HETEROCYCLES, Vol. 78, No. 9, 2009, pp. 2201 - 2208. © The Japan Institute of Heterocyclic Chemistry
Received, 8th April, 2009, Accepted, 21st May, 2009, Published online, 21st May, 2009.
DOI: 10.3987/COM-09-11728

TRANSFORMATION OF HYDROXYCYCLOALKANONES TO OXABICYCLOALKENES

Guido Krämer, Heiner Detert, and Herbert Meier*

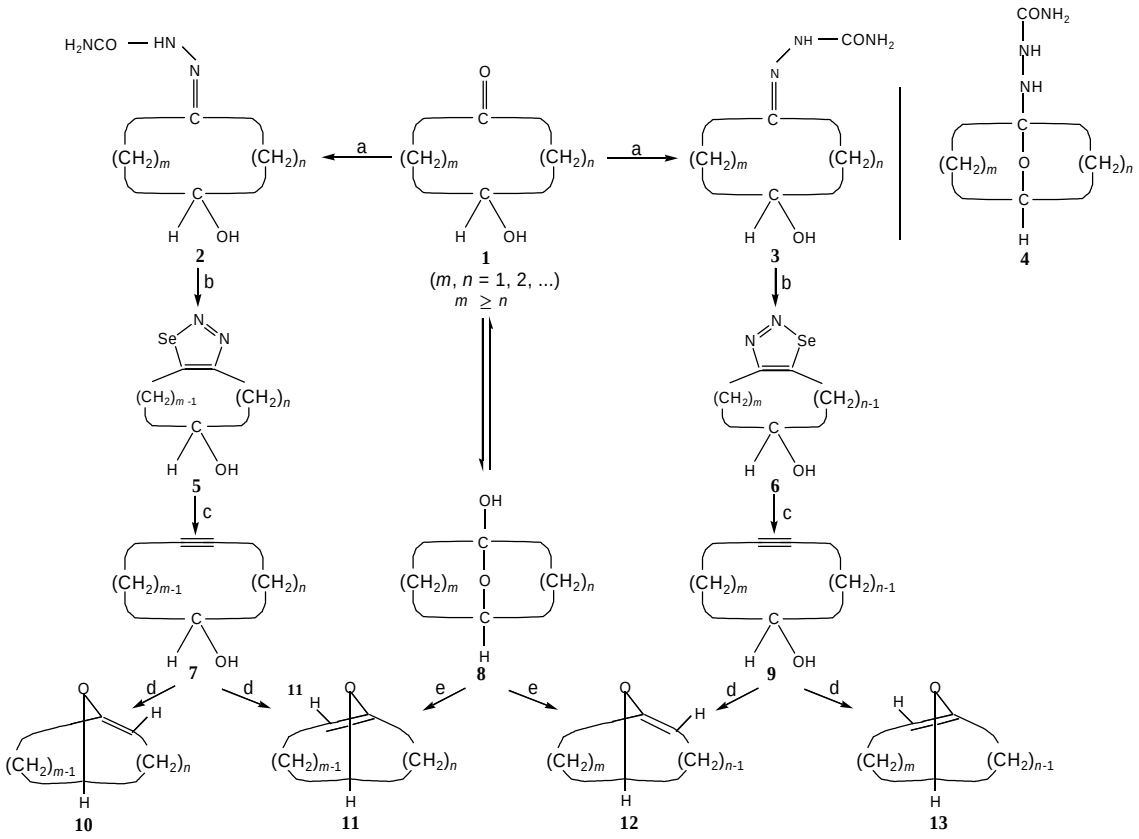
Institute of Organic Chemistry, University of Mainz, Duesbergweg 10-14, D-55099 Mainz, Germany
e-mail: hmeier@mail.uni-mainz.de

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.[1] The majority of them has the scaffold of 10-oxabicyclo [4.3.1]dec-1(9)-enes[1a,e,f,i,j,k,p] or 11-oxabicyclo[6.2.1]undec-1(10)-enes.[1c,d,l,m,n,r,t,u,v,w] Another interesting realization of such enol ether structures was achieved in the series of fullerenes.[2] The preparation of these compounds requires multi-step 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 **1** provide an easy access to *anti*-Bredt enol ethers. Scheme 1 summarizes the possible reaction routes. The cyclic hemiacetals **8**, tautomers of **1**, can be catalytically dehydrated to **11** and/or **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 SeO_2 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 **1** (*m* = *n*) yield only one enol ether **11**≡**12** and only one semicarbazone **2**≡**3**, selenadiazole **5**≡**6** and hydroxycycloalkyne

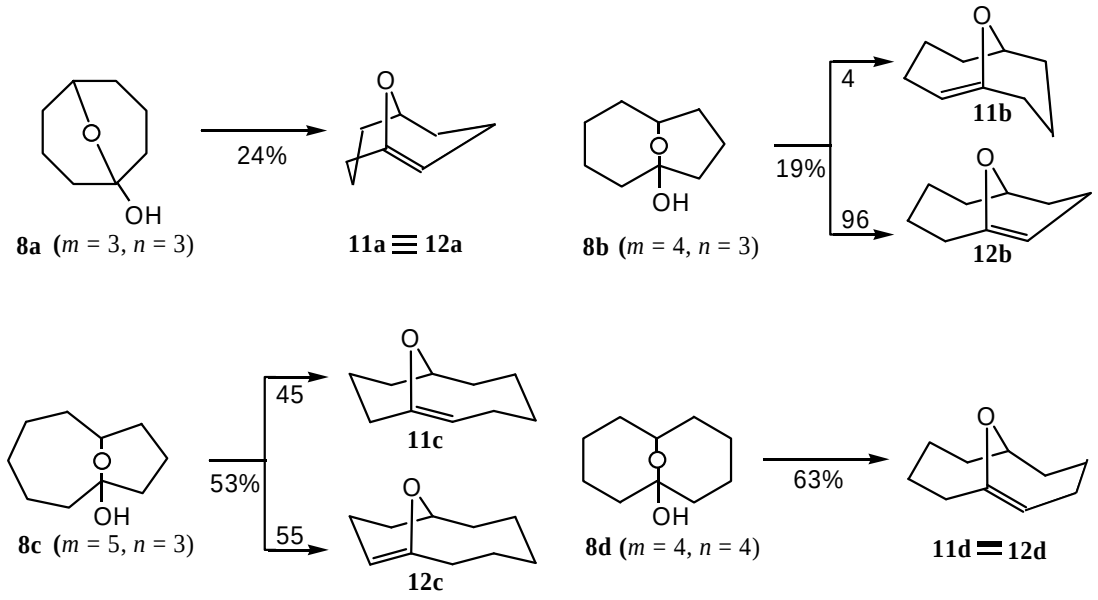
7≡9, but then two transannular addition products **10≡13** and **11≡12** can be formed. Two enol ethers can result in the case $n = m$-1 (**7** → **10≡11**) and (**9** → **12≡13**). In all other cases (m-n > 1), the ketones **1** can serve for the generation of four isomeric oxabicycloalkenes **10**–**13**. Of course, steric and/or electronic effects can influence the regioselectivity in all unsymmetrical cases, and can lead to uniform products.



Scheme 1. Generation of oxabicycloalkenes **10**-**13** from hydroxycycloalkanones **1** by route I: **1** ⇄ **8** → **11**, **12** or route II: **1** ⇄ **8** → **2**/**3** ⇄ **4** → **5**/**6** → **7**/**9** → **10**-**13**: (a) H_2N-NH-$CONH_2$, H^+; (b) SeO_2; (c) 160-180 °C; (d) 180-200 °C; (e) 90-120 °C, cat.

The β-elimination of H_2O can be performed by heating **1a-d** ⇄ **8a-d**[4-9] 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**.[3] 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.

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**.

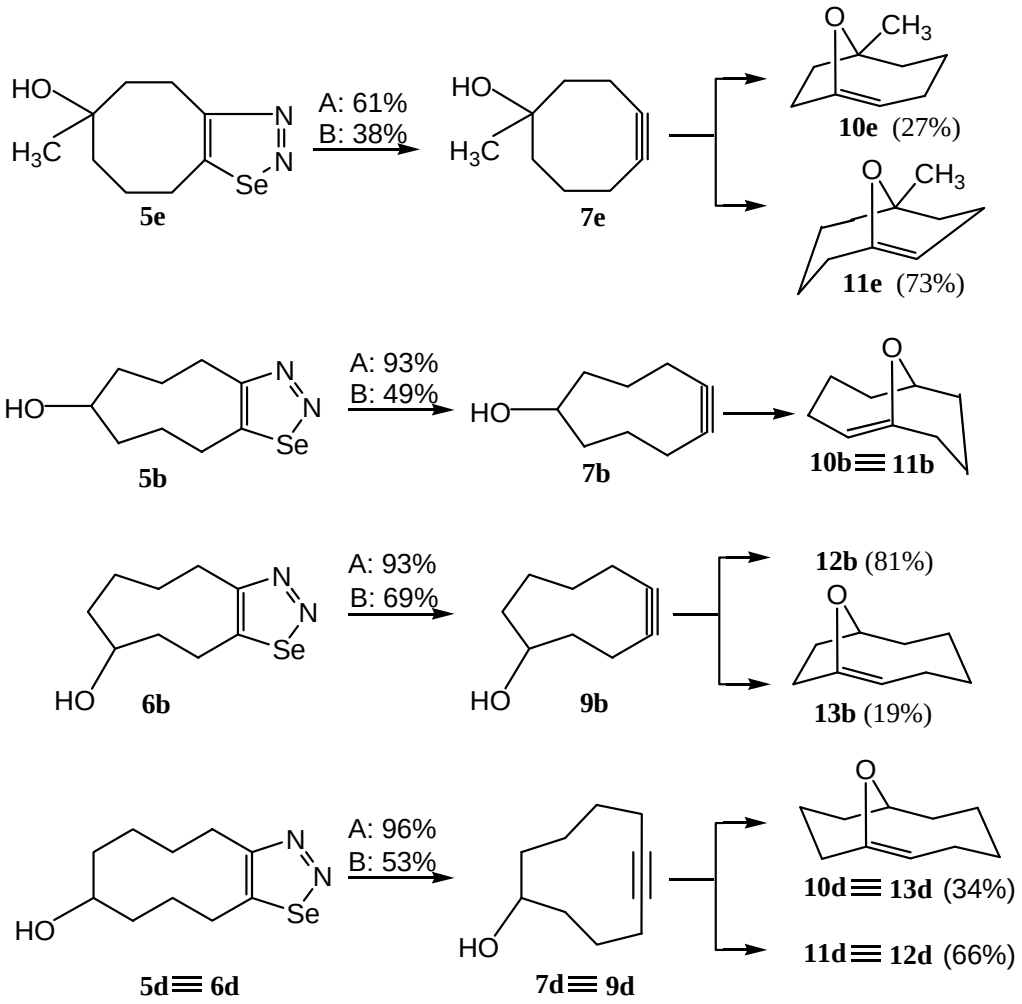


Scheme 2. Monomolecular elimination (method I) of H_2O from the hemiacetals **8**, which are in equilibrium with the corresponding hydroxycycloalkanones **1** : **8a** ⇄ **1a**[4], **8b** ⇄ **1b**[5], **8c** ⇄ **1c**[6,7], **8d** ⇄ **1d**[8] (Method A: 90-120 °C, 1-3 kPa, 0.01 equivalent of *p*-toluene-sulfonic acid

Method II in Scheme 1 makes use of the transannular addition of hydroxy groups to triple bonds in cycloalkynols.[10] 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 cupper powder enhances the yields of the alkynes. It has no influence on the transannular cyclization.

1,2,3-Selenediazole **5e**[11] was obtained in a yield of 90% by reaction of the corresponding oxo-compound[12] and H_3CMgCl. 5-Hydroxycyclononanone **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 ^{o}C, 10^{-2} -10^{-1} kPa) leads to the hydroxycycloalkynes. Method B (180-200 ^{o}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 δ 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[15], *β*-C has in **11a**,**e** a δ value of 120.0 ± 0.3 ppm, which is about 17 ppm down-field shifted. We attribute this effect to a low interaction of the p(O) orbital with the olefinic π bond, that means to a low electron density on *β*-C. A complete correlation of the ^{1}H and ^{13}C chemical shifts is given for **12b** in Figure 1.

Table 1. Characteristic ^{1}H and ^{13}C NMR data of the hydroxycycloalkynes **7**, **9** and the oxabicycloalkenes **10**-**13** (δ values in $CDCl_3$, TMS as internal standard)

Compd.	RS	C≡C	CHO	Compd.	RS	=CH	=CO	CHO
11a	8	5.70	4.65					
120.3	159.0	79.5						
7e	8		–	**10e**	8	4.84		–
95.5, 96.3	73.4			111.8	157.0	74.9		
11e	8	5.65	–					
119.8	160.6	84.9						
7b	9		4.11	**10b**	9	4.98		4.07
88.8, 88.8	74.7			111.3	154.0	76.1		
9b	9		3.94	**12b**	9	5.17		4.14
87.6, 88.0	71.8			109.7	155.3	72.6		
13b	9	4.48	4.10					
109.3	154.9	75.6						
11c	10	5.02	4.12					
111.9	151.9	80.4						
12c	10	4.72	4.02					
102.2	151.7	72.7						
7d	10		4.25	**10d**	10	5.02		4.12
84.4, 84.9	69.6			111.9	151.9	80.4		
11d	10	5.10	4.00					
113.2	156.3	74.5						

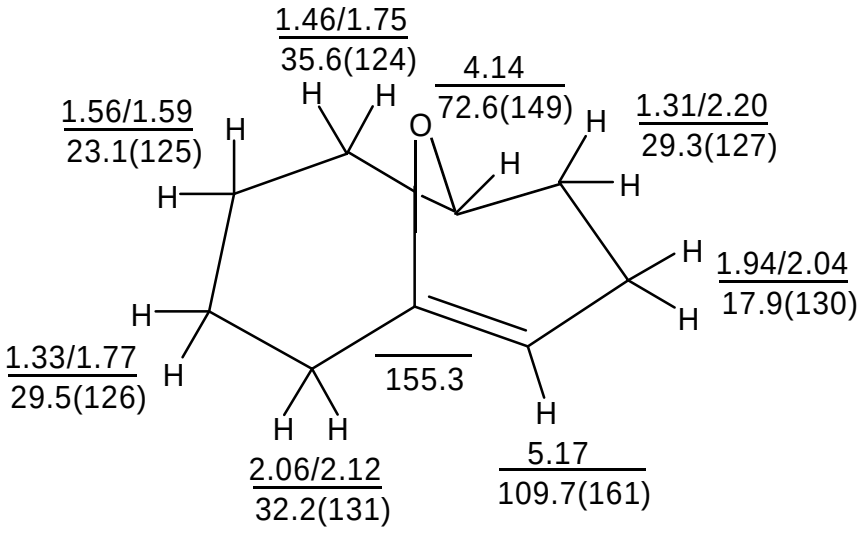


Figure 1. ^{1}H and ^{13}C NMR data of 10-oxabicyclo[4.3.1]dec-1(9)ene (**12b**); δ(^{1}H)/δ(^{13}C) values in $CDCl_3$,TMS as internal standard. The numbers in parentheses indicate the ^{1}J (C,H) coupling constants in Hz. The assignment of the signals is based on homo- and heteronuclear shift correlations and on NOE measurements

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3. In the case of **1b/8b** (Scheme 2), column chromatography (SiO_2, petroleum ether (bp 40-70 ^oC) /EtOAc 2:1) gave 17% of bis(5-oxocyclononanyl)ether as colorless oil [^{13}C NMR ($CDCl_3$): δ = 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 ($CDCl_3$): δ = 217.5 (CO), 97.5 (OC_qO), 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.
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11. **5e**: Viscous oil; ^1H NMR ($CDCl_3$): δ = 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 ($CDCl_3$): δ = 160.6, 157.0 (heteroaromat. C), 73.0 (C_qO), 40.9, 35.4, 25.3, 24.3, 23.9 (CH_2), 31.6 (CH_3). ^{77}Se NMR ($CDCl_3$) : δ = 219.7. MS (FD): *m*/*z* (%) = 247 [M + H^+, Se isotope pattern].
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13. **5b**: Viscous oil; ^1H NMR ($CDCl_3$): δ = 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 ($CDCl_3$): δ = 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 ($CDCl_3$): δ = 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 ^{o}C. ^{1}H NMR ($CDCl_3$): δ = 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 ($CDCl_3$): δ = 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 ($CDCl_3$): δ = 204.7 (SeO_2 in H_2O: δ = 0). ^{15}N NMR ($CDCl_3$): δ = 88.8, 80.5 (CH_3NO_2: δ = 0). MS (EI): *m*/*z* (%) = 261 (1) [M + H^+, Se isotope pattern], 151 (19), 133 (33), 91 (82), 81 (64), 67 (100).

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