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REACTION OF PRIMARY THIOAMIDES WITH *p*-TOLUENESULFINIC ACID

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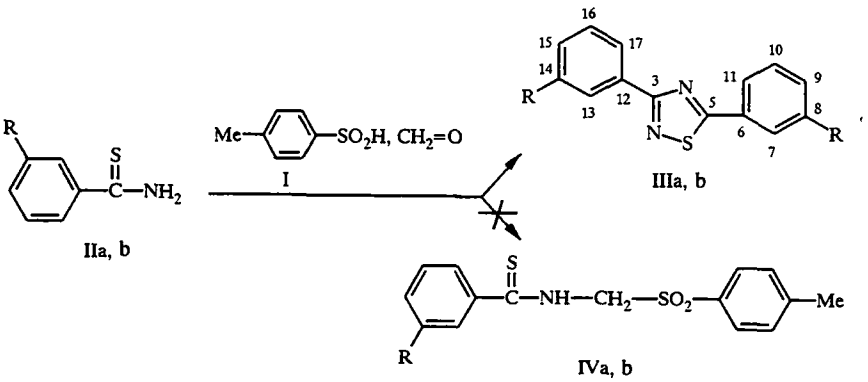
The conversion of thioamides to the corresponding 1,2,4-thiadiazoles occurs upon heating primary thioamides with formaldehyde and p*-toluenesulfinic acid in water instead of the formation of N-(tosylmethyl)thioamides.*

Our work on the synthesis of hydrogenated nitrogen heterocycles using the amidoalkylation reaction [1-3] required the preparation of N-(arylsulfonylmethyl)thioamides. The oxo analogs of these compounds, namely, N-(arylsulfonylmethyl)amides, are readily formed in the reaction of primary amides, aldehydes, and sodium arylsulfinates in the presence of excess formic acid [4, 5]. On other hand, Meijer et al. [6] have shown that the analogous reaction of primary thioamides is more complex. Thus, the reaction of *p*-toluenesulfinic acid (I), thiobenzamide, and formaldehyde or butyraldehyde gives N-(tosylmethyl)-thiobenzamide and N-(1-tosylbutyl)thiobenzamide in 20 and 38% yield, respectively. The reaction of acid I, thiobenzamide, and benzaldehyde gives 3,5-diphenyl-1,2,4-thiadiazole in 34% yield, while the mixture after conclusion of the reaction of acid I, thioacetamide, and aldehyde contains the starting compounds, (hydroxyalkyl)(*p*-tolyl)sulfones and unidentified products. In the present work, we restudied the reaction of thioamides IIa and IIb with formaldehyde and *p*-toluenesulfinic acid. The experiments were carried out under conditions similar to those described by Meijer et al. [6], although only *p*-toluenesulfinic acid I was used instead of the system containing sodium *p*-toluenesulfinate and formic acid.

We have shown that the reaction of equimolar amounts of acid I, thiobenzamide IIa, and formaldehyde in water at 80°C over 4-5 h gives 3,5-diphenyl-1,2,4-thiadiazole (IIIa) as the major nitrogen-containing product. Attempts to isolate N-(tosylmethyl)thiobenzamide (IVa) as described by Meijer [6] were unsuccessful.



II–IV a R = H, b R = Br

A more detailed study of the reaction mixture using PMR spectroscopy indicated that the major products are thiadiazole IIIa and not less than three compounds formed upon conversion of *p*-toluenesulfinic acid. The PMR spectrum has multiplets for the aromatic protons at 7.00-8.50, a set of signals for the aliphatic protons as weak multiplets at 4.00-5.50, and a series of singlets for the methyl groups bound to benzene rings at 2.30-2.50 ppm. The ratio of the integral intensities of these signals is 8.6:0.5:3, while this ratio theoretically should be 9:2:3. Thus, the extent of conversion of formaldehyde in this reaction does not exceed 25%.

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The methylene group protons of IVa appear as a PMR doublet at 5.48 ppm [6]. Only one weak doublet is found at 5.43 ppm with signals separated by 6.6 Hz in the PMR spectrum of the reaction mixture at 5.4-5.5 ppm. If we assume that this doublet belongs to IVa, its content is only 7% relative to thiadiazole IIIa.

The reaction of 3-bromothiobenzamide IIb with formaldehyde and *p*-toluenesulfinic acid in water at 80°C for 5.5 h also leads to 3,5-di(3-bromophenyl)-1,2,4-thiadiazole (IIIb) rather than the expected product, N-(tosylmethyl)-3-bromothiobenzamide (IVb).

Thus, the major reaction upon heating *p*-toluenesulfinic acid, formaldehyde, and thioamides is the oxidative condensation of the latter to give 1,2,4-thiadiazoles. This condensation is apparently promoted not by formaldehyde, which is known to react with thioamides to give only N-(hydroxymethyl)thioamides [7], but rather the sulfinic acid. Indeed, heating thioamides IIa and IIb with *p*-toluenesulfinic acid without formaldehyde in water at 80°C for 4-5.5 h gives thiadiazoles IIIa and IIIb in 69-100% yield.

The PMR spectrum of the product mixture obtained in the reaction of thiobenzamide IIa with *p*-toluenesulfinic acid in water at 80°C for 4.5 h with subsequent extraction of the reaction mixture with chloroform, drying, and evaporation shows aromatic proton multiplets at 7.04-8.44 and six methyl group protons at 2.30-2.41 ppm. The ratio of the integral intensities of these signals is 8.8:3, which is in good accord with the ratio of the aromatic protons and methyl group protons in the starting compounds (9:3). The aromatic region of the spectrum clearly shows multiplets for thiadiazole IIIa at 8.35-8.44 (2H), 8.00-8.10 (2H), and 7.46-7.56 ppm (6H). The multiplets at 7.04-7.26 and 7.34-7.47 ppm and the methyl group proton signals belong to conversion products of *p*-toluenesulfinic acid. S-(*p*-Tolyl) *p*-toluenethiosulfonate (V) is one of these products and comprises 39% of the mixture of products of the conversion of acid I. This product was identified by comparing this PMR spectrum with the spectrum of V obtained by the disproportionation of *p*-toluenesulfinic acid upon heating in acetic acid according to Kice and Bowers [8].

Similar transformations probably occur also in the reaction of thioacetamide and *p*-toluenesulfinic acid in water at 80°C. In this case, thin-layer chromatography of the reaction mixture shows that thioacetamide disappears almost entirely after 5 h. Extraction of the reaction mixture with ether, drying, and evaporation in vacuum gave a compound whose PMR spectrum showed only products of the conversion of *p*-toluenesulfinic acid. The lack of products of the conversion of thioacetamide may be attributed to the formation of 3,5-dimethyl-1,2,4-thiadiazole, which is lost during the reaction and work-up of the reaction mixture due to its volatility (bp 146-148°C [9, 10]).

EXPERIMENTAL

The IR spectra were taken on a Shimadzu IR-435 spectrometer for suspensions in Vaseline. The ^1H and ^{13}C NMR spectra were taken on Bruker MSL-200 and Varian Gemini-300 spectrometers for solutions in $CDCl_3$. The chemical shifts were assigned using the solvent signal relative to TMS (δ = 7.25 ppm in the PMR spectra and δ = 77.2 ppm for the ^{13}C NMR spectra). The signal assignment for the ^{13}C NMR spectra was carried out through an additive scheme using reported substituent increments and taking DEPT spectra with selective proton decoupling.

The reaction course and purity of the products obtained were monitored by thin-layer chromatography on Kieselgel F254 plates (Merck) using 100:1 petroleum ether—methanol as the eluent. The plates were developed with UV light or iodine vapor. Column chromatography was carried out on silica gel L40/100μ.

A sample of *p*-toluenesulfinic acid was obtained by the reduction of *p*-toluenesulfonyl chloride by sodium sulfite [11], dried over P_2O_5, and stored at 0°C.

3,5-Diphenyl-1,2,4-thiadiazole (IIIa). A. A mixture of 0.500 g (3.64 mmoles) thiobenzamide, 0.569 g (3.64 mmoles) *p*-toluenesulfinic acid, and 8 ml water was stirred at 80°C (bath temperature). An orange oil formed at the bottom of the flask soon after the reaction onset. After 4 h, the reaction mixture was cooled to room temperature and extracted with chloroform. The extract was dried over $MgSO_4$ and evaporated in vacuum. A small amount of methanol was added to the waxy residue and cooled to −5°C. The precipitate was filtered off, washed with cold methanol, and dried to give 0.237 g (54.6%) IIIa. (The yield was not optimized. Thin-layer chromatography indicated a significant amount of IIIa remaining in the mother liquor). The product was recrystallized from methanol or hexane, mp 92-92.5°C (hexane) (89-90°C (ethanol) [9]). IR spectrum: 1512, 1440, 1416, 1328, 1273, 1118, 1070, 987, 757, 703, 677 cm^{-1}. PMR spectrum: 8.35-8.44 (2H, m, 13- and 17-H), 8.00-8.10 (2H, m, 7- and 11-H), 7.46-7.56 ppm (6H, m, 8-, 9-, 10-, 14-, 15-, and 16-H). ^{13}C NMR spectrum: 188.1 ($C_{(3)}$), 173.9 ($C_{(5)}$),

133.0 ($C_{(12)}$), 131.9 ($C_{(15)}$), 130.8 ($C_{(6)}$), 130.4 ($C_{(9)}$), 129.3 ($C_{(14)}$, $C_{(16)}$), 128.7 ($C_{(8)}$, $C_{(10)}$), 128.5 ($C_{(13)}$, $C_{(17)}$), 127.5 ppm ($C_{(7)}$, $C_{(11)}$). Found: C, 70.83; H, 4.24; N, 11.52%. Calculated for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76%.

B. A mixture of 1.094 g (7.97 mmoles) thiobenzamide, 1.247 g (7.98 mmoles) *p*-toluenesulfinic acid, and 15 ml water was stirred at 80°C for 4.5 h. The reaction mixture was extracted with five 6-ml portions of chloroform. The extract was dried over $MgSO_4$ and evaporated using first a water pump and then oil pump to give 1.737 g residue. PMR spectroscopy indicated that this residue was a mixture of IIIa and the products of the conversion of *p*-toluenesulfinic acid. This residue was dissolved in a minimal amount of chloroform and the solution was placed on a column containing 45 g silica gel. Elution with ~500 ml petroleum ether gave the nonpolar products of the conversion of acid I (0.775 g) and then, elution with 100:1 petroleum ether—methanol gave 0.950 g (~100%) IIIa.

C. A mixture of 0.275 g (2.00 mmoles) thiobenzamide, 0.067 g (2.23 mmoles) paraformaldehyde, 0.345 g (2.21 mmoles) *p*-toluenesulfinic acid, and 9 ml water was stirred at 80°C for 4.5 h. The reaction mixture was extracted with five 5-ml portions of chloroform. The extract was washed with three 8-ml portions of water, dried over $MgSO_4$, and evaporated using a water pump and then oil pump to give 0.462 g residue. PMR spectroscopy showed that this residue was complex, containing mainly IIIa and the products of conversion of *p*-toluenesulfinic acid. A small amount of methanol was added to the residue and cooled to −5°C. The precipitate was filtered off, washed with cold methanol, and dried to give 0.175 g (29.4%) IIIa.

3,5-Di(3-bromophenyl)-1,2,4-thiadiazole (IIIb). A. Using procedure A described above, the reaction of 3-bromothiobenzamide IIb and *p*-toluenesulfinic acid in water at 80°C over 5.5 h gave IIIb in 68.8% yield, mp 149.5-150°C (methanol). IR spectrum: 1561, 1296, 1224, 1069, 991, 784, 721, 668 cm^{-1}. PMR spectrum: 8.52 (1H, t, $J_{13,15}$ = 2.0, $J_{13,17}$ = 1.6, $J_{13,16}$ = ~0 Hz, 13-H), 8.28 (1H, d.t, $J_{15,17}$ = 1.0, $J_{16,17}$ = 7.8 Hz, 17-H), 8.20 (1H, t, $J_{7,9}$ = 2.0, $J_{7,11}$ = 1.6, $J_{7,10}$ = ~0 Hz, 7-H), 7.91 (1H, d.d.d, $J_{9,11}$ = 1.1, $J_{10,11}$ = 7.8 Hz, 11-H), 7.66 (1H, d.d.d, $J_{15,16}$ = 8.0 Hz, 15-H), 7.60 (1H, d.d.d, $J_{9,10}$ = 8.0 Hz, 9-H), 7.38 (1H, t, 16-H), 7.36 ppm (1H, t, 10-H). ^{13}C NMR spectrum: 186.9 ($C_{(3)}$), 172.5 ($C_{(5)}$), 135.1 ($C_{(15)}$), 134.5 ($C_{(12)}$), 133.6 ($C_{(9)}$), 132.3 ($C_{(6)}$), 131.5 ($C_{(13)}$), 131.0 ($C_{(16)}$), 130.5 ($C_{(10)}$), 130.3 ($C_{(7)}$), 127.0 ($C_{(17)}$), 126.3 ($C_{(11)}$), 123.6 ($C_{(14)}$), 123.0 ppm ($C_{(8)}$). Found: C, 42.36; H, 2.11; N, 7.12%. Calculated for $C_{14}H_8Br_2N_2S$: C, 42.45; H, 2.04; N, 7.07%.

B. According to procedure B described above, the reaction of 3-bromothiobenzamide IIb, paraformaldehyde, and *p*-toluenesulfinic acid in water at 80°C over 4.5 h gave IIIb in 35.8% yield.

S-(*p*-Tolyl) *p*-Toluenesulfonate (V). According to the method of Kice and Bowers [8], the reaction of *p*-toluenesulfinic acid with glacial acetic acid at 70°C for 1 h gave V in 86% yield. PMR spectrum: 7.43 (2H, d, J = 7.83 Hz, H_{arom} in Ts), 7.21 (2H, d, J = 8.2 Hz, H_{arom} in SC_6H_4Me), 7.19 (2H, d, H_{arom} in Ts), 7.12 (2H, d, H_{arom} in SC_6H_4Me), 2.40 (3H, s, CH_3 in Ts), 2.35 ppm (3H, s, SC_6H_4Me). ^{13}C NMR spectrum: 144.7, 142.2, 140.8, 124.9 (quaternary carbon atom signals), 136.6, 130.4, 129.5, 127.7, 21.7, 21.6 ppm.

REFERENCES

1. A. D. Shutalev, Khim. Geterotsikl. Soedin., No. 10, 1389 (1993).
2. A. D. Shutalev and V. A. Kuksa, Khim. Geterotsikl. Soedin., No. 1, 97 (1995).
3. N. V. Sivova and A. D. Shutalev, Khim. Geterotsikl. Soedin., No. 2, 273 (1995).
4. T. Olijnsma, J. B. F. N. Engberts, and J. Strating, Rec. Trav. Chim., **86**, 463 (1967).
5. T. Olijnsma, J. B. F. N. Engberts, and J. Strating, Rec. Trav. Chim., **91**, 209 (1967).
6. H. Meijer, R. M. Tel, J. Strating, and J. B. F. N. Engberts, Rec. Trav. Chim., **92**, 72 (1973).
7. H. Bohme and H.-H. Hotzel, Arch. Pharm., **300**, 241 (1967).
8. J. L. Kice and K. W. Bowers, J. Am. Chem. Soc., **84**, 605 (1962).
9. G. Kresze, A. Horn, R. Phillippson, and A. Trede, Chem. Ber., **98**, 3401 (1965).
10. G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H. P. Patzschke, H. Smalla, and A. Trede, Angew. Chem., **74**, 135 (1962).
11. Weygand–Hilgetag, Experimental Methods in Organic Chemistry [Russian translation], Khimiya, Moscow (1968), p. 607.