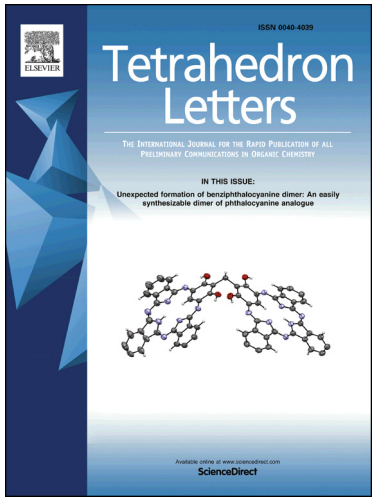
Accepted Manuscript



Effective synthesis of 6-substituted 7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines *via* a one-pot condensation/nitrosation/azide-tetrazole tautomerism reaction sequence

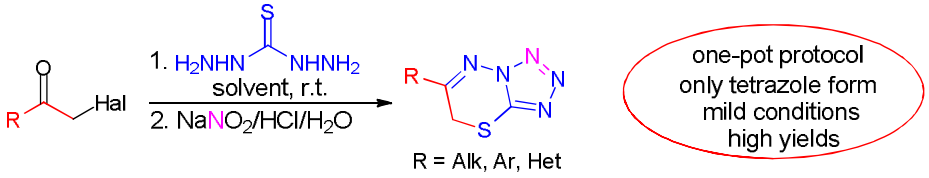
Alexander S. Kulikov, Margarita A. Epishina, Leonid L. Fershtat, Anna A. Romanova, Nina N. Makhova

PII: S0040-4039(17)31132-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.09.014
Reference: TETL 49284

To appear in: *Tetrahedron Letters*

Received Date: 20 July 2017
Revised Date: 31 August 2017
Accepted Date: 7 September 2017

Please cite this article as: Kulikov, A.S., Epishina, M.A., Fershtat, L.L., Romanova, A.A., Makhova, N.N., Effective synthesis of 6-substituted 7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines *via* a one-pot condensation/nitrosation/azide-tetrazole tautomerism reaction sequence, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.09.014



Effective synthesis of 6-substituted 7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines *via* a one-pot condensation/nitrosation/azide-tetrazole tautomerism reaction sequence

Alexander S. Kulikov,[a] Margarita A. Epishina,[a] Leonid L. Fershtat,[a] Anna A. Romanova,[b,c] Nina N. Makhova[a]*

[a]*N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47, Leninsky prosp., 119991, Moscow, Russian Federation. Phone: +7 (499) 1355326; Fax: +7 (499) 1355328. e-mail: mnn@ioc.ac.ru*

[b]*A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,28 Vavilova str., 119991 Moscow, Russian Federation. Fax: +7 (499) 135 5085.*

[c]*Higher Chemical College, Russian Academy of Sciences, 125047 Moscow, Russian Federation*

Abstract

A new, simple, and general method for the synthesis of 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines (R = Ar, Het, Alk) has been developed. The described method is based on the one-pot condensation of α-haloketones with thiocarbohydrazide, nitrosation of the formed hydrazinylthiadiazine using $NaNO_2$/HCl, and intramolecular cyclization of the nitrosation product *via* azide-tetrazole tautomerism. Spectroscopic and structural investigations revealed that the azide-tetrazole equilibrium is completely shifted to the tetrazole form both in solution and the solid state.

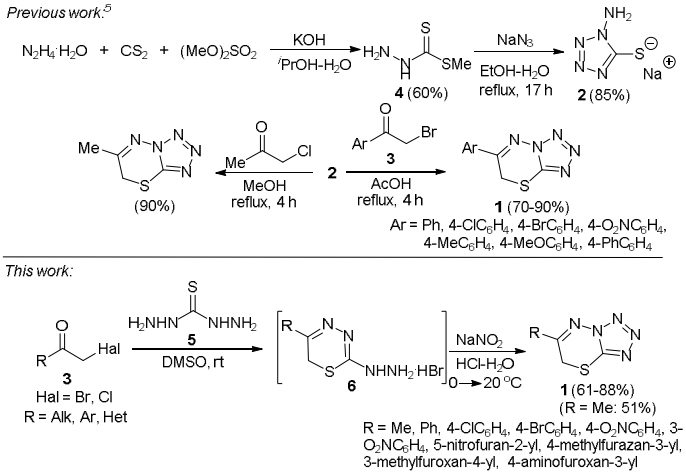
Keywords: 7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines; furoxan; α-haloketones; nitrosation; azide-tetrazole tautomerism.

During the last years, *N*-bridged fused heterocyclic systems have received significant attention owing to their diverse pharmacological activities.[1] Among them, the heterocycle-fused 1,2,4-triazole scaffold has been identified as one of the privileged structures in drug discovery.[2] In particular, 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazines are cholinesterase and other enzyme inhibitors, and can be used for the therapy of Alzheimer's disease.[3a] Additionally, they represent therapeutic agents, possessing antiproliferative and antileishmanial activities.[3b] The introduction of the thiadiazine motif makes an appreciable contribution to their biological activity, with applications as antibacterial,[4a] antifungal,[4b] and antidepressant[4c] agents.

The analogous structures containing a fused tetrazole ring, namely 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **1** (R = Ar, Alk), were previously described in only one report, along with an examination of their free radical scavenging activity.[5] Meanwhile, these structures may have potential as pharmacologically active compounds due to the tetrazole ring being an important pharmacophore in medicinal chemistry,[6] with pharmaceutical applications which have been widely explored and comprehensively documented in the literature.[7] Tetrazole-based drug candidates possess anticonvulsant,[8] antihypertensive,[9a] antiallergic,[9b] and antibiotic activities,[9c] and have also shown promising results in the treatment of various diseases, such as cancer and AIDS.[10]

The key step of the single existing method for the construction of heterocyclic systems **1** is the cyclocondensation of sodium 1-amino-1*H*-tetrazole-5-thiolate **2** with α-bromoacetophenones **3** in AcOH at reflux for 4 hours.[5] The corresponding reaction with chloroacetone was carried out at reflux in MeOH. Initial compounds **2** were, in turn, synthesized by prolonged heating of methyl dithiocarbazate **4** with NaN_3 in EtOH–H_2O. The synthesis of compound **4** is based on the condensation of hydrazine-hydrate, CS_2, and dimethyl sulfate in the presence of KOH (Scheme 1).

Herein, we present the development of a new, simple, and general approach for the synthesis of 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **1** (R = Ar, Het, Alk) *via* condensation of the corresponding α-haloketones **3** with commercially available thiocarbohydrazide **5** at room temperature, subsequent one-pot nitrosation of the formed hydrazinylthiadiazine **6**, and intramolecular cyclization of the nitrosation product *via* azide-tetrazole tautomerism to give the desired compounds **1** in good to high yields (Scheme 1).

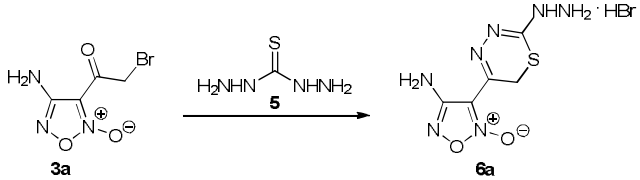


Scheme 1. Known and new methods for the synthesis of 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines.

Our ongoing scientific interests are connected with the synthesis of pharmacologically oriented structures comprising of the 1,2,5-oxadiazole 2-oxide (furoxan) scaffold, which is capable of exogenous NO release in the presence of thiol cofactors,[11] and other heterocycles with known pharmacological activities. In particular, we have recently developed effective methods for the preparation of hybrid heterocyclic structures that combine a furoxan ring with different pharmacophoric heterocycles (1,2,3-[12a-c] and 1,2,4-triazole,[12d] 1,2,4-,[12e] 1,2,5-[12f,g] and 1,3,4-oxadiazoles,[12h] tetrazole,[12i] pyridines,[12j] and others[12k-o]). In continuation of these investigations, we aimed to synthesize hybrid structures containing a furoxan ring linked to the 7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazine moiety.

Our investigation began with the development of optimal conditions for the synthesis of (2-hydrazinyl-1,3,4-thiadiazin-5-yl)furoxans **6**. We expected to nitrosate the hydrazine group in these compounds, with formation of the corresponding azides which are prone to ring-chain (azide-tetrazole) tautomerism, resulting in the target 6-furoxanyl-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **1**. The synthesis of (α-bromoacetyl)furoxans **3a,b** was previously developed by bromination of the corresponding acetylfuroxans in concentrated HCl,[13] and 4-amino-3-(α-bromoacetyl)furoxan **3a** was chosen as a model substrate. The synthesis of 5-aryl-2-hydrazinyl-1,3,4-thiadiazines is typically based on reaction of the corresponding aromatic α-haloketones **3** with thiocarbohydrazide **5** in AcOH[14a] or EtOH[14b] at reflux or under microwave irradiation in the presence of K_2CO_3.[14c] Using this approach, we carried out a search for the optimal conditions for the reaction of bromoacetylfuroxan **3a** with thiocarbohydrazide **5** in order to find milder conditions for preparation of the target thiadiazine **6a**. The solvent, temperature, and reaction time were varied (Table 1). Moderate yields were obtained in EtOH (Entries 1, 2) and decomposition was observed in 1,4-dioxane (Entry 3), while the reactions in MeCN, DMF, or DMSO were more successful (Entries 4-7). The optimal conditions were stirring for 1 h at 20 °C in DMSO (Entry 7). The possible intramolecular cyclization between the amino group and the bromoacetyl functionality can be excluded since aminofuroxans are very weak nucleophiles.[12n] Furoxan derivative **6b** was also prepared in high yield.

Table 1. Reaction conditions screening for the synthesis of 4-amino-3-(2-hydrazino-1,3,4-thiadiazin-5-yl)furoxan **6a**.[a]



Entry	Solvent	T (°C)	Time (h)	Yield **6a** (%)[b]
1	EtOH	20	12	55
2	EtOH	20	12	60[c]
3	1,4-Dioxane	20	1	-[d]
4	MeCN	0→20	2	84
5	MeCN	20	1	77
6	DMF	20	0.5	85
7	DMSO	20	0.5	90
8	DMSO	20	1	95

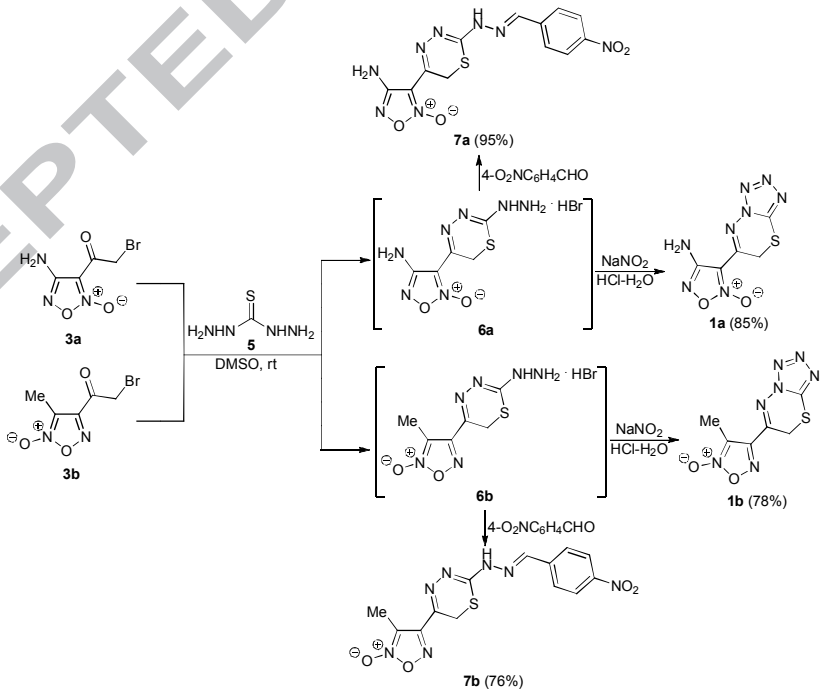
[a] Reagents and conditions: furoxan **3a** (1 mmol), thiocarbohydrazide **5** (1 mmol), solvent (2 mL) (TLC, $CHCl_3$:EtOAc =3:1).

[b] Isolated yield.

[c] conc. HCl used as an additive.

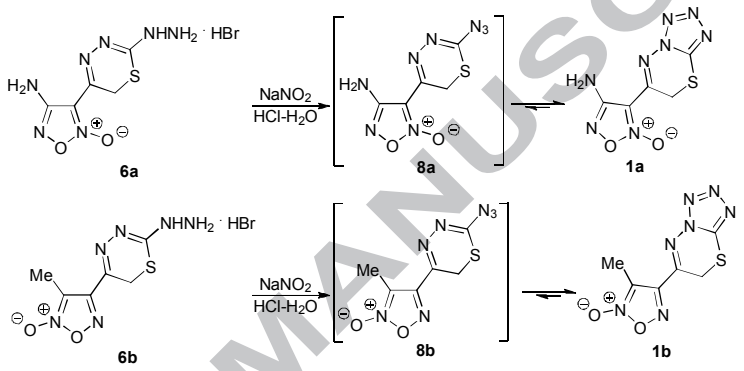
[d] Decomposition was observed.

Compounds **6a,b** proved to be insufficiently stable for storage, evidently due to the high sensitivity of the furoxan ring to strong bases[15] (hydrazine group) and, hence, they were characterized as hydrazones **7a,b**. Therefore, for further transformations, solutions of hydrazine derivatives **6a,b** in DMSO were utilized in the nitrosation reaction without isolation, and the required 6-furoxanyl-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **1a,b** were obtained in high yields (Scheme 2).

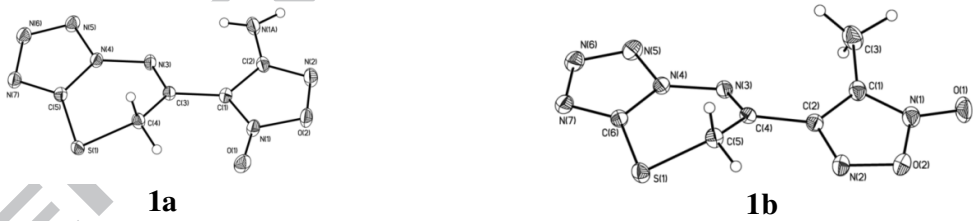


Scheme 2. One-pot synthesis of 6-furoxanyl-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **1a,b**.

Diazotization of compounds **6a,b** results in the initial formation of azides **8a,b**. The isolation of tetrazolo[5,1-*b*][1,3,4]thiadiazines **1a,b** may serve as evidence for the complete shift of the azide **8** – tetrazole **1** equilibrium towards the tetrazole in the solid state (Scheme 3). The absence of characteristic bands for the azido group in the IR spectra (2130-2150 cm^{-1}, KBr pellets) and the presence of only one singlet for the methylene group protons of the 1,3,4-thiadiazine ring in the ^1H NMR spectra (DMSO-d_6) indicated the existence of the tetrazole form of compounds **1a,b**. Finally, the structure of compounds **1a,b** was confirmed by single-crystal X-ray diffraction (Fig. 1).



Scheme 3. Azide-tetrazole tautomerism of azide **8** and tetrazole **1** forms.

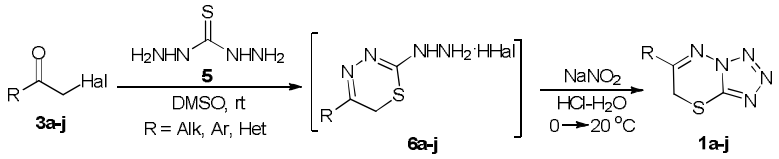


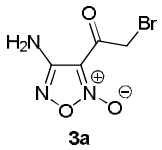
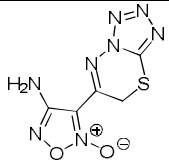
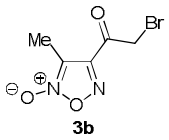
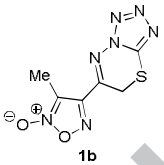
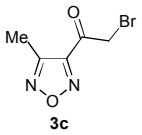
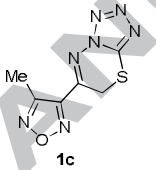
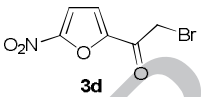
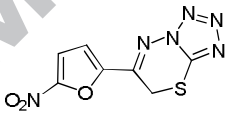
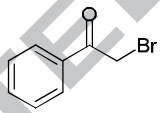
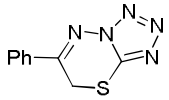
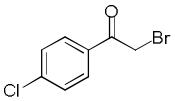
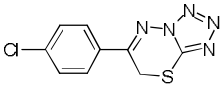
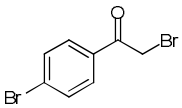
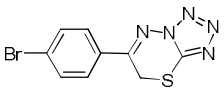
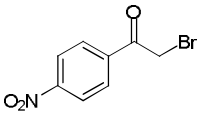
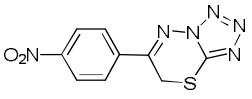
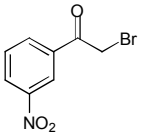
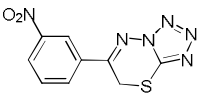
1a **1b**

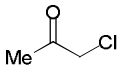
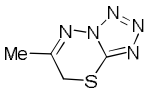
Figure 1. General view of compounds **1a,b**. Atoms are represented by probability ellipsoids of atomic vibrations (p=0.5).

The optimized conditions also proved suitable for the synthesis of further 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **1c-j** from the corresponding α-haloketones **3c-j** containing heteroaromatic, aromatic, and aliphatic substituents (Table 2). α-Haloketones **3c**,[18a] **3d**,[18b] **3e-i**,[18c] **3j**[18d] were synthesized *via* halogenation of the corresponding acetyl derivatives according to literature procedures. The intermediate hydrazine derivatives were isolated and characterized in separate experiments, either as individual compounds (**6c,h-j)** or as the acetone hydrazone **7d** (see ESI). Intermediates **6e-g** are known compounds.[19]

Table 2. Scope for the synthesis of 6-substituted 7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **1a-j**.[a]



Entry	α-Haloketone **3**	Compound **1**	Yield **1** (%)[b]
1	 **3a**	 **1a**	85
2	 **3b**	 **1b**	78
3	 **3c**	 **1c**	61
4	 **3d**	 **1d**	68
5	 **3e**	 **1e**	85
6	 **3f**	 **1f**	82
7	 **3g**	 **1g**	88
8	 **3h**	 **1h**	80
9	 **3i**	 **1i**	76

10   51

3j **1j**

[a] Reagents and conditions: haloacetyl derivative **3** (2 mmol), thiocarbohydrazide **5** (2 mmol), DMSO (2 mL), 20 °C (TLC, $CHCl_3$-EtOAc, 3:1), then conc. HCl (0.4 mL), $NaNO_2$ (3 mmol), 0 → 20 °C.

[b] Isolated yield.

The observed azide-tetrazole tautomerism is a well-known process, which has been examined by both theoretical[20] and experimental techniques.[21] The predominance of either the azide or tetrazole form depends on various factors; mainly the reaction conditions (temperature, solvents) and the structure of substituents attached to the heterocyclic system. In particular, it was found[20d] that the azide form predominates in non-polar solvents, while the tetrazole one is the major tautomer in polar solvents. To estimate the possibility for the azide form of structures **1a-j** to exist in non-polar solvents, the IR and ^{1}H NMR spectra of compounds **1b, 1g**, and **1j** were recorded as solutions in $CHCl_3$ and $CDCl_3$, respectively, because in most cases, these solvents shift the azide-tetrazole equilibrium towards the azide form.[20d] However, neither the characteristic bands of the azido group in the IR spectrum (2130-2150 cm^{-1}) nor the double set of methylene group protons of the 1,3,4-thiadiazine ring in the ^{1}H NMR spectra were observed. Therefore, the azide-tetrazole equilibrium in compounds **1a-j** is completely shifted to the tetrazole tautomer both in solution and the solid state.

In summary, a general, and highly effective method for the synthesis of diverse 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines has been developed.[22] This method is based on a sequence of one-pot reactions: condensation of substituted α-haloketones **3** with commercially available thiocarbohydrazide **5** at room temperature, nitrosation of the formed hydrazinyl-1,3,4-thiadiazine **6** using $NaNO_2$/HCl, and intramolecular cyclization of the nitrosation product *via* azide-tetrazole tautomerism to give the desired compounds **1** in good to high yields. According to IR, NMR, and single crystal X-ray data, it was established that the synthesized 6-R-7*H*-tetrazolo[5,1-*b*][1,3,4]thiadiazines **1** are not prone to ring-chain tautomerism either in solution or the solid state. To the best of our knowledge, this study represents one of the rare examples of a complete shift of the azide-tetrazole equilibrium towards the tetrazole.

Acknowledgements

This work was supported by the Russian Science Foundation (Project No 14-50-00126).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at

References and notes

1. (a) Nagamatsu, T.; Fujita, T. *Chem. Commun.* **1999**, 1461; (b) Thiel, O. R.; Achmatowicz, M. M.; Reichelt, A.; Larsen, R. D. *Angew. Chem., Int. Ed*. **2010**, *49*, 8395; (c) Tang, C.; Li, Z.; Wang, Q. *Beilstein. J. Org. Chem.* **2013**, *9*, 2629; (d) Demmer, C.; Jørgensen, M.; Jan Kehler, J.; Lennart Bunch, L. *Synlett* **2014**, *25*, 1279; (e) Tang, C.; Wang C. C.; Li, Z.; Wang, Q. *Synthesis* **2014**, *46*, 2734; (f) Zheng, H.; Wang, K.; Zhang, W.; Liu, R. *Synth. Commun.* **2015**, *45*, 2849; (g) Xu, F.; Yang, Z-Z.; Ke, Z-L.; Xi, L-M.; Yan, Q-D.; Yang, W-Q.; Zhu, L-Q.; Lin, F-L.; Lv, W-K.; Wu, H-g.; Wang, J.; Li, H-B. *Bioorg. Med. Chem. Lett.* **2016,** *26*, 8395; (h) Kamal, R.; Kumar, V.; Kumar, R. *Chem. Asian. J.* **2016**, *11*, 1988.

2. (a) Kumar, R.; Nair, R. R.; Dhiman, S. S.; Sharma, J.; Prakash, O. *Eur. J. Med. Chem.* **2009**, *44*, 2260; (b) Khan, I.; Ibrar, A.; Naeem, N. *Eur. J. Med Chem* **2013**, *63*, 854; (c) Di Braccio, M.; Grossi, G.; Alfei, S.; Ballabeni, V.; Tognolini, M.; Flammini, L.; Giorgio, C.; Bertoni, S.; Barocelli, E. *Eur. J. Med. Chem.* **2014**, *86*, 394; (d) Sahu, J. K.; Ganguly, S.; Kaushik, A. *J. Adv. Pharm. Technol. Res.* **2014**, *5*, 90; (e) Xue, D. Q.; Zhang, X. Y.; Wang, C. J.; Ma, L. Y.; Zhu, N.; He, P.; Shao, K. P.; Chen, P. J.; Gu, Y. F.; Zhang, X. S.; Wang, C. F.; Ji, C. H.; Zhang, Q. R.; Liu, H. M. *Eur. J. Med. Chem.* **2014**, *85*, 235; (f) Marathe, S.; Karnik, A. V. *Chem. Heterocycl. Compd*. **2017**, *53*, 604.

3. (a) Khan, I.; Zaib, S.; Ibrar, A.; Rama, N. H.; Simpson, J.; Iqbal, J. . *Eur. J. Med Chem.* **2014**, *78*, 167; (b) Bei Zhang, B.; Yan-Hong Li, Y-H.; Yang Liu, Y.; Yu-Rong Chen, Y-R.; En-Shan Pan, E-S.; Wen-Wei You, W-W.; Pei-Liang Zhao, P-L. *Eur. J. Med. Chem.* **2015,** *103*, 335.

4. (a) Puthiyapurayil, P.; Poojary, B.; Chikkanna, C.; Buridipad, S. K. *Eur. J. Med. Chem.* **2012**, *57*, 407; (b) Cacic, M.; Pavic, V.; Molnar, M.; Sarkanj, B.; Has-Schon, E. *Molecules* **2014**, *19*, 1163; (c) Sarapultsev, A. P.; Chupakhin, O. N.; Sarapultsev, P. A.; Sidorova, L. P.; Tseitler, T. A. *Pharmaceuticals* **2016**, *9*, 27.

5. Eftekhar, M.; Eshghi, H.; Rahimizadeh, M.; Bakavoli, M.; Saberi, S. *J. Chem. Res.* **2014**, *38*, 365-367.

6. (a) Popova, E. A.; Trifonov, R. E. *Russ. Chem. Rev.* **2015**, *84*, 891; (b) Wei, C.-X.; Bian, M.; Gong, G.-H. *Molecules* **2015**, *20*, 5528; (c) Rüger, N.; Fassauer, G. M.; Bock, C.; Emmrich, T.; Bodtke, A.; Link, A. *Molec. Divers.* **2017**, *21*, 9; (d) Zhang, H.-Z.; Gan, L.-L.; Wang, H.; Zhou, C.-H. *Mini-Rev. Med. Chem.* **2017**, *17*, 122; (e) Tazeem; Bhat, A. R.; Han, X.; Athar, F. *ChemistrySelect* **2016**, *1*, 5917; (f) Bondaryk, M.; Lukowska-Chojnacka, E.; Staniszewska, M.

Bioorg. Med. Chem. Lett. **2015**, *25*, 2657; (g) Zhang, H.-J.; Wang, S.-B.; Quan, Z.-S. *Molec. Divers.* **2015**, *19*, 817.

7. (a) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; vol. 4, pp 621-678; (b) Ostrovskii, V. A.; Koldobskii, G. I.; Trifonov, R. E. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008; vol. 6, pp 257-423;

8. (a) Dong, S.; Wang, T.; Wang, H.; Qian, K.; Zhang, Z.; Zuo, Y.; Luo, G.; Jin, Y.; Wang, Z. *Arch. Pharm.* **2017**, DOI: 10.1002/ardp.201600389; (b) Malik, S.; Khan, S. A. *Med. Chem. Res.* **2014**, *23*, 207.

9. (a) Da, Y.-J.; Yuan, W.-D.; Xin, T.; Nie, Y.-Y.; Ye, Y.; Yan, Y.-J.; Liang, L.-S.; Chen, Z.-L. *Bioorg. Med. Chem.* **2012**, *20*, 7101; (b) Edfeldt, F.; Evenäs, J.; Lepistö, M.; Ward, A.; Petersen, J.; Wissler, L.; Rohman, M.; Sivars, U.; Svensson, K.; Perry, M.; Feierberg, I.; Zhou, Z.-H.; *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2496; (c) Karabanovich, G.; Nemecek, J.; Valaskova, L.; Carazo, A.; Konecna, K.; Stolarikova, J.; Hrabalek, A.; Pavlis, O.; Pavek, P.; Vavrova, K.; Roh, J. *Eur. J. Med. Chem.* **2017**, *126*, 369.

10. (a) Shaaban, S.; Negm, A.; Ashmawy, A. M.; Ahmed, D. M.; Wessjohann, L. A. *Eur. J. Med. Chem.* **2016**, *122*, 55; (b) Babu, V. S.; Zhou, Y.; Kishi, Y. *Bioorg. Med. Chem. Lett.* **2017**, 27, 1274; (c) Tamura, Y.; Watanabe, F.; Nakatani, T.; Yasui, K.; Fuji, M.; Komurasaki, T.; Tsuzuki, H.; Maekawa, R.; Yoshioka, T.; Kawada, K.; Sugita, K.; Ohtani, M. *J. Med. Chem.* **1998**, *41*, 640.

11. (a) Ferioli, R.; Folco, G. C.; Ferretti, C.; Gasco, A. M.; Medana, C.; Fruttero, R.; Civelli, M.; Gasco, A. *Br. J. Pharmacol*. **1995**, *114*, 816; (b) Kots, A. Ya.; Grafov, M. A.; Khropov, Yu. V.; Betin, V. L.; Belushkina, N. N.; Busygina, O. G.; Yazykova, M. Yu.; Ovchinnikov, I. V.; Kulikov, A. S.; Makhova, N. N.;. Medvedeva, N. A.; Bulargina T. V.; Severina, I. S. *Br. J. Pharmacol*. **2000**, *129*, 1163; (c) Fershtat L. L.; Makhova, N. N. *ChemMedChem* **2017**, *12*, 622.

12. (a) Fershtat, L. L.; Ashirbaev, S. S.; Kulikov, A. S.; Kachala, V. V.; Makhova, N. N. *Mendeleev Commun*. **2015**, *25*, 257; (b) Fershtat, L. L.; Radzhabov, M. R.; Romanova, A. A.; Ananyev, I. V.; Makhova, N. N. *Arkivoc* **2017**, *iii*, 140; (c) Kulikov, A. S.; Larin, A. A.; Fershtat, L. L.; Anikina, L. V.; Pukhov, S. A.; Klochkov, S. G.; Struchkova, M. I.; Romanova, A. A.; Ananyev, I. V.; Makhova, N. N. *Arkivoc* **2017**, *iii*, 250; (d) Fershtat, L. L.; Epishina, M. A.; Ovchinnikov, I. V.; Kachala, V. V.; Makhova, N. N. *Chem. Heterocycl. Compd*. **2015**, *51*, 754; (e) Fershtat, L. L.; Ananyev, I. V.; Makhova, N. N. *RSC Adv*. **2015**, *5*, 47248; (f) Fershtat, L. L.; Larin, A. A.; Epishina, M. A.; Kulikov, A. S.; Ovchinnikov, I.

V.; Ananyev, I. V.; Makhova, N. N. *Tetrahedron Lett.* **2016**, *57*, 4268; (g) Fershtat, L. L.; Ovchinnikov, I. V.; Epishina, M. A.; Romanova, A. A.; Lempert, D. B.; Muravyev, N. V.; Makhova, N. N. *ChemPlusChem*, **2017**, *82*, DOI: 10.1002/cplu.201700340; (h) Fershtat, L. L.; Kulikov, A. S.; Ananyev, I. V.; Struchkova, M. I.; Makhova N. N. *J. Heterocycl. Chem.* **2016**, *53*, 102; (i) Fershtat, L. L.; Epishina, M. A.; Kulikov, A. S.; Ovchinnikov, I. V.; Ananyev, I. V.; Makhova, N. N.; *Tetrahedron* **2015**, *71*, 6764; (j) Fershtat, L. L.; Larin, A. A.; Epishina, M. A.; Ovchinnikov, I. V.; Kulikov, A. S.; Ananyev, I. V.; Makhova, N. N. *RSC Adv*. **2016**, *6*, 31526; (k) Fershtat, L. L.; Epishina, M. A.; Kulikov, A. S.; Makhova, N. N. *Mendeleev Commun*. **2015**, *25*, 36; (l) Fershtat, L. L.; Epishina, M. A.; Ovchinnikov, I. V.; Struchkova, M. I.; Romanova, A. A.; Ananyev, I. V.; Makhova, N. N. *Tetrahedron Lett*. **2016**, *57*, 5685; (m) Makhova, N. N.; Ovchinnikov, I. V.; Kulikov, A. S.; Molotov S. I.; Baryshnikova, E. L. *Pure Appl. Chem.* **2004**, *76*, 1691; (n) Makhova, N. N.; Kulikov, A. S. *Russ. Chem. Rev*. **2013**, *82*, 1007; (o) Fershtat, L. L.; Makhova. N. N. *Russ. Chem. Rev*. **2016**, *85*, 1097.

13. Kulikov, A. S.; Makhova, N. N.; Khmelnitskii, L. I. *Russ. Chem. Bull*. **1993**, *42*, 708.

14. (a) Postovskii, I. Ya.; Novikov, A. P.; Chechulina, L. A.; Sidorova, L. P. *Chem. Heterocyclic. Compd*. **1976**, *12*, 868; (b) Sreenivasa, V.; Chunduru, R.; Vedula, R. R. *Synth. Commun.* **2012**, *42*, 1454; (c) Kidwai, M.; Venkataramanan, R.; Dave, B. *J. Heterocycl. Chem*. **2002**, *39*, 1045. (a) Makhova, N. N.; Ovchinnikov, I. V.; Kulikov, A. S.; Molotov S. I.; Baryshnikova, E. L. *Pure Appl. Chem.* **2004**, *76*, 1691; (b) Makhova, N. N.; Kulikov, A. S. *Russ. Chem. Rev.* **2013**, *82*, 1007;

15. Ungnade, H. E.; Kissinger, L. M. *Tetrahedron* 1963, *19 (Suppl. 1)*, 143.

16. Taylor, R.; Allen, F. H. Statistical and Numerical Methods of Data Analysis / Structure Correlation, Weinheim, Verlag Chemie, 1994. Cambridge Structural Database, release 2017.

17. (a) Suponitsky, K. Yu.; Lyssenko, K. A.; Antipin, M. Yu.; Aleksandrova, N. S.; Sheremetev, A. B.; Novikova, T. S. *Russ. Chem. Bull., Int. Ed.*, **2009**, *58*, 2129; (b) Suponitsky, K. Yu.; Lyssenko, K. A.; Ananyev, I. V.; Kozeev, A. M.; Sheremetev, A. B. *Cryst. Growth Des.*, **2014**, *14*, 4439; (c) Espinosa, E.; Molins, E.; Lecomte, C. *Chem. Phys. Lett.*, **1998**, *285*, 170; (d) Ananyev, I. V.; Karnoukhova, V. A.; Dmitrienko, A. O.; Lyssenko, K. A. *J. Phys. Chem. A*, **2017**, *121*, 4517.

18. (a) Sheremetev, A. B.; Kulikov, A. S.; Khmel'nitskii, L. I. *Russ. Chem. Bull.* **1993**, *42*, 708; (b) Saldabol, N. O.; Giller, C. A. *Latvijas PSR Zinatnu Akademijas Vestis* **1958**, 91; *Chem.Abstr.*, **1959**, 14077; (c) Shaikh, M. S.; Palkar, M. B.; Patel, H. M.; Rane, R. A.; Alwan, W. S.; Shaikh, M. M.; Shaikh, I. M.; Hampannavar, G. A.; Karpoormath, R. *RSC Adv.* **2014**, *4*, 62308; (d) Masilamani, D.; Rogic, M. M. *J. Org. Chem.* **1981**, *46*, 4486.

19. Pfeiffer, W.-D.; Dilk, E.; Bulka, E. *Z. Chem.* **1977**, *17*, 15.

20. (a) Abu-Eittah, R. H.; El-Taher, S.; Hassan, W. M. I.; Noamaan, M. A. *Comp. Theor. Chem.* **2014**, *1033*, 52; (b) Yang, J.; Gong, X.; Wang, G. *RSC Adv.* **2015**, *5*, 9503; (c) Karakus, N.; Demirel, M. *J. Molec. Struc.* **2015**, *1093*, 65; (d) Sirakanyan, S. N.; Spinelli, D. D.; Geronikaki, A. A.; Kartsev, V. G.; Panosyan, H. A.; Armen, G. Ayvazyan, A. G.; Rafael, A.; Tamazyan, R. A.; Frenna, V.; Hovakimyan, A. A. *Tetrahedron* **2016**, *72*, 1919.

21. (a) Deev, S. L.; Shenkarev, Z. O.; Shestakova, T. S.; Chupakhin, O. N.; Rusinov, V. L.; Arseniev, A. S. *J. Org. Chem.* **2010**, *75*, 8487; (b) Shestakova, T. S.; Shenkarev, Z. O.; Deev, S. L.; Chupakhin, O. N.; Khalymbadzha, I. A.; Rusinov, V. L.; Arseniev, A. S. *J. Org. Chem.* **2013**, *78*, 6975; (c) Wentrup, C.; Lan, N. M.; Lukosch, A.; Bednarek, P.; Kvaskoff, D. *Beilstein J. Org. Chem.* **2013**, *9*, 743; (d) Waly, M. A.; El Hawary, I. I.; Hamama, W. S.; Zoorob, H. H. *J. Heterocycl. Chem.* **2013**, *50*, 12.

22. *General procedure for the synthesis of 6-substituted 7H-tetrazolo[5,1-b][1,3,4]thiadiazines **1**.* Haloacetyl derivative **3** (2 mmol) was added to a magnetically stirred solution of thiocarbohydrazide **5** (0.21 g, 2 mmol) in DMSO (2 mL). The reaction mixture was stirred for 1 h at 20 ^{o}C until substrate **3** was consumed (TLC, $CHCl_3$-EtOAc, 3:1), then water (10 mL) and conc. HCl (0.4 mL) were added. A solution of $NaNO_2$ (0.21 g, 3 mmol) in water (1.5 mL) was added dropwise to the resulting suspension at 2-4 ^{o}C over a period of 15 min. The reaction mixture was stirred for 1 h at the same temperature and for 1 h at 20 ^{o}C. The formed solid was filtered off, washed with water, dried in air and recrystallized from EtOH. Compound **1j** was extracted with $CHCl_3$ (3x15 mL), dried over $MgSO_4$, the solvent evaporated and the residue recrystallized from EtOH.

Highlights

- A novel method for the synthesis of tetrazolo[5,1-*b*]thiadiazines was developed.
- The target structures were obtained in good to high yields.
- A single tetrazole tautomer was found both in solution and in solid state.