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Reactions of Benzimidazole-2-thiol with *N*-Alkyl-1-aza-1,3-enynes

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Abstract—Reactions of *N*-alkyl-1-aza-1,3-enynes with benzimidazole-2-thiol in anhydrous dimethylformamide have been studied. The structure of the obtained compounds has been elucidated from the NMR data.

Keywords: benzimidazole-2-thiol, *N*-alkyl-1-aza-1,3-enyne, heterocyclization

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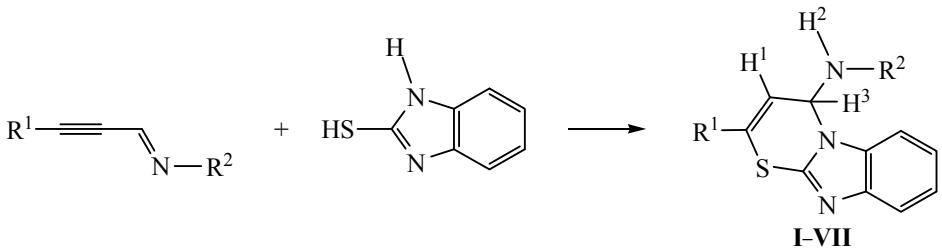
1-Aza-1,3-enynes are convenient and readily available synthons for synthesis of organic sulfur-containing polynuclear heterocyclic compounds [1–6]. Recently, considerable attention has been focused on the heterocyclization reactions of 1-aza-1,3-enynes resulting from addition of various nucleophilic reagents [3]. Benzimidazole-2-thiol derivatives readily participate in the substitution and addition (at activated double or triple bond) reactions resulting in formation of heterocyclic or acyclic products [7, 8]. Benzimidazole-2-thiol and its derivatives are known for anxiolytic activity [9]; some of them inhibit chymases (enzymes responsible for activation of interleukin-1β, serving among the major mediators of non-specific inflamematory forms of protection) [10].

It was previously shown that interaction of *N*-*tert*-butyl-1-aza-1,3-enynes with benzimidazole-2-thiol led to formation of polynuclear heterocyclic sulfur compounds, benzo[4,5]imidazole[2,1-*b*][1,3]thiazine-4-ols [11]. The reaction occurred in methanol and was accompanied by heterolytic cleavage of *tert*-butylamine; in the case of silicon-containing 1-aza-1,3-enine, desilylation was observed. However, addition of adenine-8-thiol to the silicon-containing 1-aza-1,3-enynes proceeded in absolute DMF without desilylation and allowed to preserve the secondary amino group [12].

In this work we studied reactions of benzimidazole-2-thiol with *N*-alkyl-1-aza-1,3-enynes (obtained via condensation of phenylpropiolic aldehyde and 4,4-dimethylpent-3-ynal) with aliphatic amines (*tert*-butylamine, cyclohexylamine, and benzylamine) [1] .

Similarly to the above-mentioned result [12], we found that using anhydrous DMF as solvent prevented hydrolysis and preserved the amine moiety. The obtained compounds **I**–**VII** were crystalline substances; their structure was confirmed by NMR spectroscopy (Scheme 1).

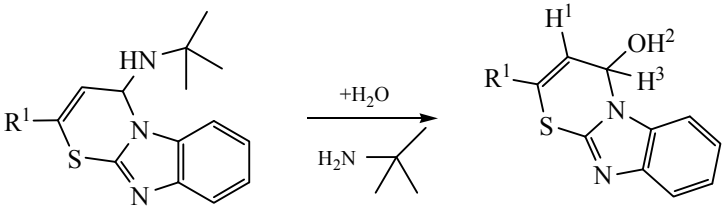
Scheme 1.



I–**VII**

R^1 = Ph, R^2 = *t*-Bu (**I**); R^1 = *t*-Bu, R^2 = *t*-Bu (**II**); R^1 = Me_3Si, R^2 = *t*-Bu (**III**); R^1 = *t*-Bu, R^2 = cyclo-C_6H_{11} (**IV**); R^1 = Me_3Si, R^2 = cyclo-C_6H_{11} (**V**); R^1 = *t*-Bu, R^2 = CH_2Ph (**VI**); R^1 = Me_3Si, R^2 = CH_2Ph (**VII**).

Scheme 2.



I, II **VIII, IX**

R^1 = Ph (**VIII**), *t*-Bu (**IX**).

In ^{1}H NMR spectrum of **II,** doublet at 6.15 ppm ($^3J_{HH}$ 5.82 Hz) was assigned to the H^1 atom. The signal of H^1 proton was observed at 2.34 ppm. The H^3 atom of 1,3-thiazine ring resonated as multiplet in the range of 6.01–6.05 ppm. The singlets at 1.11 and 1.30 ppm belonged to the protons of two *tert*-butyl groups. Signals of the aromatic protons were registered as three multiplets in their typical area.

^{1}H NMR spectra of trimethylsilyl derivatives **III**, **V,** and **VII** contained distinct singlets of nine protons in the range of 0.25–0.30 ppm [12].

According to [4, 13], addition of azoles at multiple bond of 1-aza-1,3-enynes proceeded much less readily than in the cases of aromatic thiols [1]. Apparently, thiol group was the first to react with 1-aza-1,3-enynes, and then the pyrrole nitrogen atom of benzimidazole-2-thiol followed.

Compounds **I** and **II** were hydrolyzed in aqueous ethanol (1 : 1) solution, the process being accompanied with substitution of *tert*-butylamino group to hydroxyl moiety.

^{1}H NMR spectrum of **IX** contained signals of the H^1 (6.00 ppm, J_{HH} 4.36 Hz), H^2 (6.45 ppm), and H^3 (6.78 ppm, J_{HH} 7.26 Hz) atoms. The singlet at 1.35 ppm was assigned to the *tert*-butyl protons. Aromatic protons resonated in their usual spectral region. No signals of the *tert*-butylamino group were observed in the spectrum, evidencing about its cleavage. Compounds **VIII** and **IX** were previously described in [11], but they were obtained directly by reacting *N*-*tert*-butyl-1-aza-1,3-enynes with benzimidazole-2-thiol, without isolation of the intermediates **I** and **II** (Scheme 2).

A notable feature of the described reaction is the solvent effect. In particular, performing the reaction in anhydrous DMF gives 2-substituted 4*H*-benzo[4,5]-imidazole[2,1-*b*][1,3]thiazine-4-amines **I**–**VII**, whereas with methanol as solvent it yields 2-substituted 4*H*-benzo[4,5]imidazole[2,1-*b*][1,3]thiazine-4-ols **VIII** and **IX**.

EXPERIMENTAL

NMR spectra (DMSO-d_6) were recorded with the Varian XL-300 spectrometer [300.13 MHz (^{1}H), 75.45 MHz (^{13}C)] relative to the signal of residual solvent protons. *Analytical pure* grade reagents were used for the syntheses.

***N*-*tert*-Butyl-2-phenyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole-4-amine (I).** A mixture of a solution of 0.01 mol of phenylpropiolic aldehyde *tert*-butylimine in 50 mL of anhydrous DMF and 0.01 mol of benzimidazole-2-thiol was stirred during 2 h. After the solvent removal, oily residue was crystallized from toluene–petroleum ether mixture. Pale-brown crystals were filtered off and dried in air. Yield ~75%. ^{1}H NMR spectrum, δ, ppm: 1.25 s (9H), 1.97 br.s (1H), 6.11 m (1H), 6.51 d (1H, $^3J_{HH}$ 5.8 Hz), 7.25–7.54 m (9H). ^{13}C NMR spectrum, δ_C, ppm: 30.48, 50.17, 62.71, 110.80, 117.55, 120.28, 121.00, 121.50, 121.80, 126.10, 127.20, 128.10, 128.70, 129.05, 129.31, 133.33, 143.25, 145.00. Found, %: C 71.6; H 6.5; N 12.5. $C_{20}H_{21}N_3S$. Calculated, %: C 71.6; H 6.3; N 12.5.

***N*,2-Di-*tert*-butyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole-4-amine (II).** A mixture of a solution of 0.012 mol of *N*-(4,4-dimethylpent-2-yn-1-ylidene)-2-methylpropane-2-amine in 50 mL of anhydrous DMF and 0.010 mol of benzimidazole-2-thiol was incubated during 12 h. The precipitated crystals were filtered off and dried in air. Yield ~50%, mp 155°C. ^{1}H NMR spectrum, δ, ppm: 1.11 s (9H), 1.30 s (9H), 2.34 br.s (1H), 6.03 m (1H), 6.15 d (1H, $^3J_{HH}$ 5.82 Hz), 7.12–7.17 m (2H), 7.46–7.49 m (1H), 7.58–7.60 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 29.03, 30.38, 36.40, 49.98, 62.20, 110.53, 117.11, 117.40, 120.77, 121.58, 133.28, 140.02, 143.14, 145.81. Found, %: C 68.4; H 7.9; N 13.7. $C_{18}H_{25}N_3S$. Calculated, %: C 68.5; H 8.0; N 13.3.

***N*-*tert*-Butyl-2-trimethylsilyl-4*H*-[1,3]thiazino[3,2-*a*]-benzimidazole-4-amine (III)** was obtained similarly. Yield 78%, mp 166°C. ^{1}H NMR spectrum, δ, ppm: 0.29 s (9H), 1.17 s (9H), 1.85 d (1H, $^3J_{HH}$ 10.18 Hz), 5.94–5.99 m (1H), 6.46 d (1H, $^3J_{HH}$ 5.09 Hz), 7.24–7.27 m (2H), 7.48–7.50 m (1H), 7.67–7.69 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 2.26, 30.40, 50.02, 62.85, 110.61, 117.35, 120.75, 121.70, 128.19, 129.62, 133.30, 142.53, 145.36. Found, %: C 61.4; H 7.5; N 11.7. $C_{17}H_{25}N_3SSi$. Calculated, %: C 61.5; H 7.6; N 11.6.

***N*-Cyclohexyl-2-*tert*-butyl-4*H*-[1,3]thiazino[3,2-*a*]-benzimidazole-4-amine (IV)** was obtained similarly. Yield 65%, mp 128°C. ^{1}H NMR spectrum, δ, ppm: 0.76–1.65 m (10H), 1.31 s (9H), 2.40 br.s (1H), 2.61 br.s (1H), 5.95 d (1H, $^3J_{HH}$ 5.09 Hz), 6.10 m (1H), 7.10–7.18 m (2H), 7.47–7.50 m (1H), 7.61–7.64 m (1H). Found, %: C 70.3; H 7.9; N 12.4. $C_{20}H_{27}N_3S$. Calculated, %: C 70.3; H 8.0; N 12.3.

***N*-Cyclohexyl-2-trimethylsilyl-4*H*-[1,3]thiazino-[3,2-*a*]benzimidazole-4-amine (V)** was obtained similarly. Yield 70%, mp 130°C. ^{1}H NMR spectrum, δ, ppm: 0.76–1.65 m (10H), 0.30 s (9H), 2.39 br.s (1H), 2.70 br.s (1H), 6.13 m (1H), 6.21 d (1H, $^3J_{HH}$ 4.36 Hz), 7.10–7.19 m (2H), 7.47–7.50 m (1H), 7.62–7.65 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 1.62, 23.86, 24.59, 24.88, 25.32, 30.22, 30.73, 31.19, 32.57, 109.30, 120.35, 121.80, 168.00. Found, %: C 63.7; H 7.7; N 11.7. $C_{19}H_{27}N_3SSi$. Calculated, %: C 63.8; H 7.6; N 11.8.

***N*-Benzyl-2-*tert*-butyl-4*H*-[1,3]thiazino[3,2-*a*]benz-imidazole-4-amine (VI)** was obtained similarly. Yield 70%, mp 148°C. ^{1}H NMR spectrum, δ, ppm: 1.25 s (9H), 2.39 br.s (1H), 3.30–3.33 m (1H), 3.50–3.53 m (1H), 3.57 br.s (1H), 5.90 d (1H, $^3J_{HH}$ 5.09 Hz), 6.22 m (1H), 7.10–7.21 m (7H), 7.49–7.51 m (1H), 7.69–7.71 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 29.19, 36.58, 45.47, 65.33, 110.43, 112.45, 117.35, 121.02, 121.90, 126.20, 127.35, 127.60, 133.25, 140.23, 141.80, 142.85, 145.73. Found, %: C 72.8; H 6.9; N 12.1. $C_{21}H_{23}N_3S$. Calculated, %: C 72.8; H 6.8; N 12.0.

***N*-Benzyl-2-trimethylsilyl-4*H*-[1,3]thiazino[3,2-*a*]-benzimidazole-4-amine (VII)** was obtained similarly. Yield 70%, mp 158°C. ^{1}H NMR spectrum, δ, ppm: 0.25 s (9H), 3.27–3.34 m (1H), 3.49–3.65 m (2H), 6.15 d (1H, $^3J_{HH}$ 4.36 Hz), 6.23–6.26 m (1H), 7.11–7.19 m (7H), 7.49–7.51 m (1H), 7.69–7.72 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 2.23, 45.55, 65.82, 110.48, 117.35, 121.04, 121.99, 124.90, 126.22, 127.40, 127.60, 130.53, 133.28, 140.15, 142.28, 145.17. Found, %: C 65.6; H 6.4; N 11.4. $C_{20}H_{23}N_3SSi$. Calculated, %: C 65.7; H 6.3; N 11.5.

2-Phenyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole-4-ol (VIII). 50 mL of distilled water preheated to 70°C was added to a solution of 0.0024 mol of compound **I** in 50 mL of ethanol under reflux. The resulting mixture was heated at 70°C during 2 min, slowly cooled to room temperature over 2 h and left at 4°C overnight. The obtained crystals were filtered off, washed with water, and dried. Yield 90%, mp 240°C. ^{1}H NMR spectrum, δ, ppm: 6.42 d (1H, $^3J_{HH}$ 4.4 Hz), 6.65 d. d (1H, $^3J_{HH}$ 8.7, $^3J_{HH}$ 4.4 Hz), 7.04 d (1H, $^3J_{HH}$ 8.7 Hz), 7.22–7.24 m (2H), 7.46–7.70 m (7H). ^{13}C NMR spectrum, δ_C, ppm: 73.47, 110.88, 116.60, 117.51, 121.45, 122.40, 126.08, 128.86, 129.40, 130.12, 133.30, 136.05, 142.74, 143.77. Found, %: C 68.5; H 4.4; N 9.9. $C_{16}H_{12}N_2OS$. Calculated, %: C 68.6; H 4.3; N 10.0.

2-*tert*-Butyl-4*H*-[1,3]thiazino[3,2-*a*]benzimidazole-4-ol (IX) was obtained similarly. Yield 80%, mp 210°C. ^{1}H NMR spectrum, δ, ppm: 1.36 s (9H), 6.01 d (1H, $^3J_{HH}$ 4.4 Hz), 6.40–6.50 m (1H), 6.78 d (1H, $^3J_{HH}$ 7.3 Hz), 7.14–7.23 m (2H), 7.47–7.55 m (1H), 7.59–7.67 m (1H). ^{13}C NMR spectrum, δ_C, ppm: 29.27, 36.57, 73.12, 110.64, 112.74, 117.30, 121.10, 122.15, 133.25, 141.07, 142.80, 144.55. Found, %: C 64.5; H 6.1; N 10.8. $C_{14}H_{16}N_2OS$. Calculated, % : C 64.6; H 6.2; N 10.8.

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