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Original Scientific Paper

Solvent and Temperature Effects in π-Route Cyclization†

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endo-Bicyclo[3.3.1]non-6-ene-3-carboxylic acid (**1**) was prepared and the solvent and temperature effects on the π-route cyclization were studied. The stereochemistry of the products strongly depends on the reaction temperature and the solvent used. The interpretation of the mechanism and product distribution based on experimental data is supported by theoretical investigation.

INTRODUCTION

Intramolecular cyclizations involving participation of a remote double bond have proved to be of considerable value in the synthesis of substituted adamantane derivatives.[1] The nature of the ion produced by this so-called π-route[2] cyclization depends on many structural and experimental factors and is often depicted as a »nonclassical« ion.[3] In various π-route cyclizations, the predominant isomer, produced by nucleophilic attack, displays converse stereochemistry. For example, 5-oxo-4-oxahomoadamantanone (**2**), in the reaction with 50% sulfuric acid at 90 °C, gives a mixture of *endo*- and *exo*-isomers **3**-OH and **4**-OH in a 5 : 1 ratio,[1b] (Figure 1). A similar reaction of **2** takes place with thionyl chloride at room temperature but the ratio of *endo*- and *exo*-chlorides **3**-Cl : **4**-Cl is 1 : 1.5, respectively.[4] It was also reported that the unsaturated acid **1** reacted with methanesulfonic acid at 90 °C to give a high yield of a mixture of *endo*- and *exo*-mesylates **3**-OMs and **4**-OMs in

† Dedicated to the memory of Professor Stanko Borčić, deceased on December 21, 1994.

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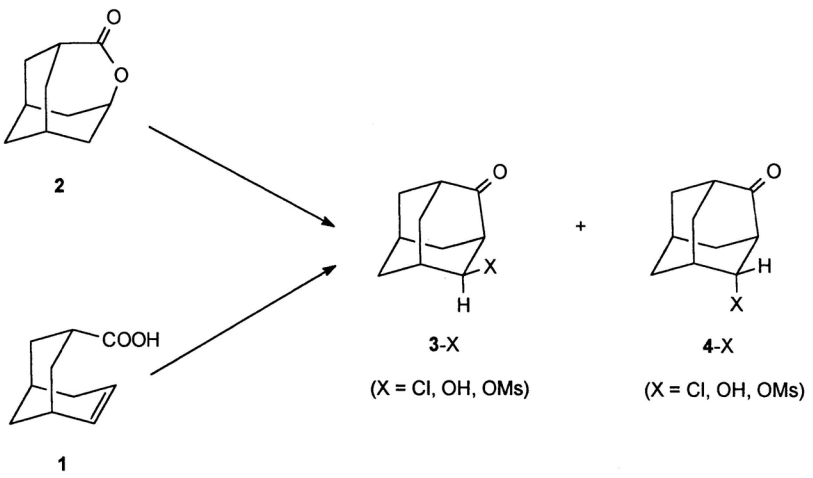


Figure 1. π-route to 2,4-substituted adamantane derivatives.

the ratio of 6 : 1.[1b] It was stated that various π-route cyclizations have initially kinetically formed *exo*-products but, when the conditions are such as to permit epimerisation, *endo*-isomers predominate.[1b,c]

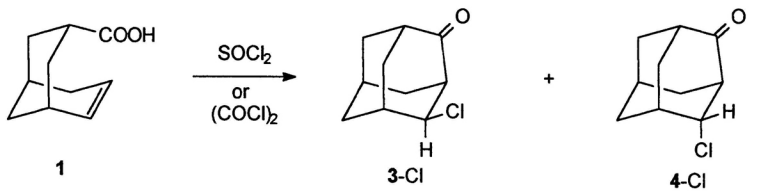
In order to obtain further information on this reaction, the cyclization of **1** was examined under various conditions. In this paper, we will offer, based on our findings, an interpretation of the product formation and the reaction mechanism.

RESULTS AND DISCUSSION

Bicyclo[3.3.1]non-6-ene-3-carboxylic acid (**1**), the compound we selected as starting material, was prepared by reaction of 2-adamantanone with sodium azide in methanesulfonic acid[5] followed by treatment of the isolated 4-methanesulfonoxyadamantan-2-one with potassium hydroxide in 60% aqueous ethanol.[6] We examined the behaviour of the unsaturated acid **1** under the conditions of π-route cyclization at different temperatures and in different solvents. In the reaction of **1** with $SOCl_2$ or $(COCl)_2$, two isomers, *endo*-4-chloro-2-adamantanone (**3**-Cl) and *exo*-4-chloro-2-adamantanone (**4**-Cl), were formed in a high yield, Scheme 1.

The product composition of the ring cyclization of **1** with thionyl chloride or oxalyl chloride under various conditions is shown in Tables I and II.

These results demonstrate the dependence of the product composition on both the temperature and the solvent. At low temperatures (–15 °C and –80 °C) the *exo*-isomer **4**-Cl was formed as the main product, while at 80 °C



1 3-Cl 4-Cl

Scheme 1.

TABLE I

Cyclization of **1** with $SOCl_2$ and $(COCl)_2$ at various temperatures

Reagent[a]	Temperature °C	Reaction time min	Ratio of products[b] 3-Cl : 4-Cl	Yield[c] %
$SOCl_2$	80	20	1.1 : 1.0	86
$SOCl_2$	25	30	1.0 : 1.9	81
$(COCl)_2$	25	30	1.0 : 1.7	82
$SOCl_2$	–5	30	1.0 : 2.2	75
$SOCl_2$	–15	120	1.0 : 3.2	83
$SOCl_2$	–80	150	1.0 : 8.2	78

[a] Reaction was carried out using a large excess of reagent (7 : 1).

[b] Based on capillary GLC-analysis.

[c] Isolated yield.

TABLE II

The influence of solvent on cyclization of **1** with $SOCl_2$ or $(COCl)_2$ at 25 °C

Solvent	Reagent[a]	Reaction time min	Ratio of products[b] 3-Cl : 4-Cl	Yield[c] %
benzene	$SOCl_2$	90	1.0 : 1.7	80
benzene	$(COCl)_2$	90	1.0 : 1.6	80
ether	$SOCl_2$	1320	1.0 : 2.7	75
ether	$(COCl)_2$	1200	1.0 : 2.5	70
CCl_4	$SOCl_2$	150	1.0 : 5.4	88
CCl_4	$(COCl)_2$	240	1.0 : 2.8	84

[a] Reaction was carried out using a large excess of reagent (7 : 1).

[b] Based on capillary GLC-analysis.

[c] Isolated yield.

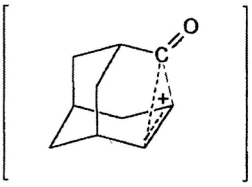
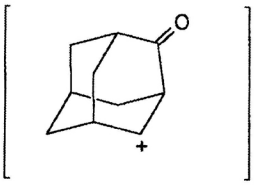
endo-isomer **3**-Cl was the major product. The rate of cyclization carried out in solvents, (Table II) was significantly reduced, particularly in ether, which suggests a polar transition state and is consistent with formation of a carbocation intermediate. Both chloro-isomers, **3**-Cl and **4**-Cl, were stable under reaction conditions for over one week.

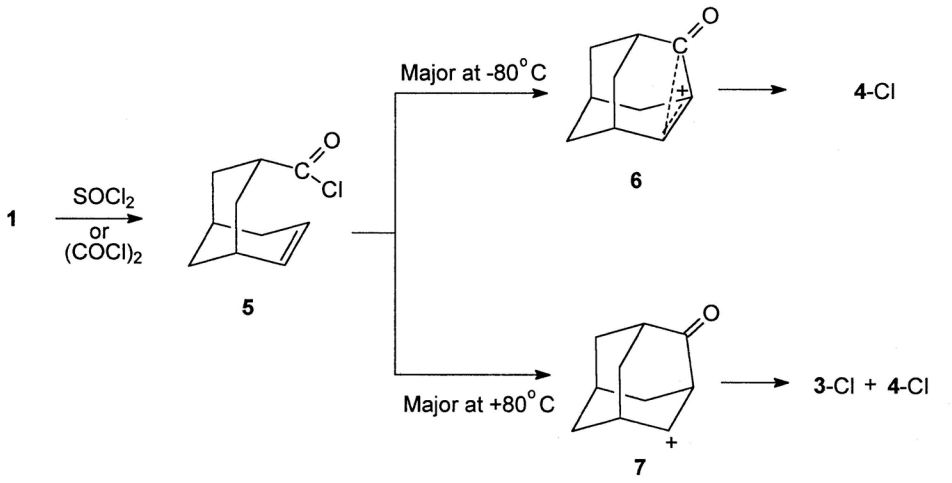
We calculated the heats of formation of isomers **3**-Cl and **4**-Cl as well as of the presumed carbocation intermediates **6** and **7** using AM1[7] and PM3[8] semiempirical methods. The results are shown in Table III.

As it can be seen, $\Delta_f H$ of both isomers **3**-Cl and **4**-Cl are practically the same. However, the »nonclassical« cation **6** is more stable by at least 3 kcal mol^{-1} than the 2-adamantyl cation **7**, and a nucleophilic attack of the chloride anion on cation **6** will occur from the *exo*-side to give *exo*-isomer **4**-Cl, while cation **7** should give both isomers **3**-Cl and **4**-Cl with equal probability or will favour the *endo*-isomer **3**-Cl by nucleophilic attack of chloride anion from the sterically less hindered *endo*-face.

TABLE III

Calculated heats of formation ($\Delta_f H$)

Compound	Cation	$\Delta_f H$/kcal mol^{-1}	
		AM1	PM3
5		–50.23	–45.43
	 **6**	150.93	155.25
	 **7**	153.98	163.69
3-Cl		–72.26	–66.82
4-Cl		–72.38	–67.57



Scheme 2.

The reaction presumably takes place according to Scheme 2. The first reaction step is the formation of unsaturated acid chloride **5**. The experiments carried out with equimolar amounts of acid **1** and oxalyl chloride showed that the formation of **5** is an instantaneous process (see experimental part). The next step strongly depends on the reaction conditions. The formation of a large amount of *exo*-isomer **4**-Cl at –80 °C could be explained by the forming of »nonclassical« cation **6** as the dominant intermediate. However, at higher temperature, both cations **6** and **7** are formed and a mixture of **3**-Cl and **4**-Cl is obtained. The ratio of products does not depend on the concentration of $SOCl_2$ or $(COCl)_2$. When the reaction was carried out with an equimolar amount of chloride reagent, the reaction rate was significantlly reduced but the ratio of products was very similar to that in the reaction with an excess of reagent.[9] An exception was the experiment carried out with $SOCl_2$ in CCl_4 (see Table II).

Although the experimental results support the proposed mechanism, we cannot completely rule out the possibility that the cyclization of **1** to **3**-Cl and **4**-Cl *via* **5** might have proceeded by a concerted process, particularly in experiments at low temperature, where an excess of $SOCl_2$ or $(COCl)_2$ was used.

In conclusion, we have demonstrated that the π-route cyclization of **1** is a kinetically controlled process and the formation of intermediates **6** and **7** strongly depends on the reaction conditions used. Since product composition can be controlled by changing the reaction conditions, our results revealed a possible preparative application of this reaction.

EXPERIMENTAL

General

GLC analyses were carried out on a Varian 3300 gas chromatograph with capillary column DB-210. ^{1}H-NMR and ^{13}C-NMR spectra were taken on a Varian Gemini 300 spectrometer. IR spectra were recorded with the Perkin-Elmer 297 spectrophotometer.

Methods of Calculation

The enthalpies of formation for optimized structures of **3**-Cl, **4**-Cl and ions **6** and **7** were calculated by the AM1[7] and PM3[8] semiempirical molecular orbital methods. Calculations were conducted using the HyperChem 4.5 program[10] running on an IBM compatible 486 (120 MHz) computer. Geometries were optimized until the root mean square value of the energy gradient was less than 0.001 kcal mol^{-1} Å^{-1}. All calculations were performed using the restricted Hartree Fock method[11] (RHF) and convergence limit of 10^{-5} kcal mol^{-1} with full optimizations of all geometrical variables (bond length, bond angles, and dihedral angles).

*Reaction of Acid **1** with $SOCl_2$ or $(COCl)_2$*

General Procedure

The reactions were carried out at different temperatures (from –80 °C to 80 °C, see Table I) and in different solvents, *ca.* 2 mL (see Table II).

A mixture composed of 0.5 g (3 mmol) of **1** and 21 mmol of $SOCl_2$ or $(COCl)_2$ was stirred under N_2 and the reaction was followed by GLC (DB-210, 150 °C). Excess of $SOCl_2$ or $(COCl)_2$ was evaporated *in vacuo* to give a solid, which was dissolved in 10 mL of ether. The ether solution was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of solvent gave a crude product which was chromatographed on silica gel column using pentane/ether (5 : 1) as the eluent. The first fractions gave pure *exo*-isomer **4**-Cl followed by *endo*-isomer **3**-Cl. The IR and ^{1}H-NMR were identical with the published spectra.[12]

3-Cl: ^{13}C-NMR ($CDCl_3$) δ/ppm: 213.25 (s), 67.59 (d), 54.37 (d), 45.89 (d), 39.56 (t), 38.95 (t), 36.31 (t), 34.63 (d), 32.67 (t), 25.78 (d).

4-Cl: ^{13}C-NMR ($CDCl_3$) δ/ppm: 213.43 (s), 63.41 (d), 54.34 (d), 45.25 (d), 39.21 (t), 34.95 (t), 34.50 (d), 33.30 (t), 29.63 (t), 26.70 (d).

*Bicyclo[3.3.1]non-6-en-3-carboxylic chloride (**5**)*

To the cooled solution (–50 °C) of 0.166 g (1 mmol) of acid **1** in 2 mL of $CDCl_3$ an equimolar amount of $(COCl)_2$ was added. According to the ^{13}C-NMR spectra, acid **1** reacted instantaneously to give pure acyl chloride **6**. Under these conditions, no products **3**-Cl and **4**-Cl were observed during a 4 hours period.

5: ^{1}H-NMR ($CDCl_3$) δ/ppm: 5.71 – 5.65 (m, 2H), 2.87 (m, 1H), 2.60 – 1.50 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ/ppm: 177.27, 130.52, 129.70, 48.14, 32.33, 31.61, 31.32, 31.08, 28.03, 25.91.

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SAŽETAK

Utjecaj otapala i temperature na ciklizaciju π-putem

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Pripravljena je *endo*-biciklo[3.3.1]non-6-en-3-karboksilna kiselina (**1**) te je proučavan utjecaj temperature i otapala na reakciju ciklizacije. Stereokemija nastalih produkata **3**-Cl i **4**-Cl u reakciji ciklizacije jako ovisi o temperaturi te o upotrijebljenom otapalu. Na osnovi eksperimentalnih podataka i teorijskih računa predložen je mehanizam nastajanja produkata.