Chemistry of Heterocyclic Compounds, Vol. 31, No. 7, 1995

BROMINATION OF 4-SUBSTITUTED THIAZOLYLHYDRAZONES

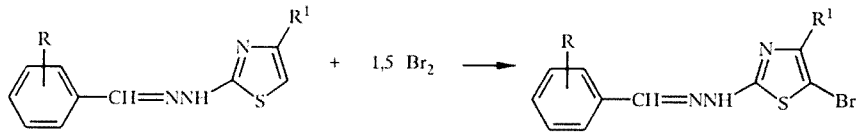
A. B. Denisova and G. P. Andronnikova

4-Phenyl- and 4-methylthiazolylhydrazones were brominated in chloroform and acetic acid. The use of 1.5 equivalents of bromine led to the exclusive formation of the 5-halo derivatives. Effects of substituents on the thiazole ring and of the hydrazone fragment aromatic ring on the course of the reaction were discovered.

In a study of the bromination of 4-carboethoxythiazolylhydrazones, we showed that this reaction depends on the amount of halogen used. The bromination proceeds both at $C_{(5)}$ of the heterocyclic ring and the methine carbon atom in the reaction of thiazole hydrazones with two bromine equivalents. The use of less than 1.5 bromine equivalents leads to the introduction of bromine only into the thiazole ring [1-3].

In order to obtain a series of 5-bromothiazolylhydrazones, we studied the bromination of 2-(R-benzylidene)hydrazino-4-phenylthiazole (I) and 2-(R-benzylidene)hydrazino-4-methylthiazole (II) in different solvents taking account of the complexity of the halogenation reaction. The starting hydrazones were obtained by the reaction of the corresponding thiosemicarbazones with bromoacetophenone or bromoacetone in ethanol.

The nature of the halogenation of these hydrazones was found to depend on the substituents in the thiazole ring and hydrazone fragment.



Ia-d, IIa-d IIIa-d, IVa-d

I, III R^1 = Ph; II—IV R^1 = CH_3; I—IV a R = H, b R = 3-NO_2, c R = 4-OCH_3, d R = 4-NO_2

2-Benzylidene- (Ia, IIa) and 2-(3-nitrobenzylidene)hydrazino-4-R^1-thiazoles (Ib, IIb) were smoothly brominated in chloroform at room temperature to give 4-phenyl- and 4-methyl-5-bromo derivatives (III, IVa, IVb).

The reaction of (4-methoxybenzylidene)hydrazino-4-R^1-thiazoles (Ic, IIc) with bromine in chloroform at room temperature leads to bromination of the phenyl ring of the hydrazone fragment in addition to halogenation of the thiazole ring as indicated by PMR spectroscopy. Products IIIc and IVc could be isolated without impurities only when the reaction of the starting compounds was carried out with 1.2 bromine equivalents in chloroform with cooling.

The least reactive 2-(4-nitrobenzylidene)hydrazinothiazoles (Id, IId) did not react with bromine in chloroform at room temperature or upon heating at reflux. The corresponding 5-bromothiazoles IIId and IVd were obtained in low yield upon heating in acetic acid at reflux.

Urals State Technical University—UPI, 620002 Yekaterinburg. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 991-995, July, 1995. Original article submitted March 1, 1995.

0009-3122/95/3107-0863$12.50

TABLE 1. PMR Spectra of I-IVa-d

Compound	Chemical shift, δ, ppm			Other signals
	H_5	CH=N	CH_3	
Ia	7,35	8,05	—	7,1...7,55 (6H, m, C_6H_5, H-5), 7,6...7,95 (6H, m, C_6H_5), 12,15 (1H, br.s, NH)
Ib*	7,05	8,43	—	7,57 (5H, br.s, C_6H_5), 7,70...8,35 (3H, m, C_6H_4), 8,74 (1H, br.s, C_6H_4)
Ic	7,28	7,98	—	3,80 (3H, s, OCH_3), 7,00 (2H, d, C_6H_4), 7,3...7,53 (3H, m, C_6H_5), 7,65 (2H, d, C_6H_4), 7,7...7,95 (2H, m, C_6H_5), 11,9 (1H, br.s, NH)
Id*	7,10	8,40	—	7,65 (5H, br.s, C_6H_5), 8,0 (2H, d, C_6H_4), 8,37 (2H, d, C_6H_4)
IIa	6,37	8,03	2,19	7,35...7,72 (5H, m, C_6H_5), 11,84 (1H, br.s, NH)
IIb	6,40	8,11	2,17	7,60...8,21 (4H, m, CH=N, C_6H_4), 8,42 (1H, br.s, C_6H_4), 12,03 (1H, br.s, NH)
IIc	6,33	7,94	2,15	3,78 (3H, s, OCH_3), 6,97 (2H, d, C_6H_4), 7,57 (2H, d, C_6H_4), 12,03 (1H, br.s, NH)
IId	6,45	8,08	2,18	7,85 (2H, d, C_6H_4), 8,25 (2H, d, C_6H_4), 12,11 (1H, br.s, NH)
IIIa	—	8,08	—	7,2...7,97 (10H, m, C_6H_5)
IIIb*	—	8,43	—	7,10...7,65 (5H, br.s, C_6H_5), 7,65...8,40 (3H, m, C_6H_4), 8,70 (1H, br.s, C_6H_4)
IIIc	—	8,00	—	3,80 (3H, s, OCH_3), 7,00 (2H, d, C_6H_4), 7,20...7,50 (3H, m, C_6H_5), 7,62 (2H, d, C_6H_4), 7,70...7,95 (2H, m, C_6H_5)
IIId*	—	8,48	—	7,60 (5H, br.s, C_6H_5), 8,05 (2H, d, C_6H_4), 8,42 (2H, d, C_6H_4)
IVa	—	8,01	2,14	7,37...7,68 (5H, m, C_6H_5)
IVb	—	8,11	2,14	7,77...8,24 (4H, m, CH=N, C_6H_4), 8,42 (1H, br.s, C_6H_4), 12,01 (1H, br.s, NH)
IVc	—	7,95	2,15	3,80 (3H, s, OCH_3), 6,97 (2H, d, C_6H_4), 7,57 (2H, d, C_6H_4)
IVd	—	8,12	2,16	7,85 (2H, d, C_6H_4), 8,28 (2H, d, C_6H_4), 12,40 (1H, br.s, NH)

*Spectrum taken in CF_3CO_2D.

The introduction of bromine at $C_{(5)}$ of the thiazole ring was indicated by PMR spectroscopy (Table 1). In previous communications, we analyzed the PMR spectra of a series of 2-hydrazino- and 2-hydrazonothiazoles and the assignment of the signals for the protons of the heterocycle and at $C_{(5)}$ and of the methine proton was carried out using these data [4].

The spectra of bromo derivatives IIIa-IIId lack singlets for the proton at $C_{(5)}$ at 7.1-7.4 ppm observed in the spectra of starting hydrazones Ia-Id. On the other hand, the azomethine signals found at 8.0-8.4 ppm remain virtually unchanged.

The PMR spectra of 4-methylthiazoles IVa-IVd also lack the quartet of the heterocyclic proton at 6.3-6.5 ppm split by the methyl group at $C_{(4)}$. The methyl proton doublet characteristic for the spectra of starting hydrazones IIIa-IIId is converted into a three-proton singlet at 2.2 ppm.

The reaction of hydrazones I and II with more than 1.5 bromine equivalents in chloroform and acetic acid leads to mixtures, from which separation of individual products was difficult. PMR spectroscopy indicated that these mixtures contained disubstitution products analogous to those obtained in our previous work [1] in addition to monosubstitution products III and IV.

Thus, the use of 1.2-1.5 bromine equivalents leads to bromination in the thiazole ring.

The greater rate of bromination of the 4-methylthiazole hydrazones in comparison with the 4-phenyl derivatives is related to the electronic effect of the methyl group, which facilitates introduction of the bromine atom into the heterocycle. The rate of the reaction was found to depend on the substituent on the aromatic ring of the hydrazone fragment. For example, the greater reactivity of 2-(*p*-methoxybenzylidene)hydrazinothiazoles Ic and IIc and reduced reactivity of *p*-nitrobenzylidene derivatives Id and IId indicates transfer of this effect through the extended $\pi-\pi-p-\pi$ conjugation chain of the aromatic ring, C=N group, amine nitrogen atom, and thiazole ring.

EXPERIMENTAL

The PMR spectra were taken on a Bruker WP-80 spectrometer at 80.13 MHz and Tesla-567A spectrometer at 100 MHz with TMS as the internal standard. The IR spectra were taken on an IR-75 spectrometer for KBr pellets. The mass spectra were taken on a Varian MAT-311A mass spectrometer. The accelerating voltage was 3 kV and the ionizing radiation energy was 70 eV. The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates using chloroform and 9:1 chloroform–ethanol as the eluents.

The elemental analysis data correspond to the calculated values (Table 2).

General Procedure for Preparation of 2-(R-Benzylidenehydrazino)-4-R^1-thiazoles (Ia-Id, IIa-IId). A sample of 0.013 mole bromoacetophenone (for Ia-Id) or bromoacetone (for IIa-IId) was added to a solution of 0.01 mole of the corresponding thiosemicarbazone in ethanol. The mixture was heated at reflux for 1 h and cooled. The precipitate formed was filtered off, dried, suspended in water, and treated with concentrated aqueous ammonia to bring the pH to 9. The free base of the hydrazone was filtered off, washed with water, dried, and recrystallized from ethanol.

2-Benzylidenehydrazino-4-phenylthiazole (Ia, $C_{16}H_{13}N_3S$) was obtained in 90% yield, mp 220°C, R_f 0.3 (chloroform). Mass spectrum, *m/z* (I > 10%): M^+ 279 (72.4), 176 (100), 134 (78), 104 (14). IR spectrum: 3440, 3300 (NH), 1595, 1590 (C=N), 1550 cm^{-1} (NH).

2-(3-Nitrobenzylidene)hydrazino-4-phenylthiazole (Ib, $C_{16}H_{12}N_4O_2S$) was obtained in 95% yield, mp 215°C, R_f 0.55 (9:1 chloroform–ethanol). Mass spectrum, *m/z* (I > 10%): M^+ 324 (70.9), 176 (99.1), 134 (100), 104 (12.9). IR spectrum: 3240 (NH), 1580 (C=N), 1520, 1340 cm^{-1} (NO_2).

2-(4-Methoxybenzylidene)hydrazino-4-phenylthiazole (Ic, $C_{17}H_{15}N_3OS$) was obtained in 87% yield, mp 196°C, R_f 0.25 (9:1 chloroform–ethanol). Mass spectrum, *m/z* (I > 10%): M^+ 309 (27.6), 176 (100), 134 (54.6). IR spectrum: 3180, 3110 (NH), 1600, 1560 (C=N), 1520 cm^{-1} (NH).

2-(4-Nitrobenzylidene)hydrazino-4-phenylthiazole (Id, $C_{16}H_{12}N_4O_2S$) was obtained in 89% yield, mp 250°C, R_f 0.25 (9:1 chloroform–ethanol). Mass spectrum, *m/z* (I > 10%): M^+ 324 (98.1), 175 (21), 134 (100), 104 (12). IR spectrum: 3295 (NH), 1580 (C=N), 1540, 1320 cm^{-1} (NO_2).

2-Benzylidenehydrazino-4-methylthiazole (IIa, $C_{11}H_{11}N_3S$) was obtained in 76% yield, mp 184°C, R_f 0.24 (chloroform). IR spectrum: 3180, 3160, 3080 (NH), 1610, 1570 cm^{-1} (C=N).

2-(3-Nitrobenzylidene)hydrazino-4-methylthiazole (IIb, $C_{11}H_{10}N_4O_2S$) was obtained in 81% yield, mp 204°C, R_f 0.3 (chloroform). IR spectrum: 3155, 3120, 3050 (NH), 1575 (C=N), 1530, 1360 cm^{-1} (NO_2).

2-(4-Methoxybenzylidene)hydrazino-4-methylthiazole (IIc, $C_{12}H_{13}N_3OS$) was obtained in 86% yield, mp 170°C, R_f 0.08 (chloroform). IR spectrum: 3200, 3030 (NH), 1570 (C=N), 1510 cm^{-1} (NH).

2-(4-Nitrobenzylidene)hydrazino-4-methylthiazole (IId, $C_{11}H_{10}N_4O_2S$) was obtained in 89% yield, mp 240°C, R_f 0.1 (chloroform). IR spectrum: 3440, 3030 (NH), 1570 (C=N), 1510, 1340 cm^{-1} (NO_2).

2-Benzylidenehydrazino-4-phenyl-5-bromothiazole (IIIa, $C_{16}H_{12}BrN_3S$). A sample of bromine was added to chloroform to give a solution containing 1 ml bromine per 10 ml solution. This bromine solution (1.55 ml, 3 mmoles) was added dropwise to a solution of 0.56 g (2 mmoles) hydrazone Ia in 30 ml dry chloroform and stirred for 3 h at room temperature. Then, 50 ml heptane was added. The precipitate of IIIa was filtered off, washed with ether, and dried. The dry precipitate was suspended in water and treated with concentrated aqueous ammonia to pH 8. The suspension was stirred, filtered, washed with water, and dried. The precipitate was redeposited from chloroform by adding heptane. The yield of IIIa was 65%, mp 114°C, R_f 0.35 (chloroform). Mass spectrum, *m/z* (I > 10%): M^+ 357 (33.6), 369 (32.6), 279 (70), 254 (30), 256 (29.7), 176 (100), 174 (66.7), 134 (77.3), 89 (27). IR spectrum: 3450 (NH), 1598, 1575 (C=N), 1565 cm^{-1} (NH).

2-(3-Nitrobenzylidene)hydrazino-4-phenyl-5-bromothiazole (IIIb, $C_{16}H_{11}BrN_4O_2S$) was obtained in 80% yield by analogy to IIIa, mp 145°C (dec.), R_f 0.5 (9:1 chloroform–ethanol). IR spectrum: 3450, 3060 (NH), 1580 (C=N), 1530, 1350 (NO_2), 1580 cm^{-1} (C–Br).

2-(4-Methoxybenzylidene)hydrazino-4-phenyl-5-bromothiazole (IIIc, $C_{17}H_{14}BRN_3S$). A sample of bromine was added to chloroform to give a solution of 1 ml bromine per 10 ml solution. The bromine solution (1 ml, 2 mmoles) was added dropwise to a solution of 0.5 g (1.6 mmole) hydrazone Ic in 20 ml chloroform with cooling to from −5 to −10°C. The reaction mixture was stirred for 15 min and, then, 50 ml cooled heptane was added. The precipitate of the hydrochloride salt of IIIc was filtered off, washed with ether, and dried. The dry precipitate was suspended in water and aqueous ammonia was added to pH 8. The solid was filtered off, washed with water, dried, and reprecipitated from chloroform by adding heptane.

TABLE 2. Elemental Analysis Data for I-IVa-d

Compound	Found, %/ Calculated, %				
	C	H	N	S	Br
Ia	69.0 68,8	4.8 4,7	15.2 15,0	11.2 11,5	—
Ib	59.4 59,3	3.9 3,7	17.4 17,3	10.0 9,9	—
Ic	66.2 66,0	5.0 4,9	13.6 13,6	10.2 10,4	—
Id	59.0 59,3	4.0 3,7	17.8 17,3	10.1 9,9	—
IIa	61.0 60,8	5.2 5,1	19.6 19,3	15.0 14,8	—
IIb	50.2 50,4	3.9 3,8	21.3 21,4	12.5 12,2	—
IIc	58.5 58,3	5.5 5,3	17.3 17,0	13.2 13,0	—
IId	50.3 50,4	4.0 3,8	21.7 21,4	12.4 12,2	—
IIIa	53.9 53,6	3.0 3,4	12.0 11,7	8.4 8,9	22.6 22,3
IIIb	48.0 47,7	3.0 2,8	14.2 13,9	8.3 8,0	20.0 19,8
IIIc	52.8 52,6	3.9 3,6	11.1 10,.8	8.6 8,3	20.9 20,6
IIId	47.9 47,7	3.1 2,8	14.1 13,9	8.3 8,0	19.9 19,8
IVa	44.9 44,6	3.6 3,4	11.5 11,2	11.1 10,8	27.3 27,0
IVb	39.0 38,7	3.0 2,7	16.7 16,4	9.6 9,4	27.3 23,4
IVc	44.5 44,2	4.0 3,7	13.2 12,9	10.0 9,8	24.7 24,5
IVd	38.9 38,7	2.9 2,7	16.6 16,4	9.6 9,4	23.5 23,4

The yield of IIIc was 75%, mp 130°C, R_f 0.3 (9:1 chloroform–ethanol). IR spectrum: 3300 (NH), 1600, 1565 (CN), 1515 cm^{-1} (NH).

2-(4-Nitrobenzylidene)hydrazino-4-phenyl-5-bromothiazole (IIId, $C_{16}H_{11}BrN_4S$). A sample of bromine was added to acetic acid to give a solution of 1 ml bromine per 10 ml solution. The bromine solution (0.85 ml, 1.6 mmole) was added dropwise to a solution of 0.35 g (1 mmole) Id in 30 ml glacial acetic acid. The reaction mixture was heated at reflux for 2 h, cooled, and poured into 50 ml cooled distilled water. The crystalline precipitate was filtered off, washed with a large amount of water, dried, and redeposited from chloroform by adding heptane. The yield of IIId was 51%, mp 180°C, R_f 0.25 (9:1 chloroform–ethanol). IR spectrum: 3430, 3080 (NH), 1560, 1325 cm^{-1} (NO_2).

2-Benzylidenehydrazino-4-methyl-5-bromothiazole (IVa, $C_{11}H_{10}BrN_3S$) was obtained by analogy to IIIa. The reaction time was 1 h. The yield of IVa was 87%, mp 138°C, R_f 0.3 (chloroform). IR spectrum: 3185, 3170 (NH), 1610, 1585 (C=N), 560 cm^{-1} (C–Br).

2-(3-Nitrobenzylidene)hydrazino-4-methyl-5-bromothiazole (IVb, $C_{11}H_9BrN_4O_2S$) was obtained by analogy to IVa in 89% yield, mp 176°C (dec.), R_f 0.3. IR spectrum: 3430, 3155 (NH), 1580 (C=N), 1530, 1360 (NO_2), 560 cm^{-1} (C–Br).

2-(4-Methoxybenzylidene)hydrazino-4-methyl-5-bromothiazole (IVc, $C_{12}H_{12}BrN_3OS$) was obtained by analogy to IIIc in 80% yield, mp 130°C, R_f 0.25 (chloroform). IR spectrum: 3180, 3070 (NH), 1605 (C=N), 1510 (NH), 585 cm^{-1} (C–Br).

2-(4-Nitrobenzylidene)hydrazino-4-methyl-5-bromothiazole (IVd, $C_{11}H_9BrN_4O_2S$) was obtained by analogy to IIId in 56% yield, mp 180°C (dec.), R_f 0.3 (chloroform). IR spectrum: 3440, 3120 (NH), 1585 (C=N), 1570, 1340 cm^{-1} (NO_2).

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