Synthesis of Ethynylglycine (FR-900130)

Robert M. Williams,* David J. Aldous, and Suzanne C. Aldous
Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

The first synthesis of racemic *N*-acetyl ethynylglycine is described.

Ethynylglycine (**1**) (FR-900130) is a novel amino acid antibiotic that was isolated[1] from *Streptomyces catenulae* at the Fujisawa Pharmaceutical Co. of Japan in 1980. This notoriously labile substance was shown to display antimicrobial activity against Gram-positive bacteria and synergy with D-cycloserine. It has also been implicated[2] as an irreversible inhibitor of alanine racemase. This deceptively simple amino acid proved to be so labile that the pure amino acid could not be isolated and purified from the fermentation medium. Its corresponding *N*-acetyl derivative (**2**) proved to be more stable, and provided a substrate from which the structure and biological properties of (**1**) were ascertained.[2] Furthermore, it was reported that (**2**) could be deacylated to (**1**) with a homogenate of rat kidney to provide material that could be detected by bioautography. In this report, we wish to describe the first synthesis of *N*-acetyl ethynylglycine (**2**). Metcalf and Casara[3,4] have previously reported the synthesis of 2-ethoxycarbonylamino-4-trimethylsilylbut-3-ynoic acid methylester, but noted that attempts to prepare the free amino acid were unsuccessful.†

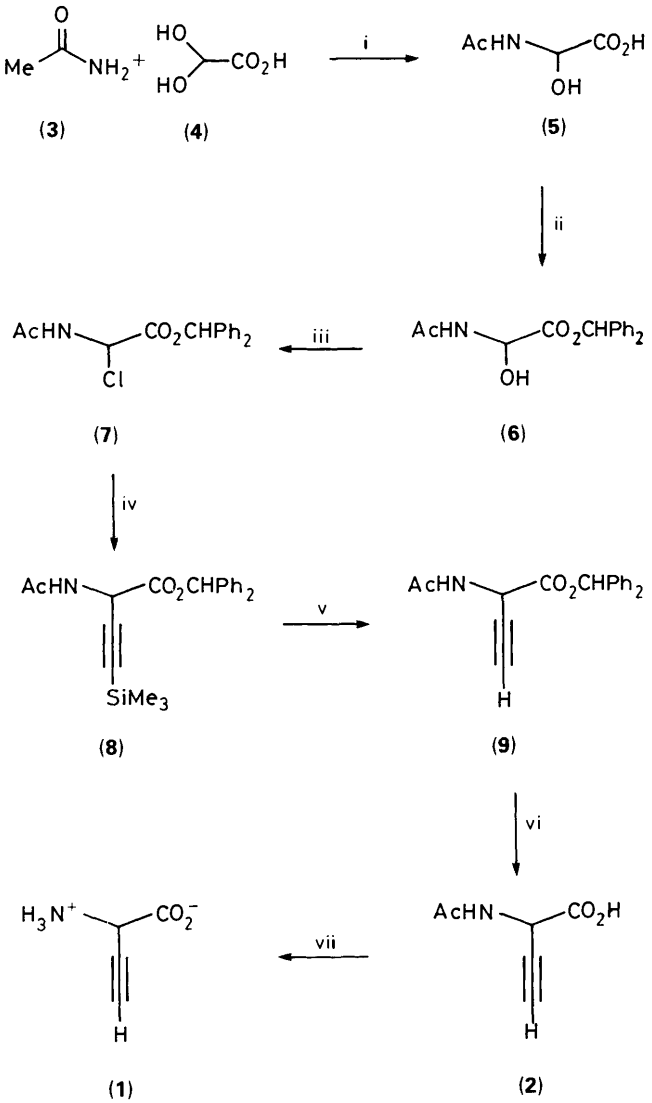
We have recently developed an efficient ethynylation of electrophilic glycinates[6] *via* coupling of alkynyl tin reagents with α-bromo glycinates in the presence of zinc chloride. In order to access this difficult amino acid, we adapted the racemic chloroglycinate system developed by Ben-ishai;[7] careful choice of amine, carboxyl, and acetylene protection was found to be necessary. The synthesis is described below according to the Scheme.

Experimental

(+)-*Benzhydryl 2-Acetylamino-4-trimethylsilylbut-3-ynoate* (**8**)—To the chloroglycinate (**7**)[8] (0.51 mmol) in refluxing dry CCl_4 (25 ml) was added trimethylsilylethynyl tributylstannane (0.52 mmol, 1.0 equiv.) followed by zinc chloride (1M; 0.52 mmol, 1.0 equiv.) in THF. The reaction was followed by TLC and quenched after 30 min by the addition of water (30 ml) then the mixture was allowed to cool to room temperature. The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 15 ml), then the combined organic phases were washed with saturated aqueous NaCl, dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (eluting with 50:1 CH_2Cl_2–MeOH) to yield (**8**) (63%), m.p. 113 °C (from EtOAc–hexanes); δ(270 MHz; $CDCl_3$) 0.21 (s, 9 H), 1.95 (s, 3 H), 5.53 (d, *J* 8.4 Hz, 1 H), 6.53 (d, *J* 8.0 Hz, 1 H), 6.92 (s, 1 H), and 7.37 (s, 10 H); $\nu_{max.}$(NaCl, $CHCl_3$) 3 445, 3 088, 3 069, 3 022, 2 956, 2 900, 2 176, 1 757, and 1 699 cm^{-1}; *m/z* (c.i., NH_3) 379 (M^+, 2.4%) and 167 (Ph_2CH, 100).

(+)-N-*Acetyl Ethynylglycine Benzhydryl Ester* (**9**).—To the protected ethynylglycine (**8**) (40 mg, 0.106 mmol) in dry THF (30 ml) at −78 °C was added a solution of $Bu_4NF{\cdot}3H_2O$ (1M; 2.11 ml, 0.211 mmol, 2 equiv.) in THF. The reaction mixture was maintained at −78 °C until starting material was consumed (TLC), then the reaction was quenched by the addition of a large excess of solid ammonium chloride (4 g). The reaction mixture was kept at low temperature and concentrated under reduced pressure, then the resulting solid was taken up into water (50 ml) and extracted with ethyl acetate (5 × 20 ml). The combined organic extracts were washed with saturated aqueous NaCl, dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (eluting with 1:1 ethyl acetate–hexane) to give the desilylated compound (**9**) (80%), m.p. 106 °C (from EtOAc–hexanes); δ(270 MHz; $CDCl_3$) 2.02 (s, 3 H), 2.39 (d, *J* 2.7

† A patent describing the preparation of (**1**) as a corrosion inhibitor has appeared.[5] In view of the subsequently reported lability of (**1**), it is unlikely that this process indeed produced (**1**).



Scheme. *Reagents and conditions:* i, acetone, reflux, 20 h, ~ quant.; ii, Ph_2CN_2, EtOAc, ~ quant; iii, $SOCl_2$, CH_2Cl_2; iv, $Me_3SiC{\equiv}CSnBu_3$, $ZnCl_2$, CCl_4, reflux 30 min, 63%; v, $Bu_4NF{\cdot}3H_2O$, THF, −78 °C, then NH_4Cl, 80%; vi, F_3CCO_2H, anisole, 84%; vii, rat kidney acylase[1]

Hz, 1 H), 5.51 (dd, *J* 2.6 Hz and 8.0 Hz, 1 H), 6.21 (d, *J* 8.0 Hz, 1 H), 6.88 (s, 1 H), and 7.33 (br s, 10 H); ν_{max}(NaCl, $CHCl_3$) 3 436, 3 304, 3 069, 3 031, 2 965, 1 754, and 1 699 cm^{-1}; *m/e* (c.i., NH_3) 308 (*M* + H, 3.1%) and 167 (PhCH, 100).

(+)-N-*Acetyl Ethynylglycine* (**2**).—To the protected compound (**9**) (32 mg, 0.11 mmol) in dry CH_2Cl_2 (4 ml) at 0 °C was added anisole (36 mg, 0.33 mmol, 3 equiv.) followed by trifluoroacetic acid (0.13 g, 1.2 mmol, 10 equiv.). The reaction mixture was allowed to warm to room temperature and quenched after 20 h by the addition of saturated aqueous $NaHCO_3$ (10 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (3 × 10 ml), and the combined aqueous phases were acidified to pH 2.3 and extracted with ethyl acetate (4 × 25 ml). The combined organic phases were washed with saturated aqueous NaCl, dried (Na_2SO_4), concentrated *in vacuo*, and recrystallized from ethyl acetate–hexane to yield (**2**) (84%, decomposed above 105 °C); δ(300 MHz; $CDCl_3$) 2.12 (s, 3 H), 2.43 (d, *J* 2.6 Hz, 1 H), 5.36 (dd, *J* 7.4 Hz and 2.6 Hz, 1 H), 6.73 (d, *J* 7.4 Hz, 1 H), and 8.02 (br s, CO_2H); *m/z* (c.i., NH_3) 142 (*M* + H, 100%) and 141 (M^+, 35). ^1H NMR and ^{13}C NMR data matched those previously reported for (**2**)[1]

Acknowledgements

The authors are indebted to the National Institutes of Health and the National Science Foundation for financial support of this work.

References

1 (*a*) Y. Kuroda, M. Okuhara, T. Goto, E. Iguchi, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiot.*, 1980, **33**, 125; (*b*) Y. Kuroda, M. Okuhara, T. Goto, M. Kohsaka, H. Aoki, and H. Imanaka, *ibid.*, p. 132.
2 C. Walsh, *Tetrahedron*, 1982, **38**, 871.
3 P. Casara and B. W. Metcalf, *Tetrahedron Lett.*, 1978, 1581.
4 B. W. Metcalf and P. Casara, *J. Chem. Soc., Chem. Comm.*, 1979, 119.
5 R. F. Monroe, F. J. Lowes, G. L. Foster, and B. D. Oaks, U.S. P. 3079345, 1963.
6 (*a*) D. Zhai, W. Zhai, and R. M. Williams, *J. Am. Chem. Soc.*, 1988, **110**, 2501; (*b*) R. M. Williams and W. Zhai, *Tetrahedron*, 1988, **44**, 5425.
7 Z. Bernstein and D. Ben-Ishai, *Tetrahedron*, 1977, **33**, 881.
8 Details of the preparation of (**3**)–(**5**) will be reported elsewhere in a full paper.

Paper 9/03445E
Received 16*th May* 1989
Accepted 14*th August* 1989