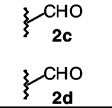
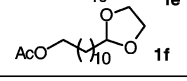
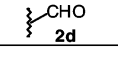


run	silylating reagent (equiv.)	R	yield (%)	2a : 3a
1	TMSOTf (1.2)	TMS	100	17 : 83
2	TMSOTf (2.0)	TMS	100	100 : 0
3	TESOTf (4.0)	TES	98	100 : 0
4	TMSCl (4.0)[b]	TMS	90	0 : 100
5	TESCl (4.0)[b]	–	n.r.	–
6	TfOH (2.0)	–	n.r.	–

[a] Equivalent of 2,6-lutidine is 1.5 times the silylating reagent. [b] Reaction was carried out at room temperature for 24 h.

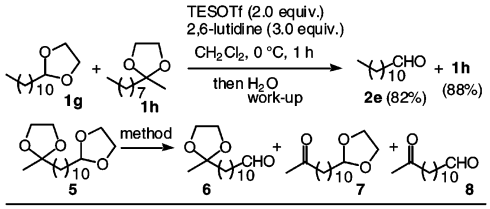
Table 2. Deprotection of Various Acetals



run	substrate	R	product	time (h)	yield (%)
1	 1b	TMS	 2b	0.5	83
2		TES		0.5	79
3	 1c	TMS	2b	0.5	79
4		TES	2b	0.5	75
5	 1d	TMS	2b	3.0	72
6		TES	 4	6.0	86
7	 1e	TES	 2c	0.5	93
8	 1f	TES	 2d	0.5	90

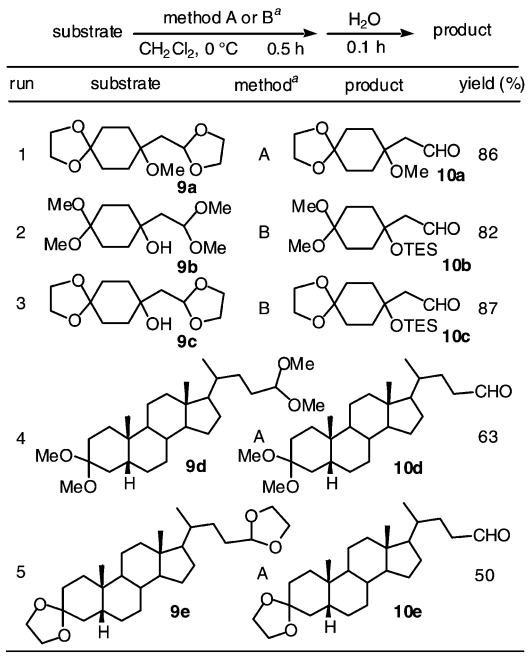
10.1021/ja046103p CCC: $27.50

Scheme 1. Chemoselective Deprotection



run	method (equiv.)	condition	yield (%)	6 : 7 : 8
1	TESOTf (2.0) 2,6-lutidine (3.0)	CH_2Cl_2, 0 °C, 1 h, then H_2O	79	100 : 0 : 0
2	*p*-TsOH (1.0)	acetone/H_2O=1:1 rt, 3.5 h	80	0 : 90 : 10
3	TMSI (1.0)	CH_2Cl_2, 0 °C, 1 h	94	0 : 77 : 23

Table 3. Chemoselective Deprotection of the Compounds Having Acetal and Ketal Units in the Same Molecule



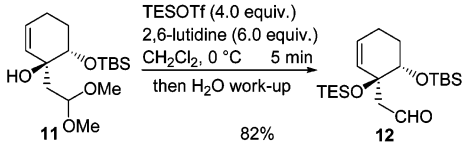
[a] Method A: 2.0 equiv of TESOTf, 3.0 equiv of 2,6-lutidine. Method B: 3.0 equiv of TESOTf, 4.0 equiv of 2,6-lutidine.

due to the stabilization of the cationic intermediates by the alkyl group.[6] This tendency was totally clarified in the reaction of compound **5**, which has ketal and acetal units in the same molecule. Our method selectively gave the ketal aldehyde **6** in good yield, whereas the other representative methods such as aqueous *p*-TsOH treatment and TMSI treatment did not give any deacetalized product **6**. It is noteworthy that the result obtained by our method is completely different from the one using *p*-TsOH or TMSI.[7,8]

Table 3 shows that our chemoselective deprotecting method is available for various compounds having acetal and ketal units in the same molecule. In the case of **9a**, the β-methoxy group remained without elimination (run 1). This shows that this method is very mild. In the cases of **9b,c** with a hydroxyl function, silylation of the hydroxyl function occurred with chemoselective deprotection of the acetal under this condition as shown (runs 2, 3). This chemoselective deprotection was also observed in steroid systems (runs 4, 5).

This method proved to be very useful for obtaining compound **12** (Scheme 2). Compound **12** is a key intermediate for our

Scheme 2



scyphostatin synthesis.[9] Although compound **11** has acid-labile *tert*-butyldimethylsilyloxy and allyl alcohol units in addition to an acetal unit, this method gave **12** in one step from **11** in high yield (82%).

In conclusion, we have developed an unprecedented, unexpected, and remarkably highly chemoselective deprotection method of acetals. This methodology can selectively deprotect acetals in the presence of ketals, although this chemoselectivity is difficult to achieve by other previously reported methods. The structures of the polar components formed during the reactions are now under investigation. The reaction conditions are usually used for the silylation of hydroxyl functions. This report cautions chemists who intend to silylate the hydroxy function of the compounds with the acetal group from an aldehyde.

Supporting Information Available: General reaction procedure using TMSOTf−2,6-lutidine and TESOTf−2,6-lutidine condition; experimental details of the reaction of **5** with TESOTf−2,6-lutidine (Scheme 1) and the transfer of **11** to **12** (Scheme 2), and the physical data of **6**, **10a**−**10e** (Table 3), and **12**; ^{1}H NMR study of the transfer from **1b** to **2b**; speculation of the reaction mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.

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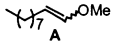
(5) The enol ether (**A**) was obtained.



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(6) See: (a) Reference 1. (b) Deslongchamps, P.; Dory, Y. L.; Li, S. *Tetrahedron* **2000**, 3533. (c) Kreevoy, M. M.; Taft, R. W., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 5590.

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(9) Total synthesis of scyphostatin is in progress, and the preparation of **11** will be presented soon. Compare Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825.

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