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SIMPLE SYNTHESIS OF IMIDAZO[1,2-*a*]PYRAZINES

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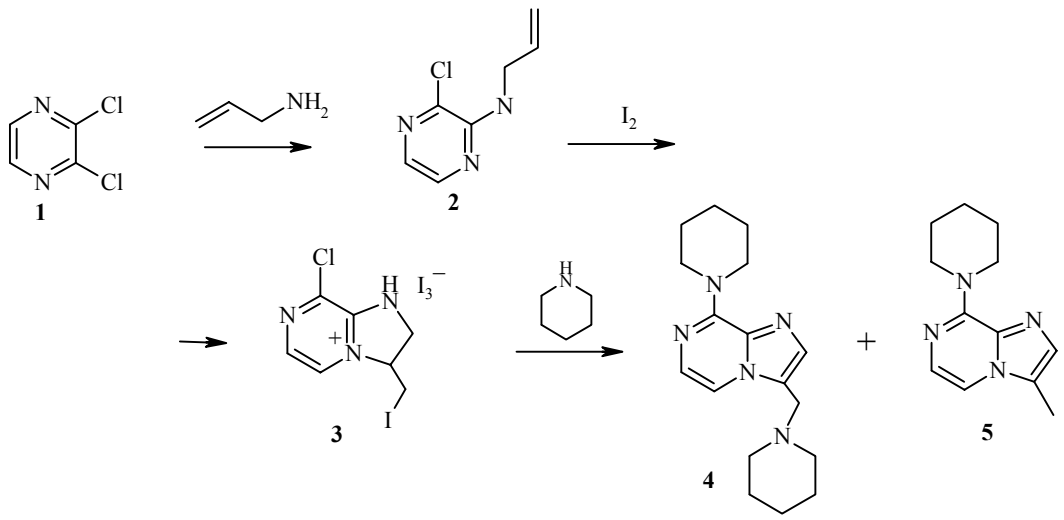
Imidazo[1,2-*a*]pyrazines are the part of luciferins (natural products responsible for bioluminescence) and display antiulcer, antibacterial, and anti-inflammatory activity [1-3]. Meurer et al. [4] have described a synthesis of substituted 2,3-dihydroimidazo[1,2-*a*]pyrazines by the action of thionyl chloride on N-(β-hydroxyethyl)pyrazines. We have carried out the cyclization of 2-allylamino-3-chloropyrazine (**2**), obtained by the reaction of 2,3-dichloropyrazine (**1**) with allylamine, by the action of iodine in diethyl ether solution. The resultant 8-chloro-3-iodomethyl-2,3-dihydro-1H-imidazo[1,2-*a*]pyrazinium triiodide (**3**) reacts with piperidine to give substitution of the halogen atoms and aromatization of the imidazoline system, leading to a mixture of 8-(1-piperidinyl)-3-(1-piperidinyl)methylimidazo[1,2-*a*]pyrazine (**4**) and 3-methyl-8-(1-piperidinyl)imidazo[1,2-*a*]pyrazine (**5**). Pyrazine **4** is probably formed through oxidation of the imidazoline fragment by the triiodide ion, while 3-methyl-8-(1-piperidinyl)imidazo[1,2-*a*]pyrazine **5** is formed due to elimination of HI and a proton shift.

The ^{1}H NMR spectrum of triiodide **3** shows a downfield shift for the pyrazine ring protons by 0.30-0.45 ppm relative to the spectrum of starting pyrazine **2**, resulting from the presence of a quaternary nitrogen atom.

The procedure for obtaining 2,3-dihydro-1H-imidazoazine salts by the cyclization of 2-allylamino derivatives of azines by action of halogens is rather common [5]. In the present work, this reaction was extended



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for the first time for pyrazine derivatives. In contrast to N-alkyl-2,3-dichloropyrazinium salts obtained through direct quaternization of dichloropyrazine **2** by the action of the strong Meerwein reagent [6], the intramolecular formation of the quaternary 8-chloro-3-iodomethyl-2,3-dihydro-1H-imidazo[1,2-*a*]pyrazinium salt proceeds smoothly under mild conditions with high yield.

2-Allylamino-3-chloropyrazine (2). A mixture of 2,3-dichloropyrazine (0.2 g, 1.34 mmol) in allylamine (3 ml) was heated at reflux for 2 h. Excess allylamine was distilled off. Then, silica gel (0.5 g) was added to the residue and stirred. The mixture obtained was extracted with three 10-ml ether portions. Evaporation of the ethereal extract gave 0.115 g (51%) **2** as a light yellow liquid. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 4.13 (2H, d, NCH_2); 5.15 (2H, m, $=CH_2$); 5.98 (1H, m, CH=); 7.58 (1H, d, *J* = 3.7, 6-H); 7.95 (1H, d, *J* = 3.7, 5-H). Found, %: C 49.74; H 4.79; N 24.90. $C_7H_8ClN_2$. Calculated, %: C 49.55; H 4.75; N 24.77.

8-Chloro-3-iodomethyl-2,3-dihydro-1H-imidazo[1,2-*a*]pyrazinium Triiodide (3). A solution of **2** (0.077 g, 0.5 mmol) in ether (3 ml) was added to a solution of iodine (0.254 g, 1 mmol) in diethyl ether (5 ml) and stirred for 12 h at room temperature. The precipitate was filtered off and washed with ether to give 0.232 g (70%) of **3**; mp 76°C (dec.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 3.81 (2H, m, CH_2I); 3.81 (1H, m, CH_2N); 4.24 (1H, dd, ^2J = 5.9, NCH_2); 5.33 (1H, m, 3-H); 7.88 (1H, d, *J* = 4.1, 6-H); 8.40 (1H, d, *J* = 4.1, 5-H); 10.3 (1H, br. s, NH). Found, %: C 12.28; H 1.01; N 6.11. $C_7H_8ClI_4N_2$. Calculated, %: C 12.41; H 1.19; N 6.20.

Reaction of 8-Chloro-3-iodomethyl-2,3-dihydro-1H-imidazo[1,2-*a*]pyrazinium Triiodide (3) with Piperidine. A sample of **3** (0.350 g, 0.52 mmol) was dissolved in piperidine (3 ml) (decoloration) with stirring and heated at reflux for 1 h. Piperidine was distilled off and the residue was treated with toluene (5 ml). The piperidine hydroiodide precipitate was filtered off. The filtrate was eluted on silica gel with 1:2 ethyl acetate–hexane as the eluent to separate **4** and **5**.

8-(1-Piperidinyl)-3-(1-piperidinyl)methylimidazo[1,2-*a*]pyrazine (4). R_f ~0.3. The yield of **4** as a yellow oil was 33 mg (22%). Mass spectrum, *m/z* (*I*, %): 299 [M^+] (10.4), 216 (100.0), 173 (3.9), 149 (5.2), 133 (8.9), 132 (8.3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.42 (2H, m, $CH_2C\underline{H}_2CH_2$); 1.53 (4H, m, $NCH_2C\underline{H}_2$); 1.72 (6H, br. s, $CH_2CH_2CH_2$); 2.35 (4H, m, $C\underline{H}_2N(CH_2)C\underline{H}_2$); 3.67 (2H, s, $CH_2C_{(3)}$); 4.18 (4H, br. s, CH_2NCH_2); 7.36 (1H, d, *J* = 4.5) and 7.70 (1H, d, *J* = 4.5, 5- and 6-H); 7.38 (1H, s, 2-H).

3-Methyl-8-(1-piperidinyl)imidazo[1,2-*a*]pyrazine (5). R_f ~0.7. The yield of **5** as a yellow oil was 18 mg (16%). Mass spectrum, *m/z* (*I*, %): 216 [M^+] (100.0), 187 (31.4), 173 (47.0), 160 (45.2), 148 (37.34), 133 (52.9), 132 (40.0), 113 (10.2), 84 (50.8). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.72 (6H, br. s, $CH_2CH_2CH_2$); 2.40 (3H, d, *J* = 0.6, CH_3); 4.20 (4H, br. s, CH_2NCH_2); 7.22 (1H, d, *J* = 4.5) and 7.39 (1H, d, *J* = 4.5, 5- and 6-H); 7.31 (1H, s, 2-H).

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