4(5)-Vinylimidazole by Dehydrobromination of 1-Triphenylmethyl-4-(2-bromoethyl)imidazole

Janina Altman and Meir Wilchek*

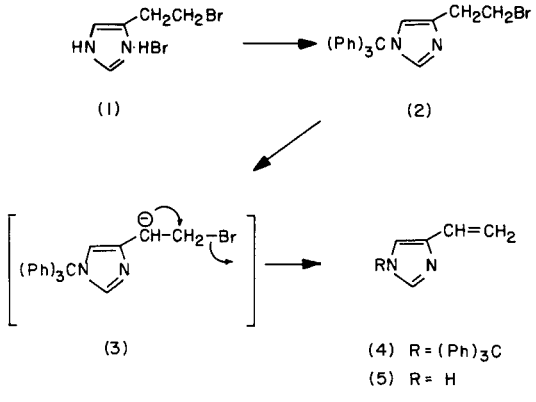
Department of Biophysics, The Weizmann Institute of Science,
Rehovot, Israel

Received November 24, 1987

1-Triphenylmethyl-4-(2-bromoethyl)imidazole undergoes elimination upon basic treatment providing an easy approach to 4(5)-vinylimidazole whereas the *N*-unsubstituted analogue leads only to substitution products.

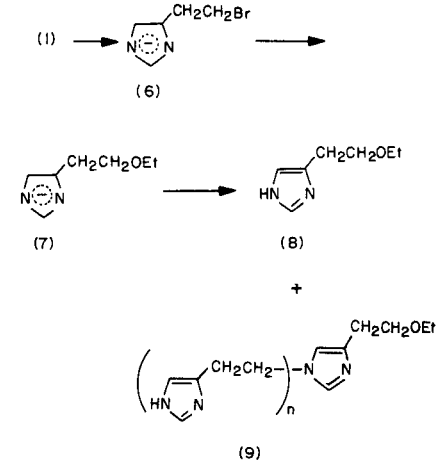
J. Heterocyclic Chem., **25**, 915 (1988).

4(5)-Vinylimidazole is used as a monomer for preparation of imidazole containing polymers [1-6] and is considered as a starting material for histamine and histidine derivatives [7]. The first attempts for its synthesis by base-induced dehydrohalogenation of 4-(2-chloroethyl)imidazole were unsuccessful [1]. Alternative methods were developed involving pyrolytic decarboxylation of urocanic acid [2] or Wittig reactions of *N*-triphenylmethylimidazole-4-carboxamide [7,8]. It appears that dehydrohalogenation can also be an easy approach to 4(5)-vinylimidazole when applied to the previously tritylated 4-(2-bromoethyl)imidazole. When **2** is treated with sodium ethoxide in ethanol at room temperature or with *n*-butyllithium or lithiumdiisopropylamide (LDA) in THF at -78° elimination involving proton abstraction from the α position to the neutral *N*-substituted imidazole ring **3** takes place as a single reaction pathway (Scheme 1). Subsequent removal of the trityl group by known procedures [7,9] gives **5** in 65% yield based on **1**.



Scheme 1

The failure of *N*-unsubstituted 4-(2-chloroethyl)imidazole to undergo elimination in a basic medium [1] is not surprising. Abstraction of a proton from the α position of the chain to the negatively-charged imidazole ring **6** (Scheme 2) seems to be unlikely; rather the β position would be expected to participate in displacement reactions. Substitution of chlorine to give phenoxy [10] or



Scheme 2

alkoxy [11] ethers and reactions with malonic acid ester carbanion derivatives have also been reported [12-14]. When **1** is treated with an excess of sodium ethoxide (one equivalent to neutralize hydrobromide, one equivalent to yield imidazolium anion and one equivalent as a reactant), 4-(2-ethoxyethyl)imidazole **8** is isolated by preparative tlc on silica as the main reaction product in 66% yield (previously reported in 24% yield [11]). In the ^{1}H nmr spectrum of the crude reaction mixture olefinic protons are not detected. There is one triplet of the CH_3 group at 1.02 ppm coupled to one quartet of CH_2O at 3.42 ppm but signals of $ImCH_2$ at the 2.76-2.86 ppm region, when irradiated, effect two triplets: one at 3.61 ppm of 2-ethoxyethyl chain and the second of low intensity at 3.71 ppm. Most likely the minor triplet derives from the methylene bound to nitrogen of the imidazole ring. Under the above reaction conditions *N*-alkylation of imidazole [15,16] leading to a dimeric or trimeric species of type **9** cannot be excluded. Maybe such compounds were present in the crude reaction mixture but we did not succeed in isolating them pure.

In summary, the elimination reaction pathway appears to be characteristic for *N*-protected 4-(2-haloethyl)imidazole, whereas when the imidazole ring is ionized upon

reaction with the base substitution occurs in the side chain.

EXPERIMENTAL

Melting points were determined on a Fisher-Johnson melting point apparatus and are uncorrected. Routine ^1H nmr spectra were recorded on a Varian FT 80A spectrometer and analytical samples on a Bruker WH-270 spectrometer. Mass spectra (electron impact, 70 ev) of **5** and **8** were obtained on a Finnigan 4500 GC-MS instrument. Microanalyses were performed by Dr. Shoshana Blum at the Microanalytical Services of the Hebrew University in Jerusalem.

1-Triphenylmethyl-4-(2-bromoethyl)imidazole (**2**).

4-(2-Bromoethyl)imidazole hydrobromide (**1**) prepared according to Bloemhoff and Kerling [17], (7.65 g, 0.03 mole) and triethylamine (3.33 g, 0.033 mole) were dissolved in absolute DMF (40 ml) under nitrogen. Upon cooling in an ice bath a solution of trityl chloride (9.2 g, 0.033 moles) in DMF (50 ml) was slowly added. The reaction mixture was stirred 2 hours at 0° and overnight at room temperature, poured into cold water (750 ml), extracted with ethyl acetate (2 x 100 ml), the organic layer was washed with water, dried (sodium sulfate) and concentrated. The residue in a small volume of dichloromethane was introduced on silica column (240 g, Woelm, 150-230 mesh) prepared with 25% ethyl acetate-hexane. Triphenylmethanol was eluted with the same solvent. Elution with ethyl acetate-hexane 1:1 gave **2** (10.2 g, 81%), mp 143° (from ethyl acetate-hexane); Rf 0.43 (tlc on silica, elution with ethyl acetate-hexane 1:1); nmr (deuteriochloroform): δ 7.47 (d, 1H, J = 1.1 Hz, ImH-2), 7.45-7.30 (m, 9 H, ArH), 7.17-7.10 (m, 6 H, ArH), 6.64 (d, 1 H, J = 1.1 Hz, ImH-5), 3.63 (t, 2 H, J = 7.2 Hz, CH_2Br), 3.07 (t, 2 H, J = 7.2 Hz, $ImCH_2$).

Anal. Calcd. for $C_{24}H_{21}BrN_2$: C, 69.06; H, 5.07; N, 6.71. Found: C, 68.75; H, 4.86; N, 6.69.

1-Triphenylmethyl-4-Vinylimidazole (**4**).

Procedure A.

Bromide **2** (834 mg, 2 mmoles) was added into a solution of sodium ethoxide (from 70 mg, 3 mmoles of sodium) in ethanol (20 ml) and left overnight at room temperature. Solid ammonium chloride (100 mg) was added, the mixture was stirred 1 hour and evaporated. The residue was treated with water and dichloromethane. The organic layer was dried (sodium sulfate) and concentrated, (634 mg, 95%), mp 203-205° (from dichloromethane-hexane) (lit 205-207° [7], 206-208° [8], tlc Rf = 0.60 (ethyl acetate-hexane 1:1); nmr (deuteriochloroform): δ 7.39 (d, 1 H, J = 0.8 Hz, ImH-2), 7.34-7.31 (m, 9 H, ArH), 7.25-7.31 (m, 9 H, ArH), 7.25-7.11 (m, 6 H, ArH), 6.77 (d, 1 H, J = 0.8 Hz, ImH-5), 6.54 (q, 1 H, J = 17.3 and 11 Hz, ImCH), 5.82 (q, 1 H, J = 17.3 and 1.7 Hz, =CH*H cis* to Im), 5.10 (q, 1 H, J = 11 and 1.7 Hz, =CH*H trans* to Im).

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.67; H, 5.99; N, 8.32. Found: C, 86.00; H, 5.69; N, 8.62.

Procedure B.

Bromide **2** (1.25 g, 3 mmoles) was dissolved in THF (15 ml) and cooled to -78° under nitrogen. 1.5*M* LDA in cyclohexane (Aldrich, 2.2 ml, 3.3 mmoles) was added. The reaction was stirred for 5 hours upon cooling, heated to room temperature, and the solvent was evaporated. After work up as above 930 mg, 93% of **4** was obtained.

4(5)-Vinylimidazole (**5**).

The removal of the trityl group was performed according to the procedure of Kokosa *et al.* [7] in THF or in acetone as a solvent, mp 80-82° (lit 83-84° [1], 80-82° [7], 80-83° [8]); nmr (deuteriochloroform): δ 8.27 (v br NH), 7.60 (s, 1 H, Im-2) 7.03 (s, 1 H, ImH-5), 6.62 (q, 1 H, J = 17.6 and 11.2 Hz, ImCH), 5.66 (q, 1 H, J = 17.6 and 1.2 Hz, =CH*H cis* to Im), 5.12 (q, 1 H, J = 11.2 and 1.2 Hz, =CH*H trans* to Im); ms: m/e 94 (M^+ 100%).

4(5)-(2-Ethoxyethyl)imidazole (**8**).

The bromide **2** (332 mg, 1.3 mmoles) was introduced into a solution of sodium ethoxide (from 100 mg, 4.3 mmoles sodium) in absolute ethanol (7.5 ml) and left overnight at room temperature. Ammonium chloride (100 mg) was added, the mixture was stirred 1 hour and evaporated, the residue was dissolved in water (2 ml), saturated with sodium carbonate and extracted 3 times with ethyl acetate. The concentrated solution was introduced on two preparative 2 mm thick tlc silica plates (Merck, 20 x 20) and eluted with ethyl acetate-ethanol 1:1. Detection was performed by spraying the edges of the plates with Pauly reagent [18] or by exposure to iodine, Rf = 0.53. The middle section of the plates was removed by scraping. This was extracted with ethyl acetate-ethanol 1:1 by stirring overnight, filtered and evaporated. To remove some silica from the product sodium carbonate anhydrous (1 g) and dichloromethane (50 ml) were added. The mixture was stirred 2 hours, filtered and concentrated giving an oil (140 mg, 66%); nmr (deuterium oxide): δ 7.61 (s, 1 H, ImH-2), 6.84 (s, 1 H, ImH-5), 3.65 (t, 2 H, J = 7 Hz, CH_2O, 3.48 (q, 2 H, J = 7 Hz, CH_2O), 2.76 (t, 2 H, J = 7 Hz, $ImCH_2$), 1.08 (t, 3 H, J = 7 Hz, CH_3); ms: m/e 140 (M^+ 7%), 111 (M-Et, 26%), 81 (M - CH_2OEt, 100%).

Anal. Calcd. for $C_7H_{12}N_2O.\frac{1}{2}H_2O$: C, 56.35; H, 8.78; N, 18.77. Found: C, 56.52; H, 8.71; N, 18.56.

Acknowledgements.

This study was supported by Makor Chemicals, Jerusalem. We wish to thank Dr. A. Tishby and Mr. R. Schlesinger for performing mass spectra. We are grateful to Mr. M. Grinberg and M. Avner for providing the 90-MHz and 270-MHz nmr spectra.

REFERENCES AND NOTES

[1] C. G. Overberger and N. Vorchheimer, *J. Am. Chem. Soc.*, **85**, 951 (1963).

[2] C. G. Overberger, R. C. Glowaky, T. J. Pacansky, and K. N. Sannes, *Macromol. Synth.*, **5**, 43 (1974).

[3] C. G. Overberger and Y. Kawakami, *J. Polym. Sci., Polym. Chem. Ed.*, **16**, 1237 (1978).

[4] C. G. Overberger and A. C. Guterl Jr., *J. Polym. Sci., Polym. Symp.*, **62**, 13 (1978).

[5] S. Morita, N. Yamashita, and T. Maeshima, *J. Polym. Sci., Polym. Chem. Ed.*, **18**, 1599 (1980).

[6] N. Yamashita, S. Morita, and T. Maeshima, *J. Polym. Sci., Polym. Chem. Ed.*, **20**, 327 (1982).

[7] M. Kokosa, R. A. Szafasz, and T. Tagupa, *J. Org. Chem.*, **48**, 3605 (1983).

[8] R. K. Griffith and R. A. DiPietro, *Synth. Commun.*, **16**, 1761 (1986).

[9] J. L. Kelly, C. A. Miller, and E. W. McLean, *J. Med. Chem.*, **20**, 721 (1977).

[10] C. F. Huebner, R. A. Turner, and C. R. Scholz, *J. Am. Chem. Soc.*, **71**, 3942 (1949).

[11] W. Schunack, *Arch. Pharm. (Weinheim)*, **307**, 517 (1974).

[12] F. Schneider, *Hoppe-Seyler's Z. Physiol. Chem.*, **334**, 26 (1963).

[13] T. C. Bruice and J. M. Sturtevant, *J. Am. Chem. Soc.*, **81**, 2860 (1959).

[14] W. Bloemhoff and K. E. T. Kerling, *Rec. Trav. Chim.*, **94**, 182 (1975).

[15] K. Hoffmann "The Chemistry of Heterocyclic Compounds", Interscience Publishers, Inc, NY, 1953, p 43.

[16] M. R. Grimmett, in *Adv. Heterocyclic Chem.*, **12**, 163 (1970); *ibid.*, **27**, 292 (1980).

[17] W. Bloemhoff and K. E. T. Kerling, *Rec. Trav. Chim.*, **89**, 1181 (1970).

[18] H. Pauly, *Hoppe-Seyler's Z. Physiol. Chem.*, **42**, 508 (1904).