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# TRIMETHYLSILYLACETYLENE-N-CARBOETHOXY GLYCINATE DIANION - A GENERAL SYNTHON FOR α-ACETYLENIC α-AMINO ACIDS.

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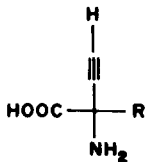
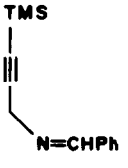
Mechanistic considerations suggest the use of α-acetylenic amino acids 1 as potential enzyme-activated irreversible inhibitors of the corresponding α-amino acid decarboxylases [1]. The recent syntheses of α-acetylenic-3,4-dihydroxyphenyl alanine [1,2], the sole known example of such an amino acid, involve the sequential alkylation and acylation of anions derived from the propargylamine synthon 2. In view of the potential utility of this class of novel amino acids, an equivalent of the nucleophile 3 would be of obvious interest, as it would allow a variety of α-acetylenic α-amino acids to be prepared from a single precursor. An apparent approach would be to directly acylate the anion derived from 2. This reaction, however, has been reported to afford an unidentified 2:1 adduct [2]. We now wish to report that the dianion prepared from the urethane 4 undergoes regioselective alkylation with a variety of electrophiles, and hence provides general synthetic access to the desired highly-funtionalized amino acids.




1

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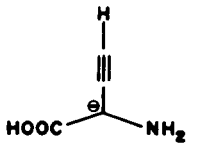


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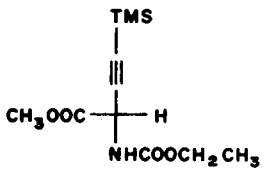
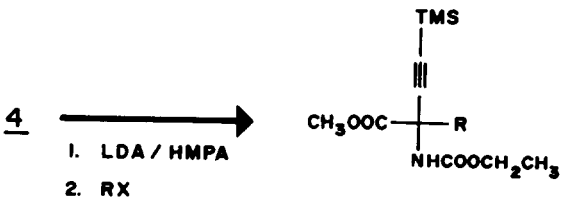



4

As shown below, the dianion which can be generated from 4 using excess lithium diisopropylamide/hexamethylphosphoramide (LDA/HMPA) undergoes alkylation with a representative series of alkyl halides. In no case were allenic products observed. The free α-acetylenic α-amino acids can be obtained from the alkylation products 5 by alkaline hydrolysis (2 M KOH, 12 hours reflux) or, more mildly, by first generating the isocyanate with $SiHCl_3$ [4], followed by alkaline hydrolysis (1 M KOH, 3 hours at 25°C).



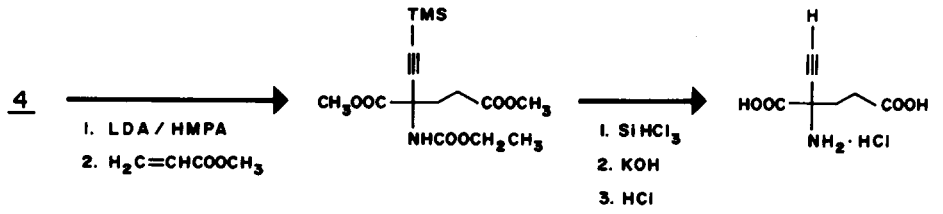

5

| | R | X | Yield of 5 |
|---|---|---|---|
| (a) | $PhCH_2$ | Br | 75 % |
| (b) | $H_2C=CHCH_2$ | Br | 70 % |
| (c) | $CH_3(CH_2)_3$ | I | 60 % |

In a typical experiment 4 (1 mmol) in THF (5 ml) is added to LDA (3 mmol) in THF (10 ml) containing HMPA (1 ml) at -70°C. After 15 minutes at -70°C benzyl bromide (1 mmol) in THF (2 ml) is added. The mixture is maintained for 3 hours at -70°C, then quenched by the addition of acetic acid (2 mmol). The alkylation product 5a (m.p. 97°C)[5] is obtained in 75 % yield after ion exchange chromatography and recrystallization. α-acetylenic phenylalanine (1 R = $CH_2Ph$ m.p. 184°C) [5] is then obtained by alkaline hydrolysis followed by ion exchange chromatography.

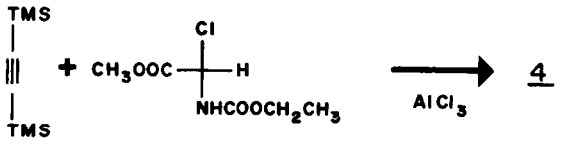
Although the alkylation by alkyl halides of the dianions derived from ethyl hippurate [6] and from N-benzylbenzamide [7] has been reported, in neither case was the conjugate addition to an α,β-unsaturated ester described. The

dianion from 4, however, undergoes a regioselective 1,4-addition with methyl acrylate to afford the Michael adduct 6 [5], in 65% yield. Removal of the protecting groups then affords α-acetylenic glutamic acid hydrochloride 7 (m.p. 160°C decomp.) [5], as depicted below.



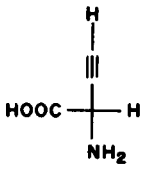

6 7

The glycinate derivative 4 (m.p. 49°C) [5] is readily prepared in 65% yield by the amidoalkylation of bis-(trimethylsilyl)-acetylene (8) [8] with the 2-chloro-N-carboethoxy glycinate (9), under Friedel-Crafts conditions ($AlCl_3$ (1 eq.) in dichloromethane for 12 hours at 25°C). The amidoalkylation of acetylenes usually leads to cyclic products which result from internal trapping of the intermediate vinyl cation [10]. This is avoided in this case, probably owing to the rapid departure of the trimethylsilyl group.

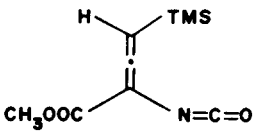



8 9

Attempts to prepare the parent amino acid of the series, α-acetylenic glycine (10), by deprotection of 4 have proven abortive. Acid or base treatment results in unidentifiable products, while gentle deprotection of the urethane function using $SiHCl_3$ [4] leads to the allene isocyanate 11, which, although unstable, could be characterised spectroscopically.




10

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