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Facile removal of 4-phenyl-oxazolidinethione auxiliary with EtSH mediated by DBU

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Abstract—In methylene chloride at 0 °C *N*-acyl-β-hydroxy-4-phenyl-oxazolidinethiones could be rapidly converted into corresponding ethyl thioesters in high yields by treatment with EtSH in the presence of a catalytic amount of DBU.

Removal of the auxiliary after completion of the chiral induction is an inevitable operation in most auxiliary-based asymmetric syntheses. Whether the auxiliary can be cleaved successfully under mild conditions may decide the fate of a particular synthetic route. Hence, the importance of developing new methods for cleavage of the auxiliaries can never be over emphasized.

Chiral 4-monosubstituted oxazolidinethiones[1] derived from those inexpensive amino acids (such as phenylglycine, valine, and phenylalanine) are a class of auxiliaries that attract[2] more and more attention in recent years, presumably because they are remarkably easier[2] to be cleaved than corresponding oxazolidinones while being highly effective in inducing new chiral centers. However, the cleavage in most cases was realized by reduction, with the *N*-acyl group being reduced to an alcohol. The only example[2a,b] of non-reductive cleavage of 4-monosubstituted oxazolidinethione auxiliaries we can find in the literature to date is an aminolysis with MeNHOMe leading to a Weinreb amide. The examples of removing other types of oxazolidinethiones are also scant. The only relevant examples appear to be those reported by Yan and co-workers,[3] which employed DMAP-catalyzed transesterifications to remove a camphor-derived auxiliary (yielding esters as products) from two non-hindered substrates. Compared with the related (Evans) oxazolidinones and thiazolidinethiones[2b] auxiliaries, the documented methods for cleaving 4-monosubstituted oxazolidinethiones auxiliaries are apparently far too few. Here in this communication we wish to report a novel method for cutting off the 4-phenyl-oxazolidinethione auxiliary, which allows for smooth transformation of the corresponding *N*-acyl-β-hydroxy-oxazolidinethiones into ethyl thioesters under very mild conditions.

The reactions were carried out at 0 °C in CH_2Cl_2 (such substrates are much less soluble in other common organic solvents). In the presence of a catalytic amount of DBU (which has never been used in removal of any chiral auxiliary up to now), the auxiliary could be cleanly and non-destructively removed by treatment with ca. 2 equiv of EtSH. The main results are outlined in Table 1. For those substrates carrying a methyl group on the α-carbon, the reactions proceeded rather fast and the yields of the thioesters were usually high (entries 1–4).

When the substituents on the auxiliary and the β-carbon were not so bulky, a substituent moderately larger than methyl group on the α-carbon could be tolerated (entries 5–7). However, when the phenyl group on the auxiliary and the methyl group on the α-carbon of **1c** were changed into *i*-Pr and *n*-Bu groups, respectively, the excessive steric hindrance around the *N*-acyl group changed the reaction course completely (entry 3 vs entry 8).

Compounds **1i** and **1j** also failed to give the expected thioesters (entries 9 and 10), in sharp contrast to the clean reactions observed with **1b**, **1k**, and **1l** (entries 2, 11, and 12). Perhaps when both the α- and β-chains are all linear simple alkyls, some unexpected steric hindrance was generated by aggregation of the alkyl chains and led to the excessive side reactions.

Keywords: Chiral auxiliaries; Cleavage; Aldols; Synthesis; Thioesters.
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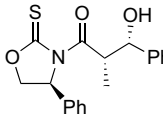
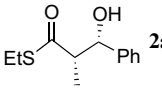
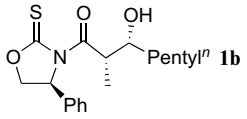
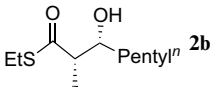
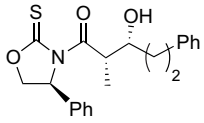
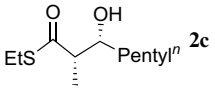
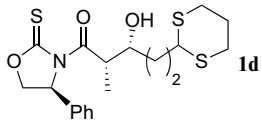
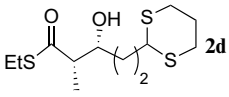
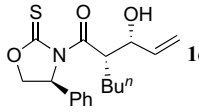
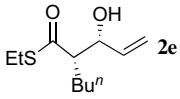
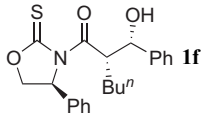
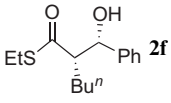
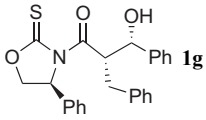
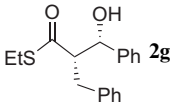
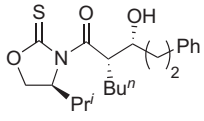
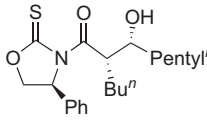
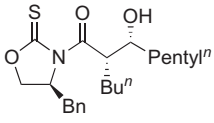
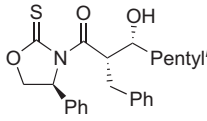
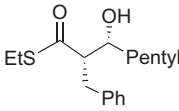
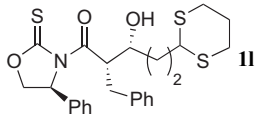
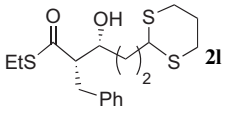
Table 1. Conversion of **1** to **2** in CH_2Cl_2 at 0 °C by treatment with EtSH in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene)[a]

Entry	Substrate	EtSH (equiv)	DBU (equiv)	Time (min)	Product	Yield (%)
1	 **1a**	2.0	0.19	30	 **2a**	92
2[b]	 **1b**	2.7	0.25	60	 **2b**	87
3[b]	 **1c**	2.3	0.23	60	 **2c**	89
4	 **1d**	2.5	0.25	30	 **2d**	87
5	 **1e**	2.2	0.21	60	 **2e**	89
6	 **1f**	2.7	0.25	30	 **2f**	85
7	 **1g**	2.1	0.21	30	 **2g**	90
8[c]	 **1h**	3.0	0.19	90	—	—
9[c]	 **1i**	2.4	0.20	60	—	—
10[c]	 **1j**	1.9	0.27	90	—	—
11	 **1k**	2.3	0.21	60	 **2k**	82
12	 **1l**	2.5	0.25	30	 **2l**	76

[a] For the general procedure, see Ref. 11.
[b] The reaction was probably already finished within 30 min.
[c] With disappearance of the starting material, extensive formation of side products was observed.

It should be mentioned that using DMAP (which was effective[3] in converting a camphor-related *N*-acyloxazolidinethione into esters) or NEt_3 to replace the DBU led to much slower reactions under otherwise identical conditions.

Thioesters are known to be more reactive than corresponding esters. They can be, for instance, easily converted into esters (without complication caused by the exocyclic attack at the auxiliary, a common side reaction if the auxiliary is not removed) under essentially neutral conditions by treatment with a proper alcohol in the presence of NBS[4] or $Ag(OCOCF_3)$,[5] or reduced to aldehydes with DIBAL-H[5] or Me_2SiH_2/Pd–C.[6] They can also be reduced to alcohols with $NaBH_4$[7] or transformed into ketones through reactions with organozinc,[8] copper,[9] or boron[10] reagents in the presence of a proper palladium catalyst. It is thus possible to manipulate the β-hydroxyl group before further elaboration of the carboxylic group (note that masking the OH before cleavage of the auxiliary often makes the auxiliary removal much more difficult).

In summary, we have described a novel very mild and convenient procedure for removing 4-phenyl-oxazolidinethione auxiliary. The *N*-acyl-β-hydroxy-4-phenyl-oxazolidinethiones can thus be readily converted in high yields into the corresponding thioesters, a class of compounds that are more reactive than esters and thus make further elaborations much easier.

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References and notes

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2. (a) See, for example: Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884; (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894–902; (c) Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084–9085; (d) Crimmins, M. T.; Katz, J. D.; McAtee, L. C.; Tabet, E. A.; Kirincich, S. J. *Org. Lett.* **2001**, *3*, 949–952; (e) Crimmins, M. T., P. J.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591–594; (f) Zhang, W.; Carter, R. G. *J. Org. Chem.* **2004**, *69*, 2569–2572.
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11. General procedure: a solution of the substrate (1 mmol), EtSH (2–2.7 mmol), and DBU (cat. amounts) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 30–90 min. When TLC showed completion of the reaction, the mixture was diluted with ether, washed in turn with 2 N HCl, aq $NaHCO_3$, H_2O and brine, and dried over Na_2SO_4. Removal of the solvent and chromatography on silica gel (eluting with EtOAc/hexanes) afforded the pure product (with the auxiliary recovered in near quantitative yields). Note that due to the presence of an excess of EtSH (a stronger acid than the proton at the α-position of the *N*-acyl group), the possibility of epimerization caused by a catalytic amount of DBU at 0 °C within a relatively short reaction period is practically negligible.