Synthesis of pentaoxaspiroalkanes and pentaoxocanes catalyzed by lanthanide compounds

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Abstract

An efficient method for the synthesis of pentaoxaspiroalkanes and pentaoxocanes by cyclocondensation of 1,1-bis(hydroperoxy)cycloalkanes and 1,1-bis(hydroperoxy)alkanes with formaldehyde catalyzed by $Sm(NO_3)_3 \cdot 6H_2O$ has been developed.

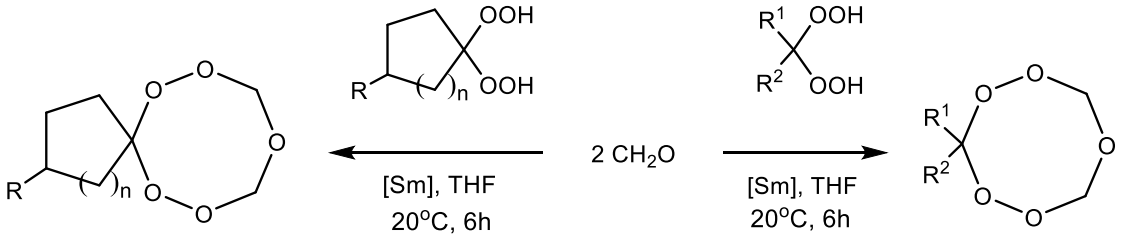
Keywords: Lanthanide catalysis, cyclocondensation, 1,1-bis(hydroperoxy)cycloalkanes, 1,1-bis(hydroperoxy)alkanes, formaldehyde, pentaoxaspiroalkanes

Introduction

Organic peroxides belong to a broad and highly demanded class of compounds.[1,2] Interest in the development of new methods for the synthesis of cyclic peroxides is due to their antimalarial activity.[3,4] We have shown earlier that pentaoxocanes are used in the synthesis of *N*-aryltetraoxazaspiroalkanes.[5] The nitrogen-containing cyclic peroxides are promising compounds with antimalarial activity.[2,6] The best known methods for the synthesis of pentaoxocanes are the acid-catalyzed reaction of α-alkoxyhydroperoxides with aliphatic aldehydes,[7-9] the acidolysis of aryl/alkyl cycloalkene ozonides with chlorosulfonic acid,[4,10-12] and the reaction of bis-silylisochromane with aromatic aldehydes.[12] Drawbacks of the known methods of pentaoxocane synthesis include the low (5%) or moderate (34%) yields and the several steps needed to obtain the desired products.

Results and Discussion

The purpose of this work is to develop a catalytic method for the selective synthesis of new spiro-coupled pentaoxocanes **1** in high yields. When starting on this problem, we assumed that if cyclocondensation of α,ω-SH acids with formaldehyde affords oxadithiacycloalkanes,[13] then cyclocondensation of 1,1-bis(hydroperoxy)cycloalkanes **2** (α,ω-OHacids) with formaldehyde would provide a synthesis of pentaoxocanes. It was shown by tentative experiments that this reaction in the absence of a catalyst does not give pentaoxaspiroalkanes **1**, while the reaction of **2** with aldehydes in the presence of traditional acid catalysts such as sulfuric acid or BF_3 Et_2O gives rise to 1,2,4,5-tetraoxanes.[14] In relation to the reaction of 1,1-bis(hydroperoxy)cyclohexane **2b** with formaldehyde, we found that in the presence of $Sm(NO_3)_3 \cdot 6H_2O$ (5 mol%) as a catalyst, the reaction carried out at ~20ºC for 6h in THF gives the pentaoxaspiroalkane **1b** in 95% yield. The $Sm(NO_3)_3 \cdot 6H_2O$ catalyst was chosen due to its successful use in our previous work to catalyze the cyclocondensation of NHacids with formaldehyde and α,ω-diols or α,ω-dithiols to afford 1,5,3-dioxazepanes[14] or 1,5,3-dithiazacycloalkanes.[15-22]



R = H, n = 1 (**1a**), 2 (**1b**), 3 (**1d**), 4 (**1e**)
R = Me, n = 2 (**1c**)

[Sm] = $Sm(NO_3)_3 \cdot 6H_2O$

$R^1 = R^2$ = Me (**3**,**7**)
R^1 = Me, R^2 = Bu^t (**4**,**8**)
$R^1 = R^2$ = Bu (**5**,**9**)
R^1,R^2 = adamantane-2,2-diyl (**6**,**10**)

Scheme. The synthesis of pentaoxaspiroalkanes and pentaoxocanes by cyclocondensation of 1,1-bis(hydroperoxy)cycloalkanes and 1,1-bis(hydroperoxy)alkanes with formaldehyde.

By NMR spectroscopic methods, compound **1b** was identified as 7,8,10,12,13-pentaoxa-spiro[5.7]tridecane based on signals at 109.98 ppm, typical of sp^3-hybridized carbon bearing two oxygen functions, and the signal at 92.30 ppm, typical of carbons in the -CH_2-O-CH_2- system. The ^{1}H NMR spectrum exhibits a singlet at 5.17 ppm due to the -O-CH_2-O-CH_2-O ring protons correlated in the HSQC experiment with the δ 92.30 ppm carbon signal. The multiplets at 1.76, 1.54, and 1.43 ppm refer to the cyclohexane ring in **1b**. The structure of 7,8,10,12,13-pentaoxaspiro[5.7]tridecane **1b** was additionally confirmed by MALDI-TOF mass spectrometry. The spectrum contains a molecular ion fragment at *m/z* 191 $[M-H]^+$, indicating the formation of compound **1b** under the reaction conditions.

It was shown by subsequent experiments that under the conditions selected (5 mol. % $Sm(NO_3)_3 \cdot 6H_2O$, 20 °C, 6 h), the yield of the target product **1b** decreases in the following sequence of solvents: THF (95%) > CH_2Cl_2 (85%) > Et_2O (79%) > C_6H_{12} (15%) > EtOAc (10%) > C_2H_5OH (7%).

Apart from $Sm(NO_3)_3 \cdot 6H_2O$, we tested some other lanthanide (Ho, Tb, Dy, Nd, La) salts as catalysts in the cyclocondensation reaction. The reactions were conducted at ~20ºC in THF in the presence of 5 mol. % of catalyst. Under these conditions, selective formation of **1b** took place in the following yields depending on the catalyst: 84% ($Ho(NO_3)_3 \cdot 5H_2O$) > 72% ($TbCl_3 \cdot 6H_2O$) > 67% ($DyCl_3 \cdot 6H_2O$) > 61% ($NdCl_3$) > 58% ($La(NO_3)_3$).

Under the optimal conditions for the preparation of **1b** (5 mol. % of $Sm(NO_3)_3 \cdot 6H_2O$, THF, 20 °C, 6 h), the cyclocondensation of 1,1-bis(hydroperoxy)cycloalkanes **2a,c-e**[14] with formaldehyde results in the selective formation of pentaoxaspiroalkanes **1a,c-e** in yields of 90% (**1a**) > 85% (**1c**) > 71% (**1d**) > 69% (**1e**) (scheme).

To determine the possibility of selective synthesis of pentaoxocanes, we studied the $Sm(NO_3)_3 \cdot 6H_2O$ catalyzed reaction of 1,1-bis(hydroperoxy)alkanes **3-6**[14] with formaldehyde. We found that this reaction provides an effective way to obtain pentaoxocanes. The yield of 1,2,4,5,7-pentaoxocanes **7-10** decreases in the sequence 2,2-dihydroperoxypropane **3** (98%) > 5,5-dihydroperoxynonane **5** (63%) > 2,2-dihydroxyadamantane **6** (53%) when using 5 mol. % of $Sm(NO_3)_3 \cdot 6H_2O$ in THF solution at 20 °C for 6 h (scheme). The reaction time for the synthesis of adamantane-2-spiro-3′-1′,2′,4′,5′,7′-pentaoxocane **10** was 10h.

Conclusions

We have developed a new selective method for the synthesis of pentaoxaspiroalkanes and pentaoxocanes by $Sm(NO_3)_3 \cdot 6H_2O$ catalyzed cyclocondensation of 1,1-bis(hydroperoxy)cyclo-alkanes and *gem*-bis(hydroperoxy)alkanes with formaldehyde.

Experimental Section

General. All reactions were performed at room temperature under an air atmosphere in a round bottom flask equipped with a magnetic stir bar. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$, internal standard was TMS. Two-dimensional homonuclear (COSY, NOESY) and heteronuclear (HSQC, HMBC) experiments were carried out under standard Bruker pulse sequences at the same operating frequencies. The mixing time for the NOESY experiments was 0.3 s. Mass spectra were recorded on a Bruker Autoflex III MALDI TOF instrument with α-cyano-4-hydroxycinnamic acid (CHCA) as a matrix. Samples of the compounds were prepared by the "dried droplet method". C/H analyses were carried out on a Carlo Erba 1108 analyzer, O analyses on a Carlo Erba 1106 analyzer. The

progress of reactions was monitored by TLC on Sorbfil (PTSKh-AF-V) plates, visualization with I_2 vapour.
The synthesis of the *gem*-bishydroperoxides **3-6** was as reported in the literature.[10]

Cyclocondensation of 1,1-bis(hydroperoxy)cycloalkanes and *gem*-bis(hydroperoxy)alkanes with formaldehyde catalyzed by $Sm(NO_3)_3·6H_2O$. General procedure A Schlenk vessel mounted on a magnetic stirrer was charged at ~20°C with tetrahydrofuran (5 ml), aqueous (37%) formaldehyde (1.46 ml, 20 mmol), and the selected bis(hydroperoxy)cycloalkane [*gem*-bis(hydroperoxy)alkane] (10 mmol). Then $Sm(NO_3)_3·6H_2O$ (0.222 g, 5 mol. % relative to 1,1-bis(hydroperoxy)cycloalkane) was added. The reaction mixture was stirred at ~20 ºC for 6 h and tetrahydrofuran was evaporated. Et_2O (10 ml) was added and the mixture was washed with water (4 × 5 ml). The ethereal layer was dried ($MgSO_4$) and concentrated to isolate pentaoxaspiroalkanes as oily liquids stable during storage at room temperature. Monitoring of the progress of reactions was effected by TLC, eluent was hexane : EtOAc, 5:1 (compounds **1a-f**, **7-10**), visualization with I_2 vapor. The residue (compounds **1a-f**, **7-10**) was chromatographed on a column with SiO_2 (eluent was hexane : EtOAc, 5:1) to isolate pure heterocyclic products.
6,7,9,11,12-Pentaoxaspiro[4.7]dodecane (**1a**). Colorless oil (1.584 g, 90%), n_D^{20} 1.4564. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 1.62-1.66 (m, 4H, H_2C), 1.86-1.89 (m, 4H, H_2C), 5.04 (s, 4H, OH_2CO) ppm. ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 24.42 (CH_2CH_2), 34.01 (CH_2CH_2), 92.31 (OCH_2O), 119.90 (C) ppm. MALDI TOF, *m/z*: 175 $[M-H]^+$. Anal. Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87; O 45.41. Found: C, 47.67; H, 6.80; O, 44.35 %.
7,8,10,12,13-Pentaoxaspiro[5.7]tridecane (**1b**). Colorless oil (1.805 g, 95%), n_D^{20} 1.5262. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 1.43-1.44 (m, 4H, H_2C), 1.54-1.55 (m, 2H, H_2C), 1.76-1.83 (m, 4H, H_2C), 5.17 (s, 4H, OH_2CO) ppm. ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 22.35 (CH_2CH_2), 25.18 (CH_2), 29.98 (CH_2CH_2), 92.30 (OCH_2O), 109.98 (C) ppm. MALDI TOF, *m/z*: 189 $[M-H]^+$. Anal. Calcd. for $C_8H_{14}O_5$: C, 50.52; H, 7.42; O 42.06. Found: C, 50.48; H, 7.34; O, 42.00 %.
3-Methyl-7,8,10,12,13-pentaoxaspiro[5.7]tridecane (**1c**). Colorless oil (1.734 g, 85%), n_D^{20} 1.4703. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 0.88-0.89 (m, 3H, CH_3), 1.11-1.15 (m, 1H, HC), 1.40-1.56 (m, 6H, H_2C), 5.04 (s, 4H, OH_2CO) ppm. ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 21.94 (CH_3), 30.17 (CH_2CH_2), 30.75 (CH_2CH_2), 31.55 (CH), 92.32 (OCH_2O), 108.85 (C) ppm. MALDI TOF, *m/z*: 203 $[M-H]^+$. Anal. Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90; O 39.17. Found: C, 52.87; H, 7.84; O, 39.09 %.
8,9,11,13,14-Pentaoxaspiro[6.7]tetradecane (**1d**). Colorless oil (1.448 g, 71%), n_D^{20} 1.4591. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 1.24-1.29 (m, 4H, H_2C), 1.45-1.51 (m, 4H, H_2C), 1.75-1.82 (m, 2H, H_2C), 2.31-2.34 (m, 4H, H_2C), 5.03 (s, 4H, OH_2CO) ppm. ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 24.15 (CH_2CH_2), 30.14 (CH_2CH_2), 43.75 (CH_2CH_2), 92.08 (OCH_2O), 113.90 (C) ppm. MALDI TOF, *m/z*: 203 $[M - H]^+$. Anal. Calcd. for $C_9H_{16}O_5$: C, 52.93; H, 7.90; O 39.17. Found: C, 52.85; H, 7.86; O, 39.11 %.

1,2,4,6,7-Pentaoxaspiro[7.7]pentadecane (**1e**). Colorless oil (1.504 g, 69%), n_D^{20} 1.4631. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 1.45-1.51 (m, 4H, H_2C), 1.77-1.79 (m, 10H, H_2C), 5.01 (s, 4H, OH_2CO) ppm. ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 25.57 (CH_2CH_2), 27.15 ($CH_2CH_2CH_2$), 41.48 (CH_2CH_2), 92.25 (OCH_2O), 113.05 (C) ppm. MALDI TOF, *m/z*: 217 $[M - H]^+$. Anal. Calcd. for $C_{10}H_{18}O_5$: C, 55.03; H, 8.31; O 36.65. Found: C, 54.98; H, 8.28; O, 36.60 %.

3,3-Dimethyl-1,2,4,5,7-pentaoxocane (**7**). Colorless oil (1.471 g, 98%), n_D^{20} 1.4013. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 1.25 (c, 6H, H_3C), 5.01 (s, 4H, OH_2CO) ppm. ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 20.05 (CH_3), 92.04 (OCH_2O), 109.03 (C) ppm. MALDI TOF, *m/z*: 149 $[M - H]^+$. Anal. Calcd. for $C_5H_{10}O_5$: C, 40.00; H, 6.71; O 53.29. Found: C, 39.95; H, 6.65; O, 53.25 %.

3-(*t*-Butyl)-3-methyl-1,2,4,5,7-pentaoxocane (**8**). Pale yellow oil (1.582 g, 82%), n_D^{20} 1.4742. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 1.05 (c, 12H, H_3C), 1.20 (c, 3H, H_3C), 5.03 (s, 4H, OH_2CO) ppm. ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 19.57 (CH_3), 22.15 (CH_3), 39.41 (C), 91.08 (OCH_2O), 109.05 (C) ppm. MALDI TOF, m/z: 191 $[M - H]^+$. Anal. Calcd. for $C_8H_{16}O_5$: C, 49.99; H, 8.39; O 41.62. Found: C, 49.94; H, 8.35; O, 41.77 %.

3,3-Dibutyl-1,2,4,5,7-pentaoxocane (**9**). Colorless oil (1.474 g, 63%), n_D^{20} 1.4654. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 0.97-1.01 (m, 6H, H_3C), 1.22-1.25 (m, 8H, H_2C), 1.36-1.41 (m, 4H, H_2C), 5.01 (s, 4H, OH_2CO) ppm. ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 19.45 (CH_3), 20.45 (CH_2), 23.76 (CH_2), 25.32 (CH_2), 29.87 (CH_2), 91.02 (OCH_2O), 109.52 (C) ppm. MALDI TOF, *m/z*: 233 $[M - H]^+$. Anal. Calcd. for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46; O 34.14. Found: C, 56.34; H, 9.40; O, 34.30 %.

Adamantane-2-spiro-3′-1′,2′,4′,5′,7′-pentaoxocane (**10**). Colorless oil (1.282 g, 53%), n_D^{20} 1.5241. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz) δ 1.18-2.27 (m, 14H, CH, H_2C), 5.09 (s, 4H, OH_2CO). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz) δ 29.74 (CH), 30.95 (CH_2), 33.57 (CH), 37.33 (CH_2), 91.07 (OCH_2O), 112.57 (C). MALDI TOF, *m/z*: 241 $[M - H]^+$. Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49; O 33.02. Found: C, 59.44; H, 7.42; O, 29.99 %.

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