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The Prop-2-ynyloxy Carbonyl Function (POC) : A New Amino-Protecting Group Removable from Sulfur-Containing Peptides by Ultrasonic Irradiation with Tetrathiomolybdate under Mild and Neutral Conditions .

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Abstract: The prop-2-ynyloxy carbonyl function (POC) which can be cleaved under mild and neutral conditions in the presence of benzyltriethylammonium tetrathiomolybdate has been developed as a new protecting group for amines.

Keywords: amino acids and derivatives; protecting groups

Most of the known amino-protecting groups are cleaved by acids[1] of varying strengths, a few other groups are cleaved by base[2] while protecting groups removable under hydrogenolytic conditions are not usually satisfactory, especially in the case of sulfur-containing peptides.[3] In a previous paper we showed that benzyltriethylammonium tetrathiomolybdate $(PhCH_2NEt_3)_2MoS_4$, **1** is a useful reagent for the selective cleavage of prop-2-ynyl groups which can be used to protect carboxylic acids.[4] These results prompted us to study the usefulness of the prop-2-ynyloxy carbonyl function (POC) as a protective group for amines in general and aminoacids in particular. Our preliminary results on the highly selective deblocking of POC group from sulfur containing amino acids and peptides under neutral conditions using tetrathiomolybdate **1** are presented in this communication.

The POC group was introduced readily by treatment of the parent amines (**3a - e**) with prop-2-ynyl chloroformate **2**[5] in aqueous dioxane in the presence of sodium hydroxide (pH = 9-10) or in dry dichloromethane in the presence of triethylamine and a catalytic amount of 4-dimethylaminopyridine. A number of POC protected amines/amino acids/peptides (**4a – e**) were obtained in very high yields (80-92%) as colourless oils.

When a simple model substrate like the POC-protected amine **4a** was treated with tetrathiomolybdate **1**, under conditions adapted for deprotection of prop-2-ynyl esters,[4] the deprotection was not very facile even after a long time (30-40 h). Even with the addition of an excess of the reagent **1** (2.0-2.5 eq), the reaction did

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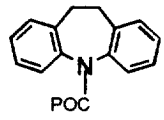
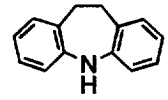
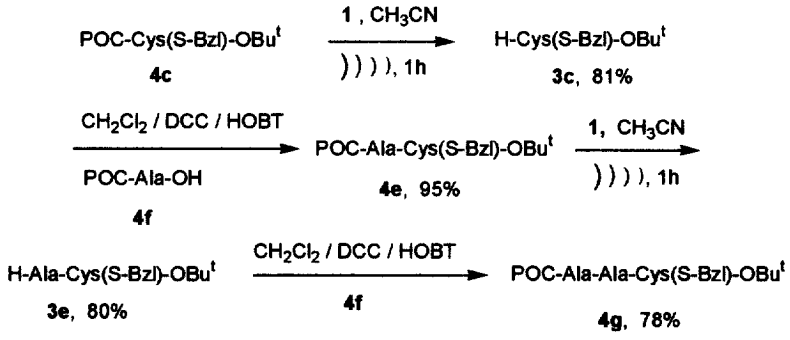
not go to completion. However, when a mixture of **4a** and tetrathiomolybdate **1** (1.0 eq) in acetonitrile was sonicated (ultrasonic cleaning bath, 25 ^{o}C, 0.75 h) as a slurry *the deprotection was very facile and the amine 3a was obtained in 88% yield.*[6] A number of N-POC protected amino acid/peptide derivatives were subjected to the same reaction conditions with tetrathiomolybdate **1** and in all the cases the deprotected amines could be isolated in very good yields. These results are summarized in Table 1.

Table 1.

	Substrate	Time (h)		Product	Yield (%)
4a		0.75	**3a**		88
4b	POC-Met-OMe	1	**3b**	H-Met-OMe	84
4c	POC-Cys(S-Bzl)-OBu^t	1	**3c**	H-Cys(S-Bzl)-OBu^t	81
4d	POC-Cys(S-Bzl)-Cys(S-Bzl)-OBu^t [14]	1	**3d**	H-Cys(S-Bzl)-Cys(S-Bzl)-OBu^t	85
4e	POC-Ala-Cys(S-Bzl)-OBu^t	1	**3e**	H-Ala-Cys(S-Bzl)-OBu^t	80

In the case of the POC protected sulfur-containing amino acid derivatives **4b** and **4c**, the reaction with **1** selectively deblocks the POC group in very good yields. The deprotected amino acid **3c** was then converted into the tripeptide **4g** stepwise using POC as the protecting group (Scheme 1). It is noteworthy that the other



Scheme 1. Preparation of a tripeptide using POC as a protecting group.

protecting groups present in the substrate (-S-Bzl and $-CO_2Bu^t$) are totally unaffected under the reaction conditions. Similarly, the POC protected dipeptide derivatives **4d** and **4e** also reacted with tetrathiomolybdate **1** to give the deprotected dipeptides **3d** and **3e**, respectively, in high yields.

It is worth mentioning that the POC group is stable to both acidic and basic conditions as evidenced by treatment of the *tert*-butyl ester, POC-Cys(S-Bzl)-OBu^t, **4c** with 98% formic acid (25 ^{0}C, 12 h) or with trifluoroacetic acid (25 ^{0}C, 1 h) which resulted in the deblocking of only the *tert*-butyl ester, leaving the POC group untouched, to provide POC-Cys(S-Bzl)-OH, **4i** (98%). This result has to be viewed in the light of the observation that selective removal of a *tert*-butyl ester in the presence of a *tert*-BOC is an intricate and long-standing problem.[7,8] Similarly, treatment of the methyl ester, POC-Cys(S-Bzl)-OMe, **4h** with 2N NaOH (25°C, 1 h) resulted in the hydrolysis of only the methyl ester leaving the POC group untouched to afford POC-Cys(S-Bzl)-OH, **4i** (96 %). The free acid, **4i** was used in the next step for coupling with H-Cys(S-Bzl)-OBu^t, **3c**.

Although at this stage the mechanism of the POC deprotection is unclear, it is very probable that a propargyl-allenic rearrangement[9,10] occurs in the reaction pathway, initiated by attack of the sulfur nucleophile **1** on the terminal carbon of the acetylenic segment. This rearrangment could not be initiated with a simple nucleophile like lithium thiophenoxide[11] and we believe that prior co-ordination of the acetylenic segment to the molybdenum is necessary.

The 1,1-dimethyl prop-2-ynyloxy carbonyl group (DMPOC),[12] a congener of POC, was claimed to be a useful protecting group for sulfur-containing peptides and was cleaved under hydrogenolytic conditions.[13] However, the yields of deprotection are mediocre. On the other hand the POC protecting group survives acidic and basic conditions and can be deprotected under mild and neutral conditions with excellent yield. Hence we believe that the POC moiety should find wide use as a protecting group in peptide chemistry, particularly for sulfur-containing amino acids and peptides.

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6. **Typical experimental procedure.** POC-amine (1 mmol) and benzyltriethylammonium tetrathio-molybdate (**1**) (1 mmol, 0.608 g) were placed in a test tube and few drops of acetonitrile (125 – 150 μL) were added to make a slurry and the mixture was sonicated in an ultrasonic cleaning bath (20 KHz) for 0.75 - 1 h. The residue was extracted with CH_2Cl_2 and diethylether (1:5, 30×5, 150 mL), the solvent removed under reduced pressure, and the crude product purified by chromatography on silica gel.

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11. Compound **4a** on treatment with lithium thiophenoxide (25 ^{o}C, sonication, CH_3CN) under the same condition was recovered unchanged.

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13. The deprotection of POC group did not occur with 5% Pd/C, H_2 (1 atm), 24 h. Even treatment with Lindlar's catalyst, H_2 (1 atm) for 24 h turned out to be unsatisfactory with a number of products ensuing.

14. Selected data for (**4d**): IR (neat, cm^{-1}) 3300, 1725, 1660; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 9H), 2.48 (t, J = 2.4 Hz, 1H), 2.75-2.88 (m, 4H), 3.70 (s, 2H), 3.77 (s, 2H), 4.22-4.39 (m, 1H), 4.62-4.66 (m, 1H), 4.69 (d, J = 2.4 Hz, 2H), 5.6 (d, 1H, NH), 6.92 (d, 1H, NH), 7.24-7.34 (m, 10H); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 27.8, 33.4, 33.9, 36.5, 52.5, 52.7, 54.0, 75.0, 77.8, 82.7, 127.0, 128.4, 128.8, 137.7, 154.8, 169.0, 169.8; MS, m/z (%): 542 [M^+] (0.4), 486 (2.8), 430 (1.5), 395 (2.8), 339 (2.8), 91 (100).