The 2-Methylsulfonyl-3-phenyl-1-prop-2-enyloxycarbonyl (Mspoc)Amino-Protecting Group

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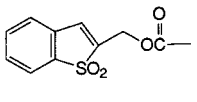
Recently a new *N*-α-amino protecting group, the 1,1-dioxobenzo[*b*]thiophene-2-ylmethyloxycarbonyl (Bsmoc) residue **1**, useful for peptide synthesis, was described.[1]



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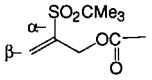

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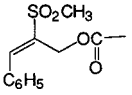

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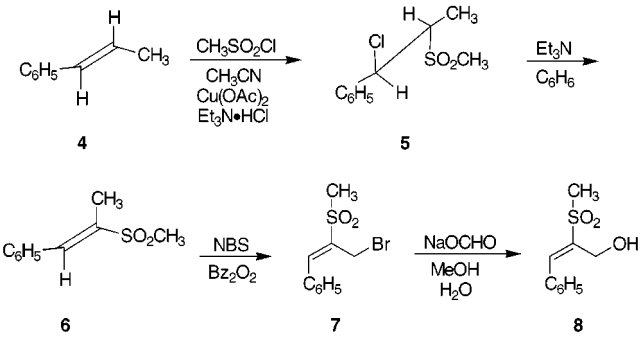
The key deblocking step in the case of amines protected by the Bsmoc group involves the addition of a nucleophilic reagent to the α,*β*-unsaturated sulfone system of **1** with the consequent ejection of the carbamate anion. Among the major advantages of such a process over systems for which the deblocking step involves a classic *β*-elimination process (e.g., the 2-(methylsulfonyl)ethoxycarbonyl, Msc,[2] or 9-fluorenylmethyloxycarbonyl, Fmoc,[3] systems) are that (a) lower concentrations of piperidine or weaker bases (e.g., morpholine) can be used for deblocking, thus minimizing base-catalyzed side reactions, and (b) application to the technique of rapid continuous solution synthesis[4] is greatly improved. Examples of peptide assembly via both solid phase and rapid solution techniques using these protecting groups have also been presented.[4]

The Bsmoc residue was conceived in response to the demonstration that the initially investigated protecting group in this category, the 2-*tert*-butylsulfonyl-2-propenoxycarbonyl (Bspoc) residue **2**, in certain cases suffered premature deblocking by the amino group liberated during the deblocking process.[5] By affixing a substituent at the *β*-position of **2**, as in the Bsmoc residue **1**, reactivity at this position is moderated and such side reactions are not observed. A second *β*-substituted system of this type, the Mspoc residue **3**, is described in this note.

Alcohol **8**, key precursor of the 2-methylsulfonyl-3-phenyl-1-prop-2-enyloxycarbonyl (Mspoc) residue, was obtained from the corresponding allylic bromide **7**[6] by formate-catalyzed hydrolysis.[7] The bromide was synthesized according to the method of Doomes and Overton,[6] which involves $Cu(OAc)_2$-catalyzed addition of the elements of methanesulfonyl chloride to *β*-methylstyrene followed by elimination of hydrogen chloride and subsequent free radical bromination of the methyl group (Scheme 1). This synthetic route, in contrast to that used for the related Bsmoc system, does not involve a low-valent, and therefore possibly unpleasant, sulfur intermediate at any stage. Another difference appears to be the greater ease with which the Mspoc acid fluorides are obtainable in crystalline form, as contrasted to undefined foams or amorphous materials. The stereochemistry of **5** and **6** was assigned on the basis of related reactions[8] and the expected two-step process of trans addition followed by trans elimination. For introduction of the Mspoc residue, alcohol **8** was converted to the chloroformate and *N*-hydroxysuccinimide carbonate.

Scheme 1



The Bsmoc and Mspoc groups, being *β*-substituted, are similar in their lesser sensitivity toward premature deblocking relative to the related 2-(*tert*-butylsulfonyl)-2-propenoxycarbonyl (Bspoc) residue but differ from each other regarding the byproducts formed upon piperidine-induced deblocking. In the case of Bsmoc, the initial Michael-like adduct quickly isomerized completely to the final stable adduct, whereas in the case of Mspoc, an equilibrium mixture of the two adducts resulted (eq 1, $n = 5$). According to ^{1}H NMR analysis the initial adduct **9**

(1)

9 **10**

predominated over **10** at the beginning (about 3/1), but after 30 min the ratio changed to 1/1.6 and did not change thereafter. Upon substitution of pyrrolidine for piperidine, deblocking was both more rapid and more specific, in that under conditions where the latter required 30 min for complete deblocking the former was complete after only 8 min. The initial adduct **9** ($n = 4$) was only fleetingly visible, and complete conversion to **10** ($n = 4$) occurred quickly. Thus for practical purposes, particularly if quantitative UV tracking is desirable, it would be preferable to adopt pyrrolidine for Mspoc deblocking.

As in the case of the Bsmoc residue, the Mspoc group was shown to be sensitive to base-catalyzed mercaptan

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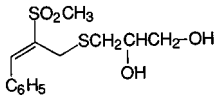
Table 1. Model Mspoc-Amino Acids and Acid Fluorides[a]

Mspoc—NHCHCOX (R)

compd		yield,%	mp, °C	recry solv	^{1}H NMR,[b] δ	mol formula	anal. data (calcd/found)		
R	X						C	H	N
H	OH	84.4	154-5	EtOAc/hexane	3.15 (s, 3), 3.70 (d, 2), 5.00 (s, 2), 7.50 (m, 5), 7.85 (s, 1)	$C_{13}H_{15}NO_6S$	49.83 49.70	4.83 5.08	4.47 4.48
Bn	OH	82	166-8	EtOAc/hexane	2.95 (m, 2), 3.05 (s, 3), 4.3 (m, 1), 7.2-7.58 (m, 10), 7.85 (s, 1)	$C_{20}H_{21}NO_6S$	59.54 59.38	5.25 5.25	3.47 3.22
CH_2-C$_6$H$_4$-$OCMe_3$	OH	75.0	140-1	EtOAc/hexane	1.3 (s, 9), 2.95 (m, 2), 3.12 (s, 3), 4.20 (m, 1), 4.98 (s, 2), 7.08 (dd, 4), 7.55 (bs, 5), 7.85 (s, 1), 7.98 (d, 1)	$C_{24}H_{29}NO_7S$	60.62 60.45	6.15 6.24	2.95 2.91
H	F[c]	82.5	98-100	DCM/hexane	3.05 (s, 3), 4.18 (m, 2), 5.18 (s, 2), 6.65 (t, 1), 7.4 (s, 5), 7.95 (s, 1)	*d*			
Bn	F[e]	81.5	122-3	DCM/hexane	3.00 (s, 3), 3.25 (m, 2), 4.90 (m, 1), 5.18 (s, 2), 5.20 (bs, 1), 7.15-7.50 (m, 10), 7.95 (s, 1)	*d*			
CH_2-C$_6$H$_4$-$OCMe_3$	F[f]	85	75(dec)	DCM/hexane	1.38 (s, 9), 3.05 (s, 3), 3.20 (m, 2), 4.86 (m, 1), 5.20 (s, 2), 5.28 (d, 1), 7.08 (dd, 4), 7.52 (s, 5), 8.0 (s, 1)	*d*			

[a] Using the isolated acid fluorides described in this table, the pentapeptide leucine enkephalin (H-Tyr-Gly-Gly-Phe-Leu-OH) was assembled in good yield according to the method described for Bsmoc chemistry[1,4] except that in these first runs deblocking was carried out via 20% piperidine/DMF. [b] Solvent was DMSO-d_6 for acids and $CDCl_3$ for acid fluorides. [c] IR (KBr) 1836 cm^{-1} (COF). [d] The acid fluorides were used as obtained and identified on the basis of their ^{1}H NMR and IR spectra. [e] IR (KBr) 1833 cm^{-1} (COF). [f] IR (KBr) 1839 cm^{-1} (COF).

deblocking. For example, 3-mercapto-1,2-propanediol caused rapid deblocking of the Mspoc derivative of *p*-chloroaniline (Mspoc-PCA) in the presence of 10 mol % of DIEA in $CDCl_3$ (^{1}H NMR test) to give an equimolar mixture of *p*-chloroaniline and adduct **11**. No thio adduct analogous to **9** was observed.



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In summary, this note describes a new amino protectant subject to deblocking via nucleophilic addition to a Michael acceptor. Relative to the previously reported Bspoc and Bsmoc residues, the Mspoc group is less sensitive to premature deblocking than the former and can be assembled from readily available materials without recourse to low-valent sulfur intermediates.

Experimental Section

(*E*)-3-(Methylsulfonyl)-3-phenyl-2-propenyl Alcohol (8). (*E*)-3-Bromo-2-(methylsulfonyl)-1-phenyl-1-propene[6] (25.6 g, 0.93 mol) and 15.82 g of sodium formate (0.23 mol) in 300 mL of methanol were refluxed for 6 h. When the starting material had disappeared (TLC) the mixture was allowed to cool and concentrated with the aid of a water aspirator. The residue was diluted with water and extracted several times with 100-mL portions of DCM. The organic layer was dried over $MgSO_4$, the solvent removed in vacuo, and the crude alcohol was recrystallized from $CHCl_3$−hexane to give 15.8 g (80.2%) of the pure alcohol as white crystals: mp 74−76 °C; IR (KBr) 3543 (OH), 1628 (C=C), 1285, 1140 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ 3.05 (t, 1), 3.15 (s, 3), 4.70 (d, 2), 7.50 (m, 5), 7.85 (s, 1). Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.59; H, 5.70. Found: C, 56.36; H, 5.82.

(*E*)-2-(Methylsulfonyl)-3-phenyl-2-propenyl Chloroformate. To a stirred solution of (*E*)-2-(methylsulfonyl)-3-phenyl-2-propenyl alcohol **8** (8.5 g, 0.04 mol) in 50 mL of THF at 0 °C was added in one portion 37.5 mL of phosgene. The reaction mixture was stirred overnight at room temperature, and excess phosgene and solvent were removed under reduced pressure with the aid of a water aspirator. The crude material was recrystallized from dichloromethane (DCM)−hexane to give 9.5 g (86.4%) of the chloroformate as colorless crystals: mp 118−120 °C; IR (KBr) 1775 (C=O), 1632 (C=C), 1293, 1155 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$) δ 3.14 (s, 3), 5.35 (s, 2), 7.40 and 7.50 (m, 5), 8.10 (s, 1). Anal. Calcd for $C_{11}H_{11}ClO_4S$: C, 48.09; H, 4.04; Cl, 12.91. Found: C, 47.98; H, 4.03; Cl, 13.10.

***N*-[(*E*)-2-(Methylsulfonyl)-3-phenyl-2-propenyloxycarbonyloxy]succinimide.** To a stirred solution of Mspoc-Cl (13.74 g, 50 mmol) in 150 mL of DCM was added 14.8 g of the dicyclohexylamine salt of *N*-hydroxysuccinimide (50 mmol) portionwise.[9] The reaction mixture was stirred overnight and filtered, and the precipitate was washed with DCM. The filtrate was washed with 10% citric acid (100 mL), 10% $NaHCO_3$ (100 mL), and water (100 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo to give the crude succinimide ester, which was recrystallized from DCM−hexane to give 13.24 g (75%) of the pure ester as white crystals: mp 152−154 °C (dec); IR (KBr) 1805, 1743 (C=O), 1295, 1141 cm^{-1} (SO_2); ^{1}H NMR ($CDCl_3$ plus a few drops of DMSO-d_6) δ 2.95 (s, 4), 3.20 (s, 3), 5.40 (s, 2), 7.55 (m, 5), 8.15 (s, 1). Anal. Calcd for $C_{15}H_{15}NO_7S$: C, 50.99; H, 4.28; N, 3.96. Found: C, 50.83; H, 4.30; N, 3.75.

(9) Compare: Paquet, A. *Can. J. Chem.* **1982**, *60*, 976.

***N*-*p*-Chlorophenyl (*E*)-2-(Methylsulfonyl)-3-phenyl-2-propenyl Carbamate (Mspoc-PCA).** To a stirred solution of *p*-chloroaniline (1.16 g, 9.1 mmol) and DIEA (1.17 g, 9.1 mmol) in 25 mL of DCM was added 2.5 g (9.1 mmol) of Mspoc-Cl portionwise. After stirring at room temperature for 1.5 h, the mixture was washed three times each with 10% HCl, 10% $NaHCO_3$, and water. After drying over $MgSO_4$ the solvent was removed in vacuo, and the residue was recrystallized from MeOH to give 3.0 g (90%) of the urethane as white crystals: mp 178−180 °C; IR (KBr) 3322 (NH), 1696 (C═O), 1615 (C═C), 1291, 1141 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$ plus a few drops of DMSO-d_6) δ 3.20 (s, 3), 5.25 (s, 2), 7.25−7.65 (m, 9), 8.05 (s, 1), 9.25 (s, 1). Anal. Calcd for $C_{17}H_{16}ClNO_4S$: C, 55.81; H, 4.41; N, 3.83. Found: C, 55.76; H, 4.46; N, 3.68.

General Procedure for the Preparation of Mspoc-Amino Acids from Mspoc-OSu.[9,10] To a stirred solution of an amino acid (10 mmol) and $NaHCO_3$ (25 mmol) in water (40 mL) was added a solution of Mspoc-OSu (10 mmol) in acetone (50 mL). After stirring for 3−5 h or overnight (TLC) the reaction mixture was extracted with DCM to remove unreacted Mspoc-OSu. The acetone was removed by means of a water aspirator. After cooling, the reaction mixture was acidified with 10% HCl to Congo red to give a white solid, which was filtered and washed with water several times to give the crude Mspoc-AA-OH. Recrystallization from a suitable solvent gave the pure acid. For individual cases see Table 1.

General Procedure for the Preparation of Mspoc-Amino Acid Fluorides.[11] To a stirred solution of the Mspoc-amino acid (2 mmol) in 5 mL of dry DCM and pyridine (2 mmol, 162 μL) kept under a N_2 atmosphere was added cyanuric fluoride (10 mmol, 900 μL) at room temperature. After 10−20 min a precipitate began to separate. After the reaction mixture was stirred for 1 h, crushed ice was added along with 15 mL of additional DCM. The organic layer was separated, and the aqueous layer was extracted with 5 mL of DCM. The combined organic layers were extracted with 10 mL of ice-cold water and dried over $MgSO_4$, and the solvent was evaporated in vacuo at room temperature. The residue was recrystallized from a suitable solvent. For individual cases see Table 1. The two acid fluorides obtained from Mspoc-phenylalanine and Mspoc-*O*-*tert*-butyltyrosine were obtained as crystalline solids and were therefore easy to dry for long-term storage. In contrast, the corresponding Bsmoc-derivatives of these two amino acid fluorides were often obtained as foamy, amorphous materials that were difficult to dry carefully.

(10) The Bolin method could also be used. See: Bolin, D. R.; Syturu, I.; Humeic, F.; Meienhofer, J. *Int. J. Pept. Protein Res.* **1983**, *33*, 353.

(11) Compare: (a) Carpino, L. A.; Sadat-Aalaee, D.; Chao, H.-G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651. (b) Carpino, L. A.; Mansour, E. M. E.; Sadat-Aalaee, D. *J. Org. Chem.* **1991**, *56*, 2611.

Table 2. Course of the Piperidine-Induced Deblocking of Mspoc-PCA

time (min)	Mspoc-PCA (%)	PCA (%)	**6** (n = 5) (%)	**7** (n = 5) (%)
0	100	0	0	0
8	23.8	76.2	57.2	19.0
15	9.1	90.9	57.9	33.0
25	3.4	96.6	41.4	55.2
30	0	100	38.5	61.5

Table 3. Course of the Pyrrolidine-Induced Deblocking of Mspoc-PCA

time (min)	Mspoc-PCA (%)	PCA (%)	**6** (n = 4) (%)	**7** (n = 4) (%)
0	100	0	0	0
8	0	100	33.3	66.7
15	0	100	18.2	81.8
20	0	100	0	100
30	0	100	0	100

Deblocking of the Mspoc Derivative of *p*-Chloroaniline (Mspoc-PCA) via Piperidine and Pyrrolidine. A solution of 0.0366 g (0.1 mmol) of Mspoc-PCA dissolved in 0.6 mL of $CDCl_3$ containing a few drops of DMSO-d_6 was prepared in an NMR tube. The spectrum was taken before and after the addition of 0.017 g (0.2 mmol) of piperidine. The course of the reaction up to a period of 30 min is shown in Table 2. A comparable run using 0.2 mmol of pyrrolidine in place of piperidine gave the results shown in Table 3.

Finally, a similar run with 2 equiv of 3-mercapto-1,2-propanediol and 10 mol % of DIEA substituted for the secondary amine showed that after 20 min complete deblocking had occurred and the only adduct visible in the NMR spectrum was **8**. A similar run with *threo*-1,4-dimercapto-2,3-butanediol and DIEA in DMSO-d_6 showed complete deblocking after about 10 min. 2-Mercaptobenzothiazole/DIEA was relatively ineffective as a deblocking agent, giving only partial deblocking after several hours.

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