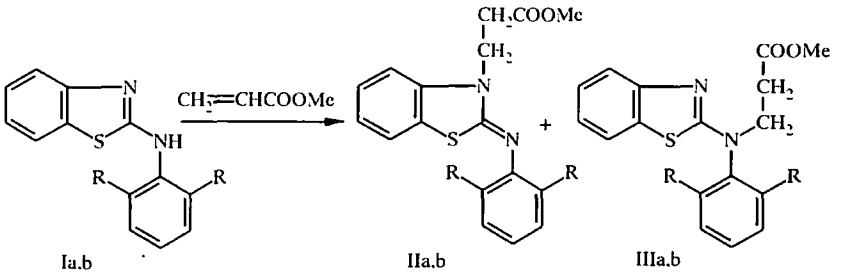
Chemistry of Heterocyclic Compounds, Vol. 35, No. 10, 1999

REACTIONS OF 2-ARYLAMINOBENZO-THIAZOLES WITH METHYL ACRYLATE

R. F. Ambartsumova

Addition of 2-arylaminobenzothiazoles to the C=C bond of methyl acrylate gives a mixture of isomeric 2-arylimino-3-(β-carbomethoxyethyl)benzothiazolines and 2-[N-aryl-N-(β-carbomethoxyethyl)amino]-benzothiazoles. Their thermal stability was studied, HPLC analysis was used to follow the dynamics of the accumulation of the compounds formed in the reaction mixtures.

Previously we have shown that the basic products in reaction of 2-alkylaminobenzothiazoles with methyl acrylate are 2-alkylamino-3-(β-carbomethoxyethyl)benzothiazolines under kinetic control and 2-[N-alkyl-N-(β-carbomethoxyethyl)amino]benzothiazoles under thermodynamic control [1]. In this report we describe the results of the reaction of 2-phenylaminobenzothiazole (Ia) and 2-(2,6-dimethylphenyl)aminobenzothiazole (Ib) with methyl acrylate. Reaction of the heterylamines Ia,b was carried out in excess, refluxing methyl acrylate and led to products of addition to the activated double bond *via* the endo- (compounds IIa,b) and the exocyclic (compounds IIIa,b) nitrogen atoms. Characteristics for the synthesized compounds are given in Table 1.



Ia,b IIa,b IIIa,b

a R = H, b R = Me

We propose that the presence of the amino esters IIIa,b in the reaction mixtures is either the result of imino-amino rearrangement of compounds IIa,b (as is observed in the case of the corresponding acids [2]) or a consequence of their partial degradation to the starting amines Ia,b and stepwise accumulation in the mixture of the aminothiazoles IIIa,b (as is the case in a series of analogous alkyl substituted esters [1]). To clear up this question, we have studied the thermal stability of the products. It was found that heating at 80°C for 15 h had no effect on the imines IIa,b and they were recovered in unchanged form. Hence, under these experimental conditions, compounds IIa,b are neither isomerized nor decomposed.

Analysing the behavior of azoles and azines in nucleophilic substitution reactions, A. F. Pozharskii has proposed [3] that alkylation of the amino form in neutral medium under conditions of kinetic control always leads to the imine. A similar dependence is, as a rule, also realized in nucleophilic addition reactions [4-7]. It therefore follows that 2-arylaminobenzothiazoles exist in the methyl acrylate solution as two tautomeric forms with some predominance of the amino form.

Institute for the Chemistry of Plant Materials, Uzbekistan Republic Academy of Sciences, Taskhkent 700170. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1428-1431, October, 1999. Original article submitted June 2, 1998.

0009-3122/99/3510-1245$22.00©1999 KluwerAcademic/Plenum Publishers

TABLE 1. Characteristics for Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f
		C	H	N		
IIa	$C_{17}H_{16}N_2O_2S$	65.17 / 65.33	5.01 / 5.16	8.97 / 8.96	51-52	0.69
IIb	$C_{19}H_{20}N_2O_2S$	67.12 / 67.01	5.85 / 5.92	8.29 / 8.23	103-104	0.65
IIIa	$C_{17}H_{16}N_2O_2S$	65.08 / 65.33	5.00 / 5.16	8.81 / 8.96	Oil	0.58
IIIb	$C_{19}H_{20}N_2O_2S$	67.15 / 67.01	6.02 / 5.92	8.18 / 8.23	144-145	0.55

It was of interest to follow the dynamics of the products accumulation during the course of the reaction. Using liquid chromatography, we were able to analyze the content of compounds Ia, IIa, and IIIa in the reaction mixtures when refluxing amine Ia in excess methyl acrylate over 0.3-20 h. It was found that, even after 20 min, both products were recorded and their amounts gradually increased reaching a maximum after 15 h (Fig. 1). Further heating led to almost no change in the composition of the reaction mixtures. As is evident from Fig. 1, the rate of the imino compound IIa formation was rather greater than that of amine IIIa.

Hence, in the reaction of aminobenzothiazoles with methyl acrylate, a crucial role is played by the electronic effects of the substituent and is not caused by steric interactions.

The structure of the synthesized compounds was proved using physicochemical methods of investigation (Table 2). Assignment to the aminobenzothiazole or iminobenzothiazoline series was made on the basis of IR, UV, and mass spectroscopic data. IR spectra indicated that compounds IIa,b have an exocyclic C=N bond. UV spectra also clearly identify the isomers. On changing from the imino compounds IIa,b to the amine structure IIIa,b a bathochromic shift of the long wavelength maximum is observed. In the mass spectra, in accordance with the method developed by us before [8], the ratio of the peaks $[M\text{-}C_2H_3COOMe]^+$ to $[M\text{-}CH_2COOMe]^+$ is much higher in the spectra of compounds IIa,b than their isomers IIIa,b. In the PMR spectra of an analogous series of aminobenzothiazole derivatives there is clearly observed a difference between the amino and imino structures [1]. However in the case of the compounds synthesized by us, even though PMR spectra were in full agreement with the proposed structure for each separate compound, they proved uninformative for the distinction of isomers.

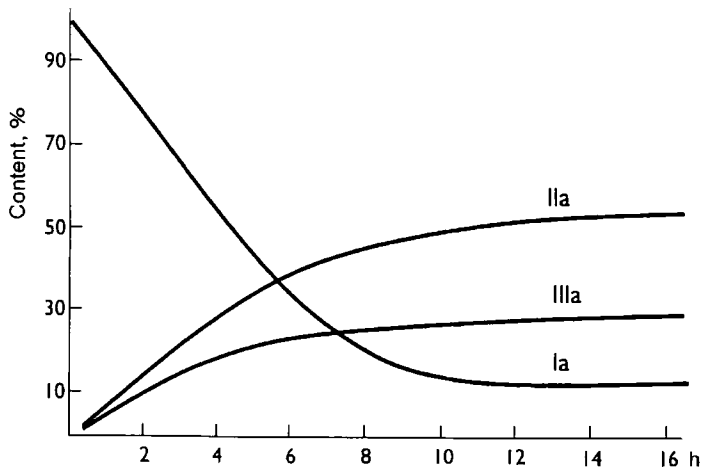
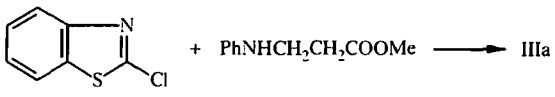


Fig. 1. Kinetic curves for formation of compounds IIa and IIIa and consumption of compound Ia in the reaction of 2-phenylaminobenzothiazole with methyl acrylate.

TABLE 2. Spectral Data for Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}		UV spectrum, λ_{max}, nm	Mass spectrum, *m/z* ($I_{rel.}$, %)				PMR spectrum, δ, ppm
	CO	C=N		M^+	$[M - C_2H_3COOMe]^+$	$[M - CH_2COOMe]^+$	other ions	
IIa	1740	1630	223.5 301.5	312 (45)	226 (100)	239 (5)	253 (27) 150 (39) 136 (9) 109 (18) 77 (17)	2.81 (2H, t) 3.59 (3H, s) 4.28 (2H, t) 6.28-7.41 (9H, m)
IIb	1730	1642	221.5 300.7	340 (59)	254 (100)	267 (2)	325 (19) 281 (24) 239 (28) 221 (16) 150 (39) 136 (30) 135 (28) 131 (31) 109 (55) 81 (80) 77 (52)	2.08 (6H, s) 2.87 (2H, t) 3.62 (3H, s) 4.37 (2H, t) 6.8-7.3 (7H, m)
IIIa	1750	1545	226 290 298.5 (sh)	312 (42)	226 (100)	239 (52)	253 (33) 225 (88) 150 (10) 136 (23) 77 (54)	2.76 (2H, t) 3.51 (3H, s) 4.26 (2H, t) 6.85-7.60 (9H, m)
IIIb	1730	1538	222 264.5 298.8 (sh)	340 (24)	254 (38)	267 (6)	325 (17) 281 (15) 150 (10) 136 (13) 132 (14) 109 (11) 77 (24) 57 (100)	2.17 (6H, s) 2.87 (2H, t) 3.58 (3H, s) 4.15 (2H, t) 6.9-7.6 (7H, m)

In addition to the spectral parameters the structure of aminothiazole IIIa was confirmed by an independent synthesis from 2-chlorobenzothiazole and the methyl ester of N-phenyl-β-alanine:



EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument for KBr tablets and UV spectra on a Hitachi EPS-3T for ethanol solutions. PMR spectra were measured on a Tesla BS-567 instrument (100 MHz, internal standard TMS, solvent $CDCl_3$). Mass spectra were taken on an MS-25 RF instrument with an electron ionization energy of 70-75 eV, source temperature of 300°C, and system temperature for direct introduction of the sample of 100-120°C. HPLC analysis of the reaction mixtures was carried out on a Millichrom chromatograph on a 6.2 × 2 mm column using Silasorb 300 sorbent and a hexane/propan-2-ol mixture (99:1). Monitoring of the course of the reaction and of compound purity were carried out on Silufol UV-254 plates in the system benzene-chloroform-acetone (4:4:1). Column chromatography used L 100/160μ silica gel with hexane, benzene eluent.

The starting materials were synthesized by the following methods: compound Ia [9], compound Ib [10], 2-chlorobenzothiazole [11], methyl ester of N-phenyl-β-alanine [12]. Commercial methyl acrylate was distilled and stabilized with NaSCN.

2-Phenylimino-3-(β-carbomethoxyethyl)benzothiazole (IIa) and 2-[N-Phenyl-N-(β-carbomethoxyethyl)aminobenzothiazole (IIIa). Amine Ia (2.26 g, 10 mmol) was refluxed in methyl acrylate

(20 ml) for 15 h. Excess of acrylate was evaporated off and the reaction mixture extracted using refluxing hexane (3 × 30 ml). The extracts were evaporated and the residue was separated on a chromatography column. The yield of compound IIa was 1.65 g (52%) and IIIa 0.66 g (21%).

In order to study the kinetics, the reaction mixture after reflux was cooled and analyzed using liquid chromatography without work up.

2-(2,6-Dimethylphenylimino)-3-(β-carbomethoxyethyl)benzothiazoline (IIb) and 2-[N-(2,6-Dimethylphenyl)-N-(β-carbomethoxyethyl)]aminobenzothiazole (IIIb). Amine Ib (1.27 g, 5 mmol) was refluxed in methyl acrylate (12 ml) for 20 h. Methyl acrylate was evaporated off and the viscous mass was extracted with hot hexane (3 × 25 ml). The extracts were evaporated and unreacted amine Ia was separated on a column.

The gathered eluate was evaporated and the residue was recrystallized from ether and then hexane to give compound IIb (0.76 g, 45%). The ether mother liquor was evaporated and the residue was recrystallized repeatedly from hexane, recovering the mother liquor each time, to give compound IIIb (0.44 g, 26%).

Independent Synthesis of Compound IIIa. 2-Chlorobenzothiazole (0.85 g, 5 mmol) and the methyl ester of N-phenyl-β-alanine (1.79 g, 10 mmol) were heated with stirring at 130-140°C. The mixture was cooled and diluted with ether and water (to 20 ml), and the layers separated. The organic layer was evaporated and the residue was chromatographed on a column to give compound IIIa (1.12 g, 72%). Samples of compound IIIa, obtained by both methods, had identical R_f values, retention times on HPLC, and spectral parameters.

REFERENCES

1. R. F. Ambartsumova, *Khim. Geterotsikl. Soedin.*, No. 7, 981 (1997).
2. V. A. Saprykina and R. F. Ambartsumova, *Uzb. Khim. Zh.*, No. 4, 65 (1987).
3. A. F. Pozharskii, *Theoretical Basis of the Chemistry of Heterocycles* [in Russian], Khimiya, Moscow (1985), p. 157.
4. C. D. Hurd, *Int. J. Sulfur Chem. A.*, **1**, 97 (1971).
5. S. I. Shul'ga and V. A. Chuiguk, *Khim. Geterotsikl. Soedin.*, No. 5, 632 (1972).
6. Z.-I. G. Beresnevichius, V. Yu. Viliunas, V. I. Raudelyunas, and R. S. Baltrushis, *Khim. Geterotsikl. Soedin.*, No. 1, 80 (1992).
7. R. F. Ambartsumova and V. A. Saprykina, *Uzb. Khim. Zh.*, No. 1, 55 (1994).
8. Ya. V. Rashkes, R. F. Ambartsumova, V. A. Saprykina, and N. K. Rozhkova, *Zh. Org. Khim.*, **14**, 1980 (1978).
9. G. Y. Sarkis and E. D. Faisal, *J. Heterocycl. Chem.*, **22**, 725 (1985).
10. T. Jen, H. Van Hoeven, W. Groves, R. A. McLean, and B. Loev, *J. Med. Chem.*, **18**, 90 (1975).
11. N. S. Drozdov and V. I. Stavrovskaya, *Zh. Obshch. Khim.*, 7, 2813 (1937).
12. W. S. Johnson, E.L. Woroch, and B. G. Buell, *J. Am. Chem. Soc.*, **71**, 1901 (1949).