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PET-Oxidative Cyclization of Unsaturated Silyl Enol Ethers. Regioselective Control by Solvent Effects.

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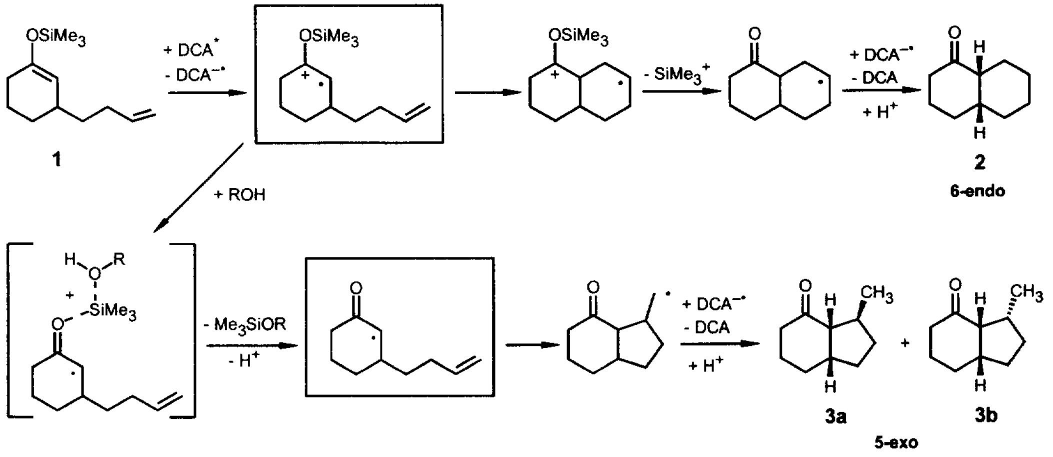
Abstract: Monocyclic silyl enol ethers tethered to an olefinic or a silylacetylenic side chain are irradiated in the presence of the electron transfer sensitizer 9,10-dicyanoanthracene (DCA). Cyclization of the initially formed silyloxy radical cations efficiently provides bicyclic and tricyclic ketones with definite stereochemistry. The *endo/exo* regiochemistry of the cyclization step can be controlled by addition of alcohol involving a radical cationic and a radical reaction pathway.

Radical ions generated by single-electron transfer from neutral compounds are known as important intermediates in a variety of interesting chemical processes and reactions. Cyclization reactions via radical cations are getting more and more popular for constructing carbocyclic and heterocyclic ring systems in a regio- and stereoselective fashion[1]. In contrast to the regioselective 1,5-ring closure (5-*exo*-trig cyclization) of the 5-hexenyl radical[2, 3], the analogous α,ω-diene radical cation cyclizes in a 6-*endo*-trig mode[4]. This often observed preference of 6-*endo*-trig cyclization is an important feature of the radical cationic cyclization reactions.



Scheme: Proposed mechanism of the PET-oxidative cyclization of **1**.

Especially substrates containing an electron-rich double bond, like enol ethers[5, 6] and enol acetates[7], and a non-activated double bond are shown to be promising starting materials for radical cationic cyclization reactions. The selective one-electron oxidation of the electron-rich double bond is easy to perform due to its lower oxidation potential[8].

Silyl enol ethers are easily oxidized either chemically[9, 10] or by means of photoinduced electron transfer (PET)[11, 12] under formation of silyloxy radical cations. We have recently reported that the PET-oxidative cyclization of various alkyl- and arylsubstituted 1-trimethylsilyloxy-1,6-heptadienes with a catalytic amount of sensitizer like DCA provides cyclohexenyl ketones as the result of 6-*endo* cyclization[11, 12].

We now report the results of the intramolecular PET-oxidative cyclization of monocyclic silyl enol ethers tethered to an olefinic or a silylacetylenic side chain. The starting materials are accessible by conjugate addition of alkenyl- and alkynyl Grignard reagents to cyclohex-2-en-1-one mediated by a catalytic amount of cuprous bromide dimethyl sulfide. Trapping the intermediate enolate with a silylating agent directly leads to 3-substituted 1-silyloxycyclohexenes[13].

A deoxygenated 0.05 M solution of the respective silyl enol ether containing about 15 mol % 9,10-dicyanoanthracene (DCA) is irradiated for at least 68 h at 419 nm in a Rayonet photochemical reactor fitted with a merry-go-round inset. Conversion and formation of products is monitored by GLC using *n*-decane as an internal standard. The products are isolated by HPLC.

Irradiation of 3-(3-butenyl)-1-trimethylsilyloxy-1-cyclohexene (**1**) in acetonitrile under oxidative PET-conditions provides bicyclic ketone *cis*-1-decalone (**2**) by 6-*endo* cyclization in an isolated yield of 25 %. Changing from pure acetonitrile to acetonitrile/alcohol as solvent we obtain an enhanced yield of cyclizied products of up to 64 %. The regioselectivity of the cyclization step changes towards 5-*exo* products, the *cis*-hexahydroindanone derivatives **3a** and **3b**.

Table 1: Irradiation of **1** under oxidative PET-conditions in MeCN/*i*-PrOH.

solvent ratio (MeCN/*i*-PrOH)	10 : 0	9 : 1	7 : 3	5 : 5	3: 7	1 : 9
endo/*exo* ratio **2**/(**3a**+**3b**)	1 : <0.2	1 : 0.9	1 : 2.1	1 : 3.1	1 : 4.0	1 : 4.9

Table 2: Irradiation of **1** under oxidative PET-conditions in MeCN/ROH (17:3).

ROH	–	*t*-BuOH	*i*-PrOH	*n*-PrOH	MeOH
isolated yields [%]					
2	25	27	30	13	14
3a, **3b**	–	11, 9	9, 11	12, 20	21, 29
total yield [%]	25	46	49	46	64
endo/*exo* ratio	–	1 : 0.7	1 : 0.7	1 : 2.4	1 : 3.6

Variation of the acetonitrile/*i*-propanol ratio and determination of the *endo*/*exo* ratio by GLC (table 1) show that changing from pure acetonitrile to acetonitrile/*i*-propanol (7:3) the formation of *cis*-1-decalone (**2**) only slidely changes, whereas the formation of 5-*exo* products **3a** and **3b** increases. At the solvent ratio of about 5:5 the maximum of total yield is reached. Irradiation in more than 50 % of *i*-propanol leads to enhanced formation of noncyclized ketone. Irradiation without sensitizer shows that this is predominantly due to the instability of **1** towards simple alcoholysis. In pure *i*-propanol almost no cyclization takes place. As shown in table 1 the *endo*/*exo* ratio changes from 1:<0.2 to 1:4.9.

Similar observations were made by using alcohols of different bulkiness. Irradiaton in the presence of *t*-butanol and *i*-propanol predominantly leads to 6-*endo* product, whereas in acetonitrile/methanol and acetonitrile/*n*-propanol 5-*exo* products are clearly favoured (table 2).

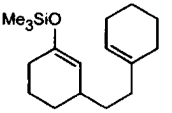
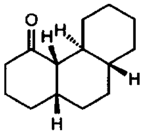
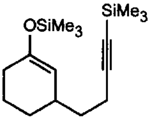
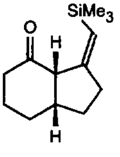
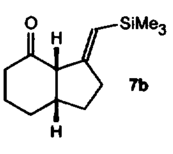
These experiments exhibit that the amount and the geometrical structure of the alcohol play an important role for the product ratio and therefore in the reaction mechanism. To our assumptions the alcohol acts as nucleophile and assists the dissoziation of the Si-O bond of the silyloxy radical cation[14]. This opens up two possible reaction pathways. On the one hand the silyloxy radical cation can cyclize in a 6-*endo* mode. Intramolecular attack and consequent desilylation lead to the product radical. On the other hand desilylation can take place before the cyclization step leading to α-keto-radicals as reactive intermediates. These cyclize according to Baldwin's rule in a 5-*exo* mode.

Deuterium labeling experiments with deuterated acetonitrile, partially deuterated methanol (MeCN/CH_3OD and MeCN/CD_3OH, respectively) and deuterated water (MeCN+10 eq. D_2O) show that only the presence of a D^+-donor leads to deuterated bicyclic ketones. This is a qualitative result by GC-MS coupling, but we can rule out that the deuterium is built in by the α-CH acidity of the ketones since the additionally formed noncyclized ketone is not deuterated. This result gives rise to the assumption that the final formation of the products occurs via back electron transfer, regenerating the DCA, followed by protonation. The alcohol presumably acts as proton donor, as well. This mechanism is also supported by the fact that a catalytic amount of DCA (15 %) is sufficient. A similar reaction mechanism has been established by Mariano concerning the oxidative cyclization of α-silylated amines[15].

Furthermore we successfully applied this PET-oxidative cyclization method to build up the tricyclic ketone **5**. The structure of dodecahydrophenanthren-4-one (**5**) has been confirmed by X-ray analysis[16]. Monocyclic silyl enol ethers tethered to a silylacetylenic side chain are also a promising entry for PET-oxidative cyclization. **6** undergoes ring-closure with a combined yields of the 5-*exo* products, the vinylsilane ketones **7a** and **7b**[17], of 47 %. For geometric reasons the linear triple bond obviously does not allow an attack on C-4, but on C-3 of the side chain. Similar observations have been reported by Snider in the radical cationic cyclization of alkynyl silyl enol ethers initiated by chemical one-electron oxidation[9].

An important feature of these cyclizations is the stereoselective ring juncture. In any case we obtain *cis*-connected rings, independent of the kinetical or thermodynamical stability.

Table 3: Bicyclic and tricyclic ketones by variation of the side chain.

silyl enol ether	cyclized product a)
 **4**	 **5** 26%
 **6**	 **7a** 24% +  **7b** 24%

a) Irradiations are carried out in acetonitrile. All yields are isolated yields.

In conclusion this oxidative cyclization method of silyl enol ethers is shown to reveal a great synthetic potential. The regiochemistry of the cyclization step can be controlled by simple addition of alcohol as nucleophile. Under mild conditions 6-*endo* products can be designed as well as products typical for radical cyclizations. In the absence of a nucleophile the reaction predominantly occurs via silyloxy radical cations as reactive intermediate. The presence of a nucleophile leads to enhanced Si-O bond cleavage. Hence the reaction pathwy via α-keto radical is favoured. Further applications of this reaction and mechanistic studies are under current investigation.

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References and Notes

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8. The oxidation potential of **1** has been determined (CH_3CN, $LiClO_4$): $E_{1/2}^{ox}$ [**1**] = +1.58 V vs. Ag/AgCl.
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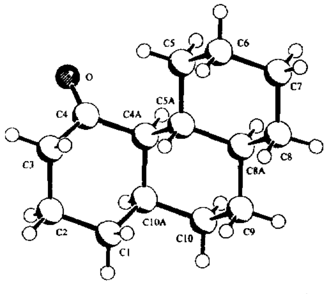
16. The crystals of **5**, $C_{14}H_{22}O$, M = 206.23 from ethanol are orthorhombic, space group $P2_12_12_1$, $a = 5.450(1)$, $b = 14.580(1)$, $c = 14.802(1)$ Å; $Z = 4$; $d_{calc} = 1.165$ g/cm^3; $\mu = 5.36$ cm^{-1}, $F(000) = 456$, crystal dimensions 0.7 x 0.1 x 0.05 mm^3, CAD4-diffractometer, $\lambda = 1.54178$ Å, 1416 independent reflections and 1182 observed reflections, $R = 0.042$ and $wR^2 = 0.115$ for the observed, $R = 0.057$ and $wR^2 = 0.128$ for all reflections. Further information can be obtained from the Fachinfomationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, on quoting the depository number CSD-404816. Characteristic bond lengths and angles:C(4)-O 1.218(3), C(4)-C(4A) 1.512(3), O-C(4)-C(3) 112.3(2), C(5A)-C(4A)-C(10A) 112.4(2).



17. All new compounds gave satisfactory spectroscopic and analytical data consistent with the indicated structures. Additionally the structures of **2**, **3a**, **3b**, **7a** and **7b** have been ascertained by 1D- and 2D-NOE, selective decoupling and ^{13}C-^1H-correlated experiments. Selected ^1H-NMR data (300 MHz, $CDCl_3$): **2**: δ 2.20 (m, 1H), 2.31 (m, 1H), 2.46 ('q', J = 5.0 Hz, C_{8a}-H). **3a**: δ 2.12 (ddd, J = 9.0, 7.7, 1.1 Hz, C_{3a}-H), 2.47 (m, C_{7a}-H). **3b**: δ 2.38 (m, C_{7a}-H), 2.70 (ddd, J = 9.1, 8.5, 1.9 Hz, C_{3a}-H). **7a**: δ 3.28 (dm, J = 7.6 Hz, C_{3a}-H), 5.51 (dt, J = 1.3, 2.3 Hz, C_8-H). **7b**: δ 3.14 (m, C_{3a}-H), 5.25 (q, J = 2.6 Hz, C_8-H).

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