TRANSFORMATION OF HYDROXYCYCLOALKANONES TO OXABICYCLOALKENES

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Abstract – Oxabicycloalkenes, which represent anti-Bredt enol ethers, can be generated by catalytic dehydration of the hemiacetals of hydroxycycloalkanones (Method I). Another option is provided by the transformation of hydroxycycloalkanones to the corresponding 1,2,3-selenadiazoles and their thermal fragmentation on Cu powder (Method II). The intermediate hydroxycycloalkynes show a transannular addition of the OH group to the triple bond. Altogether seven new oxabicycloalk-1-enes were obtained by this methods.

In recent years an increasing number of natural products and closely related synthetic analogues, which have the structures of oxabicycloalk-1-enes with an anti-Bredt enol ether functionality, have been studied. The majority of them has the scaffold of 10-oxabicyclo [4.3.1]dec-1(9)-enes or 11-oxabicyclo[6.2.1]undec-1(10)-enes. Another interesting realization of such enol ether structures was achieved in the series of fullerenes. The preparation of these compounds requires multistep syntheses in which the formation of a strained enol ether double bond is a special challenge. Bridgehead olefins with this substructure can have pyramidalized and/or twisted double bonds.

Hydroxycycloalkanones provide an easy access to anti-Bredt enol ethers. Scheme 1 summarizes the possible reaction routes. The cyclic hemiacetals, tautomers of 1, can be catalytically dehydrated to 11 and 12 (route I). Alternatively, 1 can be transformed to the stereoisomeric semicarbazones 2/3, for which cyclic tautomers 4 exist as well. The subsequent ring closure reaction with SeO₂ yields the 1,2,3-selenadiazoles 5/6. The regioselectivity of the ring closure does not depend on the preferred isomer 2, 3 or 4. Thermal cleavage of 5/6 on cupper powder gives the hydroxycycloalkynes 7/9, which perform transannular addition reactions: 7 → 10, 11 and 9 → 12, 13 (route II). Symmetric ketones (m = n) yield only one enol ether 11=12 and only one semicarbazone 2=3, selenadiazole 5=6 and hydroxycycloalkyne.
7->9, but then two transannular addition products 10<13 and 11<12 can be formed. Two enol ethers can result in the case \( n = m-1 \) (7 \( \rightarrow \) 10\( \rightarrow \)11) and (9 \( \rightarrow \) 12\( \rightarrow \)13). In all other cases (\( m-n > 1 \)), the ketones 1 can serve for the generation of four isomeric oxabicycloalkenes 10–13. Of course, steric and/or electronic effects can influence the regioselectivity in all unsymmetrical cases, and can lead to uniform products.

The \( \beta \)-elimination of H\(_2\)O can be performed by heating 1a-d \( \subseteq \) 8a-d\(^{1,9} \) in the presence of catalytic amounts of \( p \)-toluenesulfonic acid to 90-120 °C at 1 kPa (Scheme 2). In a typical procedure, 5-6 mmol of starting compound was treated with 10 mg (0.05 mmol) \( p \)-toluenesulfonic acid monohydrate. The generated water was removed under reduced pressure, so that the reverse reaction, the addition of water to the reactive double bond of the \( anti \)-Bredt enol ether, can not take place. The \( anti \)-Bredt enol ethers were then condensed in a cold trap. The residue contains bimolecular condensation products, derived from two molecules 1 or from 1 and 8.\(^{1} \) These competing reactions decrease the yields - in particular for the smaller and therefore more strained enol ethers. Due to symmetry reasons, the reactions of 8a and 8d are leading to single enol ethers, whereas 8b and 8c generate the mixtures 11b/12b and 11c/12c, respectively.

**Scheme 1.** Generation of oxabicycloalkenes 10-13 from hydroxycycloalkanones 1 by route I: 1 \( \subseteq \) 8 \( \rightarrow \) 11, 12 or route II: 1 \( \subseteq \) 8 \( \rightarrow \) 2/3 \( \subseteq \) 4 \( \rightarrow \) 5/6 \( \rightarrow \) 7/9 \( \rightarrow \) 10-13: (a) H\(_2\)N-NH-CONH\(_2\), H\(^+\); (b) SeO\(_2\); (c) 160-180 °C; (d) 180-200 °C; (e) 90-120 °C, cat.
However, the dehydration of 8b is highly regioselective in favor of 8b → 12b. Such a strong selectivity can not be found in the case 8c → 11c, 12c.

Scheme 2. Monomolecular elimination (method I) of H₂O from the hemiacetals 8, which are in equilibrium with the corresponding hydroxycycloalkanones 1: 8a ≡ 1a⁴, 8b ≡ 1b⁵, 8c ≡ 1c⁶, 8d ≡ 1d⁷ (Method A: 90-120 °C, 1-3 kPa, 0.01 equivalent of p-toluene-sulfonic acid)

Method II in Scheme 1 makes use of the transannular addition of hydroxy groups to triple bonds in cycloalkynols.⁹⁰ Scheme 3 summarizes the generation of 10b, 10d, 10e, 11d, 11e, 12b and 13b. The corresponding hydroxycycloalkanones 1 are transformed via the (Z/E)-semicarbazones 2/3 and their bicyclic isomers 4 to the 1,2,3-selenediazoles 5 and/or 6. Thermal cleavage of 5 and/or 6 on Cu powder yields at 160-180 °C the hydroxycycloalkynes 7 and/or 9. At 180-200 °C, the resulting anti-Bredt enol ethers are formed in situ by the quantitative isomerization 7/9 → 10−13. It is not necessary to isolate the hydroxycycloalkynes. The copper powder enhances the yields of the alkynes. It has no influence on the transannular cyclization.

1,2,3-Selenediazole 5e¹¹ was obtained in a yield of 90% by reaction of the corresponding oxo-compound¹² and H₃CMgCl. 5-Hydroxycyclonanone 1b yielded via its semicarbazone 2b/3b/4b 44% of a 80:20 mixture of the 1,2,3-selenediazoles 5b and 6b.¹³ Accordingly, 6-hydroxycyclodecanone 1d furnishes 47% of 1,2,3-selenediazole 5d.¹⁴
The hydroxycycloalkynes (7b,d,e; 9b) and the oxabicycloalkenes (10b,d,e; 11a,c,d,e; 12b,c; 13b) are colorless oils. To our best knowledge, 7b, 7e, 9b, and 10b, 10e, 11c, 11e, 12b, 12c and 13b are new compounds. The separation of enol ether mixtures by GC or HPLC seems to be feasible. We succeeded in the separation of 11c and 12c by column chromatography on SiO$_2$. However, a contact of pure 11c or 12c with SiO$_2$ in CDCl$_3$ over several days led again to a catalytic equilibration ($11c : 12c = 45 : 55$).

**Scheme 3.** Thermal fragmentation of the 1,2,3-selenediazoles on Cu powder. Method A (160-180 °C, $10^{-2}$-$10^{-1}$ kPa) leads to the hydroxycycloalkynes. Method B (180-200 °C, $10^{-2}$-$10^{-1}$ kPa) leads directly to the oxabicycloalkenes

Table 1 summarizes the characteristic NMR data of the hydroxycycloalkynes and the oxabicycloalkenes. The $\delta^{13}C$ values of the olefinic double bonds in the *anti*-Bredt compounds show a significant variation. High $\delta$ values for both olefinic carbon atoms were found for the systems 11a and 11e.
which have the highest strain. The double bond has therein trans configuration related to the 8-membered ring and cis configuration related to the 6-membered ring. The column RS in Table 1 contains the size of the rings in which the double bonds have trans configuration. Compared to normal enol ethers, such as (Z)-2-methoxy-2-butene, β-C has in 11a a δ value of 120.0 ± 0.3 ppm, which is about 17 ppm downfield shifted. We attribute this effect to a low interaction of the p(π) orbital with the olefinic π bond, that means to a low electron density on β-C. A complete correlation of the 1H and 13C chemical shifts is given for 12b in Figure 1.

Table 1. Characteristic 1H and 13C NMR data of the hydroxycycloalkynes 7, 9 and the oxabicycloalkenes 10-13 (δ values in CDCl3, TMS as internal standard)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>RS</th>
<th>C=CR</th>
<th>CHO</th>
<th>Compd.</th>
<th>RS</th>
<th>=CH</th>
<th>=CO</th>
<th>CHO</th>
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<tr>
<td>11a</td>
<td>8</td>
<td>5.70</td>
<td>4.65</td>
<td>120.3</td>
<td>159.0</td>
<td>79.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7e</td>
<td>8</td>
<td></td>
<td>–</td>
<td>95.5, 96.3</td>
<td>73.4</td>
<td>111.8</td>
<td>157.0</td>
<td>74.9</td>
</tr>
<tr>
<td>11e</td>
<td>8</td>
<td>5.65</td>
<td>–</td>
<td>119.8</td>
<td>160.6</td>
<td>84.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7b</td>
<td>9</td>
<td>4.11</td>
<td>4.11</td>
<td>88.8, 88.8</td>
<td>74.7</td>
<td>111.3</td>
<td>154.0</td>
<td>76.1</td>
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<tr>
<td>9b</td>
<td>9</td>
<td>3.94</td>
<td>12b</td>
<td>87.6, 88.0</td>
<td>71.8</td>
<td>109.7</td>
<td>155.3</td>
<td>72.6</td>
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<tr>
<td>13b</td>
<td>9</td>
<td>4.48</td>
<td>4.10</td>
<td>109.3</td>
<td>154.9</td>
<td>75.6</td>
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<tr>
<td>11c</td>
<td>10</td>
<td>5.02</td>
<td>4.12</td>
<td>111.9</td>
<td>151.9</td>
<td>80.4</td>
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<tr>
<td>12c</td>
<td>10</td>
<td>4.72</td>
<td>4.02</td>
<td>102.2</td>
<td>151.7</td>
<td>72.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7d</td>
<td>10</td>
<td>4.25</td>
<td>10d</td>
<td>84.4, 84.9</td>
<td>69.6</td>
<td>111.9</td>
<td>151.9</td>
<td>80.4</td>
</tr>
<tr>
<td>11d</td>
<td>10</td>
<td>5.10</td>
<td>4.00</td>
<td>113.2</td>
<td>156.3</td>
<td>74.5</td>
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Figure 1. $^1$H and $^{13}$C NMR data of 10-oxabicyclo[4.3.1]dec-1(9)ene (12b); $\delta(^1H)/\delta(^{13}C)$ values in CDCl$_3$, TMS as internal standard. The numbers in parentheses indicate the $^1J$ (C,H) coupling constants in Hz. The assignment of the signals is based on homo- and heteronuclear shift correlations and on NOE measurements.

REFERENCES AND NOTES


3. In the case of 1b/8b (Scheme 2), column chromatography (SiO$_2$, petroleum ether (bp 40-70 °C) /EtOAc 2:1) gave 17% of bis(5-oxocyclononanyl)ether as colorless oil [${^{13}}$C NMR (CDCl$_3$): $\delta = 217.6$ (CO), 74.3 (CHO), 43.8, 42.5, 31.9, 28.8, 23.8, 22.5, 20.4 (CH$_2$)] and 21% of 5-(10-oxabicyclo[4.3.1]dec-1-yloxy)cyclononanone as colorless oil [${^{13}}$C NMR (CDCl$_3$): $\delta = 217.5$ (CO), 97.5 (OC$_q$O), 74.3, 72.0 (CHO), 43.8, 42.5, 36.6, 35.5, 32.0, 29.8, 28.8, 27.4, 23.8, 22.5, 21.0, 20.4, 19.6, 17.3.


6. Obtained by oxidation of cyclodecane-1,5-diol.\(^7\)


11. 5e: Viscous oil; $^1$H NMR (CDCl$_3$): $\delta = 3.55-3.00$, m, 4H/2.20-1.85, m, 3H/1.85-1.28, m, 5H (CH$_2$), 1.27 (s, 3H, CH$_3$). $^{13}$C NMR (CDCl$_3$): $\delta = 160.6$, 157.0 (heteroaromat. C), 73.0 (C$_q$O), 40.9, 35.4, 25.3, 24.3, 23.9 (CH$_2$), 31.6 (CH$_3$). $^{77}$Se NMR (CDCl$_3$) : $\delta = 219.7$. MS (FD): $m/z$ (%) = 247 [M + H$^+$, Se isotope pattern].


13. 5b: Viscous oil; $^1$H NMR (CDCl$_3$): $\delta = 3.69$ (m, 1H, CH), 3.22 (m, 2H, CH$_2$), 3.05 (m, 2H, CH$_2$), 2.26 (br. s, 1H, OH), 2.00-1.30 (m, 8H, 4CH$_2$). $^{13}$C NMR (CDCl$_3$): $\delta = 161.2$, 160.2 (heteroaromat. C), 70.7 (CHO), 33.7, 32.1, 27.8, 26.4, 24.4, 22.5 (CH$_2$). MS (EI): $m/z$ (%) = 246 (2, M$^+$, Se pattern), 137.
(44), 116 (100); $6b$: viscous oil; $^1$H NMR (CDCl$_3$): $\delta = 3.74$ (m, 1H, CH), 3.17 (m, 2H, CH$_2$), 3.05 (m, 2H, CH$_2$), 2.48 (br. s, 1H, OH), 2.00-1.20 (m, 8H, 4CH$_2$). $^{13}$C NMR (CDCl$_3$): 161.2, 159.4 (heteroaromat. C), 70.4 (CHO), 37.1, 32.5, 27.0, 25.4, 21.2, 20.6 (CH$_2$).

14. $5d$: mp 101–103 $^\circ$C. $^1$H NMR (CDCl$_3$): $\delta = 3.91$ (m, 1H, CH), 3.20 (m, 3H), 3.05 (m, 1H), 1.95 (m, 1H), 1.89 (m, 2H), 1.63 (m, 2H), 1.48 (m, 2H), 1.38 (m, 1H), 1.33 (m, 1H), 1.15 (m, 1H), 1.02 (m, 1H) [7CH$_2$]. $^{13}$C NMR (CDCl$_3$): $\delta = 160.1$, 159.5 (heteroaromat. C), 69.8 (CHO), 33.7, 28.3, 27.2, 27.0, 26.1, 24.9, 19.5 (CH$_2$). $^{77}$Se NMR (CDCl$_3$): $\delta = 204.7$ (SeO$_2$ in H$_2$O: $\delta = 0$). $^{15}$N NMR (CDCl$_3$): $\delta = 88.8$, 80.5 (CH$_3$NO$_2$; $\delta = 0$). MS (EI): $m/z$ (%) = 261 (1) [M + H$^+$, Se isotope pattern], 151 (19), 133 (33), 91 (82), 81 (64), 67 (100).