ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 9, pp. 1923–1926. © Pleiades Publishing, Ltd., 2019.
Russian Text © The Author(s), 2019, published in Zhurnal Obshchei Khimii, 2019, Vol. 89, No. 9, pp. 1457–1461.

LETTERS TO THE EDITOR

Synthesis and Intramolecular Heterocyclization of Selected Isonicotinic Acid Thiocarbazides

O. A. Nurkenov[a]*, G. Zh. Karipova[a], T. M. Seilkhanov[b], Zh. B. Satpaeva[a], S. D. Fazylov[a], and A. Nukhuly[c]

[a] *Institute of Organic Synthesis and Coal Chemistry of the Republic of Kazakhstan, ul. Alikhanova 1, Karaganda, 100008 Kazakhstan*
**e-mail: nurkenov_oral@mail.ru*
[b] *Sh. Ualikhanov Kokshetau State University, Kazakhstan, Kokshetau, 020000 Kazakhstan*
[c] *Pavlodar State Pedagogical University, Pavlodar, Kazakhstan*

Received March 29, 2019; revised April 16, 2019; accepted April 19, 2019

Abstract—The reaction of isonicotinic acid hydrazide with ethyl-, allyl-, and cinnamoyl isothiocyanates has afforded the corresponding alkylthiosemicarbazides and the products of their intramolecular heterocyclization, 1,2,4-triazoles.

Keywords: isonicotinic acid hydrazide, thiourea, isothiocyanates, alkylthiosemicarbazides, 1,2,4-triazoles

DOI: 10.1134/S1070363219090299

It is known that antituberculous effect of nicotinic acid hydrazide and its derivatives is largely determined by the structure of pharmacophore fragments in their molecules [1–3]. In spite of numerous publications on the synthesis, properties, and structure of various hydrazide derivatives [4, 5], they are still of interest for further investigation and improvement. In view of strong antituberculous and antimicrobial activity of isonicotinic acid thiosemicarbazide and 1,2,4-triazole derivatives [6, 7], it has seemed promising to investigate the products of the reaction of nicotinic acid hydrazide with ethyl-, allyl- and cinnamoyl isothiocyanates under different conditions. The reactions were performed in ethanol to afford the corresponding alkylthiosemicarbazides **1** and **2** (Scheme 1) It was found that acidification of compounds **1** and **2** in aqueous alkaline media led to intramolecular heterocyclization into 1,2,4-triazole-5(4*H*)-thiones **3, 4** (Scheme 1).

It is known that 1,2,4-triazole-3-thiones can be obtained via sintering of a hydrazide with thiourea [8]. Analogous reaction nicotinic acid hydrazide with allyl thiourea and thiourea (sintering at 170°C during 4 h) gave compounds **4** and **5** (Scheme 2). The target products were isolated via the treatment of the reaction mixture with 20% solution of sodium hydroxide, followed by acidification.

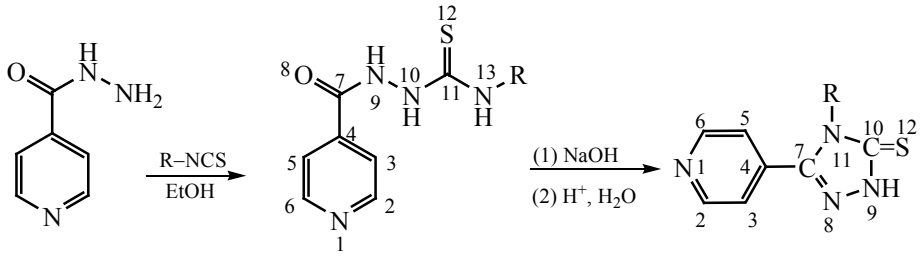
Comparison of the properties of the samples of **4** synthesized via the two methods proved their complete identity.

The obtained thiosemicarbazides **1, 2** and 1,2,4-triazole-3-thiones **3–5** after crystallization from alcohol were white crystalline compounds soluble in polar organic solvents on heating. The structure of compounds **1–5** was confirmed by means of IR, ^{1}H NMR, and ^{13}C NMR spectroscopy as well as the data of two-dimensional COSY (^{1}H–^{1}H) and HMQC (^{1}H–^{13}C) NMR experiments.

A similar heterocyclization reaction was performed using *N*-cinnamoyl-2-isonicotinoylhydrazine carbothioamide **6**. Compound **6** was synthesized via the reaction of equimolar amounts of nicotinic acid hydrazide and cinnamoyl isothiocyanate (obtained in its turn via the interaction of cinnamoyl chloride with potassium thiocyanate in acetone) in alcohol. Acidification of an alkaline solution of compound **6** also led to intramolecular heterocyclization into 7-phenyl-3-(pyridin-4-yl)-5*H*-[1,2,4]-triazolo[3,4-*b*]-[thiazine-5-one] **7** (Scheme 3).

The obtained 1,2,4-triazole-5(4*H*)-thiones **3–5**, **7** are interesting synthons for the preparation of new classes of

Scheme 1.



1, **2** **3, 4**

R = $^{13}CH_2{}^{14}CH_3$ (**1**, **3**), $^{13}CH_2{}^{14}CH{=}{}^{15}CH_2$ (**2**, **4**).

potentially bioactive compounds, due to the presence of two nucleophilic centers in the structure—the exocyclic S atom and endocyclic N atom.

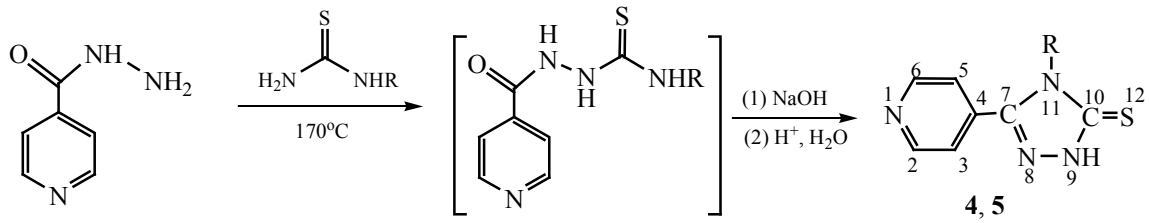
***N*-Ethyl-2-isonicotinoylhydrazinecarbothiamide (1).** A solution of 2.6 g (0.036 mol) of ethyl isothiocyanate in 5 mL of ethanol was added dropwise at stirring to a solution of 4 g (0.036 mol) of nicotinic acid hydrazide in 20 mL of ethanol. The reaction mixture was stirred for 1 h at 50°C, the reaction course was monitored by TLC. After the reaction was complete, the mixture was cooled, the precipitate was filtered off, washed with small amount of cold ethanol, and recrystallized from ethyl acetate. Yield 5.95 g (88 %), mp 235–236°C (ethanol). IR spectrum, ν, cm^{-1}: 3198 (NH), 1689 (C=O), 1248 (C=S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 t (3H, H^{15}, ^3J = 6.9), 3.41-3.45 m (2H, H^{14}), 7.78 d (2H, H^{3,5}, ^3J = 6.0), 8.72 d (2H, H^{2,6}, ^3J = 6.0), 8.16 br. s (1H, H^{13}), 9.34 br. s (1H, H^9) and 10.60 br. s (1H, H^{10}). ^{13}C NMR spectrum, δ_C, ppm: 15.00 (C^{15}), 39.08 (C^{14}), 122.19 (C^{3,5}), 140.06 (C^4), 150.71 (C^{2,6}), 164.95 (C^7) and 181.63 (C^{11}). Found, %: C 48.25; H 5.43; N 25.06. $C_9H_{12}N_4OS$. Calculated, %: C 48.20; H 5.39; N 24.98.

***N*-Allyl-2-isonicotonoylhydrazinecarbothiamide (2)** was prepared similarly. Yield 84 %, mp 220–222°C. IR spectrum, ν, cm^{-1}: 3201 (NH), 1681 (C=O), 1220 (C=S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.07 s (2H, H^{14}), 4.99–5.12 m (2H, H^{16}), 5.75–5.81 m (1H, H^{15}), 7.78 d (2H, H^{3,5}, ^3J = 5.5), 8.36 br. s (1H, H^{13}), 8.75 d (2H, H^{2,6}, ^3J = 5.5), 9.48 s (1H, H^9), 10.64 s (1H, H^{10}). ^{13}C NMR spectrum, δ_C, ppm: 46.46 (C^{14}), 115.80 (C^{16}), 122.21 (C^{3,5}), 135.43 (C^{15}), 140.07 (C^4), 150.70 (C^{2,6}), 165.00 (C^7), 182.17 (C^{11}). Found, %: C 50.88; H 5.17; N 23.78. $C_{10}H_{12}N_4OS$. Calculated, %: C 50.83; H 5.12; N 23.71.

4-Ethyl-3-(piridin-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (3). 20 mL of 2% aqueous solution of sodium hydroxide was added to 1 g (4 mmol) of compound **1**. The reaction mixture was heated at 85°C during 2 h, cooled, and neutralized to pH 6. The precipitate was filtered off. Yield 0.8 g (96%), mp 225–226°C (water). IR spectrum, ν, cm^{-1}: 3194 (NH), 1557 (C=N), 1298 (C=S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.14 t (3H, H^{14}, ^3J = 6.9), 4.06 q (2H, H^{13}, ^3J = 6.9), 7.68 d (2H, H^{3,5}, ^3J = 6.0), 8.75 d (2H, H^{2,6}, ^3J = 6.0), br. s 13.31 (1H, H^9). ^{13}C NMR spectrum, δ_C, ppm: 13.96 (C^{14}), 39.38 (C^{13}), 122.99 (C^{3,5}), 134.08 (C^4), 149.51 (C^7), 151,11 (C^{2,6}) и 167.99 (C^{10}). Found, %: C 52. 59; H 4.94; N 27.21. $C_9H_{10}N_4S$. Calculated, %: C 52.41; H 4.89; N 27.16.

4-Allyl-3-(pyridin-4-yl)-1*H*-1,2,4-triazol-5(4*H*)-thione (4) was obtained similarly. *a*. Yield 80%, mp 200–201°C. IR spectrum, ν, cm^{-1}: 3188(NH), 1604

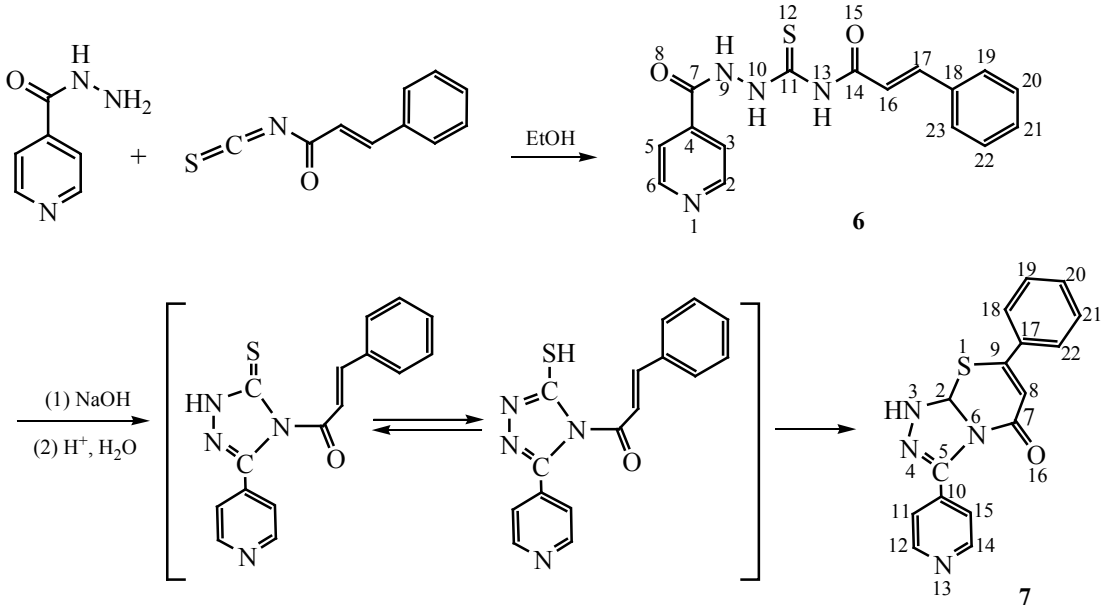
Scheme 2.



4, **5**

R = $^{13}CH_2{}^{14}CH{=}{}^{15}CH_2$ (**4**); H (**5**).

Scheme 3.



(C=N), 1301 (C=S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.75–4.85 m (3H, H$^{13, 15}$), 5.10 d (1H, H^{15}, ^3J = 10.5), 5.78–5.85 m (1H, H^{14}), 7.66 d (2H, H^{3,5}, ^3J = 5.0), 8.72 d (2H, H^{2,6}, ^3J = 5.0), 13.48 br. s (1H, H^9). ^{13}C NMR spectrum, δ_C, ppm: 46.52 (C^{13}), 117.81 (C^{15}), 122.68 (C^{3,5}), 132.21 (C^{14}), 133.93 (C^4), 149.76 (C^7), 151.01 (C^{2,6}), 168.72 (C^{10}). Found, %: C 55.10; H 4.68; N 25.70. $C_{10}H_{10}N_4S$. Calculated, %: C 55.02; H 4.62; N 25.67.

b. A mixture of 2 g (0.015 mol) of nicotinic acid hydrazide and 6.97 g (0.06 mol) of *N*-allylthiourea was thoroughly grinded in a mortar, heated to 170°C in Wood's metal and kept at that temperature for 2 h. After cooling, 20% solution of sodium hydroxide was added. The formed suspension was filtered, the filtrate was acidified with hydrochloric acid to pH = 5, the formed precipitate was isolated by filtration through a glass filter and dried. Yield 1.5 g (45.5%), mp 200-202°C.

3-(Pyridin-4-yl)-1*H*-1,2,4-triazole-5(4*H*)-thione (5) was obtained similarly to compound **4** (procedure *b*) from 2 g (0.015 mol) of isonicotinic acid hydrazide and 4.57 g (0.06 mol) of thiourea Yield 2.5 g (93.6%), mp ≥350°C. IR spectrum, ν, cm^{-1}: 3195 (NH), 1610 (C=N), 1272 (C=S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.79 d (2H, H^{3,5}, ^3J = 6.1), 8.67 d (2H, H^{2,6}, ^3J = 6.1), 13.90 br. s (2H, H^{9,11}). ^{13}C NMR spectrum, δ, ppm: 119.98 (C^{3,5}), 133.03 (C^4), 148.85 (C^7), 151.10 (C^{2,6}) and 168.19 (C^{10}). Found, %: C 47.24; H 3.45; N 31.51. $C_7H_6N_4S$. Calculated, %: C 47.18; H 3.39; N 31.44.

***N*-(2-Isonicotinoylhydrazinecarbonothioyl)-3-phenylacrylamide (6).** A mixture of 1.37 g (0.01 mol) of isonicotinic acid hydrazide and 1.89 g (0.01 mol) of cinnamoyl isothiocyanate was stirred at 70–75°C for 2 h. After cooling, the precipitate was filtered off and crystallized from isopropanol. Yield 1.3 g (40%), white solid, mp 230–231°C. IR spectrum, ν, cm^{-1}: 3194 (NH), 1686 (C=O), 1631 (C=N), 1215 (C=S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.02 d (1H, H^{16}, ^3J = 15.9), 7.42–7.44 m (3H, H^{20,21,22}), 7.60–7.62 m (2H, H^{19,23}), 7.75 d (1H, H^{17}, ^3J = 15.9), 7.78–7.79 m (2H, H^{3,5}), 8.75-8.76 m (2H, H^{2,6}), 11.42 br. s (1H, H^9), 11.75 br. s (1H, H^{13}), 12.24 br. s (1H, H^{10}). ^{13}C NMR spectrum, δ, ppm: 111.98 (C^{16}), 122.03 (C^{3,5}), 128.82 (C^{19,23}), 129.68 (C^{20,22}), 131.39 (C^{21}), 134.54 (C^{18}), 139.74 (C^4), 145.34 (C^{17}), 150.95 (C^{2,6}), 163.71 (C^7), 166.10 (C^{14}), 181.66 (C^{11}). Found, %: C 58.93; H 4.35; N 17.23. $C_{16}H_{14}N_4O_2S$. Calculated, %: C 58.88; H 4.32; N 17.17.

7-Phenyl-3-(pyridin-4-yl)-5*H*-[1,2,4]triazolo[3,4-*b*][1,3]thiazine-5-one (7) was prepared similarly to compound **3** from 1 g (3 mmol) of compound **6**. Yield 0.17 g (18 %), mp ≥320°C. IR spectrum, ν, cm^{-1}: 1641 (C=O), 1554 (C=N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.48–7.77 m (6H, H$^{2,18–22}$), 7.81 d (2H, H^{11,15}, ^3J = 5.0), 8.67 d (2H, H^{2,6}, ^3J = 5.0), 13.90 br. s (2H, H^{9,11}). ^{13}C NMR spectrum, δ, ppm: 119.26 (C^2), 119.88 (C^8), 120.02 (C^{11,15}), 128.70 (C^{18,22}), 128.96 (C^{19,21}), 129.41 (C^{20}), 133.52 (C^{17}), 133.71 (C^{10}), 134.74 (C^5), 144.34

(C^9), 151.12 ($C^{12,14}$), 171.68 (C^7). Found, %: C 62.37; H 3.98; N 18.23. $C_{16}H_{12}N_4OS$. Calculated, %: C 62.32; H 3.92; N 18.17.

^1H and ^{13}C NMR spectra were registered in DMSO-d_6 using a JNM-ECA Jeol 400 spectrometer operating at 399.78 and 100.53 MHz, respectively, with HMDS as internal reference. IR spectra were recorded using a Nicolet 5700 spectrometer (KBr pellets). Elemental analysis was performed using a Hewlett–Packard 185B analyzer. Melting points were determined in glass capillaries using a Stuart SMP 10 device. The reactions were monitored by TLC on Sorbfil plates in the isopropanol—25% aqueous ammonia–water system (7 : 2 : 1), developing with iodine vapors.

This study was financially supported by the Committee of Science of the Ministry of Education and Science of Kazakhstan Republic (grant no. AP05131054).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Mona, E.F. and Mohammed, G.A., *Egypt. J. Chem*., 2019, vol. 62, no. 2, p. 171. https://doi.org/10.21608/EJCHEM.2018.4427.1393
2. Martins, F., Santos, S., Ventura, C., Elvas-Leitao, R., Santos, L., Vitorino, S., Reis, M., Miranda, V., Correia, H.F., Sousa, J.A., Kovalishyn, V., Latino, D.A.R.S., Ramos, J., and Viveiros, M., *Eur. J. Med. Chem*., 2014, no. 81, p. 119. https://doi.org/10.1016/j.ejmech.2014.04.077
3. Machado, D., Couto, I., Perdigão, J., Rodrigues, L., Portugal, I., Baptista, P., Veigas, B., Amaral, L., and Viveiros, M., *PLoS ONE*., 2012, no. 7(4), p. e34538. https://doi.org/10.1371/journal.pone.0034538
4. Farhan, M.E. and Assy, M.G., *Egypt. J. Chem*., 2019, vol. 62, no. 2, p. 171. https://doi.org/10.21608/EJCHEM.2018.4427.1393
5. Nurkenov, O.A., Fazylov, S.D., Zhivotova, T.S., Satpayeva, Zh.B., Akhmetova, S.B., Kurmanbayeva, Zh., Karipova, G.K., and Isayeva, A.Zh., *News of NAS RK, Ser. Chem. Techn*., 2015, vol. 1, no. 409, p. 9.
6. Ali, B., Khan, K.M., Arshia, Kanwal, Hussain Sh., Hussain Sf., Ashraf, M., Riaz, M., Wadood, A., and Perveen, S., *Bioorg. Chem*., 2018, no. 79, p. 34. https://doi.org/101016/j.bioorg.2018.04.004
7. Ovsepyan T.R., Dilyan, S.V., Akopian, M.R., Minasyan, N.S., Paronikyan, R.G., Paronikyan, R.V., and Melik-Ogandzhanyan, R.G., *Khim. Zh. Arm*., 2016, vol. 69, nos. 1–2, p. 121.
8. Abdalla, S.M., Hegab, M.I., Abo Taleb, N.A., Hasabelnaby, S.M., and Goudah, A., *Eur. J. Med. Chem*., 2010, vol. 45, no. 4, p. 1267. https://doi.org/10.1016/j.ejmech.2009.10.028