Ring Opening of *N*-Tosylhistamine with Di-t-butyl Pyrocarbonate: Synthesis of 1,2-Diamino-4-tosylaminobutane Dihydrochloride[1]

Janina Altman,* Nurith Shoef, Meir Wilchek, and Abraham Warshawsky

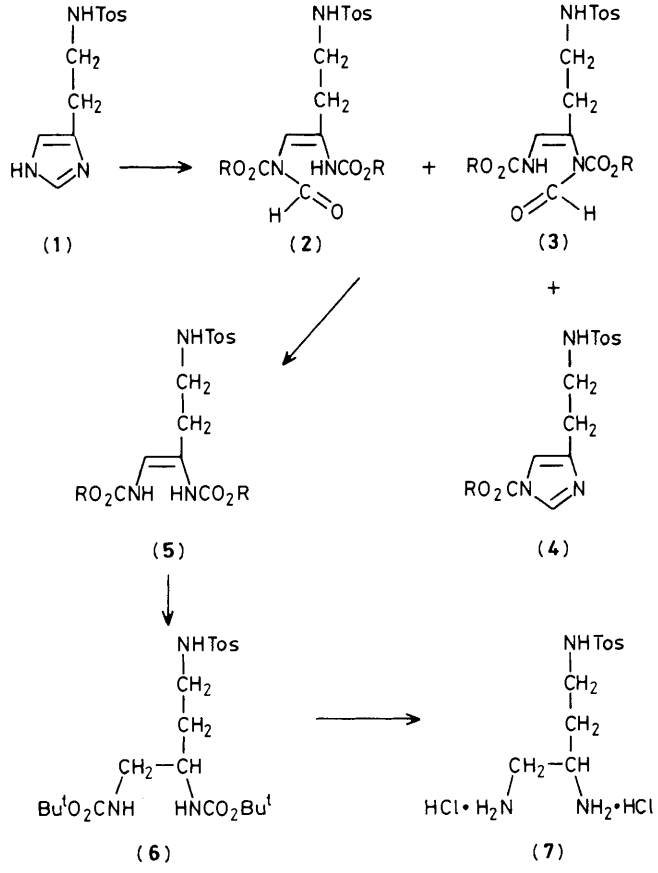
Departments of Organic Chemistry and Biophysics, Weizmann Institute of Science, 76100 Rehovot, Israel

Bamberger ring-cleavage acylation of *N*-tosylhistamine with di-t-butyl pyrocarbonate [$Bu^tOC(:O)–O–C(:O)OBu^t$] in acetonitrile–aqueous potassium acetate leads to 3,4-bis(di-t-butoxycarbonylamino)but-3-enyl(tosyl)amine, which, after hydrogenation and treatment with hydrochloric acid, gives 1,2-diamino-4-tosylaminobutane dihydrochloride.

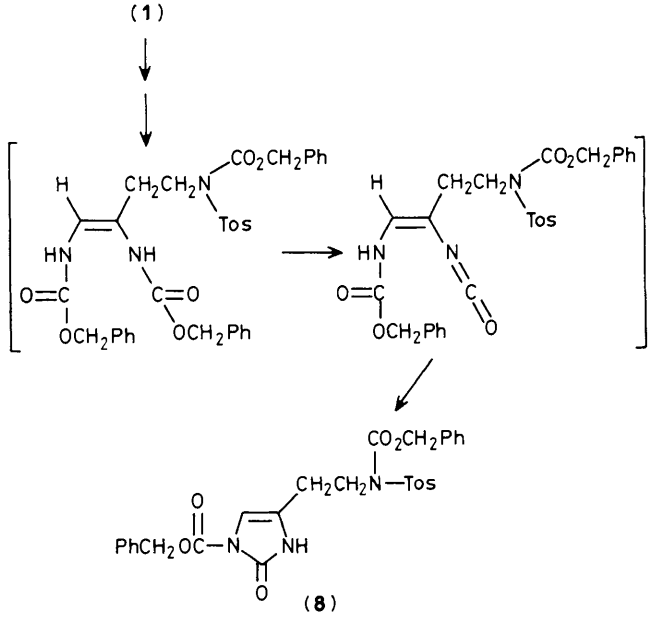
Vicinal diamines with an additional function are required as ligands for metal complex formation[2] and for synthesis of ethylenediaminetetra-acetic acid analogues which may be subsequently coupled to biological macromolecules.[3] Bamberger ring-cleavage acylation of imidazoles is a good approach to the synthesis of such compounds. Ethyl pyrocarbonate[4] or vinyl and phenyl chloroformate (the last two were considered to have good leaving groups) were used as acylating agents of imidazole, but the respective products underwent facile cyclization to the corresponding imidazol-2-one.[5]

We now report that the reaction of *N*-tosylhistamine (**1**) (1 mmol) with di-t-butyl pyrocarbonate [$Bu^tOC(:O)–O–C(:O)OBu^t$] (7.8 mmol) in acetonitrile (10 ml)–10% $MeCO_2K$ (12 ml) after 10 days at room temperature gives two isomeric open-chain products (**2a**) and (**3a**) [oil, 242 mg, 50%, purification on silica column, elution with 20% EtOAc–hexane, ^1H n.m.r. (80 MHz, $CDCl_3$) δ 9.08 (1H, CHO) and 6.41 (1H, HC=C)] together with the more polar monoacylated compound (**4a**), m.p. 98—99 °C (40%). The formyl group may be removed by methanolic ammonia giving (**5a**), m.p. 140—141 °C (80%). Catalytic reduction with Pd–C in methanol or transfer-hydrogenation with ammonium formate[6] yielded (**6**), m.p. 120—121 °C. Treatment with 26% dry HCl in MeOH at room temperature gave quantitatively the dihydrochloride (**7**) as a hygroscopic solid† (R_f 0.45, t.l.c. on silica, elution with 25% NH_4OH–EtOH, 1 : 10, spraying with ninhydrin). The cleavage of one Boc occurs during the first hour (R_f 0.69) whereas removal of the second Boc group requires several hours as the presence of one protonated amino group shields the Boc-amino group.[7] (Boc = Bu^tOC).

Compound (**1**) also reacted with benzyloxycarbonyl chloride (2 equiv.) in ethyl acetate–1M $NaHCO_3$ yielding (**2b**) and (**3b**) (oil, 69%, elution from silica column with 20% EtOAc–hexane). Refluxing in methanol (1 h) gave (**5b**) quantitatively, m.p. 20 °C. Acylation of (**1**) with benzyloxycarbonyl chloride (4 equiv.) yielded the imidazolone (**8**), m.p. 104 °C (20%), in addition to (**2b**) and (**3b**). The reaction probably proceeds *via* the triacetylated intermediate which undergoes benzyl alcohol elimination from position 3, since compound (**5b**) is stable and does not cyclize under similar reaction conditions (1M $NaHCO_3$, room temp.). Hydrogenation of (**5b**) under standard conditions does not lead to (**7**). It seems that the benzyloxycarbonyl groups are hydrogenolysed prior to hydrogenation of the double bond, and that the free



Tos = *p*-$MeC_6H_4SO_2$
a; R = Bu^t
b; R = $PhCH_2$



† All products gave satisfactory elemental analyses. Their i.r. spectra were in good agreement with data reported for analogous compounds.[9] Spectral data: (**7**) ^1H n.m.r. (80 Mhz, D_2O) δ 7.88 and 7.47 (4H, A_2B_2, *J* 10 Hz, ArH), 3.76 (1H, 9, *J* 8 Hz), 3.42—3.34 (2H, m), 3.08 (2H, t, *J* 8 Hz), 2.42 (3H, s), and 1.99 (2H, 9, *J* 8 Hz); ^{13}C n.m.r. (90 MHz, D_2O) δ 146.99, 135.77, 133.59, 128.22, 48.74 (C-2), 42.08 (C-4), 39.97 (C-1), 31.56 (C-3), and 22.15 (Me).

ene–amine system tautomerises to an imine with subsequent hydrolysis.[1] The application of di-butyl pyrocarbonate in the 90 year old Bamberger[8] reaction reveals its new synthetic potential for the preparation, under mild conditions of vicinal diamines with a third amine function still containing a protecting group.

Received, 10th May 1985; Com. 641

References

1 For previous paper in the series see J. Altman, N. Shoef, M. Wilchek, and A. Warshawsky, *J. Chem. Soc., Perkin Trans. 1*, 1984, 59.
2 J. Altman and M. Wilchek, *Inorg. Chim. Acta*, 1985, in the press; J. Altman, M. Wilchek, and A. Warshawsky, *ibid.*, 1985, **101**, 171.
3 M. W. Sundberg, C. F. Meres, D. A. Godwin, and C. I. Diamanti, *J. Med. Chem.*, 1974, **17**, 1304; J. Altman, N. Shoef, M. Wilchek, and A. Warshawsky, *J. Chem. Soc., Perkin Trans. 1*, 1983, 365.
4 M. E. Grace, M. J. Loosemore, M. L. Semmel, and R. F. Pratt, *J. Am. Chem. Soc.*, 1980, **102**, 6784.
5 R. F. Pratt and K. K. Kraus, *Tetrahedron Lett.*, 1981, **22**, 2431.
6 M. K. Anwer and A. F. Spatola, *Synthesis*, 1980, 929.
7 J. Altman, M. Gorecki, M. Wilchek, J. R. Votano, and A. Rich, *J. Med. Chem.*, 1984, **27**, 594.
8 E. Bamberger and B. Berle, *Liebigs Ann. Chem.*, 1893, **273**, 342.
9 J. Altman and D. Ben-Ishai, *J. Heterocycl. Chem.*, 1968, **5**, 679; E. Babad and D. Ben-Ishai, *ibid.*, 1969, **6**, 235.