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Zinc Mediated Addition of Active Halides to a Glycine Cation Equivalent: Synthesis of N-Boc-L-propargylglycine.

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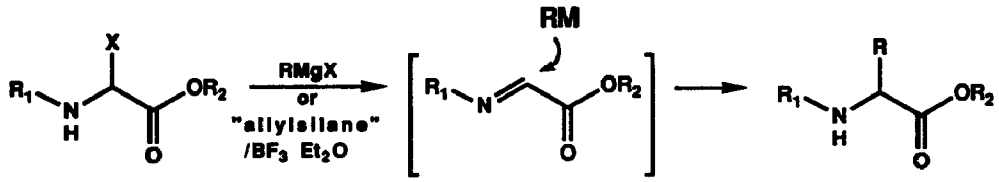
Abstract: The reaction of allylic, benzylic and propargylic halides with zinc in the presence of the glycine cation equivalent, methyl N-Boc-2-acetoxyglycine, affords Boc protected amino acid derivatives in high yield. Resolution of methyl N-Boc-propargylglycine with α-chymotrypsin affords N-Boc-L-propargylglycine in 99% e.e..

The "amidoalkylation" of C-nucleophiles with glycine cation equivalents (e.g. **1**, Scheme 1) for the synthesis of amino acid derivatives is well known.[1-10] In recent years, asymmetric modifications to this reaction have also been explored.[3,5-7] However, one limitation to this reaction is the use of highly reactive organomagnesium and organolithium reagents which can react with other sensitive functionalities. Particularly relevant to the work herein is the Lewis acid catalyzed addition of allylsilanes to glycine cation equivalents (e.g. **2**).[7-10] A potential limitation under these conditions is the sensitivity of certain amino acid protecting groups to Lewis acids. Furthermore, noticably lacking among these examples is the use of this method to synthesize propargylglycine derivatives.

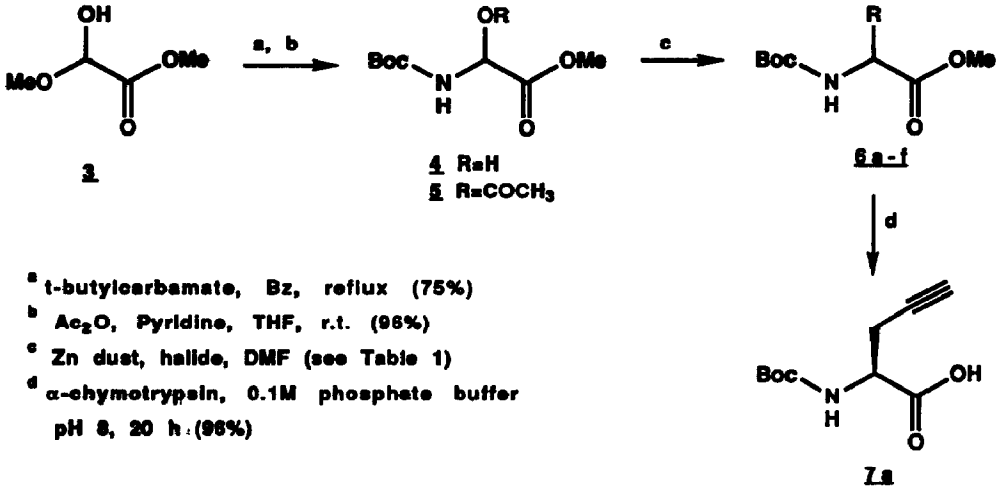
Scheme 1



1 R_1=Boc, R_2=t-Bu, X=Br
2 R_1=$MeCO_2$, R_2=Me, X=OMe

In this paper we describe a simple, efficient, one pot synthesis of a variety of natural and unnatural amino acid derivatives by reacting methyl N-Boc-2-acetoxyglycine **5** with allylic, benzylic and propargyl halides in the presence of zinc dust without the need for a Lewis acid. This reaction is essentially a Reformatsky or Barbier reaction in the presence of a glycine cation equivalent. The α-acetoxy group was selected based upon ease of synthesis and leaving group ability. Coupled with an enzyme resolution,[11] this method allows for the facile synthesis of N-Boc-L-propargylglycine.[12]

Scheme 2

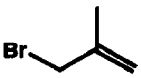
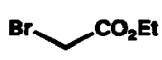
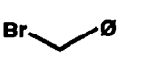


[a] t-butylcarbamate, Bz, reflux (75%)
[b] Ac_2O, Pyridine, THF, r.t. (96%)
[c] Zn dust, halide, DMF (see Table 1)
[d] α-chymotrypsin, 0.1M phosphate buffer pH 8, 20 h (96%)

Methyl N-Boc-2-acetoxyglycine 5 (Scheme 2) is easily prepared in two steps from methyl glyoxylate hemiacetal 3.[13,14] Treatment of 5 (~0.5M) and zinc dust (2 eq.) in DMF with the halide (2 eq.), while maintaining the temperature between 20-25°C for 1-2 hours affords the amino acid derivatives 6 in good to excellent yields (Table 1).[15]

Table 1

Zinc Mediated Additions to Compound 5

entry	alkyl halide[a]	product (yield)[b]	entry	alkyl halide[a]	product (yield)[b]
1		**6a** (97 %)	4		**6d** (82 %)
2		**6b** (68 %)	5		**6e** (89 %)
3		**6c** (99 %)	6		**6f** (37 %)
			7		**6g** c

[a] Two equivalents of alkyl halide were added to a 0.5 M solution of 3 (2.0 mmol) and zinc dust (4.0 mmol, 325-mesh) in DMF with cooling, at a rate to keep internal temperature between 20-25°C. [b] Isolated yield after extractive work up and silica gel chromatography. [c] See reference 18.

The solvent plays an important role in this reaction.[16] In DMF, the metallation reaction initiates quickly and the addition reaction was usually complete within 1 hour. When the reaction was carried out in THF no reaction occurred unless a Lewis acid, Me_2AlCl (0.5 eq), was present. Even under these conditions the isolated yields were high and both the Boc group and the ester

remained unaffected.

Resolution of the racemic ester **6a** with α-chymotrypsin at 25°C in 0.1M phosphate buffer (pH 8) afforded N-Boc-L-propargylglycine **7a** in 96% yield based upon 50% conversion (88% e. e.).[17] One recrystallization from Et_2O/petroleum ether gave a 67% yield of **7a** enriched to 99% e.e. [m.p. 84-85°C, $[\alpha]_D^{25}$ = +23.5° (MeOH, c = 9.1 mg/mL)].

In conclusion, an economical, high yield synthesis of Boc protected amino acid esters can be carried out by reacting methyl N-Boc-2-acetoxyglycine with a variety of organic bromides and zinc. Some of these intermediates are suitable for enzyme resolution via hydrolysis of the ester moiety.

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14. Some selected data are:

4: ^{1}H-NMR (300MHz, $CDCl_3$): δ 1.46 (s, 9H), 3.84 (s, 3H), 5.43 (m, 1H), 5.78 (d,1H, J = 8Hz). Anal calc'd for $C_8H_{15}NO_5$: C, 46.82; H, 7.37; N, 6.90. Found: C, 47.04; H, 7.71; N, 6.90. m. p. 96-97°C.

5: ^{1}H-NMR (300MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.13 (s, 3H), 3.82 (s, 3H), 5.93 (m , 1 H), 6.23 (d, 1H, J = 8Hz). Anal calc'd for $C_{10}H_{17}NO_6 \cdot 1/4\ H_20$: C, 47.71; H, 7.01; N, 5.56. Found: C, 47.68; H, 6.75; N, 5.55.

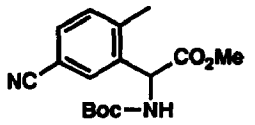
6g: ^{1}H-NMR (300MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.58 (s, 3H), 3.73 (s, 3H), 5.57 (br. d, J = 8Hz, 1H), 5.78 (br. d, J = 8Hz, 1H), 7.31 (d, J = 8Hz, 1H), 7.50 (dd, J = 8Hz, J = 1Hz, 1H), 7.55 (br. s, 1H).

15. Spectral and analyical data are consistant with the proposed strucures.

16. T. Shono, M. Ishifune, S. Kashimura, Chem. Lett., 449-452 (1990).

17. Determination of the % e. e. was made by chiral HPLC analysis using a Crownpak CR(+) column (15 cm x 4.6 mm) at 0°C and isocratic elution with 1% aq. $HClO_4$ at 0.5 mL/min. The detector was set at 205 nm.

18. This reaction did not yield the expected p-cyanophenylalanine derivative but instead gave exclusively the substituted phenylglycine derivative shown here in 57% yield.



6g

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