DOI 10.1007/s10593-019-02590-7

Chemistry of Heterocyclic Compounds **2019**, *55*(11), 1131–1134

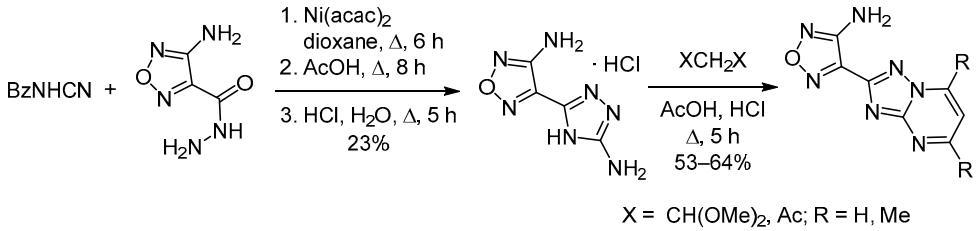
A convenient route to the 1,2,5-oxadiazole-substituted 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives

Mikhail A. Prezent[1], Sergey V. Baranin[1]*

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

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2019, *55*(11), 1131–1134

Submitted August 19, 2019
Accepted September 26, 2019



A convenient synthesis of 1,2,4-triazole and 1,2,4-triazolo[1,5-*a*]pyrimidines with 3-amino-1,2,5-oxadiazole substituent starting from available 4-amino-1,2,5-oxadiazole-3-carbohydrazide and benzoyl cyanamide has been developed.

Keywords: benzoyl cyanamide, 1,2,5-oxadiazole, 1,2,4-triazole, 1,2,4-triazolo[1,5-*a*]pyrimidine, catalytic addition reactions.

In the last few decades, one of the main trends in the design of potential drugs with improved pharmacological properties is the formation of new structures based on the molecular hybridization of diverse heterocycles with known biological activity.[1–5] Among them is the 1,2,4-triazole nucleus and its derivatives which possess a broad spectrum of pharmacological activities, in particular antiviral (ribavirin, taribavirin),[6,7] antifungal (fluconazole), and soporific (triazolam).[8,9] Recently, 5-alkyl-3-amino-1,2,4-triazoles were found to exhibit herbicidal activity[10] and showed positive results in clinical trials for the treatment of Alzheimer's disease.[11] Some 3-amino-substituted 1,2,4-triazoles possess anti-inflammatory[12] and analgesic[13] effects in the human body.

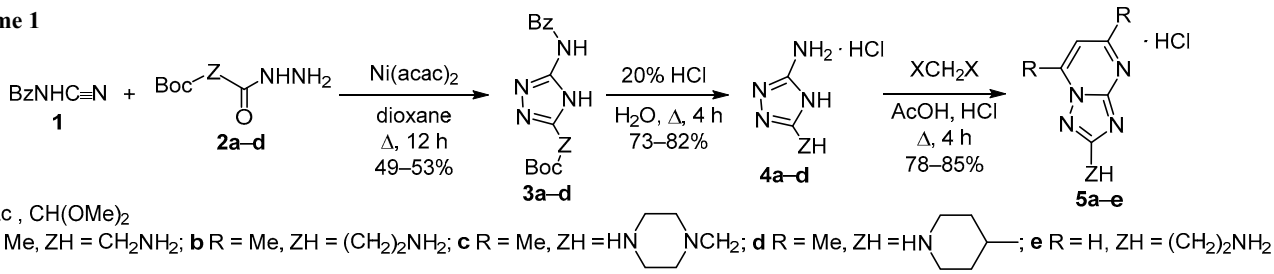
No less interesting are derivatives of 1,2,4-triazolo[1,5-*a*]-pyrimidine. Thus, some 2-(3-alkyl)-5-methyl-1,2,4-triazolo-[1,5-*a*]pyrimidines demonstrate antitumor activity,[14] 5,7-disubstituted 1,2,4-triazolo[1,5-*a*]pyrimidines show superior *in vitro* cytotoxicity to the anticancer drug doxorubicin.[15] The organotin(IV) and platinum(II) complexes of 5,7-disubstituted 1,2,4-triazolo[1,5-*a*]pyrimidines exhibit dose-dependent cytotoxic activity in multiple cancer cell lines.[16,17] In addition, 5,7-disubstituted 1,2,4-triazolo[1,5-*a*]-pyrimidines have shown promising inhibitory activities for cellular secretion of the hepatitis B virus surface antigen as potential treatment for HBV infections.[18]

Relatively recently, an interest in 1,2,5-oxadiazole derivatives as biologically active substances has arisen,[19] and some representatives of this series have been found to exhibit a wide spectrum of biological properties such as antimicrobial, antituberculosis, spasmolytic, and muscle relaxant activity.[20] In this context, a search for the new synthetic routes to the derivatives of 5,7-disubstituted 1,2,4-triazolo[1,5-*a*]pyrimidines has received significant attention due to their practical relevance.

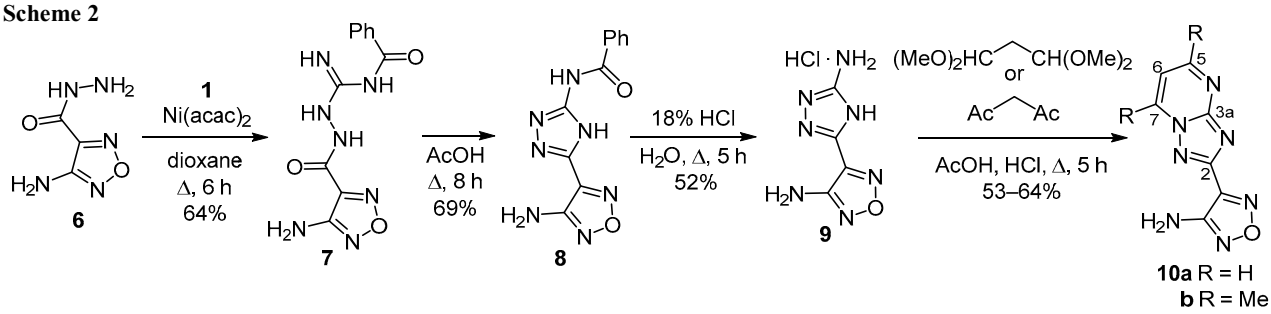
Recently, we obtained a number of 3-amino-substituted 1,2,4-triazoles **4a**–**d** by addition of benzoyl cyanamide (**1**) to the amino group of Boc-protected amino acid hydrazides **2a**–**d** in the presence of $Ni(acac)_2$ as a catalyst.[21] This was the first reported use of $Ni(acac)_2$ to promote the addition of nitriles to amino group. In the absence of $Ni(acac)_2$ the reaction did not proceed. Further,[22] 3-aminotriazoles **4a**–**d** were successfully used as convenient building blocks for the construction of 1,2,4-triazolo[1,5-*a*]pyrimidines. Triazole hydrochlorides **4a**–**d** undergo condensation with 1,3-di-electrophilic reagents, such as acetylacetone, in boiling AcOH in the presence of HCl providing high yields of 2-aminoalkyl-1,2,4-triazolo[1,5-*a*]pyrimidine hydrochlorides **5a**–**e** (Scheme 1).

In continuation of this work, new 1,2,4-triazole derivatives **8**–**10** were synthesized starting from benzoyl cyanamide (**1**) and 4-amino-1,2,5-oxadiazole-3-carbo-hydrazide (**6**) (Scheme 2). Heating the mixture of compounds **1** and **6** in dioxane in the presence of 10 mol % $Ni(acac)_2$ resulted in guanidine derivative **7** which, upon reflux in AcOH, cyclized into furazanyl-substituted triazole **8**.

Scheme 1



Scheme 2



In fact, the above reaction of Boc-protected amino acid hydrazides **2a**–**d** with benzoyl cyanamide (**1**) (Scheme 1) probably also proceeds *via* the formation of the corresponding intermediate guanidine derivatives, but unlike guanidine **7**, we found no way to isolate them due to the rapid cyclization into triazoles **3a**–**d** under the reaction conditions. Both guanidine **7** and benzoyl derivative **8** are white crystalline substances and are poorly soluble in most organic solvents while they are soluble in DMF and DMSO. Their mass spectra contain the molecular ion $[M+H]^+$ peaks. ^{1}H NMR spectra of compounds **7** and **8** indicated the presence of furazan amino group protons and the protons of the phenyl group. Further removal of the benzoyl group of triazole **8** under the action of aqueous HCl gave the corresponding 4-(5-amino-4*H*-1,2,4-triazol-3-yl)-1,2,5-oxadiazol-3-amine hydrochloride (**9**) according to the method developed by us earlier[20] (Scheme 2). Salt **9** is a white crystalline substance, poorly soluble in organic solvents, but very well soluble in H_2O, MeOH, DMF, and DMSO.

It should be noted that synthesis of free 4-(5-amino-4*H*-1,2,4-triazol-3-yl)-1,2,5-oxadiazol-3-amine (**9**) has been reported in the literature, however toxic material, cyanogen bromide, was used for its preparation.[23] Later, alternative routes for the synthesis of triazolylfurazan **9** from 3-amino-4-carbmethoxyfurazan employing aminoguanidine hydrochloride and hydrazine hydrate (in 90% yield)[24] or aminoguanidine sulfate (in 71% yield)[25] were suggested, and the structure of triazolylfurazan **9** was proved by X-ray crystallography.[25] Triazolylfurazan **9** was used as a starting compound for the synthesis of highly performant insensitive energetic materials.[25]

Similar to hydrochlorides **4a**–**d**,[22] triazolylfurazan hydrochloride **9** undergoes condensation with 1,3-dielectrophilic reagents, such as 1,1,3,3-tetramethoxypropane or acetylacetone, in boiling AcOH in the presence of HCl, providing 1,2,4-triazolo[1,5-*a*]pyrimidines **10a**,**b**, respectively (Scheme 2). Compounds **10a**,**b** are white crystalline substances soluble in DMF and DMSO, but are poorly soluble in other organic solvents. Their mass spectra contain the molecular ion $[M+H]^+$ peaks. In ^{1}H NMR spectra of compounds **10a**,**b**, the signals corresponding to furazan amino group protons and to pyrimidine protons are observed. The location of C-2 carbon signals in ^{13}C NMR spectra is in the 150.1–158.8 ppm region, which confirms the structures of compounds **10a**,**b**.[26]

In conclusion, a convenient synthesis of triazole derivatives with 3-amino-1,2,5-oxadiazole substituent from available reagents has been developed. The obtained compounds may be attractive for the investigation of their biological activity.

Experimental

IR spectra were recorded on a Bruker Alpha spectrometer in KBr. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer (300 MHz), ^{13}C NMR spectra were recorded on a Bruker Avance 600 spectrometer (150 MHz) in DMSO-d_6. Solvent residual signals were used as a standard (2.50 ppm for ^{1}H nuclei and 39.5 ppm for ^{13}C nuclei). Assignments in ^{13}C NMR spectra were made based on the ^{13}C NMR spectra of the analogs.[26] High-resolution mass spectra were recorded on a Bruker micrOTOF II instrument (ESI). Measurements were carried out in the positive ranges (capillary voltage was 4500 V). The masses were scanned in the *m*/*z* 50–3000 Da range using external and internal calibration (Electrospray Calibrant Solution, Fluka). MeCN solution of compounds was injected with a syringe, flow rate 3 μl/min, nitrogen was used as a sprayer gas (4 l/min), interface temperature was 180°C. Elemental analysis was performed on a PerkinElmer Series II CHNS/O 2400 analyzer.

Starting benzoyl cyanamide (**1**)[27] and 4-amino-1,2,5-oxadiazole-3-carbohydrazide (**6**)[28] were synthesized according to the described procedures. Commercially available $Ni(acac)_2$ and anhydrous dioxane were purchased from Sigma-Aldrich and used without additional purification.

***N*-[{2-[(4-Amino-1,2,5-oxadiazol-3-yl)carbonyl]hydrazinyl}-(imino)methyl]benzamide (7)**. A mixture of hydrazide **6**

(1.43 g, 10 mmol), benzoyl cyanamide (**1**) (1.31 g, 10 mmol), and $Ni(acac)_2$ (0.25g, 1 mmol) in anhydrous dioxane (20 ml) was refluxed with stirring for 6 h. The mixture was cooled, the precipitate formed was filtered off, washed with H_2O, and dried in air. Yield 1.85 g (64%), white crystals, mp >350°C. IR spectrum, ν, cm^{-1}: 3457, 3317 (NH, NH_2); 1710, 1685 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.35 (2H, s, NH_2); 7.40–7.70 (3H, m, H Ph); 8.05 (2H, d, *J* = 7.0, H Ph); 8.35 (2H, br. s, 2NH); 11.10 (2H, br. s, 2NH). ^{13}C NMR acceptable spectrum was not obtained: the signals of the quaternary carbon atoms could not be accumulated due to the fast migration of proton between N atoms and as a result the electron density delocalization. Found, *m*/*z*: 290.0992 $[M+H]^+$. $C_{11}H_{12}N_7O_3$. Calculated, *m*/*z*: 290.0996.

***N*-[5-(4-Amino-1,2,5-oxadiazol-3-yl)-4*H*-1,2,4-triazol-3-yl]benzamide (8)**. A solution of guanidine **7** (2.89 g, 10 mmol) in AcOH (20 ml) was refluxed with stirring for 8 h. After cooling, the solvent was removed under reduced pressure, the residue was washed with H_2O and dried in air. Yield 1.87 g (69%), white crystals, mp >350°C. IR spectrum, ν, cm^{-1}: 3454, 3340 (NH, NH_2); 1676 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.35 (2H, s, NH_2); 7.40–7.60 (3H, m, H Ph); 8.15 (2H, d, *J* = 7.0, H Ph); 12.35 (1H, s, NH); 14.35 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 126.5, 129.6 (C-2,6 Ph, C-3,5 Ph); 131.6 (C-4 Ph); 139.3 (C-4 oxadiazole); 147.3 (C-1 Ph); 152.2 (C-3 oxadiazole); 155.6, 155.7, 156.8 (C-3 triazole, C-5 triazole, C=O). Found, *m*/*z*: 272.0887 $[M+H]^+$. $C_{11}H_{10}N_7O_2$. Calculated, *m*/*z*: 272.0890.

4-(5-Amino-4*H*-1,2,4-triazol-3-yl)-1,2,5-oxadiazol-3-amine hydrochloride (9). A solution of benzoyl derivative **8** (2.71 g, 10 mmol) in 18% aqueous HCl (50 ml) was refluxed with stirring for 5 h. After cooling, the reaction mixture was filtered, the filtrate was evaporated, and the residue was crystallized from Me_2CO. The crystals were filtered off, washed with Me_2CO, and dried in air. Yield 1.06 g (52%), white crystals, mp > 350°C. IR spectrum, ν, cm^{-1}: 3557 (NH_2). ^1H NMR spectrum, δ, ppm: 6.76 (4H, br. s, $2NH_2$). ^{13}C NMR acceptable spectrum was not obtained: the signals of the quaternary carbon atoms could not be accumulated due to the fast migration of proton between N atoms and as a result the electron density delocalization. Found, *m*/*z*: 168.0626 $[M+H]^+$. $C_4H_6N_7O$. Calculated, *m*/*z*: 168.0628. Found, %: C 23.38; H 3.11; N 47.90; Cl 17.30. $C_4H_6ClN_7O$. Calculated, %: C 23.60; H 2.97; N 48.16; Cl 17.41.

Synthesis of compounds 10a,b (General method). A mixture of hydrochloride **9** (2.03 g, 10 mmol) and acetylacetone or 1,1,3,3-tetramethoxypropane (12 mmol) in glacial AcOH (15 ml) was refluxed with stirring for 5 h. The precipitate formed was filtered off, washed with H_2O, and dried in air.

4-([1,2,4]Triazolo[1,5-a]pyrimidin-2-yl)-1,2,5-oxadiazol-3-amine (10a). Yield 1.30 g (64%), white crystals, mp >350°C. IR spectrum, ν, cm^{-1}: 3461 (NH_2), 3285–3008 (CH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.58 (2H, s, NH_2); 7.25 (1H, t, *J* = 7.0, H-6); 8.80 (1H, d, *J* = 7.0, H-5); 9.21 (1H, d, *J* = 7.0, H-7). ^{13}C NMR spectrum, δ, ppm: 108.5 (C-6); 143.4 (C-4 oxadiazole); 145.1 (C-7); 150.1, 154.3, 158.8 (C-3a, C-2, C-3 oxadiazole); 164.0 (C-5). Found, *m*/*z*: 204.0628 $[M+H]^+$. $C_7H_6N_7O$. Calculated, *m*/*z*: 204.0623.

4-(5,7-Dimethyl[1,2,4]triazolo[1,5-*a*]pyrimidin-2-yl)-1,2,5-oxadiazol-3-amine (10b). Yield 1.22 g (53%), white solid, mp >350°C. IR spectrum, ν, cm^{-1}: 3458 (NH_2), 3293 (CH). ^1H NMR spectrum, δ, ppm: 2.63 (3H, s, CH_3); 2.80 (3H, s, CH_3); 6.62 (2H, s, NH_2); 7.30 (1H, s, CH). ^{13}C NMR spectrum, δ, ppm: 17.0 (CH_3); 25.2 (CH_3); 112.6 (C-6); 139.9 (C-4 oxadiazole); 148.1 (C-7); 154.3, 155.2, 156.2 (C-3a, C-2, C-3 oxadiazole); 166.6 (C-5). Found, *m*/*z*: 232.0938 $[M+H]^+$. $C_9H_{10}N_7O$. Calculated, *m*/*z*: 232.0941.

Supplementary information file, containing ^1H and ^{13}C NMR spectra of compounds **10a**,**b**, is available at the journal website http://link.springer.com/journal/10593.

References

1. Ananikov, V. P.; Khokhlova, E. A.; Egorov, M. P.; Sakharov, A. M.; Zlotin, S. G.; Kucherov, A. V.; Kustov, L. M.; Gening, M. L.; Nifantiev, N. E. *Mendeleev Commun*. **2015**, *25*, 75.
2. *Design of Hybrid Molecules for Drug Development*; Decker, M., Ed.; Elsevier: Würzburg, 2017.
3. 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.
4. Decker, M. *Curr. Med. Chem.* **2011**, *18*, 1464.
5. Tsogoeva, S. B. *Mini–Rev. Med. Chem.* **2010**, *10*, 773.
6. Glanville, A. R.; Scot, A. I.; Morton, J. M.; Aboyoun, C. L.; Plit, M. L.; Carter, I. W.; Malouf, M. A. *J. Heart Lung Transplant*. **2005**, *24*, 2114.
7. Chudinov, M. V.; Matveev, A. V; Prutkov, A. N.; Konstantinova, I. D.; Fateev, I. V.; Prasolov, V. S.; Smirnova, O. A.; Ivanov, G. A.; Galegov, A. V.; Deryabin, P. G. *Mendeleev Commun*. **2016**, *26*, 214.
8. Cha, R.; Sobel, J. D. *Expert Rev. Anti–Infect. Ther*. **2004**, *2*, 357.
9. Bel'skaya, N. P.; Demina, M. A.; Sapognikova, S. G.; Fan, Z.-J.; Zhang, H.-K.; Dehaen, W.; Bakulev, V. A. *ARKIVOC* **2008**, (xvi), 9.
10. Mitchell, G. WO Patent 144234 A1, 2013.
11. Baumann, K.; Floh, A.; Goetschi, E.; Jacobsen, H.; Jolidon, S.; Luebbers, T. US Patent 20090215759 A1, 2009.
12. Bell, K.; Sunose, M.; Ellard, K.; Cansfield, A.; Taylor, J.; Miller, W.; Ramsden, N.; Bergamini, G.; Neubauer, G. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 5257.
13. Gregory, T. F.; Wright, J. L.; Wise, L. D.; Meltzer, L. T.; Serpa, K. A.; Konkoy, C. S.; Whittemore, E. R.; Woodward, R. M. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 527.
14. Zhao, X.-L.; Zhao, Y.-F.; Guo, S.-C.; Song, H.-S.; Wang, D.; Gong, P. *Molecules* **2007**, *12*, 1136.
15. Wu, L.; Zhang, C.; Li, W. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 5002.
16. (a) Girasolo, M. A.; Canfora, L.; Sabatino, P.; Schillaci, E.; Foresti, D.; Rubino, S.; Ruisi, G.; Stocco, G. *J. Inorg. Biochem*. **2012**, *106*, 156. (b) Łakomska, I.; Fandzloch, M.; Popławska, B.; Sitkowski, J. *Spectrochim. Acta*, *Part A* **2012**, *91*, 126.
17. Sheridan, M.; Heal, J. R.; Hamilton, W. D. O.; Pike, I. WO Patent 2012080729 A2, 2012.
18. Yu, C.; Goddard, W.; Clearfield, E.; Mills, C.; Xiao, T.; Guo, H.; Morrey, J. D.; Motter, N. E.; Zhao, K.; Block, T. M.; Cuconati, A.; Xu, X. *J. Med. Chem*. **2011**, *54*, 5660.

19. Fershtat, L. L.; Epishina, M. A.; Ovchinnikov, I. V.; Kachala, V. V.; Makhova, N. N. *Chem. Heterocycl. Compd.* **2015**, *51*, 754. [*Khim. Geterotsikl. Soedin.* **2015**, *51*, 754.]
20. Paton, R. M. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996, Vol. 4, p. 229.
21. Prezent, M. A.; Daeva, E. D.; Baranin, S. V.; Dorokhov, V. A. *Russ. Chem. Bull., Int. Ed*. **2015**, *64*, 1089. [*Izv. Akad. Nauk, Ser. Khim*. **2015**, 1089.]
22. (a) Prezent, M. A.; Daeva, E. D.; Baranin, S. V.; Zavarzin, I. V. *Mendeleev Commun*. **2017**, *27*, 169. (b) Astakhov, A. V.; Suponitsky, K. Yu.; Chernyshev, V. M. *Mendeleev Commun*. **2018**, *28*, 439.
23. Shaposhnikov, S. D.; Korobov, N. V.; Sergievskii, A. V.; Pirogov, S. V.; Mel'nikova, S. F.; Tselinskii, I. V. *Russ. J. Org. Chem*. **2002**, *38*, 1351. [*Zh. Org. Khim.* **2002**, *38*, 1405.]
24. Tang, Y.; Imler, G. H.; Parrish, D. A.; Shreeve, J. M. *Org. Lett*. **2018**, *20*, 8039.
25. Xu, Z.; Cheng, G.; Yang, H.; Zhang, J.; Shreeve, J. M. *Chem.–Eur. J*. **2018**, *24*, 10488.
26. Saldago, A.; Varela, C.; Garcia Collazo, A. M.; Pevarello, P. *Magn. Reson. Chem*. **2010**, *48*, 614.
27. Crowther, A. F.; Curd, F. H. S.; Rose, F. L. *J. Chem. Soc*. **1948**, 586.
28. Aleksandrova, N. S.; Semyakin, S. S.; Anisimov, A. A.; Struchkova, M. I.; Sheremetev, A. B. *Russ. Chem. Bull., Int. Ed*. **2018**, *67*, 2035. [*Izv. Akad. Nauk, Ser. Khim*. **2018**, 2035.]