Pyridazines, LXXXVI

Some Mesoionic Mercaptoazolopyridazines

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Mercapto Anhydro Salts, Imidazo(1,2-b)pyridazines, s-Triazolo(4,3-b)pyridazines, Demethylation, Ring Opening

6-Mercapto anhydro salts of imidazo(1,2-b)- (**2**) and s-triazolo(4,3-b)pyridazines (**7**) were prepared and investigated. They were transformed into the corresponding 6-methylthio derivatives (**3** or **8**). Compounds of the type **3** are thermally demethylated into **4**, but in the case of the 2-unsubstituted compound (**3**, R = H) also ring opening occurred to give compound **5** as minor product.

The chemistry of mesoionic compounds has received increasing attention in the last years. We have recently described the first examples of mesoionic compounds in the imidazo(1,2-b)- and s-triazolo(4,3-b)pyridazine series^{1–3}. In all these cases the 6-hydroxy anhydro salts were prepared and investigated. Therefore, it seemed worthwhile to extend our investigations to the corresponding sulfur analogs, *i.e.* the mercapto anhydro salts of the above mentioned azoloazines.

As starting material 6-chloro-1-methylazolopyridazinium salts (**1** or **6**) were employed. These compounds reacted with an alcoholic solution of potassium hydrosulfide to afford the corresponding mercapto anhydro salts (**2** or **7**). These compounds are stable in hot solutions of organic solvents and are transformed with methyl iodide into the corresponding 6-methylthio-1-methylazolopyridazinium iodides (**3** or **8**). It should be mentioned that conversion of **2** into **3** required elevated temperature

and was performed under pressure. The recorded mass spectra of compounds **3** revealed an intense peak, corresponding to $m/e = M^+ - 142$, what accounts for loss of methyl iodide. This indicates that either at higher temperatures and/or under electron impact methyl iodide is split off. That this elimination takes place thermally was established in separate experiments. In this manner, 2-phenyl-1-methyl-6-methylthioimidazo(1,2-b)pyridazinium iodide (**3**, R = Ph), when sublimed at 200 °C, was transformed into **4** (R = Ph). We have also attempted to prepare the last mentioned compound from the so far unknown 2-phenylimidazo(1,2-b)pyridazine-6(5H)thione⁴ and to examine further the quaternization reactions. However, several attempts to prepare this bicyclic thione either from the corresponding 6-oxo or 6-chloro analog failed.

A similar sequence of reactions could be performed with 6-chloro-1-methylimidazo(1,2-b)pyridazinium iodide (**1**, R = H) which was transformed into **2** (R = H) and further into **3** (R = H). The later compound, when heated in vacuo at 180–190 °C, has split off methyl iodide similarly as the phenyl analog, but in addition to the compound **4** (R = H) a ring cleaved product **5** was isolated and identified. This imidazole derivative exists in the *cis*-form as evidenced from NMR and was obtained in about 15% yield. Similar ring openings of the pyridazine part of at position 6 unsubstituted azolopyridazines or at position 5 unsubstituted azolopyridines have been observed previously and take place under the influence of different nucleophiles^{5–10}.

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The reaction sequence, as outlined above, could be applied also to 3-phenyl-6-chloro-1-methyl-s-triazolo(4,3-b)pyridazinium iodide (6) which afforded the mercapto anhydro salt (7, R = Ph) and was transformed further into the methylthio compound 8 (R = Ph). The later compound could be prepared also by methylation of 3-phenyl-6-methylthio-s-triazolo(4,3-b)pyridazine (9, R = Ph) under pressure. Similar transformations were performed also with the unsubstituted analog 7 (R = H), but methylation of the 6-methylthio compound (9, R = H) did not follow the anticipated quaternization at N₁, but afforded instead the 2-methyl analog (10). The differentiation between the N₁- and N₂-methyl compounds is possible by means of NMR spectra, in an analogous manner as observed previously in quaternization studies on s-triazolo(4,3-b)pyridazines¹¹. The signal for H₃ appears at 0.2–0.6 τ for N₁-substituted compounds¹¹, whereas for compound 10 a strong paramagnetic shift is observed and the signal for H₃ appears at -1.10τ . Although it has been shown by means of calculated electron densities for the parent system, quaternization would preferentially occur at N₁, it was also shown that thermal rearrangement can take place¹¹. This appears not very likely in the case of 10 since during methylation moderately high temperature was employed and thus a direct formation of the N₂-methyl compound is anticipated.

It is interesting to note that the -S⁻ group of a mercapto anhydro salt exerts a relatively strong shielding effect on the adjacent H₇ and even on the more distant H₈ proton. Thus, with anhydro salts (2 or 7) signals for H₇ and H₈ appear at 2.50–2.65 τ and 2.15–2.37 τ , respectively, whereas with the corresponding methylthio derivatives (3 or 8) these signals appear at 1.75–2.10 τ for H₇ and at 1.1–1.41 τ for H₈, respectively. This is understandable, if we take into consideration that systems 2 or 7 represent compounds with internal charge compensation, whereas those of 3 or 8 represent quaternary salts. A comparison of anhydro salts with a different heteroatom at position 6, *i.e.* mercapto anhydro salts *versus* hydroxy anhydro salts, revealed that the sulfur atom in 2 or 7 exerts a strong deshielding effect on H₇ (about 0.8 ppm) as compared to the related hydroxy anhydro bases^{2,3}. There is practically no difference in chemical shifts of H₈ in the mercapto or hydroxy series.

Finally, the quaternized methylthio bicycle (11) when heated under reflux in an aqueous solution of potassium hydroxide for 2 h was converted in moderate yield into the corresponding hydroxy anhydro salt (12), obtained previously³ by another route.

Experimental

All melting points were determined on a Kofler micro hot stage. NMR spectra were recorded on a JEOL JNM-C-60HL spectrometer (tetramethylsilane as internal standard) and using DMSO-d₆ as solvent unless otherwise stated. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMU-6L instrument.

1. 1-Methyl-2-phenyl-6-mercaptoimidazo(1,2-b)-pyridazinium anhydro salt (2, R = Ph)

In a solution of potassium hydroxide (8 g) in ethanol (160 ml) hydrogen sulfide was introduced in slow stream for 3 hours. Thereafter the 6-chloro compound (1, R = Ph)² (4 g) was added and the reaction mixture was heated under reflux for 2 hours. The solvent was evaporated in vacuo, water (200 ml) was added and the mixture was heated to boil. After cooling and filtration the obtained product was dried *in vacuo* and crystallized from N,N-dimethylformamide and ethanol (1:2) (yield 1.95 g, 75%), m.p. 235 °C (dec.). Mass spectrum: M⁺ = 241; NMR spectrum: τ = 1.90 (s, H₃), 2.60 (d, H₇), 2.37 (d, H₈), 2.4 (m, Ph), 6.20 (s, N-Me), J_{7,8} = 9.5 Hz.

C₁₃H₁₁N₃S

Calcd	C 64.70	H 4.59	N 17.42,
Found	C 64.79	H 4.99	N 17.35.

2. 1-Methyl-6-mercaptoimidazo(1,2-b)pyridazinium anhydro salt (2, R = H)

It was obtained in a similar manner from the corresponding chloro compound (1, R = H)¹¹ in 56% yield, m.p. 215–217 °C (dec.) (from methanol). Mass spectrum: M⁺ = 165; NMR spectrum: τ = 2.05 (d, H₂), 2.0 (d, H₃), 2.65 (d, H₇), 2.25 (d, H₈), 6.10 (s, N-Me), J_{2,3} = 1.5, J_{7,8} = 9.5 Hz.

C₇H₇N₃S

Calcd C 50.88 H 4.27 N 25.44,
Found C 50.74 H 4.11 N 24.98.

3. 1-Methyl-3-phenyl-6-mercapto-s-triazolo(4,3-b)-pyridazinium anhydro salt (7, R = Ph)

The compound was prepared in the same manner as described above from the corresponding chloro compound (6, R = Ph, X = ClO₄)³ in 27% yield, m.p. 139–141 °C (from methanol). Mass spectrum: M⁺ 242, m/e 210 (M⁺–32); NMR spectrum: τ = 1.6 and 2.4 (m, 3-Ph), 2.50 (d, H₇), 2.15 (d, H₈), 5.9 (s, N–Me), $J_{7,8}$ = 9.2 Hz.

C₁₂H₁₀N₄S

Calcd C 59.48 H 4.16 N 23.13,
Found C 59.50 H 4.07 N 23.38.

4. 1-Methyl-2-phenyl-6-methylthioimidazo(1,2-b)-pyridazinium iodide (3, R = Ph)

The corresponding anhydro salt (2, R = Ph) (1 g) was treated with a solution of methyl iodide (0.6 g) in methanol (20 ml) and the reaction mixture was heated under reflux for 1 hour. The solvent was evaporated, the residue dissolved in hot chloroform (70 ml) and to the still hot solution cyclohexane was added in such a manner that no turbidity remained. Charcoal was added and after short boiling and filtration the filtrate was left to stand on ice. The separated product was filtered off and the pale yellow crystals (1.35 g, 85%) had m.p. 208–210 °C. Mass spectrum: m/e 241 (M⁺–142); NMR spectrum: τ = 0.95 (s, H₃), 2.0 (d, H₇), 1.22 (d, H₈), 2.3 (m, 2-Ph), 5.98 (s, N–Me), 7.40 (s, S–Me), $J_{7,8}$ = 9.5 Hz.

C₁₄H₁₄IN₃S

Calcd C 43.87 H 3.68 N 10.96,
Found C 43.66 H 3.89 N 11.05.

5. 1-Methyl-6-methylthioimidazo(1,2-b)-pyridazinium iodide (3, R = H)

The compound was prepared in a similar manner as described for the 2-phenyl analog from 2 (R = H) after 1 hour at room temperature in 24% yield, m.p. 187–189 °C (from methanol). Mass spectrum: m/e 165 (M⁺–142); NMR spectrum: τ = 1.48 (d, H₂), 1.37 (d, H₃), 2.10 (d, H₇), 1.41 (d, H₈), 5.96 (s, N–Me), 7.40 (s, S–Me), $J_{2,3}$ = 1.5, $J_{7,8}$ = 9.5 Hz.

C₈H₁₀IN₃S

Calcd C 31.28 H 3.28 N 13.68,
Found C 31.29 H 3.48 N 13.86.

6. 1-Methyl-3-phenyl-6-methylthio-s-triazolo(4,3-b)-pyridazinium iodide (8, R = Ph)

The compound was prepared in a similar manner as outlined above from (7, R = Ph) after 3 hours at 110 °C in 49% yield, m.p. 224–225 °C (from ethanol). Mass spectrum: m/e 242 (M⁺–142); NMR spectrum: τ = 1.6 and 2.25 (m, 3-Ph), 1.75 (d, H₇), 1.1 (d, H₈), 5.86 (s, N–Me), 7.3 (s, S–Me) $J_{7,8}$ = 9.5 Hz.

C₁₃H₁₃IN₄S

Calcd C 40.63 H 3.41 N 14.58,
Found C 40.91 H 3.70 N 14.66.

This compound could be also prepared from 3-phenyl-6-methylthio-s-triazolo(4,3-b)pyridazine (9, R = Ph)¹² and methyl iodide at 110 °C for 3 hours in 50% yield.

7. 2-Methyl-6-methylthio-s-triazolo(4,3-b)-pyridazinium iodide (10)

A mixture of 6-methylthio-s-triazolo(4,3-b)pyridazine (9, R = H)¹³ (127 mg), methyl iodide (150 mg) and methanol (3 ml) was heated in a sealed tube at 110–120 °C for 3.5 hours. The obtained product (55 mg, 23%) had m.p. 242–244 °C (from methanol). Mass spectrum: M⁺ = 308; NMR spectrum: τ = 1.10 (s, H₃), 2.2 (d, H₇), 1.55 (d, H₈), 5.80 (s, N–Me), 7.40 (s, S–Me), $J_{7,8}$ = 9.5 Hz.

C₇H₉IN₄S

Calcd C 27.28 H 2.94 N 18.18,
Found C 27.27 H 3.16 N 18.02.

8. 2-Phenyl-6-methylthioimidazo(1,2-b)pyridazine (4, R = Ph)

This compound could be obtained in 57% yield when 1-methyl-2-phenyl-6-methylthioimidazo(1,2-b)-pyridazinium iodide (3, R = Ph) was sublimed at 200 °C. M.p. 144–148 °C. Mass spectrum: M⁺ = 241; NMR spectrum: τ = 1.20 (s, H₃), 2.84 (d, H₇), 2.0 (d, H₈), 6.4 (s, SMe), 2.0 and 2.6 (m, 2-Ph), $J_{7,8}$ = 9.5 Hz.

C₁₃H₁₁N₃S

Calcd C 64.70 H 4.59 N 17.42,
Found C 64.54 H 4.89 N 17.38.

If the analog, 1-methyl-6-methylimidazo(1,2-b)-pyridazinium iodide (3, R = H), was sublimed at 180–190 °C *in vacuo*, it could be established that the sublimate consists of 85% of 6-methylthioimidazo(1,2-b)pyridazine (4, R = H) and 15% of *cis*-cyano-1-(1'-methylimidazolyl-2')ethene (5). NMR spectrum of 4 (R = H): τ = 2.20 (d, H₂), 1.67 (d, H₃), 2.78 (d, H₇), 1.90 (d, H₈), 7.40 (s, SMe), $J_{2,3}$ = 1.5, $J_{7,8}$ = 9.5 Hz. NMR spectrum of 5: τ = 2.60 (d, H₁), 4.20 (d, H₂), 2.45 and 2.75 (d, H_{4'} and H_{5'}), $J_{1,2}$ = 12, $J_{4',5'}$ = 1.0 Hz.

9. 1-Methyl-2-phenyl-6-hydroxyimidazo(1,2-b)-pyridazinium anhydro salt (12)

1-Methyl-2-phenyl-6-methylthioimidazopyridazinium iodide (11) (0.1 g) was added to an aqueous solution of potassium hydroxide (0.1 g in 15 ml of water) and the reaction mixture was heated under reflux for 2 hours. Upon cooling, the separated crystals were filtered off and crystallized from water (yield 16 mg, 27%), m.p. 270–273 °C (lit.² gives m.p. 272–273 °C) and mixed m.p. with an authentic specimen was undepressed.

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