Comparative intramolecular dehydrative lactonization of 4-oxocarboxylic acids

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Dedicated to Professor Giuseppe Bartoli on the occasion of his 65th birthday

Abstract

Reaction of 3-(*p*-toluoyl)propanoic acid, **1a** (R = H) with refluxing acetic anhydride resulted quantitatively in **2**, a β,γ-unsaturated γ-lactone, which was then converted into **3a**, an α,β-unsaturated lactone by isomerization with triethylamine. The methyl- substituted compound **1b** (R = Me), an analogue of **1a**, afforded the 2(5*H*)-furanone **3b** directly by heating with Ac_2O. Similar reaction of the cycloalkane- containing oxocarboxylic acids (**4**,**5**) led in excellent yields to the fused furanones **6** and **7**, while treatment of 2-formyl-, 2-acetyl- and 2-(*p*-toluoyl)benzoic acids (**8a-c**) with Ac_2O gave the 3-acetoxy-1-(3*H*)-isobenzofuranones, **9a-c**.

Keywords: 4-Oxocarboxylic acid, dehydration, furanones, isobenzofuranones

Introduction

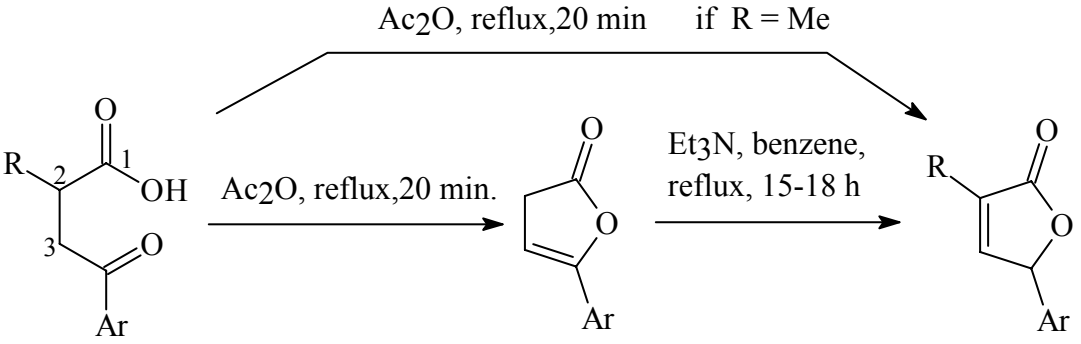
We recently described several cyclocondensation reactions of 4- and 5-oxocarboxylic acids with amines[1] and bifunctional amino derivatives, such as diamines, amino-alcohols and amino-thiols.[2] Further studies of the reactivity of *cis*- and *trans*- cyclohexane- fused 4-oxocarboxylic acids with various dehydrating agents (H_2SO_4, PPA, H_3PO_4, AcCl, Ac_2O, and DCC) led to formation of unsaturated lactones exclusively, instead of the expected saturated anthraquinone derivatives. These results prompted us to compare the reactivity of aromatic-, aliphatic-, and cycloalkane-condensed 4-oxocarboxylic acids with acetic anhydride as a mild and efficient reagent.

The chemistry, synthesis and properties of 2(3*H*)- and 2(5*H*)-furanones (butenolides) have been studied and reported in detail in the past few decades.[3-5] These ring systems serve as important moieties or precursors of several natural products (*e.g.*, avenaciolide, plumieride, digitoxin, patulin) and a series of pharmacologically active compounds (digoxin, rofecoxib, protoanemonin, phenolphthalein). A large variety of synthetic methods was reported earlier for the preparation of furanone and isobenzofuranone derivatives. Thus the readily enolized 3-

benzoylpropanoic acid was cyclized at room temperature with triphenylphosphine to the enol lactone,[6] while optically active (*ee* > 96%) γ-substituted 2-buten-4-olides were prepared by Baker's yeast reduction of alkyl 3-chloro-4-oxoalkanoates under mild conditions.[7] An efficient organoselenium-catalyzed ring-closing lactonization of butenoic acids gave alkyl- and aryl substituted 2(5*H*)-furanones, [8] and furthermore some diphenylbutenolides were prepared and studied as alkylating agents by Hashem *et al*.[9-11]

Results and Discussion

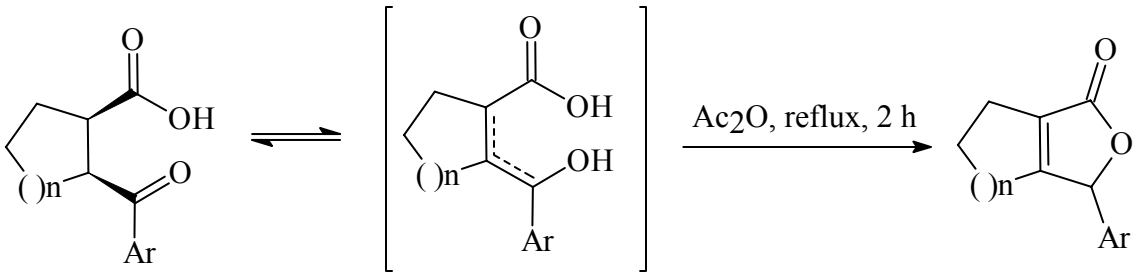
The typical reaction of 3-(*p*-toluoyl)propanoic acid, **1a** (R = H) (Scheme 1) with an excess of refluxing acetic anhydride after 20 minutes resulted in the unsaturated lactone **2** in excellent yield (88 %), then it was isomerized to the 2(5*H*)-furanone **3a** according to the method of Filler *et al* [12] in the presence of triethylamine in benzene at reflux for 15–18 hours.



Scheme 1

After purification by column chromatography on silica gel, **3a** was obtained in poor yield. On the other hand, under similar conditions, the 2-methyl- substituted analogue (**1b**) afforded the α,β -unsaturated lactone directly in good yield. In the course of the lactonization process, unexpectedly the formation of the β,γ-isomer was not observed, so further examination was aimed at relating the substituent effect on the C-2 and C-3 carbon atom. Thus, cycloalkane anellation at these positions resulted in similar cyclization and α,β-unsaturation as in the oxocarboxylic acid **1b**. When *cis*-2-(*p*-toluoyl)cyclopentane- and –cyclohexane carboxylic acids (**4**,**5**) were allowed to react in refluxing acetic anhydride the fused 2(5*H*)-furanones, **6** and **7**, were obtained almost quantitatively (Scheme 2). It is known that five- or more- membered cycloalkanones and cycloalkyl ketones are readily enolizable, and therefore intramolecular cyclization by dehydrating agents usually takes place easily. On the other hand, lactonization in this way was unsuccessful in the case of the cyclobutane- and cyclopropane- skeleton

oxocarboxylic acids, even under vigorous conditions, presumably owing to their strained and rigid cycloalkane- ring conformations.

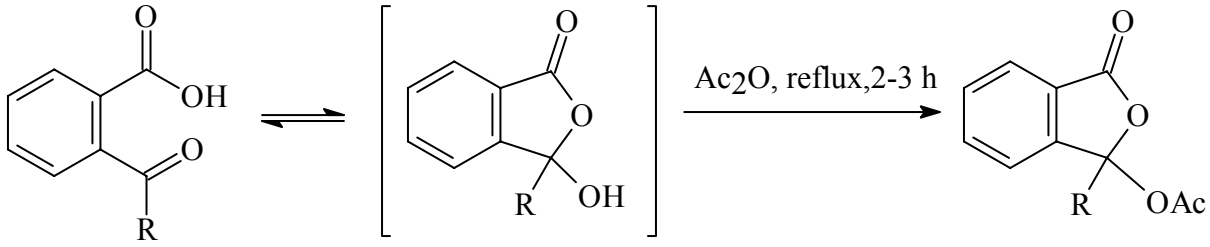


Ar = *p*- tolyl n = 1, 2

4,**5** **6**,**7**

Scheme 2

Finally, 2-formyl-, 2-acetyl-, and 2-(*p*-toluoyl)benzoic acids **8a-c**, which can exist as tautomeric mixtures of the open form or cyclic forms,[13,14] were treated with hot acetic anhydride for 2-3 hours to yield the 3-acetoxy-1-(3*H*)-isobenzofuranones, **9a-c**, after a simple workup (Scheme 3).



R = H, Me, *p*-tolyl

8a-c **9a-c**

Scheme 3

The structures of the compounds prepared were confirmed by their IR-, ^{1}H- and ^{13}C- NMR data. The structures were also studied by molecular modeling and the conformational protocol using ACD/3D ChemSketch (Version 4.01) software for compounds **2**, **3a**, **6** and **7** (Figure 1). *Ab initio*- and density functional- calculations on the ring-chain tautomerism of 4-oxocarboxylic acids were investigated recently.[15]

A relatively flexible conformation for the cyclohexene ring was observed for the lactone **7**, contrary to the cyclopentane-condensed analogue **6**, which was proved to be a rigid ring system by molecular modeling (Figure 1). The calculated structural parameters, such as distances and angles were also studied. The comparison of the computational results showed for compound **6** a

relatively shorter distance between the anellation carbon atoms, and a slightly deformed furanone ring was observed on the basis of calculated bond angles.

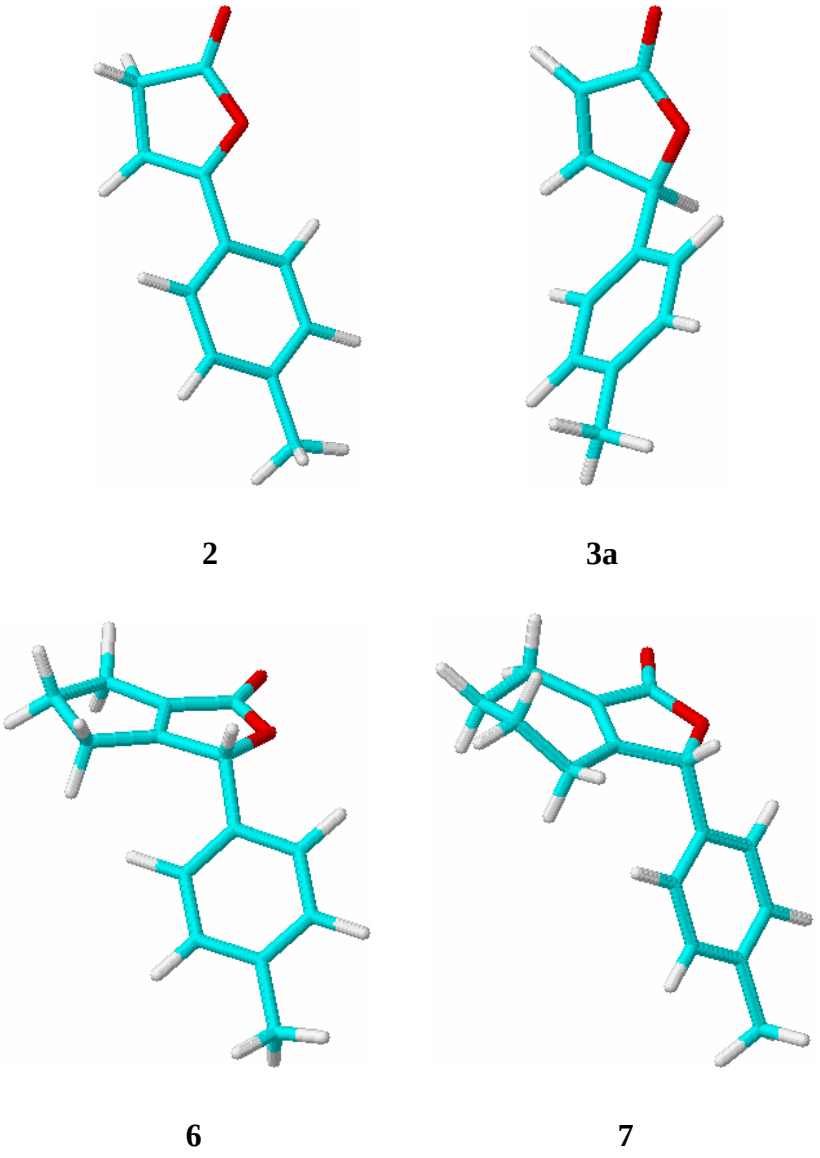


Figure 1. Final predominant minimum energy molecular structures for **2**, **3a**, **6** and **7**.

Experimental Section

General Procedures. Melting points were determined using an Electrothermal block and are uncorrected. Infrared spectra were recorded for KBr discs or films with Perkin-Elmer 177 instrument. ^{1}H- NMR and ^{13}C- NMR spectra were recorded on a Bruker *Avance* DRX 400 MHz spectrometer and $CDCl_3$ was used as solvent. Chemical shifts (δ) are in ppm from

tetramethylsilane (TMS) as internal standard, coupling constants (*J* values) are in Hz. Ascending TLC was performed on precoated plates of silica gel 60F 254 (Merck), and spots were visualized by using a UV lamp or iodine vapor. RT denotes room temperature.

Preparation of lactone (2); 5-*p*-tolylfuran-2(3*H*)-one. 3-(p-Toluoyl)propanoic acid (**1a**) (1.92 g, 10 mmol) was heated at reflux with acetic anhydride (3.06g, 30 mmol) for 20 minutes. The reaction mixture was allowed to cool to RT then it was poured into crushed ice and stirred, whereupon a solid precipitated. The solid was removed by filtration and recrystallized from benzene-diethyl ether (1:1) mixture to give pure product **2** in 88% yield. M.p. 107–109°C (lit. 111°C).[16] IR (KBr): *v* = 3111, 1800 (C=O), 1644, 1508, 1292, 1116, 1032, 893, 827, 747, 634 cm^{-1}. ^{1}H- NMR (400.13 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.40 (d, *J* = 2.1 Hz 2H), 5.71 (t, *J* = 1.8, 1.8 Hz, 1H), 7.20-7.26 (m, 2H), 7.45-7.49 (m, 2H). ^{13}C- NMR (100.62 MHz, $CDCl_3$): 21.6, 34.8, 97.3, 126.1, 129.2, 140.0, 154.2, 176.5. Anal. Calcd for $C_{11}H_{10}O_2$ (174.19): C 75.84, H 5.78; found C 75.98, H 5.85%.

Preparation of lactone (3a); 5-*p*-tolylfuran-2(5*H*)-one. The lactone **2** (0.87 g, 5 mmol) was dissolved in 20 ml of benzene and was refluxed with 10 ml of triethylamine for 15–18 hours. After evaporation the residue was purified by column chromatography on silica gel to afford **3a** in 24% yield. Colorless oil. IR (film): *v* = 3054, 1762 (C=O), 1161, 1093, 1076, 852, 810 cm^{-1}. ^{1}H- NMR: δ = 2.33 (s, 3H), 6.05 (dd, *J* = 1.9, 2.0 Hz, 1H), 6.23 (dd, *J* = 5.5, 2.0 Hz, 1H), 7.26-7.30 (m, 2H), 7.40-7.43 (m, 2H), 7.56 (dd, *J* = 5.6, 2.0 Hz 1H). ^{13}C- NMR: 84.5, 120.4, 126.3, 129.1, 129.4, 134.7, 155.8, 173.2. Calcd for $C_{11}H_{10}O_2$ (174.19): C 75.84, H 5.78; found C 75.97, H 5.88.

Preparation of lactone (3b); 3-methyl-5-*p*-tolylfuran-2(5*H*)-one. 1-methyl-3-(*p*-toluoyl)-propanoic acid (**1b;** 2.06 g, 10 mmol) was heated at reflux with 3.06g (30 mmol) of acetic anhydride for 20 min. The mixture was evaporated, and purified by column chromatography on silica gel using chloroform as eluent, to give **3b** in 76 % yield. Colorless oil. IR (film): *v* = 1795 (C=O), 1638, 1465, 1223, 876, 820, 751, 638 cm^{-1}. ^{1}H- NMR: δ = 1.88 (s, 3H), 2.34 (s, 3H), 5.66 (d, 1H, *J* = 2.0 Hz), 5.89 (d, *J* = 2.1 Hz, 1H), 7.10 (m, 2H), 7.19 (m, 2H). ^{13}C- NMR: 14.5, 21.7, 87.0, 116.7, 127.3, 129.7, 131.8, 139.9, 169.2. Calcd for $C_{12}H_{12}O_2$ (188.22): C 76.57, H 6.42; found C 76.75, H 6.49.

Preparation of lactones 6, 7 and 9b, c (General procedure)

The 4-oxocarboxylic acid (**4**, **5**, and **8b**,**c**, (10 mmol) was dissolved in acetic anhydride (20 ml) then was heated at reflux for 2 h. After evaporation under reduced pressure a mixture of diethyl ether–*n*-hexane (15:5) was added to the residue. The mixture was kept in the refrigerator for 3-5 days and the precipitated crystals filtered off.

3-*p*-Tolylcyclopenta[*c*]furan-1-one (**6**) was obtained in 87 % yield. M.p. 85-87°C. IR (KBr): *v* = 2918, 1750 (C=O), 1665, 1051, 1013, 974, 753 cm^{-1}. ^{1}H- NMR (400.13 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.44-2.47 (m, 4H), 2.57 (m, 2H), 5.84 (s, 1H), 7.13 (d, *J* = 4.3 Hz, 2H), 7.18 (d, *J* =

4.4 Hz, 2H). ^{13}C- NMR (100.61 MHz, $CDCl_3$): 20.4, 21.8, 24.9, 77.7, 82.2, 126.9, 129.6, 137.6, 170.0, 177.4. Calcd for $C_{14}H_{14}O_2$ (214.26): C 78.48, H 6.58; found C 78.70, H 6.67.

4,5,6,7-Tetrahydro-3-*p*-tolyl-1(3*H*)-isobenzofuranone (7) was obtained in 92 % yield. M.p. 79-81°C. IR (KBr): ν = 2949, 2922, 1741, 1674, 1516, 1391, 1288, 1025, 781 cm^{-1}. ^{1}H- NMR (400.13 MHz, $CDCl_3$): δ = 1.71 (m, 4H), 1.98 (m, 1H), 2.17 (m, 3H), 2.34 (s, 3H), 5.65 (s, 1H), 7.08 (d, J = 4.1 Hz, 2H), 7.17 (d, J = 4.1 Hz, 2 H). ^{13}C- NMR (100.61 MHz, $CDCl_3$): 20.5, 22.1, 23.7, 77.7, 85.0, 127.1, 129.8, 139.6, 164.4, 174.4. Calcd for $C_{15}H_{16}O_2$ (228.29): C 78.92, H 7.06; found C 79.13, H 7.10.

3-Acetoxy-3-methyl-1(3*H*)-isobenzofuranone (9b). Obtained in 85% yield. M.p. 65-67°C. IR (KBr): ν = 2995, 2941, 1781 (C=O), 1749 (C=O), 1604, 1466, 1288, 1015, 921, 768, 702, 546 cm^{-1}. ^{1}H- NMR (400.13 MHz, $CDCl_3$): δ = 1.95 (s, 3H), 2.01 (s, 3H), 7.58 (m, 2H), 7.68 (m, 1H), 7.87 (d, J = 3.8 Hz, 1H). ^{13}C- NMR (100.61 MHz, $CDCl_3$): 22.3, 25.8, 77.7, 105.7, 122.4, 126.1, 131.1, 135.1, 148.5, 168.2, 168.9. Calcd for $C_{11}H_{10}O_4$ (206.19): C 64.07, H 4.89; found C 64.22, H 4.95.

3-Acetoxy-3-(*p*-tolyl)-1(3*H*)-isobenzofuranone (9c). Obtained in 81% yield. M.p. 95-97°C. IR (KBr): ν = 1780 (C=O), 1604, 1469, 1368, 1285, 1209, 1092, 949, 761, 698, 567 cm^{-1}. ^{1}H- NMR (400.13 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 2.35 (s, 3H), 7.21 (m, 2H), 7.51 (m, 2H), 7.56-7.67 (m, 3H), 7.91 (d, J = 2.8 Hz, 1H). ^{13}C- NMR (100.61 MHz, $CDCl_3$): 21.7, 22.3, 77.7, 123.9, 128.5, 129.6, 130.0, 131.1, 133.4, 140.2, 148.5, 168.6. Calcd for $C_{17}H_{14}O_4$ (282.29): C 72.33, H 4.99; found C 72.48, H 5.08.

Preparation of the lactone, 3-acetoxy-1(3*H*)-isobenzofuranone (9a). A mixture of phthalaldehydic acid (**8a,** 1.50g, 10 mmol.) and acetic anhydride (1.53g, 15 mmol) was heated under reflux for 3 h, during which about 0.4g acetic acid distilled. The mixture was cooled and poured into crushed ice whereupon a solid precipitated. This was removed by filtration and recrystallized from benzene–diethyl ether (1:1) mixture to give pure product **9a** in 86% yield. M.p. 65-66°C. IR (KBr): ν = 1777, 1604, 1471, 1378, 1217, 1046, 968, 751, 687 cm^{-1}. ^{1}H- NMR: δ = 2.19 (s, 3H), 7.43 (s, 1H), 7.75 (m, 3H), 7.93 (d, 1H, J = 4.5 Hz). ^{13}C- NMR: 17.9, 121.0, 125.5, 129.4, 131.3, 132.2, 138.6, 163.2, 170.8. Anal. Calcd for $C_{10}H_8O_4$ (192.17): C 62.50, H 4.19; found C 62.59, H 4.24%.

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