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Direct oxidative functionalization of saturated dispiro-cyclopropanated bicyclo[3.3.1]nonanes

Kristian S. Andriasov,[a] Kseniya N. Sedenkova,[a,b] Marina G. Eremenko,[a] Igor P. Gloriosov,[a] Yuri K. Grishin,[a] Tamara S. Kuznetsova[a] and Elena B. Averina*[a,b]

[a] *Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 495 939 0290; e-mail: elaver@med.chem.msu.ru*

[b] *Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation*

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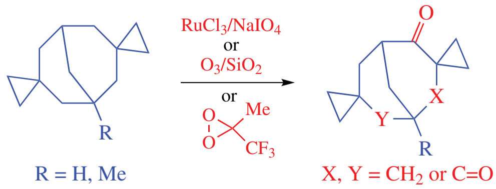
Two dispiro[cyclopropane-1,3′-bicyclo[3.3.1]nonane-7′,1′′-cyclopropanes] were treated with various oxidative systems. The conditions providing mono- or dioxidation of the CH_2 groups neighbouring to spiro-annulated cyclopropane moieties to afford the corresponding mono- or diketones were found.



Keywords: cyclopropanes, bicyclo[3.3.1]nonanes, cyclopropyl ketones, spiro compounds, 1,5-diketones, oxidation, ozone, ruthenium(VIII) oxide, methyl(trifluoromethyl)dioxirane.

This paper is dedicated to the memory of our Teacher academician N. S. Zefirov who has been heading our investigations in the field of cyclopropane chemistry for many years.

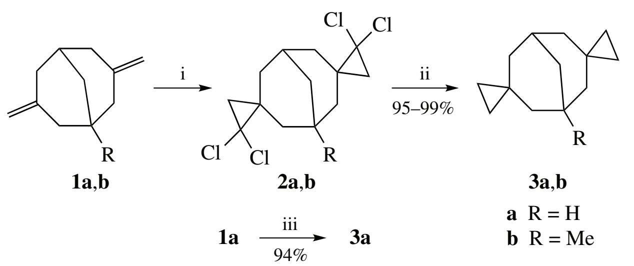
The bicyclo[3.3.1]nonane core is abundant in natural compounds including several with neuroprotective[1] and antiviral[2] properties and a wide range of other types of biological activities.[3] A number of synthetic approaches to natural bicyclo[3.3.1]nonanes and their analogues have been elaborated,[4–6] and the synthesis of novel bicyclo[3.3.1]nonane functional derivatives remains an urgent and challenging task.[7–10]

Direct oxidation of hydrocarbons, a powerful method of transformation of methylene or methine groups activated by neighbouring substituents into a carbonyl or carbinol moiety, respectively,[11] corresponds to the principle of atom economy.[12,13] Taking into account that the cyclopropyl group acts as an activating group in oxidative processes,[14] recently we applied this approach to polycyclopropanated hydrocarbons and obtained a series of cyclopropane-containing mono- and polyketones.[15,16]

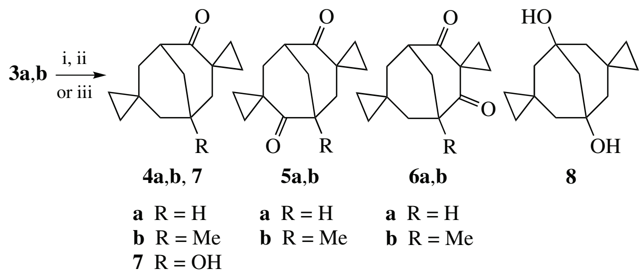
In the present work, we oxidized hydrocarbons containing a bicyclo[3.3.1]nonane core (Scheme 1) with various oxidants aiming to construct a carbonylcyclopropane moiety on this core, which may be promising for further functionalization and heterocyclization.[17–20] Hydrocarbons **3a**,**b** were obtained by reduction of *gem*-dichlorocyclopropane moieties of compounds **2a**,**b**[21] upon the treatment with lithium in the presence of *tert*-butanol. An alternative pathway, the Simmons–Smith cyclopropanation of diene **1a** with diiodomethane and diethylzinc, was also employed. Both reactions proceeded smoothly and afforded hydrocarbons **3a**,**b** in high yields.

Oxidation of compounds **3a**,**b** (Scheme 2) was performed under the conditions of 'dry' ozonolysis (method A);[16,23] upon the treatment with methyl(trifluoromethyl)dioxirane (TFDO), pre-generated from 1,1,1-trifluoroacetone (method B),[16,24] and with RuO_4, generated *in situ* from $RuCl_3$ using $NaIO_4$ as oxidant (method C).[16,25] These oxidants were chosen as the most reliable, effective and available reagents for the oxygenation of hydrocarbons, according to literature data[11] and our previous studies.[15,16]

Brief optimization for the 'dry' ozonolysis revealed that the optimal conditions yielding ketones **4a,b** as the major products were –45 °C, 30–40 min (Table 1, entries 1, 8). In the case of non-symmetrical methyl-substituted hydrocarbon **1b** the first oxidation proceeded regioselectively involving only less sterically hindered methylene group to give ketone **4b**. Diketones



Scheme 1 *Reagents and conditions*: i, [:CCl_2] (refs. 21, 22); ii, Li, Bu^{t}OH, Et_2O, 25 °C, 4 days; iii, CH_2I_2, Et_2Zn, benzene, 60 °C, 4 h.



Scheme 2 *Reagents and conditions:* i, O_3/SiO_2, –45 °C, 5–40 min (method A); ii, TFDO, $CF_3C(O)CH_3$, –20···0 °C, 2 h (method B); iii, $RuCl_3$, $NaIO_4$, CCl_4, MeCN, phosphate buffer, 25–60 °C, 0.5–16 h (method C).

Table 1 Oxidation of dispiro-cyclopropanated hydrocarbons **3a**,**b**.

Entry	Substrate	Method	T/°C	t/h	Content in the reaction mixture[a] (%)					
					3a,**b**	**4a**,**b**	**5a**,**b**	**6a**,**b**	**7**	**8**
1	**3a**	A	–45	0.67	–	70 (18)	20 (16)	10 (8)	–	–
2	**3a**	B	–20···0	2	–	42 (21)	15 (6)	5 (4)	30 (12)	8 (4)
3	**3a**	C	25	4	–	72 (38)	17 (8)	11 (6)	–	–
4	**3a**	C	25	6	–	47 (23)	33 (13)	20 (3)	–	–
5	**3a**	C	60	16	–	–	94 (25)	6	–	–
6	**3b**	A	–45	0.08	95	5	–	–	–	–
7	**3b**	A	–45	0.25	6	56	28	10	–	–
8	**3b**	A	–45	0.5	–	67 (25)	23 (13)	10 (5)	–	–
9	**3b**	A	–45	0.67	–	40	46	14	–	–
10	**3b**	B	–20···0	2	–	71 (30)	13 (4)	16 (4)	–	–
11	**3b**	C	25	0.5	31	51 (42)	13 (3)	5	–	–
12	**3b**	C	25	3	–	74 (21)	19	7	–	–
13	**3b**	C	60	6	–	14	57 (15)	29 (9)	–	–

[a] From ^{1}H NMR spectra of the reaction mixtures; isolated yields are given in parentheses.

5a,**b** and **6a**,**b**, formed by further oxidation of **4a**,**b**, were isolated as minor products. On the example of hydrocarbon **3b**, it was shown that prolongation of the ozonolysis shifted the ratio of products towards diketone **5b** (entry 9). Moderate isolated yields are resulted from the complicated chromatographic separation of complex reaction mixtures.

Oxidation of hydrocarbons **3a**,**b** with TFDO also afforded ketones **4a**,**b** as the major products, accompanied by small amounts of diketones **5a**,**b** and **6a**,**b** (see Table 1, entries 2, 10). Besides, hydroxy ketone **7** and diol **8** were formed from **3a**, in accordance with the tendency of TFDO to oxidize non-activated CH bonds.[11]

The highest monoketone/diketone ratios were achieved with the use of RuO_4 at 25 °C for 3–4 h (see Table 1, entries 3, 12). The highest preparative yields of ketones **4a**,**b** (38 and 42%, respectively) were also achieved upon the treatment with RuO_4 under mild conditions (entries 3, 11). In contrast, raising the temperature up to 60 °C and reaction time up to 6–16 h caused conversion of monoketones **4a**,**b** into diketones **5a**,**b** and **6a**,**b** (entries 5, 13).

All the oxidation products were isolated by column chromatography, and their structures were unambiguously proved by experiments (for details, see Online Supplementary Materials). The NMR data and DFT calculations for compounds **3b**, **4a**, **5b** reveal that bicyclo[3.3.1]nonane moiety consists of two 1,3-fused six-membered rings in 'chair' conformations. The structure of diketone **5a** was ultimately confirmed by X-ray analysis (Figure 1).†

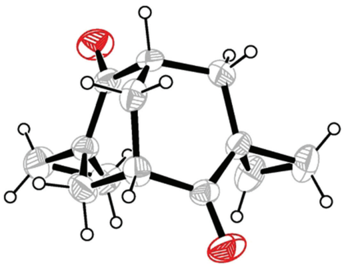


Figure 1 The molecular structure of **5a**. Displacement ellipsoids are drawn at the 50% probability level, H atoms presented as spheres with arbitrary radius.

In summary, a series of novel bicyclo[3.3.1]nonanones and bicyclo[3.3.1]nonanediones containing spiro-annulated cyclopropane moieties was accessed by oxidation of the corresponding hydrocarbons. The most selective and convenient oxidative system for this transformations was found to be RuO_4, generated *in situ*. The prepared cyclopropyl ketones are of interest as promising precursors for subsequent heterocyclizations.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.05.005.

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† *Crystal data for* **5a**. $C_{13}H_{16}O_2$ (M = 204.26), orthorhombic, space group *Fdd*2, at 295(2) K: a = 20.8300(13), b = 8.2415(5) and c = 12.6487(8) Å, V = 2171.4(2) Å^3, Z = 8, d_{calc} = 1.250 g cm^{-3}, μ = 0.658 mm^{-1}, F(000) = 880. Total of 5345 reflections were collected [981 independent reflections, R_{int} = 0.0303 (without absorption correction)] and used in the refinement, which converged to wR_2 = 0.0783, GOOF 0.957 for all independent reflections [R_1 = 0.0305 was calculated for 808 reflections with $I > 2\sigma(I)$]. Single crystals suitable for X-ray diffraction were obtained by slow evaporation of the solvent from a propan-2-ol solution of **5a**. Intensity data were collected on a Stoe STADI VARI diffractometer using focusing mirrors monochromated CuKα radiation, λ = 1.54186 Å. The data were corrected for decay, Lorentz, and polarization effects as well as absorption and beam corrections based on the multi-scan technique. The structure was solved by a combination of direct methods in SHELXS-97 and the difference Fourier technique, and refined by full-matrix least-squares procedures (SHELXL-2014/7). Non hydrogen atoms were refined with anisotropic displacement parameters. The H-atoms were calculated and subsequently treated with a riding model.

CCDC 2061507 contains 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.

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