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2-IMINOTHIOPYRANS FROM METHYLTHIOBUTADIENE AND ISOTHIOCYANATES

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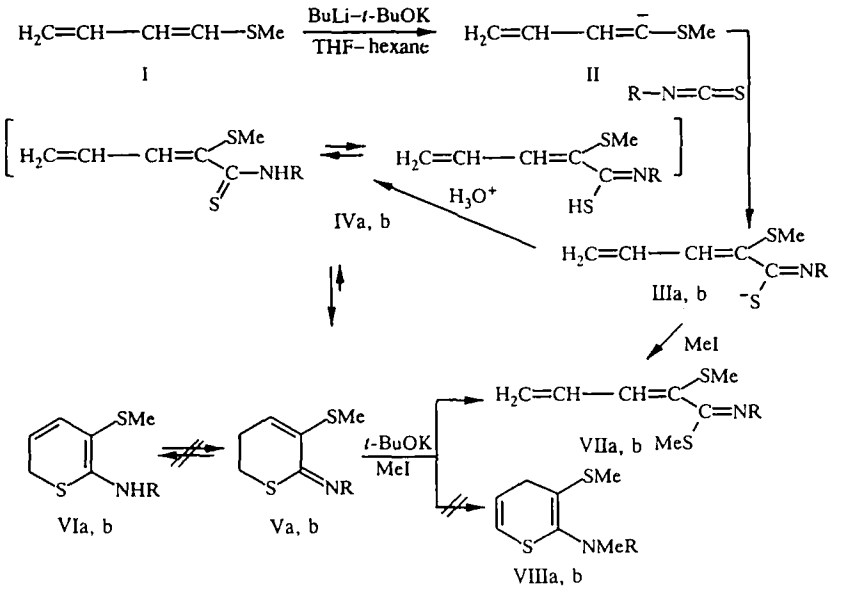
We have found a novel and simple approach to synthesis of 2-alkyl-3-(methylthio)-5,6-dihydro-2H-2-thiopyranimines by reactions of isothiocyanates with the carbanion of methylthiobutadiene, generated in situ *when treated with the superbasic system BuLi–t-BuOK. We have established that alkylation of the synthesized thiopyrans with methyliodide in the presence of t-BuOK leads to N-alkyl-1,2-di(methylthio)-2,4-pentadiene-1-imines.*

Deprotonation of methylthiobutadiene (I) by the superbasic system BuLi–*t*-BuOK in the mixed solvent THF–hexane at –70°C leads to the α-metallated derivative (II), capable of further reactions with electrophiles [1], among which, however, isothiocyanates have not been mentioned.

Continuing systematic investigations of the reactions of heterocumulenes with metallated unsaturated compounds [2-13], which have already led to opening up fundamentally new general approaches to constructing pyrrole [2-5], dihydropyridine [2-7], quinoline [8-11], and cyclobutanopyrroline [12, 13] systems, for the first time we have studied the reaction of anion II with isothiocyanates and we have found that mild hydrolysis of the adducts (III) formed easily and selectively leads, via an intermediate thioamide (IV), to iminothiopyrans (V) in high yield and in a single preparative step. These iminothiopyrans are otherwise difficult to synthesize.



III-VIII a R = Me, b R = Pr-*i*

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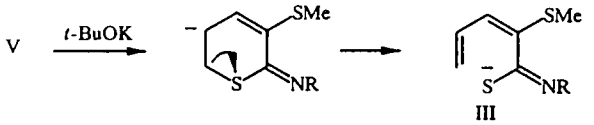
Deprotonation of methylthiobutadiene I by the system BuLi–*t*-BuOK was done as described earlier in [1]. The anion II formed is added smoothly and quantitatively to methyl- and isopropylisothiocyanates at a temperature of −50°C to −5°C and leads to the corresponding thiolates III, treatment of which with a dilute solution of hydrogen bromide ends with rapid intramolecular cyclization of the intermediates IVa, b to iminothiopyrans Va, b. Thioamide IVb was identified in a mixture with iminothiopyran Vb from the PMR spectrum (see the Experimental section) of the crude reaction product. (possibly in connection with the reversibility of cyclization). On going from methylisothiocyanate to isopropylisothiocyanate, the content of compound IV appreciably increases (thioamide IVa is present in the reaction product only in trace amounts).

No tautomeric aminothiopyrans VI were identified among the reaction products. For 2-hydroxythiophenes, for example, the existence of all three possible tautomers has been demonstrated, and usually nonaromatic γ-thiolactones are the preferred form, with predominance of the conjugated thiolen-3-one [14]. Tautomerism in the aminothiophene series, although known, has been studied much less than the tautomerism of the corresponding hydroxy derivatives [15]. Information about the tautomerism of aminothiopyrans, like that of aminothiopyrans themselves, is probably even more limited. At the same time, according to data available to us, 2-(alkylamino)-3-methylthio-thiophene exists exclusively in the amino form.

An attempt to alkylate thiopyrans Va, b with methyliodide in the presence of potassium *tert*-butoxide (in analogy with alkylation of 2-aminothiophenes) unexpectedly ended in formation of N-alkyl-1,2-di(methylthio)-2,4-pentadiene-1-imines (VIIa, b) instead of the expected methylalkylaminothiopyrans VIIIa, b; i.e., deprotonation of thiopyrans Va, b when treated with a superbase is accompanied by ring opening:



III

Alkylation of the thiolate anion III leads to the imine VII. Possibly, the reaction of cyclization of thioamide IV to thiopyran V is reversible. When treated with base, the equilibrium is shifted toward the deprotonated open form III.

For additional proof of the direction of opening of the thiopyran ring and the structure of the products formed, the imines VII were also synthesized by alkylation of thiolate III with methyliodide. Samples of imines VII obtained by different routes were completely identical (IR spectra, PMR data, and other characteristics).

The structure of thiopyrans V and imines VII were confirmed by IR and NMR spectra, and also by elemental analysis results.

EXPERIMENTAL

The IR spectra were recorded on a Specord 75-IR spectrophotometer in a thin layer. The NMR spectra were recorded on a Varian EM-390 spectrometer (90 MHz, 20% solutions of the compounds in CCl_4) and a Bruker AC-300 spectrometer (300 MHz, 20% solutions in $CDCl_3$); internal standard TMS. GLC analysis was done on a Varian 3400 gas chromatograph (flame ionization detector, capillary column 15,000 × 0.53 mm, coating 1.5 μm DB-5, nitrogen as the carrier gas).

All the operations were done under a nitrogen atmosphere. Methylthiobutadiene I was synthesized according to the procedure in [16]. Tetrahydrofuran was purified mechanically by dispersed KOH (50 g/liter) and distillation over $LiAlH_4$ in the presence of benzophenone under a nitrogen atmosphere. Butyllithium (1.6 m solution in hexane) and the rest of the reagents and solvents used in this work were commercial products.

2-Methyl-3-(methylthio)-5,6-dihydro-2H-2-thiopyranimine (Va). Methylthiobutadiene (6.0 g, 0.060 moles) was added with stirring to a solution (cooled down to −50°C) of 6.4 g (0.057 moles) *t*-BuOK in 90 ml THF. The mixture was cooled down to −95°C, and a solution of BuLi (0.056 moles) in 35 ml hexane was added carefully with vigorous cooling (in this case, the temperature abruptly increases up to −55°C). The thick, mustard-colored suspension was cooled down to −75°C; then 40 ml THF was added to it and the cooling was stopped. At −50°C, a solution of 6.0 g (0.082 moles) methylisothiocyanate in 10 ml ether was added to the reaction mass (the temperature increases up to −20°C), and then it was treated with a solution of 20 g 48% HBr in 100 ml water. The organic layer was separated, and the aqueous layer was extracted with pentane and ether; the combined extract was dried with potassium carbonate. The residue after removal of the solvent on a rotary evaporator was distilled under vacuum. Obtained: 5.5 g (63.6%) thiopyran Va (purity 91% according to GLC data). T_{bp} 100-110°C (0.5

torr), n^{20}_D 1.6360. PMR spectrum (300 MHz): 5.80 (1H, t, CH=); 3.10 (3H, s, NMe); 2.80 (2H, t, CH_2); 2.47 (2H, q, CH_2); 2.05 ppm (3H, s, SMe). Found, %: C 48.22; H 6.53; N 8.35; S 36.90. $C_7H_{11}NS_2$. Calculated, %: C 48.52; H 6.40; N 8.08; S 37.00.

2-Isopropyl-3-(methylthio)-5,6-dihydro-2H-2-thiopyranimine (Vb). Methylthiobutadiene (5.5 g, 0.055 moles) was added to a solution (cooled down to −40°C) of 6.9 g (0.062 moles) *t*-BuOK in 90 ml THF. The mixture was cooled down to −100°C and a solution of BuLi (0.059 moles) in 37 ml hexane was added carefully with vigorous cooling (in this case, the temperature rises to −55°C). At −50°C, 5.3 g (0.052 moles) isopropylisothiocyanate was added to the reaction mass (the temperature rises to −5°C), and then the reaction mixture (cooled down to −60°C) was treated with a solution of 22.9 g 48% HBr in 150 ml water. The organic layer was separated, the aqueous layer was extracted with pentane and ether, and the combined extract was dried with potassium carbonate. After removal of the solvents on a rotary evaporator, 11.1 g of residue were obtained containing 86.1% thiopyran Vb (GLC data). 4.3 g (42.6%) compound Vb was isolated by distillation. T_{bp} 137-142°C (0.7 torr), n^{20}_D 1.5880. PMR spectrum (90 MHz): 5.97 (1H, t, CH=); 3.80 (1H, m, NCH); 2.93 (2H, m, CH_2); 2.55 (2H, m, CH_2); 2.15 (3H, s, SMe); 1.20 ppm (6H, d, 2 Me). Found, %: C 53.49; H 7.63; N 7.24; S 31.64. $C_9H_{15}NS_2$. Calculated, %: C 53.69; H 7.51; N 6.96; S 31.85.

The PMR spectrum (90 MHz) of thioamide IVb (obtained by subtracting the proton signals of thiopyran Vb from the spectrum of the crude product containing 86.1% thiopyran Vb): 8.80 (1H, broad s, NH); 8.00 (1H, d, CH=C); 7.15-6.96 (1H, m, CH=); 6.00-5.60 (1H, m, CH_2=); 4.70 (1H, m, NCH); 2.15 (3H, s, SMe); 1.35 ppm (6H, d, 2Me).

N-Methyl-1,2-di(methylthio)-2,4-pentadiene-1-imine (VIIa). A. Methylthiobutadiene (5.7 g, 0.057 moles) was added to a solution (cooled down to −50°C) of 6.6 g (0.059 moles) *t*-BuOK in 60 ml THF. The mixture was cooled down to −120°C, and a solution of BuLi (0.056 moles) in 35 ml hexane was introduced. At a temperature of −45°C, a solution of 3.7 g (0.051 moles) methylisothiocyanate in 10 ml THF was added to the reaction mass (the temperature rises up to 0°C), then 11 g (0.076 moles) MeI was added (the temperature rises up to 20°C); and 10-15 min later, it was treated with 80 ml cold water. The organic layer was separated, the aqueous layer was extracted twice with a mixture of ether and pentane; the combined extract was dried with potassium carbonate. After removal of the solvents on a rotary evaporator and distillation of the residue, we obtained 7 g (74.9%) imine VIIa. T_{bp} 80-85°C (0.6 torr), n^{20}_D 1.6000. IR spectrum: 835, 870, 900 vs, 950, 960 shoulder, 1000, 1070, 1120, 1140, 1190, 1300, 1320, 1400, 1430, 1440, 1560, 1620 vs, 2760, 2860, 2900 shoulder, 2920, 2950 shoulder, 2990, 3050, 3090 cm^{-1}. PMR spectrum (90 MHz): 6.30-5.95 (2H, m, 2 CH=); 5.22-4.95 (2H, m, CH_2=); 3.12 (3H, s, NMe); 2.30 (3H, s, SMe); 2.20 ppm (3H, s, SMe). Found, %: C 55.93; H 7.88; N 6.71; S 29.48. $C_8H_{13}NS_2$. Calculated, %: C 55.77; H 7.96; N 6.50; S 29.77.

B. First a solution of 8 g (0.071 moles) *t*-BuOK in 20 ml THF and then 12 g (0.038 moles) methyliodide were added to a solution (cooled down to −20°C) of 8 g (0.046 moles) thiopyran Va in 50 ml THF. The mixture was stirred at room temperature for 15 min. After conventional treatment of the reaction mass by distillation, the imine VIIa was isolated, identical to a sample obtained by procedure A (T_{bp}, n^{20}_D, IR and PMR spectra).

N-Isopropyl-1,2-di(methylthio)-2,4-pentadiene-1-imine (VIIb). Methylthiobutadiene (5.7 g, 0.057 moles) was added to a solution (cooled down to −40°C) of 6.6 g (0.059 moles) *t*-BuOK in 90 ml THF. The mixture was cooled down to −100°C and a solution of BuLi (0.056 moles) in 35 ml hexane was introduced. At a temperature of −35°C, 5.1 g (0.050 moles) isopropylisothiocyanate was added to the reaction mass (the temperature rises to −10°C) and then at −25°C, 11 g (0.076 moles) MeI was added. The mixture was heated up to 35°C and 10-15 min later was treated with 80 ml cold water. The organic layer was separated, the aqueous layer was extracted twice with a mixture of ether and pentane. The combined extract was dried with potassium carbonate. After removal of the solvents on a rotary evaporator, we obtained 11 g residue containing 86.8% imine VIIb (GLC data). 8 g (74.4%) imine VIIb was isolated by distillation (purity 96.7%, GLC). T_{bp} 98-100°C (1 torr), n^{20}_D 1.5668. IR spectrum: 820, 900 vs, 940, 990, 1050, 1140, 1160 shoulder, 1180, 1300, 1315, 1330, 1360, 1370, 1430, 1465, 1560, 1600 vs, 2860, 2910, 2960, 3050, 3080 cm^{-1}. PMR spectrum (90 MHz): 6.50-5.85 (2H, m, 2 CH=); 5.20-4.90 (2H, m, CH_2=); 3.70 (1H, m, NCH); 2.30 (3H, s, SMe); 2.25 (3H, s, SMe); 1.10 ppm (6H, m, 2Me). Found, %: C 56.01; H 7.88; N 6.73; S 29.38. $C_{10}H_{17}NS_2$. Calculated, %: C 55.77; H 7.96; N 6.50; S 29.77.

B. A solution (cooled down to −30°C) of 6 g (0.030 moles) thiopyran Vb in 30 ml THF was treated with a solution of 5 g (0.045 moles) *t*-BuOK in 20 ml THF and then with 8.5 g (0.059 moles) methyliodide. After 20 min of stirring at room temperature, imine VIIb was isolated by conventional treatment and distillation, T_{bp} 80°C (0.7 torr), n^{20}_D 1.5674, identical to the sample synthesized by procedure A according to IR and PMR spectra.

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