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REGIOSPECIFIC 1,4 ADDITION OF A PROPARGYLIC ANION. A GENERAL SYNTHON FOR 2-SUBSTITUTED PROPARGYLAMINES AS POTENTIAL CATALYTIC IRREVERSIBLE ENZYME INHIBITORS.

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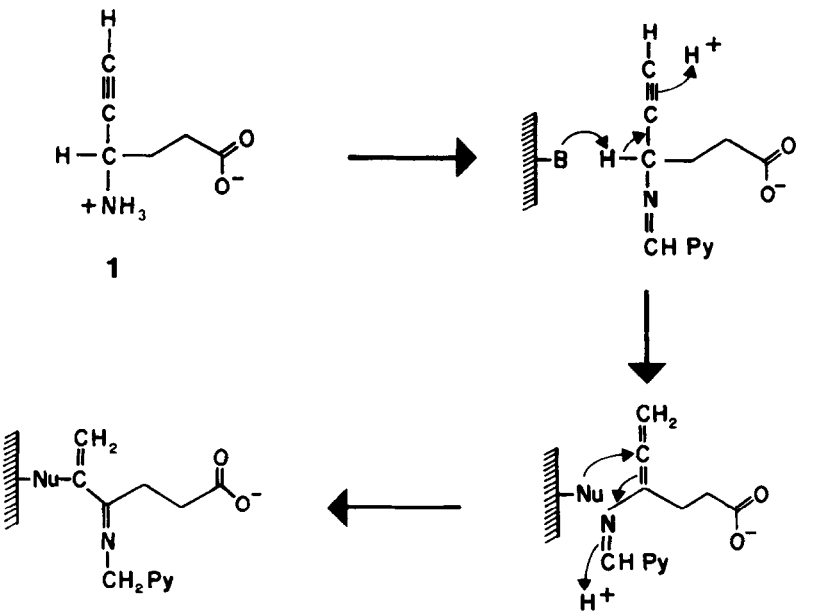
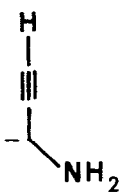
Mechanistic considerations suggest the use of α-acetylenic amines as selective irreversible inhibitors of flavine and pyridoxal-dependent enzymes which use the corresponding parent amines as natural substrates[1]. We hoped that the hitherto unknown 4-aminohex-5-ynoic acid I would selectively and irreversibly inhibit the pyridoxal phosphate-dependent γ-aminobutyric acid transaminase E.C.2.6.1.19 (GABA-T), an enzyme of prime importance in CNS function [2]. The proposed mechanism of inhibition is outlined as follows:

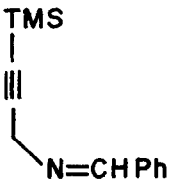


Thus abstraction by the enzyme of the proton α to the Schiff base would lead to allene formation rather than to the normal tautomerism. Inactivation could then occur via the Michael addition of a nucleophilic residue (Nu) in the active site to the conjugated allene [3].

Our synthetic strategy was to develop a synthon for the propargylic anion 2, which could then add regiospecifically in 1,4 fashion to methyl acrylate, to afford the potential enzyme inhibitor in protected form.



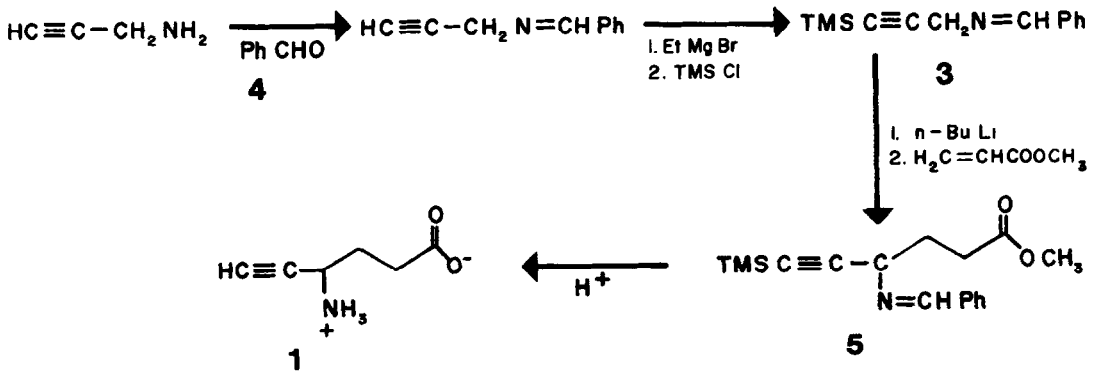
2



3

Ganem [4] has recently reported the 1,6-conjugate addition reaction of 1-trimethylsilylpropynyl copper to $\Delta^{2,4}$-dienoic esters. The addition was not regioselective, however, in that sometimes allenes were the major product; moreover, the 1,4 addition was not successful with ethyl acrylate.

We now report that the propargylic anion derived from the aldimine 3 fulfils the requirements for the desired synthon, as it undergoes a regiospecific Michael reaction to methyl acrylate in high yield [5], as is shown below:



Thus aldimine formation of propargylamine with benzaldehyde led to 4 (b.p. 100-105°C/12mm,85%), which was silylated in the usual manner to afford the key intermediate 3 (b.p. 105-110°C/0.2mm,90%) [6]. The silyl acetylene 3 (50 mM) in THF (500 ml) at -70°C was treated with n-BuLi (50 mM) to give immediately a dark-red anion. Methyl acrylate (50 mM) was then added, and 30 minutes later the mixture was quenched at -70°C with water and the product isolated by ether extraction. The n.m.r. and i.r. spectra, as well as gas chromatographic analysis of the crude reaction product showed the Michael adduct 5 to be the sole product. This 1,4 addition reaction thus appears to be regiospecific (no allene formation) and essentially quantitative. Distillation afforded the ester 5 [6] (b.p. 140-144°C/0.2mm,53%), some decomposition occurring during the distillation. The three protecting groups were then removed by acid hydrolysis (6NHCl, reflux for 12 hours) and the amino acid I (m.p. 240°C) purified by ion exchange chromatography.

The acetylenic amino acid I did indeed prove to be a specific irreversible inhibitor of GABA-T *in vitro* and *in vivo* and will be reported elsewhere [7].

In view of the potential utility of the anion derived from 3 we have briefly investigated its reaction with several other alkylating agents (see below), employing similar conditions to those described above. In all cases the reaction proceeded regiospecifically, no allenic products being detected [8].

$$\underset{3}{TMSC \equiv CCH_2N = CHPh} \xrightarrow[2.\ RX]{1.\ n\text{-}BuLi} TMSC \equiv CCH(R)N = CHPh$$

RX	b.p.of product	yield of distilled product [6,9]
CH_3I	93°C/0.05mm	49 %
n-BuBr	100-105°C/0.05mm	45 %
$HC{\equiv}CCH_2Br$	115-120°C/0.1 mm	62 %

The use of the anion derived from the aldimine 3 thus offers facile entry into a series of 2-substituted propargylamines, a class of compounds which offers potential as specific irreversible enzyme inhibitors.

2-substituted propargylamines were previously available via amine displacement of secondary propargyl halides or tosylates [10], the syntheses of which from the corresponding alcohols are often accompanied by products resulting from rearrangement or elimination.

Acknowledgements

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References

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2. E.Roberts, Biochem.Pharm., 23, 2637 (1974).
3. This scheme has also been proposed by two other groups to rationalise the inhibition of plasma amine oxidase by propargylamine. See: R.H.Abeles and C.T.Walsh, J.Amer.Chem.Soc., 95, 6125 (1973), and: R.R.Rando, Biochem.Pharm., 23, 463 (1974).
4. B.Ganem, Tetrahedron Letters, 4467 (1974).
5. The anion derived from TMS-C≡C-CH_2-N  O has been shown to add to aldehydes, however no conjugate additions were reported. Because of enzymati requirements,it was necessary in our case to produce the primary amine. See: F.Mercier, R.Epsztein and S.Holand, Bull.Soc.Chim.Fr., 690 (1972).
6. All new compounds, with the exception of the aldimine 4, gave acceptable elemental analyses. N.m.r. and i.r. spectra were consistent with the proposed structures.
7. M.Jung and B.W.Metcalf, unpublished work.
8. E.J.Corey and H.A.Kirst, Tetrahedron Letters, 5041 (1968), have described the position-specific alkylation of lithio-1-trimethylsilylpropyne with alkyl halides.
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