Unusual transformation of 4-methyldihydrofuro[2,3-h]coumarin-9-one oxime in presence of Beckmann rearrangement catalysts

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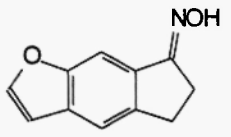
Abstract: The rearrangement of 4-methyldihydrofuro[2,3-h]coumarin-9-one oxime in presence of Beckmann catalyst (mixture of glacial acetic acid with HCl or HBr) or $POCl_3$ provides corresponding 8-halogeno-4-methyldihydrofuro[2,3-h]coumarin-9-ones formation. α-Halogenation of condensed furanone ring seems to be due to imin-amin tautomerism of the oxime. 8-Halogeno-4-methyldihydrofuro[2,3-h] coumarin-9-ones have been transformed to 9-acetoxy-8-halogeno-4-methylangelicins (due to their keto-enol tautomerism) and to 8-substituted derivatives (due to their reactivity with nucleophiles).

Introduction

Two ways of Beckmann rearrangement are known since it was discovered in 1886 (1). "Normal" way of Beckmann rearrangement of ketoximes provides a carboxylic acid amide formation via simultaneous intramolecular mechanism. "Abnormal" way of Beckmann rearrangement undergoes through intermediate carbocation and nitril formation (2-6).

Beckmann rearrangements of cyclic oximes are also known. For example, oxime **1** gives two cyclic lactam isomers **2** and **3** under different reaction conditions (7).



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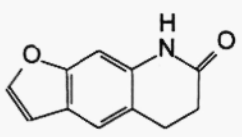

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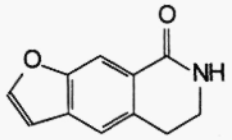
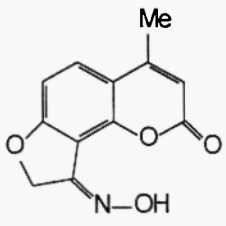


3

Looking for new ways of hetarenocoumarin synthesis (8, 9) we have studied transformations of 4-methyldihydrofuro[2,3-h]coumarin-9-one **4** oxime (**5**, oxime of **4**) in presence of $POCl_3$ and HCl.

Results and Discussion

We have found that stirring of the compound **5** in presence of $POCl_3$ or in mixture of glacial acetic acid with HCl leads to 8-chloro-4-methyldihydrofuro[2,3-h]coumarin-9-one **6a** . Use of HBr as an acid catalyst gives 8-bromo-4-methyldihydrofuro[2,3-h]coumarin-9-one **6b**. No any transformations of **5** have been found when concentrated sulfuric acid was used as Beckmann reaction catalyst.



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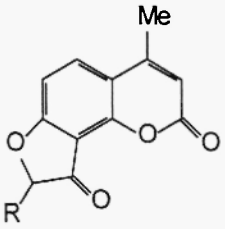
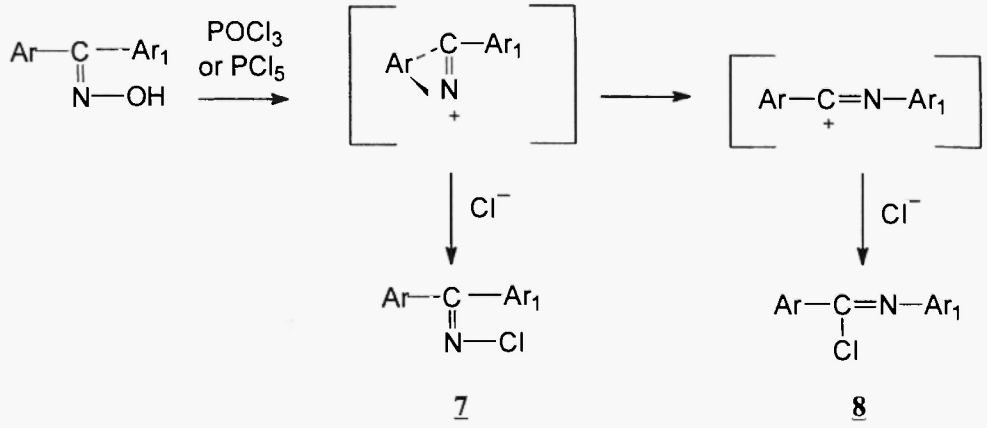


6

a: R=Cl; **b**: R=Br

Halogenated compounds formation via Beckmann rearrangement has been reported: N-chlorinated and C-chlorinated imines **7** and **8** were isolated when phosphorous chlorides had been used as catalysts (10-12). Formation of these chlorinated products has been rationalized by the scheme 1.

scheme 1

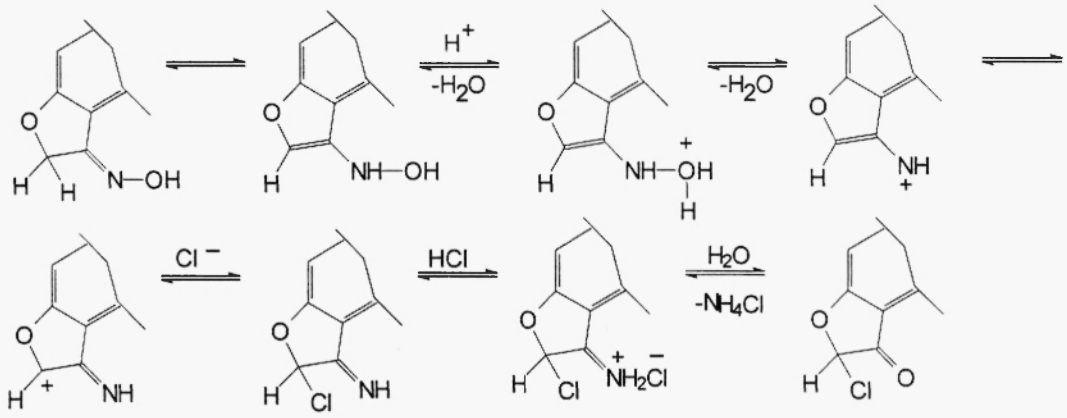


7 **8**

We have not found any rearrangement products (like **7** and **8**) when oxime **5** was treated by $POCl_3$ or HCl. One might suggest hydrolysis of oxime **5** to ketone **4** followed by a halogenation step as a way of coumarinones **6** formation. However no any transformations were detected under treatment of ketone **4** by mixture of glacial acetic acid with HCl.

We suggest the following scheme of the compound **5** transformation in presence of Beckmann reaction catalyst:

scheme 2

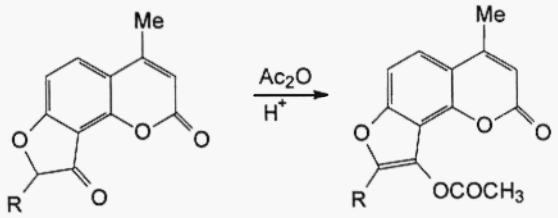


As one can see, α-halogenation of furanone **4** oxime is based on tautomerism of dihydrofuranone moiety and represents an unusual type of ketoxime reactivity in presence of Beckmann rearrangement catalysts.

We have approved compound **5** tautomeric transformations by electron absorption spectroscopy. A gradual change of the solvent composition from 100% CCl_4 - 0% CH_3OH to 0% CCl_4-100% CH_3OH provides a definite isobestic point due to intersection of the absorption spectral curves.

The suggested imin-amin tautomerism is similar to keto-enol transformations shown by compound **4**. For example, we have prepared compound **6b** by direct bromination of 4-methyldihydrofuro[2,3-h] coumarin-9-one **4** in dry dioxane. Use of excess bromine under the same conditions results in 8,8-dibromo-4-methyldihydrofuro[2,3-h]coumarin-9-one **9**. When treated by acetanhydride in presence of H_2SO_4 compounds **6** transform to enolacetates **10**, 8-substituted-9-acetoxyangelicins (see scheme 3).

scheme 3



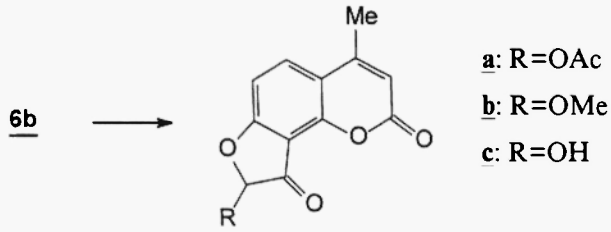
6 **10**

a: R=Cl; **b**: R=Br

Halogen atom in compounds **6** is rather reactive to nucleophilic substitution. For example, compound **6b** has been transformed to 8-acetoxy-4-methyldihydrofuro[2,3-h]coumarin-9-one **11a** when treated by CH_3COONa in dry acetone. Use methanol and Ag_2CO_3 provides transformation of **6b** to 8-methoxy-4-methyldihydrofuro[2,3-h]coumarin-9-one **11b**. Treatment of compound **6b** with aqueous

acetone in the presence of AgOH gives 8-hydroxy-4-methyldihydrofuro[2,3-h]coumarin-9-one **11c** (see scheme 4).

scheme 4



11

a: R=OAc
b: R=OMe
c: R=OH

Compound **11c** readily undergoes acetylation reaction with compound **11a** formation. Contrary to compounds **6** we have not succeeded aromatization of **11a** and **11b** by acetylation reaction. Donor acetoxy and methoxy functions at position 8 of furanone ring seem to decrease the enol content in keto-enol equilibrium.

^{1}H-NMR spectra

^{1}H-NMR spectra were recorded on a Varian Gemini-200 spectrometer at 200 MHz in acetone-d_6 or $CDCl_3$ solutions using TMS as internal standard. Chemical shifts are given in ppm.

The most characteristic signal of 8-substituted-4-methyldihydrofuro[2,3-g]coumarin-9-ones is a singlet of furanone ring 8-H proton. Its position shifts to a lower field (5.35(**11b**), 5.57(**11c**), 6.25(**11a**), 6.56(**6b**)) with increase of electron-withdrawing effect of neighbor group (OMe(**11b**), OH(**11c**), OAc(**11a**), Br(**6b**)).

^{1}H-NMR spectra of 9-acetoxyangelicins **10a** and **10b** are worth of additional comments. Under aromatization via acetylation reaction 5- and 6-H coumarin proton signals approach each other: 5-H proton signal shifts to a higher field and 6-H proton signal shifts to a lower field compared to position of these protons in nonaromatic systems **6a** and **6b**.

Mass spectra

Mass spectra were scanned on a SSQ-710 (Finnigan MAT) spectrometer at the energy of ionising electrons equal to 70 ev.

Molecular ions of compounds **6a**, **6b** and **9** have low intensity peaks (67, 39 and 26% respectively), but they produce radical-ions of the highest stability after losing halogen.

Compounds **11** also have no the highest intensity parent peaks, but their molecular ions decompose under electron impact with losing of HCO, ketene or other fragments, resulting radical-ions of the highest stability.

9-Acetoxyangelicins **10** have low intensity parent peaks (17 and 12% respectively). The base peaks were resulted after the elimination of ketene fragment.

Experimental

4-Methyldihydrofuro[2,3-h]coumarin-9-one oxime 5

The mixture of compound **4** (1 g, 4.6 mmole), hydroxylamine hydrochloride (1 g,13.8 mmole), sodium acetate (3 g, 30 mmole) and ethanol (40 ml) was refluxed for 4 hours and poured then into water. The product was filtrated off and recrystallized from ethanol as white crystals. Yield 0.74 g (70%).

5: mp 254-255 °C; ^{1}H-NMR (acetone-d_6, J/Hz), 2.47 (d, 3H, 4-Me, $J_{Me,3}$=1.4), 5.31 (s, 2H, -CH_2-), 6.18 (d, 1H, 3-H, $J_{3,Me}$=1.4), 6.97 (d, 1H, 6-H, $J_{6,5}$=8.9), 7.78 (d, 1H, 5-H, $J_{5,6}$=8.9), 10.61 (s, 1H, OH).

MS: m/z (%) 231 (M+, 100), 214 (-OH, 23), 201 (-H_2CO, 18), 186 (-H_2CO, -Me, 16), 172 (-H_2CO, -CHO, 17).

8-Chloro-4-methyldihydrofuro[2,3-h]coumarin-9-one 6a

Procedure 1. The mixture of compound **5** (0.5 g, 2.2 mmole), glacial acetic acid (20 ml) and concentrated HCl (10 ml) was stirred for 1 hour at room temperature, and poured then into water. The product was extracted by chloroform and (after chloroform evaporation) was recrystallized from the mixture of chloroform and heptane as white crystals. Yield 0.22 g (40%).

Procedure 2. The mixture of compound **5** (0.5 g, 2.2 mmole) and $POCl_3$ (20 ml) was heated for 30 min. in water bath and poured then into ice water. The product was extracted by chloroform and (after chloroform evaporation) was recrystallized from the mixture of chloroform and heptane as white crystals. Yield 0.14 g (25%).

6a: mp 207-209 °C; ^{1}H-NMR ($CDCl_3$, J/Hz), 2.45 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 6.15 (s, 1H, 8-H), 6.29 (d, 1H, 3-H, $J_{3,Me}$=1.2), 7.09 (d, 1H, 6-H, $J_{6,5}$=8.8), 7.91 (d, 1H, 5-H, $J_{5,6}$=8.8).

MS: m/z (%) 250/252 (1Cl) (M+, 67), 215 (-Cl, 100), 187 (-Cl, -CO, 44), 186 (-Cl, -HCO, 22), 171 (-Cl, -CO_2, 16).

Anal: calcd for $C_{12}H_7O_4Cl$: C, 57.45; H, 2.79; Cl, 14.14. Found: C, 57.41; H, 2.82; Cl, 14.19.

8-Bromo-4-methyldihydrofuro[2,3-h]coumarin-9-one 6b

Procedure 1. The mixture of compound **5** (3 g, 12.9 mmole), glacial acetic acid (40 ml) and concentrated HBr (25 ml) was stirred for 1 hour at 50 °C, and poured then into water. The product was

extracted by chloroform and (after chloroform evaporation) was separated by the column chromatography (silica gel 40/100, $CHCl_3$). Yield 0.76 g (20%).

Procedure 2. 4- Methyldihydrofuro[2,3-h]coumarin-9-one **4** (3 g, 14 mmole) was dissolved in dry 1,4-dioxane (130 ml). Solution of bromine (1 ml) in 1,4-dioxane (20 ml) was added drop by drop to the solution of 4 at room temperature, stirred then for 45 min. and poured into water. The product was filtrated off and recrystallized from acetone as white crystals. Yield 2.9 g (70%).

6b: mp 208-209 ^{0}C; ^{1}H-NMR ($CDCl_3$, J/Hz), 2.45 (d, 3H, 4-Me, $J_{Me,3}$=1.2), 6.29 (d, 1H, 3-H, $J_{3,Me}$=1.2), 6.56 (s, 1H, 8-H), 7.08 (d, 1H, 6-H, $J_{6,5}$=8.8), 7.91 (d, 1H, 5-H, $J_{5,6}$=8.8).

MS: m/z (%) 294/296 (1Br) (M+, 39), 215 (-Br, 100), 187 (-Br, -CO, 44), 171 (-Br, -CO_2, 5), 159 (-Br, -2CO, 12), 158 (-Br, -CO, -HCO, 10).

Anal: calcd for $C_{12}H_7O_4Br$: C, 48.80; H, 2.37; Br, 27.07. Found: C, 48.84; H, 2.39; Br, 27.08.

8,8-Dibromo-4-methyldihydrofuro[2,3-h]coumarin-9-one 9

The compound **9** has been synthesized by the procedure 2 of the compound **6b** preparation. The ratio compound **4**: bromine was equal to 1:1.7. The product was isolated by the column chromatography (silica gel 40/100, $CHCl_3$) and recrystallized from the mixture of acetone and heptane as white crystals. Yield 1 g (20%).

9: mp 230 (decom.) ^{0}C; ^{1}H-NMR ($CDCl_3$, J/Hz), 2.46 (d, 3H, 4-Me, $J_{Me,3}$=0.9), 6.32 (d, 1H, 3-H, $J_{3,Me}$=0.9), 7.07 (d, 1H, 6-H, $J_{6,5}$=8.9), 7.97 (d, 1H, 5-H, $J_{5,6}$=8.9).

MS: m/z (%) 372/374/376 (2Br) (M+, 26), 293/295 (1Br) (-Br, 100), 265/267 (1Br) (-Br, -CO, 12), 186 (-2Br, -CO, 10), 185 (-Br, -CO, -HBr, 11).

9-Acetoxy-8-halogeno-4-methylangelicins (acetylation of 8-halogeno-4-methyldihydrofuro [2,3-h]coumarin-9-ones 6) (general procedure)

The mixture of the compound **6** (3.4 mmole), acetanhydride (10 ml) and one drop of H_2SO_4 was heated in oil bath at the 110-120 ^{0}C for 1 hour and poured then into ice water. Crude product was filtrated off and recrystallized from the mixture of chloroform and heptane as white crystals.

10a: yield 70%, mp 210-211 ^{0}C; ^{1}H-NMR ($CDCl_3$, J/Hz), 2.46 (d, 3H, 4-Me, $J_{Me,3}$=0.9), 2.51 (s, 3H, Ac), 6.25 (d, 1H, 3-H, $J_{3,Me}$=0.9), 7.32 (d, 1H, 6-H, $J_{6,5}$=8.8), 7.50 (d, 1H, 5-H, $J_{5,6}$=8.8).

MS: m/z (%) 292/294 (1Cl) (M+, 17), 250/252 (1Cl) (-CH_2=C=O, 100), 222/224 (1Cl) (-CH_2=C=O, -CO, 9), 221/223 (1Cl) (-CH_2=C=O, -HCO, 8).

Anal: calcd for $C_{14}H_9O_5Cl$: C, 57.40; H, 3.07; Cl, 12.13. Found: C, 56.98; H, 3.03; Cl, 12.18.

10b: yield 75%, mp 225-227 ^{0}C; ^{1}H-NMR ($CDCl_3$, J/Hz), 2.46 (d, 3H, 4-Me, $J_{Me,3}$=0.9), 2.51 (s, 3H, Ac), 6.25 (d, 1H, 3-H, $J_{3,Me}$=0.9), 7.34 (d, 1H, 6-H, $J_{6,5}$=8.8), 7.49 (d, 1H, 5-H, $J_{5,6}$=8.8).

MS: m/z (%) 336/338 (1Br) (M+, 12), 294/296 (1Br) (-CH_2=C=O, 100), 266/268 (1Br) (-CH_2=C=O, -CO, 7), 238/240 (1Br) (-CH_2=C=O, -2CO, 23), 159 (-CH_2=C=O, -2CO, -Br, 33).

Anal: calcd for $C_{14}H_9O_5Br$: C, 49.83; H, 2.67; Br, 23.70. Found: C, 49.88; H, 2.69; Br, 23.70.

8-Acetoxy-4-methyldihydrofuro[2,3-h]coumarin-9-one 11a

The mixture of compound **6b** (1 g, 3.4 mmole), dry potassium acetate (4 g, 49 mmole) and dry acetone (100 ml) was stirred for 1 hour at room temperature. After filtration and acetone evaporation compound **11a** was recrystallized from chloroform as white crystals. Yield 4.6 g (50%).

10a: yield 70%, mp 215 °C; ^{1}H-NMR ($CDCl_3$, J/Hz), 2.22 (s, 3H, Ac), 2.45 (d, 3H, 4-Me, $J_{Me,3}$=1.0), 6.25 (s, 1H, 8-H), 6.26 (d, 1H, 3-H, $J_{3,Me}$=1.0), 7.03 (d, 1H, 6-H, $J_{6,5}$=8.5), 7.88 (d, 1H, 5-H, $J_{5,6}$=8.5).

MS: m/z (%) 274 (M+, 21), 245 (-HCO, 26), 203 (-HCO, -CH_2=C=O, 100), 159 (-HCO, -CH_2=C=O, -CO_2, 5).

Anal: calcd for $C_{14}H_{10}O_6$: C, 61.26; H, 3.65. Found: C, 61.21; H, 3.68.

8-Methoxy-4-methyldihydrofuro[2,3-h]coumarin-9-one 11b

The mixture of the compound **6b** (0.75 g, 2.5 mmole), dry Ag_2CO_3 (1.5 g) and dry MeOH (100 ml) was refluxed for 2 hours. Catalyst was filtrated off and after methanol evaporation the crude solid was recrystallized from the mixture of methanol and acetone as light yellow crystals. Yield 0.37 g (60%).

11b: mp 234-235 °C; ^{1}H-NMR ($CDCl_3$, J/Hz), 2.43 (d, 3H, 4-Me, $J_{Me,3}$=1.0), 3.66 (s, 3H, OMe), 5.35 (s, 1H, 8-H), 6.22 (d, 1H, 3-H, $J_{3,Me}$=1.0), 6.99 (d, 1H, 6-H, $J_{6,5}$=8.7), 7.85 (d, 1H, 5-H, $J_{5,6}$=8.7).

MS: m/z (%) 246 (M+, 84), 216 (-OCH_2, 26), 203 (-CH_3-C=O, 29), 186 (-CH_3O-C(H)=O, 100), 158 (-CH_3O-C(H)=O, -CO, 37), 130 (-CH_3O-C(H)=O, -2CO, 24), 102 (-CH_3O-C(H)=O, -3CO, 24).

8-Hydroxy-4-methyldihydrofuro[2,3-h]coumarin-9-one 11c

The mixture of the compound **6b** (0.5 g, 1.7 mmole), AgOH (0.75 g), acetone (50 ml) and water (10 ml) was stirred for 4 hours at room temperature. Catalyst was filtrated off and reaction mixture was poured into water. The product was extracted by chloroform and (after chloroform evaporation) was isolated by the column chromatography (silica gel 5/40, $CHCl_3$) and recrystallized then from the mixture of chloroform and heptane as light yellow crystals. Yield 0.14 g (35%).

11c: mp 209-210 °C; ^{1}H-NMR ($CDCl_3$, J/Hz), 2.43 (d, 3H, 4-Me, $J_{Me,3}$=1.0), 5.57 (d, 1H, 8-H, $J_{8,8\text{-}OH}$=8.3), 6.18 (d, 1H, 3-H, $J_{3,Me}$=1.0), 6.97 (d, 1H, 6-H, $J_{6,5}$=8.8), 7.89 (d, 1H, 5-H, $J_{5,6}$=8.8), 8.05 (d, 1H, 8-OH, $J_{8\text{-}OH,8}$=8.3).

MS: m/z (%) 232 (M+, 28), 203 (-HCO, 100), 175 (-HCO, -CO, 16), 204 (-CO, 32), 176 (-2CO, 17), 148 (-3CO, 24).

Conclusions

4-Methyldihydrofuro[2,3-h]coumarin-9-one oxime transforms to 8-halogeno-4-methyldihydrofuro[2,3-h] coumarin-9-ones in presence of Beckmann rearrangement catalysts (CH_3COOH + HCl/HBr) or $POCl_3$. Both starting oxime and final products behave reactivity based on their tautomeric transformations.

Acknowledgments

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