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Graphical abstract

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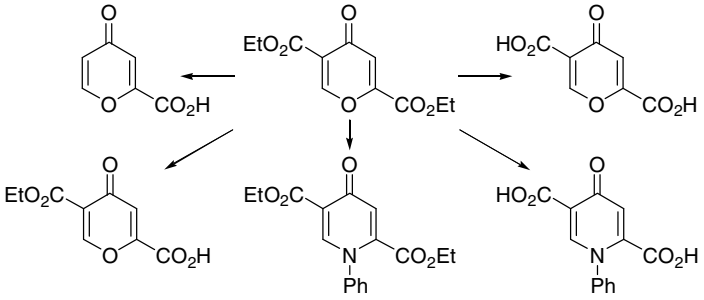

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An improved synthesis and some reactions of diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate

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A B S T R A C T

The reaction of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride in THF gave diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate, from which 4-oxo-4*H*-pyran-2,5-dicarboxylic and 4-oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylic acids and their derivatives were obtained in good yields.

Keywords: Claisen condensation; Ethyl 2-(dimethylamino)methylene-3-oxobutanoate; Diethyl oxalate; 4-Oxo-4*H*-pyran-2,5-dicarboxylic acid; 4-Oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylic acid.

Chelidonic acid, a γ-pyrone compound with the structure shown in Figure 1, is a naturally occurring compound that is widely distributed among many plants.[1] It is contained in the rhizomes of *Chelidonium majus L.* at quite high concentrations, and has multiple pharmacological effects including mild analgesic, antimicrobial, oncostatic and central nervous system sedation.[2] In addition, chelidonic acid and chelidamic acid were the most potent inhibitors of glutamate decarboxylase from rat brain,[3] and may attenuate allergic reactions by inhibition of caspase-1 activity.[4]

Unlike well-studied diethyl chelidonate,[5] diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate (diethyl isochelidonate), is much less known. Furthermore, none of the isomeric 4-pyrone dicarboxylic acids **I–III** has been recorded in the literature (Figure 1). Diethyl isochelidonate was mentioned for the first time in 2012 in the patent literature,[6] as a novel intermediate for synthesizing an anti-influenza drug exhibiting cap-dependent endonuclease inhibitory activity.

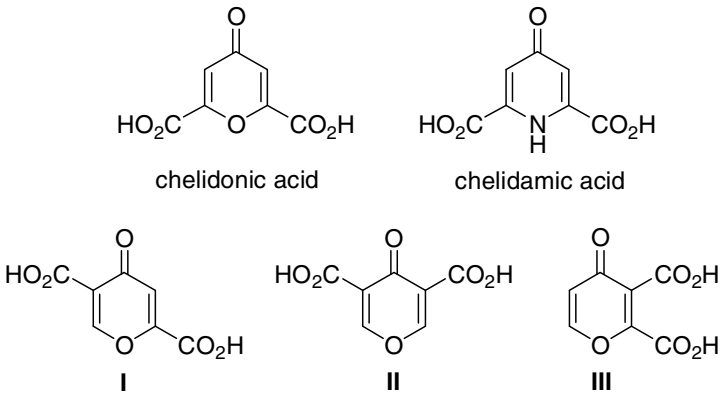


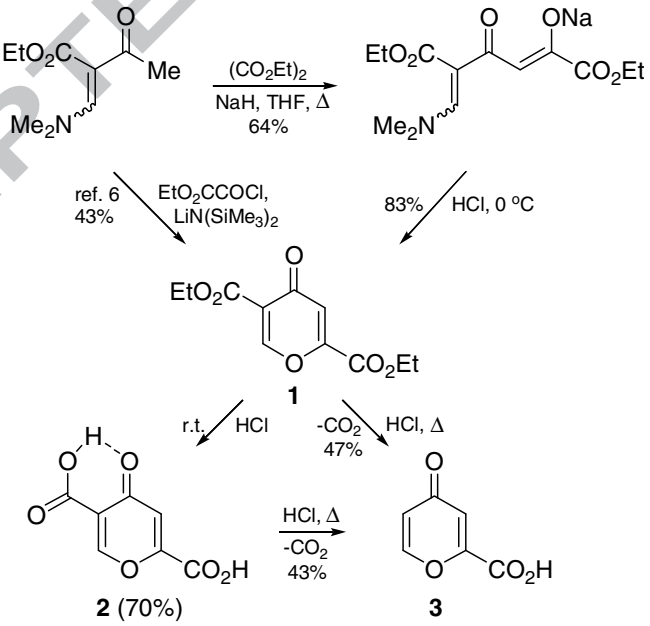
Figure 1. Some natural and unnatural γ-pyrone dicarboxylic acids.

γ-Pyrone derivatives bearing electron-withdrawing carbonyl-containing substituents at the 2- and 5-positions have, surprisingly, been poorly investigated, probably due to the limited number of methods available for their preparation.[6,7] 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 heterocyclic systems due to the presence of five electrophilic centers in their molecules (the C-2, C-4 and C-6 atoms of the pyrone system and the carbonyl carbons of the 2-COR and 5-COR' groups). The diverse range of properties of these compounds is due to the fact that, being highly reactive geminally activated push–pull alkenes with a good leaving group at the α- and α´-carbon atoms, whose role is played by the enolate anion, they acquire the ability to undergo additional transformations related to γ-pyrone ring-opening and heterocyclizations.

The present communication describes an improved synthesis of diethyl isochelidonate (**1**), which consists of the Claisen condensation of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride. Moreover, the synthesis of 4-pyrone-2,5-dicarboxylic acid [isochelidonic acid (**2**)] and its derivatives, including *N*-phenylisochelidamic acid, is presented. Although the chemistry of 4-pyrones and 4-pyridones has been well documented,[8] isochelidonic and isochelidamic acids 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 having potential interest in biomedicinal

chemistry and materials science,[9] we had a requirement for large quantities of diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate (**1**). To the best of our knowledge, there has only been one report on the preparation of diester **1** via the reaction of ethyl 2-(dimethylamino)methylene-3-oxobutanoate, prepared from ethyl acetoacetate and dimethylformamide dimethyl acetal,[10] with ethyl oxalyl chloride in the presence of hexamethyldisilazane in THF at –78 °C.[6] However, on repeating this procedure, we were unable to obtain **1** in a reasonable yield. Instead, we found that the Claisen condensation of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride in THF at reflux for five hours was the method of choice for the preparation of isochelidonic ester **1**. After cooling, the intermediate sodium salt was filtered, washed with THF (yield 64%), dissolved in water and quenched with concentrated HCl to give diester **1** in 83% yield (overall yield 53%). Note that **1** could be prepared without isolation of the sodium salt, however, a higher yield and easier purification of compound **1** was possible if the reaction was performed in a two-step approach. Unlike the previously reported method,[6] this reaction did not require a low temperature or any chromatographic purification of the final product, and thereby greatly facilitated the preparation of the target diester **1**[11] (Scheme 1).

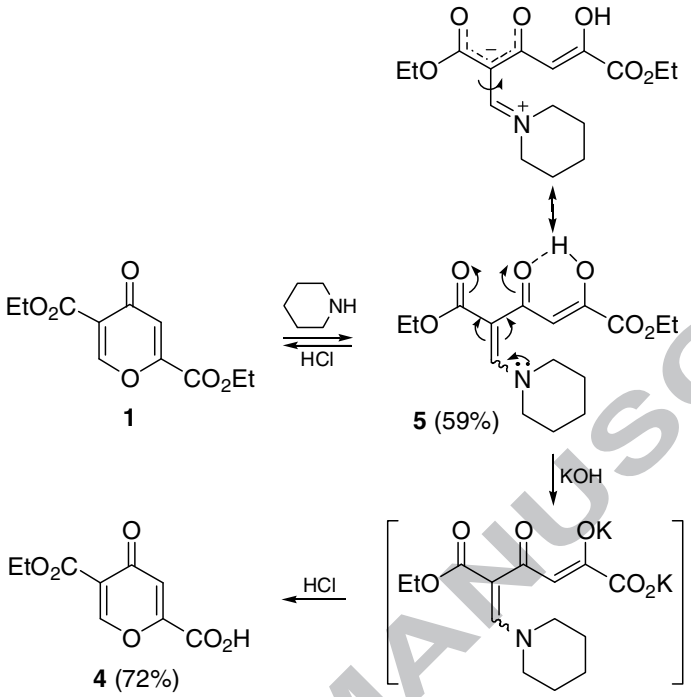


Scheme 1. Synthesis of compounds **1–3**.

As mentioned above, γ-pyrone-2,5-dicarboxylates belong to a poorly explored class of polycarbonyl compounds, the chemical properties of which have not been investigated. In connection with this, we examined the reactivity of diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate (**1**) in order to obtain potentially biologically interesting derivatives. We found that if the hydrolysis of diester **1** was carried out under milder conditions (conc. HCl, ~20 °C, 3 days), the reaction could be stopped at the diacid **2** (yield 70%),[12] whereas reflux of **1** in dilute HCl (1:1) for seven hours gave comanic acid (**3**) in 47% yield, which could also be obtained by decarboxylation of isochelidonic acid (**2**) under the same conditions (43% yield). These reactions represent an alternative route to synthesize comanic acid (**3**). Our approach makes it possible to obtain this compound from acetoacetic ester in three steps (overall yield 25%), whereas the method described in the literature[13] for the synthesis of comanic acid (**3**) consists of five steps and starts from acetone and diethyl oxalate via an acetonedioxalic ester (overall yield 33%).

There is no significant difference in the chemical reactivity of the 2- and 5-carbethoxy groups, and all our attempts to obtain the monoester starting from diester **1** were unsuccessful. Thus, an alternative method for the preparation of 5-carbethoxy-4-pyrone-2-carboxylic acid (**4**) was developed. We envisaged that the reaction of **1** with piperidine would produce the corresponding enaminone **5** with one deactivated carbethoxy group, the slow reaction of which with water could be connected with the presence of the electron-donating piperidine moiety. The second carbethoxy group of the compound **5** will be activated towards nucleophilic attack by the adjacent carbonyl group. In fact, we found that diethyl isochelidonate (**1**) reacted readily with piperidine in ethanol at 0 °C for two hours and then at –20 °C over two days to produce compound **5** in 59% yield. This reaction involved attack of the NH group at C-6 of **1** with concomitant opening of the pyrone ring to give **5**, which is a reactive polyfunctionalized intermediate with an intramolecular hydrogen bond. The ^{1}H NMR spectrum 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.[10] Treatment of amino-enone **5** with dilute HCl led to the starting pyrone **1**, however, in line with our expectations,

basic hydrolysis of compound **5** at 0 °C for 15 minutes followed by acidification successfully removed only one ethoxy group to give monoethyl isochelidonate (**4**) in 72% yield[14] (Scheme 2).



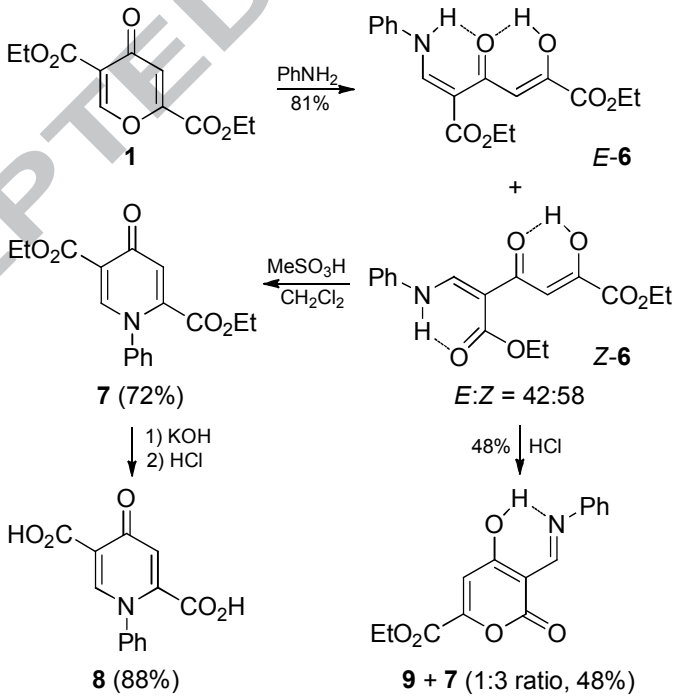
Scheme 2. Synthesis of monoester **4**.

The structures of pyrones **2** and **4** were established from their elemental analyses and spectral (^{1}H, ^{13}C NMR, and IR) data. In their ^{1}H NMR spectra, protons H-3 and H-6 appeared as singlets at δ 6.94–7.09 and δ 8.86–9.00, respectively; in the ^{13}C NMR spectra, the pyrone carbonyls appeared at δ 174.5 for monoester **4** and δ 177.5 for diacid **2** (it is well-known[15] that intramolecular hydrogen bonding causes substantial downfield shifts).

Thus, γ-pyrone **1**, due to activation of the conjugated system by two electron-withdrawing carbethoxy groups, is a highly electrophilic substrate, which is able to react with *O*- and *N*-nucleophiles, with or without affecting the pyrone ring. During the preparation of the isochelidamic acid derivatives, it was also found that treatment of **1** with aniline at 0 °C for 30 minutes gave amino-enone **6** as a 42:58 mixture of *E*- and *Z*-isomers in 81% yield. It is clear that the diester **1** reacts with aniline exclusively at its 6-position and in a 1,4-manner. The main information for the characterization of this mixture was obtained from the ^{1}H NMR spectrum in $CDCl_3$, which showed

two sets of signals. The most downfield shifted signals at δ 15.77 (s, OH), 11.37 (d, *J* = 14.2 Hz, NH), 8.79 (d, *J* = 14.2 Hz, =CHN), 7.34 (s, =CH) and at δ 14.55 (s, OH), 12.53 (d, *J* = 13.5 Hz, NH), 8.63 (d, *J* = 13.5 Hz, =CHN), 7.61 (s, =CH) were assigned tentatively to isomers *Z*-**6** and *E*-**6**, respectively. These data indicate that both labile protons are involved in the formation of strong intramolecular hydrogen bonds, thus confirming the structure of **6**.

In comparison to the reaction with piperidine, the use of methanesulfonic acid in dichloromethane at room temperature for three hours transformed amino-enone **6** irreversibly into diethyl *N*-phenylisochelidamate (**7**) in 72% yield.[16] Basic hydrolysis of **7** proceeded in the expected manner to give *N*-phenylisochelidamic acid (**8**) (yield 88%),[17] which may be of interest as a biologically valuable compound.[6] Despite their rather simple structures, neither compound **7** nor its parent acid **8** have been prepared previously; from this series of compounds only 5-carbethoxy-4-oxo-1,4-dihydropyridine-2-carboxylic acid was known.[18] Treatment of amino-enone **6** with a catalytic amount of concentrated HCl in ethanol at room temperature for 12 hours gave a mixture of compounds **9** and **7** in the ratio of 1:3 (yield 48%) (Scheme 3).



Scheme 3. Synthesis of compounds **6–9**.

In summary, we have developed an improved synthesis of biologically potent diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate, which involves the condensation of ethyl 2-(dimethylamino)methylene-3-oxobutanoate with diethyl oxalate in the presence of sodium hydride. Compared with the previously reported procedure, our method shows several advantages, the main of which are simplicity, efficiency and the ready availability of the starting materials. From this diester, for the first time, isochelidonic acid and its derivatives have been obtained in good yields. Taking into account the ability to transform an ester group into other functional groups, the 4-pyrone-2,5-dicarboxylate core is a valuable building block for the construction of a wide range of 4-pyrone derivatives.

Acknowledgment

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11. *Sodium (5E)-6-(dimethylamino)-1-ethoxy-5-(ethoxycarbonyl)-1,4-dioxohexa-2,5-dien-2-olate.* A mixture of ethyl 2-(dimethylamino)methylene-3-oxobutanoate (3.0 g, 16.2 mmol), diethyl oxalate (2.84 g, 17.3 mmol) and NaH (60% dispersion in oil) (0.84 g, 21.0 mmol) in THF (45 mL) was refluxed for 5 h. After cooling, the solid that formed was filtered, washed with THF (10 mL), and dried. Yield 3.22 g (64%), mp 220 °C (dec.), beige powder. IR (ATR): 2982, 1709, 1689, 1663, 1571 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.14 (br t, *J* = 7.0 Hz, 3H, Me), 1.20 (t, *J* = 7.0 Hz, 3H, Me), 2.88 (s, 6H, NMe_2), 3.97 (br q, *J* = 7.0 Hz, 2H, CH_2O), 4.05 (q, *J* = 7.0 Hz, 2H, CH_2O), 5.65 (s, 1H, =CH), 7.14 (br s, 1H, =CHN). *Diethyl 4-oxo-4H-pyran-2,5-dicarboxylate (**1**)*. Sodium (5*E*)-6-(dimethylamino)-1-ethoxy-5-(ethoxycarbonyl)-1,4-dioxohexa-2,5-dien-2-olate (3.0 g, 9.76 mmol) was dissolved in H_2O (10 mL) and quenched with concentrated HCl (3 mL) at 0 °C (ice bath) for 30 min. The product **1** was extracted with

EtOAc (3×7 mL) and recrystallized from hexane with the addition of small amounts of toluene. Yield 1.94 g (83%), mp 71–72 °C (in ref.[6] described as an oil), beige powder. IR (ATR): 3051, 2988, 1751, 1727, 1652, 1572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.1 Hz, 3H, Me), 1.37 (t, *J* = 7.1 Hz, 3H, Me), 4.34 (q, *J* = 7.1 Hz, 2H, CH_2O), 4.41 (q, *J* = 7.2 Hz, 2H, CH_2O), 7.18 (s, 1H, H-3), 8.53 (s, 1H, H-6).

12. *4-Oxo-4H-pyran-2,5-dicarboxylic acid (isochelidonic acid) (**2**).* A solution of diester **1** (0.20 g, 0.83 mmol) in concentrated HCl (2 mL) was stirred for 3 d at room temperature. The resulting solid was filtered, washed with H_2O, and then toluene. Yield 0.117 g (70%), mp 288–290 °C (dec.), beige powder. IR (ATR): 3530, 3428, 3084, 1751, 1713, 1662, 1605, 1560 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.09 (s, 1H, H-3), 9.00 (s, 1H, H-6), 11.0–15.0 (br s, 2H, 2OH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 119.9, 120.4, 154.8, 160.7, 163.0, 163.7, 177.5. Anal. Calcd for $C_7H_4O_6 \cdot H_2O$: C, 41.60; H, 2.99. Found: C, 41.66; H, 2.75.
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14. *5-(Ethoxycarbonyl)-4-oxo-4H-pyran-2-carboxylic acid (**4**).* A mixture of amino-enone **5** (120 mg, 0.37 mmol) and KOH (103 mg, 1.83 mmol) in H_2O (2 mL) was stirred for 15 min at 0 °C and quenched with 4 M HCl until pH = 1. The resulting solid was separated by filtering and washed with cold H_2O. Yield 56 mg (72%), mp 238–240 °C, white powder. IR (ATR): 3071, 3006, 1729, 1641, 1592, 1560 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 1.27 (q, *J* = 7.1 Hz, 3H, Me), 4.24 (q, *J* = 7.1 Hz, 2H, CH_2O), 6.94 (s, 1H, H-3), 8.86 (s, 1H, H-6) (the OH proton was not observed due to broadening); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.5, 61.4, 120.5, 121.7, 153.8, 161.0, 161.9, 162.6, 174.5. Anal. Calcd for $C_9H_8O_6$: C, 50.95; H, 3.80. Found: C, 51.07; H, 3.54.
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16. *Diethyl 4-oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylate (**7**).* A solution of amino-enone **6** (200 mg, 0.60 mmol) and $MeSO_3H$ (115 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was stirred for 3 h. The solvent was removed and the residue was diluted with H_2O. The solid that formed was filtered and recrystallized from hexane–toluene (4:1). Yield 147 mg (72%), mp 141–142 °C, colorless crystals. ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.1 Hz, 3H, Me), 1.37 (t, *J* = 7.1 Hz, 3H, Me), 4.11 (q, *J* = 7.1 Hz, 2H, CH_2O), 4.37 (q, *J* = 7.1 Hz, 2H, CH_2O), 7.06 (s, 1H, H-3), 7.28–7.32 (m, 2H, Ph), 7.50–7.54 (m, 3H, Ph), 8.27 (s, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 14.2, 61.2, 62.6, 119.5, 124.9, 125.1, 129.5, 129.8, 140.3, 142.2, 148.1, 161.3, 164.2, 174.8. Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.58; H, 5.32; N, 4.27.
17. *4-Oxo-1-phenyl-1,4-dihydropyridine-2,5-dicarboxylic acid (**8**).* To a suspension of diester **7** (100 mg, 0.32 mmol) in H_2O (2 mL) was added KOH (107 mg, 1.90 mmol) and the mixture was stirred at room temperature (30 min) and then at reflux (30 min). After cooling, the mixture was quenched with 4 M HCl until pH = 1, and the solid that formed was filtered and washed with H_2O. Yield 72 mg (88%), mp 207–208 °C, colorless powder. ^1H NMR (400 MHz, DMSO-d_6) δ 7.15 (s, 1H, H-3), 7.52–7.58 (m, 5H, Ph),

8.49 (s, 1H, H-6) (the OH protons were not observed due to broadening). Anal. Calcd for $C_{13}H_9NO_5$: C, 60.24; H, 3.50; N, 5.40. Found: C, 59.68; H, 3.14; N, 5.37.

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Graphical abstract

An improved synthesis and some reactions of diethyl 4-oxo-4*H*-pyran-2,5-dicarboxylate

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