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But-2-ynylbisoxycarbonyl Chloride: A Novel C_2-Symmetric Reagent for the Protection of Amines and Amino Acids

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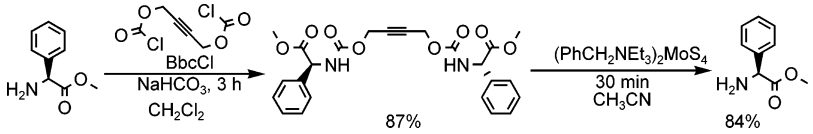
ABSTRACT

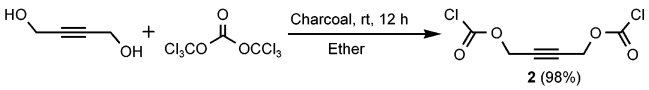


A novel C_2-symmetric protecting group for amines, the but-2-ynylbisoxycarbonyl (Bbc) group, is developed, which can be deblocked with tetrathiomolybdate under neutral conditions. One equivalent of the bischloroformate, BbcCl, is used for the protection of 2 equiv of the amine. Its application in peptide synthesis is established through the synthesis of a tripeptide, and its orthogonality with Cbz, Fmoc, and Boc groups has been studied.

The science and art of organic synthesis has not yet matured to avoid the extensive use of protective groups during the synthesis of multifunctional molecules. Therefore, the search for new and efficient protecting groups, which are stable and can be used orthogonally with a number of other protecting groups, is always underway. Previous reports from our laboratory have exploited the reactivity of benzyltriethylammonium tetrathiomolybdate (**1**) toward propargyl groups in developing protective groups for amines, alcohols, and acids.[1−6] It has been shown that alcohols and carboxylic acids can be protected as propargyl ethers[4] and esters,[5] respectively, and ultimately deblocked using tetrathiomolybdate **1**. Propargyloxycarbonyl chloride (PocCl) has been reported as an efficient reagent for the protection of amines[1,2] and alcohols.[3] The propargyl carbamates and carbonates thus formed can easily be deblocked to the amines and alcohols, respectively, using tetrathiomolybdate **1**. The Poc group has a relatively acidic alkynyl hydrogen, and it has also been observed that the reaction of propargyl carbamates with **1** is very slow and often needs ultrasonic conditions to effect the deprotection.[2] Therefore, it seemed attractive to study the reactivity of but-2-ynylbisoxycarbonyl chloride (BbcCl, **2**) as the first C_2-symmetric protecting group for amines. But-2-yne-1,4-diol on treatment with phosgene, generated in situ from triphosgene, results in the formation of but-2-ynylbisoxycarbonyl chloride (BbcCl, **2**) in high yield (Scheme 1).

The biscarbamates derived from **2** will have two propargyloxycarbonyl (Poc) groups and are expected to react with benzyltriethylammonium tetrathiomolybdate (**1**), allowing the use of Bbc group for the protection of amines. We initiated our investigations in this regard by treating **2** with 2.1 equiv of aniline in anhydrous dichloromethane in the presence of

Scheme 1. Preparation of But-2-ynylbisoxycarbonyl Chloride (BbcCl)



(1) Bhat, R. G.; Sinha, S.; Chandrasekaran, S. *Chem. Commun.* **2002**, *8*, 812.
(2) Sinha, S.; Ilankumaran, P.; Chandrasekaran, S. *Tetrahedron Lett.* **1999**, *40*, 771.
(3) Sridhar, P. R.; Chandrasekaran, S. *Org. Lett.* **2002**, *4*, 4731.
(4) Swamy, V. M.; Ilankumaran, P.; Chandrasekaran, S. *Synlett* **1997**, *5*, 513.
(5) Ilankumaran, P.; Manoj, N.; Chandrasekaran, S. *Chem. Commun.* **1996**, *16*, 1957.
(6) Ramesh, R.; Bhat, R. G.; Chandrasekaran, S. *J. Org. Chem.* **2005**, *70*, 837.

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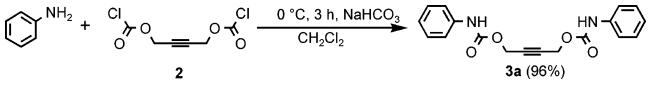
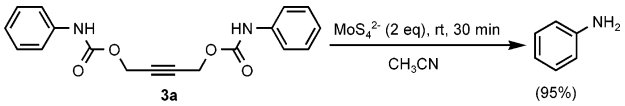
$NaHCO_3$ to yield the biscarbamate **3a** in excellent yield (Scheme 2).

Scheme 2. Preparation of the Biscarbamate of Aniline **3a** Using **2**



The Bbc-protected aniline **3a** on treatment with 2 equiv of tetrathiomolybdate **1** (CH_3CN, rt, 30 min) afforded aniline in 95% yield (Scheme 3).

Scheme 3. Deblocking of Bbc-Protected Aniline **3a** with **1**



These experiments were extended to a few other amines, which when treated with **2** (CH_2Cl_2, $NaHCO_3$, 0 °C to rt, 3 h) afforded the Bbc-protected derivatives **3a**−**i** in very good yields (Table 1). Secondary amino groups of piperidine and *N*-methylaniline reacted with **2** under the same conditions to give the corresponding carbamates in yields comparable to those of the primary amines studied (entries e and f). Even the relatively hindered amino groups of phenylglycine methyl ester and methyl 2-amino-2-methylpropanoate yielded the corresponding biscarbamates in 87% and 79% yield, respectively (**3h** and **3i**).

The biscarbamates **3a**−**i** were then treated with tetrathiomolybdate **1** (2 equiv, 28 °C, 30 min, CH_3CN), and all of them underwent deprotection to the corresponding amines in excellent yields (Table 1). In all cases, the deprotection could be effected in less than 30 min. This is a definite advantage over the deprotection of Poc-protected amines, which require ultrasonic conditions.[1]

All the biscarbamates studied were crystalline solids, except **3e**. Figure 1 shows the single-crystal X-ray structure of compound **3h**.

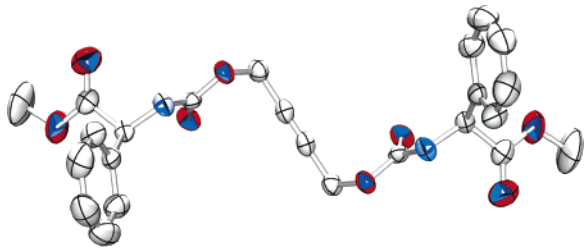
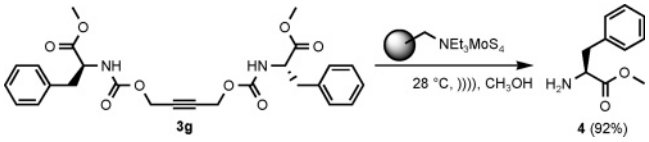


Figure 1. ORTEP diagram for **3h**.[7]

It was also observed that not all of the biscarbamates studied required 2 equiv of **1** for complete deprotection. For example, Bbc-protected aniline **3a** could be deblocked in 84% yield with 1.1 equiv of **1**, in 45 min. However, other substrates **3b**−**i** required 2 equiv of **1** for faster deprotection.

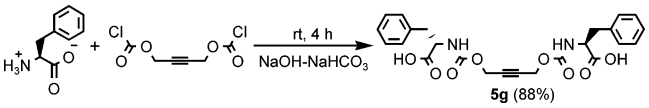
The utility of resin-bound tetrathiomolybdate for deprotecting Poc group under ultrasonic conditions has already been reported.[1] Accordingly, when **3g** was ultrasonicated (ultrasonic cleaning bath, 40 kHz, CH_3OH, 28 °C, 1 h) with 2 equiv of resin-bound tetrathiomolybdate (tetrathiomolybdate bound to Amberlite IRA-400 anion-exchange resin) the Bbc group was deblocked, yielding the corresponding amine **4** in 92% yield (Scheme 4).

Scheme 4. Deblocking of Bbc Group with Resin-Bound Tetrathiomolybdate



It is evident from the above results that the compound **2** could be used as a new reagent for protecting amines by converting them to the biscarbamates. Therefore, it was decided to extend the study to amino acids and use the Bbc-protected amino acids in peptide synthesis. Toward this goal, BbcCl was added to a precooled solution of phenylalanine (1.1 equiv) in NaOH−$NaHCO_3$ buffer (28 °C, 4 h) to get Bbc-Phe-OH (**5g**) in 88% yield (Scheme 5). Compound **5g**

Scheme 5. Preparation of Bbc-Phe-OH from Phenylalanine and BbcCl (**2**)



extracted from the reaction mixture, after acidification, was pure (from TLC) and did not require any further purification. However, a crystalline sample could be obtained by recrystallization from a ethyl acetate−hexane mixture.

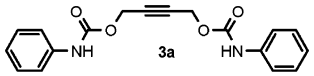
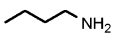
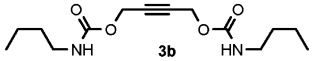
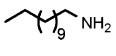
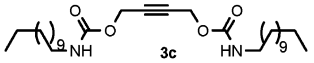
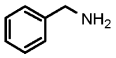
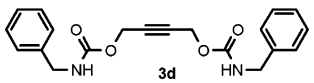
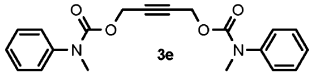
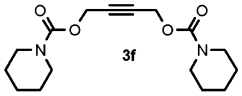
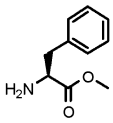
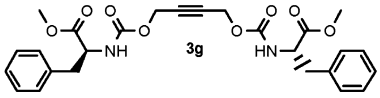
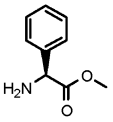
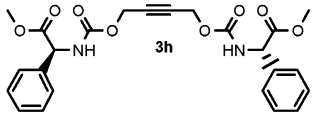
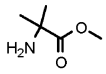
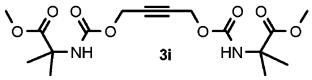
A few other amino acids were treated with BbcCl (**2**) under the above reaction conditions to get the corresponding Bbc-protected amino acids in excellent yields (Table 2). In all cases, the products obtained, **5a**−**h**, were very pure, as observed from NMR, and did not require any further purification.[8]

To use the Bbc group as a new protecting group for amines in peptide synthesis, it is necessary to establish the orthogonality of this group with the existing protective groups. We

(7) Crystal structure data for **3h**: $C_{24}H_{24}N_2O_8$, $M = 468.45$, tetragonal, space group $P4_12_12$, $a = 9.0402(2)$ Å, $c = 29.7809(10)$ Å, $V = 2433.85(11)$ Å^3, $Z = 4$, $T = 298$ K, $R = 0.0608$, $R_w = 0.1285$.

(8) All the compounds (**5a**−**h**, except **5e** and **5f**) were crystalline and could easily be purified by recrystallizing from hot ethyl acetate. Compounds **5e** and **5f** were crystallized from ethyl acetate−hexane mixture over a long period of time.

Table 1. Preparation of Bbc-Protected Amines

entry	amines	biscarbamates	yield (%) of biscarbamates[a]	yield (%) on deprotection[b]
a		 **3a**	96	95
b		 **3b**	94	96
c		 **3c**	89	93
d		 **3d**	91	95
e		 **3e**	86	95
f		 **3f**	85	88
g		 **3g**	88	90
h		 **3h**	87	84
i		 **3i**	79	82

[a] Biscarbamates **3a**−**i** were prepared from the amines by treating with 0.5 equiv of **2** in CH_2Cl_2 in the presence of $NaHCO_3$ for 3 h. [b] **3a**−**i** were deblocked to the corresponding amines by treatment with 2 equiv of **1** in CH_3CN for 30 min at 28 °C.

find that the Bbc group is extremely stable to acidic and basic conditions. Treatment of **5g** for 12 h with 6 N HCl or 4 N NaOH did not hydrolyze the Bbc group, and **5g** could be recovered unchanged.

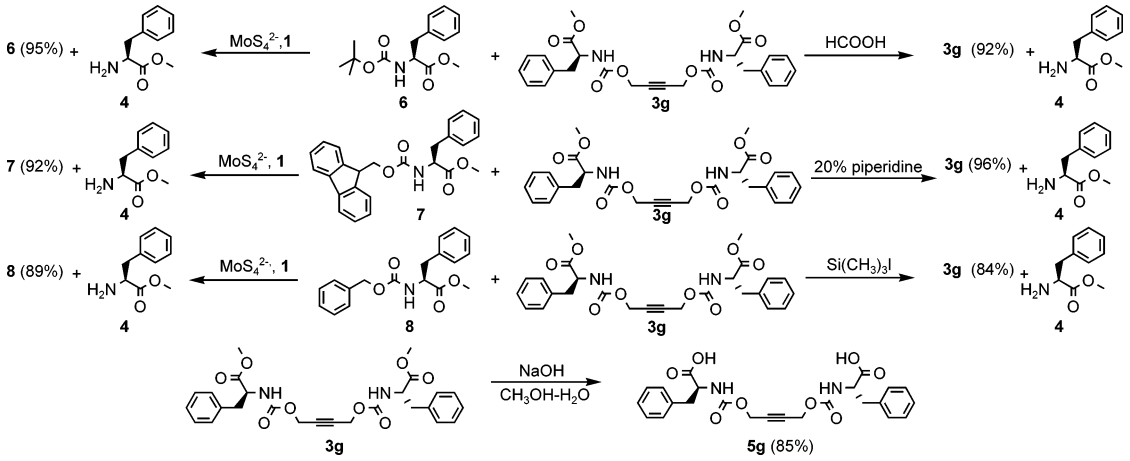
Interestingly, the reaction of Bbc group in **5g** with trimethylsilyl iodide[9] was too slow, and there was no deprotection even after 4 h at 28 °C. Trimethylsilyl iodide deprotects both Cbz and Boc groups in less than 10 min,[9] and this difference in reactivity can be exploited in developing orthogonality between these groups. It is also observed that tetrathiomolybdate **1** does not react with Cbz, Boc, or Fmoc groups, which would allow the deprotection of Bbc group selectively in their presence.

When an equimolar mixture of **3g** and the Boc derivative **6** was treated with HCOOH, only **6** was deprotected to the corresponding amine **4**. Similarly, when a mixture of **3g** and **7** was treated with 20% piperidine in dichloromethane only the Fmoc group of **7** was deblocked to yield **4**. Treatment of an equimolar mixture of **3g** and **8** with trimethylsilyl iodide removed only the Cbz group, and the Bbc group in **3g** stayed intact, whereas treatment of the above mixtures with tetrathiomolybdate **1** resulted in the deblocking of only the Bbc group in **3g** while the Boc, Fmoc, and Cbz groups were unaffected (Scheme 6). We could also establish the stability of Bbc group to conditions required for the basic hydrolysis of a methyl ester, one of the most common steps in solution-phase peptide synthesis. When **3g** was treated with 1.2 equiv of NaOH in aqueous methanol, **5g** could be obtained in 85% yield (Scheme 6).

To establish the applicability of Bbc group as a protecting group for the amino functionality in solution-phase peptide synthesis, we prepared a homo-tripeptide of phenyl alanine **9**, in which the *N*-terminus is protected with Bbc and the *C*-terminus as a methyl ester. Since the workup involved in the deprotection reaction with resin-bound tetrathiomolybdate is rather simple and since the product requires no further purification, we have used this methodology for synthesizing the tripeptide **9**. Bbc-Phe-OH (**5g**) was treated with 2 equiv of HCl·H-Phe-OCH_3 (HOBt, NMM, CH_3CN, 28 °C, 4 h) to get the dipeptide Bbc-Phe-Phe-OCH_3 (**10**) in 84% yield. Dipeptide **10** was then ultrasonicated with resin-bound tetrathiomolybdate, which yielded the amine **11** (90%), which was then coupled with 0.5 equiv of **5g** (EDC·HCl, HOBt, NMM, CH_3CN, 28 °C, 4 h) to get the tripeptide Bbc-Phe-

(9) Lott, R. S.; Chauhan, V. S.; Stammer, C. H. *J. Chem. Soc., Chem. Commun.* **1979**, 495.

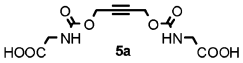
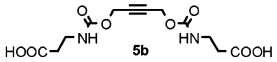
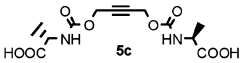
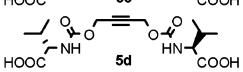
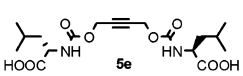
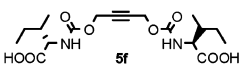
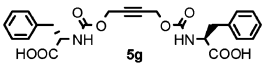
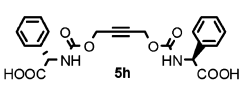
Scheme 6. Establishing the Orthogonality of Bbc Group with Boc, Fmoc, Cbz, and a Methyl Ester[a]



[a] Yields of **3g** and **6**−**8** were determined by removing the amine **4** by washing the reaction mixture with dilute acid followed by purification using column chromatography in each of the respective reactions.

Phe-Phe-OCH_3 (**9**) in 78% yield (Scheme 7), and it was purified by recrystallization from hot ethyl acetate. There is

Table 2. Protection of Amino Acids with BbcCl

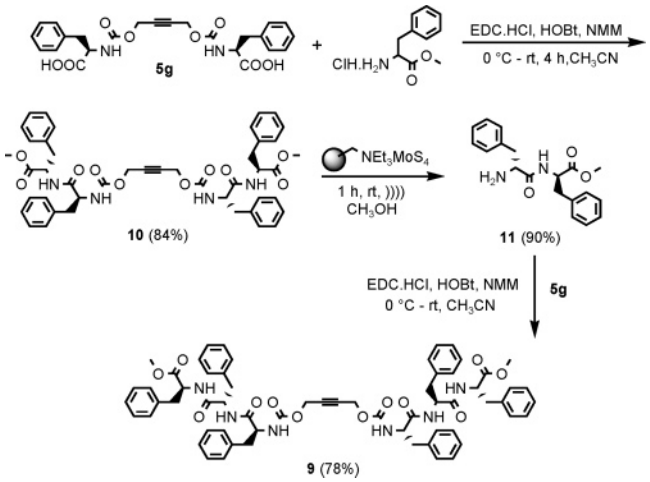
entry	amino acids	Bbc-amino acids[a]	yield (%)
a			92
b			90
c			87
d			80
e			85
f			80
g			88
h			84

[a] Bbc-amino acids **5a**−**h** were prepared by adding 0.5 equiv of BbcCl to an ice-cold solution of the amino acid in $NaHCO_3$−NaOH buffer.

no racemization of amino acids leading to diastereomerization of the peptides either during the protection of the amino group using BbcCl or during deprotection of the Bbc group with tetrathiomolybdate, **1**.[10]

In conclusion, we have developed a new C_2-symmetric protecting group, but-2-ynylbisoxycarbonyl, the Bbc group for amines, which is stable to both acidic and basic conditions and can be deprotected on treatment with tetrathiomolybdate, **1**. One equivalent of BbcCl can be used for the protection of 2 equiv of the amine. The orthogonality of Bbc group with Boc, Fmoc, and Cbz groups has been established, and the utility of this protecting group in peptide synthesis has been demonstrated.

Scheme 7. Synthesis of Bbc-Phe-Phe-Phe-OCH_3 (**9**)



Acknowledgment. R.R. thanks CSIR, New Delhi, for a Senior Research Fellowship.

Supporting Information Available: Full experimental details, characterization data, and ^1H and ^{13}C NMR spectra for all compounds. Crystallographic information file (CIF) for compound **3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051960Z

(10) NMR spectra and HPLC profile of the peptide **9** did not show the presence of any diastereomer.