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Synthesis of azolethione derivatives from 3-(phenylamino)propanehydrazide

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Heating of 3-(phenylamino)propanehydrazide with ethyl xanthogenate provided potassium salt of carbodithioate, which under the action of hydrochloric or sulphuric acid was cyclized to 5-[2-(phenylamino)ethyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione or 5-[2-(phenylamino)ethyl]-2,3-dihydro-1,3,4-thiadiazole-2-thione. In the reaction with phenacyl bromide it was transformed into *N*-(4-phenyl-2-thioxo-2,3-dihydro-1-,3-tiazol-3-yl)-3-(phenylamino)propanamide and, under treatment with hydrazine, gave 4-amino-3-[2-(phenylamino)ethyl]-4,5-dihydro-1*H*-1,2,4-triazole-5-thione, which subsequently underwent condensation reaction with phenacyl bromide to give *N*-[2-(6-phenyl-7*H*-[1,2,4]triazol[3,4-*b*][1,3,4]-3-yl)ethyl]aniline.

Key words: hydrazide, 1,2,4-triazolethione, 1,3,4-oxadiazolethione, 1,3,4-thiadiazolethione, tetraazabicyclononatriene, cyclization

INTRODUCTION

Cyclization products of carboxylic acid hydrazides, such as triazoles, oxa- and thiadiazoles, are associated with a wide range of biological activities, among which anti-inflammatory, antibacterial [1, 2], anticancer [3], and antimicrobial [4] ones have been cited in the literature. They have attracted attention as potential anti-HIV agents [5]. Previously, we have described the synthesis of azoles by the intramolecular cyclization reaction of semicarbazides and thiosemicarbazides of *N*-phenyl-β-alanine [1] and have investigated the synthesis of compounds containing two azole cycles [6, 7].

RESULTS AND DISCUSSION

Herein, we report the synthesis of azolethiones obtained from 3-(phenylamino)propanehydrazide (**1**), and some of their transformations. Carbodithio-derivatives of hydrazides are valuable synthones for synthesis of heterocyclic systems [4, 6, 7]. Potassium salt **2** was prepared by heating under reflux propanehydrazide **1** in ethanol with ethyl xanthogenate which was prepared *in situ* from CS_2 and KOH in ethanol (Scheme 1). When salt **2** was heated under reflux with phenacyl bromide, thioamide group of hydrazide participated in cyclization reaction providing *N*-(4-phenyl-2-thioxo-2,3-dihydro-1,3-thiazol-3-yl)-3-(phenylamino)propanamide (**3**) as a thick mass which turned into light-yellow crystals after washing with water and crystallization from propan-2-ol. In the ^{1}H NMR spectrum of **3** a singlet at 5.06 ppm attributed to a proton of the methyne group in the thiazole ring overlaps with the signal of the amide proton.

Acidification of an aqueous solution of carbodithioate **2** with hydrochloric or sulfuric acid caused cyclization and cleavage of H_2S resulting in formation of 5-[2-(phenylamino)ethyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione (**4**), whereas 5-[2-(phenylamino)ethyl]-2,3-dihydro-1,3,4-thiadiazole-2-thione (**5**) was obtained under treatment with concentrated sulfuric acid.

4-amino-3-[2-(phenylamino)ethyl]-4,5-dihydro-1*H*-1,2,4-triazole-5-thione (**6**) was obtained by heating under reflux salt **2** with hydrazine in dioxane and subsequently acidifying the reaction mixture. Numerous data are available in literature [8, 9] about transformation of oxadiazolethiones to 4-amino derivatives of triazolethione under treatment with hydrazine. To the best of our knowledge, there are no data on transformation of thiadiazolethiones to the respective 4-amino derivatives in the scientific literature. In this work, 4-amino derivative **6** was obtained in up to 75% yield from

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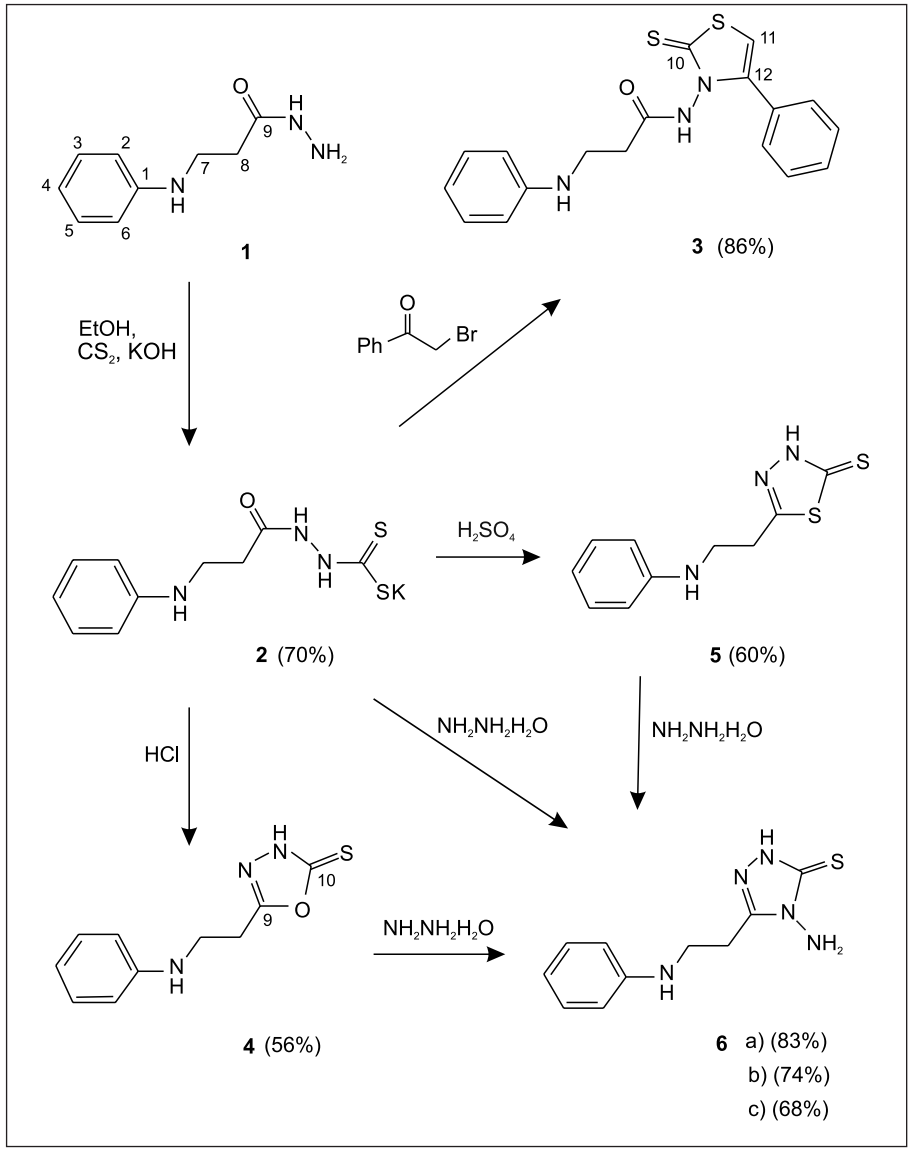


Scheme 1. Transformations of potassium salt of *N'*-[3-(phenylamino)propanehydrazide]carbodithioate to azolethiones

1,3,4-oxadiazolethione **4** and 1,3,4-thiadiazolethione **5** by heating them under reflux with hydrazine. Under the action of hydrazine, the diazole ring cleaved and replacement of oxygen or sulfur atom, respectively, took place.

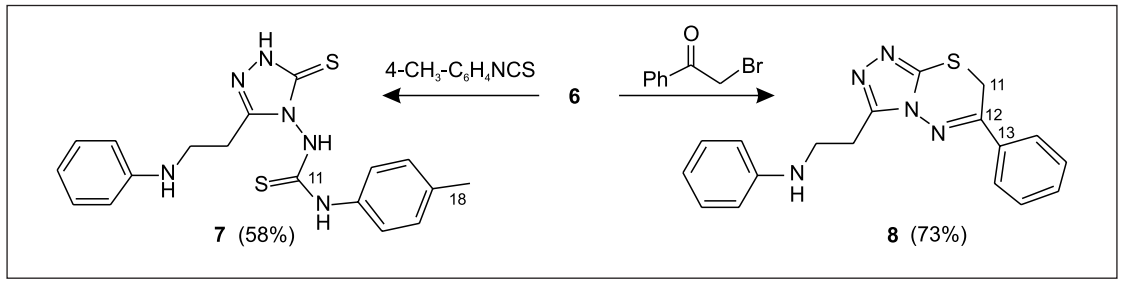
In the ^{13}C NMR spectra of **4–6**, resonances characteristic of carbon in the C = S group are present in the range of 165–180 ppm and the ones attributed to carbon in the C = N group are present in the 150–163 ppm region. Thione-thiol tautomerism is characteristic of oxa- and thiadiazoles [10, 11]. In the ^{1}H NMR spectra of these compounds recorded in DMSO-d_6 solutions, the resonance of the SH group proton is absent, therefore, the conclusion has been drawn that diazoles **4–6** existed in the thione form in this solvent.

Reaction of **6** with *p*-tolyl isocyanate provided thiocarbamide **7**, whereas *N*-[2-(6-phenyl-7*H*-[1,2,4]triazolo [3,4-*b*][1,3,4]thiadiazin-3-yl)ethyl]aniline (**8**) was synthesized by heating under reflux **6** with phenacyl bromide (Scheme 2).

In the ^{1}H NMR spectrum of **8**, two triplets attributed to methylene group protons in CH_2CN and CH_2NH are present at 2.93 and 3.39 ppm, whereas the resonances of N-NH_2 group protons observed at 5.58 ppm in the spectrum of aminotriazole **6** are absent. The protons of the methylene group in the thiadiazine ring resonated at 4.87 ppm. The spectral line at 23.76 ppm in the ^{13}C NMR spectrum confirms the presence of the CH_2 group in the thiadiazine cycle.

EXPERIMENTAL

Melting points were determined with an automatic APA1 melting point apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a *Varian Unity Inova* (300 MHz, 75 MHz) spectrometer operating in the Fourier transform mode. Chemical shifts (δ) are reported in parts per million (ppm) calibrated from TMS (0 ppm) as an internal standard for ^{1}H NMR, and DMSO-d_6 (39.50 ppm) for



Scheme 2. Reactions of 4-amino-3-[2-(phenylamino)ethyl]-4,5-dihydro-1*H*-1,2,4-triazole-5-thione with *p*-tolyl isothiocyanate and phenacyl bromide

^{13}C NMR. Mass spectra were obtained on a Waters (Micromas) ZQ 2000 Spectrometer using the chemical ionization mode (25 V). The IR spectra were measured as potassium bromide pellets using a Perkin-Elmer 1600 series FT-IR spectrometer. Elemental analyses (C, H, N) were performed with an Elemental Analyzer CE-440. The monitoring of the reaction course and the purity of the synthesized compounds were carried out using TLC on Alugram SIL G/UV$_{254}$ plates.

3-(Phenylamino)propanehydrazide (1) was synthesized as described previously [1]. M. p. 93–94 °C.

Potassium salt of N'-[3-(phenylamino)propanehydrazide] carbodithioate (2). To a solution of KOH (1.68 g, 30 mmol) in ethanol (50 ml), CS_2 (3.8 g, 3.01 ml, 50 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 15 min. Afterwards, hydrazide **1** (5.37 g, 30 mmol) dissolved in ethanol (50 ml) was added, and the reaction mixture was heated under reflux for 16 h. The liquid fraction was removed with a rotary evaporator; the residue was dissolved in ethanol (20 ml) and filtered into diethyl ether. Yield 6.2 g (70%). M. p. > 380 °C. IR-spectrum, ν/cm^{-1}: 3220–3461 (NH); 1634 (C = O); 1142 (CSS$^-$). Anal. calcd. for $C_{10}H_{12}KN_3OS_2$, %: C, 40.93; H, 4.12; N, 14.32. Found, %: C, 40.78; H, 4.53; N, 14.10.

N-(4-Phenyl-2-thioxo-2,3-dihydro-1,3-thiazol-3-yl)-3-(phenylamino)propanamide (3). To a solution of salt **2** (0.88 g, 3 mmol) in ethanol (20 ml), phenacyl bromide (0.59 g, 3 mmol) was added, and the reaction mixture was heated under reflux for 3 h. The liquid fraction was removed with a rotary evaporator; the residue was washed with water (5 × 5 ml) and crystallized from propan-2-ol. Yield 0.92 g (86%), M. p. 82–83 °C. ^{1}H NMR (DMSO-d$_6$) δ: 3.06 (t, 2H, *J* = 6.8 Hz, CH_2CO); 3.37–3.47 (m, 2H, $\underline{CH_2}NH$); 5.06 (s, 2H, NH + CH); 5.71 (s, 1H, NHAr); 6.49–6.62 (m, 3H, H-2,4,6 Ar); 7.08 (t, 2H, *J* = 7.2 Hz, H-3,5 Ar); 7.58 (t, 2H, *J* = 7.5 Hz, H Ar'); 7.71 (t, 1H, *J* = 7.5 Hz, H Ar'); 8.04 (d, 2H, *J* = 7.5 Hz, H Ar'). ^{13}C NMR (DMSO-d$_6$) δ: 24.87 (C-8); 39.62 (C-7); 112.03 (C-2, 6); 115.98 (C-4); 128.29 (C-3, 5); 128.75, 128.84, 133.82, 134.92 (C-Ar'); 147.94 (C-1); 162.58 (C-12); 166.31 (C-9); 192.41 (C-10). MS (CI, 25 V), *m/z* (%): 356 [M + H]$^+$ (100). Anal. calcd. for $C_{18}H_{17}N_3OS_2$, %: C, 60.82; H, 4.82; N, 11.82. Found, %: C, 60.78; H, 4.63; N, 11.80.

5-[2-(Phenylamino)ethyl]-2,3-dihydro-1,3,4-oxadiazole-2-thione (4). Salt **2** (14.67 g, 50 mmol) was dissolved in water (300 ml), and the solution was acidified with HCl to pH 3–4. The precipitate formed was filtered off, washed with methanol, and recrystallized from methanol. Yield 6.2 g (56%). M. p. 119–120 °C. ^{1}H NMR (DMSO-d$_6$) δ: 2.94 (t, 2H, *J* = 7.1 Hz, CH_2C = N); 3.39 (t, 2H, *J* = 7.1 Hz, $\underline{CH_2}NH$); 6.58–7.61 (m, 5H, H Ar); 5.76 (br. s, 1H, NHAr); 14.29 (s, 1H, N$\underline{NH}$). ^{13}C NMR (DMSO-d$_6$) δ: 25.22 (C-8); 39.02 (C-7); 112.09 (C-2, 6); 116.06 (C-4); 128.90 (C-3, 5); 147.96 (C-1); 162.61 (C-9), 177.68 (C-10). IR ν (cm^{-1}): 3197 (NH); 1678 (C = O); 1319 (C = S). MS (CI, 25 V), *m/z* (%): 222 [M + H]$^+$ (40%). Anal. calcd. for $C_{10}H_{11}N_3OS$, %: C, 54.28; H, 5.01; N, 18.99. Found, %: C, 54.16; H, 4.94; N, 18.78.

5-[2-(Phenylamino)ethyl]-2,3-dihydro-1,3,4-thiadiazole-2-thione (5). A solution of salt **2** (1.76 g, 6 mmol) in water (5 ml) was added in small portions to cooled down to 0 °C 98% H_2SO_4 (10 ml). The reaction mixture was cooled down and stirred for 2 h until a thick residue was formed. Afterwards, ice was added and the pH was adjusted to 3–4 with aqueous NH_3. The crystalls formed were filtered off, washed with cold water, and recrystallized from ethanol. Yield 0.85 g (60%). M. p. 161–162 °C. ^{1}H NMR (DMSO-d$_6$) δ: 3.01 (t, 2H, *J* = 6.6 Hz, CH_2C = N); 3.50 (t, 2H, *J* = 6.6 Hz, CH_2NH); 6.44 (br. s, 1H, NHAr); 6.70 (t, 1H, *J* = 7.5 Hz, H-4 Ar); 6.88 (d, 2H, *J* = 8.1 Hz, H-2, 6 Ar); 7.23 (t, 2H, *J* = 8.1 Hz, H-3, 5 Ar); 14.32 (s, 1H, N$\underline{NH}$). ^{13}C NMR (DMSO-d$_6$) δ: 25.12 (C-8); 41.66 (C-7); 112.99 (C-2, 6); 115.88 (C-4); 129.33 (C-3, 5); 146.36 (C-1); 161.82 (C-9); 177.73 (C-10). MS (CI, 25 V), *m/z* (%): 238 [M + H]$^+$ (50). Anal. calcd. for $C_{10}H_{11}N_3S_2$, %: C, 50.60; H, 4.67; N, 17.70. Found, %: C, 50.55; H, 4.61; N, 17.69.

4-Amino-3-[2-(phenylamino)ethyl]-4,5-dihydro-1H-1,2,4-triazole-5-thione (6).

Method A. A solution of salt **2** (0.9 g, 3 mmol), hydrazine hydrate (0.5 g, 0.4 ml, 10 mmol) and dioxane (30 ml) was heated under reflux for 12 h, cooled down to room temperature, and HCl was added dropwise to pH 3. The precipitate formed was filtered off, washed with cold water until the neutral medium of the washing water, and recrystallized from ethanol. Yield 0.58 g (83%). M. p. 174–175 °C. ^{1}H NMR (DMSO-d$_6$) δ: 2.88 (t, 2H, *J* = 7.2 Hz, CH_2C = N); 3.38 (t, 2H, *J* = 7.2 Hz, $\underline{CH_2}NH$);

5.58 (s, 2H, NH_2); 5.70 (br. s, 1H, NHAr); 6.51–6.63 (m, 5H, H Ar); 13.51 (s, 1H, NNH). ^{13}C NMR (DMSO-d_6) δ: 24.47 (C-8); 39.57 (C-7); 112.03 (C-2, 6); 115.83 (C-4); 128.88 (C-3, 5); 148.16 (C-1); 150.49 (C-9); 165.81 (C-10). IR ν (cm^{-1}): 3139, 3268, 3411 (NH_2, NH); 1336 (C = S). MS (CI, 25 V), *m/z* (%): 236 $[M + H]^+$ (60). Anal. calcd. for $C_{10}H_{13}N_5S$, %: C, 51.04; H, 5.57; N, 29.76. Found, %: C, 50.94; H, 5.49; N, 29.52.

Method B. The target product **6** was prepared from **4** (1.1 g, 5 mmol) according to the synthesis procedure described in Method A. Yield 0.87 g (74%).

Method C. The target product **6** was prepared from **5** (1.185 g, 5 mmol) according to the synthesis procedure described in Method A. Yield 0.81 g (68%).

The mixed samples of the compound **6**, synthesized according to Methods A–C, did not show depression of the melting point.

1-(4-Methylphenyl)-3-{3-[2-(phenylamino)ethyl]-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-4-yl}thiourea (7). A solution of **6** (0.89 g, 3.8 mmol), *p*-tolyl isothiocyanate (0.57 g, 3.8 mmol), and DMF (10 ml) was stirred at room temperature for 24 h, and afterwards water (10 ml) was added. The residue formed was crystallized from propan-2-ol. Yield 0.84 g (58%). M. p. 168–169 °C. ^{1}H NMR (DMSO-d_6) δ: 2.28 (s, 3H, CH_3); 2.47 (t, 2H, *J* = 7.1 Hz, CH_2C = N); 3.28 (t, 2H, *J* = 7.1 Hz, $\underline{CH_2}$NH); 5.69 (s, 1H, NHAr); 6.52–6.61 (m, 3H, H Ar); 7.06–7.15 (m, 4H, H Ar, Ar'); 7.27–7.32 (m, 2H, H Ar'); 9.49 (s, 1H, NH); 9.96 (s, 1H, NH); 13.50 (s, 1H, NNH). ^{13}C NMR (DMSO-d_6) δ: 20.48 (C-18); 33.14 (C-8); 39.71 (C-7); 112.14 (C-2, 6); 115.91 (C-4); 116.76 (C-13, 17); 119.86 (C-15); 128.48 (C-14, 16); 128.86 (C-3, 5); 136.40 (C-12); 148.37 (C-1); 153.39 (C-9); 171.19 (C-10); 171.87 (C-11). MS (CI, 25 V), *m/z* (%): 385 $[M + H]^+$ (50). Anal. calcd. for $C_{18}H_{20}N_6S_2$, %: C, 56.22; H, 5.24; N, 21.86 Found, %: C, 56.19; H, 5.30; N, 21.69.

N-[2-(6-Phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazin-3-yl)ethyl]aniline (8). A solution of **6** (0.47 g, 0.2 mmol), phenacyl bromide (0.396 g, 0.2 mmol), and sodium acetate (0.16 g, 0.2 mmol) in ethanol (20 ml) was heated under reflux for 2 h. The liquid fraction was removed with a rotary evaporator, the residue was crystallized from methanol. Yield 0.49 g (73%). M. p. 133–134 °C. ^{1}H NMR (DMSO-d_6) δ: 2.93 (t, 2H, *J* = 7.2 Hz, CH_2C = N); 3.39 (t, 2H, *J* = 7.2 Hz, $\underline{CH_2}$NH); 4.86 (s, 1H, S-CH_2); 6.00 (s, 1H, NH); 6.55 (dt, 1H, *J* = 1.2 Hz, *J* = 7.5 Hz, H-4 Ar); 6.62 (dd, 2H, *J* = 1.2 Hz, *J* = 7.5 Hz, H-2,6 Ar); 7.09 (dt, 2H, *J* = 1.2 Hz, *J* = 7.5 Hz, H-3,5 Ar); 7.56 (t, 2H, *J* = 7.2 Hz, H-3,5 Ar'); 7.69 (dt, 1H, *J* = 1.2 Hz, *J* = 7.2 Hz, H-4 Ar'); 8.04 (dd, 2H, *J* = 1.2 Hz, *J* = 7.2 Hz, H-2,6 Ar'). ^{13}C NMR (DMSO-d_6) δ: 23.76 (C-11); 33.18 (C-8); 39.98 (C-7); 112.13 (C-2, 6); 115.89 (C-4); 125.38 (C-14, 18); 128.33 (C-15, 17); 128.84 (C-3, 5); 133.61 (C-13); 135.43 (C-10); 141.82 (C-16); 148.26 (C-1); 150.77 (C-9); 154.76 (C-12). MS (CI, 25 V), *m/z* (%): 335 $[M + H]^+$ (60). Anal. calcd. for $C_{18}H_{17}N_5S$, %: C, 64.45; H, 5.11; N, 20.88. Found, %: C, 64.40; H, 5.10; N, 20.82.

CONCLUSIONS

Potassium salt of carbodithioate was synthesized from 3-(phenylamino)propanehydrazide. It was cyclized to derivatives of 1,2,4-triazolethione, 1,3,4-oxadiazolethione and 1,3,4-thiadiazolethione containing an aromatic cycle in the side chain. Reaction of aminotriazolethione with phenacyl bromide provided tetraazabicyclononatriene.

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AZOLTIONŲ DARINIŲ SINTEZĖ IŠ 3-(FENILAMINO) PROPANHIDRAZIDO

S a n t r a u k a

Šildant 3-(fenilamino)propanhidrazidą su etilksantogenatu gauta karboditioato kalio druska, kuri druskos arba sieros rūgščių veikimu ciklizuota į 5-[2-(fenilamino)etil]-2,3-dihidro-1,3,4-oksadiazol-2-tioną arba 5-[2-(fenilamino)etil]-2,3-dihidro-1,3,4-tiadiazol-2-tioną, o reakcijoje su fenacilbromidu susintetintas *N*-(4-fenil-2-tiokso-2,3-dihidro-1,3-tiazol-3-il)-3-(fenilamino)propanamidas. Veikiant karboditioato druską hidrazinu gautas 4-amino-3-[2- (fenilamino) etil]-4,5-dihidro-1*H*-1,2,4-triazol-5-tionas, kurį kondensuojant su fenacilbromidu išskirtas *N*-[2-(6-fenil-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-3-il)etil]anilinas.