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# Effective synthesis of 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines

**Alexander S. Kulikov[1], Margarita A. Epishina[1], Leonid L. Fershtat[1], Nina N. Makhova[1]***

[1] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Ave., Moscow 119991, Russia; e-mail: mnn@ioc.ac.ru*

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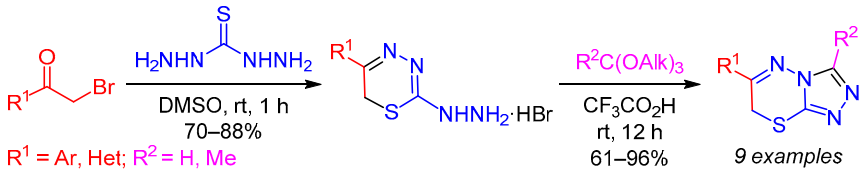



A highly effective method for the preparation of 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines was developed on the basis of condensation reaction between aryl(hetaryl) α-bromo ketones and commercially available thiocarbohydrazide, followed by treatment of the obtained 2-hydrazinyl-6*H*-1,3,4-thiadiazine hydrobromides with ortho esters in the presence of trifluoroacetic acid under mild conditions.

**Keywords**: α-bromo ketones, hydrazinylthiadiazines, ortho esters, thiocarbohydrazide, 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines, condensation.

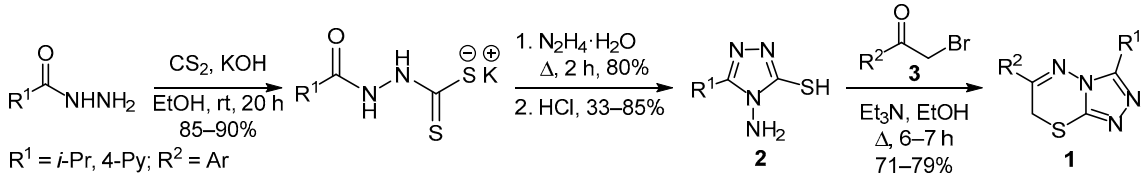
Fused nitrogenous heterocyclic systems exhibit a broad range of pharmacological activity.[1–4] Well-known examples of this class of compounds include condensed ring structures comprising of six-membered heterocycles and 1,2,4-triazole.[5–8] In particular, pharmacologically active compounds have been identified among 7*H*-1,2,4-triazolo-[3,4-*b*][1,3,4]thiadiazines **1**, which have revealed antimicrobial,[9,10] antiparasitic,[11] and antiproliferative activity.[12,13]

The most frequently used methods for building the molecular framework of compounds **1** start from the synthesis of 5-substituted 1,2,4-triazoles **2** that contain reactive vicinal amino and mercapto groups, followed by annulation of thiadiazine ring by reacting triazoles **2** with α-halo ketones **3**.[6,10,11] Synthesis of the starting 1,2,4-triazoles **2** and their subsequent transformations are performed with toxic reagents ($CS_2$, $N_2H_4 \cdot H_2O$) and at elevated temperatures (Scheme 1).

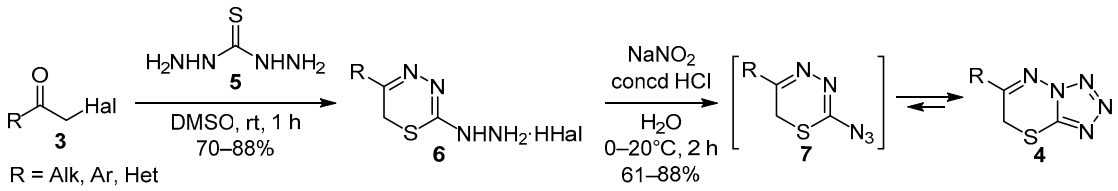
In contrast to that, we recently developed a generally applicable, highly effective method for the synthesis of 7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **4**, which relies on the initial assembly of thiadiazine ring, followed by annulation of the tetrazole ring.[14] This method includes condensation of α-bromo ketones **3** with the commercially available thiocarbohydrazide **5** at room temperature in DMSO and nitrosation of the formed 2-hydrazinyl-1,3,4-thiadiazine hydrobromide **6** by treatment with $NaNO_2$ in hydrochloric acid. The nitrosation product – azido derivative **7** undergoes intramolecular cyclization as a result of azide-tetrazole tautomerism, the equilibrium of which is completely shifted toward the tetrazole form. All of these reactions proceed under mild conditions and the final products are obtained in high yields (Scheme 2).

The goal of this work was to study the possible applications of an analogous approach for the preparation of 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines **1** with aromatic and heterocyclic substituents. The starting materials selected for this purpose were 2-hydrazinyl-6*H*-1,3,4-thiadiazine hydrobromides **6**, which were previously synthesized by us for the preparation of 7*H*-tetrazolo[5,1-*b*]-[1,3,4]thiadiazines **4**.[14] Generally, the annulation of 1,2,4-triazole ring to six-membered azines starting from their hydrazinyl derivatives **8** can be accomplished by any of the following three methods: synthesis of hydrazones **9** followed by oxidative condensation,[15,16] dehydration of acylhydrazinyl derivative **10** by refluxing in $POCl_3$,[17] and condensation with ortho esters. The third route can be

**Scheme 1**

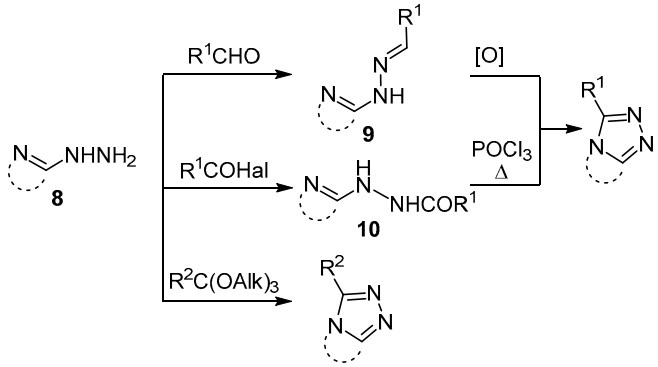


**Scheme 2**




accomplished either by refluxing the hydrazinyl derivative in mixture with an ortho ester[18] or by performing the reaction in the presence of trifluoroacetic acid[19] (Scheme 3).

**Scheme 3**




Initially, we chose to prepare the desired 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines **1** according to the first approach, based on oxidative condensation of hydrazones, which does not require harsh reaction conditions. In the role of model substrate we selected 4-nitrophenylhydrazone **11**, which was synthesized by condensation of 5-(4-bromophenyl)-2-hydrazinyl-6*H*-1,3,4-thiadiazine hydrobromide **6a** with 4-nitrobenzaldehyde (Scheme 4). This oxidation process was performed at room temperature, using such oxidizing reagents as $PhI(OAc)_2$ and $(NH_4)_2Ce(NO_3)_6$ in MeCN or $Br_2$ in AcOH. However, TLC analysis indicated that complex mixtures of products were formed under all of the tested conditions, with significant resinification occurring during the reaction. Therefore, we favored the method based on room temperature condensation of hydrazinyl derivatives with ortho esters in the presence of trifluoroacetic acid.

For the optimization of reaction conditions, we selected hydrobromide **6a** as the model compound, which was used in the reaction with $HC(OMe)_3$. The reaction parameters that were subjected to optimization included the amount of $HC(OMe)_3$, $CF_3CO_2H$ and the duration of the process. Since the starting compound was introduced into the reaction as hydrobromide and the reaction was performed in acidic medium, the conversion degree could not be observed by TLC. Therefore, the yield of each experiment using the particular reaction conditions was determined from the isolated amount of the product. The optimal conditions were found when the reaction was performed at the molar ratio **6a**:$HC(OMe)_3$:$CF_3CO_2H$ = 1:18:6.5 at 20°C for 12 h (Table 1, entry 6). The reaction did not proceed in the absence of $CF_3CO_2H$ (entry 7).

**Table 1**. Optimization of reaction conditions for the preparation of 6-(4-bromophenyl)-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazine (**1a**) from 5-(4-bromophenyl)-2-hydrazinyl-6*H*-1,3,4-thiadiazine (**6a**)*

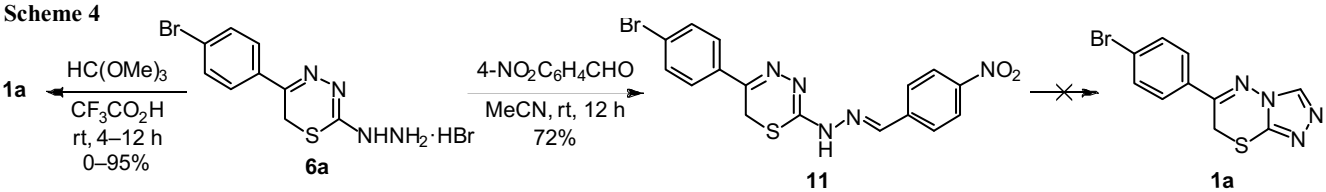
| Entry | $HC(OMe)_3$, mmol | $CF_3CO_2H$, mmol | Time, h | Yield, % |
|---|---|---|---|---|
| 1 | 9 | 26 | 12 | 53 |
| 2 | 9 | 6.5 | 12 | 80 |
| 3 | 9 | 6.5 | 8 | 67 |
| 4 | 9 | 6.5 | 4 | 46 |
| 5 | 13.5 | 6.5 | 12 | 90 |
| 6 | 18 | 6.5 | 12 | 95 |
| 7 | 18 | 0 | 12 | 0 |

* Compound **6a** (1 mmol), rt.

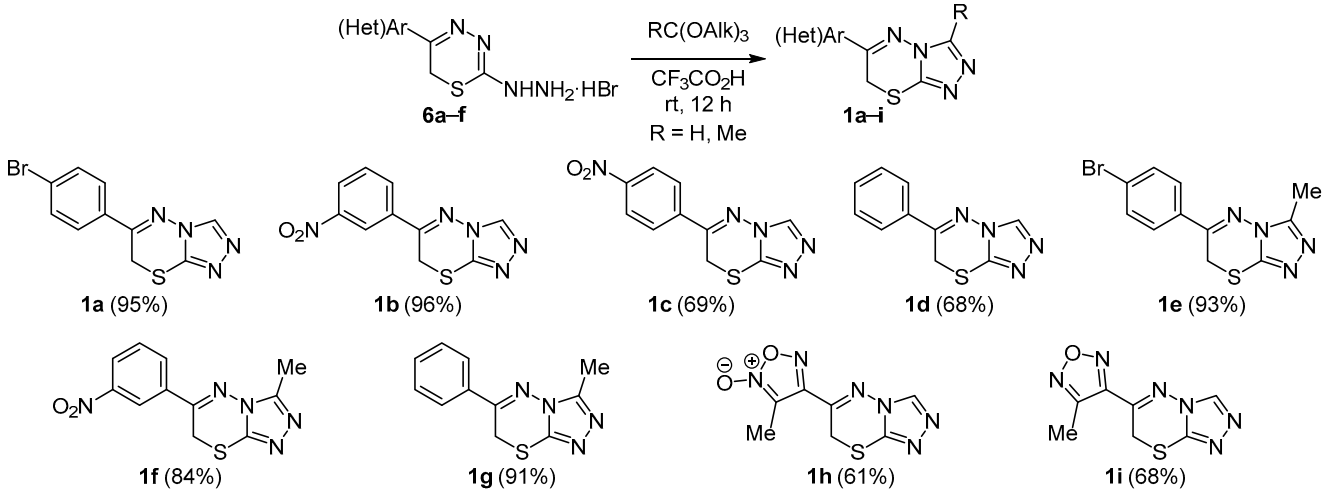
The optimized conditions were further used for reacting the rest of 2-hydrazinyl-1,3,4-thiadiazines **6b**–**f** with $HC(OMe)_3$ and $MeC(OEt)_3$, resulting in the formation of 7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines **1b**–**i** (Scheme 5). This reaction was found to be generally applicable and effective not only for 5-aryl-2-hydrazinyl-6*H*-1,3,4-thiadiazines **6b**–**d**, which reacted with both $HC(OMe)_3$ (compounds **1b**–**d**) and $MeC(OEt)_3$ (compounds **1e**–**g**). 6-Hetaryl-2-hydrazinyl-1,3,4-thiadiazines **6e**,**f** also reacted with $HC(OMe)_3$ under analogous conditions forming 6-hetaryl-7*H*-1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines **1h**,**i**. All compounds were formed in high yields and compounds **1** in the majority of cases precipitated from the reaction mixture in sufficiently pure form, without need for additional purification.

The structure of the synthesized compounds was confirmed by their spectral characteristics (IR, $^1H$ and $^{13}C$ NMR spectroscopy, high-resolution mass spectrometry). Some of the compounds have been described in the literature, but were previously obtained in lower yields and characterized only by their melting points and elemental analysis data. Therefore, we report the spectral data for all synthesized compounds in the Experimental part of this article.

**Scheme 4**



**Scheme 5**




In conclusion, a general and highly effective method for the preparation of 6-aryl-(hetaryl)-7*H*-1,2,4-triazolo[3,4-*b*]-[1,3,4]thiadiazines has been proposed. This method is based on the synthesis of 2-hydrazinyl-6*H*-1,3,4-thiadiazines by condensation of aryl(hetaryl) α-bromo ketones with commercially available thiocarbohydrazide, followed by annulation of 1,2,4-triazole ring to the 2-hydrazinyl-6*H*-1,3,4-thiadiazine intermediates using room temperature reactions with ortho esters in the presence of trifluoroacetic acid.

## Experimental

IR spectra were recorded on a Bruker Alpha instrument over 400–4000 $cm^{-1}$ range (resolution 2 $cm^{-1}$) for KBr pellets. $^1H$ and $^{13}C$ NMR spectra were acquired on a Bruker AM-300 spectrometer (300 and 75 MHz, respectively) for solutions in DMSO-$d_6$. Residual solvent signals were used as internal standards (2.50 ppm for $^1H$ nuclei and 39.5 ppm for $^{13}C$ nuclei). High-resolution mass spectra were recorded on a Bruker micrOTOF II instrument using electrospray ionization. Elemental analysis was performed on a EuroVector EA instrument. Melting points were determined on a Stuart SMP20 digital melting point apparatus. The reaction progress was controlled by thin-layer chromatography on Merck 60 $F_{254}$ plates with visualization under UV light (254 nm wavelength).

Starting 2-hydrazinyl-6*H*-1,3,4-thiadiazines **6a**–**i** were obtained according to a published procedure.[14]

**Synthesis of compounds 1a**–**i** (General method). Trifluoroacetic acid (1 ml, 13 mmol) was added dropwise to a suspension of the appropriate 2-hydrazinyl-6*H*-1,3,4-thiadiazine hydrobromide **6a**–**i** (2 mmol) in trimethyl orthoformate or triethyl orthoacetate (36 mmol), and the mixture was stirred for 12 h at room temperature. The obtained precipitate was filtered off, washed with $Et_2O$ (2×7 ml), and air-dried. Compound **1d** was isolated by evaporation of the reaction mixture at reduced pressure, followed by treatment with diethyl ether (10 ml) and additional crystallization from EtOH. Compound **1h** was isolated by evaporation of the reaction mixture at reduced pressure followed by treatment with water (10 ml) and crystallization from EtOH. Compound **1i** was additionally crystallized from EtOH.

**6-(4-Bromophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazine (1a)**. Yield 0.56 g (95%), cream-colored powder, mp 208–209°C (mp 206–208°C[18]), $R_f$ 0.28 (EtOAc). IR spectrum, ν, $cm^{-1}$: 3127, 1584, 1480, 1443, 1285, 1178, 1076, 1006, 943, 841, 811. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 4.44 (2H, s, $CH_2$); 7.79 (2H, d, $^3J$ = 8.4, H Ar); 7.92 (2H, d, $^3J$ = 8.4, H Ar); 9.15 (1H, s, CH). $^{13}C$ NMR spectrum, δ, ppm: 23.5; 125.7; 129.3; 132.0; 132.5; 140.1; 143.1; 154.7. Found, *m*/*z*: 296.9630 $[M(^{81}Br)+H]^+$, 294.9651 $[M(^{79}Br)+H]^+$. $C_{10}H_8BrN_4S$. Calculated, *m*/*z*: 296.9627 ($^{81}Br$), 294.9648 ($^{79}Br$).

**6-(3-Nitrophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (1b)**. Yield 0.50 g (96%), yellow powder, mp 233–235°C (mp 235°C[20]), $R_f$ 0.36 ($CHCl_3$–EtOAc, 3:2). IR spectrum, ν, $cm^{-1}$: 3124, 1526, 1475, 1350, 1281, 882, 732. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 4.55 (2H, s, $CH_2$); 7.88 (2H, t, $^3J$ = 8.4, H Ar); 8.39–8.46 (2H, m, H Ar); 8.76 (1H, s, H Ar); 9.23 (1H, s, CH). $^{13}C$ NMR spectrum, δ, ppm: 23.7; 121.8; 126.1; 130.7; 133.6; 135.0; 140.1; 143.2; 148.2; 153.8. Found, *m*/*z*: 262.0391 $[M+H]^+$. $C_{10}H_8N_5O_2S$. Calculated, *m*/*z*: 262.0394.

**6-(4-Nitrophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (1c)**. Yield 0.36 g (69%), light-brown powder, mp 253–254°C (254–257°C[21]), $R_f$ 0.36 ($CHCl_3$–EtOAc, 3:2). IR spectrum, ν, $cm^{-1}$: 3034, 1521, 1470, 1445, 1347, 1302, 735. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 4.51 (2H, s, $CH_2$); 8.20 (2H, d, $^3J$ = 8.8, H Ar); 8.38 (2H, d, $^3J$ = 8.8, H Ar); 9.21 (1H, s, CH). $^{13}C$ NMR spectrum, δ, ppm: 23.8; 124.0; 128.7; 139.2; 140.1; 143.2; 149.1; 153.9. Found, *m*/*z*: 262.0391 $[M+H]^+$. $C_{10}H_8N_5O_2S$. Calculated, *m*/*z*: 262.0398.

**6-Phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (1d)**. Yield 0.29 g (68%), beige powder, mp 120–121°C (EtOH) (mp 122–124°C[18]), $R_f$ 0.56 ($CHCl_3$–EtOAc, 3:2). IR spectrum, ν, $cm^{-1}$: 3128, 3064, 1481, 1450, 1283, 1182, 939, 773. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 4.44 (2H, s, $CH_2$); 7.53–7.61 (3H, m, H Ph); 7.97 (2H, d, $^3J$ = 7.1, H Ph); 9.14 (1H, s, CH). $^{13}C$ NMR spectrum, δ, ppm: 23.7; 127.3; 129.0; 131.9; 133.3; 140.2; 143.0; 155.5. Found, *m*/*z*: 217.0543 $[M+H]^+$. $C_{10}H_9N_4S$. Calculated, *m*/*z*: 217.0542.

**6-(4-Bromophenyl)-3-methyl-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazine (1e)**. Yield 0.56 g (93%), cream-colored powder, mp 228–229°C (mp 225–227°C[18]), $R_f$ 0.16 ($CHCl_3$). IR spectrum, ν, $cm^{-1}$: 1584, 1400, 1189, 1129, 1076, 1005, 721. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 2.49 (3H, s, $CH_3$); 4.37 (2H, s, $CH_2$); 7.80 (2H, d, $^3J$ = 8.4, H Ar); 7.97 (2H, d, $^3J$ = 8.4, H Ar). $^{13}C$ NMR spectrum, δ, ppm: 9.7; 22.7; 125.6; 129.3; 132.0; 132.6; 140.0; 150.5; 154.0. Found, *m*/*z*: 310.9793 $[M(^{81}Br)+H]^+$, 308.9804 $[M(^{79}Br)+H]^+$. $C_{11}H_{10}BrN_4S$. Calculated, *m*/*z*: 310.9789 ($^{81}Br$), 308.9809 ($^{79}Br$).

**3-Methyl-6-(3-nitrophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*]-[1,3,4]thiadiazine (1f)**. Yield 0.44 g (84%), yellow powder, mp 208–209°C (mp 210–211°C[22]), $R_f$ 0.13 (EtOAc). IR spectrum, ν, $cm^{-1}$: 1518, 1476, 1453, 1348, 1150, 855. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 2.51 (3H, s, $CH_3$); 4.48 (2H, s, $CH_2$); 7.88 (1H, t, $^3J$ = 7.7, H Ar); 8.50 (2H, d, $^3J$ = 7.5, H Ar); 8.77 (1H, s, H Ar). $^{13}C$ NMR spectrum, δ, ppm: 9.8; 23.0; 121.9; 126.1; 130.7; 133.5; 135.2; 139.9; 148.2; 150.6; 152.9. Found, *m*/*z*: 276.0551 $[M+H]^+$. $C_{11}H_{10}N_5O_2S$. Calculated, *m*/*z*: 276.0547.

**3-Methyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]-thiadiazine (1g)**. Yield 0.42 g (91%), cream-colored powder, mp 188–189°C (EtOH) (mp 187–188°C[18]), $R_f$ 0.26 (EtOAc). IR spectrum, ν, $cm^{-1}$: 3006, 1467, 1448, 1366, 1302, 1004, 760. $^1H$ NMR spectrum, δ, ppm: 2.48 (3H, s, $CH_3$); 4.37 (2H, s, $CH_2$); 7.58 (3H, s, H Ph); 8.01 (2H, s, H Ph). $^{13}C$ NMR spectrum, δ, ppm: 9.8; 22.9; 127.3; 128.9; 131.7; 133.5; 139.9; 150.4; 154.6. Found, *m*/*z*: 231.0707 $[M+H]^+$. $C_{11}H_{11}N_4S$. Calculated, *m*/*z*: 231.0703.

**6-(4-Methyl-5-oxido-1,2,5-oxadiazol-3-yl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (1h)**. Yield 0.29 g (61%), beige powder, mp 158–159°C, $R_f$ 0.38 ($CHCl_3$–EtOAc, 3:2). IR spectrum, ν, $cm^{-1}$: 3120, 1623, 1604, 1461, 1146, 1046, 856. $^1H$ NMR spectrum, δ, ppm: 2.39 (3H, s, $CH_3$); 4.47 (2H, s, $CH_2$); 9.25 (1H, s, CH). $^{13}C$ NMR spectrum, δ, ppm: 9.6; 22.3; 111.9; 140.3; 143.3; 146.7; 153.0. Found, *m*/*z*: 239.0348 $[M+H]^+$. $C_7H_7N_6O_2S$. Calculated, *m*/*z*: 239.0346.

**6-(4-Methyl-1,2,5-oxadiazol-3-yl)-7*H*-[1,2,4]triazolo-[3,4-*b*][1,3,4]thiadiazine (1i)**. Yield 0.30 g (68%), cream-colored powder, mp 220–221°C (EtOH), $R_f$ 0.25 ($CHCl_3$–EtOAc, 3:2). IR spectrum, ν, $cm^{-1}$: 3148, 3004, 1485, 1451, 1232, 1186, 1153, 992, 941, 911, 723. $^1H$ NMR spectrum, δ, ppm: 2.63 (3H, s, $CH_3$); 4.52 (2H, s, $CH_2$); 9.26 (1H, s, CH). $^{13}C$ NMR spectrum, δ, ppm: 10.1; 24.0; 140.1; 143.4; 146.4; 150.4; 151.1. Found, *m*/*z*: 223.0400 $[M+H]^+$. $C_7H_7N_6OS$. Calculated, *m*/*z*: 223.0397.

**5-(4-Bromophenyl)-2-[(2-(4-nitrobenzylidene)hydrazinyl]-6*H*-1,3,4-thiadiazine (11)**. 4-Nitrobenzaldehyde (0.30 g, 2 mmol) was added to a suspension of 5-(4-bromophenyl)-2-hydrazinyl-6*H*-1,3,4-thiadiazine **6a** (0.74 g, 2 mmol) in MeCN (10 ml), and the mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with water (10 ml), the precipitate was filtered off, air-dried, and recrystallized from EtOH. Yield 0.60 g (72%), orange crystals, mp 236–237°C (EtOH), $R_f$ 0.22 ($CHCl_3$). IR spectrum, ν, $cm^{-1}$: 2876, 1589, 1514, 1447, 1339, 1053, 999, 843. $^1H$ NMR spectrum, δ, ppm (*J*, Hz): 4.00 (2H, s, $CH_2$); 7.67 (2H, d, $^3J$ = 7.1, H Ar); 7.77 (2H, d, $^3J$ = 7.1, H Ar); 7.98 (2H, d, $^3J$ = 8.2, H Ar); 8.27 (2H, d, $^3J$ = 8.2, H Ar); 8.46 (1H, s, CH); 11.86 (1H, s, NH). $^{13}C$ NMR spectrum, δ, ppm: 27.5; 129.1; 129.9; 133.8; 137.6; 139.9; 147.2; 151.6; 153.5; 156.5; 169.5. Found, %: C 46.16; H 2.80; N 16.59. $C_{16}H_{12}BrN_5O_2S$. Calculated, %: C 45.95; H 2.89; N 16.74.

A Supplementary information file containing $^1H$ and $^{13}C$ NMR spectra of all obtained compounds is available at the journal website at http://link.springer.com/journal/10593.

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