


 Cite this: *RSC Adv.*, 2021, 11, 4235

 Received 17th November 2020
 Accepted 9th January 2021

DOI: 10.1039/d0ra09758f

rsc.li/rsc-advances

Catalyzed ring transformation of cyclic *N*-aryl-azadiperioxides with participation of α,ω -dithiols†

 Nataliya N. Makhmudiyarova,^{ID}* Kamil R. Shangaraev, Irina R. Ishmukhametova, Askhat G. Ibragimov and Usein M. Dzhemilev

Co(OAc)₂-catalyzed ring transformation reaction of 10-aryl-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecanes with α,ω -dithiols (ethane-1,2-, propane-1,3-, butane-1,4-, pentane-1,5-, and hexane-1,6-dithiols, 3,6-dioxaoctane-1,8-dithiol) giving 3-aryl-1,5,3-dithiazacyclanes was studied.

Cyclic peroxides attract attention for their antimalarial,¹ antibacterial,² and antitumor³ activities. Among numerous cyclic peroxides, heteroatomic cyclic peroxides occupy a special place owing to their high biological activities.⁴ The methods of synthesis of heteroatom-containing cyclic peroxides are limited. Recently,^{5–10} nitrogen- and sulfur-containing cyclic di- and triperoxides with antitumor activity have been synthesized.^{5–9} The development of efficient methods for the preparation of new cyclic hetero-di(tri)peroxides^{5–10} promotes active investigation of their transformations. It was shown that the reduction of silatriperoxycycloalkanes with PPh₃ affords siladiperoxycycloalkanes;¹¹ the reaction of spiro{adamantane-[2,3']-(pentaoxacane)} with *o*-phenylenediamine results in the synthesis of benzodioxazine.⁵ The implemented conversion of pentaoxacane with *o*-phenylenediamine to benzodioxazine⁵ suggests that cyclic *N*-containing peroxides can be involved in reactions with binucleophilic reagents, in particular α,ω -dithiols, to give new heterocycles. In contrast to the previously described methods of synthesis^{5–10} and transformation of the peroxide ring,^{5,11} this work for the first time discusses the method of catalytic conversion of tetraoxazaspirotridecane to dithiazacycloalkanes.

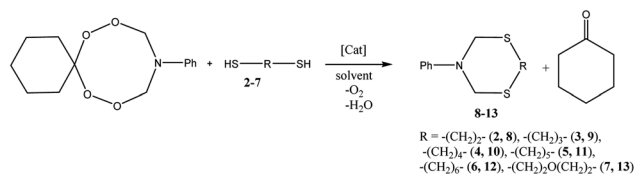
It was shown by preliminary experiments that the reaction of 10-phenyl-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecane **1** with ethane-1,2-dithiol **2** does not proceed without a catalyst. The reaction of azadiperoxide **1** with ethane-1,2-dithiol **2** catalyzed by Sm(NO₃)₃·6H₂O, H₂SO₄ or BF₃·Et₂O in THF as a solvent affords 3-phenyl-1,5,3-dithiazepane **8** in 10–15% yield (Scheme 1, Table 1). It was found that the yield of 3-phenyl-1,5,3-dithiazepane¹² is affected by the nature of the catalyst. When the reaction is carried out in a polar solvent (MeOH) in the presence of catalytic amounts of Sm(NO₃)₃·6H₂O, H₂SO₄ or BF₃·Et₂O, the yield of the target product **8** increases to 30%. In the presence of the Co(OAc)₂ catalyst, the

yield of heterocycle **8** is 85%. When AlCl₃ or CuCl catalysts are used, the yields of heterocycle **8** are 55% and 75%, respectively (Table 1). Under these conditions, cyclohexanone is formed and O₂ is released (Scheme 1). All reactions were carried out at room temperature for 20 h.

A probable pathway to the synthesis of 3-phenyl-1,5,3-dithiazepane **8** from 10-phenyl-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecane **1** includes¹³ coordination of the peroxide oxygen atom to the central atom of the catalyst, nucleophilic addition of ethane-1,2-dithiol to the resulting carbocation,^{14,15} and the subsequent ring closure giving heterocycle **8** (Scheme 2).

Under conditions including 5 mol% of Co(OAc)₂, 20 °C, MeOH, and 20 h, 10-phenyl-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecane **1** was allowed to react with propane-1,3- **3**, butane-1,4- **4**, pentane-1,5- **5**, and hexane-1,6-dithiols **6**, which furnished the corresponding 3-phenyl-1,5,3-dithiazacycloalkanes¹⁶ **9–12** in 83–89% yields (Table 1). The ring transformation reaction of azadiperoxide **1** with 3,6-dioxo-1,8-octanedithiol **7** (monooxa derivative is shown in the scheme) under the conditions described above resulted in the synthesis of 6-phenyl-1,11-dioxo-4,8-dithia-6-azacyclotridecane¹⁶ **12** in 91% yield (Scheme 1).

The discovered ring transformation reaction of azadiperoxide **1** with ethane-1,2-dithiol **2** was also carried out for 10-aryl-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecanes **14–24**, which produced 3-aryl-1,5,3-dithiazepanes¹² **25–35** in 76–90% yields (Scheme 3).



Scheme 1 Ring transformation reaction of 10-phenyl-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecane with α,ω -dithiols.

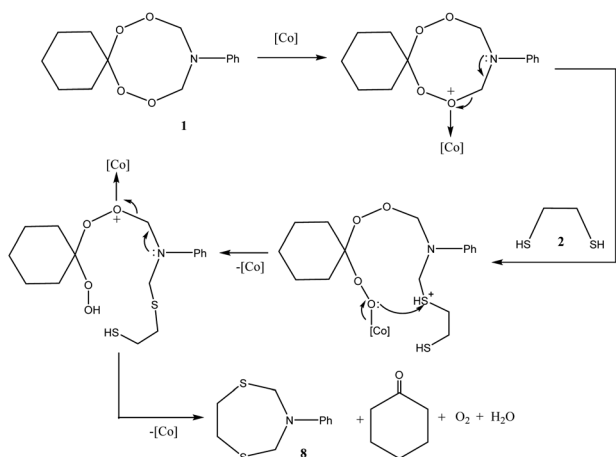
Institute of Petrochemistry and Catalysis, Russian Academy of Sciences, 141 Prospekt Oktyabrya, 450075 Ufa, Russian Federation. E-mail: natali-mnn@mail.ru

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ra09758f

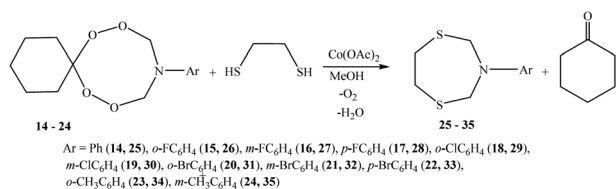


Table 1 Effect of the catalyst and solvent nature on the yield of 3-phenyl-1,5,3-dithiazacyclanes (~20 °C, 20 h)

No.	Compound	[Cat]	Solvent	Yield, %
1	8	AlCl ₃	THF	45
2	8	AlCl ₃	MeOH	55
3	8	Co(OAc) ₂	THF	79
4	8	Co(OAc) ₂	MeOH	85
5	8	BF ₃ ·OEt ₂	THF	15
6	8	BF ₃ ·OEt ₂	MeOH	30
7	8	CuCl	THF	68
8	8	CuCl	MeOH	75
9	8	H ₂ SO ₄	THF	13
10	8	H ₂ SO ₄	MeOH	25
11	8	Sm(NO ₃) ₃ ·6H ₂ O	THF	10
12	8	Sm(NO ₃) ₃ ·6H ₂ O	MeOH	20
13	8	—	THF	—
14	8	—	MeOH	—
15	9	Co(OAc) ₂	MeOH	87
16	10	Co(OAc) ₂	MeOH	79
17	11	Co(OAc) ₂	MeOH	83
18	12	Co(OAc) ₂	MeOH	89
19	13	Co(OAc) ₂	MeOH	91



Scheme 2 Probable synthesis mechanism for 3-phenyl-1,5,3-dithiazepane **8**.



Scheme 3 Ring transformation reaction of 10-aryl-7,8,12,13-tetraoxa-10-azaspiro[5.7]tridecanes with ethane-1,2-dithiol.

In conclusion, we demonstrated that on treatment with α,ω -alkanedithiols and the Co(OAc)₂ catalyst, azadiperoxides are converted to *N*-aryl-substituted 1,5,3-dithiazamacroheterocycles in high yields.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

The reported study was funded by RFBR according to the research project No. 20-33-90002/20.

Notes and references

- 1 R. Slack, A. Jacobine and G. Posner, *Med. Chem. Commun.*, 2012, **3**, 281.
- 2 V. Vil', I. Yaremenko, A. Ilovaisky and A. Terent'ev, *Molecules*, 2017, **22**, 1881.
- 3 D. Liu and J. Liu, *Nat. Prod. Bioprospect.*, 2013, **3**, 161; M. P. Crespo-Ortiz and M. Q. Wei, Antitumor Activity of Artemisinin and Its Derivatives: From a Well-Known Antimalarial Agent to a Potential Anticancer Drug, *J. Biomed. Biotechnol.*, 2012, 257597.
- 4 Y. Tu, *Nat. Med.*, 2011, **17**, 1217.
- 5 T. V. Tyumkina, N. N. Makhmudiyarova, G. M. Kiyamutdinova, E. S. Meshcheryakova, K. Sh. Bismukhametov, M. F. Abdullin, L. M. Khalilov, A. G. Ibragimov and U. M. Dzhemilev, *Tetrahedron*, 2018, **74**, 1749.
- 6 N. N. Makhmudiyarova, I. R. Ishmukhametova, L. U. Dzhemileva, T. V. Tyumkina, V. A. D'yakov, A. G. Ibragimov and U. M. Dzhemilev, *RSC Adv.*, 2019, **9**, 18923.
- 7 N. N. Makhmudiyarova, R. Sh. Rakhimov, T. V. Tyumkina, E. S. Meshcheryakova, A. G. Ibragimov and U. M. Dzhemilev, *Russ. J. Org. Chem.*, 2019, **5**, 620.
- 8 N. N. Makhmudiyarova, K. R. Shangaraev, L. U. Dzhemileva, T. V. Tyumkina, E. S. Meshcheryakova, V. A. D'yakov, A. G. Ibragimov and U. M. Dzhemilev, *RSC Adv.*, 2019, **9**, 29949.
- 9 N. N. Makhmudiyarova, I. R. Ishmukhametova, L. U. Dzhemileva, V. A. D'yakov, A. G. Ibragimov and U. M. Dzhemilev, *Molecules*, 2020, **25**, 1874.
- 10 N. N. Makhmudiyarova, I. R. Ishmukhametova, A. G. Ibragimov and U. M. Dzhemilev, *Dokl. Chem.*, 2020, **492**, 93.
- 11 N. N. Makhmudiyarova, I. R. Ishmukhametova and A. G. Ibragimov, *Russ. J. Org. Chem.*, 2020, **10**, 1495.
- 12 N. N. Murzakova, K. I. Prokof'ev, T. V. Tyumkina and A. G. Ibragimov, *Russ. J. Org. Chem.*, 2012, **48**, 588.
- 13 (a) S. Oda, J. Franke and M. Krishce, *J. Chem. Sci.*, 2016, **7**, 136; (b) S. Vojacek, K. Beese, Z. Alhalabi, S. Swyter, A. Bodtke, C. C. Schulzke, M. Jung, W. Sippl and A. Link, *Arch. Pharm.*, 2017, **350**, e1700097.
- 14 U. J. Wellmar, *Heterocyclic Chem.*, 1998, **35**, 1531.
- 15 K. Krohn and S. Cludius-Brandt, *Synthesis*, 2010, **8**, 1344.
- 16 N. N. Makhmudiyarova, L. V. Mudarisova, E. S. Meshcheryakova, A. G. Ibragimov and U. M. Dzhemilev, *Tetrahedron*, 2015, **71**, 259.
- 17 N. N. Makhmudiyarova, G. M. Khatmullina, R. Sh. Rakhimov, E. S. Meshcheryakova, A. G. Ibragimov and U. M. Dzhemilev, *Tetrahedron*, 2016, **72**, 3277.

