Preparation of *N*-(4,5-Dihydroimidazol-2-yl)azoles by Aliphatic Aldehyde Assisted Reactions of 2-Chloro-4,5-dihydroimidazole with Various Azoles

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Reaction of hemiaminals, formed by reaction of various azoles with aliphatic aldehydes, with 2-chloro-4,5-dihydroimidazole gave the title compounds as their hydrochloride salts in good yield.

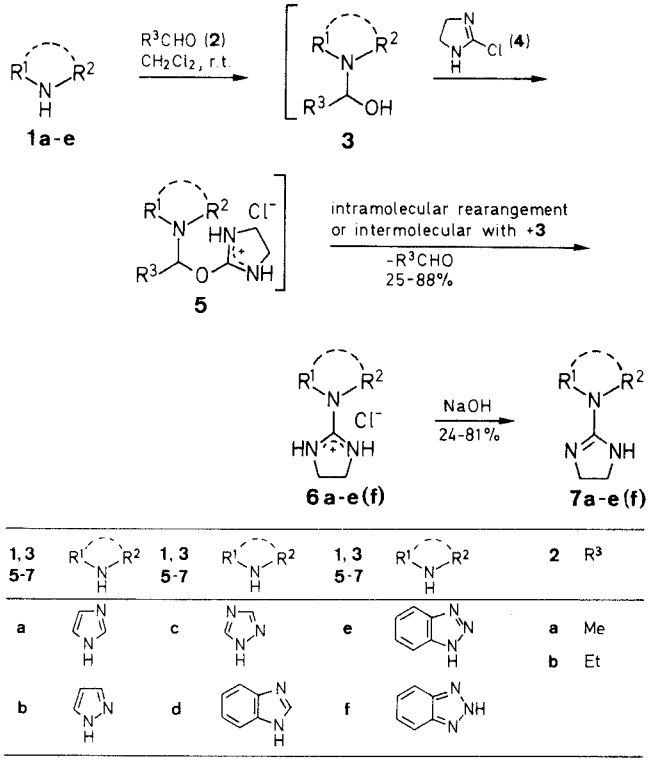
2-Chloro-4,5-dihydroimidazole (**4**) was synthesized in 1974, and since then has been successfully utilized for the incorporation of the 2-imidazoline moiety into various molecules with potential biological activity, by the nucleophilic displacement of the chlorine atom with amines, phenols, and thiophenols.[2-10] With heteroaromatic amines such as pyridine or isoquinoline, compound **4** yields polycyclic 1,3,5-triazines.[11,12]

Recently, our interest has focused on the reactions of **4** with a variety of azoles of diverse acidity and basicity. However, reactions attempted with imidazole, pyrazole or triazole using standard methods (i.e. reactions with parent heterocycles or their sodium salts) failed. The azole nitrogen atoms apparently do not induce electrophilic attack by the compound **4** under mild conditions. At elevated temperatures, the chloro derivative **4**, which possesses both an electrophilic carbon at C–2 and a nucleophilic nitrogen at N–3, undergoes self-condensation.

The solution to this problem has come from another area of our interest, namely, the chemistry of hemiaminals.[13,14] We have found that the unstable hemiaminals **3**, obtained *in situ* from azoles **1** and aliphatic aldehydes **2**, react readily with 2-chloro-4,5-dihydroimidazole (**4**), to give the desired products **6**, in high yield (Scheme **A**).

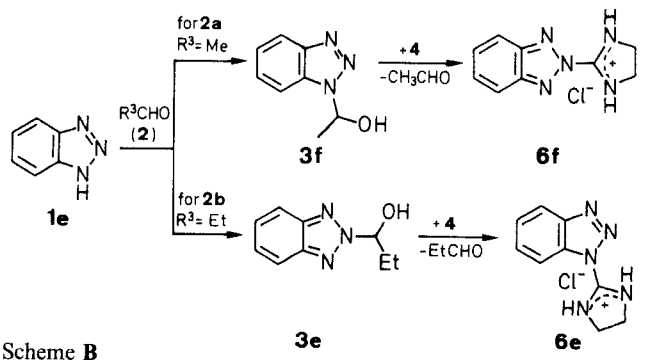
Apparently, the hemiaminals **3** possess a hydroxyl group, which is sufficiently nucleophilic to displace chloride from **4**. The intermediates **5** thus formed undergo an intra- or intermolecular rearrangement leading to **6** with simultaneous extrusion of the aldehyde. In the cases of triazole, benzotriazole, or pyrazole, intramolecular attack by the lone pair of the adjacent pyridine-like nitrogen at the carbon C–2 of the isoureide moiety in **5** is feasible. However, analogous reactions with imidazole and benzimidazole hemiaminals suggest that nucleophilic attack by the nitrogen lone pair may also proceed in an intermolecular process.

The reaction of **4** with benzotriazole adducts of aldehydes afforded a mixture of benzotriazol-1-yl **6e** and benzotriazol-2-yl **6f** isomers. The ratio of the isomers depends strongly on the concentration and ratio of the substrates and the nature of the aldehyde reactant. Acetaldehyde, for example, gave predominantly the 2-substituted benzotriazole product **6f**, while propionaldehyde apparently favors formation of the benzotriazol-1-yl isomer **6e**. The extreme instability of 2-chloro-4,5-dihydroimidazole (**4**) led to difficulties in reproducing the results. However, from the reactions carried out in the presence of acetaldehyde, we were able to isolate 85% of



Scheme **A**

pure 2-isomer **6f** (average of 3 experiments). From the reactions run in the presence of propionaldehyde, 25% of pure 1-isomer **6e** was separated (average of 3 experiments). A possible explanation for the selective formation of the isomeric products **6e** and **6f** is that acetaldehyde preferentially resides at position 1 of the benzotriazole moiety in hemiaminal **3f**, which then reacts *via* **5** to give benzotriazol-2-yl isomer **6f**. In the case of propionaldehyde, steric factors limit the attack at the position 1 of benzotriazole, and isomeric hemiacetal **3e** predominates over isomer **3f** as a substrate for the reaction with **4**. One may conclude, that increased bulk of R in benzotriazole intermediate of type **3** results in decreased amount of benzotriazol-1-yl hemiacetal **3f** due to *peri*-interactions (i.e. buttressing between benzotriazole H–7 and the hydroxyalkyl substituent, Scheme **B**).



Scheme **B**

Table. Azole Hydrochlorides **6** and Azoles **7** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	^{13}C-NMR ($CDCl_3$)[b]
6a	88	171–173	$C_6H_9ClN_4$ (172.6)	4.25 (s, 4H, CH_2CH_2), 4.95 (s, 2H, NH), 7.4, 7.75, 8.25 (3s, 1H each, $H_{imidazolyl}$)	46.46, 120.70, 133.39, 139.94, 156.10
6b	71	250–252	$C_6H_9ClN_4$ (172.6)	4.3 (s, 4H, CH_2CH_2), 4.95 (s, 2H, NH), 6.9 (dd, 1H, H-4$_{pyrazolyl}$), 8.2 (d, 1H$_{pyrazolyl}$), 8.4 (d, 1H$_{pyrazolyl}$)	46.43, 114.75, 134.06, 149.94, 157.03
6c[c]	85	169–174	$C_5H_8ClN_5$ (173.6)	4.3 (s, 4H, CH_2CH_2), 4.95 (s, 2H, NH), 8.5, 9.3 (2s, 1H each, $H_{triazolyl}$)	46.71, 145.44, 148.86, 156.66
6d	80	181–183	$C_{10}H_{11}ClN_4$ (222.7)	4.3 (s, 4H, CH_2CH_2), 4.9 (s, 2H, NH), 7.6 (m, 2H$_{arom}$), 7.7, 7.8 (2m, 1H each, H_{arom}), 8.55 (s, 1H, H-2)	46.21, 114.77, 122.62, 128.41, 128.93, 132.03, 143.95, 144.35, 155.90
6e	25	201–205 (dec)	$C_9H_{10}ClN_5$ (223.7)	4.4 (s, 4H, CH_2CH_2), 4.95 (s, 2H, NH), 7.8 (m, 1H), 7.95 (m, 2H), 8.25 (d, 1H)	46.68, 113.26, 123.21, 129.61, 132.38, 134.43, 147.83, 155.49
6f	85	195–198 (dec)	$C_9H_{10}ClN_5$ (223.7)	4.35 (s, 4H, CH_2CH_2), 4.95 (s, 2H, NH), 7.7, 7.9 (2m, 2H each, H_{arom})	46.92, 121.14, 134.18, 146.69, 156.24
7a	78	–[a]	$C_6H_8N_4$ (136.2)	3.8 (s, 4H, CH_2CH_2), 4.95 (s, 1H, NH), 7.2, 7.5, 8.15 (3s, 1H each, $H_{imidazolyl}$)	50.45, 119.95, 131.46, 138.61, 157.19
7b	70	150–152 (H_2O)	$C_6H_8N_4$ (136.2)	3.65 (m, 2H, CH_2), 3.95 (m, 2H, CH_2), 5.9 (s, 1H, NH), 6.4, 7.6, 8.25 (3s, 1H each, $H_{pyrazolyl}$)	44.91, 53.41, 108.19, 128.54, 141.80, 155.82
7c	66	178–179 (EtOH)	$C_5H_7N_5$ (137.2)	3.7 (m, 2H, CH_2), 4.0 (m, 2H, CH_2), 5.7 (s, 1H, NH), 7.95, 8.85 (2s, 1H each, $H_{triazolyl}$)	44.76, 53.75, 142.82, 152.30, 153.35
7d	77	128–130 (H_2O)	$C_{10}H_{10}N_4$ (186.2)	3.6 (m, 2H, CH_2), 4.0 (m, 2H, CH_2), 6.95 (s, 1H, NH), 7.3 (m, 2H$_{arom}$), 7.75, 8.2 (2m, 1H each, H_{arom}), 8.5 (s, 1H, H-2)	43.25, 52.77, 113.68, 118.85, 122.55, 123.36, 131.04, 140.54, 142.64, 153.53
7e[d]	24	119–121 (H_2O)	$C_9H_9N_5$ (187.2)	3.75 (m, 2H, CH_2), 4.15 (m, 2H, CH_2), 5.95 (s, 1H, NH), 7.15 (dd, 1H), 7.6 (dd, 1H), 8.1 (d, 1H, J = 7.4), 8.35 (d, 1H, J = 7.4)	44.50, 54.10, 113.86, 119.81, 125.33, 129.47, 131.41, 146.11, 154.43
7f	81	109–111[e]	$C_9H_9N_5$ (187.2)	4.0 (s, 4H, CH_2CH_2), 5.8 (s, 1H, NH), 7.4, 7.85 (2m, 2H each, H-4-7)	49.93, 118.69, 128.36, 144.81, 155.57

[a] The hydrochlorides were hygroscopic and the compounds were analysed as free bases; exceptionally the free base **7a** was more hygroscopic than the corresponding hydrochloride **6a**, and so in this case the hydrochloride was analysed. Satisfactory microanalyses (for compounds **6a** and **7b–f**) were obtained: C ±0.33, H ±0.05.

[b] Chemical shifts are referenced to $CDCl_3$, δ = 77.0.

[c] An amount of 5% of 4-(4,5-dihydroimidazol-2-yl)triazole hydrochloride was found in the crude product: ^{1}H-NMR ($CDCl_3$/TMS): δ = 4.3 (s, 4H), 4.95 (s, 2H), 9.05 (s, 2H). ^{13}C-NMR ($CDCl_3$): δ = 46.82, 143.98, 155.06.

[d] MS: m/z (%) = 187 (M^+, 27), 159 (100), 158 (43), 131 (75), 117 (16), 104 (34), 91 (39).

[e] Attempts at recrystallization led to formation of the isomeric compound **7e**.

The hydrochlorides **6a–f**, on treatment with sodium hydroxide, were converted into free bases **7a–f**. Free base **7f** proved to be rather unstable and decomposed to 1*H*-benzotriazole and 2-oxo-4,5-dihydroimidazole on attempted purification by column chromatography on silica gel. We also found that compound **7f**, heated in aqueous solution, isomerized to the thermodynamically more stable benzotriazol-1-yl derivative **7e**.

The reaction of **4** with 1,2,4-triazole **1c** in the presence of propionaldehyde gave product **6c**, which according to the ^{1}H- and ^{13}C-NMR spectra, consisted of 15:1 mixture of the 1- and 4-substituted triazole isomers, respectively. Treatment of the salt **6c** with sodium hydroxide, and recrystallization of the free base thus obtained, afforded the pure 1-isomer **7c** (Table).

The ^{1}H-NMR spectrum of pyrazole **7b** revealed the presence of two separate multiplets at δ = 3.65 and 3.95 corresponding to the protons of the CH_2CH_2 group of the imidazoline moiety. Two signals at δ = 44.91 and 53.41 for this dimethylene group were also observed in the ^{13}C-NMR spectrum. This indicates that the rotation around the C_2–N bond linking the heterocycles is hindered, probably due to intramolecular N-1′-H hydrogen bonding to N-2.

Melting points were determined with a Kofler hot stage apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were obtained on a Varian XL 300 spectrometer. All azoles used are available commercially.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)azole Hydrochlorides 6a–d; General Procedure:

A solution of 2-chloro-4,5-dihydroimidazole (**4**; 2.5 g, 0.025 mol) and the appropriate azole **1a–d** (0.025 mol) in CH_2Cl_2 (30 mL) is treated with propionaldehyde (1.45 g, 0.025 mol), and the mixture is stirred vigorously at r.t. for 1 h. The precipitate is separated by suction, washed with CH_2Cl_2 and dried over P_2O_5 (Table).

1-(4,5-Dihydro-1*H*-imidazol-2-yl)benzotriazole Hydrochloride (6e):

To a solution of **4** (2.5 g, 0.025 mol) and 1*H*-benzotriazole (**1e**; 3.0 g, 0.025 mol) in CH_2Cl_2 (50 mL) is added propionaldehyde (1.45 g, 0.025 mol), and the mixture is stirred at r.t. for 5 min. The precipitate is collected by suction, washed with CH_2Cl_2 and dried over P_2O_5 to give **6e**; yield: 1.5 g (25%).

The filtrate is treated with Et_2O (50 mL) and stirred for 0.5 h to give 3.5 g of a product which, according to ^{1}H-NMR, consists of equimolar amounts of **6e** and **6f**.

2-(4,5-Dihydro-1*H*-imidazol-2-yl)benzotriazole Hydrochloride (6f):
Acetaldehyde (1.1 g, 0.025 mol) is added to a solution of **4** (2.5 g, 0.025 mol) and benzotriazole **1e** (3.0 g, 0.025 mol) in CH_2Cl_2 (25 mL), and the mixture is stirred vigorously at r.t. for 5 min. The precipitate is separated by suction, washed with CH_2Cl_2 and dried over P_2O_5 to afford **6f**; yield: 4.7 g (85%).

***N*-(4,5-Dihydroimidazol-2-yl)azoles 7a–f:**
Compounds **7b** and **7d–f** are obtained by treatment of the appropriate hydrochloride **6** with an equimolar amount of cold aq 5% NaOH.

Derivative **7a**, which is extremely hygroscopic, and **7c** are obtained as follows:

The corresponding hydrochloride **6a** and **c**, respectively, is dissolved in abs EtOH and neutralized with an equivalent amount of NaOH. The solvent is evaporated under reduced pressure, and the solid residue is extracted with acetone. Evaporation of the solvent gives the desired free base, which is dried over KOH.

Isomerization of 2-(4,5-Dihydro-1*H*-imidazol-2-yl)benzotriazole (7f) to 1-(4,5-Dihydro-1*H*-imidazol-2-yl)benzotriazole (7e):
A suspension of benzotriazol-2-yl derivative **7f** (0.3 g, 1.6 mmol) in water (10 mL) is refluxed for 10 min. After cooling to r.t. the precipitate is collected by suction to give **7e**; yield: 0.21 g (70%).

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