2-SULFILIMINOPYRIDINES AND THEIR OXIDATION TO 2-NITROPYRIDINES

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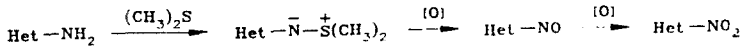
Sulfilimines of the pyridine series with electron-acceptor substituents in the ring were synthesized. It was shown that their oxidation with trifluoroperacetic acid results in the corresponding nitropyridines. The limitations of the methods were indicated.

The most common method for the synthesis of nitropyridines is the nitration of compounds of this class [1]. However, only pyridines with electron-donor substituents undergo this reaction. The synthesis of nitropyridines containing strong electron-acceptor substituents cannot be accomplished by this method [1].

Compounds with this structure could be obtained starting from the corresponding amines. However, the direct oxidation of aminopyridines with electron-acceptor groups does not lead to nitro derivatives.

In 1982, Taylor et al. [2] proposed an original method for converting aminoazines into nitro derivatives, including the successive oxidation of the sulfilimino and nitroso groups.

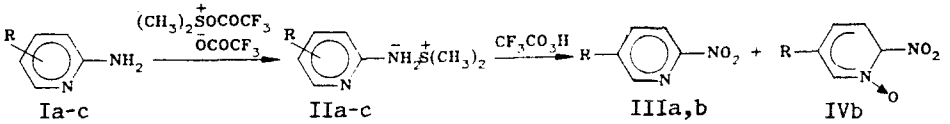


However, this reaction was carried out only with the amino derivatives of azines with electron-donor substituents or without any substituents [2-4].

The aim of the present work was to synthesize sulfilimines of the pyridine series with electron-acceptor substituents in the ring and to oxidize them to nitro derivatives.

Analysis of the literature showed that for the preparation of iminosulfuranes of the heterocyclic type, four methods of reacting the amines are most often used: 1) with dimethyl sulfide in the presence of N-chlorosuccinimide [3]; 2) with dimethyl sulfoxide and phosphorus pentoxide [5]; 3) with dimethyl sulfide bistrifluoroperacetate [6]; 4) with dimethyl sulfide bistriflate [4]. 2-Amino-5-nitropyridine (Ia) was chosen as an example of an amino pyridine. As a result of its reaction with sulfilating agents by methods 1-4, 2-dimethylsulfilimino-5-nitropyridine (IIa) was obtained in yields of 42, 81, 90, and 87%, respectively.

It is seen that the highest yield can be attained by using dimethyl sulfide bistrifluoroacetate. We used this method for the preparation of other sulfilimines of the pyridine series and prepared 2-dimethylsulfilimino-5-chloro- and 2-dimethylsulfilimino-3-nitropyridines (IIb and IIc).



Ia-c IIa-c IIIa,b IVb

Ia—IIIa R=5-NO_2; Ib—IVb R=5-Cl; Ic, IIc R=3-NO_2

It should be noted that in all cases it is necessary to use a threefold excess of the sulfilating agent. In the case of 2-amino-3,5-dinitropyridine (Id), we noted the formation of sulfilimine, but this could not be isolated in a free state, because it hydrolyzes rapidly in air to the initial amine.

The oxidation of sulfilimines IIa and IIb by trifluoroperacetic acid led to the corresponding nitro derivatives. In the second case, the corresponding pyridine N-oxide (IVb) was also formed as a by-product.

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Under similar oxidation conditions, sulfilimine IIc is hydrolyzed to amine Ic. It is possible that in this case the nitrogen atom of the sulfilimine group is attacked more rapidly by a proton of an acid than by the electrophilic oxygen atom of the peracid.

The results obtained indicate that Taylor's method is suitable only for the synthesis of nitropyridines from amines with an average basicity value (pK_{BK^+}[Ia] 2.41, pK_{BH^+}[Ib] 4.22), since sulfilimines obtained from weakly basic amines (pK_{BH^+}[Ic] 2.14, pK_{BH^+}[Id] –1.44) undergo more readily the hydrolysis than oxidation.

Thus, we synthesized sulfilimines of the pyridine series with electron-acceptor groups and showed that, by oxidizing them with trifluoroperacetic acid, the corresponding nitro derivatives can be obtained. The limitations of the method due to lower basicity were revealed.

EXPERIMENTAL

The IR spectra were recorded on a Specord spectrophotometer in KBr tablets and the PMR spectra – on a Tesla BS-467 spectrometer (60 MHz with reference to TMS), and the mass spectra – on a Varian CH-6 spectrometer. The ^{13}C and ^{14}N NMR spectra were run on a Bruker AM-300 spectrometer, using TMS as internal standard, while nitric acid was used as external standard. The basicity constants were determined spectrophotometrically on a SF-26 spectrophotometer.

Aminopyridines were obtained by methods described in [7]. The data of the elemental analyses correspond to the calculated values.

2-Dimethylsulfilimino-5-nitropyridine (IIa, $C_7H_9N_3O_2S$). A. A solution of 0.67 g (5 mmoles) of N-chlorosuccinimide in 10 ml of absolute CH_2Cl_2 was added at –20°C to a solution of 0.37 ml (5 mmoles) of dimethyl sulfide in 4 ml of absolute CH_2Cl_2. The reaction mixture was held at this temperature for 30 min, and a solution of 0.35 g (2.5 mmoles) of 2-amino-5-nitropyridine (Ia) in 5 ml of absolute CH_2Cl_2 was added. After 3 h of vigorous stirring at –20°C, 3 ml of a 10% aqueous NaOH solution was added dropwise. The temperature was raised to 0°C and the mixture was allowed to stand for 1 h. The organic layer was separated, washed with water (2 × 3 ml), and dried over $MgSO_4$. After evaporation of the solvent, the only residue was crystallized from hexane. Yield 0.21 g (42%), mp 168.0-168.5°C. IR spectrum: 3300 (CH_3), 2910 (CH_3), 1530 (NO_2), 1320 (NO_2); 980 cm^{-1} ($\overset{+}{S}–\bar{N}$). M^+ 199. PMR spectrum [in $(CD_3)_2SO$]: 2.77 [$(CH_3)_2S$]; 6.37 (H–$C_{(3)}$), 7.85 (H–$C_{(14)}$), 8.75 ppm (H–$C_{(6)}$). ^{13}C NMR spectrum: 31.49 (CH_3), 112.70 ($C_{(6)}$), 130.72 ($C_{(4)}$), 132.89 ($C_{(5)}$), 146.44 ($C_{(3)}$), 168.33 ppm ($C_{(2)}$). ^{14}N NMR spectrum –15.65 ppm (NO_2).

B. A 0.85-g portion (7.7 mmoles) of P_2O_5 was added at 2°C to 2.5 ml DMFA, and after 15 min 0.43 ml (6.1 mmoles) of DMSO was added. The mixture was allowed to stand for 1 h and a solution of 0.36 g (1.8 mmoles) of Ia in 2.5 ml DMFA was added. The mixture was stirred for another 1 h at 2°C, and after adding 2.3 ml (16 mmoles) of triethylamine, was allowed to stand for 1 h. It was then poured into 10 ml of water. The mixture was extracted with CH_2Cl_2 (3 × 5 ml), the extracts were washed with water, and dried over $MgSO_4$. The extract was evaporated and the residue was crystallized from ether. Yield 0.29 g (81%). The melting point and the IR spectrum were identical to those obtained for a sample synthesized by method A.

C. A 1.04-ml portion (7.4 mmoles) of trifluoroacetic anhydride was added at –60°C to a solution of 0.68 ml (9.5 mmoles) of DMSO in 2 ml of absolute CH_2Cl_2 in such a manner that the temperature of the reaction mixture did not rise above –50°C. After 15 min, a solution of 0.5 g (2.5 mmoles) of Ia in a mixture of 1.2 ml of DMSO and 4 ml of CH_2Cl_2 was added dropwise. The reaction mixture was allowed to stand for 3 h at –60°C, and then 12 ml of a 10% aqueous NaOH solution was added at –30°C, and the mixture was allowed to stand for 1 h at this temperature. The temperature was raised to 0°C. The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 3 ml), the extracts were washed with water (2 × 2 ml), and dried over $MgSO_4$ and evaporated to yield 0.64 g (90%) of IIa, mp 168°C. The compound does not give a depression of a mixed melting point with a sample from experiment A.

D. A solution of 1 g (3.5 mmoles) trifluoromethanesulfonic acid anhydride in 10 ml of absolute CH_2Cl_2 was added at –60°C to a solution of 0.3 ml (4.1 mmoles) of DMSO in 2 ml of absolute CH_2Cl_2 in such a manner that the temperature of the reaction mixture did not rise above –50°C. After 30 min, a solution of 0.42 g (3 mmoles) of Ia in a mixture of 2 ml of DMSO and 3 ml of CH_2Cl_2 was added dropwise. The reaction mixture was held for 15 min at –60°C, and then 10 ml of a 10% aqueous NaOH solution was added at –30°C, and the mixture was allowed to stand for 1 h at this temperature. The temperature was raised to 0°C. The organic layer was then separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 3 ml), the extracts were washed with water (2 × 2 ml), and dried over $MgSO_4$. After evaporation of the solvent, 0.52 g (87%) of crystals were obtained, which were identical to those synthesized in experiment A.

2-Dimethylsulfilimino-5-chloropyridine (IIb, $C_7H_9ClN_2S$) was obtained in a similar way as compound IIa by method C from 0.5 g (2.6 mmoles) of Ib. Yield 0.69 g (94%). mp 79-81°C (decomp.). IR spectrum: 2980 (CH_3), 2910 (CH_3), 980 cm^{-1} ($\overset{+}{S}$–$\overline{N}$). M^+ 188. PMR spectra [in $(CD_3)_2CO$]: 2.63 [$(CH_3)_2S$]; 6.38 (H–$C_{(3)}$), 7.12 (H–$C_{(4)}$), 7.73 ppm (H–$C_{(6)}$). ^{13}C NMR spectrum [in $(CD_3)_2SO$]: 32.22 ($CH_{(3)}$), 114.66 ($C_{(6)}$), 116.09 ($C_{(5)}$), 135.87 ($C_{(4)}$), 144.82 ($C_{(3)}$), 164.28 ppm ($C_{(2)}$).

2-Dimethylsulfilimino-3-nitropyridine (IIc, $C_7H_9N_3O_2S$) was obtained in a similar way as compound IIa by method C from 0.5 g (2.5 mmoles) of Ic. Yield 0.51 g (78%). mp 89-90°C (decomp.). IR spectrum: 2980 (CH_3), 2900 (CH_3), 1530 (NO_2), 1320 (NO_2), 970 cm^{-1} ($\overset{+}{S}$–$\overline{N}$). M^+ 199. PMR spectrum [in $(CD_3)_2SO$]: 2.72 [$(CH_3)_2S$], 6.47 (H–$C_{(4)}$), 8.0 ppm (H–$C_{(5)}$ and H–$C_{(6)}$).

Oxidation of Sulfilimine IIb. A 3.5-ml portion (25 mmoles) of trifluoroacetic anhydride was added dropwise at 0°C to a mixture of 0.63 ml (25 mmoles) of 83% of H_2O_2 and 20 ml of CH_2Cl_2 and after 10 min, 0.5 g (2 mmoles) of compound IIb was added. The reaction mixture was held for 1 h 30 min at 0°C, and 20 ml of a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was separated, washed with water (2 × 5 ml) and dried over $MgSO_4$. The solvent was distilled and the residue was chromatographed on a column with silica gel L 100/250 (eluent $CHCl_3$). Yield 0.26 g (62%) of compound IIIb ($C_5H_3ClN_2O_2$), mp 123-124°C, R_f 0.7 (Silufol UV-254, chloroform–acetone, 5:1). According to the data in [8], mp 120-121°C. In addition, 0.18 g (38%) of compound IVb ($C_5H_3ClN_2O_3$) was isolated, mp 96-98°C (decomp.) (R_f 0.3). IR spectrum: 1530 (NO_2), 1350 cm^{-1} (NO_2). M^+ 174.

2,5-Dinitropyridine (IIIa, $C_5H_3N_3O_4$) was obtained in a similar way as compound IIIb from 0.5 g (1.9 mmoles) of sulfilimine IIa. Yield 0.33 g (79%), mp 116-116.5 (from EtOH). IR spectrum: 1520 (NO_2), 1300 cm^{-1} (NO_2). M^+ 169. PMR spectrum (in CH_3CN): 8.38, 8.82, 9.32 ppm (pyridine protons). ^{13}C NMR spectrum [in $(CD_3)_2SO$): 120.32 ($C_{(5)}$), 137.52 ($C_{(3)}$), 145.63 ($C_{(2)}$), 148.51 ($C_{(4)}$), 159.50 ppm ($C_{(1)}$). ^{14}N NMR spectrum: –15.60 and –18.54 ppm (NO_2).

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