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Highly Selective Deblocking of Propargyl Carbonates in the Presence of Propargyl Carbamates with Tetrathiomolybdate

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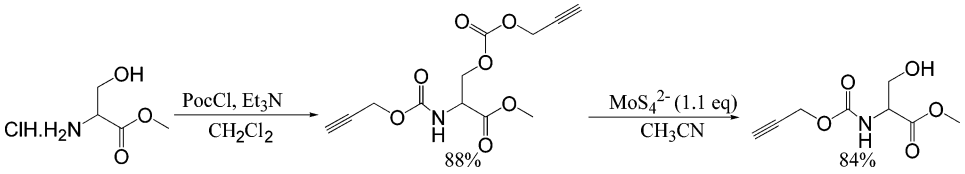

Propargyloxycarbonyl chloride, **1**, has been used to protect the hydroxyl and amino functionalities of amino alcohols and aminophenols in one pot using triethylamine or pyridine as a base. The increased reactivity of benzyltriethylammonium tetrathiomolybdate, **2**, toward propargyl carbonates over propargyl carbamates is studied in detail and has been exploited further to develop an orthogonal protection strategy for the hydroxyl and amino functionalities. For example, 2-amino-1-butanol, **6a**, was treated with **1** to get the *N*,*O*-diPoc compound **7a** in 90% yield, which when treated with 1.1 equiv of **2** at room temperature removes the Poc group attached to oxygen while leaving the one attached to nitrogen intact to yield compound **8a** in 85% yield. This particular observation offers a new protecting strategy where an amine and an alcohol group can be protected simultaneously in one pot, and in a later synthetic step, if the alcohol group has to be deprotected selectively, it can be achieved with 1 equiv of **2**.

Introduction

One of the most convenient methods used for the protection of amines is by forming the corresponding carbamates.[1] *tert*-Butyl, benzyl, and 9-fluorenylmethyl carbamates are by far the most commonly used as Boc, Cbz, and Fmoc, respectively. Alcohols are generally protected as the corresponding ethers, esters, acetals, or ketals.[1] Protection of alcohols as carbonates is not uncommon. Carbonates are relatively less stable than carbamates, and most of them are not sufficiently stable to a variety of conditions to meet the needs of a protecting group. The increased stability of carbamates over carbonates has not been comprehensively studied to develop a methodology for orthogonal protection in the case of such protecting groups.

We have earlier reported our results on the protection of alcohols and amines as propargyl carbonates[2] and carbamates,[3] respectively. The protection is achieved by treating the alcohol or amine with propargyloxycarbonyl chloride (PocCl, **1**) in the presence of a suitable base. The use of this reagent for protection of the amino group in peptide synthesis[4] and for the hydroxyl function in carbohydrate synthesis[2] has already been demonstrated. The propargyloxy carbonyl (Poc) group is stable to a variety of acidic and basic conditions. For instance, it has been shown that methyl esters of Poc-protected amino acids could be hydrolyzed with methanolic NaOH in good yields, keeping the Poc group intact.[4] The orthogonality of the Poc group with a number of acid- and base-labile protecting groups used commonly in carbohydrate synthesis has also been reported.[2] However, propargyl carbonates/carbamates are deprotected effectively using benzyltriethylammonium tetrathiomolybdate **2** as the reagent[2−5] (Figure 1). It has also been shown that most of the commonly used protecting groups for amines and alcohols, including the allyloxycarbonyl group, do not react with **2**.

Results and Discussion

We decided to carry out a systematic study of deprotection of propargyl carbonates and propargyl carbamates

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(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons, Inc.: New York, 1999.
(2) Sridhar, P. R.; Chandrasekaran, S. *Org. Lett.* **2002**, *4*, 4731.
(3) Sinha, S.; Ilankumaran, S.; Chandrasekaran, S. *Tetrahedron Lett.* **1999**, *40*, 771.
(4) Bhat, R. G.; Sinha, S.; Chandrasekaran, S. *Chem. Commun.* **2002**, *8*, 812.
(5) Ramesha, A. R.; Chandrasekaran, S. *Synth. Commun.* **1992**, *22*, 3277.

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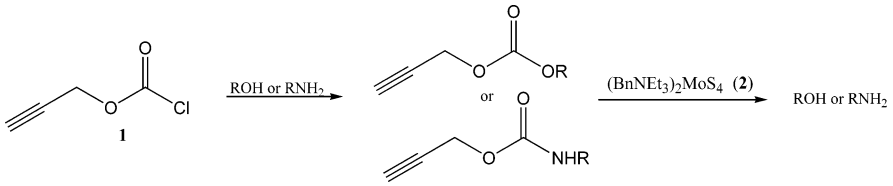
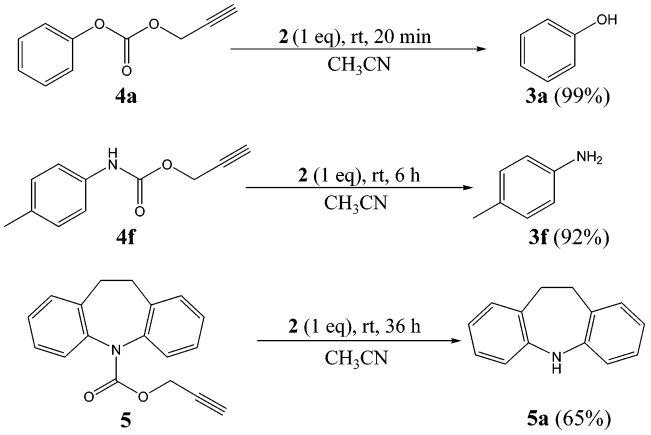


FIGURE 1. Protection of an amine or alcohol with propargyloxycarbonyl chloride, **1**, and subsequent deprotection of Poc group with benzyltriethylammonium tetrathiomolybdate, **2**.

SCHEME 1. Comparison of the Reactivity of 2 with Propargyl Carbonates and Propargyl Carbamates (28 °C, CH_3CN)

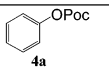
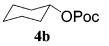
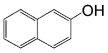
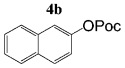
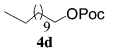
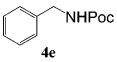
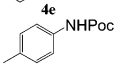
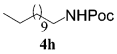


with benzyltriethylammonium tetrathiomolybdate **2** with a view to develop a simple protocol for orthogonal protection. Propargyl carbonates have been shown to react with **2** at a faster rate than propargyl carbamates, and the difference in reactivity is marked. Generally, the reaction times are less than an hour for propargyl carbonates, and it varies from 6 h to 1 day for propargyl carbamates. For example, phenyl propargyl carbonate **4a** reacts with 1 equiv of **2** to give phenol in almost quantitative yield (20 min, rt), whereas *p*-toluidylpropargyl carbamate **4f** takes about 6 h for complete deprotection, and interestingly, the carbamate **5** did not react completely even after 36 h[3] with **2** under the same reaction conditions (Scheme 1).

However, the carbamates **4f** and **5** cleaved readily to give the corresponding amines **3f** and **5a** in very good yields when treated with 1 equiv of **2** under ultrasonication (ultrasonic cleaning bath, 28 °C, CH_3CN, 30−45 min). It is to be noted that the same results cannot be achieved by increasing the temperature. Though the reaction is faster at elevated temperatures, it is observed that increasing the temperature above 60 °C results in gradual decomposition of the reagent **2**. There are reports dealing with the deprotection of Poc group with trifluoroacetic acid in the presence of metal complexes such as $Co_2(CO)_8$, but no difference in the reactivities of propargyl carbonates and carbamates has been observed.[6]

The drastic difference in the reactivity of propargyl carbonates and carbamates toward tetrathiomolybdate **2**, as evident from Scheme 1, prompted us to study the selective deblocking of propargyl carbonates in the presence of propargyl carbamates. We began our experiments by treating 1 equiv each of phenyl propargyl carbonate **4a** and *p*-toluidyl propargyl carbamate **4f** with 1.1 equiv of **2** in dry acetonitrile at room temperature. The reaction was monitored by thin-layer chromatography (TLC) until the carbonate **4a** disappeared completely (25 min) to give phenol **3a** (89%) and the unreacted carbamate **4f** (87%) as shown in Scheme 2.

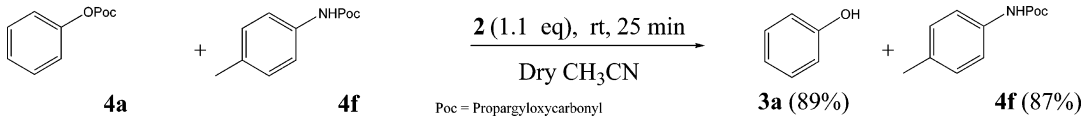
TABLE 1. Preparation of Propargyl Carbonates and Carbamates

Entry	Alcohol/Phenol/Amine	Carbonate/Carbamate	Time (h)	Temperature (°C)	Yield (%)
i	 **3a**	 **4a**	3	-78	95
ii	 **3b**	 **4b**	3	-78	93
iii	 **3c**	 **4c**	3	-78	97
iv	 **3d**	 **4d**	3	-78	96
v	 **3e**	 **4e**	1.5	0	97
vi	 **3f**	 **4f**	1.5	0	97
vii	 **3g**	 **4g**	1.5	0	97
viii	 **3h**	 **4h**	1.5	0	96

A few simple propargyl carbonates and carbamates were prepared for further study by treating the corresponding alcohols, or phenols, and amines with **1** (CH_2Cl_2, Et_3N). The desired carbonates **4a**−**d** and carbamates **4e**−**h** were obtained in excellent yields (Table 1).

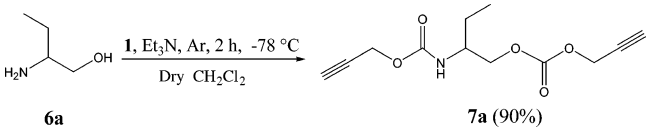
The selective deblocking of carbonates **4a**−**d** in the presence of carbamates **4e**−**h** using **2** was studied with different combinations of substrates. In all cases, propargyl carbonates **4a**−**d** could be deblocked completely (15−45 min) and propargyl carbamates **4e**−**h** could be recovered in high yields, as listed in Table 2. The general observation is that the deprotection of alkyl propargyl carbonates **4b** and **4d** takes longer time than aryl propargyl carbonates **4a** and **4c**, when treated with **2**.

SCHEME 2. Selective Reaction of 2 with Propargyl Carbonate in the Presence of Propargyl Carbamate



4a **4f** **3a** (89%) **4f** (87%)

SCHEME 3. Simultaneous Protection of Amino and Hydroxyl Groups as Corresponding Carbamate and Carbonate



SCHEME 4. Selective Deprotection of Propargyl Carbonate in the Presence of Propargyl Carbamate Using 2

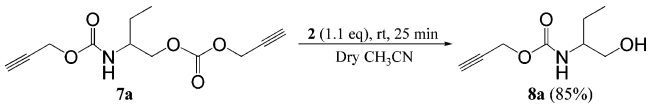
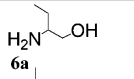
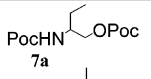
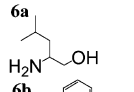
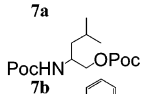
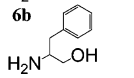
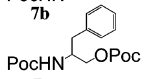
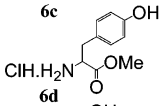
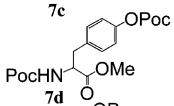
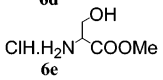
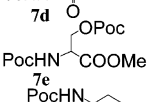
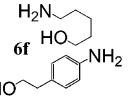
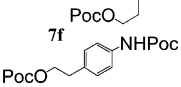
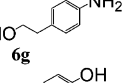
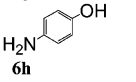
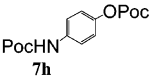


TABLE 2. Selective Deblocking of Propargyl Carbonates in the Presence of Propargyl Carbamates with 2

entry	carbonate + carbamate	time (min)	products[a]
i	**4a** + **4e**	25	**3a** (89) + **4e** (87)
ii	**4c** + **4e**	15	**3c** (88) + **4e** (91)
iii	**4a** + **4h**	25	**3a** (89) + **4h** (88)
iv	**4c** + **4g**	15	**3c** (88) + **4h** (90)
v	**4c** + **4h**	15	**3c** (89) + **4h** (88)
vi	**4b** + **4e**	35	**3b** (89) + **4e** (86)
vii	**4b** + **4f**	35	**3b** (89) + **4f** (88)
viii	**4b** + **4g**	35	**3b** (90) + **4g** (92)
ix	**4d** + **4h**	45	**3d** (88) + **4h** (85)
x	**4d** + **4f**	45	**3d** (88) + **4f** (84)

[a] Percentage yields for the products are given in parentheses.

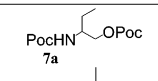
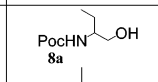
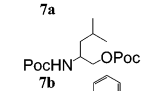
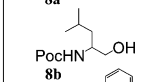
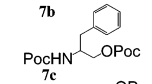
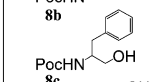
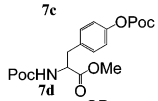
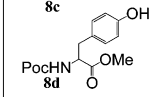
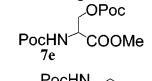
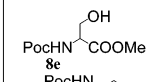
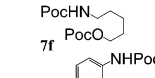
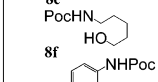
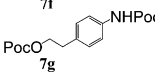
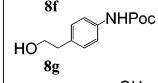
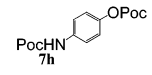
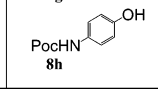
TABLE 3. Di-Poc Derivatives of Amino Alcohols and Aminophenols

Entry	Amino alcohols/Amino phenols	Time (h)	Product	Yield (%)
i	 **6a**	2.5	 **7a**	90
ii	 **6b**	2.5	 **7b**	89
iii	 **6c**	2.5	 **7c**	90
iv	 **6d**	2	 **7d**	90
v	 **6e**	2.5	 **7e**	88
vi	 **6f**	2	 **7f**	90
vii	 **6g**	1.5	**7g**	91
viii	 **6h**	1.5	 **7h**	92

However, all the propargyl carbonates are completely deblocked in less than 45 min.

Encouraged by the success achieved in selective deblocking of Poc-protected hydroxyl groups over Poc-protected amino groups, we decided to study the reaction of **7a**, with **2**, where both the amino and hydroxyl groups are protected with a Poc group. The protected derivative **7a** was easily prepared (90%) by the reaction of 2-aminobutanol **6a** with **1** (Scheme 3).

TABLE 4. Selective Deprotection of Propargyl Carbonates with 2

Entry	Diprotected Amino alcohols/Amino phenols	Time (min)	Products	Yield (%)
i	 **7a**	25	 **8a**	85
ii	 **7b**	30	 **8b**	83
iii	 **7c**	30	 **8c**	86
iv	 **7d**	20	 **8d**	90
v	 **7e**	30	 **8e**	84
vi	 **7f**	30	 **8f**	81
vii	 **7g**	30	 **8g**	78
viii	 **7h**	20	 **8h**	82

The protected derivative **7a** was then treated with **2** (1.1 equiv, 25 min, 28 °C, CH_3CN) to yield **8a** (85%), where the propargyl carbonate alone was deblocked leaving the propargyl carbamate unaffected (Scheme 4).

To ascertain the scope of this methodology a number of amino alcohols **6b**−**h** were converted to the corresponding Poc-protected derivatives **7b**−**h**, respectively, in very good yields (Table 3).

The selective deblocking of these di-Poc derivatives **7b**−**h** with **2** was then studied under similar conditions (1.1 equiv, rt, 20−30 min), and in all cases the reaction was quite selective and efficient to produce the corresponding alcohols **8b**−**h** respectively in excellent yields. These results are summarized in Table 4.

Conclusion

In conclusion, the utility of propargyloxycarbonyl chloride in simultaneous protection of alcohols and amines has been explored and the selective deblocking of propargyl carbonates in the presence of propargyl carbamates with benzyltriethylammonium tetrathiomolybdate **2** under mild conditions has been achieved. These results add a new dimension to selective protection strategies by providing an efficient method for the one pot protection of alcohol and amine functionalities with the same reagent **1**. In a later synthetic step, if the alcohol group has to be deprotected selectively it can be achieved with 1 equiv of **2**, leaving the amino protection intact, which can then be removed at a later step with an additional 1 equiv of **2** under ultrasonic conditions.

Experimental Section

General Procedure for the Protection of Amines, Alcohols, and Phenols with PocCl, 1. To a well-stirred solution of phenol (10 mmol) and triethylamine (10.5 mmol)

(6) Fukase, Y.; Fukase, K.; Kusumoto, S. *Tetrahedron Lett.* **1999**, *40*, 1169.

in anhydrous dichloromethane (30 mL), at −78 °C, was added dropwise PocCl (10 mmol). The reaction mixture was stirred at the same temperature until completion of the reaction (as shown by TLC). It was then washed with water and dried over anhydrous Na_2SO_4. The carbonate **4a** was then purified, to get a pale yellow oil, using flash column chromatography on a silica gel (230−400 mesh) column using 10% ethyl acetate in hexane for elution.

^{1}H NMR ($CDCl_3$): δ 7.37−7.15 (m, 5H), 4.8 (d, J = 2.7, 2H), 2.6 (t, J = 2.7, 1H). ^{13}C NMR ($CDCl_3$): δ 152.8, 150.7, 129.3, 126.0, 120.7, 76.4, 76.1, 55.6. IR (neat): 3293 (s), 3069 (w), 2130 (w), 1759 (s). ESMS: HRMS calcd for $C_{10}H_8O_3$ + Na 199.0371, found 199.0390.

Procedure for the Selective Deblocking of Propargyl Carbonates in the Presence of Propargyl Carbamates. To a solution of propargyl carbonate and carbamate (2 mmol each) in anhydrous CH_3CN (2 mL) was added tetrathiomolybdate **2** (2.2 mmol) at room temperature (28 °C). Reaction was monitored using TLC. On complete disappearance of the propargyl carbonate, stirring was stopped and the solvent was removed under vacuum. The residue was extracted with a 9:1 mixture of dichloromethane and diethyl ether three times and filtered over a Celite pad. The compounds were separated by flash column chromatography on silica gel (230−400 mesh) using a ethyl acetate/hexane solvent system.

General Procedure for the Preparation of 7a−h. To a well-stirred solution of the 2-amino-1-butanol **6a** (5 mmol) and triethylamine (11 mmol) in anhydrous dichloromethane (20 mL) at −78 °C was added dropwise PocCl, **1** (10.5 mmol). The reaction mixture was stirred at the same temperature until completion of the reaction (as shown by TLC). It was then washed with water and dried over anhydrous Na_2SO_4. The diprotected compound **7a** was then purified to get a pale yellow oil, using flash column chromatography on a silica gel (230−400 mesh) column using 20% ethyl acetate in hexane for elution.

^{1}H NMR ($CDCl_3$): δ 5.2 (db, J = 8.4, 1H), 4.7 (d, J = 2.4, 2H), 4.7 (sb, 2H), 4.2 (d, J = 4.2, 2H), 3.77−3.87 (m, 1H), 2. 6 (t, J = 2.4, 1H), 2.5 (t, J = 2.1, 1H), 1.48−1.69 (m, 2H), 0.97 (t, J = 7.2, 3H). ^{13}C NMR ($CDCl_3$): δ 155.0, 154.3, 78.0, 76.7, 75.8, 74.6, 69.2, 55.3, 52.4, 51.5, 24.2, 10.1. IR (neat): 3295 (s), 2129 (w), 1747 (s), 1714 (s). ESMS: HRMS calcd for $C_{12}H_{15}NO_5$ + Na 276.0848, found 276.0851.

Procedure for the Selective Deblocking of Propargyl Carbonates from Di-Poc-Protected Amino Alcohols and Aminophenols. To a stirred solution of **7a** (2 mmol) in anhydrous CH_3CN (1.5 mL) at room temperature was added tetrathiomolybdate **2** (2.2 mmol). The reaction mixture was stirred until the disappearance of the starting material (25 min, as shown by TLC). The solvent was removed under vacuum. The residue was extracted with a 9:1 mixture of dichloromethane and diethyl ether three times and filtered over a Celite pad. The compound **8a** was purified, to get a colorless oil, by flash column chromatography on a silica gel (230−400 mesh) column using 20% ethyl acetate in hexane for elution.

^{1}H NMR ($CDCl_3$): δ 5.3 (sb, 1H), 4.6 (sb, 2H), 3.55−3.69 (m, 3H), 3.1 (sb, 1H), 2.5 (sb, 1H), 1.42−1.62 (m, 2H), 0.95 (t, J = 6.9, 3H). ^{13}C NMR ($CDCl_3$): δ 155.8, 78.1, 74.7, 64.5, 54.7, 52.5, 24.2, 10.3. IR: 3404 (s), 3297 (s), 2966 (m), 2127 (w), 1714 (s), 1697 (s). IR (neat): 3395 (br), 2131(w), 1714 (s). ESMS: HRMS calcd for $C_8H_{13}NO_3$ + Na 194.0793, found 194.0795.

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Supporting Information Available: Characterization data and ^{1}H and ^{13}C spectra for reference compounds **4a**−**h**, **7a**−**h** and **8a**−**h** and experimental procedures including those for the synthesis of **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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