Beckmann Fragmentation of Camphor-4-carboxylic and Camphor-4-acetic Acid Oximes

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A mild and efficient recyclization reaction of bornanone-4-carboxylic and bornanone-4-acetic acid oximes in aqueous hydrochloric acid has been developed. Beckmann fragmentation followed by hydrolysis provides a straightforward method for the preparation and isolation of functionalized [2.2.1] and [3.3.0] bicyclic lactones in nearly quantitative yields. These simple transformations offer the opportunity to obtain a wide range of more complex functionalized bicyclic terpenoids on a large-scale, starting from readily available camphor derivatives.

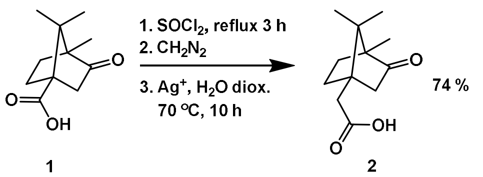
Introduction

The Beckmann rearrangement of camphor oxime has been studied by generations of chemists for more than 135 years [1]. Under different acidic conditions, camphor oxime usually forms a complicated mixture of various rearrangement and fragmentation products [2-4]. Even in the most successful cases, using preliminarily sulfonated oximes, the desired lactam was obtained only as one of the minor products with a yield of just a few percent [5,6]. Solid-state supported catalytic processes under microwave irradiation led to the formation of both possible lactams *via* primary methylene and tertiary bridgehead migration [7,8]. Like many other small or strained ring ketoximes, these molecules tend to form Beckmann fragmentation products instead of undergoing Beckmann rearrangement (lactams). Beckmann fragmentation processes usually involve the formation of carbocationic intermediates that can yield unsaturated compounds or undergo various complex nucleophilic skeletal rearrangements. Bridgehead methyl group in the case of camphor facilitates the formation of tertiary carbocation, but under the reaction conditions numerous side reactions took place [4].

The carboxylic group is known to be an effective trap for electrophilic intermediates in numerous intramolecular lactonization reactions, forming oxygen-containing cycles of different sizes [9-13]. In most cases, electrophilic intermediates are formed during additions to multiple bonds or dissociation processes. A wide variety of electrophiles can initiate lactonization of unsaturated carboxylic acids forming various functionalized lactones that have found wide application in the synthesis of more complex organic compounds [11].

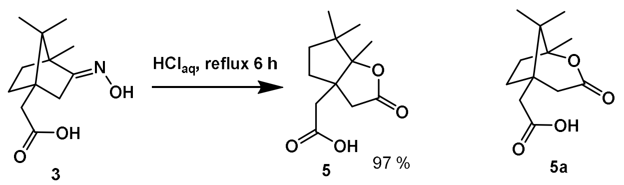
Here we report the intramolecular lactonization of carbocations formed during the Beckmann fragmentation of camphor-derived oximes bearing carboxylic groups at the bridgehead position.

Camphor-4-acetic acid (**2**) was prepared from the camphor-4-carboxylic acid (**1**) by the Arndt-Eistert homologation reaction sequence (Scheme 1). Corresponding oximes were prepared in almost quantitative yields by the reaction with hydroxylamine.



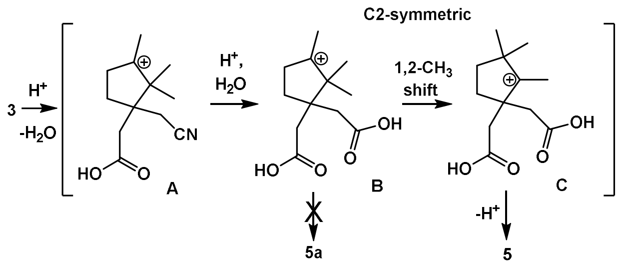
Scheme 1. Synthesis of camphor-4-acetic acid.

Oxime of camphor-4-acetic acid (**3**) under reflux for 6 hours in constantly boiling hydrochloric acid yields *cis*-(6,6,6a-trimethyl-2-oxohexahydro-3aH-cyclopenta[b]furan-3a-yl)acetic acid (**5**) (Scheme 2). When the single enantiomer of **3** was used in this reaction only the racemic **5** was obtained.



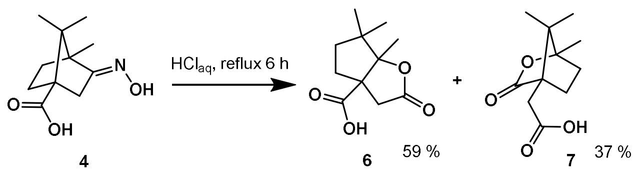
Scheme 2. Recyclization of camphor-4-acetic acid oxime.

Both compounds **5** and **5a** have the same molecular formula and can be formed *via* C2-symmetric (achiral) carbocationic intermediates (Scheme 3). HRMS and 2D-NMR experiments prove the structure of **5**.



Scheme 3. Plausible mechanism of the formation of **5**.

Oxime of camphor-4-carboxylic acid (**4**) under reflux for 6 hours in constantly boiling hydrochloric acid yields the mixture of *cis*-6,6,6a-trimethyl-2-oxohexahydro-3aH-cyclopenta[b]furan-3a-carboxylic acid (**6**) and (1,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]hept-4-yl)acetic acid (**7**) (Scheme 4).



Scheme 4. Recyclization of camphor-4-carboxylic acid oxime.

These two compounds can be easily separated by flash chromatography. The molecular formula of each compound was determined by HRMS and the structure was proved by 2D-NMR experiments (please see supplementary materials).

Experimental part

Solvents were purified according to the standard procedures. ^{1}H, ^{13}C, and two-dimensional (NOESY, COSY, HSQC, and

HMBC) NMR spectra were recorded on Bruker Avance III 600 HD spectrometer (600 MHz). Chemical shifts are reported in ppm downfield from TMS as the internal standard. HRMS were recorded on Infinity 1260 UHPLC system coupled to an 6224 Accurate Mass TOF LC/MS system (Agilent Technologies, Singapore). The synthesis of **1** was performed using a previously described procedure [14].

*(4,7,7-Trimethyl-3-oxobicyclo[2.2.1]hept-1-yl)acetic acid (**2**).* Camphor-4-carboxylic acid (15.7 g, 80 mmol) and thionyl chloride (25 mL) were heated under reflux for 3 h in a 500 mL round-bottomed flask, cooled to a room temperature and concentrated to dryness under reduced pressure using a rotary evaporator. The crude product was placed under high vacuum for 3 hours. The crude material was used directly in the next step. Resulting carboxylic acid chloride was dissolved in anhydrous tetrahydrofuran (100 mL) under argon atmosphere. An ethereal solution of diazomethane (0.2 mol) was added at 0 ºC and the solution allowed to react for 3 hrs. without stirring at room temperature (20 ºC). With stirring, 75 mL of 0.5 N acetic acid was added carefully to destroy unreacted diazomethane and saturated aqueous sodium bicarbonate solution (75 mL) was added carefully. The organic layer was dried over magnesium sulfate, filtered, and the solvents were removed under vacuum on a rotary evaporator. The crude product was placed under high vacuum for 3 hr. The crude material was used directly in the next step. The crude diazo ketone was dissolved in dioxane (200 mL) and distilled water (30 mL) was added. Silver trifluoroacetate (2.72 g, 12.3 mmol) was placed in a 50-mL Erlenmeyer flask and dissolved in triethylamine (39 mL, 280 mmol). The resulting solution was added to the diazo ketone solution in one portion. The solution was heated to 70 ºC with stirring for 10 h. The solution was evaporated to dryness with a rotary evaporator and the residue was extracted with saturated aqueous sodium bicarbonate solution (3x50 mL). Excess of 5 N hydrochloric acid was added dropwise and the product extracted with three portions of ethyl acetate (40 mL each), dried over magnesium sulfate, filtered, and the solvent was removed under vacuum. Yield of 74%, a white solid. Mp 77–78 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.85 (br s, 1H), 2.45 (s, 2H), 2.27-2.16 (m, 2H), 1.82-1.60 (m, 3H), 1.46-1.37 (m, 1H), 0.92 (s, 3H), 0.85 (s, 3H), 0.72 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 218.1, 178.4, 59.3, 49.1, 46.7, 46.6, 36.2, 31.8, 29.3, 17.6, 16.1, 9.9. HRMS calcd for $C_{12}H_{18}O_3$: 210.1256; found: 210.1253.

General procedure for the synthesis of oximes.

Hydroxylamine hydrochloride (6 mmol) and pyridine (12 mmol) were added to a stirred solution of 5 mmol of keto acid in 50 mL of 2-propanol in a round-bottomed flask. The reaction mixture was heated under reflux for 5 h, cooled to a room temperature and concentrated under reduced pressure using a rotary evaporator. Distilled water (20 mL) was added to the residue. Resulting mixture evaporated again under the reduced pressure. Then 50 mL of distilled cold water and 15 mL of 1 M hydrochloric acid were added to the residue. The product was filtered, washed with distilled water and dried. Analytical samples were prepared by crystallization from 2-propanol/hexane (1:10) mixture.

*3-(Hydroxyimino)-4,7,7-trimethylbicyclo[2.2.1]heptane-1-carboxylic acid (**4**).*

Yield of 95 %, a white solid, mp 245–247 °C [15]. ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.33 (br s, 1H), 10.16 (br s, 1H), 2.67 (d, J = 18 Hz, 1H), 2.20-2.05 (m, 2H), 1.80-1.65 (m, 1H), 1.49-1.38 (m, 1H), 1.35-1.25 (m, 1H), 0.92 (s, 3H), 0.89 (s, 3H), 0.70 (s, 3H). ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 174.5, 164.3, 54.7, 53.4, 51.2, 35.7, 32.1, 30.4, 17.9, 17.0, 11.7. HRMS calcd for $C_{11}H_{17}NO_3$: 211.1208; found: 211.1204.

*[3-(Hydroxyimino)-4,7,7-trimethylbicyclo[2.2.1]hept-1-yl]acetic acid (**3**).*

Yield of 96 %, a white solid, mp 231–232 °C. ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.04 (br. s, 1H), 10.02 (s, 1H), 2.26-2.14 (m, 3H), 2.10 (d, J = 18 Hz, 1H), 1.66-1.57 (m, 2H), 1.47-1.38 (m, 1H), 1.33-1.23 (m, 1H), 0.93 (s, 3H), 0.74 (s, 3H), 0.58 (s, 3H). ^{13}C-NMR (150 MHz, DMSO-d$_6$): δ = 173.8, 165.7, 52.6, 50.0, 47.1, 37.4, 36.6, 32.5, 32.3, 17.3, 16.1, 12.3. HRMS calcd for $C_{12}H_{19}NO_3$: 225.1365; found: 225.1363.

General procedure for the Beckmann fragmentation.

4.5 Mmol of the oxime from the previous stage was placed in a 100 mL round-bottomed flask equipped with a magnetic stirring bar and reflux condenser. Constantly boiling hydrochloric acid (50 mL) was added and the mixture was heated under reflux for 6 hours with continuous stirring. Reaction mixture was cooled to room temperature and evaporated to dryness under reduced pressure using a rotary evaporator. The residue was dissolved in 50 mL of ethyl acetate, washed twice with 20 mL of distilled water, dried over magnesium sulfate, filtered, and the solvent was removed under vacuum on a rotary evaporator.

*cis-(6,6,6a-Trimethyl-2-oxohexahydro-3aH-cyclopenta[b]furan-3a-yl)acetic acid (**5**).*

Yield of 97 %, a white solid, mp 168–169 °C. ^{1}H-NMR (600 MHz, DMSO-d$_6$):δ = 12.25 (br s, 1H), 2.89(d, J = 18 Hz, 1H), 2.62(d, J = 15.6 Hz, 1H), 2.58 (d, J = 18 Hz, 1H), 2.41(d, J = 15.6 Hz, 1H), 1.90-1.75 (m, 2H), 1.54-1.39 (m, 2H), 1.18 (s, 3H), 0.98 (s, 3H), 0.87 (s, 3H). ^{13}C-NMR (150 MHz, DMSO-d$_6$): δ = 175.7, 173.0, 99.2, 48.7, 45.8, 44.1, 43.6, 40.2, 37.4, 23.8, 23.5, 16.1. HRMS calcd for $C_{12}H_{18}O_4$: 226.1205; found: 226.1199.

*cis-6,6,6a-Trimethyl-2-oxohexahydro-3aH-cyclopenta[b]furan-3a-carboxylic acid (**6**).*

Yield of 59%, a white solid, mp193–194°C. ^{1}H-NMR (600 MHz, CDCl$_3$): δ = 9.79 (br. s, 1H), 3.69 (d, J=18 Hz, 1H), 2.81-2.73 (m, 1H), 2.53

(d, J = 18 Hz, 1H), 1.78-1.72 (m, 1H), 1.70-1.60 (m, 2H), 1.34 (s, 3H), 1.09 (s, 3H), 1.02 (s,3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 178.8, 174.8, 99.9, 58.8, 46.3, 41.6, 37.9, 35.5, 23.2, 23.1, 17.4. HRMS calcd for $C_{11}H_{16}O_4$: 212.1049; found: 212.1045.

(1,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]hept-4-yl)acetic acid (7). Yield of 37%, a white solid, m.p. 175–176 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$): δ =10.25 (br s, 1H), 2.72 (d, J = 15.6 Hz, 1H), 2.39 (d, J = 15.6 Hz, 1H), 2.13-2.07 (m, 1H), 1.96-1.81 (m, 3H), 1.34 (s, 3H), 0.92 (s, 3H), 0.88 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 179.7, 175.1, 93.4, 55.2, 52.4, 32.4, 31.7, 25.9, 16.5, 16.3, 13.8. HRMS calcd for $C_{11}H_{16}O_4$: 212.1049; found: 212.1046.

Conclusions

The intramolecular lactonization of carbocations formed during the Beckmann fragmentation of camphor-4-carboxylic and camphor-4-acetic acid oximes leads to the formation of functionalized [2.2.1] and [3.3.0] bicyclic lactones in good yields. These simple transformations give the opportunity to obtain more complex terpenoids in large-scale synthesis, starting from easily available derivatives of camphor.

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