Preparative synthesis of ethyl 5-acyl-4-pyrone-2-carboxylates and 6-aryl-, 6-alkyl-, and 5-acylcomanic acids on their basis*

D. L. Obydennov, A. O. Goncharov, and V. Ya. Sosnovskikh*

Institute of Natural Sciences of the Ural Federal University named after the first President of Russia B. N. Yeltsin, 51 prosp. Lenina, 620000 Ekaterinburg, Russian Federation.
E-mail: dmitry.obydennov@urfu.ru

A simple and efficient method for the synthesis of ethyl 5-alkanoyl- and 5-aroyl-4-pyrone-2-carboxylates was developed, which is based on the condensation of 1-R-2-(dimethylaminomethylidene)butane-1,3-diones, obtained from 1,3-diketones and dimethylformamide dimethyl acetal, with diethyl oxalate in the presence of NaH in THF. Ethyl 5-acyl-4-pyrone-2-carboxylates were used in the synthesis of 6-R- and 5-RCO-comanic acids.

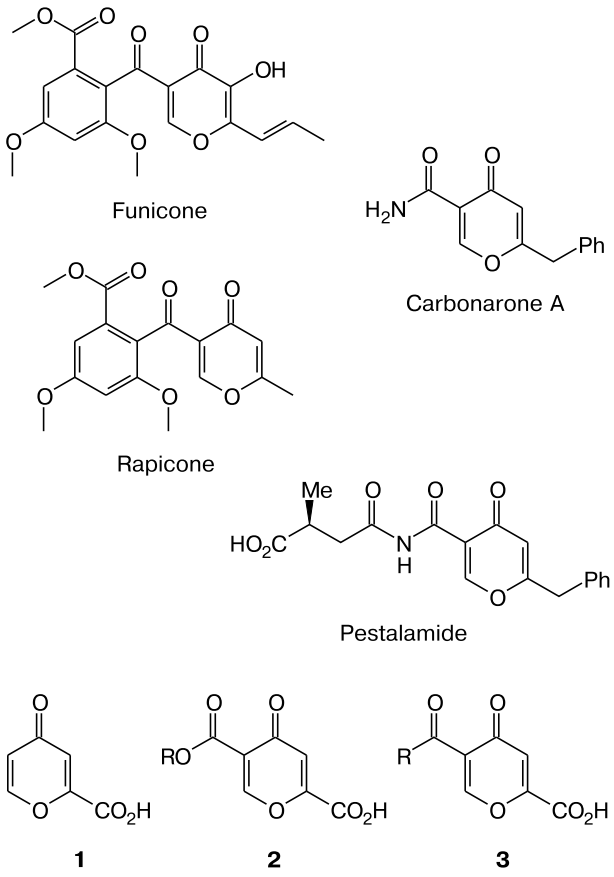
Key words: Claisen condensation, dimethylformamide dimethyl acetal, 1,3-diketones, enaminodiones, ethyl 5-acylcomanoates, comanic acids.

4-Pyrones are an important class of oxygen-containing heterocyclic compounds, which simultaneously are masked polycarbonyl systems and cyclic enones. The structural specific features of 4-pyrones determine their large synthetic potential, due to which they are widely used as building blocks for the preparation of pharmaceutical agents[1] and materials for electronics.[2]

3-Acyl-4-pyrone derivatives in their reactivity, prevalence in the nature, and useful properties take a special place among numerous representatives of γ-pyrones. They include such natural compounds, as funicone,[3] rapicone,[3] carbonarone A,[4] and pestalamide A[4]. Many funicones, 3-aroyl-4-pyrone derivatives, manifest antifungal, anticancer, and anti-HIV activity.[3] Apart from that, 3-hydroxy-4-pyrone-2,5-dicarboxylic acid derivatives are used for the preparation of dolutegravir, which is a second generation inhibitor of HIV integrase.[5—7]

However, despite the importance of 3-acyl-4-pyrones, the scope of methods for the synthesis of these compounds remains very limited, apparently, due to their high chemical activity related to the electron density deficiency on the atom C(2). It is obvious that the introduction of ester or acyl substituent into 4-pyrone-2-carboxylic acid (comanic acid, **1**) should even further increase the heterocycle electrophilicity and develop additional difficulties in the preparation of isochelidonic **2** and 5-acylcomanic acid esters **3**, which are prone to ready γ-pyrone ring opening.

5-Carbalkoxy- and 5-acyl-4-pyrone-2-carboxylic acids **2** and **3** contain five carbonyl groups, two of which are in the masked state and appear only after the pyrone ring opening upon treatment with water molecule. There are only several literature examples of the synthesis of esters **2** and **3** *via* acylation of enaminodiones formed by the reaction of 1,3-dicarbonyl compounds with dimethylformamide dimethyl acetal (DMF DMA).[5—9] Isochelidonic



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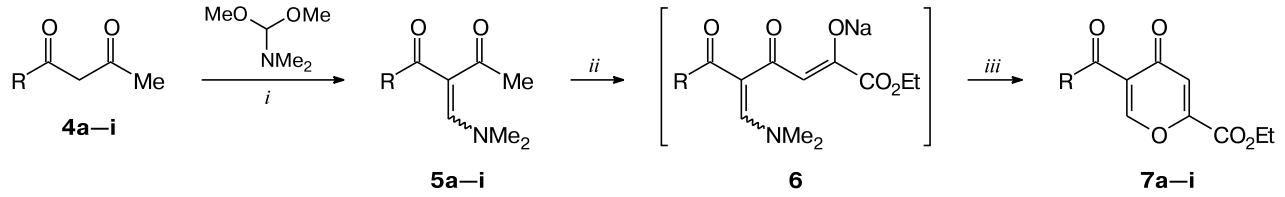
Scheme 1



Reagents and conditions: *i*. C_6H_6, ~20 °C (24 h), reflux (1 h); *ii*. THF, $(CO_2Et)_2$, NaH; *iii*. HCl, 0 °C.

esters **2** have been obtained earlier[5–7] from enaminodiones with ethyloxalyl chloride in THF in the presence of lithium hexamethyldisilazane at −78 °C, whereas 5-acyl-4-pyrone-2-carboxylic esters **3** were obtained by the condensation of enaminodiones with diethyl oxalate in the presence of EtONa upon heating in ethanol.[8,9] However, despite synthetic significance of the last mentioned compounds, no detailed procedures for their preparation are available, whereas all our attempts to reproduce the synthesis of 5-acylcomanic esters **3**, the yields for which were not reported,[8,9] did not lead to the desirable results.

The present work deals with the search for simple and reliable method for the synthesis of ethyl 5-acylcomanoates in order to obtain these compounds on a multi-gram scale, avoiding chromatographic isolation and purification of the final products (for preliminary communication, see Ref. 10). We report the full data on ethyl 5-alkanoyl- and 5-aroyl-4-pyrone-2-carboxylates obtained by a new procedure *via* the condensation of the corresponding enaminodiones with diethyl oxalate in the presence of NaH in THF. The hydrolysis of these esters gave 6-aryl(alkyl)- and 5-acylcomanic acids, depending on the reaction conditions.

Results and Discussion

In continuation of our studies in the area of substituted comanic acids,[11–14] we attempted to synthesize little known, but very promising for synthetic purposes ethyl 5-acylcomanoates. First of all, it was necessary to study in greater details than so far[8,9] the reaction of 1,3-diketones **4** with DMF DMA, that would provide us with a wide spectrum of starting enaminodiones **5**. Then, we had to develop a new procedure for carrying out the condensation at the acetyl group of enamines **5** with diethyl oxalate, which would give us a possibility of obtaining ethyl 5-acylcomanoates **7** in good yields and make these useful building blocks available for preparative purposes.

It is known that 1-R-butane-1,3-diones **4** react with DMF DMA at the methylene group with the formation of push-pull enaminodiones **5**. Despite the fact that these enamines are widely used in the synthesis of various heterocycles,[15] they have been obtained only based on diketones **4a**—**c**,**i** and described without indication of yields for the products **5b**,**c** (see Ref. 9). Note also the illustrative fact that in the last large review devoted to the synthesis and chemical properties of 1,3-diketones, the information on the reaction of 1-R-butane-1,3-diones **4** with DMF DMA is completely absent.[16] We found that the stirring of diketones **4a**—**i** with DMF DMA (1.3 equiv.) in anhydrous benzene for 24 h at room temperature with subsequent reflux of the reaction mixture for 1 h are the optimal conditions for their enamination. In this case, 1-R-2-(dimethylaminomethylidene)butane-1,3-diones **5a**—**i** were obtained as yellow or orange powders in from 59 to 88% yields (Scheme 1, Table 1).

The reaction gives high yields of the products with both aromatic and aliphatic substituents, whereas the lowest yield (59%) was observed for compound **5e** with the electron-withdrawing *p*-nitrophenyl substituent. Since we failed to obtain corresponding enaminodiones from 1-trifluoromethyl- and 1-(pyrid-2-yl)butane-1,3-diones under the indicated above conditions (the formation of a complex mixture of products or resinification was always observed), a conclusion can be drawn on the unfavorable influence of the electron-withdrawing substituents in 1,3-diketones **4** on the course of their reaction with DMF DMA. It is interesting that the bulky *tert*-butyl group not only does not hinder this reaction, but, *vice versa*, promotes the formation of pivaloyl enamine **5h** in the highest yield (88%). In the ^{1}H NMR spectra of products **5a**—**g**, the methyl groups of the Me_2N fragment are observed in the

Table 1. Yields of products **5** and **7**

Diketone **4**	R	Enamine **5**	Yield of **5** (%)	Pyrone **7**	Yield[a] of **7** (%)
4a	Ph	**5a**	64	**7a**	73
4b	4-ClC_6H_4	**5b**	80	**7b**	82
4c	4-$MeOC_6H_4$	**5c**	86	**7c**	69
4d	4-MeC_6H_4	**5d**	76	**7d**	78
4e	4-$NO_2C_6H_4$	**5e**	59	**7e**	42[b]
4f	2-$C_{10}H_7$	**5f**	68	**7f**	68
4g	2-C_4H_3S	**5g**	77	**7g**	73
4h	Bu^t	**5h**	88	**7h**	53[b]
4i	Me	**5i**	87	**7i**	31[b]

[a] Salt **6** was treated with dilute HCl (1 : 2).
[b] The condensation was carried out at ~20 °C for 5 days.

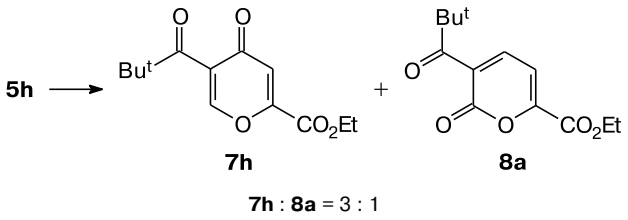
region of δ 2.3—3.6 as strongly broadened signals because of the hindered rotation of the amino group around the double bond.[17] In enaminodione **5h**, the Me_2N group was found as a sharp singlet at δ 2.91 (6 H), which, most likely, is related to the stabilization of the *E*-isomeric form by the *tert*-butyl substituent.

As it was noted above, the known methods[8,9] for acylation of the methyl group in enaminodiones **5** with diethyl oxalate gave low yields of ethyl 5-acylcomanoates **7** and required chromatographic isolation of the products. In this connection, we carried out a thorough search for the condensation system, which would allow us to eliminate these disadvantages and make pyrones **7** available in the multi-gram scaled amounts. The following systems were studied: EtONa—EtOH, Bu^tOK—Et_2O, Bu^tOK—THF, and NaH—THF, of which the latter turned out to be the most efficient (a 60% suspension of NaH in mineral oil and anhydrous THF). It was found that the condensation of enaminodiones **5** with diethyl oxalate can be carried out both upon reflux for 8 h and upon continuos stirring at ~20 °C for 5 days (the reaction begins in the second or even third day). Both methods give close results (except for enamines **5e,h,i**), but the second method (stirring at room temperature) is more preferable. This reaction turned out to be very sensitive to the reagents quality, especially to that of sodium hydride, and the probability of proceeding side processes related to stale or low-quality NaH decreases under milder conditions. In the case of enamines **5e**,**i**, at room temperature the yields of products **7e**,**i** are 42 and 31%, respectively, while heating leads either to the decrease in the yield to 9% (for **7e**), or strong resinification (for **7i**). The initially formed sodium salts **6** were not isolated in the pure state, but were subjected to hydrolysis with dilute HCl (1 : 2) at 0 °C to acyclic polycarbonyl intermediates, which under these conditions spontaneously cyclize to pyrones **7a**—**i** in 31—82% yields (see Scheme 1, Table 1).

Reflux of enaminodione **5h** (R = Bu^t) with diethyl oxalate in the system NaH—THF for 8 h unexpectedly gave a mixture of the target pyrone **7h** with the isomeric product in the ratio of 3 : 1, from which pyrone **7h** and its isomer were isolated in the pure form by fractional recrystallization from ethanol at −20 °C in 33 and 11% yields, respectively. Based on the spectral data, the side isomer was identified as 6-carbethoxy-3-pivaloyl-2-pyrone (**8a**) (Scheme 2). Since no formation of the rearrangement products was detected with other enaminodiones **5** under similar conditions, it can be suggested that this specific feature of compound **5h** is related to the presence of a bulky *tert*-butyl group, affecting its reactivity. Carrying out the reaction at room temperature for 5 days allowed us to completely avoid the formation of 2-pyrone **8a** and to increase the yield of 4-pyrone **7h** from 33 to 53%.

The structure of compound **8a** was established based on elemental analysis, which confirmed its isomeric composition, as well as from the ^1H and ^{13}C NMR spectroscopy data (Tables 2 and 3). The most relevant examples of such compounds described in the literature are methyl 3-phenyl-2-pyrone-6-carboxylate (**8b**)[18] and ethyl 6-phenyl-2-pyrone-3-carboxylate (**8c**).[19] It should be noted that in the series of 2-pyrones, the spin-spin coupling constant between the protons of the C(3)=C(4) double bond has the value within the 8—10 Hz range, whereas for the C(5)=C(6) bond it is considerably smaller (*J* = 5—6 Hz), that allows us to exclude such structures from consideration.[20,21]

Scheme 2



Reagents and conditions: 1) $(CO_2Et)_2$, NaH, THF, Δ; 2) HCl, 0 °C.

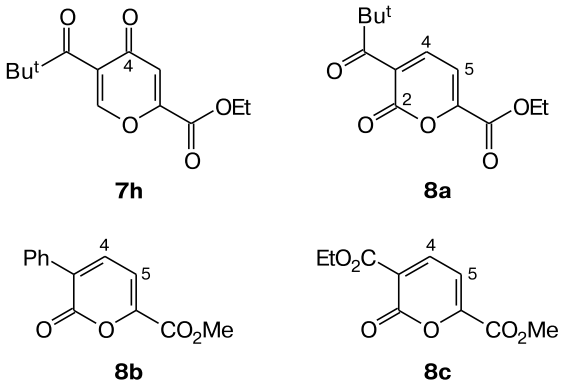


Table 2. Chemical shifts for protons H(3) and H(6) in pyrones **7a—i** and for protons H(4) and H(5) in 2-pyrones **8a—c** ($CDCl_3$)

Compound	δ_H, *J*/Hz	Assignment
7a—g	7.22—7.28	C(3)H
	8.11—8.31	C(6)H
s-trans-**7h**	7.13	C(3)H
	7.80	C(6)H
s-cis-**7i**	7.22	C(3)H
	8.44	C(6)H
8a	7.61 (d, 1 H, *J* = 6.7)*	C(4)H
	7.20 (d, 1 H, *J* = 6.7)*	C(5)H
8b	7.54 (d, 1 H, *J* = 7.0)	C(4)H
	7.23 (d, 1 H, *J* = 7.0)	C(5)H
8c	8.29 (d, 1 H, *J* = 7.4)	C(4)H
	6.77 (d, 1 H, *J* = 7.4)	C(5)H

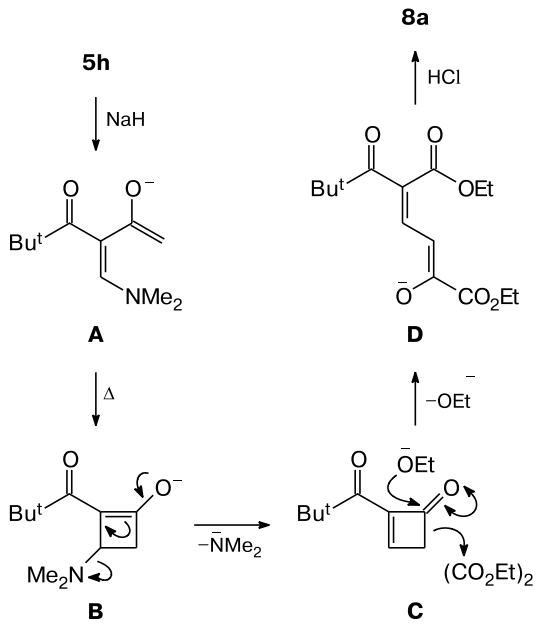
* DMSO-d_6.

Table 3. Chemical shifts for the C=O group in pyrones **7h** and **8a**

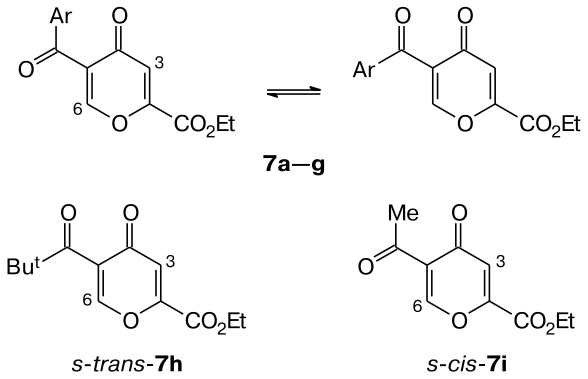
Compound	δ_C		
	Bu^{t}C=O	EtOC=O	C_{pyr}=O
7h	206.7	159.5	175.6
8a	207.4	159.0	157.4

The photochemical isomerization of 4-pyrones to 2-pyrones is a well known process,[22] however, in our case, when taking into account drastic enough reaction conditions, it can be suggested that the isomerization process is explained by the reaction center transition in the initially formed enolate **A** and the emergence of cyclobutene intermediates **B** and **C** (Scheme 3). The latter sequentially undergoes the ring opening reaction upon treatment with ethoxide anion and the condensation with diethyl oxalate to form intermediate **D**, the cyclization of which under acidic conditions gives 2-pyrone **8a**.

Scheme 3



The structure of 4-pyrones **7a—i** also deserves a brief comment. The analysis of chemical shift values for protons H(3) and H(6) in the ^{1}H NMR spectra of these compounds recorded in solution of $CDCl_3$ leads to certain conclusions about conformation preferences of the acyl substituent (see Table 2). In compound **7i**, the proton H(6) is found in the lowest field as a singlet (δ 8.44) because of the deshielding influence of the carbonyl group of the acetyl substituent, which indicates that pyrone **7i** predominantly exists as a *s-cis*-conformer. In the pivaloyl derivative **7h**, an opposite picture is observed: the high-field signal (δ 7.80) for proton H(6) indicates the *s-trans*-conformation. 5-Aroylcomanoates **7a—g** with averaged chemical shifts for this proton exist in solution of deuterochloroform as mixtures of approximately equal amounts of *s-cis*- and *s-trans*-conformers, the equilibrium between which begins to shift to the side of the former conformer as the electron-withdrawing character of substituent in the benzene ring increases (for *p*-nitrophenyl derivative **7e**, $\delta_{H(6)}$ 8.31).



In the next step of the work, already having a simple, efficient, and easily reproducible procedure for the synthesis of ethyl 5-acylcomanoates **7**, we set a goal to convert esters **7** to the corresponding acids. It is known that comanic acids containing aliphatic or aromatic substituents exhibit antiprolipherative activity[23] and can be used for treatment of metabolic syndrome.[24] Apart from that, they are active substrates in the synthesis of various heterocyclic systems, including 3-pyrazolylindoles,[25,26] 3-(hetarylmethyl)quinoxalinones,[27] and 3-(1*H*-1,5-benzodiazepin-2(3*H*)-ylidenemethyl)quinoxalin-2(1*H*)-ones.[14] In connection with high biological activity and synthetic importance of γ-pyrone-derived carboxylic acids, the suggested hydrolysis of the ethoxycarbonyl group in comanoates **7** is a relevant synthetic problem, which seems simple only at first glance. In fact, taking into account the readiness of γ-pyrone ring opening in both the acidic and the basic media, as well as the absence in the literature of any data on chemical properties of compounds **7** (the oxidation of esters **7a**,**i** with *m*-chloroperbenzoic acid to epoxydes is only described[8]), the transformation of ethyl 5-acylcomanoates **7** to 5-acylcomanic acids deserves special attention, since it does not mean just a routine hydrolysis of the ester group.

We found that esters **7a—h** upon heating in dilute hydrochloric acid at 100 °C underwent rearrangement and gave, instead of expected 5-RCO-comanic acids, 6-R-comanic acids **9a—h** in high yields (68—94%), of which acids **9f—h** were obtained for the first time. In the case of esters **7a—e**,**g**,**h**, the reaction proceeded in HCl (1 : 1) during 8 h, whereas for 2-naphthyl derivative **7f** more prolonged heating was required (32 h) and more concentrated hydro-

chloric acid (2 : 1), that can be explained by the low solubility of pyrone **7f** in HCl because of the presence of large and hydrophobic naphthyl residue. A plausible mechanism of the reaction includes the addition of a water molecule at the atom C(6) with subsequent pyrone ring opening and deformylation (Scheme 4, Table 4). The structure of 6-aroylcomanic acids **9a**—**g** was unambiguously inferred from their ^{1}H NMR spectra, which exhibited characteristic doublets for protons H(5) and H(3) with J = 2.1—2.3 Hz at δ 6.84—6.92 and 6.93—7.29, respectively; in pivaloyl derivative **9h**, the signal for the proton H(5) is upfield shifted by 0.55 ppm (δ 6.29) and that of H(3) by 0.16 ppm (δ 6.77) (DMSO-d_6).

Scheme 4

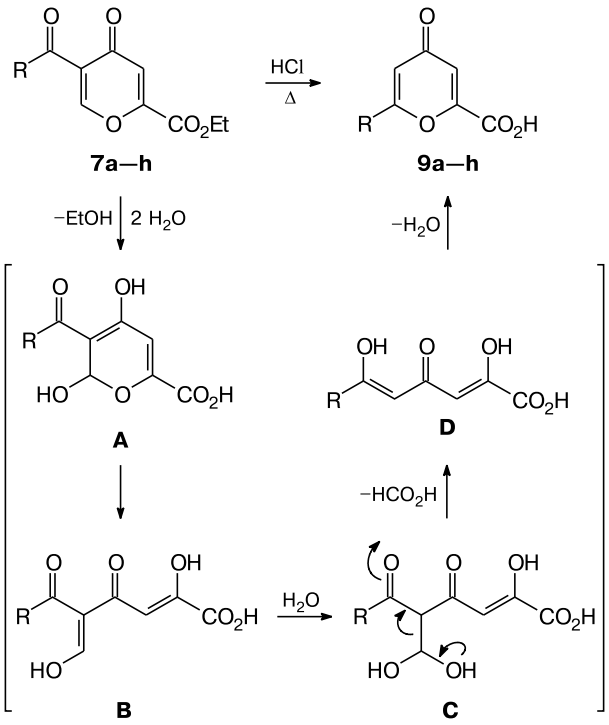


Table 4. Yields of 6-R-comanic acids **9**

Acid **9**	R	Yield[a] (%)
9a	Ph	68
9b	4-ClC_6H_4	85
9c	4-$MeOC_6H_4$	92
9d	4-MeC_6H_4	92
9e	4-$NO_2C_6H_4$	81
9f	2-$C_{10}H_7$	94[b]
9g	2-C_4H_3S	89
9h	Bu^t	68

[a] The reactions were carried out upon standing of pyrones **7** at 100 °C in HCl (1 : 1).
[b] The reaction was carried out in HCl (2 : 1) for 32 h.

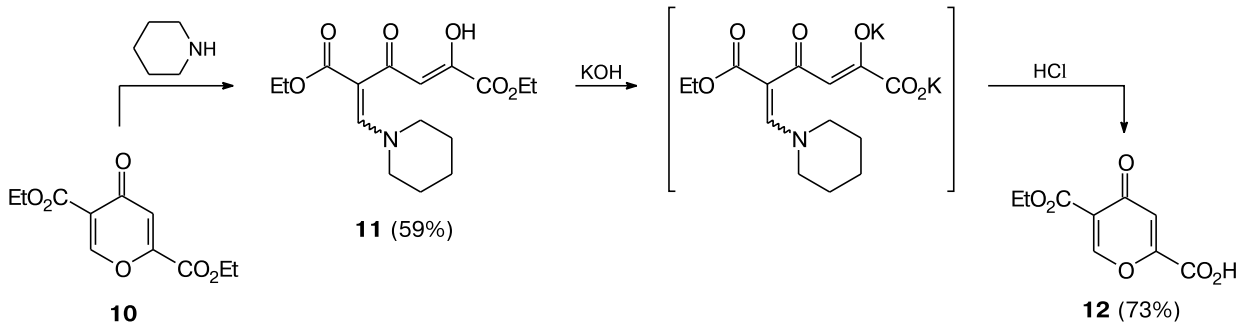
The described reaction constitutes a new three-step method for the synthesis of a wide number of 6-R-comanic acids from 1,3-diketones in 20—56% total yield. Enamination with DMF DMA protects the active methylene group and promotes selective acylation, whereas treatment with hydrochloric acid removes this protection. Earlier, 6-arylcomanic acids were obtained by a four-step transformation of benzylideneacetones,[28] whereas direct acylation of 1-R-butane-1,3-diones (R = Ar, Het, Alk) with oxalic esters is known only for a limited number of examples.[28,29] The method for the preparation of 6-substituted comanic acids suggested in this work includes fewer number of steps and allows one to obtain not only 6-aryl-, but also 6-hetaryl- and 6-alkylcomanic acids. At the same time, these results show that ethyl 5-acylcomanoates **7** cannot be converted to 5-acylcomanic acids in acidic medium.

Earlier,[30] we have developed a method for selective hydrolysis of one of two carbethoxy groups in diethyl isochelidonate **10**. The essence of the method consists in the following: the reaction of diester **10** with piperidine gives enamine **11** stables under basic conditions, in which the 5-CO_2Et group is deactivated because of the electron-donating influence of the nitrogen atom. As a result, only 2-CO_2Et group undergoes alkaline hydrolysis. This allows one to obtain monoethyl ester of isochelidonic acid **12** under mild conditions and in good yield (Scheme 5).

We decided to use this approach for the preparation of 5-acylcomanic acids from esters **7**, which allowed us to protect atom C(6) from the secondary attack by the nucleophile and, thus, to avoid the undesirable step of deformylation. Treatment of esters **7a**—**c**,**f**,**g** with piperidine at 0 °C for 1 h led to polycarbonyl enamines **13a**—**c**,**f**,**g** (66—82% yields) as a result of the attack at the atom C(6) with subsequent pyrone ring opening. Hydrolysis of these enamines in the presence of KOH at 0 °C for 15—20 min with subsequent acidification with HCl to pH 1 gave the target 5-acyl-4-pyrone-2-carboxylic acids **14a**—**c**,**f**,**g** in 54—89% yields (Scheme 6, Table 5). This sequence of reactions constitutes a simple method for obtaining earlier unknown 5-aroylcomanic acids **14**. In the ^{1}H NMR spectra of the push-pull enamines **11** and **13**, the signals from the piperidine fragment are strongly broadened, that indicates its hindered rotation around the double bond; in acids **14**, two singlets for the protons H(3) and H(6) are observed at δ 6.97—7.02 and 8.56—8.71, respectively (DMSO-d_6). The strongly deshielded signal for the proton H(6) leads to a conclusion that 5-aroylcomanic acids **14** in solution predominantly exist in the form of *s-cis*-conformer.

In conclusion, we have developed a simple and efficient synthesis of ethyl 5-alkanoyl- and 5-aroyl-4-pyrone-2-carboxylates from 1,3-diketones, DMF DMA, and diethyl oxalate. We showed that these compounds in acidic medium can readily undergo rearrangement to 6-substituted comanic acids, whereas their treatment with piperi-

Scheme 5



Scheme 6

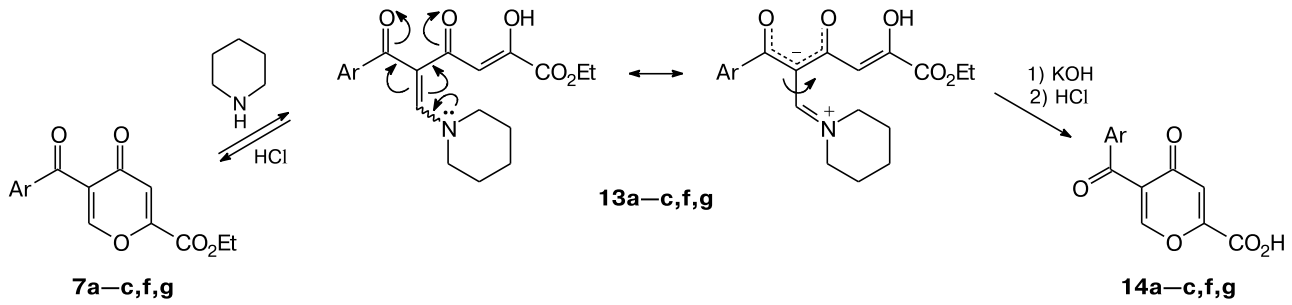


Table 5. Yields of products **13** and **14**

R	Yield (%)	
	13	**14**
Ph	82	69
4-ClC_6H_4	71	89
4-$MeOC_6H_4$	79	61
2-$C_{10}H_7$	82	54
2-C_4H_3S	66	80

dine with subsequent basic hydrolysis gives 5-aroyl-4-pyrone-2-carboxylic acids.

Experimental

IR the spectra were recorded on a Perkin—Elmer Spectrum BX-II spectrometer using a frustrated total internal reflection (FTIR) appliance. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance II spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 and $CDCl_3$, using $SiMe_4$ an internal standard. Elemental analysis was performed on a PE 2400 automated analyzer. Melting points were determined on a SMP30 heating stage. Solvents used in the work were distilled, NaH (a 60% suspension in mineral oil) and DMF DMA were purchased from Sigma Aldrich. Benzene and THF were refluxed over sodium metal and distilled. Benzoylacetone[31] and other 1,3-diketones[32] were obtained according to the known procedures.

Synthesis of enaminodiones 5a—i (general procedure). Dimethylformamide dimethyl acetal (15.49 g, 0.13 mol) was added to 1,3-diketone **4** (0.1 mol) in anhydrous benzene (46 mL), the reaction mixture was stirred for 24 h at room temperature and then refluxed for 1 h, using a reflux condenser equipped with a calcium chloride drying tube. Then the solvent and an excess of DMF DMA were removed at reduced pressure, the residue was recrystallized from a proper solvent.

2-(Dimethylaminomethylene)-1-phenylbutane-1,3-dione (5a). The yield was 13.91 g (64%), yellow crystals, m.p. 83—84 °C (Et_2O) (Ref. 33: m.p. 72—74 °C). ^1H NMR corresponded to the literature data.[33,34]

2-(Dimethylaminomethylene)-1-(4-chlorophenyl)butane-1,3-dione (5b). The yield was 20.14 g (80%), a yellow powder, m.p. 115—116 °C (toluene : hexane, 1 : 1) (Ref. 9: m.p. 122 °C). ^1H NMR (DMSO-d_6), δ: 2.08 (s, 3 H, Me); 2.45—3.30 (m, 6 H, NMe_2); 7.52 (d, 2 H, H(3), $H_{Ar}(5)$, J = 8.5 Hz); 7.73 (s, 1 H, =CH); 7.85 (d, 2 H, H(2), $H_{Ar}(6)$, J = 8.5 Hz).

2-(Dimethylaminomethylene)-1-(4-methoxyphenyl)butane-1,3-dione (5c). The yield was 21.27 g (86%), a yellow powder, m.p. 126—127 °C (toluene) (Ref. 9: m.p. 126 °C). ^1H NMR ($CDCl_3$), δ: 2.00 (s, 3 H, Me); 2.32—3.51 (m, 6 H, NMe_2); 3.87 (s, 3 H, MeO); 6.93 (d, 2 H, H(3), $H_{Ar}(5)$, J = 8.7 Hz); 7.73 (s, 1 H, =CH); 7.85 (d, 2 H, H(2), $H_{Ar}(6)$, J = 8.7 Hz).

2-(Dimethylaminomethylene)-1-(4-methylphenyl)butane-1,3-dione (5d). The yield was 17.58 g (76%), a yellow powder, m.p. 113—115 °C (toluene : hexane, 2 : 1). Found (%): C, 72.85; H, 7.33; N, 6.07. $C_{14}H_{17}NO_2$. Calculated (%): C, 72.70; H, 7.41, N, 6.06. IR, ν/cm^{-1}: 2922, 1647, 1573, 1393, 1302, 930, 837, 758. ^1H NMR ($CDCl_3$), δ: 1.99 (s, 3 H, Me); 2.41 (s, 3 H, Me); 2.52—3.28 (m, 6 H, NMe_2); 7.24 (d, 2 H, H(3), $H_{Ar}(5)$,

J = 7.8 Hz); 7.73 (s, 1 H, =CH); 8.24 (d, 2 H, H(2), H_{Ar}(6), J = 8.7 Hz).

2-(Dimethylaminomethylene)-1-(4-nitrophenyl)butane-1,3-dione (5e). The yield was 15.47 g (59%), orange crystals, m.p. 146—148 °C (toluene). Found: m/z 263.1030 $[MH]^+$. $C_{13}H_{14}N_2O_4$. Calculated: M = 263.1032. IR, ν/cm^{-1}: 2927, 1646, 1577, 1511, 1301, 935, 850. ^{1}H NMR (DMSO-d_6), δ: 2.11 (s, 3 H, Me); 2.31—3.64 (br.s, 6 H, NMe_2); 7.77 (s, 1 H, =CH); 7.86 (d, 2 H, H(3), H_{Ar}(5), J = 8.7 Hz); 8.24 (d, 2 H, H(2), H_{Ar}(6), J = 8.7 Hz).

2-(Dimethylaminomethylene)-1-(2-naphthyl)butane-1,3-dione (5f). The yield was 18.18 g (68%), yellow crystals, m.p. 102—104 °C (Et_2O). Found (%): C, 76.50; H, 6.68; N, 5.01. $C_{17}H_{17}NO_2$. Calculated (%): C, 76.38; H, 6.41, N, 5.24. IR, ν/cm^{-1}: 3013, 2954, 2924, 1652, 1616, 1308, 925. ^{1}H NMR ($CDCl_3$), δ: 2.01 (s, 3 H, Me); 2.44—3.39 (br.s, 6 H, NMe_2); 7.54 (td, 1 H, H_{Naph}(6), J = 8.0 Hz, J = 1.3 Hz);* 7.59 (td, 1 H, H_{Naph}(7), J = 8.0 Hz, J = 1.3 Hz); 7.82 (s, 1 H, =CH); 7.86—7.94 (m, 3 H, H(4), H(5), H_{Naph}(8)); 7.98 (dd, 1 H, H_{Naph}(3), J = 8.5 Hz, J = 1.5 Hz); 8.32 (s, 1 H, H_{Naph}(1)).

2-(Dimethylaminomethylene)-1-(2-thienyl)butane-1,3-dione (5g). The yield was 17.19 g (77%), yellow crystals, m.p. 71—72 °C (Et_2O). Found (%): C, 59.33; H, 5.69; N, 6.22. $C_{11}H_{13}NO_2S$. Calculated (%): C, 59.17; H, 5.87, N, 6.27. IR, ν/cm^{-1}: 3101, 3053, 2924, 1643, 1578, 1307, 847, 728. ^{1}H NMR (DMSO-d_6), δ: 2.07 (s, 3 H, Me); 2.55—3.19 (m, 6 H, NMe_2); 7.17 (dd, 1 H, H_{Th}(4), J = 4.9 Hz, J = 3.8 Hz);** 7.52 (dd, 1 H, H_{Th}(3), J = 3.7 Hz, J = 1.2 Hz); 7.67 (s, 1 H, =CH); 7.92 (dd, 1 H, H_{Th}(5), J = 4.9 Hz, J = 1.2 Hz).

3-(Dimethylaminomethylene)-5,5-dimethylhexa-2,4-dione (5h). The yield was 17.36 g (88%), yellowish crystals, m.p. 68—69 °C (benzene). Found (%): C, 66.82; H, 7.73; N, 7.18. $C_{11}H_{19}NO_2$. Calculated (%): C, 66.97; H, 9.71, N, 7.10. IR, ν/cm^{-1}: 2966, 2870, 1653, 1581, 1300, 999. ^{1}H NMR ($CDCl_3$), δ: 1.22 (s, 9 H, Bu^t); 2.17 (s, 3 H, Me); 2.91 (s, 6 H, NMe_2); 7.16 (s, 1 H, =CH).

3-(Dimethylaminomethylene)pentane-2,4-dione (5i). The yield was 13.50 g (87%), yellow crystals, m.p. 51—53 °C (Et_2O—hexane) (Ref. 35: m.p. 52—54 °C). ^{1}H NMR corresponded to the literature data.[35]

Synthesis of ethyl 5-acylcomanoates 7a—i (general procedure). A mixture of enaminodione **5** (5 mmol), diethyl oxalate (0.88 g, 6 mmol), and NaH (0.24 g, 6 mmol, a 60% dispersion in mineral oil) in anhydrous THF (15 mL) was stirred for 5 days (refluxed for 8 h). Then, the reaction mixture was treated with 4 M HCl to pH = 1 with cooling and stirred for 30 min at 0 °C. The product was extracted with EtOAc (3×15 mL), the extract was sequentially washed with H_2O (10 mL) and saturated aqueous solution of NaCl (5 mL) and dried with Na_2SO_4. The solvent was evaporated at reduced pressure, the residue was diluted with EtOH. A precipitate formed was filtered, washed with cold EtOH, and, if necessary, recrystallized from EtOH.

Ethyl 5-benzoyl-4-oxo-4*H*-pyrane-2-carboxylate (7a)[8]. The yield was 0.95 g (73%), light yellow crystals, m.p. 88—89 °C. ^{1}H NMR ($CDCl_3$, δ: 1.43 (t, 3 H, Me, J = 7.1); 4.46 (q, 2 H, CH_2O, J = 7.1); 7.24 (s, 1 H, H_{pyr}(3));*** 7.47 (t, 2 H, H(3), H(5) Ph, J = 7.7); 7.60 (tt, 1 H, H_{Ph}(4), J = 7.4, J = 1.2); 7.81 (dd, 2 H, H(2), H_{Ph}(6), J = 8.0, J = 1.4); 8.15 (s, 1 H, H_{pyr}(6)). ^{13}C NMR ($CDCl_3$, δ: 14.1, 63.5, 121.3, 128.7, 129.7, 130.6, 134.2, 136.2, 152.9, 157.5, 159.4, 175.8, 190.6.

Ethyl 5-(4-chlorobenzoyl)-4-oxo-4*H*-pyrane-2-carboxylate (7b). The yield was 1.26 g (82%), a beige powder, m.p. 113—114 °C (Ref. 9: m.p. 108—109 °C). IR, ν/cm^{-1}: 3085, 1740, 1654, 1621, 1580. ^{1}H NMR ($CDCl_3$), δ: 1.43 (t, 3 H, Me, J = 7.1 Hz); 4.46 (q, 2 H, CH_2O, J = 7.1 Hz); 7.23 (s, 1 H, H_{pyr}(3)); 7.44 (d, 2 H, H(3), H_{Ar}(5), J = 8.3 Hz); 7.75 (d, 2 H, H(2), H_{Ar}(6), J = 8.3 Hz); 8.18 (s, 1 H, H_{pyr}(6)).

Ethyl 5-(4-methoxybenzoyl)-4-oxo-4*H*-pyrane-2-carboxylate (7c). The yield was 1.04 g (69%), light yellow crystals, m.p. 89—90 °C (Ref. 9: m.p. 81—84 °C). IR, ν/cm^{-1}: 3072, 1731, 1655, 1594. ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, 3 H, Me, J = 7.1 Hz); 3.88 (s, 3 H, MeO); 4.46 (q, 2 H, CH_2O, J = 7.1 Hz); 6.93 (d, 2 H, H(3), H_{Ar}(5), J = 9.0 Hz); 7.23 (s, 1 H, H_{pyr}(3)); 7.82 (d, 2 H, H(2), H_{Ar}(6), J = 9.0 Hz); 8.11 (s, 1 H, H_{pyr}(6)).

Ethyl 5-(4-methylbenzoyl)-4-oxo-4*H*-pyrane-2-carboxylate (7d). The yield was 1.12 g (78%), light yellow crystals, m.p. 127—128 °C. Found (%): C, 67.31; H, 4.89. $C_{16}H_{14}O_5$. Calculated (%): C, 67.13; H, 4.93. IR, ν/cm^{-1}: 3209, 3032, 1754, 1651, 1614, 1309, 1001, 796. ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, 3 H, Me, J = 7.2 Hz); 2.42 (s, 3 H, Me); 4.46 (q, 2 H, CH_2O, J = 7.2 Hz); 7.22 (s, 1 H, H_{pyr}(3)); 7.26 (d, 2 H, H(3), H_{Ar}(5), J = 8.0 Hz); 7.72 (d, 2 H, H(2), H_{Ar}(6), J = 8.0 Hz); 8.12 (s, 1 H, H_{pyr}(6)).

Ethyl 5-(4-nitrobenzoyl)-4-oxo-4*H*-pyrane-2-carboxylate (7e). A precipitate obtained after the dilution with EtOH was refluxed with toluene (50 mL) for removal of polymeric impurities. Then, the toluene solution was decanted, concentrated to 10 mL, and diluted with hexane (20 mL), a precipitate formed was collected by filtration. The yield was 0.67 g (42%), an orange powder, m.p. 164—165 °C. Found (%): C, 57.06; H, 3.45; N, 4.49. $C_{15}H_{11}NO_7$. Calculated (%): C, 56.79; H, 3.49; N, 4.42. IR, ν/cm^{-1}: 3117, 3075, 2990, 1746, 1649, 1596, 1519, 849. ^{1}H NMR ($CDCl_3$), δ: 1.43 (s, 3 H, Me, J = 7.2 Hz); 4.48 (q, 2 H, CH_2O, J = 7.2 Hz); 7.25 (s, 1 H, H_{pyr}(3)); 7.93 (d, 2 H, H(3), H_{Ar}(5), J = 8.9 Hz); 8.30 (d, 2 H, H(2), H_{Ar}(6), J = 8.9 Hz); 8.31 (s, 1 H, H_{pyr}(6)).

Ethyl 5-(2-naphthoyl)-4-oxo-4*H*-pyrane-2-carboxylate (7f). The yield was 1.10 g (68%), a beige powder, m.p. 148—149 °C. Found (%): C, 70.84; H, 4.39. $C_{19}H_{14}O_5$. Calculated (%): C, 70.80; H, 4.38. IR, ν/cm^{-1}: 3078, 3059, 2989, 1737, 1646, 1572, 1296, 935, 784. ^{1}H NMR ($CDCl_3$), δ: 1.44 (t, 3 H, Me, J = 7.1 Hz); 4.48 (q, 2 H, CH_2O, J = 7.1 Hz); 7.28 (s, 1 H, H_{pyr}(3)); 7.54 (td, 1 H, H_{Naph}(7), J = 7.6 Hz, J = 1.1 Hz); 7.62 (td, 1 H, H_{Naph}(6), J = 7.6 Hz, J = 1.2 Hz); 7.88 (d, 1 H, H_{Naph}(4), J = 8.0 Hz); 7.90—7.95 (m, 3 H, H_{Ar}); 8.20 (s, 1 H, H_{pyr}(6)); 8.29 (d, 1 H, H_{Naph}(1), J = 0.8 Hz).

Ethyl 4-oxo-5-(2-thenoyl)-4*H*-pyrane-2-carboxylate (7g).[10] The yield was 1.02 g (73%), colorless crystals, m.p. 97—98 °C. Found (%): C, 56.02; H, 3.53. $C_{13}H_{10}O_5S$. Calculated (%): C, 56.11; H, 3.62. IR, ν/cm^{-1}: 3087, 2983, 2923, 2853, 1728, 1655, 1641, 1621, 1578. ^{1}H NMR ($CDCl_3$), δ: 1.42 (t, 3 H, Me, J = 7.1 Hz); 4.45 (q, 2 H, CH_2O, J = 7.1 Hz); 7.14 (dd, 1 H, H_{Th}(4), J = 4.9 Hz, J = 3.9 Hz); 7.24 (s, 1 H, H_{pyr}(3)); 7.67 (dd, 1 H, H_{Th}(3), J = 3.9 Hz, J = 1.1 Hz); 7.75 (dd, 1 H, H_{Th}(5), J = 4.9 Hz, J = 1.1 Hz); 8.18 (s, 1 H, H_{pyr}(6)). ^{13}C NMR (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.

Ethyl 4-oxo-5-pivaloyl-4*H*-pyrane-2-carboxylate (7h) was obtained from enaminodione **5h** by the reaction at 20 °C for

* H_{Naph} are the protons of the naphthaline ring.

** H_{Th} are the protons of the thiophene ring.

*** H_{pyr} are the protons of the pyrone ring.

5 days. After extraction and evaporation of the solvent at reduced pressure, the residue was diluted with EtOH (4 mL) and allowed to stand for 24 h at −20 °C. A precipitate was collected by filtration, washed with cold EtOH, and dried. The yield was 0.67 g (53%), colorless crystals, m.p. 106—107 °C. Found (%): C, 62.30; H, 6.75. $C_{13}H_{16}O_5$. Calculated (%): C, 61.90; H, 6.39. IR, ν/cm^{-1}: 3055, 2974, 2924, 2855, 1739, 1699, 1646, 1615, 1463, 1086, 935, 783. ^{1}H NMR ($CDCl_3$), δ: 1.24 (s, 9 H, Bu^t); 1.41 (t, 3 H, Me, J = 7.1 Hz); 4.44 (q, 2 H, CH_2O, J = 7.1 Hz); 7.13 (s, 1 H, H(3)); 7.80 (s, 1 H, H(6)). ^{13}C NMR ($CDCl_3$), δ: 14.1, 26.1, 45.1, 63.3, 120.5, 132.9, 152.8, 153.3, 159.5, 175.6, 206.7.

Ethyl 5-acetyl-4-oxo-4*H*-pyrane-2-carboxylate (7i).[8] After evaporation of the solvent from the extract, EtOH (4 mL) was added, and the resulting mixture was allowed to stand for 1 days at −20 °C. A precipitate was collected by filtration, washed with cold EtOH, and dried. The yield was 0.33 g (31%), orange crystals, m.p. 65—67 °C. ^{1}H NMR ($CDCl_3$), δ: 1.41 (t, 3 H, Me, J = 7.1 Hz); 2.66 (s, 3 H, Me); 4.44 (q, 2 H, CH_2O, J = 7.1 Hz); 7.22 (s, 1 H, H(3)); 8.44 (s, 1 H, H(6)). ^{13}C NMR ($CDCl_3$), δ: 14.1, 31.5, 63.5, 122.4, 127.8, 152.6, 159.3, 160.9, 176.3, 195.9.

Ethyl 2-oxo-3-pivaloyl-2*H*-pyrane-6-carboxylate (8a) was obtained from enaminodione **5h** upon reflux for 8 h. After extraction and evaporation of the solvent at reduced pressure, the residue was diluted with EtOH (4 mL) and allowed to stand for 1 h at −20 °C, a precipitate of **7h** was filtered off. The filtrate was additionally allowed to stand for 24 h at −20 °C. A precipitate was collected by filtration and recrystallized from hexane with a small amount of toluene. The yield was 0.14 g (11%), colorless crystals, m.p. 78—81 °C. Found (%): C, 61.86; H, 6.48. $C_{13}H_{16}O_5$. Calculated (%): C, 61.90; H, 6.39. IR, ν/cm^{-1}: 2989, 2970, 1734, 1689, 1270, 1129, 767. ^{1}H NMR (DMSO-d_6), δ: 1.20 (s, 9 H, Bu^t); 1.37 (t, 3 H, Me, J = 7.0 Hz); 4.36 (q, 2 H, CH_2O, J = 7.0 Hz); 7.20 (d, 1 H, H(5), J = 6.7 Hz); 7.61 (s, 1 H, H(4), J = 6.7 Hz). ^{13}C NMR ($CDCl_3$), δ: 14.2, 26.5, 45.1, 62.9, 109.4, 133.8, 139.3, 150.3, 157.4, 159.0, 207.4.

Synthesis of 6-substituted comanic acids 9a—h (general procedure). A suspension of ethyl ester **7** (0.400 g) in HCl (4 mL) (1 : 1) was heated in a bath at 100 °C for 8 h, a precipitate formed was collected by filtration and dried.

4-Oxo-6-phenyl-4*H*-pyrane-2-carboxylic acid (9a). The yield was 0.216 g (68%), a grey powder. m.p. 247—248 °C (Ref. 29: m.p. 250—252 °C). ^{1}H NMR (DMSO-d_6), δ: 6.89 (d, 1 H, H(5), J = 2.2 Hz); 7.13 (d, 1 H, H(3), J = 2.2 Hz); 7.50—7.62 (m, 3 H, Ph); 7.98 (dd, 2 H, Ph, J = 8.6 Hz, J = 1.9 Hz); 13.0—16.0 (br.s, 1 H, OH).

6-(4-Chlorophenyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (9b). The yield was 0.278 g (85%), a grey powder, m.p. 284—285 °C (Ref. 28: m.p. 264—265 °C). ^{1}H NMR (DMSO-d_6), δ: 6.88 (d, 1 H, H(5), J = 2.1 Hz); 7.15 (d, 1 H, H(3), J = 2.1 Hz); 7.65 (d, 2 H, H(3), H_{Ar}(5), J = 8.6 Hz); 7.99 (d, 2 H, H(2), H_{Ar}(6), J = 8.6 Hz); 13.0—16.0 (br.s, 1 H, OH).

6-(4-Methoxyphenyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (9c). The yield was 0.300 g (92%), a grey powder, m.p. 266—267 °C (Ref. 28: m.p. 250—253 °C). ^{1}H NMR (DMSO-d_6), δ: 3.85 (s, 3 H, MeO); 6.84 (d, 1 H, H(5), J = 2.3 Hz); 7.00 (d, 1 H, H(3), J = 2.3 Hz); 7.11 (d, 2 H, H(3), H_{Ar}(5), J = 8.9 Hz); 7.92 (d, 2 H, H(2), H_{Ar}(6), J = 8.9 Hz); 12.0—16.0 (br.s, 1 H, OH).

6-(4-Methylphenyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (9d). The yield was 0.296 g (92%), a colorless powder, m.p. 246—248 °C (Ref. 28: m.p. 237—238 °C). ^{1}H NMR (DMSO-d_6), δ: 2.42 (s, 3 H, Me); 6.85 (d, 1 H, H(5), J = 2.3 Hz); 6.93 (d, 1 H, H(3), J = 2.3 Hz); 7.33 (d, 2 H, H(3), H_{Ar}(5), J = 8.2 Hz); 7.83 (d, 2 H, H(2), H_{Ar}(6), J = 8.2 Hz); the OH proton was not detected.

6-(4-Nitrophenyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (9e). The yield was 0.267 g (81%), a grey powder, m.p. 253—254 °C (Ref. 28: m.p. 248—250 °C). ^{1}H NMR (DMSO-d_6), δ: 6.92 (d, 1 H, H(5), J = 2.2 Hz); 7.29 (d, 1 H, H(3), J = 2.2 Hz); 8.25 (d, 2 H, Ar, J = 9.0 Hz); 8.36 (d, 2 H, Ar, J = 9.0 Hz); the OH proton was not detected.

6-(2-Naphthyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (9f). The reaction used HCl (6 mL, 2 : 1) and was carried out for 32 h. The yield was 0.311 g (94%), a grey powder, m.p. 283—284 °C. Found (%): C, 71.67; H, 3.69. $C_{16}H_{10}O_4$. Calculated (%): C, 72.18; H, 3.79. ^{1}H NMR (DMSO-d_6), δ: 6.91 (d, 1 H, H(5), J = 2.3 Hz); 7.23 (d, 1 H, H(3), J = 2.3 Hz); 7.57—7.67 (m, 2 H, H(6), H_{Naph}(7)); 7.96—8.10 (m, 4 H, H_{Naph}); 8.57 (d, 1 H, H_{Naph}(1), J = 1.2 Hz); 13.9—15.2 (br.s, 1 H, OH).

4-Oxo-6-(2-thienyl)-4*H*-pyrane-2-carboxylic acid (9g).[10] The yield was 0.285 g (89%), a grey powder, m.p. 252—253 °C. Found (%): C, 54.03; H, 2.75. $C_{10}H_6O_4S$. Calculated (%): C, 54.05; H, 2.72. IR, ν/cm^{-1}: 3108, 3085, 1730, 1623, 1594, 1573. ^{1}H NMR (DMSO-d_6), δ: 6.84 (d, 1 H, H(5), J = 2.3 Hz); 6.98 (d, 1 H, H(3), J = 2.3 Hz); 7.27 (dd, 1 H, H_{Th}(4), J = 5.0 Hz, J = 3.9 Hz); 7.93 (dd, 1 H, H_{Th}(3), J = 3.9 Hz, J = 1.1 Hz); 7.95 (dd, 1 H, H_{Th}(5), J = 5.0 Hz, J = 1.1 Hz); 12.0—15.5 (br.s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 110.6, 118.4, 129.4, 129.9, 132.4, 133.7, 153.2, 159.5, 161.3, 178.8.

6-(*tert*-Butyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (9h). The yield was 0.212 g (68%), a colorless powder, m.p. 235—237 °C. Found: m/z 197.0819 $[MH]^+$. $C_{10}H_{13}O_4$. Calculated: M = = 197.0814. IR, ν/cm^{-1}: 3055, 2974, 2924, 2855, 1739, 1699, 1646, 1655, 1463, 1292, 1244, 1086, 935, 783. ^{1}H NMR (DMSO-d_6), δ: 1.26 (s, 9 H, Bu^t); 6.29 (d, 1 H, H(5), J = 2.3 Hz); 6.77 (d, 1 H, H(3), J = 2.3 Hz); 13.9—15.0 (br.s, 1 H, OH).

Diethyl 2-hydroxy-4-oxo-5-(piperidin-1-ylmethylidene)hex-2-enedioate (11). Diester **10** (0.242 g, 1.0 mmol) was added to a solution of piperidine (0.102 g, 1.20 mmol) in EtOH (2 mL) at 0 °C. The resulting suspension was stirred for 2 h at 0 °C and then allowed to stand for 2 days at −20 °C. A precipitate formed was collected by filtration and washed with cold EtOH. The yield was 0.192 g (59%), a yellow powder, m.p. 71—72 °C. Found (%): C, 59.06; H, 7.29; N, 4.27. $C_{16}H_{23}NO_6$. Calculated (%): C, 59.06; H, 7.13; N, 4.31. IR, ν/cm^{-1}: 3144, 2986, 2929, 2852, 1740, 1686, 844, 785. ^{1}H NMR (DMSO-d_6), δ: 1.31 (t, 3 H, Me, J = 7.1 Hz); 1.32 (t, 3 H, Me, J = 7.1 Hz); 1.62—1.82 (br.s, 6 H, 3 CH_2); 2.8—3.8 (br.s, 4 H, $(CH_2)_2N$); 4.18 (q, 2 H, CH_2O, J = 7.1 Hz); 4.24 (q, 2 H, CH_2O, J = 7.1 Hz); 6.70 (s, 1 H, =CH); 7.91 (s, 1 H, =HCN); 14.0—16.0 (br.s, 1 H, OH).

Synthesis of enamines 13a—c,f,g (general procedure). A thoroughly triturated pyrone **7a** (1.0 mmol) was added to a solution of piperidine (0.102 g, 1.20 mmol) in EtOH (3 mL) at 0 °C. The resulting suspension was stirred for 1 h at 0 °C, a precipitate formed was collected by filtration and washed with cold EtOH.

Ethyl 5-benzoyl-2-hydroxy-4-oxo-6-(piperidin-1-yl)hexa-2,5-dienoate (13a). The yield was 0.293 g (82%), a yellow powder, m.p. 127—128 °C. Found (%): C, 67.20; H, 6.35; N, 3.86. $C_{20}H_{23}NO_5$. Calculated (%): C, 67.21; H, 6.49; N, 3.92. IR, ν/cm^{-1}: 2994, 2947, 1786, 1577, 941, 779. ^{1}H NMR (DMSO-d_6), δ: 1.26 (t, 3 H, Me, J = 7.1 Hz); 1.34—1.74 (br.s, 6 H, 3 CH_2); 2.70—3.30 (br.s, 4 H, $(CH_2)_2N$); 4.17 (q, 2 H, CH_2O, J = 7.1 Hz); 6.17 (s, 1 H, =CH); 7.48 (t, 2 H, H(3), H_{Ph}(5), J = 7.5 Hz); 7.57 (tt, 1 H, H_{Ph}(4), J = 7.3 Hz, J = 1.2 Hz); 7.78 (d, 2 H, H(2),

$H_{Ph}(6)$, J = 7.5 Hz); 8.04 (s, 1 H, =HCN); 15.0—16.0 (br.s, 1 H, OH).

Ethyl 5-(4-chlorobenzoyl)-2-hydroxy-4-oxo-6-(piperidin-1-yl)hexa-2,5-dienoate (13b). The yield was 0.278 g (71%), a yellow powder, m.p. 123—124 °C. Found (%): C, 61.24; H, 5.63; N, 3.35. $C_{20}H_{22}ClNO_5$. Calculated (%): C, 61.30; H, 5.66; N, 3.57. IR, ν/cm^{-1}: 2949, 2856, 1721, 1582, 941, 781. ^{1}H NMR (DMSO-d_6), δ: 1.24 (t, 3 H, Me, J = 7.2 Hz); 1.30—1.68 (br.s, 6 H, 3 CH_2); 2.60—3.90 (br.s, 4 H, $(CH_2)_2N$); 4.17 (q, 2 H, CH_2O, J = 7.2 Hz); 6.24 (s, 1 H, =CH); 7.51 (d, 2 H, H(3), $H_{Ar}(5)$, J = 8.5 Hz); 7.76 (d, 2 H, H(2), $H_{Ar}(6)$, J = 8.5 Hz); 8.06 (s, 1 H, =HCN); 14.0—16.0 (br.s, 1 H, OH).

Ethyl 2-hydroxy-5-(4-methoxybenzoyl)-4-oxo-6-(piperidin-1-yl)hexa-2,5-dienoate (13c). The yield was 0.313 g (79%), a yellow powder, m.p. 107—108 °C. Found (%): C, 63.27; H, 6.67; N, 3.43. $C_{21}H_{25}NO_6 \cdot 0.5H_2O$. Calculated (%): C, 63.62; H, 6.61; N, 3.53. IR, ν/cm^{-1}: 2941, 2857, 1721, 1589, 902, 767. ^{1}H NMR (DMSO-d_6), δ: 1.23 (t, 3 H, Me, J = 7.1 Hz); 1.32—1.72 (br.s, 6 H, 3 CH_2); 2.9—3.7 (br.s, 4 H, $(CH_2)_2N$); 3.85 (s, 3 H, MeO); 4.18 (q, 2 H, CH_2O, J = 7.2 Hz); 6.14 (s, 1 H, =CH); 7.00 (d, 2 H, H(3), $H_{Ar}(5)$, J = 8.5 Hz); 7.76 (d, 2 H, H(2), $H_{Ar}(6)$, J = 8.5 Hz); 8.01 (s, 1 H, =HCN); 15.0—16.0 (br.s, 1 H, OH).

Ethyl 2-hydroxy-5-(2-naphthoyl)-4-oxo-6-(piperidin-1-yl)-hexa-2,5-dienoate (13f). The yield was 0.334 g (82%), a light yellow powder, m.p. 130—132 °C. Found (%): C, 70.39; H, 6.15; N, 3.40. $C_{24}H_{25}NO_5$. Calculated (%): C, 70.74; H, 6.18, N, 3.44. IR, ν/cm^{-1}: 3060, 2938, 2858, 1730, 1617, 1236, 966. ^{1}H NMR (DMSO-d_6), δ: 1.19 (t, 3 H, Me, J = 7.1 Hz); 1.2—1.8 (br.s, 6 H, 3 CH_2); 2.7—3.9 (m, 4 H, $(CH_2)_2N$); 4.14 (q, 2 H, CH_2O, J = 7.1 Hz); 6.24 (s, 1 H, =CH); 7.56 (td, 1 H, H_{Naph}, J = 7.2 Hz, J = 0.7 Hz); 7.62 (td, 1 H, H_{Naph}, J = 7.6 Hz, J = 0.8 Hz); 7.88 (dd, 1 H, H_{Naph}, J = 8.6 Hz, J = 1.3 Hz); 7.94 (dd, 1 H, H_{Naph}, J = 8.1 Hz); 7.98 (dd, 1 H, H_{Naph}, J = 8.6 Hz); 8.04 (d, 1 H, H_{Naph}, J = 8.0 Hz); 8.13 (s, 1 H, $H_{Naph}(1)$); 8.34 (s, 1 H, =CHN); 15.0—16.2 (s, 1 H, OH).

Ethyl 2-hydroxy-4-oxo-6-(piperidin-1-yl)-5-(2-thenoyl)-hexa-2,5-dienoate (13g).[10] The yield was 0.291 g (66%), a yellow powder, m.p. 125—126 °C. Found (%): C, 59.45; H, 5.72, N, 3.72. $C_{18}H_{21}NO_5S$. Calculated (%): C, 59.49; H, 5.82; N, 3.85. IR, ν/cm^{-1}: 3131, 3069, 2998, 2984, 2951, 1725, 1604, 1586. ^{1}H NMR (DMSO-d_6), δ: 1.22 (t, 3 H, Me, J = 7.1 Hz); 1.35—1.70 (br.s, 6 H, 3 CH_2); 2.9—3.8 (br.s, 4 H, $(CH_2)_2N$); 4.19 (q, 2 H, CH_2O, J = 7.1 Hz); 6.29 (s, 1 H, =CH); 7.21 (dd, 1 H, $H_{Th}(4)$, J = 4.9 Hz, J = 3.9 Hz); 7.65 (dd, 1 H, $H_{Th}(3)$, J = 3.9 Hz, J = 1.2 Hz); 8.03 (dd, 1 H, $H_{Th}(5)$, J = 4.9 Hz, J = 1.2 Hz); 8.06 (s, 1 H, =CHN); 15.0—16.5 (br.s, 1 H, OH). ^{13}C NMR (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.

Synthesis of 5-acylcomanic acids 14a—c,f,g (general procedure). Enamine **13** (107 mg, 0.3 mmol) was added to a solution of KOH (84 mg, 1.50 mmol) in water (2 mL) with cooling to 0 °C. The resulting suspension was stirred until complete dissolution of the precipitate over 15—20 min at 0 °C, then the reaction mixture was acidified with 4 M HCl to pH = 1, a precipitate of the target acid was collected by filtration.

5-Benzoyl-4-oxo-4*H*-pyrane-2-carboxylic acid (14a). The yield was 52 mg, 69%), a yellowish powder, m.p. 197—198 °C. Found (%): C, 61.63; H, 3.03. $C_{13}H_8O_5 \cdot 0.5H_2O$. Calculated (%): C, 61.66; H, 3.58. IR, ν/cm^{-1}: 3074, 1734, 1656, 1638, 1287, 902, 781. ^{1}H NMR (DMSO-d_6), δ: 7.01 (s, 1 H, $H_{pyr}(3)$); 7.53 (t, 2 H, H(3), $H_{Ph}(5)$, J = 7.7 Hz); 7.69 (tt, 1 H, $H_{Ph}(4)$, J = 7.5 Hz, J = 1.2 Hz); 7.85 (dd, 2 H, H(2), $H_{Ph}(6)$, J = 8.4 Hz, J = 1.3 Hz); 8.65 (s, 1 H, $H_{pyr}(6)$); the OH proton was not detected.

5-(4-Chlorobenzoyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (14b). The yield was 77 mg (89%), a yellowish powder, m.p. 230—232 °C. Found (%): C, 54.43; H, 2.65. $C_{13}H_7ClO_5 \cdot 0.5H_2O$. Calculated (%): C, 54.80; H, 2.80. IR, ν/cm^{-1}: 3071, 2878, 2609, 1738, 1656, 1632, 1584, 1289, 905. ^{1}H NMR (DMSO-d_6), δ: 7.02 (s, 1 H, $H_{pyr}(3)$); 7.60 (d, 2 H, H(3), $H_{Ar}(5)$, J = 8.6 Hz); 7.86 (d, 2 H, H(2), $H_{Ar}(6)$, J = 8.6 Hz); 8.67 (s, 1 H, $H_{pyr}(6)$); the OH proton was not detected.

5-(4-Methoxybenzoyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (14c). The yield was 50 mg (61%), a light yellow powder, m.p. 125—126 °C (acetone—H_2O). Found (%): C, 61.23; H, 3.51. $C_{14}H_{10}O_6$. Calculated (%): C, 61.32; H, 3.68. IR, ν/cm^{-1}: 3069, 2872, 2602, 1738, 1651, 1586, 1293, 909. ^{1}H NMR (DMSO-d_6), δ: 3.87 (s, 3 H, CH_3O); 7.00 (s, 1 H, $H_{pyr}(3)$); 7.05 (d, 2 H, H(3), $H_{Ar}(5)$, J = 8.8 Hz); 7.83 (d, 2 H, H(2), $H_{Ar}(6)$, J = 8.8 Hz); 8.59 (s, 1 H, $H_{pyr}(6)$); the OH proton was not detected.

5-(2-Naphthoyl)-4-oxo-4*H*-pyrane-2-carboxylic acid (14f). The reaction was carried out in H_2O—THF (2.5 mL, 4 : 1) for 20 min, the product **14f** was additionally refluxed with toluene for 1 min. The yield was 50 mg (54%), a light yellow powder, m.p. 243—244 °C. Found (%): C, 66.40; H, 3.34. $C_{17}H_{10}O_5 \cdot \cdot 0.67H_2O$. Calculated (%): C, 66.65; H, 3.73. IR, ν/cm^{-1}: 3078, 2923, 1742, 1670, 1647, 1300. ^{1}H NMR (DMSO-d_6), δ: 6.97 (s, 1 H, $H_{pyr}(3)$); 7.57 (t, 1 H, $H_{Naph}(6)$, J = 7.3 Hz); 7.64 (t, 1 H, $H_{Naph}(7)$, J = 7.2 Hz); 7.90 (d, 1 H, H_{Naph}, J = 8.5 Hz); 7.96 (m, 2 H, H_{Naph}); 8.03 (d, 1 H, H_{Naph}, J = 8.1 Hz); 8.40 (s, 1 H, $H_{Naph}(1)$); 8.56 (s, 1 H, $H_{pyr}(6)$); the OH proton was not detected.

4-Oxo-5-(2-thenoyl)-4*H*-pyrane-2-carboxylic acid (14g).[10] The yield was 64 mg (80%), a light yellow powder, m.p. 218—220 °C. Found (%): C, 49.51; H, 2.98. $C_{11}H_6O_5S \cdot H_2O$. Calculated (%):C, 49.25; H, 3.01. IR, ν/cm^{-1}: 3452, 3097, 1727, 1651, 1627. ^{1}H NMR (DMSO-d_6), δ: 7.02 (s, 1 H, $H_{pyr}(3)$); 7.26 (dd, 1 H, $H_{Th}(4)$, J = 4.8 Hz, J = 4.0 Hz); 7.83 (dd, 1 H, $H_{Th}(3)$, J = 4.0 Hz, J = 1.2 Hz); 8.15 (dd, 1 H, $H_{Th}(5)$, J = 4.8 Hz, J = 1.2 Hz); 8.71 (s, 1 H, $H_{pyr}(6)$); the OH proton was not detected. ^{13}C NMR (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.

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