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Divergent oriented synthesis of 2*H*-1,2,3-triazoles *via* rearrangement of furoxanylhydrazones

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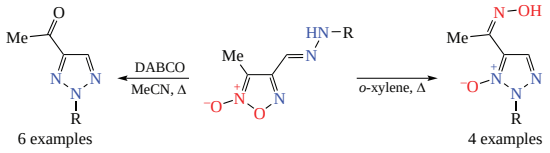
Base- and thermally induced rearrangements of readily available furoxanylhydrazones were investigated. Variation of reaction conditions enables a preparation of structurally diverse functionally substituted 2*H*-1,2,3-triazoles from the same starting materials.



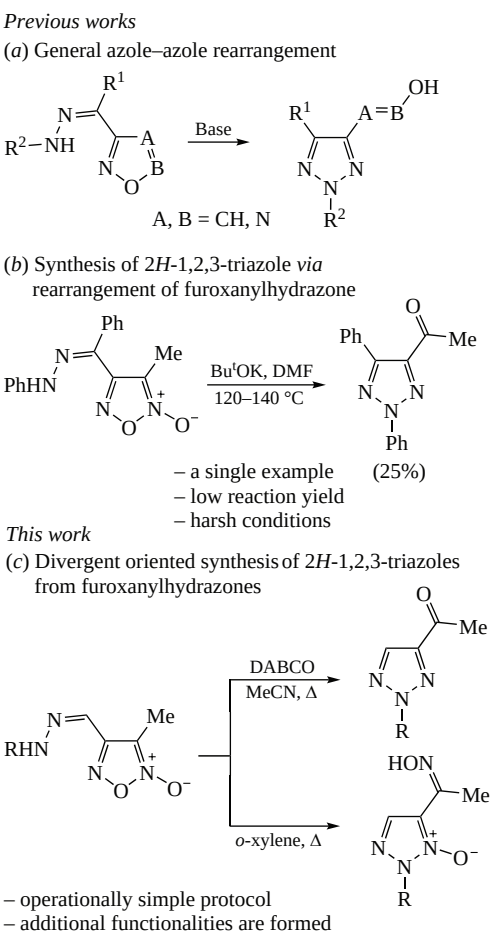
Keywords: furoxan, nitrogen heterocycles, rearrangement, triazole, azole.

Dedicated to the leader of Zelinsky Institute of Organic Chemistry, Academician M. P. Egorov on the occasion of his 70th birthday.

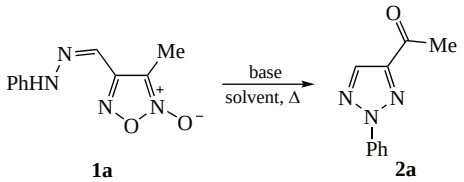
Nitrogen heterocycles are the most frequently occurred structural motifs in various pharmaceuticals and promising drug candidates.[1] According to the U.S. FDA database, >59% of clinically used small-molecule medicines incorporate a nitrogen heterocycle subunit.[2] However, the construction of individual pharmaceutical scaffolds using known synthetic methodologies often involves multi-step and energy-consuming procedures or suffers from a lack of reproducibility and scalability. Therefore, a creation of novel step-economy protocols for the assembly of various nitrogen-containing heterocyclic scaffolds remains highly urgent.[3]

In a broad series of nitrogen heterocycles, 1,2,3-triazoles have been known as a desired aim in click chemistry featuring exquisite selectivity and bioorthogonality.[4] Moreover, 1,2,3-triazoles find myriad applications as approved pharmaceuticals or promising drug candidates with a broad range of biological activities,[5] effective inhibitors of the corrosion process of metals or their alloys,[6] components of functionalized polymeric materials[7] or high-energy substances.[8] Closely related 2*H*-1,2,3-triazole 1-oxides are far less explored in spite of their structural similarity. Recently, our team created a novel, environmentally benign strategy for the electrooxidative formation of 1,2,3-triazole 1-oxides.[9] Taking into account the presence of the *N*-oxide moiety, 1,2,3-triazole 1-oxides may provide not only useful insights into the development of novel functional organic materials,[10] but also serve as exogenous nitric oxide (NO) donors for various biomedical applications.[11] Therefore, the development of diverse synthetic protocols for an assembly of 2*H*-1,2,3-triazole and their *N*-oxides remains desired.

Previously, it was shown, that 2*H*-1,2,3-triazoles can be prepared from other functionally substituted heterocycles through a so-called azole-to-azole interconversion. To accomplish this rearrangement, the initial azole has to contain a ring-conjugated side chain reacting as a nucleophile (*e.g.*, hydrazone moiety) toward the pivotal annular nitrogen atom in the S_N^i-type reaction followed by a cleavage of the adjacent bond to form a new azole [Scheme 1(*a*)].[12] There is a single example of the preparation of 5-acetyl-2,4-diphenyl-2*H*-1,2,3-triazole *via* base-induced rearrangement of the corresponding furoxanylhydrazone followed by one-pot Nef reaction [Scheme 1(*b*)].[13] However, the described synthetic procedure required harsh reaction conditions and exhaustive preparative TLC purification, which is rather inconvenient. Herein, we present divergent oriented synthesis of 2*H*-1,2,3-triazoles and their 1-oxides *via*



Scheme 1



1a **2a**

Scheme 2

Table 1 Optimization of the synthesis of 2*H*-1,2,3-triazole **2a**.[a]

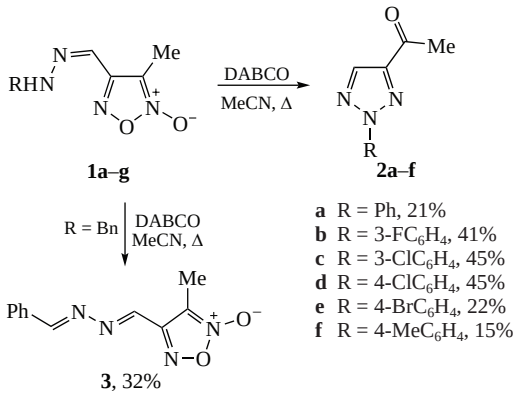
Entry	Base	Solvent	Yield of **2a** (%)[b]
1	NaOH	MeOH	4
2	K_2CO_3	DMF	4
3	K_2CO_3	MeCN	10
4	MeONa	MeOH	15
5	Cs_2CO_3	MeCN	18
6	CsF	MeCN	13
7	NaHMDS	THF	–[c]
8	NaH	THF	–[c]
9	DBU	MeCN	20
10	DABCO	MeCN	21
11	DABCO	dioxane	11
12	Py	–[d]	–[c]
13	DMAP	MeCN	11

[a] Reaction conditions: furoxanylhydrazone **1a** (0.5 mmol), base (0.5 mmol), solvent (2.5 ml), reflux for 2–24 h. [b] Isolated yields. [c] Trace amounts of **2a** were detected by TLC. [d] Neat reaction.

rearrangement of readily available furoxanylhydrazones [Scheme 1(*c*)].

Our investigations toward rearrangement of furoxanylhydrazones started from the optimization of the reaction conditions. Hydrazone **1a** was used as a suitable substrate and various bases and solvents were screened (Scheme 2, Table 1). Since the reaction did not proceed at temperatures below 50 °C, all experiments were performed under reflux. It was found that utilization of common inorganic bases (NaOH, K_2CO_3) in different solvents resulted in low yields of 2*H*-1,2,3-triazole **2a** (entries 1–3). Rearrangement of substrate **1a** promoted by MeONa, Cs_2CO_3 or CsF provided somewhat better yields of the product **2a** (entries 4–6), while utilization of NaHMDS or NaH gave only trace amounts of **2a** (entries 7, 8). Strong sterically hindered organic bases (DBU, DABCO) also provided 2*H*-1,2,3-triazole **2a** (entries 9–11) and the highest yield of **2a** (21%) was achieved upon conducting the reaction in MeCN (entry 10). Pyridine and DMAP were less efficient (entries 12, 13). Thus, optimal conditions for the synthesis of **2a** were utilization of DABCO in refluxing MeCN (entry 10).

Under optimized conditions, substrate scope for base-induced rearrangement of furoxanylhydrazones **1** was studied. It was found that hydrazones **1a–f** bearing aryl fragment at the hydrazone moiety underwent rearrangement affording target



1a–g **2a–f**

3, 32%

a R = Ph, 21%
b R = 3-FC_6H_4, 41%
c R = 3-ClC_6H_4, 45%
d R = 4-ClC_6H_4, 45%
e R = 4-BrC_6H_4, 22%
f R = 4-MeC_6H_4, 15%

Scheme 3

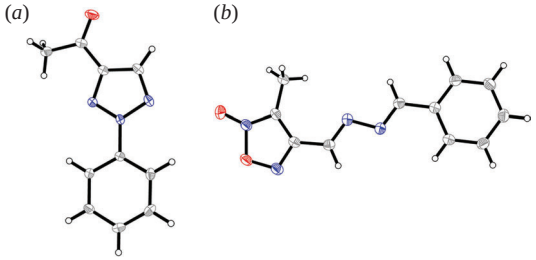
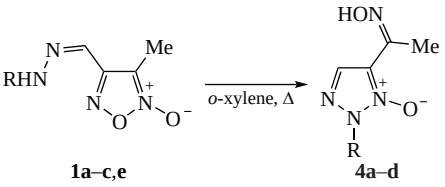


Figure 1 Molecular structures of compounds (*a*) **2a** and (*b*) **3** with atoms shown as thermal ellipsoids at 50% probability level.

2*H*-1,2,3-triazoles **2a–f** in fair yields. At the same time, an introduction of hydrazone **1g** incorporating benzyl motif gave unexpectedly azine **3** as a sole reaction product (Scheme 3). Arguably, in this case aerobic oxidation of the substrate **1g** is a favorable process due to the formation of a prolonged conjugated system in azine **3**. On the other hand, conducting rearrangement of hydrazone **1g** in argon atmosphere led to azine **3** in a very low yield (3%) and no other products were detected, which may serve as evidence for aerial oxidation of the substrate **1g**. It should also be noted that the studied reaction showed good scalability and conducting rearrangement of hydrazone **1a** on 5 mmol scale resulted in almost the same yield of 1,2,3-triazole **2a** (20%). All compounds were characterized by NMR spectroscopy and high-resolution mass spectrometry. The conclusive data on the structures of 2*H*-1,2,3-triazole **2a** and azine **3** were obtained by the single-crystal X-ray diffraction study (Figure 1; for details, see Online Supplementary Materials).†

Interestingly, upon prolonged heating in *o*-xylene in the absence of any bases furoxanylhydrazones **1** underwent a similar rearrangement, albeit resulting in a formation of 2*H*-1,2,3-triazole 1-oxides **4** (Scheme 4). Although large amounts of



1a–c,e **4a–d**

a R = Ph, 10%
b R = 3-FC_6H_4, 9%
c R = 3-ClC_6H_4, 9%
d R = 4-BrC_6H_4, 18%

Scheme 4

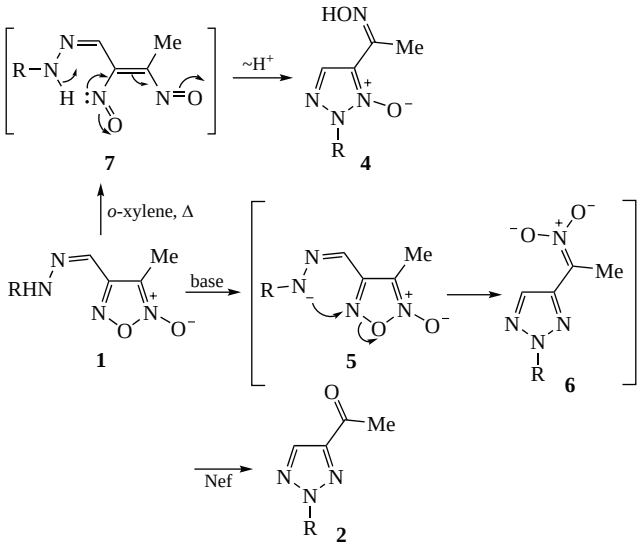
† *Crystal data for* **2a**. $C_{10}H_9N_3O$ (M_r = 187.20), triclinic, space group *P*1, *a* = 5.6693(3), *b* = 7.2303(3) and *c* = 11.6096(5) Å, *V* = 443.38(4) Å^3, *Z* = 2, d_x = 1.402 g cm^{-3}, absorption coefficient: 0.096 mm^{-1}, *F*(000) = 196, the final *R* = 0.0535, *wR* = 0.1129 for 2404 observed reflections with $I > 2\sigma(I)$.

Crystal data for **3**. $C_{11}H_{10}N_4O_2$ (M_r = 230.23), monoclinic, space group $P2_1/n$, *a* = 6.9334(2), *b* = 12.2596(4) and *c* = 12.9102(4) Å, *V* = 1070.43(6) Å^3, *Z* = 4, d_x = 1.429 g cm^{-3}, absorption coefficient: 0.858 mm^{-1}, *F*(000) = 480, the final *R* = 0.0346, *wR* = 0.0982 for 4147 observed reflections with $I > 2\sigma(I)$.

X-ray diffraction data in both experiments were collected at 100 K on a Bruker Quest D8 diffractometer equipped with a Photon-III area-detector (graphite monochromator, shutterless ϕ- and ω-scan technique), using MoK_α-radiation. The intensity data were integrated by the SAINT program[14] and corrected for absorption and decay using SADABS.[15] The structure was solved by direct methods using SHELXT[16] and refined on F^2 using SHELXL-2018.[17] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters. The SHELXTL program suite[14] was used for molecular graphics.

Crystal data and structure refinement parameters are given in Online Supplementary Materials.

CCDC 2287317 (**2a**) and 2289518 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.



Scheme 5

starting material decomposed under these conditions, we were able to isolate 2*H*-1,2,3-triazole 1-oxides **4** bearing a (hydroxyimino)ethyl moiety at the C(5) position of the heterocyclic ring.

Plausible mechanisms of both studied base- and thermally-induced rearrangements of furoxanylhydrazones are outlined in Scheme 5. Substrate **1** undergoes deprotonation under the action of a strong base and thus generated nitrogen-centered anion **5** rearranges into the 2*H*-1,2,3-triazole **6** *via* azole-to-azole interconversion. Subsequent Nef reaction furnishes the formation of acetyl-1,2,3-triazoles **2**. In the case of thermal rearrangement, it is known that the furoxan ring is capable of thermal ring cleavage at elevated temperatures (>110 °C) to generate unstable dinitrosoethylene intermediate, which may undergo cyclization to another furoxan regioisomer. This feature is usually applied to regulate ratios of furoxan regioisomers.[18] However, there are a few reports on trapping dinitrosoethylene intermediates to form structurally diverse nitrogen-containing species.[19] In our case, we suppose that upon heating in *o*-xylene furoxanylhydrazones **1** generate dinitrosoethylene intermediates **7** and hydrazone moiety is served as a nucleophilic trap for a closer nitroso group resulting in the formation of 2*H*-1,2,3-triazole 1-oxides **4**.

In conclusion, divergent oriented synthesis of 2*H*-1,2,3-triazoles and their 1-oxides *via* rearrangement of readily available furoxanylhydrazones was realized. It was shown that base-induced rearrangement of furoxanylhydrazones provided a direct access to acetyl-2*H*-1,2,3-triazoles, while thermal rearrangement of the same substrates gave (hydroxyimino)ethyl-2*H*-1,2,3-triazole 1-oxides, albeit in low yields. These results supplement known approaches in azole-to-azole interconversions to increase the availability of functionally substituted polynitrogen heterocycles.

Crystal structure determination was performed in the Department of Structural Studies of Zelinsky Institute of Organic Chemistry, Moscow.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.10.008.

References

1 (*a*) J. M. Smith, J. A. Dixon, J. N. deGruyter and P. S. Baran, *J. Med. Chem.*, 2019, **62**, 2256; (*b*) S. W. Krska, D. A. DiRocco, S. D. Dreher and M. Shevlin, *Acc. Chem. Res.*, 2017, **50**, 2976; (*c*) Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai and J.-Q. Yu, *Nature*, 2014, **515**, 389; (*d*) E. C. Hansen, D. J. Pedro, A. C. Wotal, N. J. Gower, J. D. Nelson, S. Caron and D. J. Weix, *Nat. Chem.*, 2016, **8**, 1126; (*e*) M. C. Hilton, X. Zhang, B. T. Boyle, J. V. Alegre-Requena, R. S. Paton and A. McNally, *Science*, 2018, **362**, 799.

2 (*a*) P. Das, M. D. Delost, M. H. Qureshi, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2019, **62**, 4265; (*b*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257.

3 (*a*) Y. Kawamata, J. C. Vantourout, D. P. Hickey, P. Bai, L. Chen, Q. Hou, W. Qiao, K. Barman, M. A. Edwards, A. F. Garrido-Castro, J. N. deGruyter, H. Nakamura, K. Knouse, C. Qin, K. J. Clay, D. Bao, C. Li, J. T. Starr, C. Garcia-Irizarry, N. Sach, H. S. White, M. Neurock, S. D. Minteer and P. S. Baran, *J. Am. Chem. Soc.*, 2019, **141**, 6392; (*b*) X. Zhang and A. McNally, *ACS Catal.*, 2019, **9**, 4862; (*c*) A. J. Boddy, D. P. Affron, C. J. Cordier, E. L. Rivers, A. C. Spivey and J. A. Bull, *Angew. Chem., Int. Ed.*, 2019, **58**, 1458; (*d*) R. Dorel and A. M. Echavarren, *Chem. Rev.*, 2015, **115**, 9028; (*e*) K. C. Nicolaou, C. R. H. Hale, C. Nilewski and H. A. Ioannidou, *Chem. Soc. Rev.*, 2012, **41**, 5185.

4 (*a*) N. Z. Fantoni, A. H. El-Sagheer and T. Brown, *Chem. Rev.*, 2021, **121**, 7122; (*b*) J. Totobenazara and A. J. Burke, *Tetrahedron Lett.*, 2015, **56**, 2853; (*c*) M. S. Ziegler, K. V. Lakshmi and T. D. Tilley, *J. Am. Chem. Soc.*, 2017, **139**, 5378.

5 (*a*) P. Prasher and M. Sharma, *Med. Chem. Commun.*, 2019, **10**, 1302; (*b*) M. Xu, Y. Peng, L. Zhu, S. Wang, J. Ji and K. P. Rakesh, *Eur. J. Med. Chem.*, 2019, **180**, 656; (*c*) L. Chen, L. J. Keller, E. Cordasco, M. Bogyo and C. S. Lentz, *Angew. Chem., Int. Ed.*, 2019, **58**, 5643; (*d*) M. Serafini, T. Pirali and G. C. Tron, *Adv. Heterocycl. Chem.*, 2021, **134**, 101; (*e*) D. Lengerli, K. Ibis, Y. Nural and E. Banoglu, *Expert Opin. Drug Discov.*, 2022, **17**, 1209.

6 (*a*) M. Faisal, A. Saeed, D. Shahzad, N. Abbas, F. A. Larik, P. A. Channar, T. A. Fattah, D. M. Khan and S. A. Shehzadi, *Corros. Rev.*, 2018, **36**, 507; (*b*) Yu. I. Kuznetsov, *Int. J. Corros. Scale Inhib.*, 2020, **9**, 1142; (*c*) E. Armelin, R. Whelan, Y. M. Martinez-Triana, C. Aleman, M. G. Finn and D. D. Diaz, *ACS Appl. Mater. Interfaces*, 2017, **9**, 4231.

7 (*a*) J. Huo, C. Lin and J. Liang, *React. Funct. Polym.*, 2020, **152**, 104531; (*b*) Y. Chen. H. Chen and H. Tian, *Chem. Commun.*, 2015, **51**, 11508.

8 (*a*) S. Feng, P. Yin, C. He, S. Pang and J. M. Shreeve, *J. Mater. Chem. A*, 2021, **9**, 12291; (*b*) S. Feng, F. Li, X. Zhao, Y. Qian, T. Fei, P. Yin and S. Pang, *Energ. Mater. Front.*, 2021, **2**, 125; (*c*) L. Pei, Q. Lai, P. Yin and S. Pang, *Cryst. Growth Des.*, 2023, **23**, 3595.

9 K. Titenkova, A. D. Shuvaev, F. E. Teslenko, E. S. Zhilin and L. L. Fershtat, *Green Chem.*, 2023, **25**, 6686.

10 (*a*) A. A. Larin and L. L. Fershtat, *Mendeleev Commun.*, 2022, **32**, 703; (*b*) S. G. Zlotin, A. M. Churakov, M. P. Egorov, L. L. Fershtat, M. S. Klenov, I. V. Kuchurov, N. N. Makhova, G. A. Smirnov, Yu. V. Tomilov and V. A. Tartakovsky, *Mendeleev Commun.*, 2021, **31**, 731; (*c*) P. Yin, Q. Zhang and J. M. Shreeve, *Acc. Chem. Res.*, 2016, **49**, 4; (*d*) A. A. Larin, A. V. Shaferov, K. A. Monogarov, D. B. Meerov, A. N. Pivkina and L. L. Fershtat, *Mendeleev Commun.*, 2022, **32**, 111.

11 (*a*) L. L. Fershtat and E. S. Zhilin, *Molecules*, 2021, **26**, 5705; (*b*) L. L. Fershtat and N. N. Makhova, *ChemMedChem*, 2017, **12**, 622; (*c*) K. Schönafinger, *Il Farmaco*, 1999, 54, 316; (*d*) A. Gasco and K. Schönafinger, in *Nitric Oxide Donors*: *For Pharmaceutical and Biological Applications*, eds. P. G. Wang, T. B. Cai and N. Taniguchi, Wiley-VCH, Weinheim, 2005, pp. 131–175; (*e*) A. S. Kulikov, M. A. Epishina, E. S. Zhilin, A. D. Shuvaev, L. L. Fershtat and N. N. Makhova, *Mendeleev Commun.*, 2021, **31**, 42; (*f*) L. L. Fershtat and F. E. Teslenko, *Synthesis*, 2021, **53**, 3673.

12 (*a*) N. N. Makhova, I. V. Ovchinnikov, A. S. Kulikov, S. I. Molotov and E. L. Baryshnikova, *Pure Appl. Chem.*, 2004, **76**, 1691; (*b*) A. J. Boulton and P. B. Ghosh, *Adv. Heterocycl. Chem.*, 1969, **10**, 1; (*c*) A. R. Katritzky and M. F. Gordeev, *Heterocycles*, 1993, **35**, 483.

13 E. L. Baryshnikova and N. N. Makhova, *Mendeleev Commun.*, 2000, **10**, 190.

14 *Bruker, APEX-III*, Bruker AXS, Madison, WI, USA, 2018.

15 L. Krause, R. Herbst-Irmer, G. M. Sheldrick and D. Stalke, *J. Appl. Crystallogr.*, 2015, **48**, 3.

16 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **A71**, 3.

17 G. M. Sheldrick, *Acta Crystallogr.*, 2015, **C71**, 3.

18 (*a*) N. N. Makhova and L. L. Fershtat, *Tetrahedron Lett.*, 2018, **59**, 2317; (*b*) D. M. Bystrov, L. L. Fershtat and N. N. Makhova, *Chem. Heterocycl. Compd.*, 2019, **55**, 1143; (*c*) A. A. Larin, D. D. Degtyarev, I. V. Ananyev, A. N. Pivkina and L. L. Fershtat, *Chem. Eng. J.*, 2023, **470**, 144144.

19 S.-C. Chan, J. England, K. Wieghardt and C.-Y. Wong, *Chem. Sci.*, 2014, **5**, 3883.

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