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GENERAL SYNTHETIC ACCESS TO α-ALLENYL AMINES AND α-ALLENYL-α-AMINOACIDS AS POTENTIAL ENZYME ACTIVATED IRREVERSIBLE INHIBITORS OF PLP DEPENDENT ENZYMES

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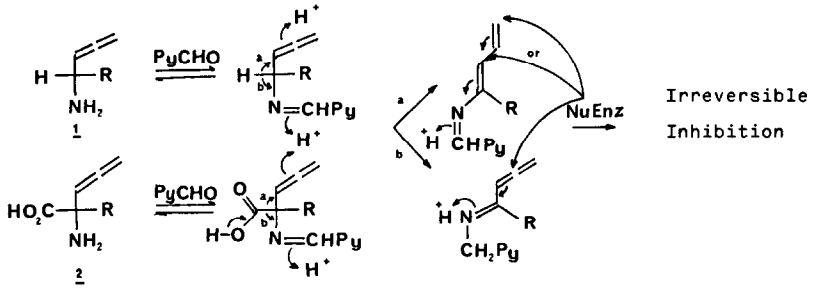
The entitled allene derivatives have been prepared from the parent α-ethynyl amines and α-amino acids. The corresponding derivative of GABA, putrescine and phenylalanine have been found to be irreversible and time dependent inhibitors of GABA-T, ODC and bacterial AADC, respectively.

Enzyme-activated irreversible inhibition of pyridoxal-phosphate (PLP) dependent enzymes has been achieved with α-fluoromethyl[1], α-vinyl[2] and α-ethynyl[1a,3] derivatives of amino acid substrates and/or amine products of the enzyme reaction. Mechanistic considerations suggest that the hitherto unknown allenyl derivatives 1 and 2 of the parent amine products and α-amino acid substrates, respectively, of PLP dependent enzymes, could also generate electrophilic Michael acceptors during their enzymic turnover and consequently irreversibly inactivate the enzymes as indicated in Scheme I (Nu-Enz represents a nucleophilic residue of the enzyme's active site, R the side chain of natural substrate or product of the target enzyme and Py the pyridoxal phosphate ring system).

Scheme I

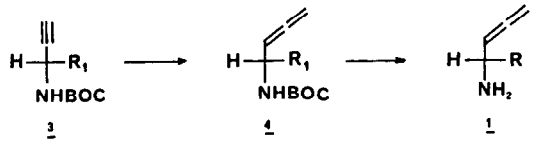
Proposed mechanism for inactivation of PLP dependent-transaminase and α-amino acid decarboxylases by α-allenyl derivatives of their substrates and/or products by either of path a or b.



Except for a cumbersome retro Diels Alder reaction requiring high temperature (t > 450°C)[4], there is no synthetic access to α-allenyl-α-alkyl primary amines reported in the literature. We have found that the procedure described by Crabbé et al[5] for the conversion of α-ethynyl alcohols into α-allenyl alcohols can be used to prepare in good yield N-tertiobutyl-oxycarbonyl-α-allenyl amines 4[6] from the corresponding N-protected α-ethynyl amines 3 which are easily available from propargyl amines[1a,3b,c].A typical experimental procedure is as follows: a

dioxane solution (100 ml) of 3 (0.05 mol), diisopropyl amine (8.5 ml, 0.06 mol), formaldehyde (6.5 ml of a 37% aqueous solution, 0.08 mol) and freshly prepared CuBr (2 g, 0.015 mol) was heated under a nitrogen atmosphere for 12 h. The heterogeneous brown reaction mixture was quenched with 1 N aqueous AcOH (100 ml) and stirred until a green homogeneous solution was obtained. Extraction with diethyl ether (3 x 100 ml) and usual work-up of the organic layers yielded crude 4 which was purified by flash chromatography on silica gel. Specific examples of such transformation are listed in table 1. Removal of the protective group(s) of 4 under standard conditions (excess ethereal HCl, r.t., 12 h) proceeded in good yield to give 1. In the case of 1d and 1e, the ester group was hydrolyzed first with 1 equivalent of lithium hydroxide at r.t. for 2 h in a 1:1 mixture of DME:H_2O. It is notable that the chirality at the carbon bearing the amine function is fully retained during the transformation of 3 to 1 (see entries b', b", c' and c" in table 1)[7].

Scheme II



3 4 1

a : R_1 = H
b : R_1 = $(CH_2)_2CO_2Me$
c : R_1 = $(CH_2)_3NHBOC$
d : R_1 = CH_2CO_2Me
e : R_1 = $(CH_2)_3CH(NHBOC)-CO_2Me$

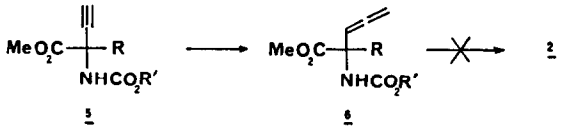
a : R = H
b : R = $(CH_2)_2CO_2H$
c : R = $(CH_2)_3NH_2$
d : R = CH_2CO_2H
e : R = $(CH_2)_3CH(NH_2)CO_2H$

TABLE 1

	3 → 4[12]			→ 1[12]		
	mp °C	yield %	mp °C	yield %	mp °C	$[\alpha]_D^{25}$
a	45	63	oil[13]	100	120	
b (R,S)	43	66	43	75	170	
b' (R)	69	65	< 50	80	169	-38° (c:0.25, H_2O)
b'' (S)	68	60	< 50	80	170	+44° (c:0.25, H_2O)
c (R,S)	94	80	92	100	210 (2 HCl)	
c' (R)	103	75	82	100	206 (2 HCl)	-44° (c:0.15, H_2O)
c'' (S)	105	80	85	100	205 (2 HCl)	+44° (c:0.15, H_2O)
d	52	60	< 50	80	123 (HCl)	
e	88	79	oil	90	107 (2 HCl)	

The Crabbé's conditions also allowed the synthesis of N-alkyloxycarbonyl ester of α-allenyl-α-amino acids 6 from the corresponding α-ethynyl derivatives 5 which, with the exception of N-tertiobutyloxycarbonyl analogues are available from the parent α-amino acids[3d]. The preparation of the α-allenyl-α-amino acids 2 was however frustated at the level of the deprotection of the amine function (Scheme III). The allene function proved to be unstable under the reaction conditions required for the cleavage of alkyl carbamate group. Eventually 2 were obtained from the benzamide derivatives 9 by a sequential deprotection sequence involving a) formation of an imidate with the Meerwein reagent (1 eq., CH_2Cl_2, reflux 12 h) followed by a mild acidic hydrolysis (1N AcOH:dioxane, 1:1, reflux 12 h); b) reprotection of the amine function with a tertiobutyloxycarbonyl group (1 eq., BOC_2O, 1 eq NEt_3, $CHCl_3$, 2 h reflux); c) hydrolysis of the ester group (1 eq. lithium hydroxide, r.t., 2 h, $DME:H_2O$, 1:1); and d) cleavage of the tertiobutyloxycarbonyl group (excess ethereal HCl, 12 h, r.t.). The benzamide derivatives 9 were most conveniently prepared via a Claisen rearrangement on N-benzoyl propargylic ester of α-amino acids as described by Steglich et al[9]. It is interesting that all attempts to hydrolyse 9 or the allenyl oxazolidone precursor 8 directly to 2 afforded, even under mild conditions, up to 30 % of side product(s) which contain(s) no allene function.

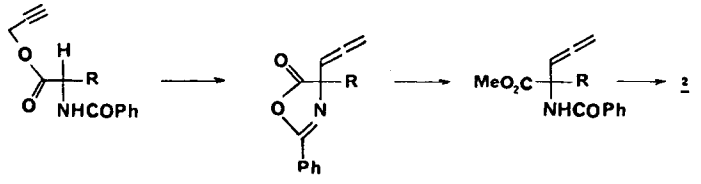
Scheme III



5 6 2

R' = Me, Et R = CH_2Ph

Scheme IV



7 8 9

TABLE 2

	R	7 → 9[12]		→ 2[12]		
		mp °C	yield %	mp °C	yield %	mp °C
a	CH_3	78	55	140	70	188
b	CH_2Ph	117	48	102	58	196

As anticipated, (S)-allenyl GABA 1b" and (R)-allenyl-putrescine 1c' proved to be potent enzyme-activated irreversible inhibitors of mammalian 4-amino-butyrate-2-oxoglutarate aminotransferase (EC 2.6.1.19, GABA-T)[10] and bacterial ornithine decarboxylase (EC 4.1.1.17, ODC)[11] respectively. Preliminary results indicate that (R,S)-allenyl phenylalanine 2c is also a time-dependent inhibitor of bacterial L-aromatic-α-amino acid decarboxylase (EC 4.1.1.26, AADC)[10]. Full biological data on these compounds will be reported elsewhere.

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6. A. DOUTHEAU, A. SABA, J. GORE, Tetrahedron Lett., 2461, 1982 have mentionned the preparation of N-2,3-butadienyl phthalimide from N-propargylic phthalimide by a similar route.
7. The enantiomeric purity was assesed on a Chirasil-Val capillary column (J. P. HINCKEL, J. WAGNER, unpublished results) according to the method described by Bayer and coll., J. Chromatog., 146, 187, 1978. The isomers 1b' and 1b" were esterified with EtOH-HCl gas and N-acylated with pentafluoropropionic anhydride and 1c' and 1c" were N-acylated with trifluoroacetic anhydride. In each case, the enantiomeric excess was greater than 99.5%.
8. These compounds were obtained by standard protection of the corresponding enantiomers of the parent aminoacid and amine described in P. CASARA, C. DANZIN, B. METCALF, M. JUNG, Chem. Comm., 1190, 1982 and references cited herein. The enantiomeric excess of each starting material assessed as described in ref. 7 was greater than 99.5%.
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11. C. DANZIN, unpublished results.
12. All new compounds with the exception of the compound 4a, gave acceptable elemental analyses. N.m.r. and i.r. spectra were consistent with the proposed structures.
13. Some decomposition occured during distillation.

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