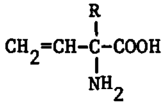
Tetrahedron Letters No. 42, pp 3999 - 4002.
© Pergamon Press Ltd. 1978. Printed in Great Britain.

0040-4039/78/1015-3999$02.00/0

A GENERAL SYNTHESIS OF α-VINYL-α-AMINO ACIDS

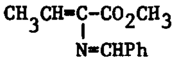
W. J. Greenlee,* D. Taub, and A. A. Patchett
Merck Sharp & Dohme Research Laboratories, Division of
Merck & Co., Inc., P. O. Box 2000, Rahway, New Jersey 07065

In connection with our experiments directed toward the design of specific enzyme inhibitors,[1] we desired an efficient route to vinyl amino acids of type 1.[3] Although these might be obtained by partial reduction of the corresponding ethynyl amino acids as has been shown for α-vinyl DOPA (R = 3,4-dihydroxyphenylmethyl),[1,2] we sought a more direct method for their preparation. We now wish to report the use of dehydroamino acid derivative 2 as a synthon for α-vinyl amino acids. The recently reported route to α-amino acids by alkylation of the anion derived from benzalglycinate 3[5] coupled with the well-known deconjugative alkylation of enolates derived from α,β-unsaturated carbonyl systems, suggested that the anion formed upon deprotonation of 2 would undergo alkylation at the α-position.



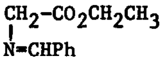
$CH_2{=}CH{-}\overset{R}{\underset{NH_2}{C}}{-}COOH$

1



$CH_3CH{=}\underset{N=CHPh}{C}{-}CO_2CH_3$

2



$\underset{N=CHPh}{CH_2}{-}CO_2CH_2CH_3$

3

Lithium hexamethyldisilazide (1.1 equiv.) in THF at -70°C converts Schiff base 2 (60:40 E:Z mixture - see below) to the anion 4, which reacts smoothly with alkylating agents (1.0 equiv.), providing exclusively the α-alkylated products 5. These were purified with concomitant hydrolysis of the Schiff base function by chromatography on acid-washed silica gel, allowing isolation of pure aminoesters 6 in good yield (Table 1). The remaining protecting groups were removed by treatment with 6N HCl (2 hours, reflux), providing α-vinyl amino acids as the hydrochlorides 7.

In a typical experiment synthon 2 (5.0 mmol) in THF (12.5 ml) was added to lithium hexamethyldisilazide (5.5 mmol) in THF (12.5 ml) containing HMPA (3.5 ml) at -70°C. After 30 minutes p-benzyloxybenzyl bromide (5.0 mmol) in THF (7.5 ml) was added. The mixture was stirred for one hour at -70°C and then at room temperature for three hours. After workup with aqueous ammonium chloride-ether, the resulting crude alkylation product was chromatographed on 25 g of acid-washed silica gel,[6] providing p-benzyloxy-α-vinyl phenylalanine methyl ester in 77.5% yield. The amino ester was combined with 50 ml of 6N HCl and the mixture was heated at reflux for 2 hours with rapid stirring. The cooled solution was extracted with methylene chloride (3 x 5 ml), treated with activated charcoal, and evaporated to dryness, giving essentially pure α-vinyl tyrosine hydrochloride as an amorphous solid in 82.0% yield.

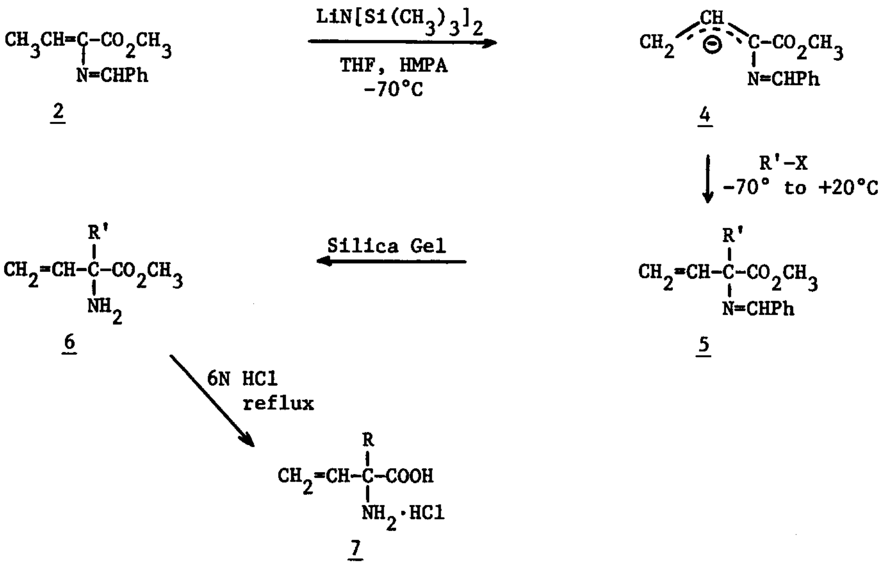
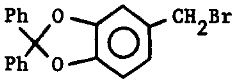
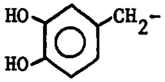
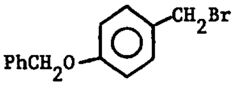
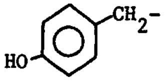
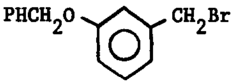
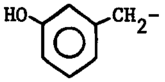
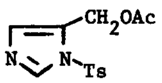
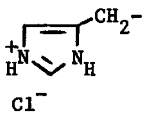
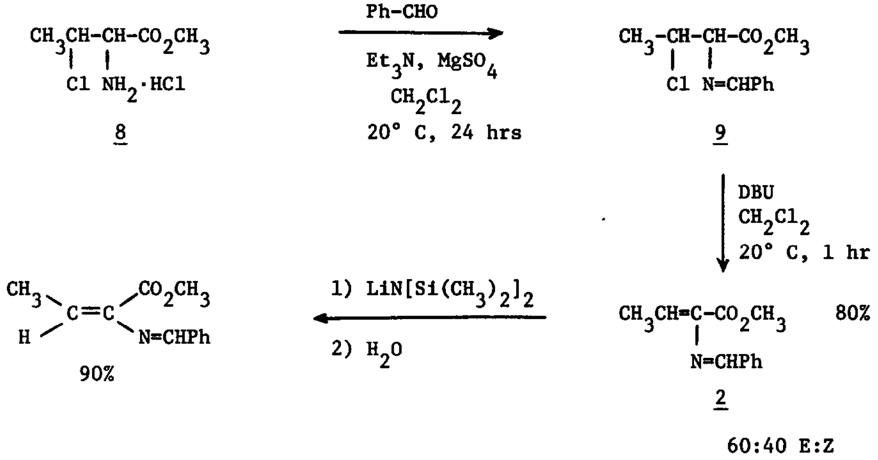


Table 1

R'X	Yield of 6[8]	R	Yield of 7[8]
	80.4%		92.7%
	77.5		82.0
	65.6		82.4
 [9]	74.1		72.3 [10]
$CH_2{=}CH{-}CH_2Br$	76.3	$CH_2{=}CH{-}CH_2{-}$	94.3
$CH_3O_2C{-}CH_2Br$	72.6	$HO_2C{-}CH_2{-}$	96.6
$(CH_3)_2CHI$	79.0	$(CH_3)_2CH{-}$	66.0
$PhCH{=}N{-}(CH_2)_3{-}Br$ [11]	-	$^{+}H_3N{-}(CH_2)_3{-}$ Cl^{-}	50.2 [12]

Schiff base 2[13] was conveniently prepared from (DL)-β-chloro-α-aminobutyric acid methyl ester hydrochloride (8).[14]



Attempts to prepare α-vinylglycine (1, R=H)[4a,b] by quenching anion 4 with water or acetic acid at either -70°C or at room temperature led instead to isolation of the pure E isomer of 2. Unlike the anion derived from benzalglycinate 3,[5] anion 4 does not undergo Michael addition to methyl acrylate or acrylonitrile at -70°C. Reaction of 4 with other electrophiles is now being studied.

References

1. D. Taub and A. A. Patchett, Tetrahedron Lett., 2745 (1977).
2. B. W. Metcalf and K. Jund, Tetrahedron Lett., 3689 (1977).
3. Although numerous examples of β,γ-unsaturated-α-amino acids are known, only two α-vinyl compounds (1, R = H[4a,b] and R = CH_3[4c]) in addition to α-vinyl DOPA[1,2] have been reported.
4. (a) P. Friis, P. Helboe and P. Olesen Larsen, Acta Chem. Scand., Ser. B., 28, 317 (1974); (b) J. E. Baldwin, S. B. Haber, C. Hoskins and L. I. Kruse, J. Org. Chem., 42, 1239 (1977); (c) S. Terashima, N. Takamura, S. Yamada, Chem. Abstr., 73, 44909q (1970).
5. G. Stork, A. Y. W. Leong and A. M. Touzin, J. Org. Chem., 41, 3491 (1976).
6. Silica gel 60 (E. Merck Cat. No. 7736) was slurried with 6N HCl and collected on a fritted funnel. It was washed with water until neutral, with saturated disodium EDTA solution, water, and then 0.3N HCl and allowed to dry in air for 48 hours.[7] Columns were slurry-packed in hexane and eluted with hexane, ether, 10:1 ether:acetonitrile, and then 100:10:2 ether:acetonitrile:triethylamine, the latter solvent bringing about elution of the amino-esters 6.
7. A. Y. W. Leong, Ph.D. Thesis, Columbia University, 1977.

8. All new compounds give ir, pmr, and mass spectra in accord with the assigned structures.
9. M. Suzuki, T. Miyahara, R. Yoshioka, M. Miyoshi and K. Matsumoto, Agr. Biol. Chem., 38, 1709 (1974).
10. The aminoester 6 (R = N-tosylimidazolylmethyl) was treated with conc. HCl at reflux (4 hours). The resulting crude product was purified by ion-exchange chromatography on Dowex 50W-X4 resin.
11. B. W. Metcalf, P. Bey, C. Danzin, M. J. Jung, P. Casara, J. P. Vevert, J. Amer. Chem. Soc., 100, 2551 (1978).
12. Overall yield. The crude alkylation product was treated directly with 6N HCl (2 hours at reflux) and the resulting amino acid hydrochloride was purified on Dowex 50W-X4 resin (eluted with water and then 2N HCl).
13. Schiff base 2 was stored at 0°C after purification by filtration through activity 3 neutral alumina (Woelm) in 10:1 hexane:ether. It is stable at this temperature, but undergoes slow isomerization to the pure E isomer.
14. P. A. Plattner, A. Boller, H. Frick, A. Furst, B. Hegedus, H. Kirchensteiner, St. Majnoni, R. Schlapfer and H. Spiegelberg, Helv. Chim. Acta, 40, 1531 (1957).

(Received in USA 4 August 1978; received in UK for publication 29 August 1978)