Synthetic Access to α-Substituted Prop-2-ynylamines and α-Acetylenic Amino Acids *via* the t-Butyl *N*-Trimethylsilylprop-2-ynylcarbamate Dianion

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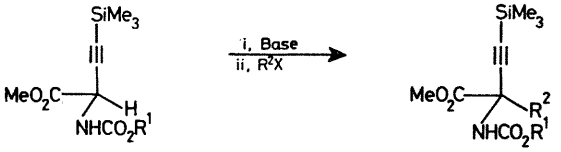
Summary The dianion derived from t-butyl *N*-trimethylsilylprop-2-ynylcarbamate undergoes alkylation and carboxylation at the propynylic position, leading to derivatives of acetylenic amines and amino acids.

WE recently reported that the alkylation reactions of the dianion derived from the acetylenic glycinate (**1a**), with a variety of electrophiles, including a Michael acceptor, proceed invariably in a regiospecific sense to afford acetylenic and not allenic products.[1] Such regiospecificity,



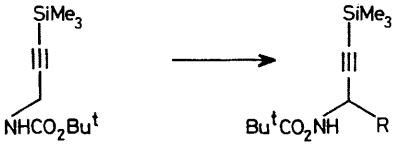
(1) a; R = Et
b; R = Bu^t

(2)

useful because the deprotected α-acetylenic amino acids are potential irreversible enzyme inhibitors,[2] was not unexpected, as the ester function could exert a dominant directing effect.

The reactions of the dianion generated from the prop-2-ynylcarbamate derivative (**3**), were examined, in order to ascertain the role of the ester function in controlling the position of alkylation. If regiospecificity were retained to afford acetylenic products, the prop-2-ynylcarbamate (**3**) would offer a synthon complementary to the corresponding imines,[3] for the synthesis of 2-substituted prop-2-ynylamines, several examples of which are now proven irreversible enzyme inactivators.[4,5]

When the t-butyl carbamate (**3**) is treated with an excess of lithium di-isopropylamide (LDA) or t-butyl-lithium in the presence of tetramethylethylenediamine at −78 °C, the dianion which results can undergo alkylation with a variety of electrophiles. Although traces of allenic products can be detected by i.r. spectroscopy, the products (**4**)‡§ which result from alkylation at the prop-2-ynylic position of (**3**) can be isolated in high yield by silica gel chromatography.¶



(3) (4)

The high-yielding regiospecific 1,4-addition of (**3**) to methyl acrylate is noteworthy, because on deprotection the Michael adduct would lead to 4-aminohex-5-ynoic acid, an enzyme-activated inhibitor of 4-aminobutyrate 2-oxoglutarate aminotransferase (GABA-T).[4]

The prop-2-ynylcarbamate (**3**) (m.p. 61 °C)‡§ is readily available in two steps from prop-2-ynylamine. Treatment with t-butylcarbonyl azide in the presence of triethylamine yields the corresponding t-butyl carbamate (m.p. 43 °C),‡§ the acetylene group of which can be silylated by acetylide formation with 2 equiv. of EtMgBr, followed by reaction with Me_3SiCl (2 equiv., acid workup), both reactions proceeding in high yield. We have been unable to achieve dianion formation from the products of alkylation (**4**) under a variety of conditions. Carboxylation, however, of the dianion derived from (**3**) leads to a mixture of the

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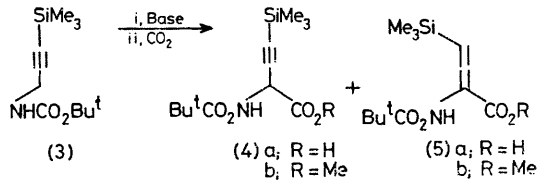
‡ N.m.r. and i.r. spectra were in agreement with the proposed structure.

§ Acceptable elemental analyses were obtained for this compound.

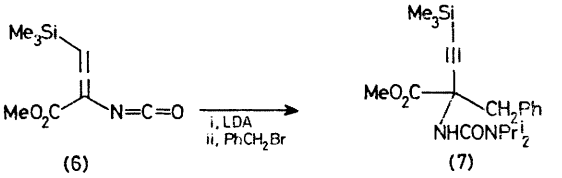
¶ Yields obtained were 65, 75, 90, and 89% when $H_2C{=}CHCH_2Br$, $PhCH_2Br$, Bu^nI, and $H_2C{=}CHCO_2Me$ respectively, were used as alkylating agent for (**3**).

unstable acetylenic and allenic acids, (**4a**) and (**5a**), and when this mixture is treated immediately with diazomethane it affords the corresponding methyl esters (**4b**)§ and (**5b**)‡ in a ratio of 4:1.



That the allenic acid has the structure (**5a**)‡ and results from isomerism *in situ* of (**4a**)‡ is evident from an examination of the ^{1}H n.m.r. spectrum of the mixture of methyl esters, where the allenic hydrogen appears as a singlet at δ 5·7. With the alternative possibility, the allenic hydrogen would be expected to appear as a doublet. While separation of the unstable isomeric esters (**4b**) and (**5b**) has not been carried out, treatment of the mixture with an excess of base, followed by benzyl bromide, leads to the α-acetylenic amino acid derivative (**2b**) ($R^2 = CH_2Ph$)‡§ in 70% yield. The chemistry of the dianion derived from the t-butyl carbamate (**1b**) is thus similar to that of the corresponding ethyl carbamate (**1a**),[1] but offers the advantage of greater facility of deprotection.

As the allenic ester (**5b**)‡ may be susceptible to double deprotonation to afford the same dianion as that generated from the prop-2-ynylic ester (**4b**),‡§ the alkylation of the allenyl isocyanate (**6**)[1] with benzyl bromide in the presence of an excess of LDA was examined. The urea (**7**)‡ can be



isolated in low yield, its formation probably resulting from initial attack of LDA on the isocyanate function, the intermediate anion then undergoing deprotonation to generate a dianion analogous to that derived from (**1**).

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