Methyl Iodide as a Cyclodeaminating Agent

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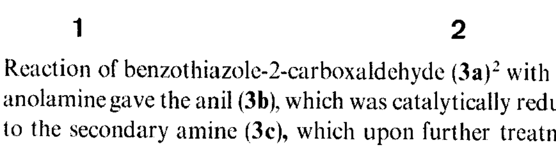
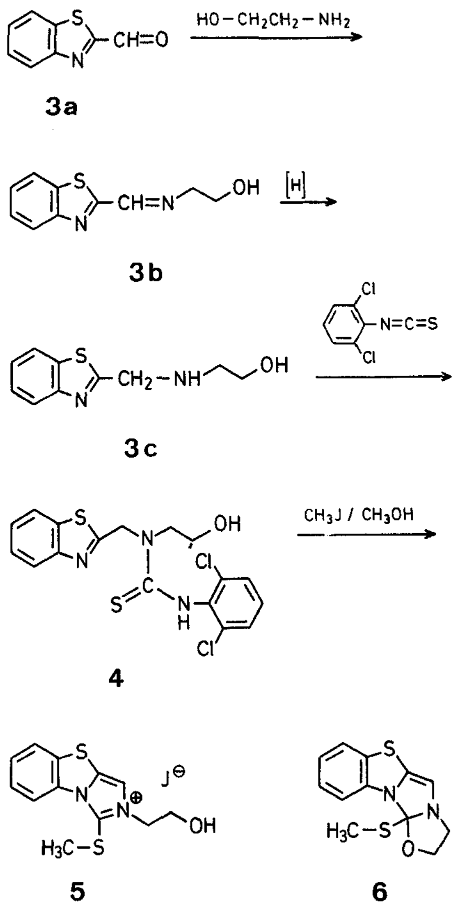
Recently Omar[1] described the reaction of several *o*-aminophenylthioureas (**1**) with methyl iodide which resulted in cyclodesulphurisation to give the corresponding 2-(substituted-amino)benzimidazoles (**2**). As a cautionary note we here draw attention to an analogous thiourea/methyl iodide cyclisation which proceeded with sulphur retention and aniline elimination (e.g. **4**→**5**)



Reaction of benzothiazole-2-carboxaldehyde (**3a**)[2] with ethanolamine gave the anil (**3b**), which was catalytically reduced to the secondary amine (**3c**), which upon further treatment with 2,6-dichlorophenylisothiocyanate gave the thiourea (**4**). Treatment of (**4**) with methyl iodide in methanol under reflux for 20 hours resulted in the formation of the imidazolium iodide (**5**).

When a solution of **5** in pyridine-d_5 was allowed to stand at room temperature for several hours almost complete conversion of **5** to **6** was indicated by the ^{1}H-N.M.R. spectrum. This conversion is consistent with base-assisted intramolecular attack by the hydroxyethyl side-chain on the immonium function. Closely related examples of this behaviour have been reported (e.g. conversion of 1-(2-hydroxyethyl)-2,3,3-trimethyl-2,3-dihydroindolium iodide[3] under action of sodium carbonate to 1a,2,3,9-tetrahydro-1a,9,9-trimethyloxazolo-[3,2-*a*]indole.



Two alternative syntheses of unquaternised imidazo[5.1-*b*]-benzothiazoles have recently appeared[4,5].

N.M.R. spectra were obtained on a Varian HA 100 spectrometer (TMS internal standard), mass spectra on an AEI MS 9 spectrometer, and the infrared spectra on a Perkin Elmer 157 spectrometer.

2-(2-Hydroxyethyliminomethyl)benzothiazole (3b):
A mixture of benzothiazole-2-carboxaldehyde[2] (**3a**; 2.5 g, 16.5 mmol) and ethanolamine (1.0 ml, 16.5 mmol) was heated at 80° for 10 minutes, the water formed being removed under vacuum. Upon cooling the solid product was washed with light petroleum and crystallised from toluene/light petroleum; yield: 2.6 g (77%); m.p. 89°.

$C_{10}H_{10}N_2OS$	calc.	C 58.2	H 4.9	N 13.6
(206.3)	found	58.2	4.9	13.5

2-(2-Hydroxyethylaminomethyl)benzothiazole (3c):
To a solution of the imine (**3b**; 0.9 g, 4.4 mmol) in glacial acetic acid (30 ml) was added palladium on charcoal (10%; 0.25 g) and the mixture shaken under an atmosphere of hydrogen at room temperature until hydrogen uptake ceased (~3 h). The resulting solution was filtered and evaporated yielding an oil which was distributed between dilute ammonium hydroxide (12 ml) and ether (25 ml). The ether layer was separated and the aqueous phase re-extracted with ether. The combined extracts were dried and evaporated yielding the product as an oil. Treatment of this oil with an excess of oxalic acid in ethyl acetate gave a solid oxalate salt which was washed with ether; yield: 0.45 g (34%); m.p. 181–183° (decomp.).

$C_{10}H_{12}N_2OS.(CO_2H)_2$	calc.	C 48.3	H 4.7	N 9.4
(298.3)	found	47.9	5.1	9.2

3-(2,6-Dichloromethyl)-1-(benzothiazol-2-ylmethyl)-1-(2-hydroxyethyl) thiourea (4):
A sample of the oxalate of **3c** was treated with 2*N* sodium hydroxide and extracted with ether to give a sample of the free base

3c. A mixture of this base (**3c**; 0.7 g, 3.3 mmol) and 2,6-dichlorophenyl isothiocyanate (0.68 g, 3.3 mmol) in dry toluene (50 ml) was refluxed for 4 h and the solvent was then evaporated *in vacuo*. Crystallisation of the resulting solid from toluene gave the product; yield: 1.1 g (81%); m.p. 168°.

$C_{17}H_{15}Cl_2N_3OS_2$	calc.	C 49.8	H 3.7	N 10.0
(412.3)	found	49.5	3.7	10.2

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.98$ (s, hydroxyethyl CH_2), 5.52 (s, benzylic CH_2), 7.2–8.1 (m, aromatic protons plus OH or NH), 9.24 ppm (s, NH or OH).

I.R. (nujol): $\nu = 1540$ (thioamide), 3200, and 3400 cm^{-1} (NH and OH).

2-(2-Hydroxyethyl)-1-methylthioimidazo[5,1-*b*]benzothiazolium iodide (5):

A solution of the thiourea (**4**; 0.8 g, 2 mmol) in dry methanol (50 ml) containing methyl iodide (2.0 g, 14 mmol) was refluxed under nitrogen for 20 h after which the solvent was evaporated to leave a brown oil. Trituration of this oil with ether (2 × 50 ml) followed by ethanol (2 × 25 ml) gave the product as a pale brown solid; yield: 0.38 g (51%), m.p. 151–152° (decomp.); raised to 155° upon recrystallisation from ethanol/water.

$C_{12}H_{13}N_2OS_2 . J$	calc.	C 36.7	H 3.3	N 7.1
(392.3)	found	36.7	3.4	6.8

^{1}H-N.M.R. (pyridine-d_5): $\delta = 2.3$ (s, S—CH_3), 3.5 and 3.8 (sym. m, hydroxyethyl CH_2), 6.5–7.2 ppm (m, aromatic protons).

I.R. (nujol): $\nu = 1650$ ($C{=}\overset{\oplus}{N}$), 2800–3200 cm^{-1} (broad OH).

Mass spectrum: $m/e = 265.0431$ ($M^{\oplus} - HJ$, 5%, $C_{12}H_{13}N_2OS$ requires 265.0469), 264.0411 ($M^{\oplus} - HJ - 1$, 37%, $C_{12}H_{12}N_2OS$ requires 264.0393), 189.0487 ($m^* = 135.3$, $M^{\oplus} - HJ - COSCH_3$, 100%, $C_{10}H_9N_2S$ requires 189.0487), 148.0210 ($m^* = 115.9$, 189 − CH_3CN, 12%, C_8H_6NS requires 148.0220).

After 2 h standing of a solution of **5** in pyridine-d_5 the resonance at $\delta = 2.3$ ppm was almost completely replaced by a singlet at $\delta = 2.35$ ppm and a change in shape of the hydroxyethyl methylenes was observed, indicative of the conversion **5**→**6**.

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[1] A. M. M. E. Omar, *Synthesis* **1974**, 41.

[2] V. M. Zubarovskii, *Dokl. Akad. Nauk SSSR* **87**, 759 (1952); *C.A.* **48**, 164 (1954).

[3] E. L. Zaitseva, et al., *Khim. Geterotsikl. Soedin* **1973**, 1362; *C.A.* **80**, 27149 (1974).

[4] V. V. Avidon, M. N. Shchukina, *Khim. Geterotsikl. Soedin* **1965**, 64; *C.A.* **63**, 4271 (1965).

[5] V. V. Avidon, M. N. Shchukina, *Khim. Geterotsikl. Soedin* **1965**, 349; *C.A.* **63**, 16333 (1965).