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REGIOSELECTIVITY OF HETEROCYCLIZATION OF 2-SUBSTITUTED 3,3-BIS(METHYLSULFANYL)ACRYLONITRILES WITH 2-BENZIMIDAZOLEACETONITRILE

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Functionalized pyrido[1,2-a]benzimidazoles have been synthesized by the interaction of 2-substituted 2-cyano-3,3-bis(methylsulfanyl)acrylonitriles with 2-benzimidazoleacetonitrile under S_NVin reaction conditions.

Keywords: 2-benzimidazoleacetonitrile, 2-cyano-3,3-bis(methylsulfanyl)acrylonitriles, pyrido[1,2-*a*]benzimidazole, regioselective heterocyclization.

It has been shown for the first time that the condensation of 2-(benzimidazol-2-yl)acetonitrile (**1**) with an activated alkene under S_NVin reaction conditions [1] proceeds regioselectively through the corresponding transition state **A** with the formation of pyrido[1,2-*a*]benzimidazole **3**. Regioselectivity was also observed in the case of the interaction of compound **1** with 2-cyano-3,3-bis(methylsulfanyl)acrylic acid ethyl ester **4**, leading to the formation of pyrido[1,2-*a*]benzimidazole **5**.

At the same time the unexpected formation of the heterocyclic system **5** occurs on condensing compound **1** with 2-cyano-3,3-bis(methylsulfanyl)acrylamide **6**.

It has therefore been established that the anilide fragment of 2-cyano-N-(2-methoxyphenyl)-3,3-bis(methylsulfanyl)acrylamide (**2**) is transferred into compound **3**, and the amide fragment of alkene **6** undergoes an intramolecular rearrangement forming pyrido[1,2-*a*]benzimidazole **5**.

The synthesized compounds **3, 5** fluoresce on UV irradiation.

The biological activity of the obtained compounds has been predicted with the aid of the PASS programs [2]. The probability that the obtained compounds **3, 5** may display antiasthmatic activity was 67.3-92.9%, antiallergic 65.3-91.2%, and as antagonists of chemoxin receptors CXCRI 53.5-64.8%

EXPERIMENTAL

The IR spectra were recorded on a Perkin-Elmer FIR Spectrum One instrument in KBr. The ^{1}H NMR spectra were recorded on Bruker Avance II 400 (400 MHz) (compound **3**) and Varian Mercury-500 (500 MHz)

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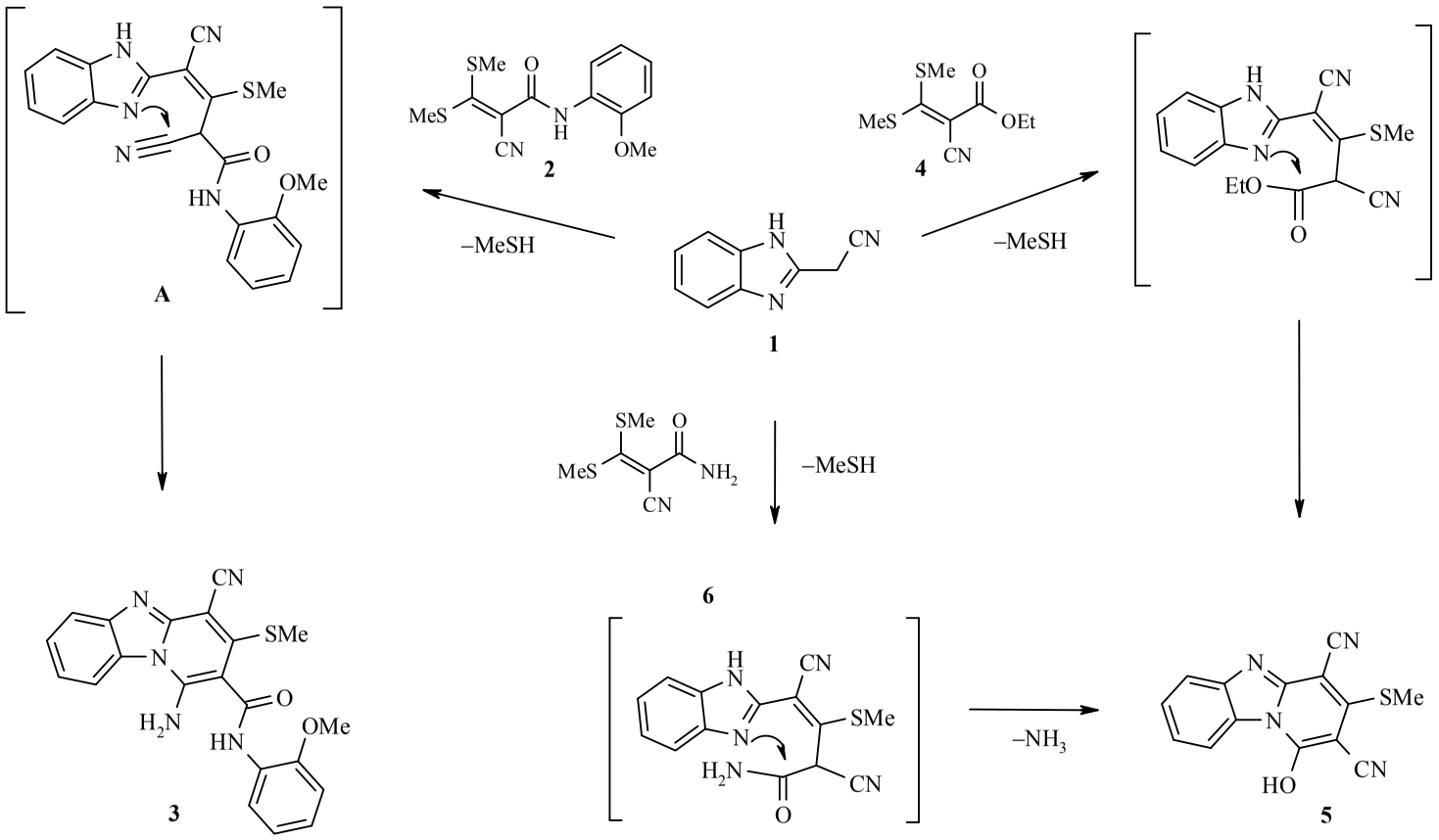
A
2
4
1
–MeSH
–MeSH
6
–MeSH
3
–NH3
5

(compound **5**) instruments in DMSO-d_6, internal standard was TMS. The EI mass spectra were obtained on a MX-1321 (70 eV) (compound **3**) with direct insertion of substance into the ion source (70 eV) and on a Chrommas GC/MS Hewlett-Packard 5890/5972 with HP-5MS column (compound **5**).

The melting points of compounds were determined on a Kofler block. A check on the progress of reactions and the homogeneity of compounds was carried out by TLC on Silufol UV 254 plates in the system acetone–hexane, 3:5, visualization was with iodine vapor and in UV light.

2-cyano-N-(2-methoxyphenyl)-3,3-bis(methylsulfanyl)acrylamide (2) was obtained by the procedure of [3].

1-Amino-4-cyano-3-methylthio-N-(2-methoxyphenyl)pyrido[1,2-*a*]benzimidazole-2-carboxamide (3). 2-(Benzimidazol-2-yl)acetonitrile (**1**) (1.57 g, 10 mmol) was added to a suspension of KOH (0.56 g, 10 mmol) in DMSO (10 ml) and the mixture stirred for 15 min. 2-cyano-N-(2-methoxyphenyl)-3,3-bis(methylsulfanyl)-acrylamide (**2**) (2.94 g, 10 mmol) was then added to the reaction mixture, which was stirred for 1 h, and heated at 80°C for 15 min. The mixture was then left for 2 h, poured into cold water, the mixture was acidified with an equimolar quantity of 30% HCl solution, the resulting solid was filtered off, and washed with water. Yield 2.41 g (60%); mp 126-130°C (butanol). IR spectrum, ν, cm^{-1}: 1556 (NH_2, NH), 1643 (C=O), 2216 (C≡N), 3234, 3334. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.63 (1H, br. s, NH); 8.45 (1H, d, *J* = 8.1, H benzimidazole); 8.20 (1H, d, *J* = 8.1, H arom); 7.89 (2H, br. s, NH_2); 7.80 (1H, d, *J* = 8.1, H benzimidazole); 7.53 (1H, t, *J* = 7.7, H benzimidazole); 7.34 (1H, t, *J* = 7.7, H benzimidazole); 7.11 (1H, t, *J* = 7.7, H arom); 7.02 (1H, d, *J* = 8.1, H arom); 6.96 (1H, t, *J* = 7.7, H arom); 3.88 (3H, s, OCH_3); 2.63 (3H, s, SCH_3). Mass spectrum, *m/z* (I_{rel}, %): 108 $[M]^+$ (24), 206 (9), 281 (7), 403 (13). Found, %: C 62.52; H 4.25; N 17.36. $C_{21}H_{17}N_5O_2S$. Calculated, %: C 62.59; H 4.09; N 17.36.

1-Hydroxy-3-methylsulfanylpyrido[1,2-*a*]benzimidazole-2,4-dicarbonitrile (5) was obtained analogously to compound **3** using as ketenedithioacetal the diethyl ester of 2-cyano-3,3-bis(methylsulfanyl)-acrylic acid (**4**) or 2-cyano-3,3-bis(methylsulfanyl)acrylamide (**6**). Yield 2.02 g (72%) and 2.24 g (80%) respectively, mp 290-297°C (butanol). IR spectrum, ν, cm^{-1}: 2215 (C≡N), 3450 (OH). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 8.45 (1H, d, *J* = 8.0, H arom); 7.64 (1H, d, *J* = 7.8, H arom.); 7.45 (1H, t, *J* = 7.6, H arom); 7.30 (1H, t, *J* = 7.6, H arom.); 2.74 (3H, s, SCH_3). The signal of the OH group proton was not displayed, probably as a result of rapid deuterium exchange. Mass spectrum, *m/z* (I_{rel}, %): 279 $[M-1]^+$ (100). Found, %: C 59.99; H 2.88; N 19.99. $C_{14}H_8N_4OS$. Calculated, %: C 60.05; H 2.97; N 19.86.

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