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RECYCLIZATION OF BENZIMIDAZO[2,1-*b*]THIAZANIUM SALTS INTO 1-(2,3-EPITHIOPROPYL)BENZIMIDAZOL-2-ONES UNDER THE ACTION OF EPICHLORHYDRIN

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It has been shown that the reaction of epichlorhydrin with 3-hydroxybenzimidazo[2,1-b]thiazanium salts leads to recyclization of the thiazanium ring with the formation of substituted 1-(2,3-epithiopropyl)benzimidazol-2-ones in high yield. The proposed method enables the introduction of functional groups unstable in alkaline medium into the structure of thiirane derivatives.

Keywords: 3-hydroxybenzimidazo[2,1-*b*]thiazanium salts, thiiranes, 1-(2,3-epithiopropyl)benzimidazol-2-ones, epichlorhydrin, recyclization.

In spite of the fact that the chemistry of thiiranes has attracted the attention of investigators for a long time [1-4], the number of efficient approaches to the synthesis of their derivatives containing functional groups is limited [5-7]. An important method of obtaining derivatives of hetarylthiiranes **2** is the recyclization of 3-hydroxy- and 3-halo-substituted thiazanium salts **2** under the action of alkali [8, 9]. Thiirane derivatives of azolones with alkyl and aralkyl substituents may be obtained by such a method. However, this method is not suitable for obtaining compounds containing, apart from the thiirane ring, fragments sensitive to the action of alkalis (esters, amides, ketone groups).

We have established that in the cases when the counter-ion in the condensed thiazanium salts **1** is halide, heating the salts with an excess of epichlorhydrin leads directly to recyclization into thiirane derivatives – 1-(2,3-epithiopropyl)benzimidazol-2-ones **2** in high yield and without affecting functional groups in position 3 of the ring. Phenacyl, aminocarbonylmethyl, and alkoxycarbonylmethyl were used as functional groups in this work.

The conversion of compounds **1** → **2** is caused by the fact that epichlorhydrin is able to bind halide anions forming the alkoxide anion of glycerin dihalohydrin **1B** which is rapidly protonated as a result of the hydroxyl group of thiazanium salt **1**, assisting the irreversible course of recyclization of the latter to thiirane through the oxidothiazanium zwitterion **2A** and its covalent form **2C**. The synchronous occurrence of a reaction with addition of chloride ion to the oxirane with cleavage of proton from the thiazanium salt is also possible. If the OH

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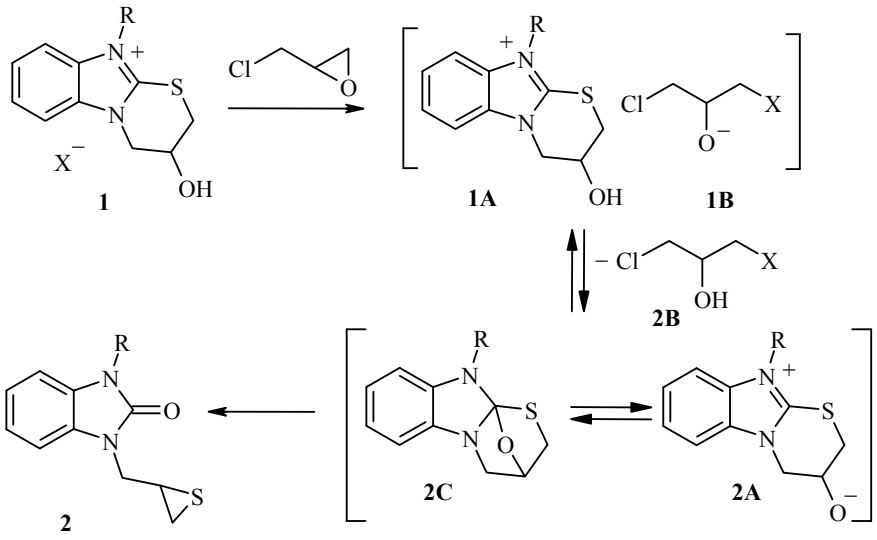
group is protected by acylation then recyclization does not occur, which is caused by the impossibility of carrying out the stage of forming intermediate **2A**. It is interesting that with perchlorate salts of **1**, obtained analogously [9], the reaction also does not proceed due to the low nucleophilicity of this anion.



1, **2 a** R = $PhCOCH_2$, **b** R = *p*-$BrC_6H_4COCH_2$, **c** R = (piperidino)$COCH_2$, **d** R = (morpholino)$COCH_2$, **e** R = $MeOCOCH_2$, **f** R = $EtOCOCH_2$

In the ^1H NMR spectra of thiazanium salts **1a-f** the most characteristic signal is that of the OH group protons in the 5.95-6.15 region and of the methylene group of the substituent in position 1 (6.21-6.31 for phenacyl derivatives **1a,b** and 5.49-5.53 ppm for the aminoalkoxy derivatives **1c-f**). The signals of the propylene fragment were observed in the regions 3.42-3.76 (CH_2S), 4.63-4.75 (CHO), and 4.33-4.58 ppm (CH_2N). The characteristic signals of the 2,3-epithiopropyl group of compounds **2a-f** are the two multiplets of the thiirane rings (in the resolved form of two dd in the 2.37-2.51 and 2.46-2.60 ppm regions, caused by the geminal and vicinal splitting of the small ring protons), the multiplet signals of the CHS (3.14-3.31), and the multiplets of the CH_2N fragment protons (3.88-4.20 ppm).

A new approach has therefore been developed for obtaining azacyclic derivatives of thiiranes containing functional groups unstable in alkaline medium, which comprises recyclization of benzimidazo-[2,1-*b*]-1,3-thiazanium halides **1a-f** on heating in epichlorhydrin. The derivatives obtained may be useful in the search for new biologically active substances, which is confirmed by predictions of the PASS program. Thus it forecast high activity of thiiranes **2a-f** as inhibitors of prolylaminopeptidases and limonene synthetase, as cardiovascular analeptics, peripheral vasodilotators, antagonists of acetylcholine receptors, nootropic preparations, anticonvulsants, etc.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) instrument in DMSO-d_6, internal standard was TMS. Chromatography in a thin layer of silica gel was carried out on Silufol plates (Czech Republic), eluent was chloroform–methanol, 10:1, visualization was with iodine vapor.

3-Hydroxy-10-R-benzimidazo[2,1-*b*]-1,3-thiazanium Salts 1a-f (General Method). A mixture of 3-hydroxybenzimidazo[2,1-*b*]thiazane (1 g, 5 mmol), alkylating agent (5.5 mmol), and DMF (1 ml) was heated

at 150°C for 40 min. For the isolation of compounds **1a,b** precipitated after cooling, the solid was filtered off, washed with DMF, and with acetonitrile, and dried. For the isolation of compounds **1c-f** after cooling, ether (5 ml) was added, the precipitated solid was filtered off, washed with acetonitrile, and dried.

3-Hydroxy-10-phenacylbenzimidazo[2,1-*b*]-1,3-thiazanium Bromide (1a). Yield 84%; mp 237-238 °C (DMF). R_f 0.09. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.42 (1H, dd, $^3J_{cis}$ = 5.0, $^2J_{gem}$ = 12.4, CH_2S); 3.58 (1H, d, $^2J_{gem}$ = 12.4, CH_2S); 4.33 (1H, d, $^2J_{gem}$ = 13.4, NCH_2); 4.47 (1H, d, $^2J_{gem}$ = 13.4, NCH_2); 4.63 (1H, m, CHO); 5.95 (1H, d, *J* = 3.4, OH); 6.21 (2H, d, *J* = 6.8, CH_2CO); 7.43 (2H, m, CH arom.); 7.52 (2H, m, CH arom.); 7.68 (1H, m, CH arom.); 7.83 (2H, m, CH arom.); 8.05 (2H, m, CH arom.). Found, %: C 53.5; H 4.3; N 6.7. $C_{18}H_{17}BrN_2O_2S$. Calculated, %: C 53.3; H 4.2; N 6.9.

10-(4-Bromophenacyl)-3-hydroxybenzimidazo[2,1-*b*]-1,3-thiazanium Bromide (1b). Yield 90%; mp 232-233°C (DMF). R_f 0.08. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.54 (1H, dd, $^3J_{cis}$ = 4.8, $^2J_{gem}$ = 12.5, CH_2S); 3.69 (1H, d, $^2J_{gem}$ = 12.5, CH_2S); 4.45 (1H, dd, J_{cis} = 2.4, $^2J_{gem}$ = 13.5, NCH_2); 4.58 (1H, dd, $^3J_{trans}$ = 2.7, $^2J_{gem}$ = 13.5, NCH_2); 4.74 (1H, m, CHO); 6.07 (1H, s, OH); 6.31 (2H, dd, *J* = 6.9, CH_2CO); 7.57 (2H, m, CH arom.); 7.92 (2H, d, *J* = 8.6, CH arom.); 7.94 (2H, m, CH arom.); 8.09 (2H, d, *J* = 8.6, CH arom.). Found, %: C 44.5; H 3.4; N 5.9. $C_{18}H_{16}Br_2N_2O_2S$. Calculated, %: C 44.7; H 3.3; N 5.8.

3-Hydroxy-10-(piperidinocarbonylmethyl)benzimidazo[2,1-*b*]-1,3-thiazanium Bromide (1c). Yield 76%; mp 197-198°C (DMF). R_f 0.07. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39-1.71 (6H, m, CH_2 piperidino); 3.41-3.71 (6H, m, CH_2S, CH_2N piperidino); 4.41 (1H, dd, $^3J_{cis}$ = 2.4, $^2J_{gem}$ = 13.4, NCH_2); 4.52 (1H, dd, $^3J_{trans}$ = 2.6, $^2J_{gem}$ = 13.4, NCH_2); 4.71 (1H, m, CHO); 5.49 (2H, s, CH_2CO); 6.15 (1H, s, OH); 7.59 (2H, m, CH arom.); 7.91 (2H, m, CH arom.). Found, %: C 49.7; H 5.3; N 10.1. $C_{17}H_{22}BrN_3O_2S$. Calculated, %: C 49.5; H 5.4; N 10.2.

3-Hydroxy-10-(morpholinocarbonylmethyl)benzimidazo[2,1-*b*]-1,3-thiazanium Bromide (1d). Yield 75%; mp 237-238°C (DMF). R_f 0.06. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.45-3.76 (10H, m, CH_2S, CH_2 morpholino); 4.42 (1H, dd, $^3J_{cis}$ = 2.3, $^2J_{gem}$ = 13.4, NCH_2CH); 4.54 (1H, dd, $^3J_{trans}$ = 2.6, $^2J_{gem}$ = 13.4, NCH_2CH); 4.72 (1H, m, CHO); 5.53 (2H, s, CH_2CO); 6.11 (1H, s, OH); 7.59 (2H, m, CH arom.); 7.90 (2H, m, CH arom.). Found, %: C 46.7; H 4.8; N 10.2. $C_{16}H_{20}BrN_3O_3S$. Calculated, %: C 46.4; H 4.9; N 10.1.

3-Hydroxy-10-(methoxycarbonylmethyl)benzimidazo[2,1-*b*]-1,3-thiazanium Iodide (1e). Yield 60%; mp 212-213°C (DMF). R_f 0.08. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.58 (1H, dd, $^3J_{cis}$ = 4.9, $^2J_{gem}$ = 12.4, CH_2S); 3.72 (1H, d, $^2J_{gem}$ = 12.4, CH_2S); 3.78 (3H, s, OCH_3); 4.42 (1H, d, $^2J_{gem}$ = 13.4, NCH_2); 4.57 (1H, d, $^2J_{gem}$ = 13.4, NCH_2); 4.75 (1H, m, CHO); 5.51 (2H, d, *J* = 7.2, CH_2CO); 6.07 (1H, s, OH); 7.60 (2H, m, CH arom.); 7.93 (2H, m, CH arom.). Found, %: C 38.6; H 3.8; N 6.8. $C_{13}H_{15}IN_2O_3S$. Calculated, %: C 38.4; H 3.7; N 6.9.

10-(Ethoxycarbonylmethyl)-3-hydroxybenzimidazo[2,1-*b*]-1,3-thiazanium bromide (1f). Yield 71%; mp 179-180°C (DMF). R_f 0.09. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, t, *J* = 7.1, CH_3); 3.58 (1H, dd, $^3J_{cis}$ = 4.8, $^2J_{gem}$ = 12.5, CH_2S); 3.71 (1H, d, $^2J_{gem}$ = 12.5 CH_2S); 4.24 (2H, q, *J* = 7.1, OCH_2); 4.41 (1H, dd, $^3J_{cis}$ = 2.4, $^2J_{gem}$ = 13.5, NCH_2); 4.55 (1H, dd, $^3J_{trans}$ = 2.7, $^2J_{gem}$ = 13.5, NCH_2); 4.75 (1H, m, CHO); 5.49 (2H, d, *J* = 8.0, CH_2CO); 6.07 (1H, d, *J* = 3.4, OH); 7.61 (2H, m, CH arom.); 7.95 (2H, m, CH arom.). Found, %: C 45.3; H 4.5; N 7.6. $C_{14}H_{17}BrN_2O_3S$. Calculated, %: C 45.1; H 4.6; N 7.5.

1-R-3-(2,3-Epithiopropyl)benzimidazol-2-ones 2a-f (General Method). The 3-hydroxybenzimidazo-[2,1-*b*]thiazanium salt **1a-f** was boiled in a 20-fold molar excess of epichlorhydrin until solution and then for an additional 5 min, cooled, the solid was filtered off, and recrystallized from alcohol. In the cases when the reaction product was soluble (compounds **2c-f**), the epichlorhydrin was evaporated in vacuum, the residue was dissolved in chloroform, passed through a layer of silica gel, the chloroform was evaporated in vacuum, and the obtained substance recrystallized from hexane–2-propanol, 10:1.

3-(2,3-Epithiopropyl)-1-phenacylbenzimidazol-2-one (2a). Yield 80%; mp 134-135°C (2-propanol). R_f 0.72. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50 (1H, d, $^3J_{cis}$ = 5.4, CH_2S); 2.59 (1H, d, $^3J_{trans}$ = 6.2, CH_2S); 3.28 (1H, m, CHS); 4.02 (1H, dd, $^3J_{trans}$ = 6.5, $^2J_{gem}$ = 14.7, NCH_2); 4.19 (1H, dd, $^3J_{cis}$ = 5.6, $^2J_{gem}$ = 14.7, NCH_2); 5.52

(2H, s, CH_2CO); 7.01-7.14 (3H, m, CH arom.); 7.34 (1H, m, CH arom.); 7.57-7.71 (3H, m, CH arom.); 8.09 (2H, m, CH arom.). Found, %: C 66.9; H 5.1; N 8.5. $C_{18}H_{16}N_2O_2S$. Calculated, %: C 66.7; H 5.0; N 8.6.

1-(4-Bromophenacyl)-3-(2,3-epithiopropyl)benzimidazol-2-one (2b). Yield 85%; mp 209-210°C (2-propanol). R_f 0.65. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (1H, m, CH_2S); 2.60 (1H, d, $^3J_{trans}$ = 6.2, CH_2S); 3.31 (1H, m, CHS); 4.03 (1H, dd, $^3J_{trans}$ = 6.5, $^2J_{gem}$ = 14.8, NCH_2); 4.20 (1H, dd, $^3J_{cis}$ = 5.6, $^2J_{gem}$ = 14.8, NCH_2); 5.53 (2H, s, CH_2CO); 7.03-7.10 (2H, m, CH arom.); 7.14 (1H, d, *J* = 7.5, CH arom.); 7.35 (1H, d, *J* = 7.6, CH arom.); 7.83 (2H, d, *J* = 8.3, CH arom.); 8.03 (2H, d, *J* = 8.3, CH arom.). Found, %: C 53.8; H 3.7; N 7.1. $C_{18}H_{15}BrN_2O_2S$. Calculated, %: C 53.6; H 3.8; N 7.0.

3-(2,3-Epithiopropyl)-1-(piperidinocarbonylmethyl)benzimidazol-2-one (2c). Yield 78%; mp 157-158°C (hexane–2-propanol, 10:1). R_f 0.64. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39-1.68 (6H, m, CH_2 piperidino); 2.48 (1H, m, CH_2S); 2.58 (1H, d, $^3J_{trans}$ = 6.2, CH_2S); 3.27 (1H, m, CHS); 3.39-3.56 (4H, m, CH_2 piperidino); 4.01 (1H, dd, $^3J_{trans}$ = 6.5, $^2J_{gem}$ = 14.8, NCH_2); 4.16 (1H, dd, $^3J_{cis}$ = 5.6, $^2J_{gem}$ = 14.8, NCH_2); 4.72 (2H, s, CH_2CO); 7.03 (3H, m, CH arom.); 7.28 (1H, m, CH arom.). Found, %: C 61.9; H 6.2; N 12.5. $C_{17}H_{21}N_3O_2S$. Calculated, %: C 61.6; H 6.4; N 12.7.

3-(2,3-Epithiopropyl)-1-(morpholinocarbonylmethyl)benzimidazol-2-one (2d). Yield 80%; mp 161-162°C (hexane–2-propanol, 10:1). R_f 0.59. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.50 (1H, m, CH_2S); 2.59 (1H, d, $^3J_{trans}$ = 6.2, CH_2S); 3.28 (1H, m, CHS); 3.40-3.71 (8H, m, CH_2 morpholino); 4.02 (1H, dd, $^3J_{trans}$ = 6.5, $^2J_{gem}$ = 14.7, NCH_2); 4.17 (1H, dd, $^3J_{cis}$ = 5.6, $^2J_{gem}$ = 14.7, NCH_2); 4.79 (2H, s, CH_2CO); 7.06 (3H, m, CH arom.); 7.29 (1H, m, CH arom.). Found, %: C 57.3; H 5.8; N 12.7. $C_{16}H_{19}N_3O_3S$. Calculated, %: C 57.6; H 5.7; N 12.6.

3-(2,3-Epithiopropyl)-1-(methoxycarbonylmethyl)benzimidazol-2-one (2e). Yield 85%; mp 100-101°C (hexane–2-propanol, 10:1). R_f 0.70. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.49 (1H, m, CH_2S); 2.57 (1H, d, $^3J_{trans}$ = 6.2, CH_2S); 3.26 (1H, m, CHS); 3.68 (3H, s, OCH_3); 3.99 (1H, dd, $^3J_{trans}$ = 6.5, $^2J_{gem}$ = 14.8, NCH_2); 4.15 (1H, dd, $^3J_{cis}$ = 5.6, $^2J_{gem}$ = 14.8, NCH_2); 4.75 (2H, s, CH_2CO); 7.06 (2H, m, CH arom.); 7.17 (1H, d, *J* = 7.2, CH arom.), 7.32 (1H, d, *J* = 7.0, CH arom.). Found, %: C 56.4; H 5.2; N 10.2. $C_{13}H_{14}N_2O_3S$. Calculated, %: C 56.1; H 5.1; N 10.1.

3-(2,3-Epithiopropyl)-1-(ethoxycarbonylmethyl)benzimidazol-2-one (2f). Yield 75%; mp 127-129°C (hexane–2-propanol, 10:1). R_f 0.74. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 7.1, CH_3); 2.37 (1H, m, CH_2S); 2.46 (1H, d, $^3J_{trans}$ = 6.2, CH_2S); 3.14 (1H, m, CHS); 3.88 (1H, dd, $^3J_{trans}$ = 6.5, $^2J_{gem}$ = 14.8, NCH_2); 4.01-4.07 (3H, m, NCH_2, CH_2O); 4.61 (2H, s, CH_2CO); 6.95 (2H, m, CH arom.); 7.05 (1H, d, *J* = 7.5, CH arom.); 7.21 (1H, d, *J* = 7.0, CH arom.). Found, %: C 57.7; H 5.3; N 9.5. $C_{14}H_{16}N_2O_3S$. Calculated, %: C 57.5; H 5.5; N 9.6.

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