Tetrahedron Letters,Vol.26,No.32,pp 3807-3810,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

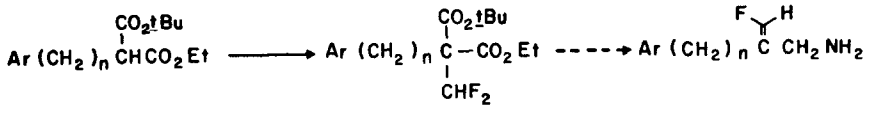
A GENERAL PREPARATION OF FLUOROALLYLAMINE ENZYME INHIBITORS INCORPORATING A β-SUBSTITUTED HETEROATOM

Ian A. McDonald*, Philippe Bey+

Merrell Dow Research Institute, Strasbourg Center, 67084 Strasbourg, France

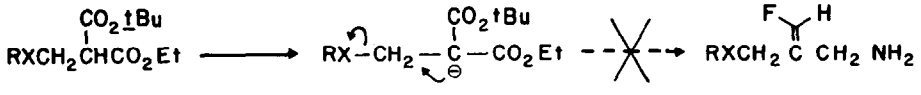
Abstract: A general route to β-heteroatom substituted fluoroallylamines is described. This has led to the synthesis of new time-dependent inhibitors of monoamine oxidase, diamine oxidase and γ-aminobutyric acid transaminase.

We have recently reported[1,2] that derivatives of 2-aryl-3-fluoroallylamine (1, n = 0) are potent enzyme-activated inhibitors of the metabolic enzyme monoamine oxidase (MAO). These substances are readily prepared[1] from an appropriately susbstituted malonate (2) by reaction of the sodium salt with $ClCHF_2$, affording 3 in essentially quantitative yield.



2 3 1

For cases in which a heteroatom is present in a position β to the malonate functionality (4), however, this procedure is not suitable due to the propensity of the anion 5 to undergo β-elimination.

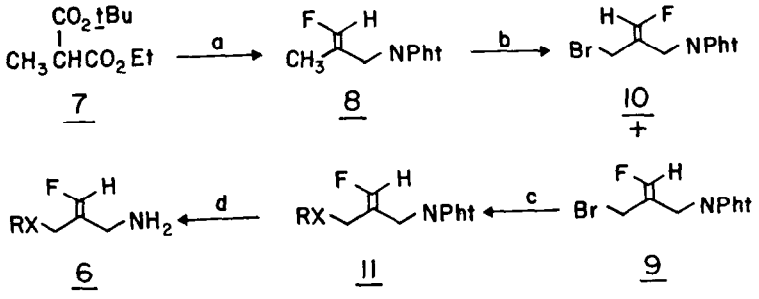


4 5 6

This letter discloses a modified synthetic route (Scheme) to compounds of general formula 6, opening up the possibility of preparing a number of substances having potential as enzyme-activated inhibitors of various flavin- and pyridoxal phosphate- dependent enzymes.

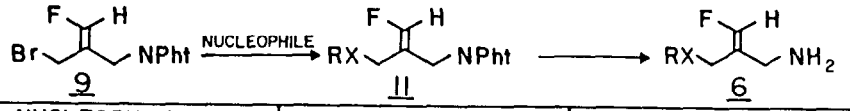
+ Present address: Merrell Dow Research Institute, Cincinnati, Ohio 45215, USA

Thus the phthalimide 8 (mp 57-58 °C), prepared from the mixed malonate ester 7 according to a slight modification[3] of the published procedure[1], underwent allylic bromination with N-bromosuccinimide (NBS) in refluxing CCl_4 affording a mixture of bromides (9 and 10) together with small amounts of unidentified material. The Z-isomer 9 (mp 81-83 °C) could be crystallized directly from the mixture; further purification of the mother liquors by silica chromatography yielded more 9 (total yield 35%) and 10 (mp 86-87 °C, 9% yield). Treatment of 9 with a series of nucleophiles (see Table) afforded 12a-c which were converted to 6a-c by standard methods. When the crude mixture of 9 and 10 was reacted directly with potassium phthalimide in N,N-dimethylformamide (DMF) a single product (6d) was isolated.



Scheme: a) Ref. 1; b) NBS, CCl_4, reflux; c) and d) see Table. Pht = phthalimido

The bromide 9 turned out to be an useful synthon for the preparation of various amines and amino acids. To date, time-dependent inhibitors of MAO, diamine oxidase (DAO) and γ-aminobutyric acid transaminase (GABA-T) have been prepared. The unexpected biochemical porperties of some of these compounds will be discussed elsewhere[4].



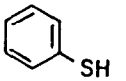
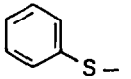
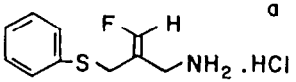
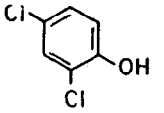
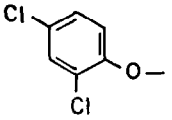
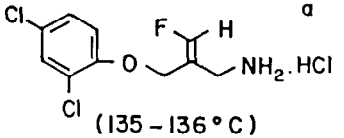
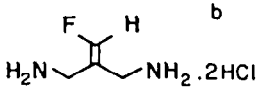
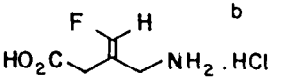
ENTRY	NUCLEOPHILE (BASE, SOLVENT)	11 RX (mp)	6 (mp)	TARGET ENZYME
a	 SH (NaH, DMF)	 (80 – 81 °C)	 [a] (164 – 165 °C)	MAO[5]
b	 OH (NaH, DMF)	 (115 – 116 °C)	 [a] (135 – 136 °C)	MAO[5]
c	Potassium phthalimide (DMF)	– NPht (147 – 148 °C)	 [b] (230 – 231 °C)	DAO[6]
d	NaCN (DMSO)	– CN (104 – 105 °C)	 [b] (139 – 140 °C)	GABA-T[7]

Table: a) Prepared by deprotection with hydrazine, followed by treatment with aq. HCl.
b) Prepared by treatment with refluxing 6 M aq. HCl.

References and Notes

1. I.A. McDonald, J.M. Lacoste, P. Bey, M.G. Palfreyman, and M. Zreika, J. Med. Chem., 28, 186 (1985).
2. P. Bey, I.A. McDonald, and M.G. Palfreyman. Presented at: Amine Oxidases: A Cambridge Workshop (1984), J. Pharm. and Pharmacol., 36, 38W (1984).
3. The decarboxylative-fluoride elimination step was carried out in a two phase system using an excess of $NaHCO_3$ in $CHCl_3$ and water. The mixture was refluxed for 5.5 h, the organic phase separated, dried and distilled at atmosphere pressure, then at 80 mm to collect the product [(E)-ethyl 2-methyl-3-fluoroacrylate; bp 60-70 °C/80 mm].
4. I.A. McDonald, M.G. Palfreyman, M. Zreika, J. Fozard, and P. Bey, Biochem. Pharmacol., submitted (1985).
5. These compounds inhibited MAO (M.G. Palfreyman et al, unpublished results).
6. 6c was an inhibitor of DAO. N. Seiler, S. Sarhan, personal communication.
7. 6d inhibited GABA-T. M. Jung, personal communication.

(Received in France 4 June 1985)