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SYNTHESIS OF α-ETHYNYLHISTAMINE, AN INACTIVATOR OF HISTIDINE DECARBOXYLASE

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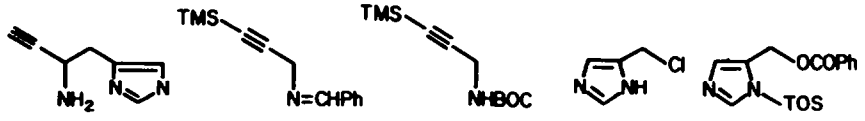
Abstract - α-Ethynylhistamine, an inactivator of histidine decarboxylase, has been synthesized via addition of the t-butyl N-trimethysilyl-prop-2-ynylcarbamate dianion to epibromohydrin to afford the epoxide 6. 6 was converted to the corresponding bromoketone 8 which underwent imidazole formation to give 9 on treatment with S-phenylisothiourea. Desulfurization and deprotection then gave the title compound.

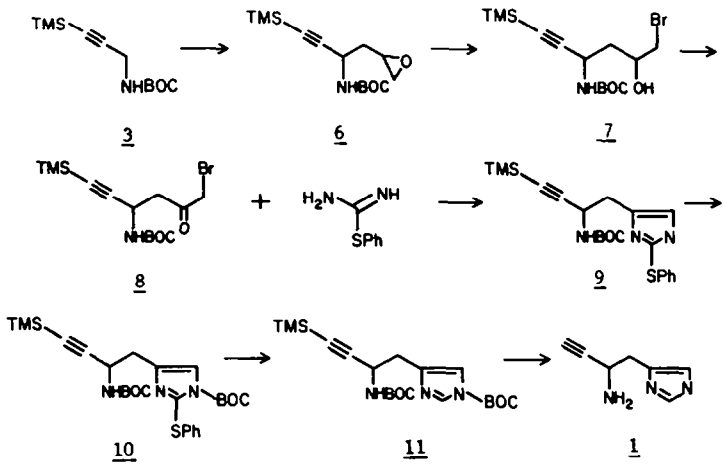
In connection with an ongoing program directed towards the synthesis and biochemical evaluation of suicide enzyme inhibitors, we initiated the synthesis of α-ethynylhistamine (1). It was proposed that this compound, being an analogue of histamine, would inactivate histidine decarboxylase. By analogy with previous work such an inactivation process could be a consequence of the microscopic reversibility principle[1-3] or of a transamination mode[4].

Our initial approach involved the attempted addition of either the monoanion of 2[5] or the dianion of 3[6], which we had developed previously, to a derivative of the preformed imidazole nucleus 4[7] or 5[8]. We were unsuccessful in obtaining alkylated products for unknown reasons using 4, or possibly owing to the acidity of the proton at position 2 of the imidazole nucleus[9] with 5. As a result we turned to approaches involving alkylation of either 2 or 3 with alkylating agents bearing latent functionalities destined for conversion to the imidazole ring at a later stage.



1 2 3 4 5

Imidazoles may be formed from α-haloketones using ammonia in formamide[10]. Alternatively the use of S-benzylisothiourea leads to thioimidazoles[11]. The α-bromoketone 8 (Scheme 1) thus became a desired intermediate from which a variety of approaches to the imidazole 1 could be explored.



Scheme 1

Treatment of the dianion derived from 3[6] with epibromohydrin produced the epoxide 6 as a mixture of diastereomers in 70% yield. Epoxide opening of 6 (KBr/H_2O/HOAc/THF)[12] followed by Jones oxidation of the resulting crude bromohydrin 7 afforded the bromoketone 8 as an oil in 75% yield. 8 underwent cyclization to imidazole 9 on treatment with S-phenylisothiourea[13] (DMF, Na_2CO_3, 47%). Use of S-benzylisothiourea lead to the analogous S-benzylthioimidazole, however, difficulties in reductive removal of the S-benzyl group in the presence of the acetylene function dictated S-phenylisothiourea as the reagent of choice. While aluminum amalgam[9] reduction of 9 was unsuccessful, prior conversion to the biscarbamate 10 allowed satisfactory desulfurization to 11 in 75% yield. Desilylation of 11 ($Bu_4N^+F^-$/THF, 82%) gave 12 which on treatment with HCl/ethanol afforded 1 as the dihydrochloride in 50% yield after recrystallization.

An irreversible component has been observed in the inhibition of histidine decarboxylase from hamster placenta with pure 1, however, the inactivation process does not follow pseudo first-order kinetics.[14]

EXPERIMENTAL SECTION

General Methods

Proton NMR spectra were recorded on a Varian EM390 spectrometer; chemicals shifts are reported in δ units with Me_4Si as the internal standard using deuterochloroform as the solvent unless stated otherwise. IR spectra were taken on a Perkin-Elmer 337 infrared spectrophotometer and are reported in reciprocal centimeters with polystyrene as the reference standard. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

1,1-Dimethylethyl[1-(oxiranylmethyl)-3-(trimethylsilyl)-2-propynyl]carbamate (6). To a solution of LDA, prepared by the addition of n-BuLi (185 mL of 1.43 M soln, 264 mmol) to DIA (37 mL, 264 mmol) in THF (250 mL) at -78° was added TMEDA (40 mL, 264 mmol) followed by the carbamate 3[6] (20.0 g, 88.1 mmol) in THF (200 mL) during 30 min. After 45 min at -78°, a solution of epibromohydrin (22.6 mL, 264 mmol) in THF (50 mL) which had been prechilled to -78°, was added via transfer needle. After being stirred for 30 min at -78° the mixture was quenched with HOAc (50 mL) in THF (50 mL) and allowed to warm to room temperature. The solution was diluted with ether, washed with H_2O and brine and dried ($MgSO_4$). The residue, after concentration was subjected to flash chromatography on silica gel. Elution with 10% EtOAc-hexane afforded the epoxide 6 (17.3 g, 70%) as an oil as a mixture of diastereomers. NMR ($CDCl_3$): δ 4.72 (m, 2H), HN and methine; 3.10 (m, 1H), 2.86 (t, J=5, 1H) and 2.56 (m, 1H), epoxide; 1.85 (m, 2H), CH_2; 1.48 (s, 9H), t-butyl; 0.15 (s, 9H), TMS.

1,1-Dimethylethyl[4-bromo-3-oxo-1-[(trimethylsilyl)ethynyl]butyl]carbamate (8). To a mixture of a saturated solution of KBr in water (21 mL) and HOAc (140 mL) at 0° was added a cold solution of the epoxide 6 (9.2 g, 32.5 mmol) in THF (30 mL). The mixture was maintained to 0° for 18 hours then the product isolated by ether extraction to afford an oil (11.2 g).

This was dissolved in acetone (50 mL) and treated with Jones reagent until the brown color persisted for 15 min. Excess reagent was reduced with isopropanol and the product isolated by chloroform extraction. The ketone 8 (7.6 g, 69%) was obtained as an oil by HPLC using 16% ether-hexane as eluant. NMR ($CDCl_3$): 5.20 (broad d, 1H), HN; 4.80 (m, 1H), methine; 3.96 (s, 2H), CH_2Br; 3.08 (broad d, 2H, J=6) CH_2; 1.48(s, 9H), t-butyl; 0.16 (s, 9H), TMS. IR (film): 3340, 2160, 1720.
Anal. Calcd for $C_{14}H_{24}BrNO_3Si$: C, 46.41; H, 6.68; N, 3.87; Br, 22.05.

Found: C.46.43; H, 6.56; N, 3.91; Br, 21.92.

1,1-Dimethylethyl[1-[[2-(phenylthio)-1H-imidazol-4-yl]methyl]-3-(trimethylsilyl)--2-propynyl]carbamate (9). To a solution of the bromoketone 8 (19.7 g, 54.4 mmol) in DMF (115 mL) was added Na_2CO_3 (28.8 g, 272 mmol) and S-phenylisothiourea (9.9 g, 65.3 mmol) and the mixture heated to 70°.[3] After 1-1/2 h at 70°, the mixture was cooled and treated with H_2O (5 mL). The solvent was then distilled off at aspirator pressure and the crude product isolated by ether extraction. Flash chromatography on silica gel using 30% then 40% EtOAc-hexane as eluant afforded the imidazole 9 (10.7 g, 47%), m.p. 65°. NMR ($CDCl_3$): 7.15 (s, 5H), SPh; 6.91 (s, 1H), imidazole; 5.05 (broad d, J=9, 1H), NH; 4.60 (m, 1H), methine; 2.92 (d, J=6, 2H), CH_2; 1.41 (s, 9H), t-butyl; 0.12 (s, 9H), TMS. IR (KBr): 2170, 1700. M.S. (e.i.): m/e 415 (M^+), 190 (100%).
Anal. Calcd $C_{21}H_{29}N_3O_2SSi$: C, 60.69; H, 7.03; N, 10.11; S, 7.71.

Found: C, 60.45; H, 7.02; N, 10.03; S, 7.71.

1,1-Dimethylethyl 4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]-4-(trimethyl-silyl)-3-butynyl]-2-(phenylthio)-1H-imidazole-1-carboxylate (10). A solution of the imidazole 9 (4.2 g, 10.1 mmol) and Et_3N (1 mL, 10.1 mmol) in CH_2Cl_2 (10 mL) was chilled to 0°. Di-t-butyldicarbonate (5.8 mL, 25.3 mmol) was added, and the solution was stirred at room temperature overnight. The mixture was concentrated and the crude product isolated by ether extraction, then purified by flash chromatography using 20% EtOAc-hexane as eluant to afford 10 (5.2 g, 100%) as an oil. NMR ($CDCl_3$): 7.58 (m, 2H) and 7.36 (m, 3H), SPh; 7.17 (s, 1H), imidazole; 5.35 (broad d, J=9, 1H), NH; 4.59 (m, 1H), methine; 2.71 (d, J=6, 2H), CH_2; 1.60 (s, 9H) and 1.40 (s, 9H), t-butyl; 0.10 (s, 9H), TMS. IR (film): 3380, 2165, 1745, 1710. MS (e.i.): m/e 516 (M+1), 190 and 57 (100%).
Anal. Calcd $C_{26}H_{37}N_3O_4SSi$: C, 60.55; H, 7.23; N, 8.15; S, 6,22.

Found: C, 60.05; H, 7.22; N, 7.89; S, 6.14.

1,1-Dimethylethyl 4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]-4-(trimethylsilyl)-3-butynyl]-1H-imidazole-1-carboxylate (11). Aluminum amalgam was prepared as described[15] from aluminum granules (2.7 g, 8-16 mesh) and added to a solution of 10 (2.57 g, 5 mmol) in 15% H_2O/EtOH (100 mL). After 48 hours a further sample of aluminum amalgam prepared from aluminum granules (5 g) was added and the mixture stirred for a further 24 hours. The mixture was filtered and concentrated. Flash chromatography using 35% EtOAc/hexane afforded 11 (1.9 g, 93%). It was not possible to obtain satisfactory elemental analyses on 11 probably due to facile cleavage of the Im-Boc bond. NMR ($CDCl_3$): 7.96 (d, J=1.5, 1H) and 7.20 (broad s, 1H) imidazole; 5.33 (broad d, J=9, 1H), NH; 4.66 (m, 1H) methine; 2.88 (d, J=6, 2H) CH_2; 1.60 (s, 9H) and 1.43 (s, 9H), t-butyl; 0.12 (s, 9H), TMS. IR (film): 3350, 2160, 1750, 1700.

1,1-Dimethylethyl 4-[2-[[(1,1-dimethylethoxy)carbonyl]amino]-3-butynyl]-1H-imidazole-1-carboxylate (12). To a solution of 16 (3.1 g, 7.6 mmol) in THF (15 mL) was added $(n\text{-}Bu)_4NF$ (15.2 mL of 1M soln) and the solution was stirred at room temperature for 3-1/2 h. It was then diluted with ether and washed with water and brine. 12 (2.1 g) was obtained in 82% by flash chromatography using 40% EtOAc/hexane as eluant. NMR ($CDCl_3$): 7.96 (s, 1H) and 7.20 (s, 1H), imidazole; 5.60 (broad d, J=8, 1H), HN; 4.67 (m, 1H), methine; 2.92 (d, J=6, 2H), CH_2; 2.15 (d, J=1, 1H), acetylene; 1.60 (s, 9H) and 1.43 (s, 9H), t-butyl. IR (film): 3340, 3310, 1760, 1710.

α-Ethynylhistamine dihydrochloride (1). The carbamate 12 (5.0 g, 18 mmol) in ethanol (50 mL) was treated with conc. HCl (5 mL) and the solution stirred at room temperature for 4 h then concentrated and diluted with water. This solution was then washed with ether, the aqueous phase filtered and concentrated. The residue was then dissolved in hot EtOH (200 mL), while adding sufficient water to obtain a solution. The solution was then concentrated to 50 mL, more EtOH (200 mL) added and the solution concentrated to 5 mL then allowed to cool. The crystals of 1 (2.3 g, 62%) which formed were collected, redissolved in hot 95% EtOH and treated with charcoal, then filtered and concentrated. The crystals which formed on cooling were recrystallized from 95% EtOH to afford the analytical sample, m.p. 214-216° (decomp). NMR (D_2O): 8.66 (d, J=1.5, 1H) and 7.46 (broad s, 1H), imidazole; 4.51 (m, 1H), methine; 3.36 (s) and 3.33 (d, J=1), methylene; 3.13 (d, J=1), acetylene. IR (KBr); 2120.
Anal. Calcd $C_7H_9N_3 \cdot 2HCl$: C, 40.40; H, 5.33; N, 20.19; Cl, 34.07.

Found: C.40.35; H, 5.43; N, 20.16; Cl, 33.93.

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