Synthesis of Mesoionic Anhydro-3-mercapto-1-methyl-8-oxo-7,8-dihydro-1,2,4-triazolo[4,3-*a*]pyrazine-1-ium Hydroxide

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As part of an investigation on the synthesis of cephalosporin antibiotics,[1,2] we needed various heterocyclic thiols, in particular, of bridgehead-nitrogen heterocycles containing the 1,2,4-triazole moiety, and we recently reported[3,4] the novel synthesis of 8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazines **2** based upon the simple annulation of the pyrazinone ring onto the triazole ring precursor **1**.

Another method reported[5,6] for the preparation of these ring systems is based on the annulation of the triazole ring onto 2,3(1*H*,4*H*)-pyrazinedione **3** precursor. This method is based upon the reaction of 3-chloro-2(1*H*)-pyrazinone[7] **4** with hydrazine to give the 3-hydrazinopyrazinone, further treatment with carbon disulfide under basic conditions to give the corresponding 8-oxo-3-thioxo-2,3,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazines **2**.

We herein report a synthesis of new mesoionic, anhydro-3-mercapto-1-methyl-8-oxo-7,8-dihydro-1,2,4-triazolo[4,3-*a*]pyrazine-1-ium hydroxide **6** by using the latter methodology (Scheme 1). While a great number of monocyclic mesoionic compounds are known,[8] congeners containing fused rings are much less common.[9]

The reaction of 3-chloro-2(1*H*)-pyrazinone **4** with methylhydrazine was carried out in dioxane at room temperature and gave a regioselective product, 3-(1-methylhydrazino-2(1*H*)-pyrazinone **5** in good yield. Treatment of **5** with carbon disulfide in the presence of potassium hydroxide in ethanol at reflux temperature for 2 h afforded a mesoionic, anhydro-3-mercapto-1-methyl-8-oxo-7,8-dihydro-1,2,4-triazolo[4,3-*a*]pyrazine-1-ium hydroxide **6**.

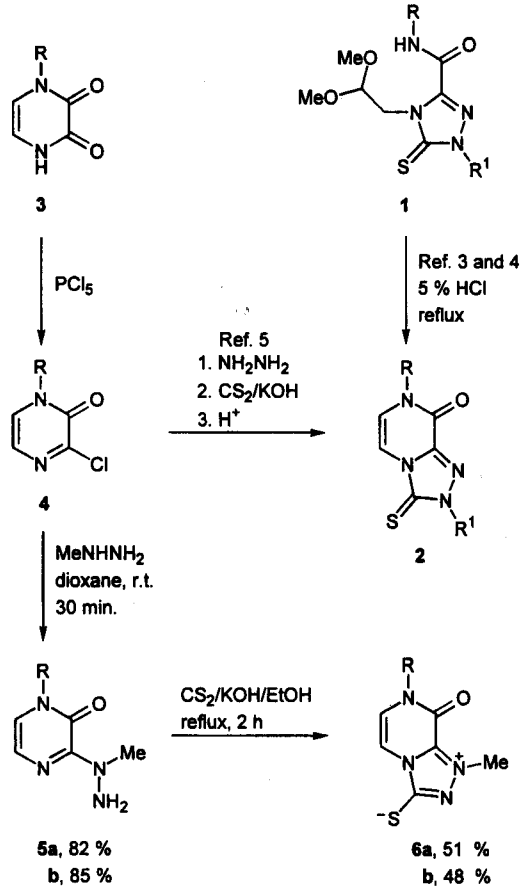
The structural elucidation of compounds **6** was accomplished on the basis of spectral data. Compounds **6** showed in the IR spectral absorption due to the C=O stretching at 1687 cm^{-1}, together with the characteristic absorption of the C=N bond at 1640-1641 cm^{-1}. Mass spectra showed the molecular ion peak as a base peak. The characteristic ^1H NMR absorptions of the *N*-methyl protons at deshielded region δ 4.48-4.51 were indication that mesoionic compounds had made.[9d]

Experimental Section

All reagents were of commercial quality from freshly opened containers. Reagent quality solvents were used without further purification. Analytical TLC plates and silica gel (230-400 mesh) were purchased from EM Reagents. Melting points were taken using a Electrothermal melting point apparatus and are uncorrected. Mass spectra were obtained using a Hewlett Packard model 5985 B spectrometer. IR spectra were recorded on a Analect FX 6160 Infrared spectrophotometer. The NMR spectra were measured on a Varian Gemini 300 spectrometer.

3-Chloro-1-methyl-2(1*H*)-pyrazinone (**4a**) and 3-chloro-1-ethyl-2(1*H*)-pyrazinone (**4b**) were prepared following the literature procedure.[7]

1-Methyl-3-(1-methylhydrazino)-2(1*H*)-pyrazinone (5a). To a stirred solution of 3-chloro-1-methyl-2(1*H*)-pyrazinone (**4a**; 3.56 g, 24.5 mmol) in dioxane (30 mL) was added methylhydrazine (4.61 g, 98 mmol) in a dropwise manner at room temperature. After stirring for 30 min at r.t., the mixture was neutralized with potassium carbonate (5.0 g, 36.1 mmol). Dichloromethane (50 mL) was then added and the mixture was dried ($MgSO_4$) and the or-



4, 5, 6	R
a	Me
b	Et

Scheme 1.

ganic phase was separated by suction, concentrated to dryness under reduced pressure. The residual crystalline solid was separated by filtration using petroleum ether to give **5a**; yield 3.08 g (82%); mp 116-118 °C; ^{1}H NMR ($CDCl_3$) δ 3.47 (s, 3H, CH_3NN), 3.50 (s, 3H, CH_3N), 4.70 (br s, 2H, NH_2), 6.62 (d, 1H, *J*=4.6 Hz, CH), 6.94 (d, 1H, *J*=4.6 Hz, CH).

1-Ethyl-3-(1-methylhydrazino)-2(1*H*)-pyrazinone (5b). With the same procedure for the preparation of **5a**, compound **5b** was obtained by the treatment of 3-chloro-1-ethyl-2(1*H*)-pyrazinone (**4b**; 3.88 g, 24.5 mmol) with methylhydrazine (4.61 g, 98 mmol): yield 3.52 g (85%); mp 45-46 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, 3H, *J*=7.0 Hz, $CH_2\underline{CH_3}$), 3.45 (s, 3H, CH_3NN), 3.87 (q, 2H, *J*=7.0 Hz, $\underline{CH_2}CH_3$), 4.70 (br s, 2H, NH_2), 6.55 (d, 1H, *J*=4.6 Hz, CH), 6.90 (d, 1H, *J*=4.6 Hz, CH).

Anhydro-3-mercapto-1,7-dimethyl-8-oxo-7,8-dihydro-1,2,4-triazolo[4,3-*a*]-pyrazin-1-ium hydroxide (6a). To a stirred solution of 1-methylhydrazinopyrazinone (**5a**; 0.98 g, 6.35 mmol) in ethanol (30 mL) were added dropwise carbon disulfide (1.15 mL, 19.0 mmol) and 20 mL of ethanolic potassium hydroxide solution (0.53 g, 8.30 mmol) at room temperature. The mixture was heated at reflux temperature for 2 h. After cooling, the precipitated solid, which was gradually separated during the reaction, was filtered off, washed with ethanol (5 mL), ether (10 mL) and dried *in vacuo* to give a mesoionic compound **6a** as a pale yellow solid; yield 0.63 g (51%); mp 274 °C (decomp.); MS (70 eV) m/z 196 (M^+, 100), 128 (30), 96 (28), 64 (45); IR (KBr) 1687, 1640, 1579, 1494, 1428, 1397, 1363, 1244, 1165, 986 cm $^{-1}$; ^{1}H NMR ($CDCl_3$+ CF_3COOH) δ 3.65 (s, 3H, CH_3N), 4.48 (s, 3H, CH_3N^+), 7.20 (d, 1H, *J*=6.0 Hz, CH), 7.54 (d, 1H, *J*=6.0 Hz, CH).

Anhydro-3-mercapto-7-ethyl-1-methyl-8-oxo-7,8-dihydro-1,2,4-triazolo[4,3-*a*]-pyrazin-1-ium hydroxide (6b). With the same procedure for the preparation of **6a**, compound **6b** was obtained by the treatment of 1-methylhydrazinopyrazinone (**5b**; 1.07 g, 6.35 mmol) with carbon disulfide (1.15 mL, 19.0 mmol) and 20 mL of ethanolic potassium hydroxide solution (0.53 g, 8.30 mmol): **6b**; yield 0.64 g (48%); mp 259-260 °C (decomp.); MS (70 eV) m/z 210 (M^+, 100), 152 (83), 124 (79), 123 (23), 96 (54), 69 (49), 68 (42); IR (KBr) 1687, 1641, 1575, 1493, 1444, 1378, 1341, 1238, 1161, 999 cm $^{-1}$; ^{1}H NMR ($CDCl_3$+ CF_3COOH) δ 1.42 (t, 3H, *J*=7.2 Hz, $CH_2\underline{CH_3}$), 4.12 (q, 2H, *J*=7.2 Hz, $\underline{CH_2}CH_3$), 4.51 (s, 3H, CH_3N^+), 7.20 (d, 1H, *J*=6.0 Hz, CH), 7.56 (d, 1H, *J*=6.0 Hz, CH).

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