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A Novel and Highly Efficient Two-Carbon Ring Expansion

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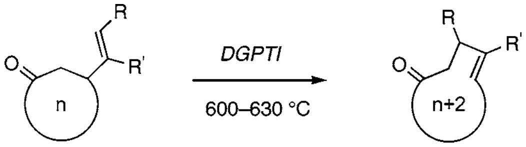
ABSTRACT



n = 8–10,12,13,15: R,R' = H

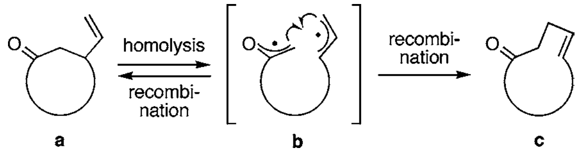
n = 12: R,R' = CH_3/H

Dynamic gas-phase thermoisomerization (DGPTI) of medium- and large-ring 3-vinylcycloalkanones at 600–630 °C produces isomeric γ,δ-unsaturated cycloalkanones expanded by two carbon atoms. A reaction mechanism involving an open-chain diradical intermediate, followed by intramolecular recombination under insertion of the vinyl group is proposed. Substituents on the vinyl moiety are transferred locospecifically to the ring-expanded ketones as corresponding β- and γ-substituents, respectively. The preparation of extraordinary cyclic allenes can be accomplished by DGPTI (540 °C) of 3-ethinylcyclododecanone.

Methods for expanding carbocyclic rings of different sizes are important tools for the preparation of various biologically active macrocyclic target molecules as well as synthetically useful intermediates.[1] We recently described the transformation of medium- and large-ring 1-vinylcycloalkanols into the isomeric, ring-expanded bishomologous macrocyclic ketones by means of dynamic gas-phase thermoisomerization (DGPTI) in a flow reactor at 650 °C.[2] Promoted by the synthetic and mechanistic importance associated with radical-mediated ring expansion reactions,[3] we report herein the first two-carbon ring expansion reaction from 3-vinylcycloalkanones **1** to nicely functionalized ring-expanded 3-cycloalkenones **2** and the first studies of the scope and regiochemistry of this remarkably efficient transformation.

The design of this new ring expansion reaction was based on the mechanistic hypothesis outlined in Scheme 1.

Scheme 1



Considering the reactor temperatures of about 600 °C, initial cleavage of the weakest single bond[4] in molecule **a** would result in the formation of a stabilized α-acyl ω-allyl diradical species **b**.[5] Intramolecular recombination within the open-chain diradical intermediate would then be expected to occur in the terminal vinylogous position, leading to the two-carbon ring-expanded γ,δ-unsaturated cyclic ketone **c**. This sequence, corresponding to a nonconcerted thermal 1,3-C shift

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(1) (a) Zhang, W.; Dowd, P. *Tetrahedron Lett.* **1996**, *37*, 957. (b) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991. (c) Stach, H.; Hesse, M. *Tetrahedron* **1988**, *44*, 1573. (d) Wovkulich, P. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamom Press: Oxford, 1991; Vol. 1, Chapter 3. (e) Gutsche, C. D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, 1968.

(2) (a) Nagel, M.; Fráter, G.; Hansen, H.-J. *Chimia* **2003**, *57*, 196 and references therein. (b) Nagel, M.; Fráter, G.; Hansen, H.-J. *Synlett* **2002**, 275, 280.

(3) (a) Yet, L. *Tetrahedron* **1999**, *55*, 9649. (b) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091.

(4) (a) Rüedi, G.; Nagel, M.; Hansen, H.-J. *Org. Lett.* **2003**, *5*, 2691. (b) Rüedi, G.; Nagel, M.; Hansen, H.-J. *Synlett* **2003**, 1210.

(5) (a) McNab, H. *Contemp. Org. Synth.* **1996**, *3*, 373. (b) Cadogan, J. I.; Hickson, C.; McNab, H. *Tetrahedron* **1986**, *42*, 2135.

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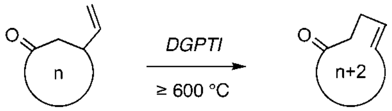
reaction, generally allows the formation of both possible diastereoisomers, i.e., the (*E*)- as well as the (*Z*)-forms.

We started our studies with 3-vinylcyclododecanone (**1d**), which was easily prepared from α,*β*-unsaturated cyclododecanone by 1,4-addition of vinylmagnesium bromide in the presence of cuprous iodide in 90% yield.[6] Subjecting **1d** to DGPTI in a flow reactor system under reduced pressure (2−4 × 10^{-2} mbar) at 580 °C delivered ring-expanded 3-cyclotetradecenone **2d** as a 1:1 mixture of (*E*)- and (*Z*)-isomers in 78% yield.[7] Additional studies on the influence of the reaction temperature on the thermal isomerization revealed optimal conversion to occur at 600 °C providing **2d** in 85% yield.[8] However, at higher temperatures (>600 °C), the efficiency of the reaction decreases due to the formation of decarbonylation products as well as complex product mixtures with mainly low molecular mass components.

To more fully explore the generality of this finding, we systematically investigated the effect of the ring size on this amazing transformation. In agreement with the results obtained with substrate **1d**, the homologous 3-vinylcyclotridecanone **1e** was thermally isomerized at 600 °C into 3-cyclopentadecenone **2e** in 87% yield, which upon hydrogenation quantitatively afforded the valuable macrocyclic musk odorant cyclopentadecanone.[9] The 17-membered *γ*,*δ*-unsaturated compound **2f** was easily obtained from 15-membered ketone **1f** in the same manner in good yields (75%).[10] In sharp contrast to the smoothly convertible macrocyclic substrates **1d**−**f**, thermolysis under the same reaction conditions of medium ring-sized 3-vinylcycloalkanones **1b** and **1c** afforded the corresponding ring-expanded products **2b** and **2c**, respectively, only in moderate yields (entries 2 and 3). Almost no conversion could be detected in the case of the eight-membered analogue **1a** (entry 1), even at elevated temperatures (>650 °C). However, besides 5% of the expected 3-cyclodecenone (**2a**), only starting material and low-boiling fragmentation products could be detected. The findings summarized in Table 1 reflect the ring strain in the range of 8- to 17-membered carbocyclic systems.

Table 1. DGPTI of 3-Vinylcycloalkanones in Dependence of the Ring Size



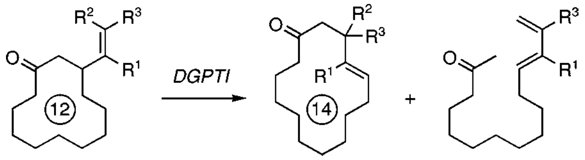
1 **2**

entry	*n*	product	*T* (°C)	yield (%)[a]	*E*/*Z* ratio[b]
1	8	**a**	630	ca. 5[c]	1.0
2	9	**b**	620	35[d]	1.3
3	10	**c**	610	6d[e]	1.7
4	12	**d**	600	85[e]	2.0
5	13	**e**	600	87[e]	1.6
6	15	**f**	600	75[d]	1.7

[a] Based on isolated material. [b] *E*/*Z* ratio was determined by ^{1}H NMR spectroscopic analysis. [c] Not isolated. [d] Isolated as an *E*/*Z* mixture. [e] Both (*E*)- and (*Z*)-forms could be separated by column chromatography.

In contrast to the smooth reaction conditions of cyclic 3-vinyl-substituted ketones, DGPTI of comparable acyclic substrates under the same conditions, to yield open-chain 3-enones, yielded only low molecular weight products (according to GC/MS analysis), which were not further characterized. Also no reaction or only tar formation was observed by heating **1d** under static conditions in an ampule at 400 °C.

Table 2. Influence of Methyl Substituents on the Vinyl Moiety on DGPTI of 3-Vinylcyclododecanones



3 **4** **5**

R^1	R^2	R^3	product	*T* (°C)	**4** yield (%)[a]	**5** yield (%)[a]
CH_3	H	H	**a**	600	87[b]	0
H	CH_3/H	H/CH_3	**b**	580	55[c]	10[c]
CH_3	CH_3/H	H/CH_3	**c**	580	46[c]	21[b]
H	CH_3	CH_3	**d**	590	0	38[b]

[a] Based on isolated material. [b] As a 1:1 mixture of (*E*)- and (*Z*)-isomers. [c] Exclusively (*E*)-isomer.

To gain additional insight into regiochemical aspects and to obtain a clear picture of how substituents on the alkene moiety effect the isomerization process, we have further studied the thermal behavior of selected *γ*-substituted cyclododecanones **3a**−**d** (Table 2).[11] In accord with the parent structure **1d**, DGPTI of 3-(isopropenyl)cyclododecanone (**3a**) at 600 °C produced 4-methylcyclotetradec-4-enone (**4a**) as

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[6] Williams, D. R.; Benbow, J. W.; McNutt, J. G.; Allen, E. E. *J. Org. Chem.* **1995**, *60*, 833.

[7] Both isomers could be separated by column chromatography and/or by crystallization from 60:1 hexane/AcOEt.

[8] In a representative procedure, 3-vinylcyclododecanone (**1d**) (4.82 g, 23.14 mmol) was evaporated in a kugelrohr oven and directly distilled under reduced pressure (2 mbar) through a preheated (600 °C) quartz tube (110 cm length, 3 cm i.d., contact time estimated at about 1−2 s) applying a flow of N_2 (1.4 L/h). At the outlet part of the reactor, the ring expansion product was collected in a cooling trap (−196 °C). Purification by flash chromatography (silica gel, 40:1 hexanes/ethyl acetate) gave (*E*)-**2d** (2.75 g, 57%) as a first fraction, followed by (*Z*)-**2d** (1.35 g, 28%). Both isomers could be crystallized from 60:1 hexanes/ethyl acetate, affording colorless needles. All new compounds were fully characterized.

[9] For leading references on musk odorants, see: (a) Fráter, G.; Bajgrowicz, J. A.; Kraft, P. *Tetrahedron* **1998**, *54*, 7633. (b) Fráter, G.; Lamparsky, D. In *Perfumes: Art, Science and Technology*; Müller, P. M., Lamparsky, D., Eds.; Elsevier: London, New York, 1991; Chapter 20, pp 533−555. (c) Ohloff, G. *Riechstoffe und Geruchssinn. Die Molekulare Welt der Düfte*; Springer: Berlin, 1990; Chapter 9, pp 195−219. (d) Mookherjee, B. D.; Wilson, R. A. In *Fragrance Chemistry: The Science of the Sense of Smell*; Theimer, E. T., Ed.; Academic Press: New York, 1982; Chapter 12, pp 433−494.

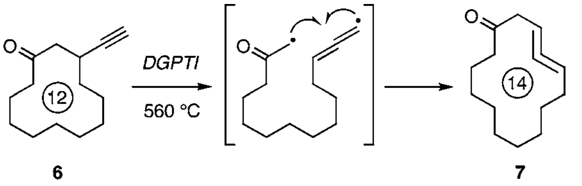
[10] Decrease in yield might be explained by side reactions taking place in the kugelrohr oven (static conditions) during the evaporation process, which requires higher temperatures for the rather high-boiling substrate **1f**.

[11] Compounds **3a**−**d** were prepared in excellent yields (90−98%) by conjugate 1,4-addition of the corresponding freshly prepared vinyllithium reagents and cuprous iodide in ether at −78 °C, see: (a) Leonard, J.; Mohialdin, S.; Reed, D.; Ryan, G.; Swain, P. A. *Tetrahedron* **1995**, *51*, 12843. (b) Linstrumelle, G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103.

a 2:1 mixture of (*E*)- and (*Z*)-isomers (87%) that could easily be separated by column chromatography or crystallization from hexane. In remarkable contrast, a methyl substituent at the terminal position of the vinyl moiety such as that present in **3b**,**c** led to the corresponding ring-expanded cyclic ketones **4b**,**c** (55 and 46%, respectively) only in (*E*)-configuration along with open-chain methyl ketones **5b**,**c** (10 and 21%, respectively), which are valuable intermediates in synthesis but undesired products in the current study. Interestingly, no 5,6-dihydro-2*H*-pyrane derivatives formed via intramolecular hetero Diels−Alder reaction could be detected.[12] The starting materials **3b** and **3c**, respectively, were mixtures of (*E*)- and (*Z*)-isomers. However, both pure isomers react to give exclusively the corresponding (*E*)-cycloalkenones **4b** and **4c**, respectively. Hydrogenation of **4b** quantitatively afforded (±)-normuscone. An additional methyl group at the recombination center affected, as expected, the course of the reaction: thermal isomerization of 3-(2-methyl-1-propenyl)cyclododecanone (**3d**) at 590 °C afforded only the thermodynamically most favorable open-chain diene **5d** (38%) besides a considerable amount of recovered starting material.[13] It seems that in this case, the formed diradical of type **b** only undergoes recombination to the starting material and disproportionation to the observed diene **5d**.[14]

These results demonstrate that substrates bearing a 1-propenyl substituent adversely effect the facility of this reaction. Furthermore, it could be established that the methyl substituents on the vinyl moiety are transferred to the ring-expanded products as corresponding β- and γ-substituents, respectively.

Scheme 2. Diradical-Mediated Formation of a Cyclic Allene



Finally, we have extended our investigations by varying the C_2-insertion unit starting from 3-ethinylcyclododecanone **6**.[15] DGPTI at 540 °C provided the extraordinary cyclic allene **7** in 56% yield (based on recovered starting material), which showed in its IR spectrum a characteristic absorption at 1962 cm^{-1}.[16] In comparison with the vinyl analogues, rather low temperatures were necessary for optimal conversion. More elevated temperatures, however, resulted in the formation of open-chain products and additional low-boiling side products, which were not further characterized. In summary, we have demonstrated the first example of a ring expansion reaction of 3-vinyl/ethinyl-substituted medium- and large-ring cycloalkanones to the isomeric bishomologous γ,δ-unsaturated cyclic ketones by means of DGPTI. Moreover, this method provides a novel strategy for the synthesis of functionalized macrocyclic systems. Further synthetic studies of DGPTI processes involving other substrates are in progress.

Acknowledgment. This work was generously supported by the Swiss National Science Foundation (SNF).

Supporting Information Available: Experimental conditions and complete spectral data for all products of the ring expansion reaction **2a−f**, **4a−d**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] Brouard, C.; Pornet, J.; Miginiac, L. *Synth. Commun.* **1994**, *21*, 3047.

[13] At temperatures below 590 °C, almost no conversion occurred, whereas higher temperatures gave rise to a broad variety of low-boiling products.

[14] In agreement with this finding, first experiments with optically active (*Z*)-**3b** gave racemic **4b** as well as racemic starting material (details will be provided in an upcoming publication).

[15] (a) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182. (b) Bergdahl, M.; Eriksson, M.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1993**, *58*, 7238.

[16] Johnson, R. P. *Chem. Rev.* **1989**, *89*, 1111.