6-Aza-, 6-Oxa-and 6-Thia-4,5,6,7-Tetrahydrobenzimidazoles by Electrophilic Intramolecular Ring Closure of Imidazoles

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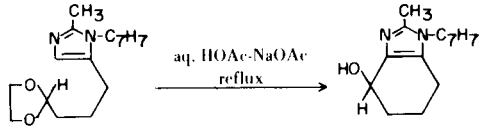
It is well known that imidazoles are quite unreactive towards electrophilic substitution under the common strongly acidic conditions usually required (1a,b). However, under mildly acidic conditions (aqueous sodium acetate-acetic acid buffer), a facile hydroxymethylation of 1,2-disubstituted imidazoles with formaldehyde could be achieved, leading to the corresponding 5-hydroxymethyl derivatives (2).

Recent work showed that under similar conditions benzimidazoles could be synthesized from imidazoles by intramolecular ring closure. An example was presented of the formation of a tetrahydrobenzimidazole (**10**) from the open-chain precursor (**9**) (3). In order to demonstrate the



9 **10**

C_7H_7 = benzyl

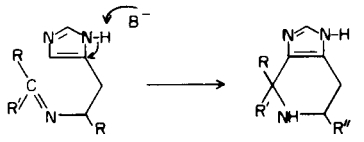
generality of this reaction, we now wish to report the synthesis of 6-oxa-, 6-thia- and 6-azatetrahydrobenzimidazoles (**2a-d**) by means of intramolecular electrophilic ring closure of functionalized imidazoles (**1a-d**).

1a-d **2a-d**

C_7H_7 = benzyl

a: X = O R = C_2H_5
b: X = N-CH_3 R = CH_3
c: X = N-C_7H_7 R = CH_3
d: X = S R = C_2H_5

At present only some 6-aza-4,5,6,7-tetrahydrobenzimidazoles (**12**) are known and have been obtained by base catalyzed cyclization of Schiff bases (**11**) derived from histamine and histidine (4a-e). Essential in this approach was the absence of any substituent at the imidazole nitrogen.

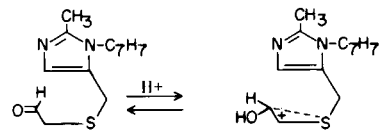


11 **12**

The preparation of the required substrates for cyclization (**1a-d**) is outlined in scheme I. The cyclizations were monitored with thin layer chromatography. On refluxing **1a** in an aqueous solution containing acetate buffer (*p*H $\sim$ 5) after about 7 hours starting material had disappeared. Together with a considerable amount of tarry material two products were formed. Work-up and chromatography showed one compound to be the desired cyclic ether **2a**, obtained in 28% yield. The other product proved to be alcohol **3**, which must undoubtedly be the result of ether cleavage.

Cyclization reactions of compounds **1b** and **1c** under identical conditions as for **1a** were also completed after seven hours.

In both cases relatively large amounts of tarry material were formed. Chromatography of the reaction products afforded 23% of **2b** from **1b** and 21% of **2c** from **1c**. The structures could be easily confirmed with nmr, ir and elemental analyses. On reacting **1d** in buffered solution reaction was completed after two hours and one single product had been formed. Chromatography over a short column afforded in 65% yield the cyclic thioether **2d**. The high rate and relative cleanliness of this reaction might be atrributed to anchimeric assistance of sulfur in stabilizing the intermediate carbonium ion in **13**. To the best of our knowledge such a pronounced effect has hitherto never been reported for a similar electrophilic substitution reaction.



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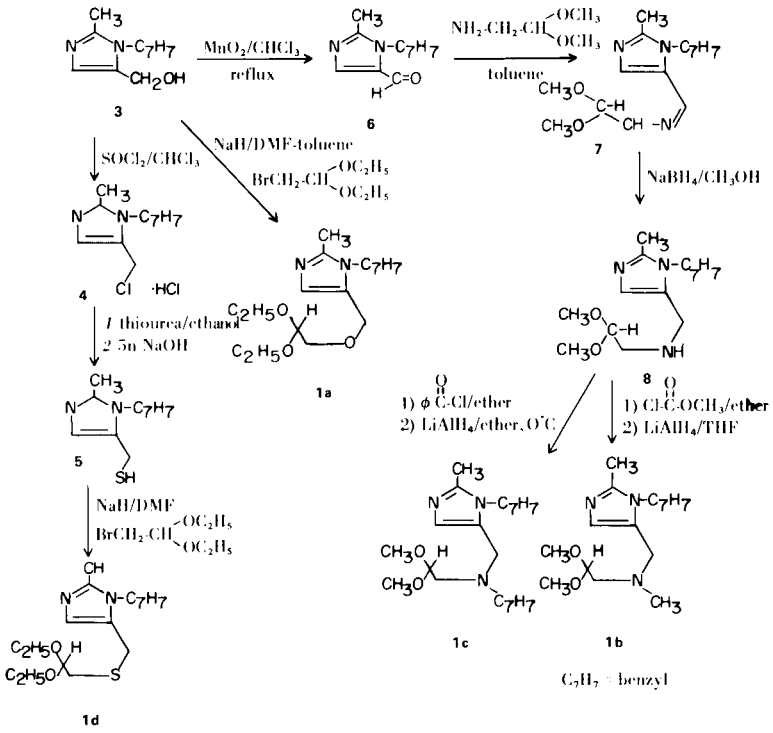
(SCHEME I)



EXPERIMENTAL

General.

Melting points were determined on a Mettler apparatus and are uncorrected. Nmr data were obtained with a Varian T-60A spectrometer (solutions in deuteriochloroform). Infrared spectra were recorded on a Perkin-Elmer 237. 1-Benzyl-2-methyl-5-hydroxymethylimidazole (**3**) was synthesized by a known method (2).

1-Benzyl-2-methylimidazole-5-carboxaldehyde (**6**).

A mixture of 70 g. (0.35 mole) of **3** and 200 g. of active manganese dioxide (5) in 400 ml. of chloroform was stirred under reflux for 4 hours. The residual oil, obtained after filtering of the reaction mixture over Celite and subsequent evaporation of the solvent, was distilled *in vacuo*, yield, 56.2 g. (81%), b.p. 124-128° (0.03); m.p. 51-52° (lit (2) 48-50°).

1-Benzyl-2-methyl-5-(2,2-dimethoxyethyliminomethyl)imidazole (**7**).

A solution of 40 g. (0.2 mole) of **6** and 21 g. (0.2 mole) of aminoacetaldehyde-dimethylacetal in 200 ml. of toluene was refluxed for 4 hours under continuous removal of water with a Dean-Stark trap. Evaporation of the solvent and subsequent distillation afforded 51.4 g. (90%) of **7**, b.p. 165-170° (0.04); nmr: δ 2.28 (s, 3, CH_3), 3.60 (d, 2, =N-CH_2-), 8.18 (s, 1, -N=C*H*-); ir (nujol): 1650 cm^{-1} ν(C=N).

Anal. Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found: C, 66.75; H, 7.37; N, 14.62.

1-Benzyl-2-methyl-5-(2,2-dimethoxyethylaminomethyl)imidazole (**8**).

To a solution of 72 g. (0.25 mole) of **7** in 700 ml. of methanol was added with stirring at room temperature 12.5 g. (0.63 mole) of sodium borohydride. The mixture was refluxed for 3 hours. The solvent was then removed, water was added and the product extracted with benzene. Distillation gave 57 g. (79%) of **8**, b.p. 185-195° (0.03); nmr: δ 2.32 (s, 3, CH_3), 3.70 (s, 2, -NH-CH_2-imidazole), 6.96 (s, 1, H-4 imidazole).

Anal. Calcd. for $C_{18}H_{27}N_3O_2$: C, 66.41; H, 8.01; N, 14.52. Found: C, 66.37; H, 8.06; N, 14.52.

1-Benzyl-2-methyl-5-*N*-(2,2-dimethoxyethyl)-*N*-methylaminomethylimidazole (**1b**).

To a solution of 20.2 g. (0.07 mole) of **8** and 7.7 g. (0.08 mole) of triethylamine in 100 ml. of ether was added at 0-5° a solution of 6.6 g. (0.07 mole) of methylchloroformate in 20 ml. of ether. After stirring for 1 hour the precipitate was filtered and the solvent removed. The residue consisted of nearly pure carbamate ester; nmr: δ 2.30 (s, 3, CH_3), 3.22 (s, 6, OCH_3), 3.50 (s, 3, $COOCH_3$), 7.00 (s, 1, H-4 imidazole). The crude oil was dissolved in 35 ml. of THF and added dropwise under reflux to a stirred suspension of lithium aluminohydride (5 g.) in 60 ml. of THF. After 2 hours the mixture was worked up in the usual manner and afforded 10.3 g. (49% of **1b**; b.p. 160-170° (0.02); nmr: δ 2.20 (s, 3, N-CH_3), 2.29 (s, 3, CH_3), 3.22 (s, 6, OCH_3), 5.31 (s, 2, CH_2-C_6H_5), 6.85 (s, 1, H-4 imidazole).

Anal. Calcd. for $C_{17}H_{25}N_3O_2 \cdot 2HCl$: C, 54.26; H, 7.23; N, 11.27. Found: C, 54.35; H, 7.26; N, 11.13.

1-Benzyl-2-methyl-5-(2,2-dimethoxyethyl,benzylaminomethyl)-imidazole (**1c**).

A solution of 25.3 g. (0.18 mole) of benzoyl chloride in 200 ml. of ether was added dropwise with stirring at 5-10° to a solution of 52 g. (0.18 mole) of **8** in 400 ml. of ether, containing 20.2 g. (0.2 mole) of triethylamine. After stirring for 2 hours at room temperature 630 ml. of 1*N* sodium hydroxide was added and the

product was extracted with benzene. Washing, drying and evaporation of the solvent afforded the benzoyl compound as an oil; nmr: δ 2.30 (s, 3, CH_3), 3.29 (s, 6, OCH_3), 4.77 (s, 2, N-$CH_2C_6H_5$), 7.08 (s, 1, H-4 imidazole); ir (nujol): 1700 cm^{-1} ν (C=O). Reduction of the crude oil with lithium aluminohydride in ether at 0° gave 38.2 g. (56%) of **1c** as an oil; nmr: δ 2.25 (s, 3, CH_3), 3.15 (s, 6, OCH_3), 3.53 (s, 2, -N-CH_2-imidazole), 3.61 (s, 2, CH_2-N-$CH_2C_6H_5$), 6.92 (s, 1, H-4 imidazole).

Anal. Calcd. for $C_{23}H_{29}N_3O_2 \cdot 2HCl$: C, 61.06; H, 6.91; N, 9.29. Found: C, 60.79; H, 6.93; N, 9.24.

1-Benzyl-2-methyl-5-(2,2-diethoxyethoxymethyl)imidazole (**1a**).

To a solution of 50 g. (0.25 mole) of **3** in 250 ml. of DMF was added 9 g. (*ca* 0.3 mole) of sodium hydride (80% dispersion in mineral oil). The mixture was stirred and heated at 60-80° until hydrogen evolution had ceased. Then 400 ml. of toluene was added and 65 g. (0.33 mole) of bromoacetaldehyde-diethylacetal and the mixture was refluxed for 24 hours. After that period 2 l. of water was added; the toluene layer was separated and the water phase was extracted twice with ether. The combined organic phases were washed, dried and evaporated. The residual oil was chromatographed (silica gel; chloroform-2% methanol as eluent) and distilled, yield 31.8 g. (40%) of **1a** as an oil; b.p. 170-175° (0.01); nmr: δ 2.32 (s, 3, CH_3), 4.45 (s, 2, -O-CH_2- imidazole), 5.25 (s, 2, -N-CH_2-C_6H_5), 7.02 (s, 1, H-4 imidazole).

Anal. Calcd. for $C_{16}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.63; H, 8.06; N, 8.60.

1-Benzyl-2-methyl-5-chloromethylimidazole Hydrochloride (**4**).

A solution of 13.1 g. (0.11 mole) of thionyl chloride was added with stirring at 10° to a solution of 20.2 g. of **3** in 100 ml. of chloroform. After one hour the solvent was removed and the residue was treated with 150 ml. of ether, thus affording 24 g. (93%) of **4**, m.p. (2-propanol) 182-183°.

Anal. Calcd. for $C_{12}H_{13}ClN_2 \cdot HCl$: C, 56.01; H, 5.48; N, 10.89. Found: C, 56.28; H, 5.66; N, 10.87.

1-Benzyl-2-methyl-5-mercaptomethylimidazole (**5**).

A mixture of 25.7 g. (0.1 mole) of **4** and 7.6 g. (0.1 mole) of thiourea in 150 ml. of ethanol was refluxed for 6 hours. Evaporation of the solvent left a viscous oil, which upon treatment with diisopropylether afforded 28.1 g. (85%) of essentially pure thiouronium salt, m.p. 198-202°.

Anal. Calcd. for $C_{13}H_{16}N_4S \cdot 2HCl$: C, 46.85; H, 5.41; N, 16.82. Found: C, 47.01; H, 5.42; N, 16.81.

The thiouronium salt was dissolved in 350 ml. of 5*N* sodium hydroxide and refluxed for 1 hour. The reaction mixture was then neutralized with acetic acid and extracted with chloroform. After washing, drying and evaporation of the solvent 16.4 g. (74%) of **5** left as an oil which rapidly decomposed on standing. The crude product was pure enough for the next step (more than 90% based upon nmr); nmr: δ 2.38 (s, 3, CH_3), 3.58 (s, 2, -S-CH_2-imidazole), 6.90 (s, 1-H-4 imidazole).

1-Benzyl-2-methyl-5-(2,2-diethoxyethylmercaptomethyl)imidazole (**1d**).

To a suspension of 2.4 g. (0.08 mole) of sodium hydride (80% dispersion in mineral oil) in 50 ml. of DMF was added with stirring a solution of 16.5 g. (0.076 mole) of **5** in 30 ml. of DMF. After hydrogen evolution had ceased stirring was prolonged for 1 hour. Then a solution of 16.7 g. (0.085 mole) of 2-bromoacetaldehyde-diethylacetal in 20 ml. of DMF was added dropwise at 30°. After stirring for additional 5 hours water (500 ml.) was added and the product was extracted with ether. Chromatography and subsequent distillation yielded 12.1 g. (48%) of **1d** as a viscous oil, b.p. 185-195° (0.02); nmr: δ 1.20 (t, 6, -OCH_2-CH_3), 2.33 (s, 3, CH_3), 3.70 (s, 2, -S-CH_2-imidazole).

Anal. Calcd. for $C_{18}H_{26}N_2O_2S$: C, 64.67; H, 7.78; N, 8.38. Found: C, 64.88; H, 7.77; N, 8.57.

1-Benzyl-2-methyl-4-hydroxy-6-thia-4,5,6,7-tetrahydrobenzimidazole (**2d**).

A mixture of 3.34 g. (0.01 mole) of **1d**, 12 g. of sodium acetate, 10 ml. of acetic acid and 40 ml. of water was refluxed for 2 hours. The solution was rendered basic with 3*N* sodium hydroxide and extracted with chloroform. Chromatographing the product (silica gel; chloroform-10% methanol as eluent, Rf 0.24) afforded 1.69 g. (65%) of **2d**, m.p. (toluene) 161-162°; nmr: δ 2.39 (s, 3, CH_3), 3.00 (m, 2, -S-CH_2-CHOH-), 3.40 (s, 2, -S-CH_2-imidazole), 5.45 (s, 1, *OH*); ir (potassium bromide): 3120 cm^{-1} ν (OH).

Anal. Calcd. for $C_{14}H_{16}N_2OS$: C, 64.58; H, 6.19; N, 10.76. Found: C, 64.31; H, 6.11; N, 10.50.

1,6-Dibenzyl-2-methyl-4-hydroxy-6-aza-4,5,6,7-tetrahydrobenzimidazole (**2c**).

A mixture of 3.79 g. (0.01 mole) of **1c**, 12 g. of sodium acetate, 10 ml. of acetic acid and 40 ml. of water was refluxed for 8 hours. The solution was neutralized with 3*N* sodium hydroxide and extracted with chloroform. After washing, drying and stripping off the solvent, the residual oil was chromatographed (silica gel; chloroform-10% methanol as eluent, Rf 0.15) and afforded 0.70 g. (21%) of **2c** as an oil; nmr: δ 2.33 (s, 3, CH_3), 2.92 (d, 2, -N-CH_2-CHOH-), 3.34 (d, 2, -N-CH_2-imidazole), 3.71 (s, 2, -N-CH_2-C_6H_5); m.p. (bis HCl-salt) 228-230° (2-propanol).

Anal. Calcd. for $C_{21}H_{23}N_3O \cdot 2HCl$: C, 62.07; H, 6.20; N, 10.34. Found: C, 61.60; H, 6.38; N, 10.77.

1-Benzyl-2,6-dimethyl-4-hydroxy-6-aza-4,5,6,7-tetrahydrobenzimidazole (**2b**).

A solution of 3.03 g. of **1b** (0.01 mole), 12 g. of sodium acetate and 10 ml. of acetic acid in 40 ml. of water was refluxed for 8 hours. The mixture was made basic with 3*N* sodium hydroxide and extracted with chloroform. The product obtained after washing, drying and stripping off the solvent, was chromatographed over silica gel (chloroform-10% methanol as eluent, Rf 0.11) and gave 0.59 g. (32%) of pure **2b**, m.p. (dioxane-diisopropylether) 152-153°; nmr: δ 2.32 (s, 3, CH_3), 2.45 (s, 3, CH_3), 2.80 (m, 2, NCH_2-CHOH), 3.28 (d, 2, -N-CH_2-imidazole), 4.30 (s, 1, OH), 4.80 (t, 1, *CH*OH).

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.90; H, 7.44; N, 16.27.

1-Benzyl-2-methyl-4-hydroxy-6-oxa-4,5,6,7-tetrahydrobenzimidazole (**2a**).

A solution of 2.94 g. (0.01 mole) of **1a**, 12 g. of sodium acetate and 10 ml. of acetic acid in 40 ml. of water was refluxed for 8 hours. After cooling, the reaction mixture was brought to *p*H 8 with 3*N* sodium hydroxide and extracted with chloroform. Washing, drying and evaporation of the solvent left an oil which upon chromatographing over silica gel (chloroform-10% methanol as eluent, Rf 0.20) yielded 0.68 g. (28%) of **2a**, m.p. (toluene) 153-154°; nmr: δ 2.38 (s, 3, CH_3), 3.95 (q, 2, -O-CH_2-CHOH), 4.48 (d, 2, -O-CH_2-imidazole), 4.78 (t, 1, *CH*OH), 4.93 (s, 2, -N-CH_2-C_6H_5), 5.32 (s, 1, *OH*).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.76; H, 6.54; N, 11.42.

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