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A New Approach to Hydroazulenes via Olefin Metathesis

Heiko Junga, Siegfried Blechert*

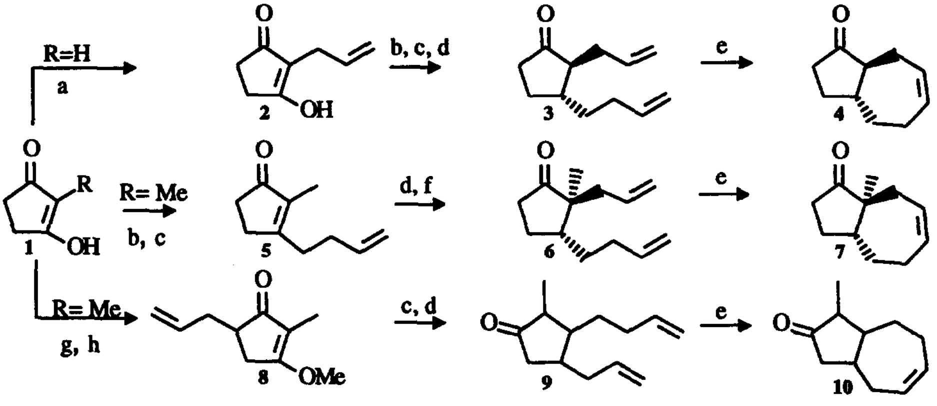
Institut für organische Chemie der Technischen Universität Berlin,
Straße des 17. Juni 135, D-1000 Berlin 12, Germany

Abstract: Several functionalized diolefins cyclize to hydroazulenes (among others) via olefin metathesis with CH_3ReO_3. These conversions are regioselective and occur with high diastereoselectivity.

The heterogeneous catalyst system methyltrioxorhenium (MTO) on silica gel/aluminum oxide as a carrier was developed by Herrmann et al. It presents itself as well-suited for the intermolecular olefin metathesis of various functionalized olefins. [1]

We were interested in testing olefin metathesis in connection with an MTO catalyst as a method for the preparation of functionalized perhydroazulenes. These ring systems occur in many natural products, which are also of pharmacological interest.

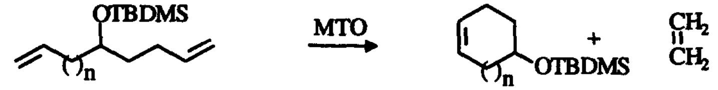
Starting with 1,3-cyclopentanedione derivatives, different perhydroazulene precursors are easily obtained via standard reactions such as the vinylogous ester trick, Birch reduction, or α-alkylation. The allyl and homoallyl chains of the precursors (i. e. **3**, **6**, **9**) could then be cyclized by olefin metathesis reaction with MTO giving rise to the hydroazulene ring system.



a) KOH, H_2O, $CH_2{=}CHCH_2Br$ b) EtOH, p-TosOH, benzene c) $CH_2{=}CHCH_2CH_2MgBr$, Et_2O, then H_3O^+ d) liq. NH_3, Li, t-BuOH, then H_2O e) MTO/(SiO_2, Al_2O_3), 1,1,2-trichlorotrifluoroethane, CH_2Cl_2 f) KH, THF, $CH_2{=}CHCH_2Br$ g) MeOH, p-TosOH, benzene h) LDA, THF, $CH_2{=}CHCH_2Br$ [2]

The precursors **3**, **6** and **9** cyclized diastereoselectively to hydroazulenes with satisfactory to very good yields. The stereochemistry of the precursors **3**, **6** and hydroazulenes **4**, **7** was determined by NOE - experiments.[3] These successful cyclizations show that intramolecular metathesis reactions of functionalized olefins using MTO as catalyst are possible and highly useful for the preparation of hydroazulenes.

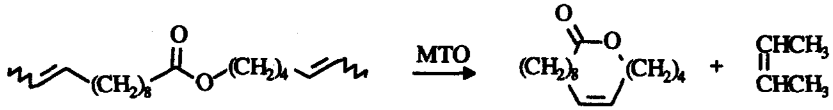
Further, we were interested in whether other functionalities are tolerated by the catalyst and which other ring sizes could be achieved. In order to examine this topic 1,8-nonadiene-5-ol [4] protected as a silyl ether was subjected to the conditions of the metathesis. This compound as well as an analagous 1,7-octadiene [5] derivative were cyclizable with moderate to good yields.



11 n= 1, **12** n= 2 **13** n=1, **14** n= 2

The successful cyclization of precursors **11** and **12** shows that silylethers are also tolerated in diolefins for the preparation of functionalized six and seven-membered rings. 1,7-Octadiene could be quantitatively transformed with visible release of ethene gas into cyclohexene and in trace amounts to the dimer cyclododecadiene.

In addition, macrocyclic lactone **16** was easily obtainable via the olefin metathesis of 10-dodecenoicacid-5-heptenylester **15** using MTO as catalyst, shown in the scheme below. For this reaction methyl-substituted double bonds were necessary in order to prevent isomerization of the double bonds during metathesis. Hydrogenation of this lactone afforded the natural product Exaltolid. Previously, lactone **16** was synthesized by Villemin through metathesis of a similar precursor. [6]



15 **16** **17**

Cyclization yields (isolated).

Substrate	Product	Solvent	Mol% cat.	Conditions	Yield [%]
3	4	CH_2Cl_2	18	RT	51
3	4	CH_2Cl_2, TTE [a]	8	refl.	80
6	7	CH_2Cl_2, TTE	8	refl.	58
6	7	CH_2Cl_2, TTE	45	RT	90
9	10	CH_2Cl_2, TTE	13	refl.	67
11	13	CH_2Cl_2	6	RT	57
12	14	CH_2Cl_2	4	RT	30
12	14	CH_2Cl_2, TTE	13	RT	79
15	16	CH_2Cl_2	16	RT	35

[a] 1,1,2-trichlorotrifluoroethane

References and Notes

1 W. A. Herrmann, F. E. Kühn, R. W. Fischer, W. R. Thiel, C. C. Romao, *Inorganic Chem.* **1992**, 31, 4431.

2 Compounds **2**, **5** and **8** are mentioned in previous literature: L. Novák, G. Baán, J. Marosfalvi, C. Szántay, *Chem. Ber.* **1980**, 113, 2939; K. Antczak, J. F. Kingston, S. J. Alward, A. G. Fallis, *Can. J. Chem.* **1984**, 62, 829; W. H. Parsons, R. H. Schlessinger, M. L. Quesada, *J. Am. Chem. Soc.* **1980**, 102, 889.

3 The stereochemistry of the main diastereomer is specified. For **9** and **10** the stereochemistry was not determined but GC showed that there is a main diastereomer. All new compounds exhibited ^1H, ^{13}C NMR , IR and mass spectra consistent with the assigned structure. Typical procedure: methyltrioxorhenium (14 mg) in 1 ml CH_2Cl_2 was added to a (1g) suspension of finely ground Strem carrier (87% SiO_2, 13% Al_2O_3 , Strem Chemicals, Inc.) in 8 ml 1,1,2-trichlorotrifluoroethane under argon atmosphere (inert gas box). After stirring for 10 min at room temperature **6** (130 mg) in 6 ml 1,1,2-trichlorotrifluoroethane was added. The reaction mixture was heated to reflux for 7 d and its progress was monitored by GC/MS. The catalyst was then filtered and the solvent evaporated to afford 64 mg **7** (58%) as a colourless oil after flash chromatography (ether/ pentane 1:40 -> 1:20).
IR ($CHCl_3$) : ν = 3025 (vs), 1731 (vs), 1438 (m), 1205 (vs), 1061 (m) cm^{-1}; ^1H-NMR (400 MHz, C_6D_6) : δ = 5.76 (m, 1H), 5.67 (m, 1H), 2.67 (dd, 1H, J= 15.5 Hz, 8.5 Hz), 2.16-1.73 (m, 5H), 1.38 (m, 2H), 1.22 (m, 2H), 1.13 (m, 1H), 0.72 (s, 3H) ppm; ^{13}C-NMR (100.64 MHz, C_6D_6) : d = 219.1 (s), 131.6 (d), 128.0 (d), 51.0 (d), 48.4 (s), 35.5 (t), 35.1 (t), 29.0 (t), 26.2 (t), 25.5 (t), 13.9 (q) ppm; MS : m/e = 164 (M^+, 63%), 149 (76%), 106 (100%), 93 (66%), 79 (47%), 67 (31%) calcd. for $C_{11}H_{16}O$: 164.1201 found: 164.1201

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