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LETTERS TO THE EDITOR

Addition of 4-Phenyl-2-imidazole-2-thione to *N*-Alkyl-1-aza-1,3-enynes

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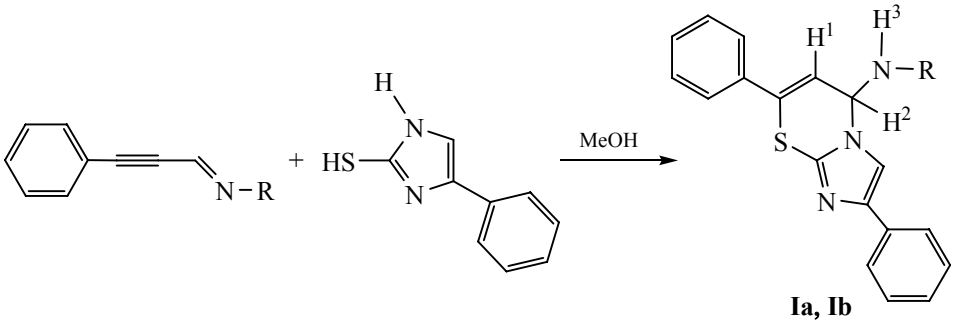
Imidazole-2-thione derivatives are promising inhibitors of mitogen-activated protein kinase p38 (MAP p38) [1, 2], which plays a key role in the biosynthesis of tumor necrosis factor [2], and inflammatory cytokine interleukin 1β. 4-Substituted imidazole-2-thiones are selective agonists of adrenergic alpha-2-receptors [3]. In this regard, the synthesis of new compounds with potential biological activity based on the substituted imidazole-2-thiones is of interest.

Previously, it has been shown that structural analogs of imidazole-2-thiones like benzimidazole-2-thiol and adenine-8-thiol reacted with 1-aza-1,3-enynes to form polynuclear sulfur-containing compounds, benzo[4,5]imidazolo[2,1-*b*][1,3]thiazine-4-amines [4, 5].

In this work we showed that the interaction of *N*-alkyl-1-aza-1,3-enynes with 4-phenylimidazole-2-thione as a model compound leads to the formation of fused heterocyclic compounds: imidazolo[2,1-*b*][1,3]thiazine-5-amine. The reaction proceeds while stirring equimolar amounts of starting reactants in methanol at room temperature for 30 min. The reaction products are crystalline compounds.

The composition and structure of the synthesized compounds were confirmed by elemental analysis, ^{1}H and ^{13}C NMR spectra. Thus, the ^{1}H NMR spectrum of compound **Ia** contained a doublet signal at 6.31 ppm (J 4.7 Hz) corresponding to the proton H^1. The H^2 proton resonated as a doublet of doublets at 6.03 ppm (J 6.9, 4.7 Hz). The signal of the H^3 proton of the secondary amino group appeared as multiplet signals in the range of 3.30–3.04 ppm. The proton resonances of the cyclohexyl substituents and aromatic moieties were registered in their characteristic areas.

Scheme 1.



Ia, Ib

R = *cyclo*-Hex (**Ia**), Bn (**Ib**).

Thiol-thione tautomerism is typical of imidazole-2-thiones [6]. In the case of the reaction with 1-aza-1,3-enynes, 4-phenylimidazole-2-thione reacted in a thiol form. Along with a thiol group, the second nucleophilic site, "pyrrole" nitrogen of 4-phenyl-2-imidazole-2-thione, participates in the reaction. It attacks the electrophilic carbon atom of the azomethine group [7]. Probably, heterocyclization proceeds according to the scheme of [3 + 3]-binucleophilic addition.

The reaction can result in the formation of two regioisomers. Previously, using DFT calculation we have shown that interaction of 1-aza-1,3-enynes with adenine-8-thiol [5] afforded only one regioisomer for which the effect of the steric factor is minimum. Therefore, the structure of 2,7-diphenyl-5*H*-imidazo-[2,1-*b*][1,3]thiazine-5-amine was ascribed to the resulting compounds **Ia** and **Ib** (Scheme 1).

Hence, the reaction of *N*-alkyl-1-aza-1,3-enynes with 4-phenylimidazole-2-thione is a convenient approach towards of modification of imidazole-2-thiones.

***N*-Cyclohexyl-2,7-diphenyl-5*H*-imidazo[2,1-*b*]-[1,3]thiazine-5-amine (Ia)**. 4-Phenylimidazole-2-thione (5 mmol) was added with stirring to a solution of 5 mmol of phenylpropiolic aldehyde cyclohexylimine in 25 mL of anhydrous methanol. The reaction mixture was stirred at room temperature for 30 min. The crystalline precipitate was filtered off and dried in air. Yield 65%, mp 131–132°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 7.94 s (1H), 7.77 d (2H, *J* 7.2 Hz), 7.72–7.61 m (1H), 7.61–7.32 m (6H), 7.26 d.t (1H, *J* 14.7, 7.4 Hz), 6.31 d (1H, *J* 4.7 Hz), 6.03 d.d (1H, *J* 6.9, 4.7 Hz), 3.30–3.04 m (1H), 2.52 d.d (1H, *J* 9.5, 7.8 Hz), 2.03 m (1H), 1.71–1.42 m (5H), 1.33–0.92 m (5H). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 141.29, 136.97, 136.00, 134.27, 130.79, 129.87, 129.58, 129.06, 127.10, 126.54, 124.70, 117.71, 115.76, 67.21, 52.07, 34.92, 33.86, 25.95, 24.98. Found, %: C 74.1; H 6.6; N 10.7. $C_{24}H_{25}N_3S$. Calculated, %: C 74.4; H 6.5; N 10.8.

***N*-Benzyl-2,7-diphenyl-5*H*-imidazo[2,1-*b*][1,3]-thiazine-5-amine (Ib)** was prepared similarly. Yield 80%, mp 147–148°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 7.95 d (1H, *J* 31.6 Hz), 7.83–7.72 m (2H), 7.59–7.11 m (13H), 6.24 d (1H, *J* 4.4 Hz), 6.20–6.10 m (1H), 3.98 d.d (1H, *J* 13.4, 5.8 Hz), 3.69 d.d (1H, *J* 13.7, 7.8 Hz), 3.54 d.d (1H, *J* 13.7, 5.3 Hz). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 141.58, 140.84, 136.93, 136.39, 134.24, 131.86, 129.90, 129.48, 129.10, 128.56, 128.22, 127.14, 126.58, 124.74, 116.79, 115.53, 68.63, 46.66. Found, %: C 75.8; H 5.6; N 10.9. $C_{25}H_{21}N_3S$. Calculated, %: C 75.9; H 5.4; N 10.6.

NMR spectra were recorded on a Bruker 400 spectrometer [400 (^{1}H), 100 MHz (^{13}C)]. Elemental analysis was performed on a Perkin-Elmer 2400 CHN-analyzer. Melting points were determined on a Koeffler heating block.

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