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PII: S0040-4039(14)01943-1
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.11.050
Reference: TETL 45434

To appear in: *Tetrahedron Letters*

Received Date: 19 September 2014
Revised Date: 4 November 2014
Accepted Date: 13 November 2014

Please cite this article as: Ryabukhin, S.V., Fominova, K.I., Sibgatulin, D.A., Grygorenko, O.O., Synthesis of three-dimensional fused and spirocyclic oxygen-containing cyclobutanone derivatives, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.11.050

Graphical Abstract

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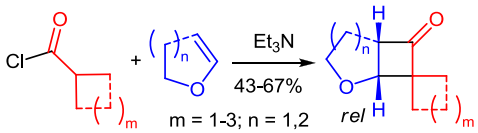

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Synthesis of three-dimensional fused and spirocyclic oxygen-containing cyclobutanone derivatives

Sergey V. Ryabukhin,[a] Kateryna I. Fominova,[a] Dmitriy A. Sibgatulin,[b] Oleksandr O. Grygorenko[a]*

[a]*National Taras Shevchenko University of Kyiv, Volodymyrska Street, 64, Kyiv 01601, Ukraine*
[b]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, Kyiv 02660, Ukraine*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

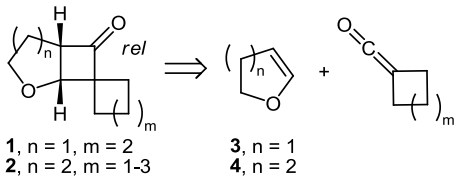
Keywords:
Three-dimensional frameworks
Cyclobutanes
[2+2] Cycloaddition
Oxygen heterocycles
Spiro compounds

ABSTRACT

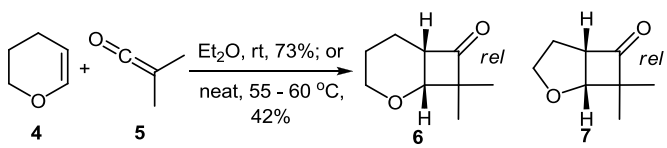
An approach to fused and spirocyclic oxygen-containing cyclobutanone derivatives based on ketene [2+2] cycloaddition with vinyl ethers is described. Using alicyclic chloroanhydrides as ketene sources as well as cyclic vinyl ethers in the reaction resulted in the formation of three-dimensional conformationally restricted building blocks of interest to medicinal chemistry and organic synthesis. In particular, 2-oxaspiro(bicyclo[3.2.0]heptane-7,1'-cycloalkane)-6-ones and 2-oxaspiro(bicyclo[4.2.0]octane-8,1'-cycloalkane)-6-ones were obtained. The procedure involves readily available and inexpensive starting materials and allows construction of complex molecular architectures on large scale in a single run.

Fused and spirocyclic ring systems are the key structural elements of numerous important organic molecules, including many natural products and marketed drugs. Many synthetic efforts in heterocyclic chemistry have been directed towards the synthesis of heteroaromatic ring systems; apart from certain cases such as steroid-like molecules and some other natural products, fused and spirocyclic heteroaliphatic frameworks have received less attention. The situation has since changed and recent trends in medicinal chemistry have shifted towards three-dimensional scaffolds as the central cores of potential drugs.[1] Conformationally restricted templates, including spirocyclic ones, have advantages for drug discovery, since, due to their pre-organizaion, they have increased chance of potent and selective binding with their biological targets. It is not surprising therefore, that spirocyclic heteroaliphatic molecules have attracted signifiacnt attention from synthetic and medicinal chemists.[2] Furthermore, special attention has been paid to oxygen-enriched molecules since it was shown that many compound collections have less oxygen content compared to natural products and marketed drugs.[3] Therefore, fused and spirocyclic ring systems based on saturated oxygen heterocycles are of particular interest.

In this work, we have turned our attention to fused and spirocyclic oxygen-containing ring systems based on the cyclobutanone motif, namely, 2-oxaspiro(bicyclo[3.2.0]heptane-7,1'-cycloalkane)-6-ones (**1**) and 2-oxaspiro(bicyclo[4.2.0]-octane-8,1'-cycloalkane)-6-ones (**2**). Since the classical method for the construction of the polysubstituted cyclobutanones relies on [2+2] cycloaddition with ketenes,[4] cyclic vinyl ethers **3** and **4** would be the starting materials of choice for the construction of ring systems **1** and **2**, respectively (Scheme 1). Surprisingly, vinyl ethers **3** and **4** are virtually unstudied in reactions with ketenes. Most of the literature involved reactions of 3,6-dihydro-2*H*-pyran (**4**) with more reactive aryl-substituted ketenes.[5] Only a single example described the [2+2]cycloaddition of **4** with gaseous dimethylketene (**5**) (generated by pyrolysis of either 1,1,3,3-trimethylcyclobutanedione[6] or isobutyryl anhydride[5a]), leading to 2-oxabicyclo[4.2.0]octane derivative **6** (Scheme 2).



Scheme 1.



Scheme 2.

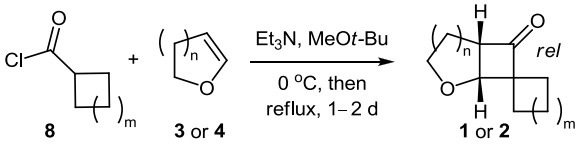
First of all, we have checked if compound **6** could be obtained using dimethylketene generated *in situ* from isobutyryl chloride and triethylamine. It was found that a complex mixture was obtained when a 1:1.5 ratio of **4** and **5** (as described by Martin and co-workers[5a]) was used. We found that compound **6** did form

* Corresponding author. Tel.: +38-044-239-3315; fax: +38-044-573-2643; e-mail: gregor@univ.kiev.ua

in a substantial amount in the presence of at least a three-fold excess of **4**; increasing the ratio of **4** and **5** further improved the reaction outcome, such that when using a 10:1 ratio of the starting materials, the isolated yield of **6** was 43% (after fractional distillation)[7] – a result very similar to that obtained by Krapcho and Lesser.[6] The method was also amenable to the preparation of adduct **7**[8] (64% yield) starting from 2,3-dihydrofuran (**3**).

It was found that the procedure was efficient with alicyclic acyl chlorides **8b–d**: the corresponding fused and spirocyclic cyclobutanones **1** and **2** were obtained in 56–67% yields (Table 1). No product **2a** was formed in the reaction of cyclopropanecarbonyl chloride (**8a**) and **4**; obviously, the corresponding ketene was too strained to be formed efficiently under the reaction conditions.

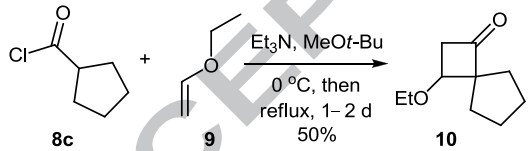
Table 1. Synthesis of fused, spirocyclic cyclobutanones **1** and **2**



Entry	Starting materials[a]	m	n	Product	Yield (%)	Ref.
1	**8c** + **3**	2	1	**1c**	56	9
2	**8a** + **4**	0	2	**2a**	0	–
3	**8b** + **4**	1	2	**2b**	57	10
4	**8c** + **4**	2	2	**2c**	62	11
5	**8d** + **4**	3	2	**2d**	67	12

[a] Ratio of **8**, **3**(**4**) and Et_3N = 1:10:1.3

Since alicyclic ketenes have rarely been used in reactions with vinyl ethers previously,[13] we also checked if the method worked with acyclic substrates, namely, ethyl vinyl ether (**9**) (Scheme 3). Reaction of **9** with the ketene generated from **8c** gave the corresponding adduct **10** in 50% yield.[14]



Scheme 3.

In conclusion, a convenient method for the preparation of oxygen-containing fused and spirocyclic cyclobutanone derivatives, in particular, 2-oxaspiro(bicyclo[3.2.0]heptane-7,1'-cycloalkane)-6-ones and 2-oxaspiro(bicyclo[4.2.0]octane-8,1'-cycloalkane)-6-ones, is described. The procedure involves readily available and inexpensive starting materials and could be scaled up to prepare 100 g of the product in a single run. The building blocks obtained are of particular interest in medicinal chemistry as three-dimensional scaffolds for the generation of lead-like libraries, as well as in other areas of chemistry as versatile synthetic intermediates.

Acknowledgments

The authors thank Mr. Dmytro Granat for his help with synthetic experiments.

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7. General procedure for the [2+2] cycloadditions: To a solution of the vinyl ether **3**, **4**, or **9** (20 mol) in dry methyl *tert*-butyl ether (1.8 L), Et_3N (2.6 mol) was added. The reaction mixture was cooled to 0 °C and the acyl chloride (2 mol) was added dropwise at this temperature with stirring. The resulting mixture was stirred at rt for 0.5 h and at reflux for 1–2 d. The precipitate was filtered off, and the filtrate was washed with H_2O (0.5 L), sat. aq $NaHCO_3$ (0.5 L), and brine (0.5 L), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was subjected to fractional distillation in *vacuo* to give the corresponding cyclobutanones **1**, **2**, **6**, **7**, or **10**.
8. 7,7-Dimethyl-2-oxa-bicyclo[3.2.0]heptan-6-one (**7**). Yield 13.5 g (64%). Colorless liquid. Bp 42–43 °C / 1 mmHg. Anal. Calcd for $C_8H_{12}O_2$ C 68.55, H 8.63. Found C 68.38, H 8.84. MS (EI, *m/z*): 140 (M^+), 112, 97, 70, 41. ^{1}H NMR (500 MHz, DMSO-d_6), δ 4.32 (d, J = 5.8 Hz, 1H), 4.09 (ddd, 9.1 Hz, 6.0 Hz and 1.3 Hz, 1H), 4.01 (td, J = 8.4 Hz and 2.9 Hz, 1H), 3.70–3.63 (m, 1H), 2.04–1.98 (m, 1H), 1.89–1.78 (m, 1H), 1.14 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 217.6, 79.6, 69.6, 60.9, 60.7, 27.8, 21.6, 14.2.
9. 2-Oxaspiro[bicyclo[3.2.0]heptane-7,1'-cyclopentan]-6-one (**1c**): Yield 11.3 g (56%). Colorless liquid. Bp 50–52 °C / 0.07 mmHg. Anal. Calcd for $C_{10}H_{14}O_2$ C 72.26, H 8.49. Found C 72.53, H 8.28. MS (EI, *m/z*): 166 (M^+), 138, 98. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.38 (d, J = 5.7 Hz, 1H), 4.04 (t, J = 8.4 Hz, 1H), 3.82 – 3.75 (m, 1H), 3.67 – 3.58 (m, 1H), 2.16 – 2.08 (m, 1H), 1.90 – 1.79 (m, 2H), 1.79 – 1.70 (m, 2H), 1.70 – 1.55 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 218.8, 79.6, 71.1, 68.6, 61.5, 35.9, 28.4, 26.3, 25.8, 25.5.
10. 2-Oxaspiro[bicyclo[4.2.0]octane-8,1'-cyclobutan]-7-one (**2b**): Yield 12.5 g (57%). Colorless liquid. Bp 54–55 °C / 0.08 mmHg. Anal. Calcd for $C_{10}H_{14}O_2$ C 72.26, H 8.49. Found C 72.40, H 8.71. MS (EI, *m/z*): 166 (M^+), 138, 110, 84. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.09 (d, J = 5.5 Hz, 1H), 3.73 (d, J = 10.9 Hz, 1H), 3.23 (td, J = 11.2, 3.2 Hz, 1H), 3.06 (t, J = 5.6 Hz, 1H), 2.28 – 2.18 (m, 1H), 2.16 – 2.03 (m, 3H), 2.00 – 1.93 (m, 1H), 1.93 – 1.78 (m, 2H), 1.56 – 1.45 (m, 1H), 1.44 – 1.32 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 70.9, 65.0, 64.4, 52.3, 29.2, 21.8, 20.9, 18.0, 15.8.
11. 2-Oxaspiro[bicyclo[4.2.0]octane-8,1'-cyclopentan]-7-one (**2c**): Yield 10.8 g (62%). Colorless liquid. Bp 63–64 °C / 0.1 mmHg. Anal. Calcd for $C_{11}H_{16}O_2$ C 73.30, H 8.95. Found C 73.09, H 9.24. MS (EI, *m/z*): 180 (M^+), 152, 96. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.96 (d, J = 5.7 Hz, 1H), 3.76 (d, J = 11.0 Hz, 1H), 3.29 – 3.19 (m, 2H), 2.09 – 1.99 (m, 1H), 1.91 – 1.83 (m, 1H), 1.83 – 1.64 (m,

4H), 1.64 – 1.48 (m, 4H), 1.48 – 1.34 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.8, 72.4, 71.9, 64.4, 53.6, 35.6, 25.9, 25.4, 25.2, 21.8, 18.2.

12. 2-Oxaspiro[bicyclo[4.2.0]octane-8,1'-cyclohexan]-7-one (**2d**): Yield 14.6 g (67%). Colorless liquid. Bp 70–71 °C / 0.09 mmHg. Anal. Calcd for $C_{12}H_{18}O_2$ C 74.19, H 9.34. Found C 73.88, H 9.62. MS (EI, *m/z*): 194 (M^+), 166, 110. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.10 (d, *J* = 6.1 Hz, 1H), 3.79 (d, *J* = 11.0 Hz, 1H), 3.29 (t, *J* = 6.3 Hz, 1H), 3.24 (td, *J* = 11.1, 2.4 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.76 – 1.28 (m, 13H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9, 70.2, 67.7, 64.4, 51.4, 32.4, 25.3, 24.8, 22.6, 22.6, 21.9, 18.1.
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14. 3-Ethoxyspiro[3.4]octan-1-one (**10**): Yield 12.3 g (50%). Colorless liquid. Bp 36–38 °C / 0.1 mmHg. Anal. Calcd for $C_{10}H_{16}O_2$ C 71.39, H 9.59. Found C 71.06, H 9.63. MS (CI, *m/z*): 169 (MH^+). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (dd, *J* = 6.9, 5.6 Hz, 1H), 3.54 – 3.38 (m, 2H), 3.11 (dd, *J* = 17.6, 6.9 Hz, 1H), 2.91 (dd, *J* = 17.6, 5.5 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.95 – 1.85 (m, 1H), 1.74 – 1.55 (m, 6H), 1.21 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.2, 73.2, 72.5, 64.9, 50.5, 34.5, 28.1, 25.8 (2C), 14.9.