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Two New Procedures for the Introduction of Benzyl-type Protecting Groups for Thiols

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Abstract: Two new methods for the benzylation of thiols are described: a) direct S–alkylation with *para*-substituted benzylic cations; and b) reductive S–alkylations of 2-aminothiols. Both methods provide efficient routes for the introduction of benzyl-type protecting groups in high yields.

In the course of work on S-alkylations of sulfur-containing amino acids with diphenylmethyl- and triphenylmethyl-cations[1], we observed that both 4-methoxybenzyl alcohol **1a** and 4–methoxybenzyl chloride **1b** gave a pink color upon treatment with trifluoroacetic acid (TFA) in CH_2Cl_2, indicating the formation of the 4-methoxybenzyl cation. Although the TFA-induced rearrangement of N-(4-methoxybenzyloxycarbonyl)-cysteine to S-(4-methoxybenzyl)-cysteine and the S-alkylation of cysteine by 4–methoxybenzylcarbazate have been described[2], the cationic S–alkylation of thiols by the inexpensive reagents **1a** and **1b** has not yet been investigated in detail.

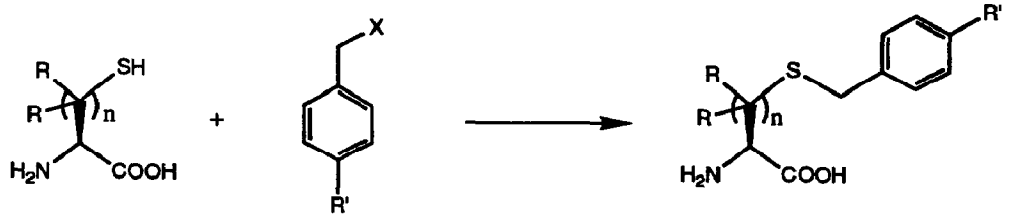

Table 1.

amino acid			benzyl derivative		product (isolated yield
	R	n	R'	X	or substitution level)
2	H	1	OMe(1b)	Cl	4 (81%)
D-3	Me	1	OMe	Cl	D-5 (66%)
D,L-6	H	2	OMe	Cl	D,L-7 (78%)
2	H	1	Me	OH	8 (37%) [a]
2	H	1	H	OH	9 (0%) [a]
2	H	1	Wang resin	OH	10 (0.30meq/g)
2	H	1	Polystyrene	OH or Cl	11 (0.01 meq/g)
12(Cystine)		1	OMe	Cl	4 (78%) [b]

a) 2 equiv. of benzyl alcohol, 50% TFA/ CH_2Cl_2, 1h. b) after reduction with Ph_3P.

We found that both L-cysteine **2** and the tertiary thiol D-penicillamine, D-**3**, are readily S-alkylated by either the chloride **1b** or the alcohol **1a** in a solution of TFA and CH_2Cl_2. However, considerable amounts of by-products, due to Friedel-Crafts-alkylation of the aromatic ring by the 4-methoxybenzyl cation, were formed when using the more reactive alcohol **1a** or at high concentrations (>15 vol.%) of TFA. The amount of by-products was significantly decreased with the more selective chloride **1b** in low concentrations of TFA (<15 vol.%), and after aqueous work-up and extraction of the contaminants with CH_2Cl_2, the optically pure compounds **4** and D-**5** were isolated in high yields[3] (Table 1). DL-homocysteine **6** could be transformed into its 4-methoxybenzyl thioether **7** under the same conditions as L-cysteine in 78% yield. We also found that 4-methylbenzyl alcohol alkylates cysteine in TFA/ CH_2Cl_2, whereas the corresponding chloride forms smaller amounts (<25%) of the desired product **8**. We were not able to prepare S–benzylcysteine **9** utilizing either benzyl alcohol or chloride. Unlike trityl and diphenylmethyl protected materials, the 4-methyl- and 4-methoxybenzyl protected materials proved to be stable to either 50%TFA or 50%TFA/Et_3SiH[4] at r.t.. These observations indicate that the the stability of the benzylic cation is critical to the rate of product formation as well as product stability. The described S-alkylation with 4–methoxybenzyl chloride was used for the protection of ^{15}N enriched L-cysteine required for NMR studies of the solution phase conformations of a series of cyclic peptides[5].

Under similar reaction conditions, L-cysteine was coupled to commercially available *p*-alkoxybenzyl alcohol polystyrene resin (Wang-resin[6], 0.64 meq/g) to afford the corresponding resinlinked cysteine thioether **10** with a substitution grade of 0.30 meq/g. The reaction with either hydroxymethyl polystyrene resin or chloromethyl polystyrene resin was unsatisfactory, furnishing a product **11** with a substitution grade of only 0.01 meq/g.

The described procedure also offers a method for the transformation of disulfides into 4-methoxybenzylthioethers without isolation of the intermediate thiol. Thus, L-cystine **12** was reduced with triphenylphosphine[7] and, after extraction of the triphenylphosphine oxide, converted into the corresponding thioether in 78% overall yield.

For the preparation of S-benzyl- and S-(4-methylbenzyl)cysteines, another new route proved to be more efficient. When thiazolidines of type **14** are treated with Et_3SiH in 50%TFA/CH_2Cl_2, the thioethers **4** and **8-9** are formed in practically quantitative yields[8]. Since the thioazolidines **14** form readily from cysteine and the aromatic aldehydes **13a-c** in 50%TFA/CH_2Cl_2, the thioethers **4** and **8-9** were prepared in a one-pot-reaction. The crude thioethers **4** and **8-9** were Boc-protected using standard conditions, and the Boc–derivatives **16a-c** were isolated in high overall yields (Table 2).

However, we were not able to reduce thiazolidines from cysteine and either paraformaldehyde or acetaldehyde under the described conditions. Presumably, the stabilization of the cationic intermediate **15** by an aromatic substituent is essential to enable the ring-opening of the thiazolidine **14**. Reductive S–alkylations of penicillamine via the analoguous thiazolidines were unsuccessful.

The methods we have studied offer a simple alternative to the basic methods currently in use[9].

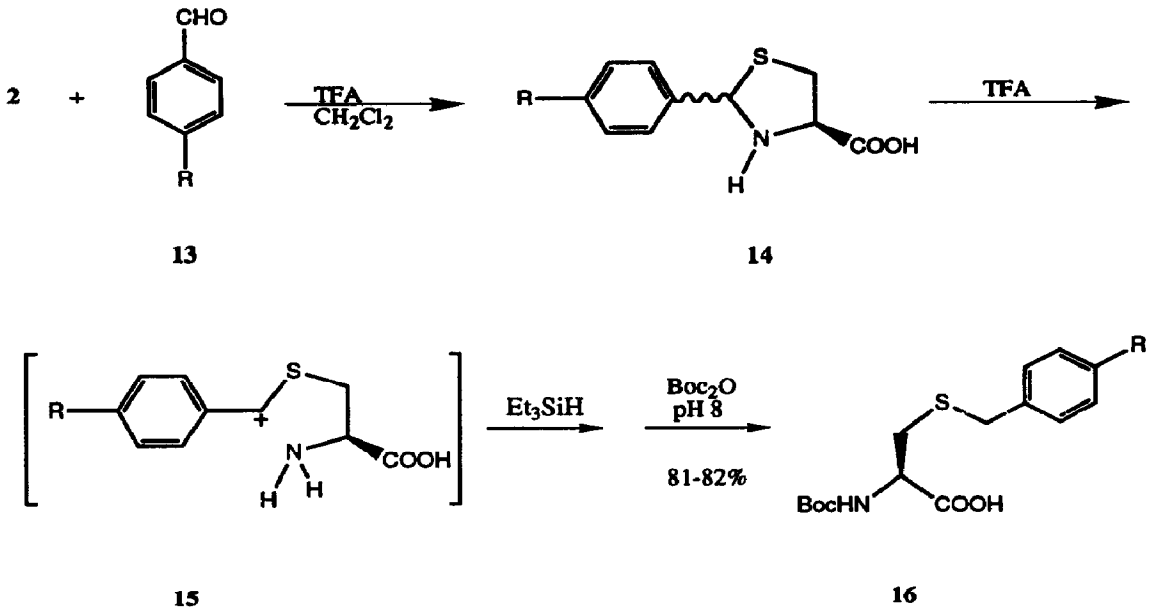

Table 2

Aldehyde	R	N-Boc amino acid	isolated overall yield
13a	H	**16a**	82%
13b	Me	**16b**	82%
13c	OMe	**16c**	81%

Typical procedures:

1. To a stirred solution of L-cysteine (363.5 mg, 3.0 mmol) in TFA/CH_2Cl_2 (3 ml/18 ml), a solution of 4–methoxybenzyl chloride (470 mg, 3.0 mmol) in CH_2Cl_2 (18 ml) was added dropwise over a period of 1 h at 0°C, and stirring was continued for 30 min at r.t.. Then MeOH (10 ml) and water (40 ml) were added, the layers were separated, and the organic layer was reextracted with water (30 ml). The combined aqueous layers were washed with CH_2Cl_2 (30 ml), filtered, and the solvents were removed in vacuo. The residue was dissolved in water, brought to pH 6 with a 10% aqueous solution of $NaHCO_3$, and the product was recrystallized from MeOH/water (3:1). Yield 586 mg (2.42 mmol, 81%) of **4**; m.p. 208-209°C, $[\alpha]_D^{20}$= +24.5 (c=1.0, 1 N NaOH).

2. To a stirred suspension of D-Penicillamine (12.60 g, 84.4 mmol) in TFA/CH_2Cl_2 (15 ml/ 75 ml), a solution of 4-methoxybenzyl chloride (13.22 g, 84.4 mmol) in CH_2Cl_2 (115 ml) was added

dropwise over a period of 1 h at 0°C. Stirring was continued for 60 min at r.t., and MeOH (20 ml) was added. The crude reaction mixture was evaporated, dissolved in CH_2Cl_2 (40 ml), and extracted with water (5 portions of 80 ml). The combined aqueous layers were filtered and evaporated. The crude product was dissolved in MeOH/ H_2O, brought to pH 6 with $NaHCO_3$, and recrystallized from MeOH/H_2O (1:3). Yield 15.0 g (56 mmol, 66%) of **D-5**; m.p.=169-170°C[10], $[\alpha]_D^{20}$= –63.1 (c=1.0, 1 N NaOH).

3. To a stirred solution of cysteine (363 mg, 3.0 mmol) in TFA/CH_2Cl_2 (5 ml each), the aromatic aldehyde **13b** (397 mg, 3.3 mmol) was added dropwise, and stirring at r.t. was continued for 90 min. Et_3SiH (698 mg, 6.0 mmol) was added dropwise at 0°C, and stirring at r.t. was continued for 16 h. MeOH (10 ml) was added, the crude reaction mixture was poured into H_2O (40 ml)/ CH_2Cl_2 (30 ml), and the organic layer was reextracted with water (30 ml). The combined aqueous layers were evaporated to dryness, and the reaction product was neutralized and recrystallized as described above or transformed into its N–Boc-derivative with Boc_2O in THF/H_2O (40 ml each) at pH 8.5 (r.t., 2 h). The reaction mixture was acidified to pH 3-4 with dilute H_2SO_4, extracted with ether (2 x 50 ml), and the combined organic extracts were washed with brine and dried. The solvent was removed *in vacuo* and the protected amino acid was precipitated with petroleum ether and recrystallized from hexane/ethyl acetate. Yield: 800 mg (82%) of analytically pure **16b**; $[\alpha]_D^{20}$=–47.1 (c=1.0 HOAc), m.p.= 81°C.

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2. C. Ressler, S.N. Banerjee, *J. Org. Chem.* **1976**, *41*, 1336.
3. All compounds were characterized by their ^1H NMR, IR and mass spectra. In addition, correct combustion analyses were obtained for compounds **4**, **D-5**, D,L-**7** and **16 a-c.**
4. In contrast to S-(4-methoxybenzyl) protected thiols, S-diphenymethyl and S-triphenylmethyl-protected thiols are cleaved by TFA/Et_3SiH; see D.A. Pearson, M. Blanchette, M.L. Baker, C.A. Guindon, *Tetrahedron Lett.* **1989**, *30*, 2739.
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9. For examples, see a) M.J. Brown, P.D. Milano, D.C. Lever, W.W. Epstein, D.C. Poulter, *J. Am. Chem. Soc.* **1991**, *113*, 3176. b) C.-C. Yang, C.K. Marlowe, R. Kania, *J. Am. Chem. Soc.* **1991**, *113*, 3177. c) M. D. Bachi, O. Goldberg, *J. Chem. Soc. Perkin I*, **1974**, 1184; d) M. Shin, K. Inouye, N. Higuchi, Y. Kyogoku, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2211.
10. Ref. 9c) reports 192-195°C as the melting point of **D-5**. In our hands, **D-5** repeatedly melted at 169-170°C and was analytically pure by combustion analysis, HPLC, ^1H NMR and mass spectrum.

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