RSC Advances

PAPER

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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-azadiperoxides with participation of α,ω-dithiols†

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$Co(OAc)_2$-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.

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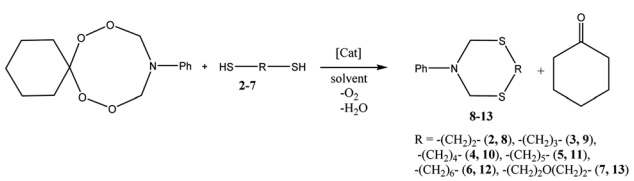
Cyclic peroxides attract attention for their antimalarial,[1] antibacterial,[2] and antitumor[3] activities. Among numerous cyclic peroxides, heteroatomic cyclic peroxides occupy a special place owing to their high biological activities.[4] The methods of synthesis of heteroatom-containing cyclic peroxides 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 PPh_3 affords siladiperoxycycloalkanes;[11] the reaction of spiro{adamantane-[2,3′]-(pentaoxacane)} with *o*-phenylenediamine results in the synthesis of benzodioxazocine.[5] The implemented conversion of pentaoxacane with *o*-phenylenediamine to benzodioxazocine[5] 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 $Sm(NO_3)_3 \cdot 6H_2O$, H_2SO_4 or $BF_3 \cdot Et_2O$ 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-dithiazepane[12] 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 $Sm(NO_3)_3 \cdot 6H_2O$, H_2SO_4 or $BF_3 \cdot Et_2O$, 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 $AlCl_3$ or CuCl catalysts are used, the yields of heterocycle **8** are 55% and 75%, respectively (Table 1). Under these conditions, cyclohexanone is formed and O_2 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** includes[13] 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-dithiaazacycloalkanes[16] **9–12** in 83–89% yields (Table 1). The ring transformation reaction of azadiperoxide **1** with 3,6-dioxa-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-dioxa-4,8-dithia-6-azacyclotridecane[16] **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-dithiazepanes[12] **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.

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

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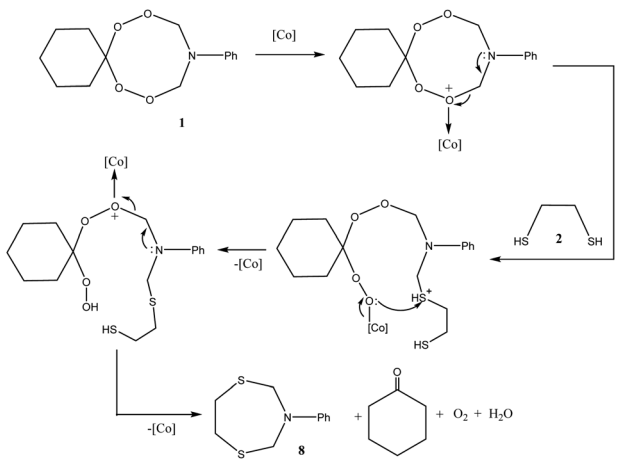
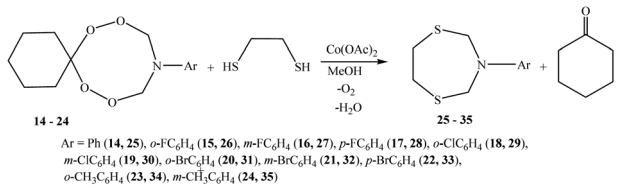
Table 1 Effect of the catalyst and solvent nature on the yield of 3-phenyl-1,5,3-dithiazacyclanes (~20 °C, 20 h)

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**	$BF_3 \cdot OEt_2$	THF	15
6	**8**	$BF_3 \cdot OEt_2$	MeOH	30
7	**8**	CuCl	THF	68
8	**8**	CuCl	MeOH	75
9	**8**	H_2SO_4	THF	13
10	**8**	H_2SO_4	MeOH	25
11	**8**	$Sm(NO_3)_3 \cdot 6H_2O$	THF	10
12	**8**	$Sm(NO_3)_3 \cdot 6H_2O$	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.

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