Beckmann Rearrangement of 3-carboxybicyclo[3.3.1]nonane and [3.2.1]octane Oximes

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Regiospecific Beckmann rearrangement of substituted 2-hydroximinonorbornanone carboxylic acids has been investigated. Selective formation of new functionalized 10-oxo-9-azabicyclo[3.3.2]decanes and 7-oxo-6-azabicyclo[3.2.2]nonanes in good yield has been demonstrated. Presence of neighboring carboxylic group allows conducting of Beckmann rearrangement of strained bicyclic compounds.

Introduction

Beckmann rearrangement, discovered 130 years ago, has been widely used for the purposes of modern organic synthesis of large variety of natural products, pharmaceuticals and products of bulk industrial processes [1-3]. Nevertheless strained cyclic systems undergo abnormal rearrangement (Beckmann fragmentation) which is often accomplished with different carbocation rearrangements resulting in complex mixture of products [4-10]. Thus norbornanone oximes, among them the investigated are terpenoid derivatives, showed very poor ability to form classic rearrangement products. Camphor oxime can give up to 12 products under different reaction conditions, but no formation of desired lactame was observed [11]. Substituted norbornanone oximes have been reported to form a mixture of fragmentation products under various acidic, basic and photochemical conditions. Bicyclic lactames were detected as minor byproducts only in a few cases [12-15].

Results and discussion

We have chosen two pairs of model substrates in order to examine the assumption, that carboxyl group in proper position can be involved in Beckmann rearrangement by influencing on its products or on the kinetics of our studies we investigated *anti-* and *syn-*8-oximinobicyclo[3.2.1]octane- and 9-oximinobicyclo[3.3.1]nonane-3-carboxylic acids (**1.1, 1.2, 2.1, 2.2**) (**Figure 1**).
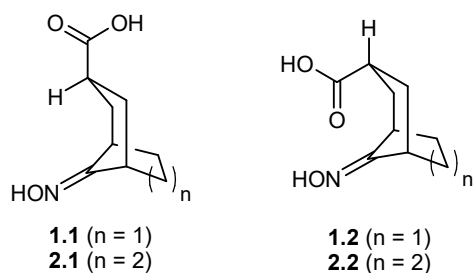
Figure 1. Bicyclic oximinocarboxylic acids.

Compounds **1.1** and **2.1** contain significantly distant carboxyl group, which probably does not affect the reaction behavior. In turn, compounds **1.2** and **2.2** have close carboxyl group, which is probably able to stabilize the transition state of the Beckman rearrangement by overlapping of vacant orbitals of intermediate carbocations with the lone pairs of oxygen atoms of carboxyl groups and contribute to obtaining products of normal rearrangement or influence the reaction, resulting in recyclization or fragmentation products. In addition, it should be noted that both types of bicyclic oximes have features that allow using them as convenient model compounds. Firstly, these oximes are not able to deuterium exchange of the bridgehead α-protons according to the Bredt`s rule. This greatly facilitates rearrangement monitoring in a solution of deuterated trifluoroacetic acid. Secondly, in the case of Beckmann rearrangement regioisomeric products should not be expected due to the symmetry of the molecules, which contributes to easier identification of the reaction products.

All the oximino acids were prepared from corresponding keto acids and hydroxylamine hydrochloride in presence of pyridine. Ketoacids **3**, **4**, **5** and **6** were synthesized by alkylation of 1-pyrrolidino-1-cyclopentene (**7**) or 1-pyrrolidino-1-cyclohexene (**8**) with ethyl 3-bromo-2-bromometylpropionate (**9**) [16-18]. As a result we obtained bicyclic esters of *anti*-configuration (**10**, **11**) due to steric factors. These esters was subjected to hydrolysis in aqueous LiOH resulting *anti*-keto acids **3** and **4**, another part of the esters **10** and **11** was isomerized in MeONa to *syn*-keto esters **12**, **13** and then also hydrolyzed to *syn*-keto acids **5** and **6** (**Scheme 1**).
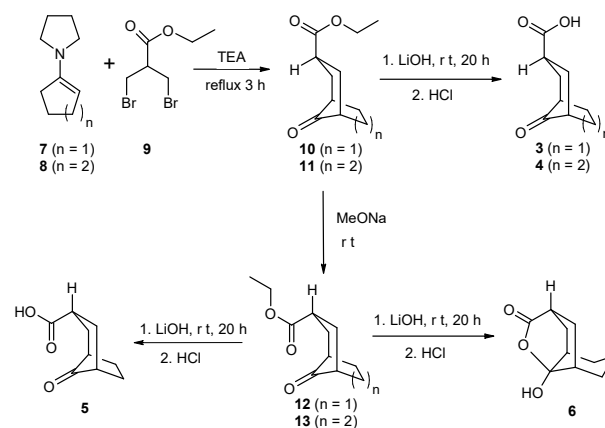

Scheme 1. Synthesis of *syn*- and *anti*-keto acids.

Spectral measurements showed differences between these acids. *Syn*-keto acid **6** exists in the lactole form, which shows the spatial proximity of carbonyl and carboxylic groups. In turn, *anti*-keto acid **4** does not have such proximity of functional groups and lactole is not formed. Despite the more electrophilic character of carbonyl group in keto acid **5** than in **6**, bicyclo[3.2.1]octane-carboxylic acid **5**

does not form lactole. This obviously indicates a greater spatial distance between carboxyl and carbonyl groups.

Beckman rearrangement was carried out by heating of oximino acids in trifluoroacetic acid (**Scheme 2**).
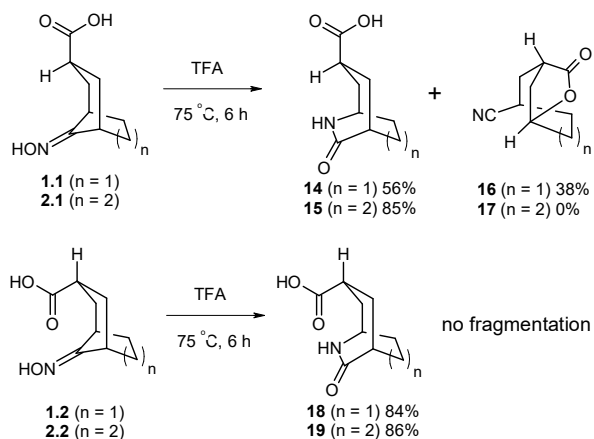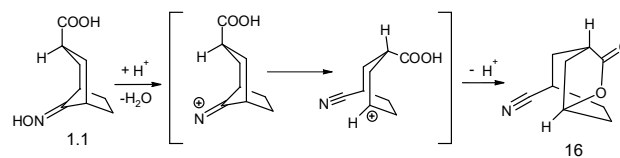

Scheme 2. Beckmann rearrangement of bicyclic oximes.

The obtained data indicate that oximes **2.1** and **2.2** in solution of trifluoroacetic acid at a temperature of 73-75 °C after 6 hours completely converted to the corresponding lactams **15** and **19**. Intermediate probes in deuterated trifluoroacetic acid show that the *syn*-oxime **2.2** reacts slightly faster than *anti*-oxime **2.1.** Conversion ratio for *syn*-/*anti*-oximes was 31.5/23 after 1 h heating and 79/68 after 3 h heating**.**

Bicyclo[3.2.1]octane oximes **1.1** and **1.2** react with the same speed, but in different directions. *syn*-Oxime **1.2** underwent classical Beckmann rearrangement forming lactam 18. However, *anti*-oxime **1.1** gave a mixture of products - lactam **14** (rearrangement product) and lactone **16** (recyclization product) in the

ratio of 3: 2. The appearance of the lactone **16** could be explained by fragmentation process of oxyme **1.1** and recovering of cation by neighboring carboxyl group (**Scheme 3**).

Scheme 3. Plausible mechanism of formation of lactone **16.**

Conclusions

We can conclude that bicyclo[3.3.1]nonane skeleton is large enough to stabilize the 9-azabicyclo[3.3.2]decene carbocation transition state of normal Beckmann rearrangement, unlike the above mentioned bicyclo[2.2.1]heptanes. Therefore, several cationic transition states may exist, which promotes Beckmann rearrangement similar to oxime of cyclohexanone. Carboxyl group in compounds **2.1** and **2.2** does not participate significantly in the reaction, although likely contributes to more rapid progress in *syn*-oxime **2.2.** Considering that there is no fragmentation of *syn*-oxime **1.2** it is arguable that spatially contiguous carboxyl group stabilizes the transition state, showing anchimeric assistance, promotes the formation of lactam.

Experimental part

All starting materials were purchased from Acros, Merck, Aldrich and Fluka chemicals. All solvents were distilled before use [19]. All experiments, unless otherwise stated,

were carried under Argon atmosphere. The ^{1}H and ^{13}C NMR spectra were recorded on a "Mercury 400" Varian and Bruker AM 400 (400 MHz) spectrometers. Tetramethylsilane was used as an internal standard. Mass spectra ware recorded on Agilent 1100 LSMS SL instrument with chemical ionization. Melting points are uncorrected.

General method of preparation. anti- and syn-8-oximinobicyclo[3.2.1]octane- and 9-oximinobicyclo[3.3.1]nonane-3-carboxylic acids (1.1, 1.2, 2.1, 2.2). Hydroxylamine hydrochloride (6 mmol) and pyridine (6 mmol) was added to a stirred solution of 5 mmol of keto acid (compounds **3-6**) in 2-propanol. The reaction mixture was heated under reflux for 5 h. After that, the reaction was evaporated under reduced pressure and 100 ml of distilled water was added to the residue. The product was filtered, washed with water, dried and recrystallized from methanol to give compounds **1.1**, **1.2**, **2.1**, **2.2**.

anti-8-oximinobicyclo[3.2.1]octane-3-carboxylic acid (**1.1**). Yield of 88 %, a white solid, m.p. 125–127 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 12.35 (br s, 1H, COOH), 10.00 (br s, 1H, N-OH), 3.13 (s, 1H), 2.59-2.51 (m, 1H), 2.50-2.41 (m, 2H), 2.39-2.33 (m, 1H), 1.90-1.79 (m, 1H), 1.66-1.53 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 176.98, 167.23, 37.36, 35.83, 34.14, 33.42, 31.63, 24.17, 24.16.

Anal. calcd. for C$_9$H$_{13}$NO$_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.89; H, 7.24; N, 7.59.

syn-8-oximinobicyclo[3.2.1]octane-3-carboxylic acid (**1.2**). Yield of 93 %, a white solid, m.p. 135–138 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 12.15 (br s, 1H, COOH), 10.07 (br s, 1H, N-OH), 3.18 (br s, 1H), 2.74 (pent, 1H, J = 7.4 Hz), 2.52 (s, 1H), 1.96–1.92 (m, 1H), 1.85–1.82 (m, 1H), 1.67–1.59 (m, 6H). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 176.17, 166.86, 38.13, 37.46, 35.42, 34.14, 31.61, 25.27, 25.12. Anal. calcd. for C$_9$H$_{13}$NO$_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.86; H, 7.25; N, 7.57.

anti-9-oximinobicyclo[3.3.1]nonane-3-carboxylic acid (**2.1**). Yield of 89 %, a white solid, m.p. 185–187 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 11.87 (br s, 1H, COOH), 9.95 (br s, 1H, N-OH), 3.54 (d, J = 10.8 Hz, 1H), 2.52 (t, J = 7.8 Hz, 1H), 2.20–2.08 (m, 2H), 2.04–1.97 (m, 1H), 1.92–1.86 (m, 1H), 1.71–1.59 (m, 4H), 1.54–1.42 (m, 3H). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 176.08, 161.96, 37.31, 34.29, 33.25, 32.25, 30.76, 30.05, 25.66, 15.19. Anal. calcd. for C$_{10}$H$_{15}$NO$_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.82; H, 7.76; N, 7.01.

syn-9-oximinobicyclo[3.3.1]nonane-3-carboxylic acid (**2.2**). Yield of 91 %, a white solid, m.p. 176–179 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 12.16 (br s, 1H, COOH), 10.14

(br s, 1H, N-OH), 3.44 (s, 1H), 3.15 (pent, $J =$ 7.8 Hz, 1H), 2.42 (s, 1H), 2.07-1.97 (m, 2H), 1.88-1.85 (m, 2H), 1.77-1.65 (m, 5H), 1.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d$_6$): $\delta = 176.31$, 162.17, 37.61, 35.70, 34.91, 33.99, 32.48, 30.92, 27.29, 20.98. Anal. calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.78; H, 7.77; N, 7.02.

General method of Beckmann rearrangement of anti- and syn-8-oximinobicyclo[3.2.1]octane- and 9-oximinobicyclo[3.3.1]nonane-3-carboxylic acids (1.1, 1.2, 2.1, 2.2). Solution of 2 mmol of hydroxylamino acid (compounds **1.1**, **1.2**, **2.1**, **2.2**) in trifluoroacetic acid (20 ml) was heated under reflux for 6 h. The reaction was evaporated under reduced pressure and 20 ml of distilled water was added to the residue. Resulting mixture was evaporated under reduced pressure again and 20 ml of distilled water was added to the residue. The product was filtered, washed with water and dried to give compounds **14-19**.

syn-6-aza-7-oxobicyclo[3.2.2]nonane-3-carboxylic acid (**18**). Yield of 84 %, a white solid, m.p. 218–220 °C; ^{1}H NMR (400 MHz, CD$_3$OD): $\delta = 3.55$ (s, 1H), 2.83 (s, 1H), 2.42 (s, 1H), 2.03-1.99 (m, 2H), 1.89-1.76 (m, 4H), 1.63-1.52 (m, 2H). ^{13}C NMR (125 MHz, CD$_3$OD): $\delta = 180.93$, 178.34, 48.57, 40.36, 39.84, 37.20, 31.12, 25.12, 22.33. HRMS (CI,

CH$_4$) calcd for $C_9H_{14}NO_3$: 184.0974 (MH$^+$); found: 184.0969.

anti-6-aza-7-oxobicyclo[3.2.2]nonane-3-carboxylic acid (**14**). Yield of 56 %, a white solid, m.p. 207–209 °C; ^{13}C NMR (125 MHz, CD$_3$OD): $\delta = 180.60$, 177.29, 48.02, 40.92, 39.15, 36.23, 32.73, 28.68, 26.74. HRMS (CI, CH$_4$) calcd for $C_9H_{14}NO_3$: 184.0974 (MH$^+$); found: 184.0971.

8-oxo-7-oxabicyclo[4.2.1]nonane-3-carbonitrile (**16**). Yield of 38 %, a colorless oil. ^{13}C NMR (125 MHz, CD$_3$OD): $\delta = 178.55$, 123.21, 80.86, 39.54, 34.65, 32.53, 30.96, 28.34, 26.82. HRMS (CI, CH$_4$) calcd for $C_9H_{12}NO_2$: 166.0868 (MH$^+$); found: 166.0866.

anti-9-aza-10-oxobicyclo[3.3.2]decane-3-carboxylic acid (**15**). Yield of 85 %, a white solid, m.p. 203–205 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): $\delta = 12.28$ (br s, 1H, COOH), 7.60 (d, $J = 6.4$ Hz, 1H, NH), 3.47 (s, 1H), 3.38 (s, 1H), 2.69 (s, 1H), 2.24 (t, $J = 7.2$ Hz, 1H), 2.12-2.05 (m, 2H), 1.86-1.80 (m, 1H), 1.68-1.64 (m, 1H), 1.55-1.41 (m, 5H). ^{13}C NMR (125 MHz, DMSO-d$_6$): $\delta = 176.73$, 176.18, 44.64, 42.16, 39.84, 34.44, 29.13, 27.93, 25.10, 18.34. HRMS (CI, CH$_4$) calcd for $C_{10}H_{16}NO_3$: 198.1130 (MH$^+$); found: 198.1124.

syn-9-aza-10-oxobicyclo[3.3.2]decane-3-carboxylic acid (**15**). Yield of 86 %, a white

solid, m.p. 88–90 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 12.24 (br s, 1H, COOH), 7.57 (d, J = 8.0 Hz, 1H, NH), 3.45 (s, 1H), 2.92 (t, J = 7.4 Hz, 1H), 2.70-2.60 (m, 1H), 1.96-1.92 (m, 1H), 1.88-1.68 (m, 4H), 1.64-1.45 (m, 3H), 1.43-1.34 (m, 2H). ^{13}C NMR (125 MHz, DMSO-d$_6$): δ = 177.09, 176.56, 44.97, 42.64, 36.93, 36.62, 30.20, 27.72, 23.40, 22.11. HRMS (CI, CH$_4$) calcd for $C_{10}H_{16}NO_3$: 198.1130 (MH$^+$); found: 198.1134.

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