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Deprotection of 1,3-oxathiolanes to ketones promoted by base

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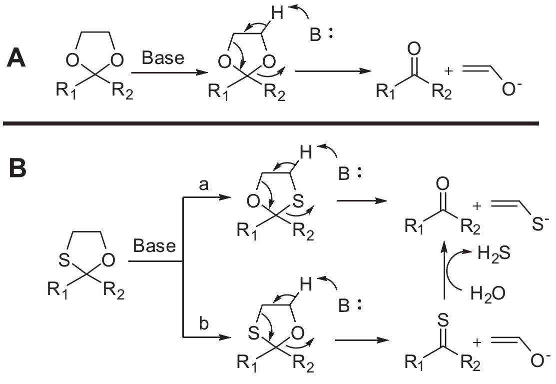
ABSTRACT

A variety of 1,3-oxathiolanes can be easily converted to the corresponding ketones in good yields with LTMP in THF. This deprotection methodology shows satisfactory chemoselectivity when other protecting groups, such as dimethylketal, 1,3-dioxolane, 1,3-dithiane, and other acid-sensitive groups, are present within the same substrates.

Protection and deprotection play important roles and are usually unavoidable in the synthesis of complex molecules. Among the various protecting groups for carbonyl, 1,3-oxathiolane is very useful because of its stability under mild acidic condition, in which the *O,O*-acetals are often not tolerant. Accordingly, many methods have been exploited for the deprotection of 1,3-oxathiolanes. These usual reagents include Lewis acids,[1] oxidants,[2] and those resulting in sulfonium intermediates,[3] such as NBS,[3a–c] I_2–$AgNO_2$,[3d,3e] and $Bi(NO_3)_3$.[3h] Moreover, other special reagents[4–10] proved effective for this deprotection as well, including Raney nickel,[4] Chloramine-T,[5] BSP/Tf_2O,[6] HgO,[7] and benzyne.[8] However, to the best of our knowledge, deprotection of 1,3-oxathiolane solely with base has never been explored.

We have previously reported an interesting base-promoted deprotection of 1,3-dioxolanes (Scheme 1A),[11] adventitiously discovered during the total synthesis of lindenane-type sesquiterpenoids.[12] In view of reaction mechanism, we anticipated that treating 1,3-oxathiolanes with base should potentially provide the corresponding ketones via either path a or path b (Scheme 1B). Herein we present our results on this deprotection with lithium 2,2,6,6-tetramethylpiperidide (LTMP).

Initially, 1,3-oxathiolane of α-tetralone (**1a**) was selected as the test substrate and treated with various bases in THF (Table 1, entries 1–8). Although potassium *tert*-butoxide and potassium and lithium bis(trimethylsilyl)amides proved ineffective to deprotect **1a** even at 0 °C (entries 1–3), lithium diisopropylamide (LDA) led to a satisfactory 61% yield as a stronger base (entry 4). To our delight, LTMP behaved as the optimal base, affording 79% yield at −78 °C (entry 5). However, inferior yields were obtained when we attempted *n*-butyl lithium, *s*-butyl lithium, and *t*-butyl lithium (entries 6–8). To probe the possibility of further optimization, we studied deprotection in different solvents. Interestingly, in the ethereal solvents other than THF, the reaction proceeded sluggish even at 0 °C, as was the situation in toluene (entries 9–12). Finally, we achieved 84% yields with 5.0 equiv of LTMP in THF, while a lower yield was obtained with a less amount of base even at higher reaction temperatures (entries 13–14).



Scheme 1.

Based on the above optimization, we investigated the substrate scope for this reaction with 5.0 equiv of LTMP in THF. The results are summarized in Table 2. First, aromatic substrates with a different *para*-substituent were screened, showing that both electron-donating and electron-withdrawing groups are tolerable (entries 2–4). Similarly, the *ortho*-substituted bromide also

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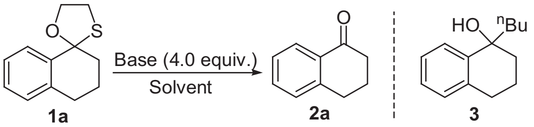
Table 1
Optimization of the reaction condition[a]



Entry	Solvent	Base	Temperature (°C)	Yield of **2a**[b] (%)
1	THF	*t*-BuOK	−78 to 0	NR[c]
2	THF	KHMDS	−78 to 0	NR
3	THF	LHMDS	−78 to 0	NR
4	THF	LDA	−78	61
5	THF	LTMP	−78	79
6	THF	*n*-BuLi	−78	14[d]
7	THF	*s*-BuLi	−78	59
8	THF	*t*-BuLi	−78	25
9	DME	LTMP	−78 to 0	15
10	*t*-BuOMe	LTMP	−78 to 0	29
11	Et_2O	LTMP	−78 to 0	25
12	Toluene	LTMP	−78 to 0	14
13	THF	LTMP[e]	−78	84
14	THF	LTMP[f]	−78 to rt	69

[a] Unless otherwise specified, the reaction was carried out with **1a** (0.5 mmol) and the corresponding base (2.0 mmol) in solvent (4 mL) under argon atmosphere.

[b] Isolated yields.

[c] NR = no reaction.

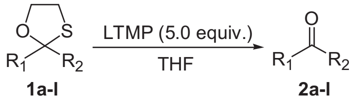
[d] By-product **3** formed in 58% yield.

[e] 2.5 mmol of LTMP was used.

[f] 1.5 mmol of LTMP was used.

Table 2
Deprotection of 1,3-oxathiolane of ketones

[a]



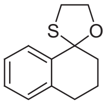
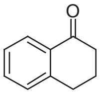
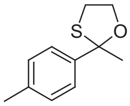
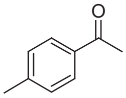
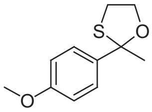
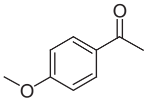
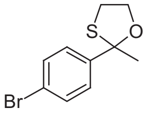
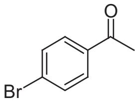
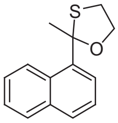
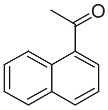
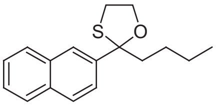
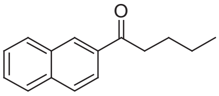
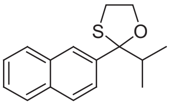
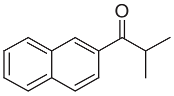
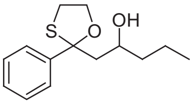
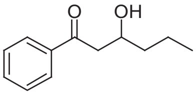
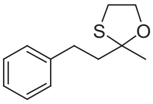
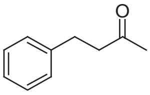
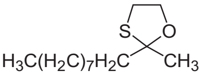
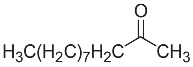
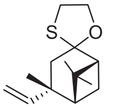
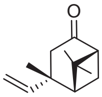
Entry	Starting material[b]		Temperature (°C)	Product		Yield[c] (%)
1		**1a**	−78		**2a**	84
2		**1b**	−78		**2b**	77
3		**1c**	−78		**2c**	79
4		**1d**	−78		**2d**	81
5		**1e**	−78		**2e**	74
6		**1f**	−78		**2f**	88

Table 2 (*continued*)

Entry	Starting material[b]		Temperature (°C)	Product		Yield[c] (%)
7		**1g**	−78		**2g**	89
8		**1h**	−78		**2h**	72
9		**1i**	−78		**2i**	86
10		**1j**	−30		**2j**	82
11		**1k**	−30		**2k**	86
12		**1l**	0		**2l**	76

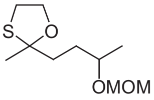
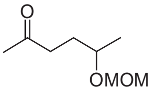
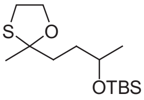
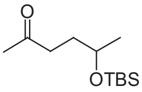
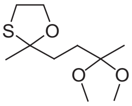
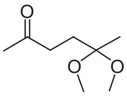
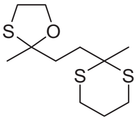
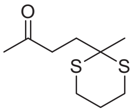
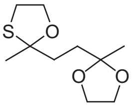
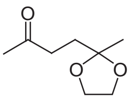
[a] Unless otherwise specified, the reaction was carried out with **1** (0.5 mmol) and LTMP (2.5 mmol) in THF (4 mL) under argon atmosphere. The reaction time is not more than 5 h (see Supplementary data).

[b] All starting materials were prepared in the presence of trimethyl orthoformate and a catalytic amount of tetrabutylammonium tribromide (TBATB) in 2-mercaptoethanol.

[c] Isolated yields.

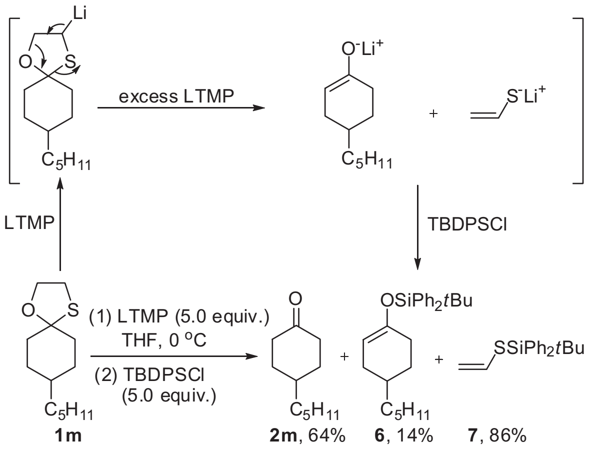
furnished satisfactory yield (entry 5). When extending the benzyl to the α- or β-substitutednaphthyl, the corresponding ketones are obtained smoothly as well, although compound **1h** afforded a lower yield probably due to the bulkiness of isopropyl group (entries 6–8). Notably, compound **1i** provided β-hydroxyl ketone **2i** very cleanly in the typical condition (entry 9), which is potentially unstable in the alkaline environment. As for aliphatic substrates, the reactions went well along at elevated temperatures (entries 10–12), manifesting the wide scope of this deprotection.

Table 3
Chemoselective deprotection of 1,3-oxathiolane[a]

Entry	Starting material		Temperature (°C)	Product		Yield[b] (%)
1		**4a**	0		**5a**	72
2		**4b**	0		**5b**	75
3		**4c**	−30		**5c**	72
4		**4d**	0		**5d**	76
5		**4e**	0		**5e**	74

[a] The reaction was carried out with **4** (0.5 mmol) and LTMP (2.5 mmol) in THF (4 mL) under argon atmosphere.

[b] Isolated yields.



Scheme 2. Trapping experiment.

Chemoselectivity is crucial for the applicability of a protection or deprotection strategy. Thus, to illustrate the selectivity of our methodology, we prepared and examined several compounds embracing other functional groups coexisting with 1,3-oxathiolane (Table 3). In the presence of MOM ether and TBS ether, 1,3-oxathiolane could be selectively converted to the ketone (entries 1 and 2). Dimethyl ketal and 1,3-dithiane showed also their stability under the condition (entries 3 and 4). Importantly, even the chemo-selectivity between 1,3-dioxolane and 1,3-oxathiolane could be realized due to the difference of their deprotection rates (entry 5). It is worth noting that those selectivities cannot be implemented in the presence of acid (for compounds **4a–c**, **4e**) or mercury salt or oxidants (for compound **4d**).

The deprotection of 1,3-oxathiolane can be initiated from the deprotonation at either S-attached carbon or O-attached carbon (path a or path b, Scheme 1B). Considering that the reactions with 1,3-oxathiolanes are generally faster than those with 1,3-dioxalane even at lower temperatures, we prefer a mechanism through the path of a sulfur-stabilizing anion, which results in the decomposition or 1,3-oxathiolane. To testify our assumption, a trapping experiment was conducted. After compound **1m** was treated with LTMP, TBDPSCl was added to trap the intermediates, resulting in the formation of compounds **6** and **7**, which supports our preliminary mechanistic suppose (Scheme 2)[11].

In general, we have developed an effective methodology for deprotecting various 1,3-oxathiolanes to the corresponding ketones, showing admirable chemoselectivity in the presence of dimethylketal, 1,3-dioxolane, 1,3-dithiane, and other acid-labile protecting groups. We believe it would get potentially a wide application in organic synthesis.

Acknowledgments

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Supplementary data

Supplementary data (characterization data for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.053.

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