Synthesis of Vicinally Substituted by Halogen 4-Methylthio and Methylsulfonyl Derivatives of 2,6-Dimethylpyridine and Their 1-Oxides

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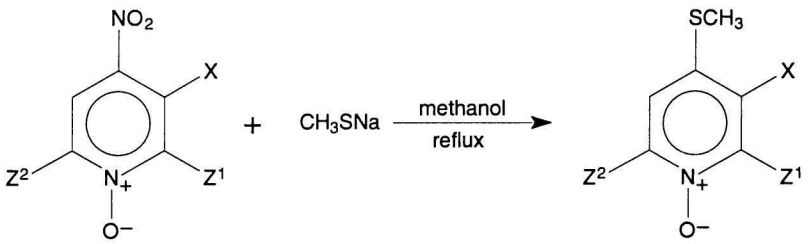
3-Halo-2,6-dimethyl-4-nitropyridine 1-oxides react with sodium methanethiolate giving 3-halo-2,6-dimethyl-4-methylthiopyridine 1-oxides which are oxidized into respective methylsulfonyl derivatives and reduced to 3-halo-2,6-dimethyl-4-methylthiopyridines.

Sulfur-containing derivatives of 1-oxides of heteroaromatic amines, especially of pyridine, are known to possess antifungal and antibacterial properties [1—4]. It has been reported recently that sulfonyl derivatives of pyridine 1-oxides have found wide applications as herbicides and plant growth regulators and as phase-transfer catalysts of S_N2 reactions [5—8]. In addition, chloropyridylsulfone 1-oxide was used as toxicant of *Escherichia coli* in agar [9].

For many years investigations have been carried out in our laboratory on the reactivities of 1-oxides of halonitropyridines [10—13]. Particular attention has been paid to the nucleophilic exchange reactions of substituents at positions 2 and 4 as these positions are very strongly activated towards this substitution through mesomerism by the *N*-oxide group. Among the reactions of this type the preparation of 3-halo-2,6-dimethyl-4-ethylthiopyridine 1-oxides was described [12]. This paper is a continuation of our studies on the syntheses of sulfur-containing pyridine derivatives and their 1-oxides *via* easy replacement of the nitro group in position 4 of pyridine 1-oxides.

The 3-halo-2,6-dimethyl-4-nitropyridine 1-oxides were prepared by oxidation of the respective 3-substituted 2,6-dimethylpyridines and by subsequent nitration of the resulting 1-oxides [14, 15]. Starting from these 1-oxides (*Ia*, *Ib*) in the first step, through the reaction with sodium methanethiolate exclusively the corresponding methylthio derivatives (*IIa*, *IIb*) were prepared in good yields; the presence of the halogen atom at a vicinal position to the nitro group seems to additionally facilitate this type of exchange of this group (Scheme 1). It is worth noting that in contrast to the 3-methylthio derivatives [16], the sulfur atom in *IIa*, *IIb* is very susceptible to oxidation. As it is shown in Scheme 2, only methylsulfonyl derivatives *IIIa*, *IIIb* were obtained from the above-mentioned reactions.

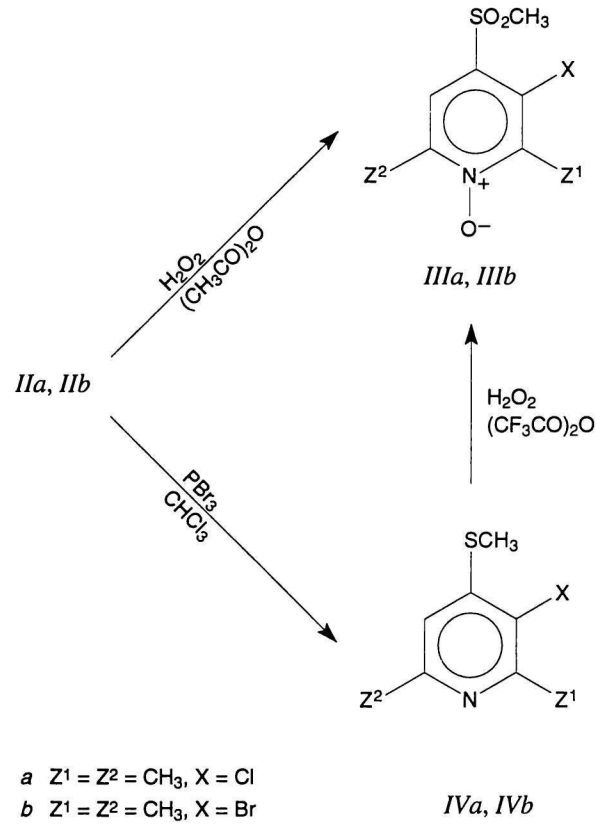
When compounds *IIa*, *IIb* were treated with phosphorus tribromide the corresponding 4-methylthiopyridines were obtained (*IVa*, *IVb*) in which the nitrogen atom of the ring showed also susceptibility to the oxidation in contrast to the nitrogen atom in 2,6-dimethyl-3-methylthiopyridine [16]. Consequently, there is an additional pathway to *IIIa*, *IIIb* through the oxidation of



Ia, *Ib* — *IIa*, *IIb*

a $Z^1 = Z^2 = CH_3$, X = Cl
b $Z^1 = Z^2 = CH_3$, X = Br

Scheme 1



a $Z^1 = Z^2 = CH_3$, X = Cl
b $Z^1 = Z^2 = CH_3$, X = Br

Scheme 2

IVa, IVb with trifluoroperacetic acid. In conclusion, this increase of susceptibility to the oxidation of the sulfur atom, as well as of the nitrogen atom seems to be the result of mutual interaction between these atoms through the ring.

The structures of all the prepared compounds were characterized by their elemental analyses and by IR and ^{1}H NMR spectra.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The infrared spectra were taken on a Specord IR 75 (Zeiss, Jena) spectrophotometer. ^{1}H NMR spectra were recorded on a Tesla BS-598 A spectrometer (100 MHz) using $CDCl_3$ as solvent and TMS as the internal standard. Chemical shifts are expressed as δ.

3-Chloro-2,6-dimethyl-4-methylthiopyridine 1-oxide (*IIa*) and 3-bromo-2,6-dimethyl-4-methylthiopyridine 1-oxide (*IIb*) were prepared from *Ia* and *Ib* as described in [12].

IIa: Colourless crystals (67 %), m.p. = 161 °C (from H_2O). For $C_8H_{10}ClNOS$ (M_r = 203.69) w_i(calc.): 47.17 % C, 4.94 % H, 6.87 % N; w_i(found): 46.66 % C, 4.92 % H, 6.64 % N.

IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 2983, 2920 $\nu(CH_3)$, 1593 (ring), 1441, 1422, 1370, 1355 $\delta(CH_3)$, 1234 ν(NO), 1018 ν(C—Cl), 790, 647, 542 ν(CS). ^{1}H NMR spectrum, δ: 6.93 (s, 1H), 2.60 (3H, C-2—CH_3), 2.45 (s, 3H, C-6—CH_3), 2.98 (s, 3H, S—CH_3).

IIb: Colourless crystals (59 %), m.p. = 169—170 °C (from H_2O). For $C_8H_{10}BrNOS$ (M_r = 248.15) w_i(calc.): 38.72 % C, 4.06 % H, 5.64 % N; w_i(found): 38.25 % C, 3.91 % H, 5.45 % N.

IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 2980, 2960, 2918 $\nu(CH_3)$, 1591 (ring), 1442, 1420, 1370, 1354 $\delta(CH_3)$, 1237 ν(NO), 1005 ν(C—Br), 773, 633, 545 ν(C—S). ^{1}H NMR spectrum, δ: 6.89 (s, 1H), 2.65 (s, 3H, C-2—CH_3), 2.41 (s, 3H, C-6—CH_3), 2.94 (s, 3H, S—CH_3).

3-Chloro-2,6-dimethyl-4-methylsulfonylpyridine 1-Oxide (*IIIa*)

To a mixture of *IIa* (2 g; 9.8 mmol) and 30 % H_2O_2 (8 cm^3) $(CF_3CO)_2O$ (8 cm^3) was added dropwise under vigorous stirring with external cooling. The resulting mixture was subsequently heated at 90 °C for 10 min and left to stand at room temperature. Afterwards a small quantity of H_2O was added and it was neutralized with K_2CO_3, evaporated under reduced pressure to dryness and extracted several times with $CHCl_3$. After distilling off the solvent the crude product was recrystallized from CH_3COCH_3 yielding 2 g (87 %) of colourless crystals, m.p. = 193—195 °C. For $C_8H_{10}ClNO_3S$ (M_r = 235.69) w_i(calc.): 40.76 % C, 4.27 % H, 5.94 % N; w_i(found): 40.71 % C, 4.08 % H, 5.73 % N.

IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 3004, 2927 $\nu(CH_3)$, 1593 (ring), 1450, 1400 $\delta(CH_3)$, 1309 $\nu(SO_2)$, 1272 ν(NO), 1136 $\nu(SO_2)$, 1015 ν(C—Cl), 786, 658, 550 ν(C—S), 510 $\gamma(SO_2)$. ^{1}H NMR spectrum, δ: 7.68 (s, 1H), 2.67 (s, 3H, C-2—CH_3), 2.50 (s, 3H, C-6—CH_3), 3.28 (s, 3H, S—CH_3).

3-Bromo-2,6-dimethyl-4-methylsulfonylpyridine 1-Oxide (*IIIb*)

Using the same procedure as described above, *IIb* (2.43 g; 9.8 mmol) gave *IIIb* (2.08 g, 76 %), m.p. = 201—204 °C.

For $C_8H_{10}BrNO_3S$ (M_r = 280.15) w_i(calc.): 34.72 % C, 3.59 % H, 5.00 % N; w_i(found): 34.52 % C, 3.38 % H, 4.94 % N.

IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 3000, 2920 $\nu(CH_3)$, 1590 (ring), 1450, 1400, 1375 $\delta(CH_3)$, 1307 $\nu(SO_2)$, 1273 ν(NO), 1137 $\nu(SO_2)$, 1002 ν(C—Br), 787, 641, 555 ν(C—S), 515 $\gamma(SO_2)$. ^{1}H NMR spectrum, δ: 7.62 (s, 1H), 2.73 (s, 3H, C-2—CH_3), 2.47 (s, 3H, C-6—CH_3), 3.25 (s, 3H, S—CH_3).

3-Chloro-2,6-dimethyl-4-methylthiopyridine (*IVa*)

To a solution of compound *IIa* (9 g; 44 mmol) in $CHCl_3$ (95 cm^3) PBr_3 (7 cm^3) was added carefully. The

mixture was boiled for 1 h and then additional portion of PBr_3 (7 cm^3) was added and heated for additional 30 min. After distilling off $CHCl_3$ and the excess of PBr_3 under reduced pressure, a small quantity of H_2O-ice was added, neutralized with $NaHCO_3$ to alkaline reaction and steam distilled. The distillate was extracted with $(C_2H_5)_2O$. The solution was dried over $MgSO_4$. After evaporating of solvent the crude product was twice recrystallized from benzine to afford 4.9 g of *IVa* (60 %), m.p. = 96—97 °C.

For $C_8H_{10}ClNS$ (M_r = 187.69) w_i(calc.): 51.19 % C, 5.37 % H, 7.46 % N; w_i(found): 51.31 % C, 5.59 % H, 7.33 % N.

IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 2980, 2917 ν(CH_3), 1550 (ring), 1432, 1420, 1376 δ(CH_3), 1043 ν(C—Cl), 637, 568 ν(C—S): ^{1}H NMR spectrum, δ: 7.03 (s, 1H), 2.77 (s, 3H, C-2—CH_3), 2.56 (s, 3H, C-6—CH_3), 2.86 (s, 3H, S—CH_3).

3-Bromo-2,6-dimethyl-4-methylthiopyridine (*IVb*)

Compound *IIb* (10.4 g; 44 mmol) was subjected to the same procedure as described above for the preparation of *IVa* to afford 7.44 g of *IVb* (73 %), m.p. = 87—90 °C.

For $C_8H_{10}BrSN$ (M_r = 232.15) w_i(calc.): 41.39 % C, 4.34 % H, 6.03 % N; w_i(found): 41.44 % C, 4.49 % H, 5.91 % N.

IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 2980, 2930 ν(CH_3), 1553 (ring), 1433, 1378 δ(CH_3), 1020 ν(C—Br), 607, 565 ν(C—S). ^{1}H NMR spectrum, δ: 6.98 (s, 1H), 2.80 (s, 3H, C-2—CH_3), 2.54 (s, 3H, C-6—CH_3), 2.92 (s, 3H, S—CH_3).

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