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LETTERS TO THE EDITOR

Cyanoethylation and Carboxyethylation of 5-Benzofuryl-4-substituted 4*H*-1,2,4-Triazole-3-thiols

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Abstract—Base-catalyzed reactions of 5-benzofuryl-4-substituted 4*H*-1,2,4-triazole-3-thiols with acrylonitrile and acrylic acid afforded 2-(2-cyanoethyl)- or 2-(2-carboxyethyl)triazoline-3-thiones. Attempts to obtain the corresponding sulfanyl derivatives failed.

Keywords: benzofuryl-1,2,4-triazole-3-thiol, acrylonitrile, cyanoethylation, acrylic acid, carboxyethylation, *S*-alkylation

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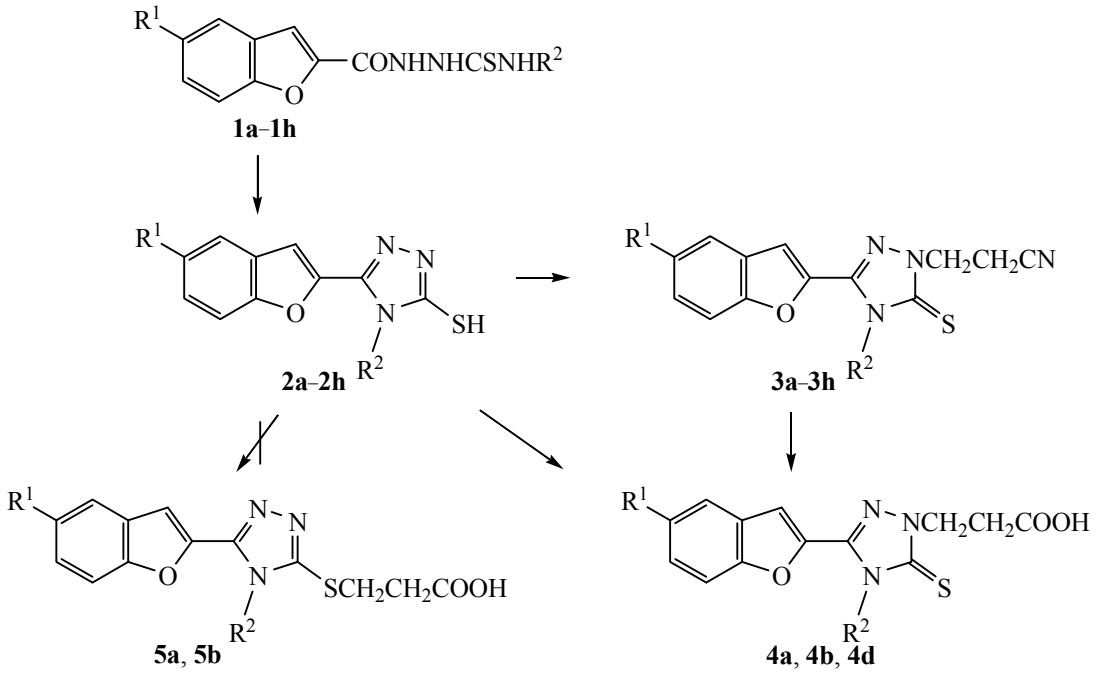
Triazole is one of the five-membered heterocycles that are present in many natural products and medications. A number of 1,2,4-triazole-based drugs is currently known. Thus, ribavirin shows a strong antiviral effect [1, 2]; rizatriptan is effective for the treatment of migraine headaches [3]; anastrozole is an antitumor drug [4]. Synthesis, reactions, and biological activity of a number of 1,2,4-triazole derivatives containing various pharmacophore fragments in the positions *3, 4*, and *5* of the heterocycle have been reported, some of which have a pronounced or moderate antitumour or antibacterial activity, and the ability to influence DNA methylation [5–8]. These results and data on previously synthesized 1,2,4-triazole derivatives showing significant antitumor activity [9–12] confirm the practical importance and scientific significance of continuing a targeted search for biologically active compounds among the new triazole derivatives.

Here we studied the reactions of cyanoethylation and carboxyethylation of 5-benzofuryl-4-substituted 4*H*-1,2,4-triazole-3-thiols.

The starting 1,2,4-triazole-3-thiols **2a**–**2h** were obtained by intramolecular cyclization of the corresponding 1,4-disubstituted thiosemicarbazides **1** in an alkaline medium [9–11]. Cyanoethylation and carboxyethylation of 1,2,4-triazole-3-thiols with acrylonitrile and acrylic acid were carried out in the presence of triethylamine or NaOH as a catalyst.

Alkylation and cyanoethylation of 1,2,4-triazole-3-thiols are of interest due to the search for new biologically active triazole derivatives. However, data on the structure of the products of alkylation and cyanoethylation are not consistently reliable and sometimes contradictory [13, 14]. We have previously shown that the reaction of 5-(4-alkoxyphenyl)-4-phenyl(benzyl)-4*H*-triazole-3-thiol with acrylonitrile in the presence of triethylamine resulted in the formation of the corresponding 2-*N*-(2-cyanoethyl)triazole-3-thiones. We did not succeed in obtaining the 3-cyanoethylsulfanyl derivative [13]. However, the reaction of acrylonitrile with 1,2,4-triazole-3-thiol in a 2% NaOH solution afforded 3-(2-cyanoethylsulfanyl)-1,2,4-triazole as a sole product, whose formation was proven only by elemental analysis data [14]. In this regard, we performed the cyanoethylation reaction of triazole-3-thiols **2a**–**2h** with acrylonitrile in the presence of both triethylamine and NaOH [14]. It was found that in both cases the reaction proceeded exclusively with the formation of 2-*N*-cyanoethyltriazoline-3-thiones **3a**–**3h** (Scheme 1). Structure of the compounds obtained was

Scheme 1.



R^1 = H, R^2 = C_6H_5 (**a**); R^1 = H, R^2 = $CH_2C_6H_5$ (**b**); R^1 = H, R^2 = C_6H_{11} (**c**); R^1 = H, R^2 = CH_2 = $CHCH_2$ (**d**); R^1 = CH_3, R^2 = C_6H_5 (**e**); R^1 = CH_3, R^2 = $CH_2C_6H_5$ (**f**); R^1 = CH_3, R^2 = C_6H_{11} (**g**); R^1 = CH_3, R^2 = CH_2=$CHCH_2$ (**h**); R^1 = H, R^2 = C_6H_5 (**a**); R^1 = H, R^2 = $CH_2C_6H_5$ (**b**); R^1 = H, CH_2=$CHCH_2$ (**d**).

confirmed by ^{1}H and ^{13}C NMR spectra. Thus, in the ^{1}H NMR spectrum of compound **3a** there were triplet signals of the CH_2CN and NCH_2 groups at 3.10 and 4.59 ppm, respectively. The ^{13}C NMR spectrum of compound **3a** contained the signal of the NCH_2 moiety (44.6 ppm) and no signal of the SCH_2 group, which would appear in a stronger field when *S*-cyanoethylation occurs.

In a similar manner, acrylic acid reacted with triazole-3-thiols **2a**, **2b**, and **2d** in the presence of triethylamine to give exclusively 2-(2-carboxyethyl)triazoline-3-thiones **4a**, **4b**, and **4d**. The sructure of the resulting compounds was additionally confirmed by an authentic synthesis of **4a** from nitrile **3a**. The melting point of a mixture of two samples obtained was not depressed. We did not succeed in isolating 3-(2-carboxyethyl)sulfanyl derivatives **5a**, **5b**, and **5d**. Attempts to alkylate triazole-3-thiols **2a**, **2b**, and **2d** with 2-chloropropionic and 2-bromopropionic acids in both alcoholic and aqueous KOH solution were not successful (Scheme 1).

The purity, individuality, and structure of the synthesized compounds were confirmed by TLC, elemental analysis, ^{1}H and ^{13}C NMR spectroscopy data.

5-Benzofuryl-4-substituted 2-cyanoethyl-2*H*-1,2,4-triazole-3-thiones 3a–3h (general procedure). A mixture of the corresponding 1,2,4-triazole-3-thiol **2** (0.01 mol), 10 mL of freshly distilled acrylonitrile, 20 mL of triethylamine, and 20 mL of water or 40 mL of a 2% solution of NaOH was refluxed for 8–10 h. Excess of acrylonitrile was distilled off, then 40 mL of water was added. The crystals formed were filtered off and dried.

5-Benzofuryl-4-phenyl-2-(2-cyanoethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3a). Yield 94.5%, mp 174–175°C, R_f 0.73. ^{1}H NMR spectrum, δ, ppm: 3.16 t (2H, CH_2CN, J = 6.7 Hz), 4.58 t (2H, NCH_2, J = 6.7 Hz), 6.30 d (1H, =CH, J = 0.8 Hz), 7.22 d.d.d (1H, C_6H_4, J = 8.0, 7.3, 0.9 Hz), 7.35 d.d.d (1H, C_6H_4, J = 8.2, 7.3, 1.4 Hz), 7.45–7.51 m (4H, C_6H_4 + C_6H_5), 7.62–7.68 m (3H, C_6H_5). Found, %: N 17.26; S 9.42. $C_{19}H_{14}N_4OS$. Calculated, %: N 16.17; S 9.25.

5-Benzofuryl-4-benzyl-2-(2-cyanoethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3b). Yield 90%, mp 126–127°C, R_f 0.68. ^{1}H NMR spectrum, δ, ppm: 3.14 t (2H, CH_2CN,

J = 6.6 Hz), 4.58 t (2H, NCH_2, J = 6.6 Hz), 5.67 s (2H, NCH_2), 7.18–7.32 m (6H, C_6H_4 and C_6H_5), 7.36 d (1H, =CH, J = 0.8 Hz), 7.39 d.d.d (1H, C_6H_4, J = 8.3, 7.2, 1.2 Hz), 7.56 d.d.d (1H, C_6H_4, J = 8.3, 1.6, 0.8 Hz), 7.65 br.d (1H, C_6H_4, J = 7.8 Hz). Found, %: N 15.75; S 8.56. $C_{20}H_{16}N_4OS$. Calculated, %: N 15.54; S 8.29.

5-Benzofuryl-4-cyclohexyl-2-(2-cyanoethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3c). Yield 85.7%, mp 194–195°C, R_f 0.67. ^{1}H NMR spectrum, δ, ppm: 1.10–1.27 m (2H), 1.36–1.53 m (2H), 1.66–1.93 m (4H, C_6H_{11}), 2.04–2.21 m (2H, C_6H_{11}), 3.07 t (2H, CH_2CN, J = 6.7 Hz), 4.71–4.83 m (1H, NCH, C_6H_{11}), 7.34 t.d (1H, C_6H_4, J = 7.5, 1.1 Hz), 7.40 d (1H, =CH, J = 0.8 Hz), 7.41–7.47 m (1H, C_6H_4), 7.60–7.64 m (1H, C_6H_4), 7.75 d.d (1H, C_6H_4, J = 7.7, 1.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.6 (CH_2), 24.4 (CH_2), 25.3 ($2CH_2$), 28.9 ($2CH_2$), 44.4 (NCH_2), 57.8 (NCH), 110.5 (CH), 110.9 (CH), 126.6 (C), 140.8 (C), 141.3 (C), 154.4 (C). Found, %: N 15.68; S 9.28. $C_{19}H_{20}N_4OS$. Calculated, %: N 15.89; S 9.09.

4-Allyl-5-benzofuryl-2-(2-cyanoethyl)-2*H*-1,2,4-triazole-3(4H)-thione (3d). Yield 85.5%, mp 109–110°C, R_f 0.72. ^{1}H NMR spectrum, δ, ppm: 3.10 t (2H, CH_2CN, J = 6.6 Hz), 4.53 t (2H, NCH_2, J = 6.6 Hz), 5.06 d.t (2H, NCH_2, J = 5.3, 1.5 Hz), 5.17–5.25 m (2H, $=CH_2$), 5.99 d.d.t (1H, =CH, J = 17.0, 10.5, 5.3 Hz), 7.31 d.d.d (1H, C_6H_4, J = 7.8, 7.3, 1.0 Hz), 7.42 d.d.d (1H, C_6H_4, J = 8.2, 7.3, 1.3 Hz), 7.51 d (1H, =CH, J = 0.9 Hz), 7.61 br.d (1H, C_6H_4, J = 8.2 Hz), 7.72 br.d (1H, C_6H_4, J = 7.8 Hz). Found, %: N 18.26; S 10.57. $C_{16}H_{14}N_4OS$. Calculated, %: N 18.05; S 10.33.

5-(5-Methylbenzofuryl)-4-phenyl-2-(2-cyanoethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3e). Yield 97.2%, mp 161–162°C, R_f 0.72. ^{1}H NMR spectrum, δ, ppm: 2.39 br.s (3H, CH_3), 3.16 t (2H, CH_2CN, J = 6.7 Hz), 4.58 t (2H, NCH_2, J = 6.7 Hz), 6.20 d (1H, =CH, J = 0.9 Hz), 7.15 br.d.d (1H, C_6H_3, J = 8.4, 1.6 Hz), 7.25–7.27 m (1H, C_6H_3), 7.34 br.d (1H, C_6H_3, J = 8.4 Hz), 7.44–7.49 m (2H, C_6H_5), 7.60–7.68 m (3H, C_6H_5). Found, %: N 15.31; S 8.58. $C_{20}H_{16}N_4OS$. Calculated, %: N 15.54; S 8.89.

5-(5-Methylbenzofuryl)-4-benzyl-2-(2-cyanoethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3f). Yield 74.0%, mp 148–149°C, R_f 0.60. ^{1}H NMR spectrum, δ, ppm: 2.44 s (3H, CH_3), 3.13 t (2H, CH_2CN, J = 6.6 Hz), 4.57 t (2H, NCH_2, J = 6.6 Hz), 5.65 s (2H, $NC\underline{H}_2C_6H_5$), 7.17–7.31 m (7H) and 7.40–7.45 m (2H, C_6H_5, C_6H_3, H_{furyl}). Found, %: N 14.75; S 8.74. $C_{21}H_{18}N_4OS$. Calculated, %: N 14.96; S 8.56.

5-(5-Methylbenzofuryl)-4-cyclohexyl-2-(2-cyanoethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3g). Yield 97.0%, mp 123–124°C, R_f 0.70. ^{1}H NMR spectrum, δ, ppm: 1.14–1.26 m (2H, C_6H_{11}), 1.35–1.52 m (2H, C_6H_{11}), 1.66–1.92 m (4H, C_6H_{11}), 2.02–2.16 m (2H, C_6H_{11}), 2.49 s (3H, CH_3), 3.06 t (2H, CH_2CN, J = 6.7 Hz), 4.49 t (2H, NCH_2, J = 6.7 Hz), 4.70–4.82 m (1H, C_6H_{11}), 7.24 d.d (1H, C_6H_3, J = 8.5, 1.9 Hz), 7.30 d (1H, =CH, J = 0.8 Hz), 7.49 d (1H, C_6H_3, J = 8.5 Hz), 7.51 d.d (1H, C_6H_3, J = 1.9, 0.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 15.6 (CH_2), 20.7 (CH_2), 24.4 (CH_2), 25.3 ($2CH_2$), 28.9 ($2CH_2$), 44.4 (NCH_2), 57.8 (NCH), 110.3 (CH), 110.5 (CH), 116.3 (CN), 121.4 (CH), 126.7 (C), 127.3 (CH), 140.8 (C), 141.4 (C), 152.9 (C), 166.7 (C). Found, %: N 15.52; S 8.96. $C_{20}H_{22}N_4OS$. Calculated, %: N 15.28; S 8.74.

4-Allyl-5-(5-methylbenzofuryl)-2-(2-cyanoethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (3h). Yield 90.5%, mp 102–103°C, R_f 0.74. ^{1}H NMR spectrum, δ, ppm: 2.47 s (3H, CH_3), 3.09 t (2H, CH_2CN, J = 6.6 Hz), 4.52 t (2H, NCH_2, J = 6.6 Hz), 5.04 d.t (2H, NCH_2, J = 5.3, 1.5 Hz), 5.16–5.24 m (2H, $=CH_2$), 5.97 d.d.t (1H, =CH, J = 17.0, 10.5, 5.3 Hz), 7.22 d.d (1H, C_6H_3, J = 8.4, 1.7 Hz), 7.40 d (1H, =CH, J = 0.8 Hz), 7.45–7.49 m (2H, C_6H_3). Found, %: N 17.48; S 9.62. $C_{17}H_{16}N_4O_6$. Calculated, %: N 17.27; S 9.88.

5-Benzofuryl-4-substituted 2-(2-carboxyethyl)-1,2,4-triazole-3(4*H*)-thiones 4a, 4b, 4d *(general procedure).* A mixture of 1,2,4-triazole-3-thiol **2a**, **2b** or **2d** (0.001 mol), 2 mL of acrylic acid, 4 mL of triethylamine and 4 mL of water was refluxed for 15–20 h. Water was added to quench the reaction. Upon cooling, the formed crystals were filtered off, washed with water and dried.

5-Benzofuryl-4-phenyl-2-(2-carboxyethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (4a). Yield 72%, mp 171–172°C, R_f 0.56. ^{1}H NMR spectrum, δ, ppm: 2.92 t (2H, $COCH_2$, J = 7.5 Hz), 4.50 t (2H, NCH_2, J = 7.5 Hz), 6.26 d (1H, =CH, J = 0.7 Hz), 7.17–7.24 m (1H, C_6H_4), 7.34 t.d (1H, C_6H_4, J = 7.8, 1.3 Hz), 7.42–7.50 m (4H, C_6H_4 + C_6H_5), 7.60–7.67 m (3H, C_6H_4), 12.25 br.s (1H, COOH). Found, %: N 11.64; S 8.92. $C_{19}H_{15}N_3O_3S$. Calculated, %: N 11.50; S 8.77.

5-Benzofuryl-4-benzyl-2-(2-carboxyethyl)-2*H*-1,2,4-triazol-3(4*H*)-thione (4b). Yield 65.8%, mp 85–86°C, R_f 0.51. ^{1}H NMR spectrum, δ, ppm: 2.87 t (2H, $COCH_2$, J = 7.5 Hz), 4.50 t (2H, NCH_2, J = 7.5 Hz), 5.65 s (2H, $C\underline{H}_2C_6H_5$), 7.19–7.32 m (7H), 7.38 d.d.d (1H, C_6H_4, J = 8.3, 7.9, 1.2 Hz), 7.55 d.d (1H, C_6H_4,

J 8.3, 1.2 Hz), 7.64 d.d (1H, C_6H_4, *J* = 7.9, 1.5 Hz), 12.27 br.s (1H, COOH). Found, %: N 13.35; S 8.67. $C_{20}H_{17}N_3O_3S$. Calculated, %: N 13.07; S 8.45.

4-Allyl-5-benzofuryl-2-(2-carboxyethyl)-2*H*-1,2,4-triazole-3(4*H*)-thione (4d). Yield 74.5%, mp 148–149°C, R_f 0.52. ^{1}H NMR spectrum, δ, ppm: 2.83 t (2H, CH_2OH, *J* = 7.5 Hz), 4.44 t (2H, NCH_2, *J* = 7.5 Hz), 5.04 d.t (2H, NCH_2, *J* = 5.3, 1.5 Hz), 5.18 d.q (1H, $=CH_2$, *J* = 17.1, 1.5 Hz), 5.20 d.q (1H, $=CH_2$, *J* = 10.2, 1.5 Hz), 5.98 d.d.t (1H, =CH, *J* = 17.1, 10.2, 5.3 Hz), 7.31 d.d.d (1H, C_6H_4, *J* = 8.2, 7.2, 1.1 Hz), 7.41 d.d.d (1H, C_6H_4, *J* = 7.8, 7.2, 1.1 Hz), 7.51 d (1H, =CH, *J* = 0.9 Hz), 7.60 br.d (1H, C_6H_4, *J* = 8.2 Hz), 7.71 br.d (1H, C_6H_4, *J* = 7.8 Hz). Found, %: N 12.56; S 9.46. $C_{16}H_{15}N_3O_3S$. Calculated, %: N 12.75; S 9.73.

5-Benzofuryl-4-phenyl-2-(2-carboxyethyl)-2*H*-1,2,4-triazol-3(4*H*)-thione (4a) (authentic synthesis). A mixture of 2-(2-cyanoethyl)-1,2,4-triazole-3-thione **3a** (0.001 mol) and 5 mL of conc. hydrochloric acid was refluxed for 8–10 h. After cooling, water was added, and the mixture was kept overnight. The formed crystals were filtered off, washed with water, and dried. Yield 55.5%, mp 171–172°C (no melting point depression was observed in a mixed sample with above described compound **4a**).

^{1}H and ^{13}C NMR spectra (DMSO-d_6) were recorded on a Mercury-300 spectrometer, internal reference TMS. Melting points were measured on a Boetius apparatus. TLC analysis was performed on Silufol UV-254 plates, eluent benzene–acetone, 1 : 0.25 (**3a**–**3h**) or benzene–acetone–ethanol, 1 : 1 : 0.1 (**4a**, **4b**, **4d**).

REFERENCES

1. Sidwell, R.W., Hofman, J.H., Khore, G.P., Allen, L.B., Witkowski, J.T., and Robins, R.K., *Science*, 1972, vol. 177, no. 4050. p. 705. doi 10.1126/science.177.4050.705
2. Sidwell, R.W., Bailey, K.W., Wong, M.H., Bernard, D.L., and Smee, D.F., *Antiviral Res*., 2005, vol. 68, no. 1, p. 10. doi 10.1016/j. antiviral.2005.06.003
3. Williamson, D.J., Hill, R.G., Shepheard, S.J., and Hargreaves, R.J., *Br. J. Pharmacol*., 2001, vol. 133, p. 1029. doi 10.1038/sj.bjp. 0704162
4. Coombes, R.C., Wynne, C.H., and Dowse, A.M., *Endocrine-Related Cancer*, 1999, vol. 6, p. 259. doi 10.1677/erc.0.0060259
5. Ovsepyan, T.R., Arsenyan, F.G., Nersesyan, L.E., Aharonyan, A.S., Danielyan, I.S., Paronikyan, R.V., and Melik-Ohanjanyan, R.G., *Pharm. Chem. J*., 2015, vol. 49, p. 251. doi 10.1007/s11094-015-1261-5
6. Ovsepyan, T.R., Dilanyan, S.V., Minasyan, N.S., and Melik-Ohanjanyan, R.G., *Russ. J. Org. Chem*., 2014, vol. 50, p. 736. doi 10.1134/s1070428014050194
7. Ovsepyan, T.R., Grboyan, S.V., Arsenyan, F.G., and Melik-Ohanjanyan, R.G., *Pharm. Chem. J*., 2012, vol. 45, p. 705. doi 10.1007/s11094-012-0706-3
8. Ovsepyan, T.R., Melik-Ogandzhanyan, R.G., Panosyan, G.A., Arsenyan, F.G., and Garibdzhanyan, B.T., *Pharm. Chem. J*., 2009, vol. 43, no. 12, p. 645. doi 10.1007/s11094-010-0371-3
9. Kaldrikyan, M.A., Grigoryan, L.A., Melik-Ohanjanyan, R.G., and Arsenyan, F.G., *Pharm. Chem. J*., 2009, vol. 43, no. 5, p. 242. doi 10.1007/s11094-009-0287-y
10. Kaldrikyan, M.A., Grigoryan, L.A., Melik-Ohanjanyan, R.G., and Arsenyan, F.G., *Pharm. Chem. J*., 2011, vol. 45, no. 4, p. 211. doi 10.1007/s11094-011-0596-9
11. Kaldrikyan, M.A., Melik-Ohanjanyan, R.G., and Arsenyan, F.G., *Pharm. Chem. J*., 2013, vol. 47, no. 4, p. 191. doi 10.1007/s11094-013-0924-3
12. Kaldrikyan, M.A., Minasyan, N.S., and Melik-Ohanjanyan, R.G., *Russ. J. Org. Chem*., 2013, vol. 49, no. 10, p. 1550. doi 10.1134/s1070428013/00254
13. Kaldrikyan, M.A., Minasyan, N.S., and Melik-Ohanjanyan, R.G., *Russ. J. Gen. Chem*., 2016, vol. 86, no. 2, p. 305. doi 10.1134/s10736321602017
14. Azaryan, A.S., Iradyan, N.S., and Aroyan, A.A., *Arm. Khim. Zh.*, 1975, vol. 28, no. 9, p. 709.