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Expanding the scope of methyl xanthate esters - From Barton-McCombie reaction auxiliary to versatile protective group

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ABSTRACT

The methyl xanthate ester is presented as a versatile protective group for alcohols. Hydroxyl groups can easily be transformed into methyl xanthate esters by several methods and are commonly used as an auxiliary in the Barton-McCombie reaction. We show that these methyl xanthate esters can readily and chemoselectively be cleaved under mild conditions by the action of diethylenetriamine using microwave heating. This method is orthogonal to many common hydroxyl protective groups that can be introduced and cleaved in the presence of methyl xanthate ester.

1. Introduction

Protective group chemistry is an important field within synthetic organic chemistry. New protective groups as well as methods for introduction and removal of well-known protective groups are frequently published, with reference to special requirements for reactivity, selectivity, and compatibility.[1] Xanthate esters have been used for decades as auxiliary groups in the Barton-McCombie radical deoxygenation reaction where hydroxyl groups are transformed into xanthate esters and then deoxygenated with the aid of a radical initiator and a hydrogen atom source (Scheme 1).[2] Furthermore, methyl xanthate esters are used in the Chugaev elimination reaction, which forms olefins by pyrolysis.[3] Hence, the xanthate ester is a useful functional group, commonly employed in total synthesis.[4–13]

Methyl xanthate esters are generally formed in high yields by treatment of an alcohol in THF with NaH, CS_2, and MeI, successively. Imidazole may also be present to promote alkoxide formation.[2] Variations such as the use of other strong bases, e.g. *n*-BuLi,[14] *t*-BuOK,[15] and NaHMDS,[16] and other conditions, e.g. Na,[17] NaOH and TBAHS under phase transfer conditions,[18] cesium base/TBAI in DMF,[19,20] KF-Al_2O_3,[21] Triton-B[22] or basic resin[23] in DMSO, and KO_2/Et_4NBr in DMF,[24] have been employed. Selective monoprotection of a diol can be achieved using either CsOH·H_2O/TBAI[20] or DBN[25] in DMF.

To our knowledge, there is no comprehensive study of the use of the methyl xanthate ester as a protective group, and there are only a limited number of examples of its removal, usually under quite harsh conditions. In 1960 it was reported that xanthate esters could be cleaved from carbohydrates by the action of $Hg(OAc)_2$.[26] Reductive removal using $LiAlH_4$ has also been presented,[25,27] as well as hydrolysis.[28,29] Furthermore, the methyl xanthate ester has mediated the removal of the Evans auxiliary using H_2O_2/LiOH, resulting in cleavage of the xanthate functionality as well.[30] The methyl xanthate ester is an electron-withdrawing group with low polarity, no stereogenic centers, and a simple NMR spectroscopic signature (i.e. a singlet at around 2.56 ppm in the ^1H NMR spectrum and signals at around 216 and 19 ppm in the ^{13}C NMR spectrum), which makes it appealing as a protective group. Herein, we present the methyl xanthate ester as a versatile protective group for alcohols that can be cleaved under mild conditions.

2. Results and discussion

In our efforts to find a chemoselective method for cleaving methyl xanthate esters, we developed a mild and efficient procedure using diethylenetriamine. Diethylenetriamine was recently reported to cleave unactivated carbamates and ureas in the

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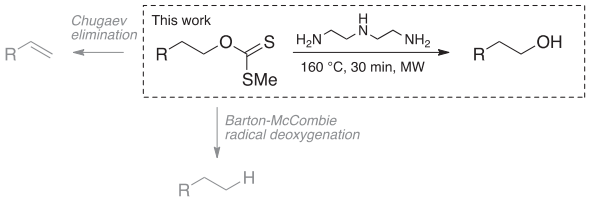


Scheme 1.

presence of amides, including a few thio derivatives.[31] However, reaction temperatures of 130–140 °C for 2–48 h were required. In contrast, we show that methyl xanthate esters can be cleaved in 30 min at 160 °C using microwave heating, and after aqueous work-up, pure alcohols are obtained. The mechanism of the diethylenetriamine-mediated deprotection is not known. However, we envision that the methyl xanthate ester undergoes a nucleophilic attack on the thiocarbonyl by diethylenetriamine. The by-products of the reaction, although the identities are unknown, are believed to be polar and therefore water-soluble. Even if the nucleophilic attack would generate methanethiol, this is a gas and thus causes no purification issues. Diethylenetriamine is water-soluble and excess reagent is thus easily removed by aqueous wash. Indeed, aqueous work-up of the reaction mixtures resulted in pure alcohols characterized by NMR spectroscopy.

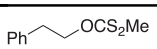
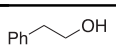
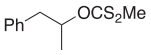
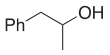
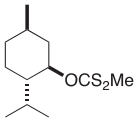
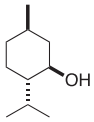
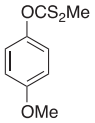
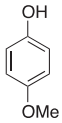
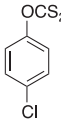
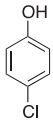
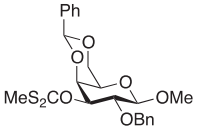
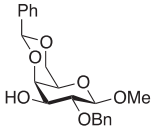
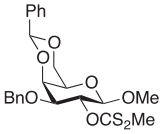
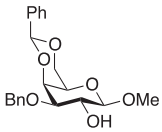
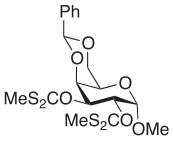
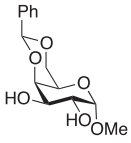
With this new deprotection method in hand, we first examined the substrate scope (Table 1). Primary (entry 1) and secondary (entries 2 and 3) methyl xanthate esters, as well as phenolic xanthate esters (entries 4 and 5), were readily cleaved in excellent yields. To verify the mildness of the method, three carbohydrate substrates (entries 6–8), including a disubstituted compound (entry 8), were subjected to the deprotection protocol, with excellent yields.

To investigate the versatility of the method, 1,6-hexanediol was monosubstituted as methyl xanthate ester and a range of representative alcohol protective groups were introduced and subsequently chemoselectively cleaved (Table 2). The syntheses of the diprotected compounds were conducted using standard procedures. The benzylated derivative (entry 4) has been synthesized before, but by a reversed synthetic procedure, i.e. benzylation followed by xanthylation.[32] Performing the benzylation with the methyl xanthate ester already present proved difficult because of the reactivity of the xanthate unit towards alkoxides.

Removal of the acetate using either catalytic NaOMe or guanidine/guanidinium nitrate gave only modest yields, due to partial cleavage of the methyl xanthate ester. However, aqueous LiOH in THF preserved the xanthate ester moiety (entry 1). The THP (entry 2) and MOM (entry 3) groups were cleaved under mild acidic conditions. Debenzylation by hydrogenation using Pd/C did not regenerate the alcohol, as expected. Most likely, the sulfur containing xanthate moiety poisons the catalyst. However, $BF_3 \cdot Et_2O$ and TBAI smoothly cleaved the benzyl protective group (entry 4). As a precaution, equimolar amounts of acetic acid were added when the silyl ethers were cleaved with TBAF (entries 5 and 6).

Finally, we investigated the removal of the methyl xanthate ester in the presence of other hydroxyl protective groups using our newly developed diethylenetriamine protocol (Table 3). As anticipated, the acetate group did not tolerate these conditions, and 1,6-hexanediol was obtained as the major product. Otherwise, all investigated protective groups were kept intact under these conditions and the corresponding alcohols were isolated in excellent yields. As reported by Noshita et al.,[31] diethylenetriamine cleaves carbamates. Hence, the methyl xanthate ester cannot be considered orthogonal to carbamate protective groups using this deprotection protocol.

Table 1
Scope of the cleavage of methyl xanthate ester.[a]

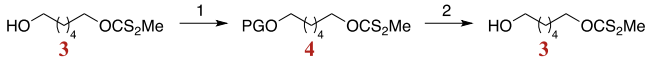
Entry	Substance		Product		Yield
1		**1a**		**2a**	92%
2		**1b**		**2b**	97%
3		**1c**		**2c**	94%
4		**1d**		**2d**	94%
5		**1e**		**2e**	88%
6		**1f**		**2f**	99%
7		**1g**		**2g**	99%
8		**1h**		**2h**	96%

[a] Diethylenetriamine, 160 °C, 30 min, MW.

3. Conclusion

To conclude, the methyl xanthate ester is a versatile protective group for alcohols. We have shown that it can be utilized in the presence of a range of common alcohol protective groups as well as

Table 2
Introduction and chemoselective cleavage of alcohol protective groups in the presence of methyl xanthate ester.



Entry	PG	Introduction		Cleavage	
		Reagents 1	Yield	Reagent(s) 2	Yield
1	Ac (**4a**)	Ac_2O, Py	98%	1 M LiOH	87%
2	THP (**4b**)	DHP, *p*TSA	94%	*p*TSA, THF	93%
3	MOM (**4c**)	$CH_2(OMe)_2$, LiBr, *p*TSA	89%	1 M HCl, MeOH	96%
4	Bn (**4d**)		cf. ref.[32]	$BF_3 \cdot Et_2O$, TBAI	96%
5	TBDPS (**4e**)	TBDPSCl, DMAP, Py	90%	TBAF, AcOH	96%
6	TIPS (**4f**)	TIPSOTf, 2,6-lutidine	96%	TBAF, AcOH	84%