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Synthesis of *C*-Propargylic Esters of N-Protected Amino Acids and Peptides

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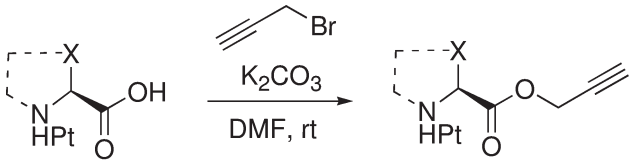


Pt = Boc, Cbz, Bom, COPh and POC

X = -H, alkyl, aryl, -CH_2aryl and -CH_2heteroaryl

Recent years have seen a huge surge of interest in the application of alkyne-derived motifs for so-called "click" chemistry. Given the critical importance of amino acids in organic synthesis as well as their myriad of applications in "click" chemistry it is interesting to note that the synthesis of *C*-propargyl derived amino acid esters has not been particularly well served. We report a convenient, straightforward, and high-yielding synthesis of structurally diverse *C*-propargyl-derived N-protected amino acid esters.

A search of SciFinder reveals that to date over 1700 papers have been published on "click chemistry". Critical to its continued success and development is the ready availability of structurally diverse alkyne (and azide) starting materials.

In an ongoing extension of a Trøger base project[1] we required an efficient, cheap, reliable, and straightforward synthesis of structurally diverse N-protected α-amino acid propargyl esters suited to "click" chemistry. Given the widespread availability of structurally diverse natural and unnatural amino acids and the extensive interest in "click" chemistry we were surprised that a search on SciFinder afforded a limited number of α-amino acid propargyl esters. Furthermore upon closer inspection many of the proposed syntheses employed elevated reaction temperatures, i.e., 70 °C,[2] multistep reaction processes, i.e., synthesis of propargyl ester **3** from methyl ester **1** via acid **2**,[3] and the use of relatively expensive reagents, i.e., synthesis of esters **5** and **6** utilized

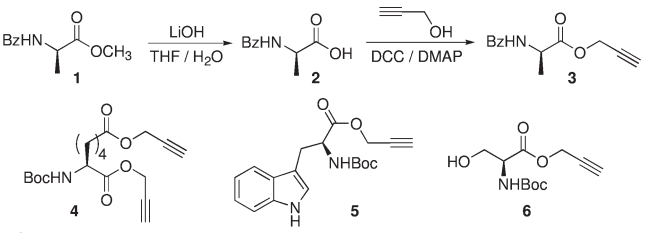
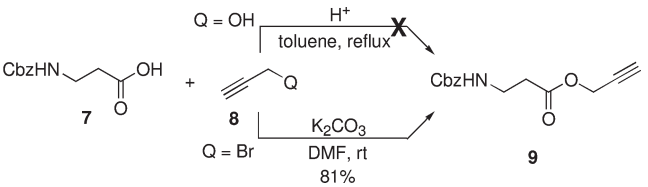


FIGURE 1. Previously synthesized N-protected *O*-propargylic α-amino acid esters.

SCHEME 1. Synthetic Routes to *N*-Cbz-*β*-aminoalanine Propargyl Ester 9



N-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride ($22 per gram), were low yielding, i.e., 14% for **6**,[4] required long reaction times, i.e., **5** took 48 h to go to completion,[5] or employed DCC (dicyclohexylcarbodiimide), necessitating flash chromatography for the efficient and complete removal of the DCU (*N*,*N*′-dicyclohexylurea) byproduct, i.e., synthesis of **3** and **4** (Figure 1).[6]

Attempting the synthesis of ester **9** a solution of acid **7** was warmed with propargyl alcohol **8** (Q = OH) and 10 mol % tosic acid (Scheme 1). After 6 h an intractable brown tar had formed. Subsequent analysis (^{1}H NMR) indicated ~10% of ester **9** had formed but that this was embedded within a complex unidentifiable mixture.

An alternative procedure was required. The O-propargylation of α-amino carboxylic acids with use of propargyl bromide and base has been reported with (*S*)-tyrosine and (*S*)-aspartic acid.[7] Reinvestigating the synthesis of ester **9** we stirred acid **7** in dimethylformamide with propargyl bromide and anhydrous potassium carbonate (1.2 equiv). After a simple workup, i.e., dilute with aqueous citric acid, extract with ethyl acetate, and filter through a Varian SPE cartridge (NH_2), an unoptimized 81% yield of ester **9** was afforded that was pure enough (^{1}H NMR indicated > 95%) to be used for a subsequent reaction.

With this result we set about investigating the scope of the reaction with alternative N-protected α-amino acids. Both aryl and alkyl side chain equipped α-amino acids such as *N*-Cbz-(*S*)-phenylalanine and *N*-Bz leucine (entries A and B, Table 1) afforded the corresponding propargyl esters **10** and

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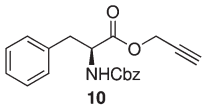
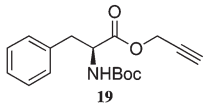
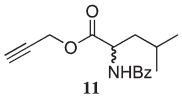
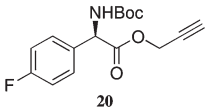
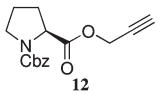
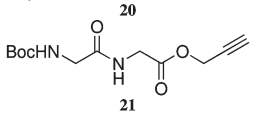
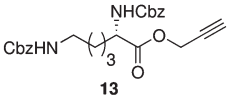
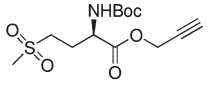
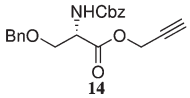
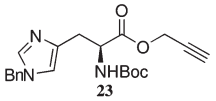
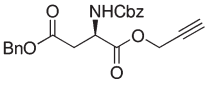
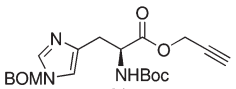
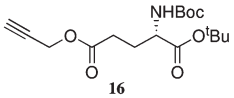
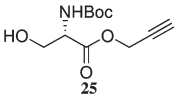
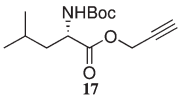
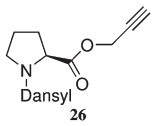
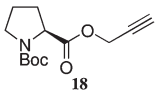
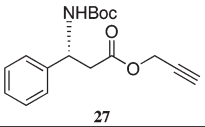
TABLE 1. Examples of Structurally Diverse N-Protected *O*-Propargylic Amino Acid Esters and Peptides Synthesized in This Study

Entry No	N-protected α-amino propargyl ester	Yield	Entry No	N-protected α-amino propargyl ester	Yield
A	 **10**	86%	J	 **19**	91%
B	 **11**	83%	K	 **20**	86%
C	 **12**	95%	L	 **21**	67%
D	 **13**	85%	M	 **22**	71%
E	 **14**	81%	N	 **23**	41%
F	 **15**	82%	O	 **24**	43%
G	 **16**	89%	P	 **25**	65%
H	 **17**	92%	Q	 **26**	85%
I	 **18**	96%	R	 **27**	75%

11 in 86% and 83% yields, respectively. Similarly the cyclic α-amino acid *N*-Cbz-(*S*)-proline derived propargyl ester (**12**, entry C) was returned in an excellent 95% yield and without recourse to flash chromatography. The synthesis of propargyl ester **13** derived from the doubly *N*-Cbz protected (*S*)-lysine was achieved in a pleasing 85% yield (entry D), again no column chromatography was required. Subjecting differentially N,O-diprotected *N*-Cbz-(*S*)-serine-*O*-benzyl to propargylation afforded the desired ester **14** (Table 1, entry E, 81% yield) with both *N*-Cbz and *O*-benzyl protecting groups remaining intact. Similarly the diprotected mono-*O*-benzyl ester *N*-Cbz aspartic acid precursor afforded the corresponding α-amino propargylic ester **15** in an 82% yield (entry F).

Incorporating an *N*-Boc protecting group within (*S*)-glutamic acid, (*S*)-leucine, (*S*)-proline, and (*S*)-phenylalanine afforded (Scheme 1) the expected *N*-Boc protected α-amino acid propargylic esters **16**−**19** in 89%, 92%, 96%, and 91% yields, respectively (entries G−J), without recourse to column chromatography. Similarly incorporating an unnatural, aryl containing α-amino acid, i.e., *N*-Boc-4-fluoro-(*S*)-phenylglycine, afforded the corresponding propargylic ester **20** in a pleasing 86% yield (entry K).

All attempts at transforming *N*-acetylglycine, *N*-Fmoc-(*S*)-valine, *N*-Fmoc-(*S*)-phenylalanine, *N*-Fmoc-*β*-alanine, or *N*-Fmoc-(*S*)-alanine into the corresponding propargylic esters (not shown) employing the reaction conditions outlined in Scheme 1 failed to return any of the desired products. Seemingly the use of base labile N-protecting groups resulted in their cleavage during the reaction process.

A particularly useful application would focus on the ability to generate propargylic esters of dipeptides. With this in mind we subjected the simple monoprotected *N*-Boc-gly gly dipeptide to our standard propargylation reaction conditions (Scheme 1). After a simple workup we were delighted to isolate the desired propargyl ester of *N*-Boc-gly-gly (**21**) in an unoptimised 67% yield (entry L, Table 1).

The application of our O-propargylation reaction to α-amino acids that have heteroatoms embedded within their side chains was deemed worthy of investigation. Initiating this study we probed the O-propargylation of *N*-Boc-(*S*)-methionine sulfone. The desired ester (**22**) was afforded in an unoptimized but pleasing 71% yield (entry M). Similarly incorporating imidazole equipped α-amino acids such as 3-*N*-benzyl-α-*N*-Boc-(*S*)-histidine (entry N), 3-*N*-BOM-α-*N*-Boc-(*S*)-histidine (entry O) afforded the corresponding propargyl esters **23** and **24** in 41% and 43% yields, respectively.

The synthesis of (*S*)-serine derived propargylic ester **25** has been previously reported; however, the yield was a very poor 14%.[4] We felt our procedure may offer this potentially valuable α-amino acid building block in a higher yield. Consequently we were delighted that subjecting *N*-Boc-(*S*)-serine to the reaction conditions outlined in Scheme 1 afforded ester **25** in a significantly improved 65% yield (entry P).

The dansyl group is routinely employed as a fluorogenic agent for the N-derivatization and analysis of α-amino acids and peptides.[8] Furthermore Borthwick et al. has demonstrated that a series of *N*-dansyl-(*S*)-proline α-methylpyrrolidine-5,5-lactam derivatives display single-figure μM inhibition of human cytomegalovirus (HCMV) protease.[9] Thus the ability to generate a *N*-dansyl-(*S*)-proline propargyl ester **26** may have significant applications in the spectroscopic determination of amino acids or peptides as well as acting as a valuable tool for probing biological systems. With this in mind we subjected commercially available *N*-dansyl-(*S*)-proline to our standard propargylic reaction conditions. We were delighted that ester **26** (entry Q) was afforded in an 85% yield and, similar to previous examples, the product was pure enough to be used "as is".

Our study to date had focused on, in the majority of cases, investigating N-protected α-amino acids derived from natural sources. Although we did not envisage any issues it was thought prudent to establish that the procedure outlined in Scheme 1 also worked for unnatural N-protected β-amino acids. With this in mind we took commercially available (*R*)-3-(Boc-amino)-3-phenylpropionic acid and subjected it to our standard conditions with propargyl bromide and potassium carbonate in dimethylformamide. The corresponding propargyl ester (**27**) was afforded as a white powder in a 75% yield (entry R).

In summary, the efficient synthesis of C-propargylated α-amino acids has been achieved by using very mild reaction conditions that tolerate the majority of commonly used amino acid protecting groups. Utilizing cheap reagents the desired products are afforded, in the majority of cases, pure enough to be employed as is, thus negating the cost and environmental impact of purification. It is envisaged that this protocol will be widely applicable, affording valuable C-propargylated amino acids building blocks that should find significant use in the synthetic chemistry community.

Experimental Section

General Procedure. A flame-dried 25-mL round-bottomed flask was charged with *N*-Cbz-(*S*)-proline (1 g, 4 mmol) and anhydrous potassium carbonate (830 mg, 6 mmol) in DMF (5 mL). The resulting suspension was stirred for 30 min under an atmosphere of nitrogen. Propargyl bromide (80% in toluene, 710 mg, 6 mmol) was added and the reaction was stirred for 16 h at ambient temperature. The resulting mixture was diluted with water (5 mL), acidified with citric acid (1 mL), and extracted with ethyl acetate (2 × 2 mL). The combined organic extracts were washed with brine (2 mL), dried with magnesium sulfate, and filtered through NH_2 loaded silica. Solvent removal afforded **12** (1.1 g, 3.8 mmol) as a yellow oil in a 95% yield, with the following physicochemical properties.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (m, 5H, ArH), 5.03 (m, 2H, $CH_{2(cbz)}$), 4.62 (m, 1H, $CHH_{(yne)}$), 4.45 (s, 1H, $CHH_{(yne)}$), 4.28 (m, 1H, αCH), 3.41 (m, 2H, δCH_2), 2.41 (1H, $CH_{(yne)}$), 2.12 (d, J = 7.42 Hz, 1H, βCHH), 1.85 (m, 3H, βCHH, γCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 171.9, 154.9, 154.2, 136.7, 136.6, 128.5, 128.4, 128.0, 127.9, 127.9, 127.8, 77.2, 75.3, 66.9, 66.9, 58.9, 58.6, 52.4, 52.3, 46.8, 46.3, 30.6, 29.6, 24.1, 23.3; FT-IR (KBr neat) 3285, 2956, 2883, 1753, 1704, 1452, 1417, 1353, 1167; m/z [ES] M + Na (found) 310.0, (calcd) 310.11; HRMS (NSI) calcd for $C_{16}H_{21}N_2O_4$ 305.1496, found 305.1496; $[\alpha]^{25}_D$ −80.3 (c 1.0, $CHCl_3$).

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Supporting Information Available: General experimental methods, additional experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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