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THIOETHER PROTECTION VIA SELECTIVELY CLEAVABLE SULFONIUM SALTS

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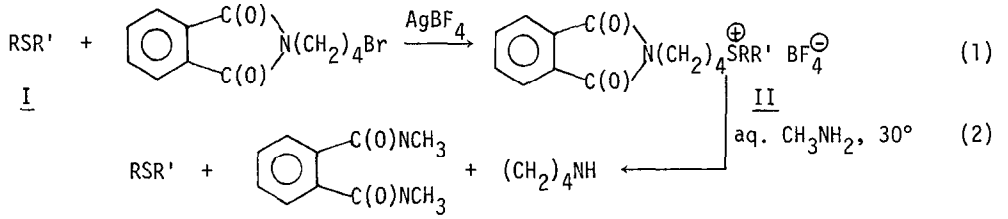
ABSTRACT: There are few protecting groups available for the thioether functionality. The selective cleavage of 4-phthalimidobutyl- and *p*-methoxybenzylsulfonium salts make these derivatives ideal for thioether protection.

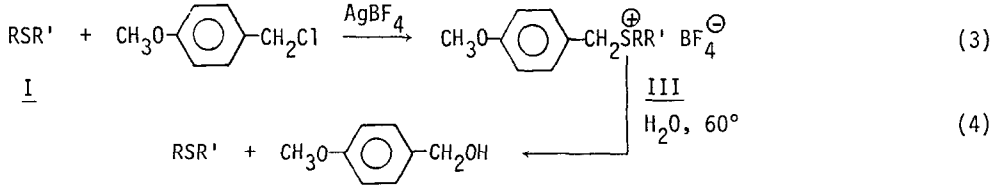
A mildly reversible means of protecting the thioether group is often critical when polyfunctional molecules are synthesized. An effective protecting group Z must add quantitatively to the thioether, RSR'; the product, RSR'Z must be resistant to metal catalysts, electrophiles and oxidizing reagents, and in the end, it must be cleaved selectively. Our approach was to develop a protecting group which would be selectively cleaved using the well-established phenomena of neighboring-group participation[2] (protected 4-aminobutylsulfonium salts, Eq. 1,2)



(1)

(2)

and the stabilization of benzylic cations by electron donating groups[3] (*p*-methoxybenzylsulfonium salts, Eq. 3,4).



(3)

(4)

In order to prevent premature cleavage of the 4-aminobutyl group as pyrrolidine, the amine group itself had to be protected. This was accomplished by alkylating the thioether with 4-bromobutylphthalimide[4] using $AgBF_4$[5] to promote the reaction. Subsequent treatment of the phthalimide with aqueous methylamine[6] freed the aminobutyl group prior to release of the thioether. Conversion by stepwise hydrolysis of the phthalimide group was also successful,[7] but more tedious. The more widely used HBr/CH_3CO_2H[8] and NH_2NH_2[8] in aq. alcohol did not yield the desired products. The sulfonium salts and their yields are listed in Table I.

Table I. Sulfonium Salts

RSR'	% Yield (time at 81°C) II	III	Salt
thiane (Ia)	84 (20 hr)	—	IIa,[a] m. 242-50 (d)
benzyl methyl sulfide (Ib)	74 (20 hr)	—	IIb,[b] m. 160-1
di-*n*-butylsulfide (Ic)	53 (20 hr)	99 (30 min)	IIc,[c] m. 114-5 IIIc,[d] m. 49-51
N-acetylmethionine methyl ester (Id)	—	97 (30 min)	IIId·1½H_2O,[e] oil

[a] IIa, Anal. Calcd. for $C_{17}H_{22}NO_2SBF_4$; C, 52.2; H, 5.67; N, 3.58. Found: C, 52.02; H, 5.79; N, 3.63. ^{1}H-NMR (CD_3CN) δ 3.35 (-CH_2-S). [b] IIb, Anal. Calcd. for $C_{20}H_{22}NO_2SBF_4$; C, 56.2; H, 5.19; N, 3.28. Found: C, 56.14; H, 5.26; N, 3.22. ^{1}H-NMR (CD_3CN) δ 2.65 (CH_3S). [c] IIc, Anal. Calcd. for $C_{20}H_{30}NO_2SBF_4$; C, 55.2; H, 6.94; N, 3.22. Found: C, 54.92; H, 7.03; N, 3.20. ^{1}H-NMR (CD_3CN) δ 3.35 (-CH_2-S). [d] IIIc, purified by column chromatography C_2H_5OH-$CHCl_3$ on Merck Silica Gel. Anal. Calcd. for $C_{16}H_{27}OSBF_4$; C, 54.2; H, 7.63. Found: C, 54.44; H, 7.81. ^{1}H-NMR ($CDCl_3$) δ 3.25, 3.7 (-CH_2S). [e] IIId, Anal. Calcd. for $C_{16}H_{24}NO_4S\cdot 1\frac{1}{2}H_2O$; C, 43.6; H, 6.18; N, 3.18. Found: C, 43.84; H, 6.02; N, 3.26. IR 3390, 3300 (-OH); ^{1}H-NMR ($CDCl_3$ δ 2.75 (CH_3-S).

Table II. Selective Cleavage

Salt	Method	% Yield thioether
IIa	A	71
IIb	A	74
IIc	A	70
IIIc	B	quantitative
IIId	B	quantitative; N-acetylmethionine[9]

Although the yields were satisfactory with the unhindered thioethers Ia,b, they were lowered when acyclic dialkylthioethers, e.g. Ic, were used. Noting that most high-yield sulfonium salt preparations[10] involve the reaction of thioethers with methylating agents or with other highly reactive alkylating reagents, e.g. allyl, prenyl, benzyl, we protected thioethers Ic,d by use of equimolar quantities of *p*-methoxybenzyl chloride/$AgBF_4$ in CH_3CN. With the *p*-

methoxybenzyldialkyl sulfonium salts, selective hydrolysis to the dialkylthioether and *p*-methoxybenzyl alcohol was observed.[3] In all cases, including cleavage of the benzyl methyl sulfonium salt IIb, the only thioether recovered was the original thioether, RSR' (Table II). The only exception was the methyl N-acetylmethionyl salt IIId which decomposed to N-acetylmethionine, undergoing facile ester hydrolysis during the selective sulfonium salt cleavage.

Both these synthetic schemes are particularly attractive methods for thioether protection and subsequent deprotection. The only other method which may offer certain advantages in some cases is the methylation-demethylation of the methionyl group on a heptapeptide,[11a] but variable results are reported with other molecules.[11b]

Methods

Method A: The sulfonium salt IIa or IIb, 2×10^{-3} moles is stirred with 4 mL 20-40% aq. CH_3NH_2 at 30° for 20 hr. The thioether is extracted into CH_2Cl_2. The organic layer is washed with 3 portions of 1 M HCl and then with water. The dried organic solution is first distilled to remove the solvent, then vacuum transferred to obtain the thioether. The yield of thioether IIc, obtained by extraction into CCl_4, is determined by NMR integration by comparison with a known standard.

Method B: The sulfonium salt, 2×10^{-3} moles is stirred with 6 mL of 1.5% aq. CH_3NH_2 at 60° for 10 hr. To the cooled mixture is added K_2CO_3 and CH_2Cl_2. From salt IIIc, thioether Ic is in the organic layer which is passed through 2 g dry silica gel (Baker 60-200 M), followed by an equal volume of CH_2Cl_2. The CH_2Cl_2 is distilled off and the thioether vacuum transferred. In contrast, the N-acetylmethionine produced from salt IIId is in the aqueous layer which is made more basic with K_2CO_3 and extracted with $CHCl_3$. The aqueous layer is acidified (HCl) and dried under vacuum. The residue is triturated with warm $CHCl_3$, the $CHCl_3$ is removed under vacuum to give N-acetylmethionine.

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5. Franzen, V.; Schmidt, H.-J.; Mertz, C. *Chem. Ber.* 1961, *94*, 2942: II; The thioether is refluxed with 1.0-1.2 molar equivalents of 4-bromobutylphthalimide and $AgBF_4$ (Aldrich Chem.) in 50 mL CH_3CN. The AgBr is separated by centrifugation. The solvent is removed under vacuum and the residue washed with Et_2O and CCl_4. The salt is recrystallized from CH_3CN/Et_2O. Use of AgOTS yields only 4-phthalimidobutyl tosylate. III; Equimolar quantities of *p*-methoxybenzyl chloride, thioether and $AgBF_4$ are refluxed for 30 min in CH_3CN. The AgCl is separated by centrifugation; the solvent is removed under vacuum; the residue is washed with Et_2O and vacuum dried.
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