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"GREEN CHEMICAL" METHODS FOR THE REGIOSELECTIVE SYNTHESIS OF 1-HETARYLSULFANYL-ω-CYANOALKANES

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Novel „green chemical" methods for the synthesis of 1-hetarylthio-ω-cyanoalkanes were elaborated. Phase transfer catalyst ($(CH_3)_4NBr$) effect on yield of alkylation reaction was demonstrated. 1-Hetarylthio-ω-cyanoalkanes were isolated in 49–86% yields.

Key words: *„green chemical" synthesis, phase transfer catalysis, alkali hydroxides, 1-hetarylthio-ω-cyanoalkanes.*

INTRODUCTION

Heterocyclic oxime derivatives exhibit wide range of biological activity [1–11]. Nitrile derivatives are known to be the excellent synthons for the preparation of different biologically active amidoxime derivatives [12]. The aim of the present work is elaboration of a novel "green chemical" method for the preparation of 1-hetarylthio-ω-cyanoalkanes of type $HetS(CH_2)_nCN$ (where Het is 2-substituted 1,3,4-thiadiazol-2-ylamine, quinazolin-4-one and 4,6-dihydroxy-pyrimidine, n = 3–5). There are some data concerning alkylation of thiols of 1,3,4-thiadiazol-2-ylamine, quinazolin-4-one and 4,6-dihydroxypyrimidine by alkyl halides in the chemical literature. Thus, 5-sulfanyl-1,3,4-thiadiazol-2-ylamine was successfully S-alkylated in the presence of aqueous KOH [13, 14] or Na_2CO_3 [15]. Some articles are dedicated to S-methylation of 2-mercapto-4(3H)-quinazolinone in the systems MeI/ EtOH KOH or methyl tosylate / DMF [16] and MeI / H_2O [17]. 4,6-Dihydroxy-2-mercaptopyrimidine was successfully S-methylated in the system MeI / KOH / H_2O [18]. However, there are no data in literature concerning the synthesis of 1-hetarylthio-ω-cyanoalkanes.

EXPERIMENTAL

^1H NMR spectra were recorded on a *Varian 200* Mercury instrument using $CDCl_3$ or DMSO-d_6 as a solvent and hexamethyldisiloxane (HMDSO) as an internal standard. Mass spectra were registered on a GC-MS HP 6890 (70 eV). LC-MS spectra were recorded on MS *Waters 3100* Mass detector. Thiols **1**–**3** (*Acros*), **4** (*Aldrich*), 4-bromobutyronitrile, 5-bromovaleronitrile or 6-bromo-hexanenitrile (*Alfa Aesar*) were used without additional purification.

Synthesis of 5-(4-cyanobutylsulfanyl)-1,3,4-thiadiazol-2-ylamine (2) using phase transfer catalytic method. KOH (0.5 g, 9 mmol) solution in water (1 ml) was added to the mixture of thiol **1** (0.4 g, 3 mmol), Me_4NBr (0.23 g, 1.5 mmol) in water (2 ml). Reaction mixture was cooled to 0 °C and 5-bromo-valeronitrile (0.25 ml, 3 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. Water (6 ml) was

added and the precipitate of the product was filtered off, washed with water and dried. Yield 0.55 g (86%) of white crystals with melting point 111 °C. ^{1}H NMR spectrum, δ: 1.65–1.99 (m, 4H, $(CH_2)_2$); 2.38 (t, 2H, J = 6 Hz, CCH_2); 3.18 (t, 2H, J = 7 Hz, SCH_2); 7.32 (bs, 2H, NH_2). Mass spectrum, *m/z* (relative intensity): 214 (M^+, 22), 167 (24), 147 (19), 133 (100), 114 (10), 74 (28), 80 (23).

Synthesis of 5-(5-cyanopentylsulfanyl)-1,3,4-thiadiazol-2-ylamine (3). Aqueous KOH (2 ml) solution (6 *N*) was added under stirring to the mixture of thiol **1** (1.0 g, 7.5 mmol) in water (5 ml). Reaction mixture was cooled to 0 °C and 6-bromohexanenitrile (1.0 ml, 7.5 mmol) was added dropwise. The reaction mixture was allowed to warm up to room temperature and stirred for 12 h at room temperature and the precipitate of the product was filtered off, washed with water and dried. Yield 1.22 g of white crystals (71%). ^{1}H NMR spectrum, δ: 1.44–1.66 (m, 6H, $(CH_2)_3$); 2.49 (t, 2H, J = 6 Hz, CCH_2); 3.05 (t, 2H, J = 7 Hz, SCH_2); 7.29 (bs, 2H, NH_2). Mass spectrum, *m/z* (relative intensity): 228 (M^+, 17), 181 (21), 160 (11), 147 (14), 133 (100), 74 (20), 60 (14).

General procedure for the synthesis of 1-hetarylthio-ω-cyanoalkanes 5, 6, 8, 9, 11–13 in water. Solid NaOH or KOH (27.8 mmol) was added under stirring to the mixture of thiols **4, 7** or **10** (27.8 mmol) in water (50 ml). Reaction mixture was refluxed for 30 minutes and 4-bromobutyronitrile, 5-bromovaleronitrile or 6-bromohexanenitrile (27.8 mmol) was added. The reaction mixture was refluxed for 2 h, cooled to room temperature and the precipitate of the product was filtered off, washed with water and dried.

The properties of obtained compounds were as followed.

4-Hydroxy-2-(4-cyanobutylsulfanyl)pyrimidine (5). Yield 75%.^{1}H NMR spectrum, δ: 1.61–1.73 (m, 4H, $CH_2(C\underline{H}_2)_2$); 2.54 (t, 2H, J = 6 Hz, CH_2); 3.14 (t, 2H, J = 6 Hz, SCH_2); 6.09 and 7.85 (both d, 2H, J = 4 Hz, pyrimidine protons).

4-Hydroxy-2-(5-cyanopentylsulfanyl)pyrimidine (6). Yield 77%. ^{1}H NMR spectrum, δ: 1.61–1.73 (m, 6H, $CH_2(C\underline{H}_2)_3$); 2.41 (t, 2H, J = 6 Hz, CH_2); 3.17 (t, 2H, J = 6 Hz, SCH_2); 6.99 and 8.36 (both d, 2H, J = 6 Hz, pyrimidine protons).

4,6-Dihydroxy-2-(4-cyanobutylsulfanyl)pyrimidine (8). Yield 49%. M.p. >230 °C. ^{1}H NMR spectrum, δ: 1.64–1.76 (m, 4H, $CH_2(C\underline{H}_2)_2$); 2.55 (t, 2H, J = 6 Hz, CCH_2); 3.12 (t, 2H, J = 8 Hz, SCH_2); 5.13 (s, 1H, pyrimidine proton).

4,6-Dihydroxy-2-(5-cyanopentylsulfanyl)pyrimidine (9). Yield 52%. M.p. 165 °C. ^{1}H NMR spectrum, δ: 1.47–1.65 (m, 6H, $CH_2(C\underline{H}_2)_3$); 2.50 (t, 2H, J = 6 Hz, CCH_2); 3.09 (t, 2H, J = 6 Hz, SCH_2); 5.12 (s, 1H, CH).

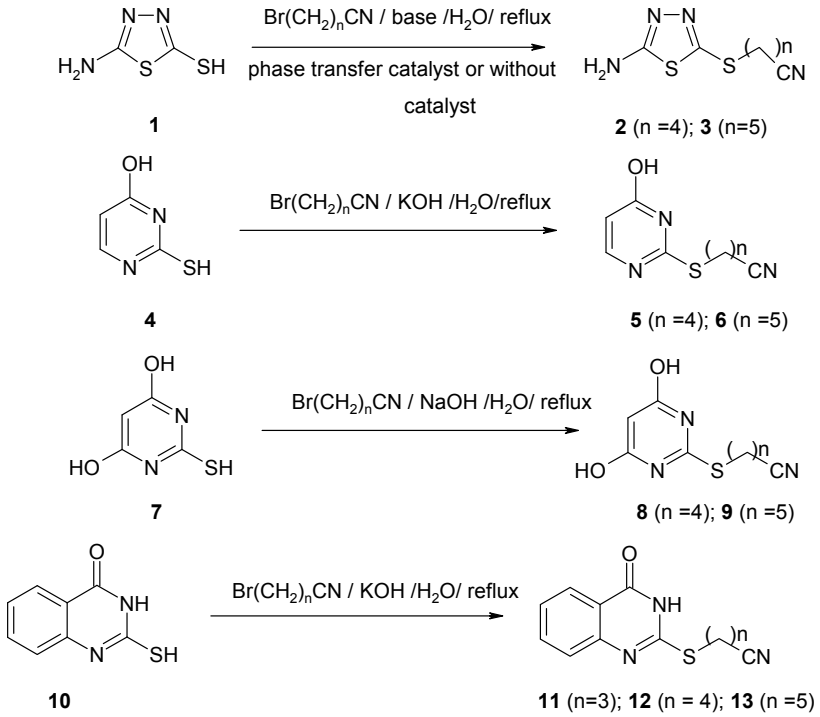
2-(3-Cyanopropylsulfanyl)quinazolin-4(3H)-one (11). Yield 70%. M.p. 160 °C. ^{1}H NMR spectrum, δ: 2.19 (m, 4H, $CH_2C\underline{H}_2$); 2.58 (t, 2H, J = 6 Hz, CCH_2); 3.43 (t, 2H, J = 6 Hz, SCH_2); 7.37–7.73 and 8.23–8.27 (both m, 4H, quinazoline protons); 11.65 (bs, 1H, NH). Mass spectrum, *m/z* (relative intensity): 245 (M^+, 15), 205 (100), 192 (31), 178 (41), 146 (30), 119 (36), 90 (40), 63 (11).

2-(4-Cyanobutylsulfanyl)quinazolin-4(3H)-one (12). Yield 65%. M.p. 140 °C. ^{1}H NMR spectrum, δ: 1.72 (m, 4H, $CH_2(C\underline{H}_2)_2$); 2.58 (t, 2H, J = 6 Hz, CCH_2); 3.24 (t, 2H, J = 6 Hz, SCH_2); 7.36–8.05 (m, 4H, quinazoline protons); 12.56 (bs, 1H, NH). LC-MS: 260 (M^++1).

2-(5-Cyanopentylsulfanyl)quinazolin-4(3H)-one (13). Yield 63%. M.p. 130 °C. ^{1}H NMR spectrum, δ: 1.47–1.76 (m, 6H, $CH_2(C\underline{H}_2)_3$); 2.50 (t, 2H, J = 6 Hz, CCH_2); 3.21(t, 2H, J = 6 Hz, SCH_2); 7.13–8.03 (m, 4H, quinazoline protons); 11.13 and 12.51 (both bs, 1H, NH and OH of tautomeric form). Mass spectrum, *m/z* (relative intensity): 273 (M^+, 7), 233 (20), 205 (41), 192 (41), 178 (100), 145 (23), 120 (52), 90 (44). LC-MS: 274 (M^++1).

RESULTS AND DISCUSSION

Sometimes the phase transfer catalysts (for example, ammonium salts) are added to aqueous reaction mixture with an aim to increase the yields and formation selectivity of the proposed products. Such type "green chemical" environment-friendly phase transfer reactions have been recently reviewed [19]. Therefore we carried out the alkylation of 5-sulfanyl-1,3,4-thiadiazol-2-ylamine (**1**) with 5-bromovaleronitrile in the system KOH (3 equivalents) / 50 mol.% of Me_4NBr in water at room temperature. The corresponding product **2** was isolated in 86% yield as white crystals. The product **2** was isolated in 80% yield, when this reaction was carried out in the presence of K_2CO_3 as base. Interestingly, that alkylation of thiol **1** with 5-bromovaleronitrile was successfully realized also in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene, 1 equivalent) as a base. In this case, the product **2** was isolated in 78% yield. Alkylation of the substrate **1** with $Br(CH_2)_4CN$ in 6 N KOH in the absence of any catalyst has lead to the formation of product **2** in 76% yield. Therefore, in the further alkylation of substrates **1**, **4**, **7** and **10** with 4-bromobutyronitrile, 5-bromovaleronitrile or 6-bromohexanenitrile the system KOH or NaOH / water was used. 1-Hetarylsulfanyl-ω-cyanoalkanes **3**, **5**, **6**, **8**, **9**, **11**–**13** were isolated in 49–77% yields.



1 **2** (n =4); **3** (n=5)

4 **5** (n =4); **6** (n =5)

7 **8** (n =4); **9** (n =5)

10 **11** (n=3); **12** (n = 4); **13** (n =5)

CONCLUSION

Novel „green chemical" methods for the synthesis of 1-hetarylthio-ω-cyanoalkanes were elaborated. In all cases reactions proceeds S-selectively and leads to desired products in yields up to 86%.

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R E F E R E N C E S

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REGIOSELEKTĪVA 1-HETARILSULFANIL-ω-CIANOALKĀNU SINTĒZE, PIELIETOJOT "ZAĻĀS ĶĪMIJAS" METODES

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K O P S A V I L K U M S

Izstrādātas jaunas 1-hetarilsulfanil-ω-cianoalkānu "zaļās ķīmijas" sintēzes metodes ūdens šķīdumos. Demonstrēta pievienotā starpfāžu katalizatora ($(CH_3)_4NBr$) ietekme uz reakcijas iznākumu. Iegūti 1-hetarilsulfanil-ω-cianoalkāni ar 49–86% iznākumiem.

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