Pergamon

Tetrahedron Letters 40 (1999) 1811–1814

TETRAHEDRON LETTERS

Conversion of 2-(trimethylsilyl)ethyl sulfides into thioesters.

Hans Grundberg, Magnus Andergran, and Ulf J. Nilsson*

Organic Chemistry 2, Lund Institute of Technology, Lund University, P.O.B. 124, SE-221 00 Lund, Sweden

Received 25 November 1998; accepted 23 December 1998

Abstract: Treatment of 2-(trimethylsilyl)ethyl sulfides with a carboxylic acid chloride and $AgBF_4$ in CH_2Cl_2 furnishes the corresponding thioesters in high yields and purities. The conversion of 2-(trimethylsilyl)ethyl sulfides into synthetically versatile thioesters allows such sulfides to be used as sulfhydryl protective groups, since such sulfides are easily prepared and are stable towards many reaction conditions encountered in organic syntheses. © 1999 Elsevier Science Ltd. All rights reserved.

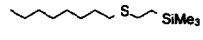
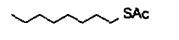
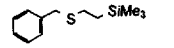
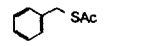
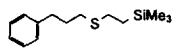
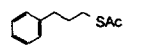
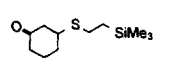
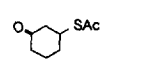
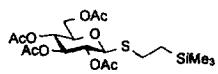
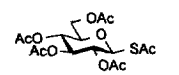
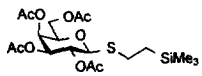
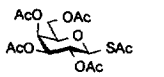
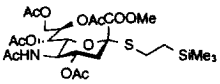
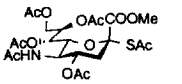
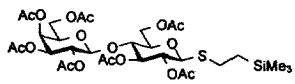
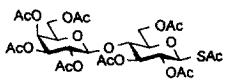
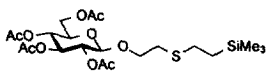
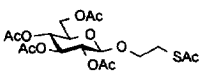
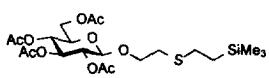
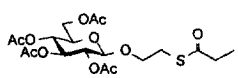
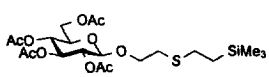
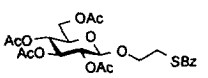
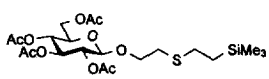
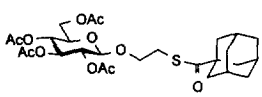
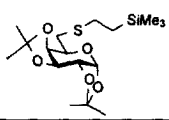
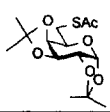
Numerous reagents exists for nucleophilic introduction of sulfhydryl moieties into electrophilic substrates (e.g. alkyl halides and α,β-unsaturated carbonyl compounds). However, a majority of these reagents yield either an unprotected thiol (e.g. with thiophosphate,[1] sulfhydride,[2] sulfide,[3] and hydrogen sulfide[4] as nucleophiles) or a thiol carrying less stable protective groups (e.g. thioacetates, thiocyanates, Bunte salts, *S*-alkyl thiouronium salts[4]). In our laboratory arose the need for a sulfur nucleophile, which gave stable protected thiols upon reaction with electrophiles. Our attention turned to 2-(trimethylsilyl)ethane thiol, which gives 2-(trimethylsilyl)ethyl sulfides in high yields in reactions with electrophiles.[5] However, the stability of 2-(trimethylsilyl)ethyl sulfides has hitherto somewhat limited their use as sulfhydryl protective groups. They do, for example, not undergo fluoride ion-mediated cleavage.[5] A two-step method for cleavage of 2-(trimethylsilyl)ethyl sulfides to thiols has been reported,[5] which involved conversion of the 2-(trimethylsilyl)ethyl sulfides to disulfides using (methylthio)dimethylsulfonium tetrafluoroborate and dimethyl disulfide. Subsequent reduction of disulfides furnished unprotected thiols.

We wish to report an alternative method for the cleavage of 2-(trimethylsilyl)ethyl sulfides and 1-thio-glycosides; treatment with carboxylic acid chlorides in the presence of silver tetrafluoroborate as promoter gives the corresponding thioesters in high yields (table 1). Other promoters (TMSOTf, $BF_3{\cdot}Et_2O$, or AgOTf) may be used, but silver tetrafluoroborate proved to be the most general and mildest promoter and gave the highest yields. Reactions were complete within 2-25 min and the crude thioesters were in most cases sufficiently pure (>90%) to be used directly in the next reaction step without the need for chromatographic purification. However, in a few cases with substrates carrying more acid-sensitive functionalities, the method was less successful in providing thioester products; [i]two of the initially formed, less stable, anomeric *S*-acetate products (table 1, entries 6 and 7) were further slowly converted into the corresponding *O*-acetates or glycals and [ii]isopropylidene acetals were acetolysed (table 1, entry 13) under the reaction conditions. 2-(Trimethylsilyl)ethyl glycosides have been reported

*E-mail: ulf.nilsson@orgk2.lth.se

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00016-7

Table 1. Conversion of 2-(trimethylsilyl)ethyl sulfides into thioesters.

Entry	Substrate[a]	Conditions[b]	Product[c]	Yield
1		**A** **B**		93% 94%
2	 *(ref. 14)*	**A**		quant.
3	 *(ref. 5)*	**A**		quant.
4	 *(ref. 5)*	**A** **C**		55%[d] <5%
5	 *(ref. 14)*	**A** **B** **D**		81%[d] <20%[e] 64%[d]
6		**A** **B**		35%[d,f] <5%[d,g]
7		**A**		<5%[d,h]
8		**A** **D**		85%[d] 71%[d]
9		**A** **C**		99%[d] 99%[d]
10		**E**		95%[d]
11		**F**		65%[d]
12		**G**		68%[d]
13		**A**		<5%[d,i]

[a]Substrate preparation entry 1; octyl bromide, $Me_3SiCH_2CH_2SH$, Cs_2CO_3, DMF (93%), entry 6; 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galactopyranosyl bromide, $Me_3SiCH_2CH_2SH$, NaH, DMF (78%), entry 7; methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero-β-D-galacto-2-nonulopyranosyl chloride)onate,[6] $Me_3SiCH_2CH_2SH$, NaOEt, EtOH (63%), entry 8; lactose octaacetate, $Me_3SiCH_2CH_2SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (90%), entry 9; 2-bromoethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside,[7] $Me_3SiCH_2CH_2SH$, Cs_2CO_3, DMF (81%), entry 13; 1,2:3,4-di-*O*-isopropylidene-6-*O*-trifluoromethanesulfonyl-D-galactopyranose[8] $Me_3SiCH_2CH_2SH$, Cs_2CO_3, DMF (89%). [b]**A**; AcCl, $AgBF_4$, CH_2Cl_2, 2-25 min. **B**; Ac_2O, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 18 min[9]. **C**; AcCl, TMSOTf, CH_2Cl_2, 7 min. **D**; AcCl, AgOTf, CH_2Cl_2, 3-7 min. **E**; Propionyl chloride, $AgBF_4$, CH_2Cl_2, 25 min. **F**; Benzoyl chloride, $AgBF_4$, CH_2Cl_2, 15 min. **G**; 1-Adamantanecarbonyl chloride, $AgBF_4$, CH_2Cl_2, 60 min. [c]All new compounds had satisfactory ^{1}H-NMR-spectra and HRMS-spectra. [d]Yield after column chromatography (SiO_2, heptane/EtOAc). [e] ^{1}H-NMR showed a mixture of substrate, product, β-1-*O*-acetate, and α-1-*O*-acetate in a ratio of 20:10:4:1 after 22h reaction time. [f]The product was not stable under the reaction conditions, but was further converted to the corresponding 1-*O*-acetate. [g]The corresponding 1-*O*-acetate was the major product. [h]The product was not stable under the reaction conditions, but was further converted to the corresponding 2,3-glycal. [i]The isopropylidene acetals were acetolysed under the reaction conditions.

Table 2. Stability of 2-(trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glycopyranosides toward various reagent combinations.

Lewis acids:		Acylation:	
$AlCl_3(EtOH/CH_2Cl_2$[a]	+[c]	Ac_2O/pyridine[a]	+
$HgBr_2/MeCN$[b]	+	De-silylation:	
$BF_3{\cdot}Et_2O/CH_2Cl_2$[a]	+	Bu_4NF/THF[b]	+
$SnCl_4/CH_2Cl_2$[b]	+	$Bu_4NF/MeCN$[b]	+
$ZnCl_2/MeCN$[b]	+	Bu_4NF/CH_2Cl_2[b]	+
$BF_3{\cdot}Et_2O/MeCN$[a]	+/-	$LiBF_4/MeCN$[b]	+
TFA/CH_2Cl_2[a]	+/-	Acetal hydrolysis:	
NIS/TMSOTf[a]	-	$HOAc/H_2O$[b]	+
MeSBr/AgOTf[a]	-	TFA/H_2O[a,d]	+
Br_2/CH_2Cl_2[b]	-	Trichloroacetimidate synthesis:	
Transesterfication:		CH_2Cl_2/DBU/Cl_3CCN[a]	+
NaOMe/MeOH[a]	+		

[a]Reactions were analysed with TLC and ^{1}H-NMR. [b]Reactions were analysed with TLC. [c]Stability is indicated by +, reaction is indicated by -, and slow reaction is indicated by +/-. [d]Conditions were successfully employed for the hydrolysis of isopropylidene acetals of 1,2:3,4-di-*O*-isopropylidene-6-*S*-[2-(trimethylsilyl)ethyl]-D-galactopyranose (table 1, entry 13).

to undergo clean acetolysis upon treatment with $BF_3{\cdot}Et_2O/Ac_2O$[9] and this reagent combination was compared with AcCl/$AgBF_4$ for the acetolysis of 2-(trimethylsilyl)ethyl sulfides. The $BF_3{\cdot}Et_2O/Ac_2O$ reagent nicely cleaved simple 2-(trimethylsilyl)ethyl sulfides (table 1, entry 1), while an interfering formation of the corresponding 1-*O*-acetates occurred in case of 2-(trimethylsilyl)ethyl 1-thio-glycosides (table 1, entries 5 and 6).

Conversions of 2-(trimethylsilyl)ethyl sulfides into thioesters are particularly useful, since thioesters are readily transformed into thiols[10] or cleaved and alkylated in one-pot by treatment with an alkylating reagent in the presence of diethylamine or piperidine.[11,12] Additional attractive features of the present method are that the unpleasant odours associated with the earlier reported conditions for cleavage of 2-(trimethylsilyl)ethyl sulfides[5] [(methylthio)dimethylsulfonium tetrafluoroborate and dimethyl disulfide] are avoided and that different thioesters may be prepared from one 2-(trimethylsilyl)ethyl sulfide (table 1, entries 9-12) using commercially available acid chlorides.

In order to investigate the potential of 2-(trimethylsilyl)ethyl sulfides as sulfhydryl protective groups, a small stability study was performed by subjecting 2-(trimethylsilyl)ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-galacto- and glucopyranosides to a selection of reaction conditions often encountered in organic synthesis (table 2). 2-(Trimethylsilyl)ethyl 1-thio-glycosides were chosen for the stability study, since they were expected to be among the least stable 2-(trimethylsilyl)ethyl sulfides. The 2-(trimethylsilyl)ethyl 1-thio-glycosides were stable towards most reaction conditions employed, except for strong and soft Lewis acids (table 2). In addition, 2-(trimethylsilyl)ethyl sulfides have previously been shown to be stable towards de-arylsulfonylation conditions; $Na(Hg)/THF/CH_3OH$[5].

Finally, 2-(trimethylsilyl)ethyl sulfides can be prepared by other means than reaction of 2-(trimethylsilyl)ethane thiol with electrophiles; [i]an electrophilic reagent, 2-(trimethylsilyl)ethane thioltosylate, has been shown to sulfenylate nucleophilic carbons,[5] [ii]radical additions of 2-(trimethylsilyl)ethane thiol to olefins

yield 2-(trimethylsilyl)ethyl sulfides,[13] and [iii]radical additions of vinyltrimethylsilane to thiols yield 2-(trimethylsilyl)ethyl sulfides (i.e. protecting a thiol).[13,14] The different possible synthetic routes towards 2-(trimethylsilyl)ethyl sulfides and the stability of 2-(trimethylsilyl)ethyl sulfides towards many reaction conditions encountered in organic synthesis, together with our method for their facile transformation into thioesters, renders such sulfides particularly useful as sulfhydryl protective groups.

Typical experimental procedure for acetolysis of 2-(trimethylsilyl)ethyl sulfides: To octyl 2-(trimethylsilyl)ethyl sulfide (91.4 mg, 0.37 mmol) and acetyl chloride (0.5 mL, dist. from PCl_5) in dry CH_2Cl_2 (2 mL) under argon, was added $AgBF_4$ (75 mg, 0.39 mmol). TLC analysis showed the reaction to be complete within 5 min. The mixture was diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$, filtered through Celite (to remove the silver chloride precipitate), the CH_2Cl_2 was dried over Na_2SO_4, and concentrated to give octyl thioacetate (64.6 mg, 93%) in >98% purity according to ^{1}H-NMR analysis.

Acknowledgements: This work was supported by the Swedish Natural Science Research Council and The Swedish Foundation for Strategic Research.

References

1 Bieniarz, C.; Cornwell, M. J. *Tetrahedron Lett.* 1993, *34*, 939.
2 Reid, E. E. *Organic Chemistry of Bivalent Sulfur*; Chemical Publishing Company: New York, 1963; Vol. 1, pp 21.
3 Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, pp 1104.
4 March, J. *Advanced Organic Chemistry*; Fourth ed.; John Wiley & Sons: New York, 1992, pp 406.
5 Anderson, M. B.; Ranasinghe, M. G.; Palmer, J. T.; Fuchs, P. L. *J. Org. Chem.* 1988, *53*, 3127.
6 Kuhn, R.; Lutz, P.; MacDonald, D. L. *Chem. Ber.* 1966, *99*, 611.
7 Marquez, F.; Mesquida, A. *An. Quim.* 1974, *70*, 833.
8 Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* 1989, *30*, 1281.
9 Jansson, K.; Ahlfors, S.; Frejd, T.; Kihlberg, J.; Magnusson, G. *J. Org. Chem.* 1988, *53*, 5629.
10 For a recent example; Wallace, O. B.; Springer, D. M. *Tetrahedron Lett.* 1998, *39*, 2693.
11 Bennett, S.; von Itzstein, M.; Kiefel, M. J. *Carbohydr. Res.* 1994, *259*, 293.
12 Nilsson, U. J.; Fournier, E. J.-L.; Hindsgaul, O. *Bioorg. Med. Chem.* 1998, *6*, 1563.
13 Schwan, A. L.; Brillon, D.; Dufault, R. *Can. J. Chem.* 1994, *72*, 325.
14 Mahadevan, A.; Li, C.; Fuchs, P. l. *Synth. Commun.* 1994, *24*, 3099.