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Mild, Selective Cleavage of Amino Acid and Peptide β-(Trimethylsilyl)ethoxymethyl (SEM) Esters by Magnesium Bromide

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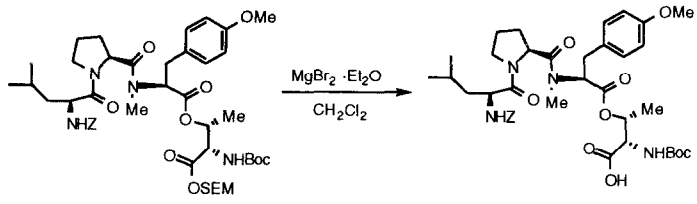
Abstract: Magnesium bromide etherate has been previously shown to cleave β-(trimethylsilyl)ethoxymethyl (SEM) esters of aliphatic acids. This methodology has now been extended to amino acid and peptide derivatives in the presence of protecting groups typically encountered in peptide chemistry, including the Boc, Cbz, Fmoc and Troc carbamates as well as benzyl-, *tert*-butyl- and *tert*-butyldimethylsilyl ethers. The stability of fluoride sensitive protecting groups to magnesium bromide allows for added selectivity in the removal of SEM esters in organic synthesis. © 1997 Elsevier Science Ltd.

The selective protection and deprotection of functional groups is an important strategic element of organic synthesis. The β-(trimethylsilyl)ethoxymethyl (SEM) ester is an attractive protecting group for carboxylic acids whenever a mild, non-hydrolytic deprotection is required. The SEM ester is usually removed under acidic conditions or with a fluoride ion source.[1,2] These conditions may be incompatible with other protecting groups in peptide chemistry such as acid sensitive *tert*-butyldimethylsilyl (TBDMS) and *tert*-butoxycarbonyl (Boc) groups as well as the fluoride sensitive *N*-9-fluorenylmethoxycarbonyl (Fmoc) group.

Kim and co-workers have demonstrated the mild cleavage of SEM and other acetal-type esters using magnesium bromide in ether.[3] In our laboratory, the SEM ester has been used to protect the carboxyl terminus of a tetrapeptide which occurs in the natural products of the didemnin family. While selective removal of this SEM ester can be achieved with HF in acetonitrile,[4] we have successfully substituted magnesium bromide as a milder alternative, as shown in eq. 1.



1 2 (eq. 1)

The success of this mild deprotection prompted us to study the use of magnesium bromide to cleave SEM esters of highly protected amino acid derivatives. We were especially interested in the use of magnesium bromide as an alternative to fluoride sources such as HF and TBAF, allowing SEM esters to be removed in the presence of silyl ethers and Fmoc carbamates. We have demonstrated the complete compatibility of the magnesium bromide method with several protecting groups commonly used in amino acid and peptide chemistry. The experimental results are summarized below.

Table. Magnesium Bromide Cleavage of Protected SEM Esters of Amino Acids.

	Substrate	Product	Time	Yield	[a][α]$_D^{25}$ (solvent)°	[α]$_{ref}$
1	Boc-Leu-SEM	Boc-Leu-OH	2.5h	71%	-26.1 (HOAc)	-25[5]
2	Boc-Phe-OSEM	Boc-Phe-OH	2.5h	78%	+24.3 (EtOH)	+25[5]
3	Boc-Pro-OSEM	Boc-Pro-OH	2.5h	70%	-57.5 (HOAc)	-61[5]
4	Fmoc-Ile-OSEM	Fmoc-Ile-OH	2.5h	83%	-10.9 (DMF)	-12[5]
5	Cbz-Leu-OSEM	Cbz-Leu-OH	2h	87%	-13.9 (EtOH)	-16[5]
6	Fmoc-Thr(*t*Bu)-OSEM	Fmoc-Thr(*t*Bu)-OH	3h	67%	+12.8 (EtOAc)	+16[5]
7	Boc-Thr(Bn)-OSEM	Boc-Thr(Bn)-OH	3h	83%	+14.9 (MeOH)	+16.5[5]
8	Boc-Thr(OH)-OSEM	Boc-Thr(OH)-OH	4h	80%	- 9.7 (HOAc)	- 8.5[5]
9	Fmoc-Thr(TBDMS)-OSEM	Fmoc-Thr(TBDMS)-OH	12h	61%	+13.3 ($CHCl_3$)	+15.0[6]
10	Troc-Lys(Cbz)-OSEM	Troc-Lys(Cbz)-OH	12h	quant.	+10.0 ($CHCl_3$)	+8.0[6]
11	Fmoc-Lys(Cbz)-OSEM	Fmoc-Lys(Cbz)-OH	12h	88%	- 2.7 (MeOH)	- 2.0[7]
12	**1**	**2**	7h	quant.	-57.0 ($CHCl_3$)	-55.0[4]

[a] The temperatures and concentrations used for determining the optical rotations were similar to those used in the determination of the reported optical rotations.

The results shown in the Table illustrate the efficient magnesium bromide-mediated removal of SEM esters from amino acids containing other protecting groups. In entries 1 through 5, the SEM esters of various amino acids were removed while the carbamates Boc, Fmoc and Cbz remained unaffected. The hydroxyl protecting groups *tert*-butyl-, benzyl-, and *tert*-butyldimethylsilyl and the free hydroxyl group of threonine were all stable during the magnesium bromide deprotection (entries 6 through 9). Entry 9 illustrates the potential of magnesium bromide as an alternative to TBAF and HF. The SEM ester was removed while the fluoride-sensitive Fmoc and TBDMS groups were left intact. Entry 10 shows the stability of the Troc group, which is usually removed by reductive fragmentation with zinc. Entry 11 shows the smooth deprotection of a lysine derivative in which both carbamate groups remained intact. The lowest yields obtained were for entries 6 and 9. In both cases, starting material was recovered. The extent of any possible racemization was not studied directly. However, the products obtained had optical rotations which were in reasonable agreement with reported values. These results demonstrate the general compatibility of magnesium bromide with amino acids containing several common protecting groups.

In conclusion, the removal of SEM esters with magnesium bromide has been successfully applied to amino acids and peptides without affecting several other protecting groups. In some cases (e.g. entries 4, 6, 9 and 11), magnesium bromide allowed for a selectivity in deprotection that would be difficult to achieve using conventional fluoride, hydrogenolysis, saponification or acidic conditions. This mild and selective deprotection reaction may make the SEM ester a more attractive choice for protection of substituted carboxylic acids in peptide synthesis.

General Procedure for SEM Ester Preparation: The synthesis of SEM esters was carried out by stirring a mixture of 0.25M of the protected amino acids in DMF with 0.8 equivalent of 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) and 1.1 equivalent of lithium carbonate at room temperature overnight. Another 0.4 equivalent of SEM-Cl was added, and the reaction was stirred for another 4 h. The reaction mixtures were diluted with brine, and the products were extracted with ethyl ether. After evaporation of the solvent under reduced pressure and flash silica gel chromatography, the SEM esters were usually obtained as a pale-yellow oils or white solids with yields ranging from 60-80%. A catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP) was used to increase the yield when no base-sensitive groups were present.

General Procedure for SEM Ester Cleavage: Cleavage was accomplished by adding three equivalents of magnesium bromide etherate to the SEM ester solutions (0.0178M in dichloromethane) at -20°C. After stirring for 0.5 h, the temperature of the reactions was raised to 0°C. Further warming to room temperature allowed the reactions to go to completion. After the solutions were concentrated under reduced pressure, pure products could be obtained in either of two ways. In the first protocol, the residues were dissolved in saturated sodium bicarbonate solution, followed by acidification of the aqueous layer, and subsequent extractions of the free acids with ethyl acetate. An alternative procedure consisted of washing the reaction mixtures with dilute HCl

and brine, concentrating the organic layer, and isolating the products by silica gel flash chromatography. The NMR spectra and optical rotations of the products were in agreement with the reported values.

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