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Graphical abstract

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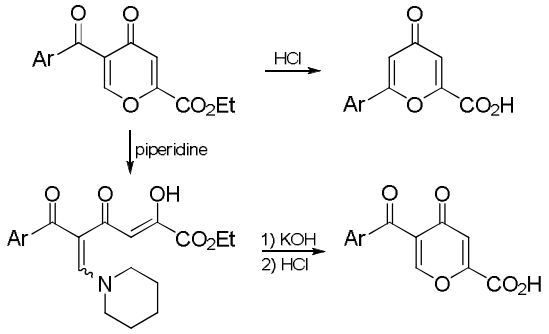


* Corresponding author. Fax: +7 343 261 59 78;
e-mail: dobydennov@mail.ru

Synthesis of 6-aryl- and 5-aroylcomanic acids from 5-aroyl-2-carbethoxy-4-pyrones via a deformylative rearrangement and ring-opening/ring-closure sequence

Dmitrii L. Obydennov [a,*], Gerd-Volker Röschenthaler [b], Vyacheslav Ya. Sosnovskikh [a]

dobydennov@mail.ru

[a] *Department of Chemistry, Ural Federal University, prosp. Lenina 51, 620000 Ekaterinburg, Russia*

[b] *School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, 28759 Bremen, Germany*

A B S T R A C T

The reaction of 1-aryl-2-(dimethylaminomethylene)butane-1,3-diones with diethyl oxalate in the presence of sodium hydride in THF gave ethyl 5-aroyl-4-oxo-4*H*-pyran-2-carboxylates, from which 4-oxo-6-aryl-4*H*-pyran-2-carboxylic acids (6-arylcomanic acids) were obtained in high yields via acid-catalyzed deformylative rearrangement. 5-Aroyl-4-oxo-4*H*-pyran-2-carboxylic acids (5-aroylcomanic acids) were prepared via a ring-opening/ring-closure sequence by the reaction of 5-aroyl-2-carbethoxy-4-pyrones with piperidine and subsequent basic hydrolysis and acidification.

Keywords: Claisen condensation; 1-Aryl-2-(dimethylaminomethylene)butane-1,3-diones; Diethyl oxalate; 5-Aroyl-2-carbethoxy-4-pyrones; Rearrangement; 6-Arylcomanic acids; Hydrolysis; 5-Aroylcomanic acids.

It is known that certain derivatives of 4-oxo-6-phenyl-4*H*-pyran-2-carboxylic acid (6-phenylcomanic acid) selectively inhibit cyclooxygenase-2 enzymes (COX-2) in preference to COX-1, and are useful in the treatment of COX-2 mediated diseases, such as inflammation, pain, fever, and asthma, with fewer side effects.[1] At the same time, these compounds are an important class of γ-pyrones which can serve as the starting materials for the syntheses of a broad range of important heterocycles due to the presence of four electrophilic centers in their molecules (the C-2, C-4 and C-6 atoms of the pyrone system and the carbonyl carbon of the 2-CO_2R group).[2] The diverse range of properties of substituted γ-pyrones is due to the fact that, being highly reactive enones with a good leaving group at the α- and α´-carbon atoms, whose role is played by the enolate anion, they

have the ability to undergo additional transformations related to γ-pyrone ring-opening and heterocyclizations.[3]

Earlier, 6-phenylcomanic acid was obtained by cyclodehydrobromination of ethyl 5,6-dibromo-2,4-dioxo-6-phenylhexanoate at reflux with KOAc in anhydrous ethanol with subsequent acid hydrolysis of the ethyl 6-phenylcomanate thus formed,[4] as well as by cyclodehydration of 6-phenyl-2,4,6-trioxohexanoic acid, prepared from benzoylacetone and dimethyl oxalate, on heating in acetic acid,[5] and by condensation of 4-phenylbut-3-yn-2-one with diethyl oxalate in the presence of NaOEt.[6] The synthesis of 6-phenylcomanic acid derivatives with a substituent on the aromatic ring, from the corresponding ethyl 6-aryl-5,6-dibromo-2,4-dioxohexanoates under the action of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[7] and diisopropylamine,[2c] has also been described.

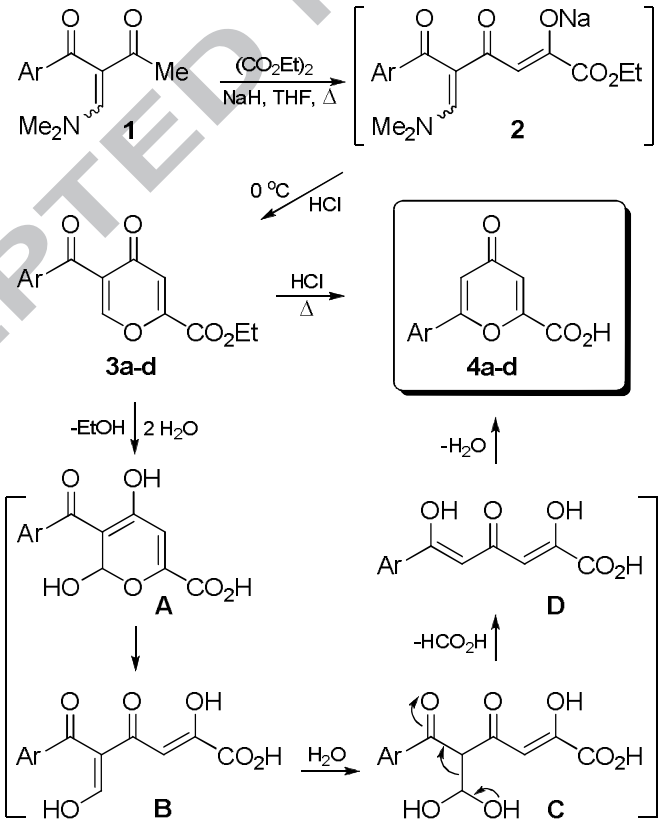
The present communication reports a novel synthesis of 6-arylcomanic acids **4** via acid-catalyzed deformylative rearrangement of ethyl 5-aroyl-4-oxo-4*H*-pyran-2-carboxylates **3**. Additionally, the preparation of 5-aroyl-4-pyrone-2-carboxylic acids (5-aroylcomanic acids, **6**) from **3** via a ring-opening/ring-closure sequence is presented. Although the chemistry of comanic acid derivatives has been well documented,[8] compounds **6** are hitherto unreported.

Within the framework of a research program on the synthetic opportunities offered by the γ-pyrone system in the preparation of organic molecules of potential interest in biomedicinal chemistry and materials science,[9] we required large quantities of ethyl 5-aroyl-4-oxo-4*H*-pyran-2-carboxylates **3**. To the best of our knowledge, there has only been one report on the preparation of these compounds via the reactions of 1-aryl-2-(dimethylaminomethylene)butane-1,3-diones **1** with diethyl oxalate in the presence of sodium ethoxide in ethanol (no product yields were reported).[10] This is the reason why pyrones **3** belong to a poorly explored class of polycarbonyl compounds, the chemical properties of which have not been investigated.

We found that the Claisen condensation of enaminodiones **1** with diethyl oxalate in the presence of sodium hydride in THF at reflux for eight hours was the method of choice for the preparation of pyrones **3**. After cooling, the reaction mixture was quenched with hydrochloric acid to give 5-aroyl-

2-carbethoxy-4-pyrones **3a–d** in 73–82% yields. It turned out that if the hydrolysis of the sodium salts **2** was carried out under milder conditions (4 M HCl, 0 °C, 30 min), the reaction could be stopped at the pyrones **3**, whereas reflux of **3** in dilute HCl (1:1) for eight hours gave 6-arylcomanic acids **4a–d** in 68–85% yields. In the ^{1}H NMR spectra of **3**, protons H-3 and H-6 appeared as singlets at δ 7.23–7.25 and δ 8.13–8.20 ($CDCl_3$), while H-3 and H-5 in **4** appeared as doublets with J = 2.2 Hz at δ 6.98–7.16 and δ 6.84–6.90 (DMSO-d_6), respectively.

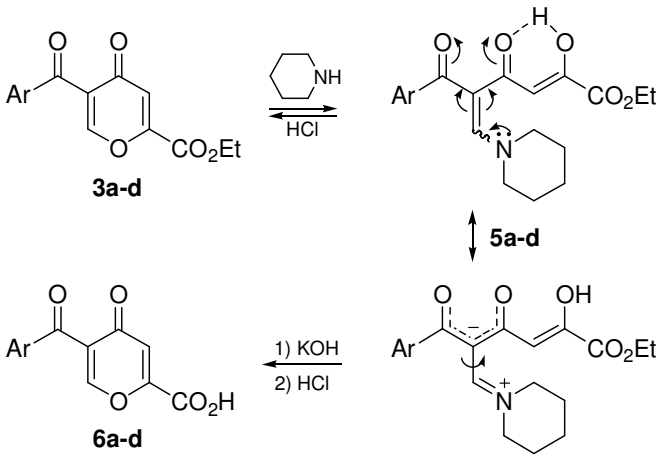
A plausible pathway leading to the formation of acids **4** via intermediates **A**–**D** is outlined in Scheme 1. It is clear from this reaction that the ester **3** reacts with water exclusively at its 6-position and in a 1,4-manner, followed by deformylative rearrangement. This transformation represents an alternative route to synthesize acids **4** and makes it possible to obtain these compounds from 1,3-diketones in three steps in 25–60% overall yields. Previously, ethyl 5-chloro- and 5-hydroxy-6-phenyl-4-oxo-4*H*-pyran-2-carboxylates were prepared from epoxypyrones using a similar rearrangement in the presence of formic or perchloric acid.[10a]



Ar	Pyrone **3**	Yield (%)	Pyrone **4**	Yield (%)
Ph	**3a**	73	**4a**	68
4-$MeOC_6H_4$	**3b**	69	**4b**	72
4-ClC_6H_4	**3c**	82	**4c**	85
2-C_4H_3S	**3d**	73	**4d**	79

Scheme 1. Synthesis of 4-pyrones **3** and **4**.

In connection with this simple rearrangement, the direct hydrolysis of **3** into 5-aroyl-4-pyrone-2-carboxylic acids (5-aroylcomanic acids, **6**) proved impossible, therefore an alternative method for the preparation of compounds **6** was required. We envisaged that the reaction of **3** with piperidine would produce the corresponding enaminotriones **5** bearing a carbethoxy group activated towards nucleophilic attack. In fact, we found that pyrones **3** reacted readily with piperidine in ethanol at 0 °C for one hour to produce enamines **5** in 57–82% yields. This reaction involved attack of the NH group at C-6 of **3** with concomitant opening of the pyrone ring to give compounds **5**, which are reactive polycarbonyl intermediates with an intramolecular hydrogen bond. The ^{1}H NMR spectra of **5** displayed broad signals for the piperidine function as a result of its only slightly hindered rotation and there was no evidence of two geometric isomers.[11] Treatment of enamines **5** with dilute HCl led to the starting pyrones **3**, however, in line with our expectations, basic hydrolysis of **5** at 0 °C for 15 minutes in the presence of KOH followed by acidification with HCl successfully removed the ethoxy group to give 5-aroylcomanic acids **6** in 61–89% yields[12] as a result of a ring-opening/ring-closure sequence (Scheme 2). Despite their rather simple structures, neither compounds **6** nor their acyclic precursors **5** have previously been prepared. It is pertinent to note that the behavior of compounds **5** closely resembles that already reported by us for 2,5-dicarbethoxy-4-pyrone, which under the same conditions gives 5-carbethoxy-4-pyrone-2-carboxylic acid.[13] Thus, γ-pyrones **3**, due to activation of the conjugated system by two electron-withdrawing groups, are highly electrophilic substrates, which are able to react with *O*- and *N*-nucleophiles, with opening of the pyrone ring.



Ar	Aminoenone **5**	Yield (%)	Pyrone **6**	Yield (%)
Ph	**5a**	82	**6a**	69
4-$MeOC_6H_4$	**5b**	79	**6b**	61
4-ClC_6H_4	**5c**	57	**6c**	89
2-C_4H_3S	**5d**	66	**6d**	80

Scheme 2. Synthesis of compounds **5** and **6**.

In summary, we have developed a novel synthesis of biologically potent 6-arylcomanic acids, which involves the deformylative rearrangement of 5-aroyl-2-carbethoxy-4-pyrones in the presence of hydrochloric acid. Compared with the previously reported procedures, our method shows several advantages, the main of which are simplicity, efficiency and the ready availability of the starting materials. In addition, 5-aroylcomanic acids were obtained in good yields, for the first time. Taking into account the ability to transform the γ-pyrone system into other compounds, the comanic acid derivatives described here are valuable building blocks for the construction of various heterocyclic systems.

Acknowledgment

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12. *General procedure for the synthesis of compounds* ***3a–d***. A mixture of enaminodione **1** (5.0 mmol), diethyl oxalate (0.88 g, 6.0 mmol) and NaH (60% dispersion in oil, 0.24 g, 6.0 mmol) in THF (15 mL) was refluxed for 8 h. After cooling, the reaction mixture was treated with 4 M HCl until pH = 1, stirred at 0 °C for 30 min, extracted with EtOAc (3 × 15 mL), and evaporated under reduced pressure. The resulting residue was quenched with EtOH to give pyrones **3** as colorless or yellowish crystals.

General procedure for the synthesis of compounds ***4a–d***. A suspension of the pyrone **3** (1.0 mmol) in dilute HCl (1:1, 2 mL) was stirred at 100 °C for 8 h. The solid that formed was filtered and dried to give pyrones **4** as a white or grey powders.

*Ethyl 4-oxo-5-(2-thienoyl)-4H-pyran-2-carboxylate (**3d**).* Yield 73%, mp 97–98 °C, colorless crystals. IR (ATR): 3087, 2983, 2923, 2853, 1728, 1655, 1641, 1621, 1578 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, *J* = 7.1 Hz, 3H, Me), 4.45 (q, *J* = 7.1 Hz, 2H, CH_2O), 7.14 (dd, *J* = 4.9, 3.9 Hz, 1H, H-4′), 7.24 (s, 1H, H-3), 7.67 (dd, *J* = 3.9, 1.1 Hz, 1H, H-3′), 7.75 (dd, *J* = 4.9, 1.1 Hz, 1H, H-5′), 8.18 (s, 1H, H-6); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.3, 63.3, 120.2, 129.5, 129.7, 137.4, 137.6, 143.5, 153.3, 157.7, 159.7, 175.6, 182.5. Anal. Calcd for $C_{13}H_{10}O_5S$: C, 56.11; H, 3.62. Found: C, 56.02; H, 3.53.

*4-Oxo-6-(2-thienyl)-4H-pyran-2-carboxylic acid (**4d**).* Yield 79%, grey powder, mp 252–253 °C. IR (ATR): 3108, 3085, 1730, 1623, 1594, 1573 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.84 (d, *J* = 2.3 Hz, 1H, H-5), 6.98 (d, *J* = 2.3 Hz, 1H, H-3), 7.27 (dd, *J* = 5.0, 3.9 Hz, 1H, H-4′), 7.93 (dd, 1H, *J* = 3.9, 1.1 Hz, H-3′), 7.95 (dd, 1H, *J* = 5.0, 1.1 Hz, H-5′), 12.0–15.5 (br s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 110.6, 118.4, 129.4, 129.9, 132.4, 133.7, 153.2, 159.5, 161.3, 178.8. Anal. Calcd for $C_{10}H_6O_4S$: C, 54.05; H, 2.72. Found: C, 54.03; H, 2.75.

*Ethyl 2-hydroxy-4-oxo-6-(piperidin-1-yl)-5-(2-thienoyl)hexa-2,5-dienoate (**5d**).* Yield 66%, yellow powder, mp 125–126 °C. IR (ATR): 3131, 3069, 2998, 2984, 2951, 1725, 1604, 1586 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.22 (t, *J* = 7.1 Hz, 3H, Me), 1.35–1.70 (br s, 6H, $3CH_2$), 2.9–3.8 (br s, 4H, $(CH_2)_2N$), 4.19 (q, *J* = 7.1 Hz, 2H, CH_2O), 6.29 (s, 1H, =CH), 7.21 (dd, *J* = 4.9, 3.9 Hz, 1H, H-4′), 7.65 (dd, *J* = 3.9, 1.2 Hz, 1H, H-3′), 8.03 (dd, *J* = 4.9, 1.2 Hz, 1H, H-5′), 8.06 (s, 1H, =CHN), 15.0–16.5 (br s, 1 H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.4, 22.8, 22.9, 44.3, 61.9, 100.0, 107.0, 129.3, 134.6, 136.2, 146.4, 154.7, 161.9, 163.0, 187.6, 188.6. Anal. Calcd for $C_{18}H_{21}NO_5S$: C, 59.49; H, 5.82; N, 3.85. Found: C, 59.45; H, 5.72, N, 3.72.

*4-Oxo-5-(2-thienoyl)-4H-pyran-2-carboxylic acid (**6d**).* Yield 80%, yellowish powder, mp 218–220 °C. IR (ATR): 3452, 3097, 1727, 1651, 1627 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ ^1H NMR (400 MHz, DMSO-d_6) δ 7.02 (s, 1H, H-3), 7.26 (dd, *J* = 4.8, 4.0 Hz, 1H, H-4′), 7.83 (dd, *J* = 4.0, 1.2 Hz, 1H, H-3′), 8.15 (dd, *J* = 4.8, 1.2 Hz, 1H, H-5′), 8.71 (s, 1H, H-6) (the OH proton was not observed due to broadening); ^{13}C NMR (100 MHz, DMSO-d_6): δ 119.9, 129.5, 129.6, 137.4, 137.5, 143.5, 154.4, 157.8, 161.1, 175.9, 182.7. Anal. Calcd for $C_{11}H_6O_5S·H_2O$: C, 49.25; H, 3.01. Found: C, 49.51; H, 2.98.

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