Chemistry of Heterocyclic Compounds, Vol. 38, No. 8, 2002

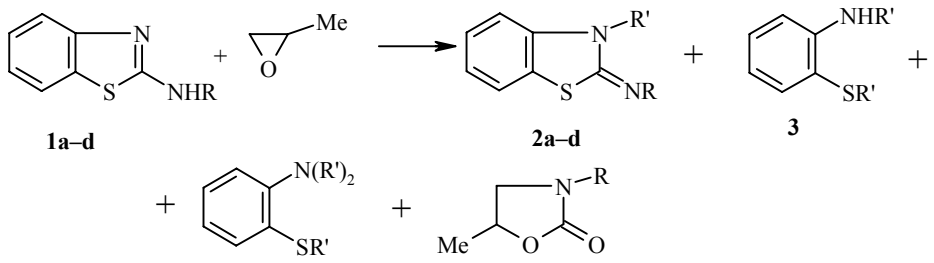
EFFECT OF VARIOUS FACTORS ON THE REACTION OF 2-AMINOBENZO-THIAZOLES WITH PROPYLENE OXIDE

R. F. Ambartsumova and L. P. Kosmacheva

We have shown that when 2-substituted 2-aminobenzothiazoles react with propylene oxide in proton-donor solvents, products of hydroxyalkylation of both the heterocycle and o-aminothiophenol formed as a result of its cleavage are synthesized. We have traced the effect of the nature of the solvent, various additives, the reaction temperature, and the heating time on this process.

Keywords: 2-aminobenzothiazoles, propylene oxide, hydroxyalkylation.

In development of our studies on synthesis of heterocyclic amino alcohols [1, 2] and also study of the characteristic features of cleavage of the heterocycle of aminobenzazoles on reaction with oxiranes [3-5], it seemed of interest to study the effect of the nature of the substituents in the 2 position of the aminobenzothiazole system, and also a number of other factors, on the reaction of 2-aminobenzothiazoles **1a-d** with propylene oxide. We have shown that when amines **1-d** are held with excess propylene oxide in methanol, 3-(β-hydroxypropyl)-2-(R-imino)benzothiazolines **2a-d** are formed, and also hydroxypropyl derivatives of *o*-aminothiophenol **3-4**, which we obtained previously by reaction of unsubstituted 2-aminobenzothiazole with propylene oxide [3]. Compounds **2a-c** were separated from the reaction mixtures and characterized. Compound **2d**, formed in very low yield (Table 1), could not be isolated in pure form. Using TLC to compare with known samples, in addition to compounds **2-4** we detected 3-R-5-methyloxazolidin-2-ones **5a-d** in the reaction mixtures, the formation of which was hypothesized by analogy with previously studied reactions [3-5].



1a–d **2a–d** **3** **4** **5a–d**

1, 2, 5 a R = Me, **b** R = Et, **c** R = COMe, **d** R = Ph; **2–4** R' = CH_2CHMe (OH)

Institute of Plant Chemistry, Academy of Sciences of the Republic of Uzbekistan, Tashkent 700170; e-mail: timal@online.ru. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1135-1140, August, 2002. Original article submitted November 24, 1999.

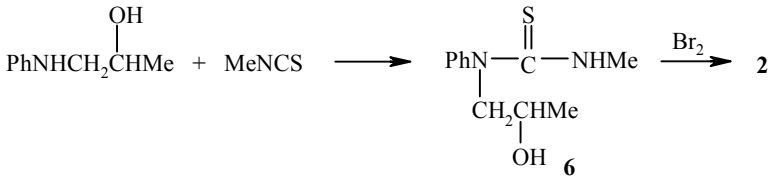
 0009-3122/02/3808-0994$27.00

TABLE 1. Yield of Products of Interaction Between Compounds **1a-d** and Propylene Oxide

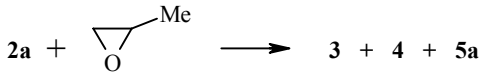
Starting amine	Product yield, %			
	2	**3**	**4**	**2 + 3 + 4**
1a	30	40	6	76
1b	44	25	5	74
1c	22	37	20	79
1d	4	1	<< 1	5

HPLC analysis of the reaction mixtures (Table 1) showed that when methyl, ethyl, or acetyl substituent was introduced into 2-aminobenzothiazole molecule, the total yield of products **2-4** was approximately the same (compounds **5a-d** were not observed under the given conditions). However, when we go from amine **1a** to amine **1b**, the yield of products of cleavage of the benzothiazole ring decreases, while on the other hand when we go from amine **1a** to amide **1c**, the reaction proceeds at a higher conversion rate. From this it follows that the low yield of products in the reaction of amine **1d** with propylene oxide is more likely due to steric hindrances created by the phenyl substituent rather than by electronic factors. On the whole, amines **1a-d** react analogously to unsubstituted 2-aminobenzothiazole [3] and 3-substituted 2-iminobenzothiazolines [4].

The structure of compounds **2a-c** was established on spectral data basis and confirmed by elemental analysis. Compound **2d** was identified by TLC, HPLC, and liquid matrix secondary ion mass spectrometry (LSIMS). Compound **2a** was also obtained by an alternate synthesis to verify its identity: cyclization of thiourea **6**, formed in reaction of N-(β-hydroxypropyl)aniline with methyl isothiocyanate.



Since we previously [4] have shown that 2-methylimino-3-methylbenzothiazoline (**7**), which does not have any mobile hydrogen atoms, reacts with propylene oxide, we carried out the reaction of amino alcohol **2a** with propylene oxide. We found that in this case, a similar reaction occurs, and cleavage of the benzothiazole ring occurs much more vigorously than for compound **7** (the yield of products **3** and **4** is 48% and 15% respectively).



Probably introduction of hydroxyl group into the alkyl chain of the substituent at the endocyclic nitrogen atom of 2-iminobenzothiazoline intensifies the process of opening of the heterocycle due to redistribution of electron density in the N–C=N system, induced by formation of a hydrogen bond of the type

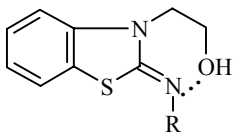


TABLE 2. Solvent Dependence of the Product Yield from Reaction of Amine **1b** with Propylene Oxide

Solvent	Product yield, %		
	2b	**3**	**4**
Methanol	44	25	5
Ethanol	48	5	1
Propanol	50	3	1
Isopropanol	48	1	< 1
Butanol	50	2	< 1
Glycerol	70	15	10
Ethylene glycol	50	26	19
Acetone	< 1	—	—
DMF	< 1	—	—
Methanol–acetone, 3:1	33	4	< 1
Water–acetone, 3:1	61	10	5
Water–acetone, 1:3	61	2	< 1
Phenol–acetone, 1:3	27	—	—
Ethylene glycol–acetone, 3:1	51	21	11
Glycerol–acetone, 3:1	46	6	3
Acetic acid	78	—	—

For the case of amine **1b** as an example, using HPLC we studied the effect of various factors on this process. In Table 2, we present the results of the effect of the nature of the solvent (reaction time 30 days, temperature 25-30°C, mole ratio of amine **1b** to propylene oxide 1:5, amount of the solvent, 1 ml/mmol of amine **1b**). In a number of solvents, amine **1b** did not dissolve (water, phenol) or dissolved poorly, so we used mixtures of these solvents with acetone, and for comparison we took a methanol—acetone mixture. As hypothesized, cleavage of the heterocycle occurs only in protic solvents. The reaction generally does not occur in such aprotic solvents as benzene, chloroform, dioxane. In acetone and DMF, we observed only trace amounts of the alkylation product **2b**. The maximum product yield was observed when using water and polyols. In simple alcohols, the cleavage product yield decreases as we go from the lower homologs to the higher homologs. It is interesting to note that in acetic acid, the products **3** and **4** are generally not observed while the yield of amino alcohol **2b** is high. The results of studying the effect of some agents which might affect the course of the

TABLE 3. Dependence of the Product Yield from Reaction of Amine **1b** with Propylene Oxide on Additives

Solvent	Additive	Amount of additive, mol/mol of amine	Product yield, %		
			2b	**3**	**4**
Methanol	—	—	44	25	5
Methanol	CH_3ONa	2	< 1	—	—
Methanol	NaOH	1	< 1	—	—
Methanol	HCl	1	65	17	5
Methanol	Et_4NI	0.05	36	18	4
Methanol	$ZnCl_2$	0.05	48	18	4
Methanol	$CoCl_2$	0.05	20	2	1
Methanol	$FeBr_2$	0.05	31	12	3
Acetone	—	—	< 1	—	—
Acetone	BF_3OEt_2	0.5	51	—	—

TABLE 4. Dependence of the Product Yield From Reaction of Amine **1b** with Propylene Oxide (mole ratio 1:5) on Temperature and Heating Time

Solvent	Temperature, °C	Time, h	Product yield, %		
			2b	**3**	**4**
Methanol	70	5	25	—	—
Water	70	5	35	—	—
Methanol	70	20	49	13	2
Water	70	20	53	6	2
Methanol	100	10	17	42	5
Ethylene glycol	100	10	15	21	28

reaction are presented in Table 3 (the same conditions). Hydrogen chloride and boron trifluoride etherate, like acetic acid, catalyze synthesis of amino alcohol **2b**, while basic agents almost completely inhibit the process of both alkylation of the heterocycle and its cleavage. Salt additives mainly slightly inhibit both processes.

As we see from Table 4, raising the reaction temperature up to 70°C leads to formation of appreciable amounts of product **2b** even after 5 h, but the cleavage products **3** and **4** appear only with more prolonged interaction or with further increase of temperature. We should note that carrying out the reaction with heating is complicated very considerably by polymerization of oxirane.

EXPERIMENTAL

The IR spectra were taken on an UR-20 apparatus in KBr disks. The UV spectra were recorded on a Perkin-Elmer Lambda 16 spectrometer in ethanol. The mass spectra were taken on a double focusing MKh 1310 spectrometer with direct sample injection SVP 5, ionization chamber temperature 150-170°C, ionizing potential 70 eV. The conditions for obtaining the LSIMS spectrum were similar to those given in [5]. The ^{1}H NMR spectra of the solutions of compounds **2a** and **2c** in $CDCl_3$ and compound **2b** in C_5H_5N-d_5 were measured on a Jeol C-60 HL spectrometer (60 MHz), internal standard TMS.

The composition of the reaction mixtures was determined by HPLC on a Milikhrom-1 chromatograph using a steel column (64 × 2 mm) packed with Silasorb 600. As the mobile phase, we used hexane–chloroform–isopropanol mixture, 80:15:5 (A) and 70:20:10 (B) by volume, elution rate was 100 ml/min, UV detection at 250 nm. The course of the reactions and the purity of the compounds were monitored by TLC (Silufol UV-254, acetone–benzene–chloroform, 2:1:1). The substances were separated and purified by column chromatography (CC) on silica gel L 100/160 μm, eluting successively with hexane, benzene, and acetone.

The starting amines **1a-d** were obtained by the procedures [6-9]. Known samples of oxazolidinones **5a-d** were synthesized by the procedures [10-12]. The characteristics of *o*-aminothiophenols **3** and **4** are given in [3]. In HPLC analysis, the retention times for compounds **3** and **4** are respectively 8'37" and 12'25" in system (A) and 3'58" and 5'52" in system (B).

3-(β-Hydroxypropyl)-2-methyliminobenzothiazoline (2a). Propylene oxide (2.9 g, 50 mmol) was added to solution of 2-methylaminobenzothiazole (**1a**) (1.64 g, 10 mmol) in methanol (10 ml) and held at 25-30°C for 30 days with periodic shaking. Then methanol and excess propylene oxide were removed under vacuum, the residue was analyzed by HPLC, and the products were isolated by column chromatography. Obtained compound **2a**; mp 69-70°C (hexane), R_f 0.59, retention time 7'15" (A). IR spectrum, ν, cm^{-1}: 3325 (OH), 1630 (C=N). UV spectrum, λ_{max}, nm (log ε); 224 (4.74), 263 (4.34), 304 (4.12). ^{1}H NMR spectrum, δ, ppm: 1.16 (3H, d, CH_3); 2.96 (3H, d, CH_3); 3.90 (2H, d, CH_2N); 4.11 (1H, m, CH); 5.10 (1H, br. s, OH); 6.58-7.53 (4H, m, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %); 222 (14) $[M]^+$; 207 (10); 177 (20) $[M–CH(OH)CH_3]^+$;

173 (17); 165 (18); 164 (100) [M–$CH_2CH(OH)CH_3$]$^+$; 163 (28); 150 (20); 149 (16); 138 (12); 137 (12); 136 (96); 135 (28); 109 (31); 95 (18); 81 (16); 77 (17). Found, %: C 59.68; H 6.22; N 12.92. $C_{11}H_{14}N_2OS$. Calculated, %: C 59.46; H 6.31; N 12.61.

Compounds **2b-d** were synthesized similarly.

2-Ethylimino-3-(β-hydroxylpropyl)benzothiazoline (2b) was obtained from 2-ethylamino-benzothiazole (**1b**). Oil, R_f 0.57, retention time 5'41" (A). IR spectrum, ν, cm^{-1}: 3280 (OH), 1630 (C=N). UV spectrum, λ_{max}, nm (log ε): 224 (4.99), 265 (4.56), 298 (4.21). ^{1}H NMR spectrum, δ, ppm: 1.05-1.45 (6H, m, $2CH_3$); 3.05-3.39 (2H, m, CH_2); 4.40 (3H, m, CH_2N, CH); 6.95-7.61 (4H, m, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 236 (22) [M]$^+$; 221 (13); 192 (10); 191 (22) [M–$CH(OH)CH_3$]$^+$; 179 (19); 178 (100) [M–$CH_2CH(OH)CH_3$]$^+$; 164 (15); 163 (49); 150 (53); 149 (16); 136 (17); 135 (11); 109 (20). Found, %: C 61.15; H 6.55; N 12.13. $C_{12}H_{16}N_2OS$. Calculated, %: C 61.02; H 6.78; N 11.86.

2-Acetimido-3-(β-hydroxypropyl)benzothiazoline (2c) was obtained from 2-acetamidobenzothiazole (**1c**); mp 129-130°C (benzene–hexane, 1:1), R_f 0.77, retention time 4'29" (B). IR spectrum, ν, cm^{-1}: 3425 (OH), 1588 (C=N–C=O). UV spectrum, λ_{max}, nm (log ε): 218 (4.47), 227 inflection (4.37), 258 (3.86), 279 (3.90), 312 (4.38). ^{1}H NMR spectrum, δ, ppm: 1.25 (3H, d, CH_3); 2.20 (3H, s, CH_3); 4.15-4.35 (3H, m, CH_2, CH); 4.81 (1H, br. s, OH); 7.15-7.65 (4H, m, H_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 250 (4) [M]$^+$; 235 (10); 205 (8) [M–$CH(OH)CH_3$]$^+$; 193 (52); 192 (36) [M–$CH_2CH(OH)CH_3$]$^+$; 191 (20); 177 (32); 164 (20); 163 (26); 151 (32); 150 (100); 149 (22); 136 (32); 109 (24); 105 (16); 104 (12). Found, %: C 57.62; H 5.33; N 11.25. $C_{12}H_{14}N_2O_2S$. Calculated, %: C 57.58; H 5.64; N 11.19.

3-(β-Hydroxypropyl)-2-phenyliminobenzothiazoline (2d) was obtained from 2-phenylamino-benzothiazole (**1d**), retention time in HPLC analysis was 2'46" (B), LSIMS mass spectrum: *m*/*z* 285 [M+H]$^+$.

Reaction of amine **1b** with propylene oxide was carried out similarly in various solvents (Table 2) and in the presence of various additives (10 mmol) (Table 3). The excess propylene oxide and the low-boiling solvent were removed under vacuum; the residue was analyzed by HPLC.

The reaction of amine **1b** with propylene oxide at different temperatures was carried out with the same ratio of reagents in a sealed ampoule placed in a rotary oven (Table 4).

Alternate Synthesis of Imine 2a. Solution of methyl isothiocyanate (1.14 g, 16 mmol) in absolute benzene (2 ml) was added dropwise to a solution of N-(β-hydroxypropyl)aniline (2.28 g, 15 mmol) in absolute benzene (7 ml). The mixture was stirred at room temperature for 5 h, then boiled for 4 h. The unreacted amine was extracted with dilute hydrochloric acid, then the benzene layer was washed with water and dried with Na_2SO_4. The solvent was removed at reduced pressure; thiourea **6** (2.73 g) was obtained, dissolved in absolute chloroform (30 ml). Solution of bromine (3.04 g, 19 mmol) in chloroform (10 ml) was added dropwise with stirring to the solution cooled down to 0°C, at a rate so that the temperature of the mixture did not rise above 10°C. The reaction mixture was stirred for 2 h at room temperature, then boiled for 2 h. The solvent and excess bromine were removed at reduced pressure, the residue was treated with 25% $NaHSO_3$ solution (20 ml), and the aqueous solution was neutralized by NH_4OH to pH 8. The precipitated oil was extracted with chloroform, the organic layer was dried with Na_2SO_4, the solvent was removed and the residue was recrystallized from hexane. Yield of product **2a** 1.19 g (36%); mp 69-70°C. A mixed sample of imine **2a** with the previously synthesized sample did not result in a depression of the melting point.

REFERENCES

1. R. F. Ambartsumova and L. P. Kosmacheva, *Khim. Geterotsikl. Soedin.*, 685 (1991).
2. M. K. Makhmudov, R. F. Ambartsumova, and B. Tashkhodzhaev, *Khim. Geterotsikl. Soedin.*, 1273 (1996).
3. E. G. Mil'grom, L. P. Kosmacheva, Ya. V. Rashkes, and R. F. Ambartsumova, *Khim. Geterotsikl. Soedin.*, 1139 (1994).

4. L. P. Kosmacheva, E. G. Mil'grom, and R. F. Ambartsumova, *Khim. Geterotsikl. Soedin.*, 1279 (1996).
5. L. P. Kosmacheva, R. F. Ambartsumova, and E. G. Mil'grom, *Khim. Geterotsikl. Soedin.*, 1132 (2000).
6. S. G. Ryklis and R. P. Vel'tman, *Ukr. Khim. Zh.,* **18**, 102 (1952).
7. J. A. VanAllan and G. A. Reynolds, *J. Heterocycl. Chem.*, **5**, 471 (1968).
8. R. Hunter, *J. Chem. Soc.*, 1385 (1926).
9. L. R. Davidenkov and B. A. Porai-Koshits, *Zh. Obshch. Khim.*, **26**, 868 (1956).
10. A. V. Steele, US Pat. 2868801; *Chem. Abstr.,* **53**, 10261 (1959).
11. D. Braun and J. Weinert, *Liebigs Ann. Chem.*, 210 (1979).
12. W. J. Close, *J. Am. Chem. Soc.*, **73**, 95 (1951).