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FACILE PREPARATION OF 2-OXO-2*H*-1-PYRAN-3-CARBOXYLATES WITH THE ELECTRON-WITHDRAWING GROUP AT THE 5-POSITION

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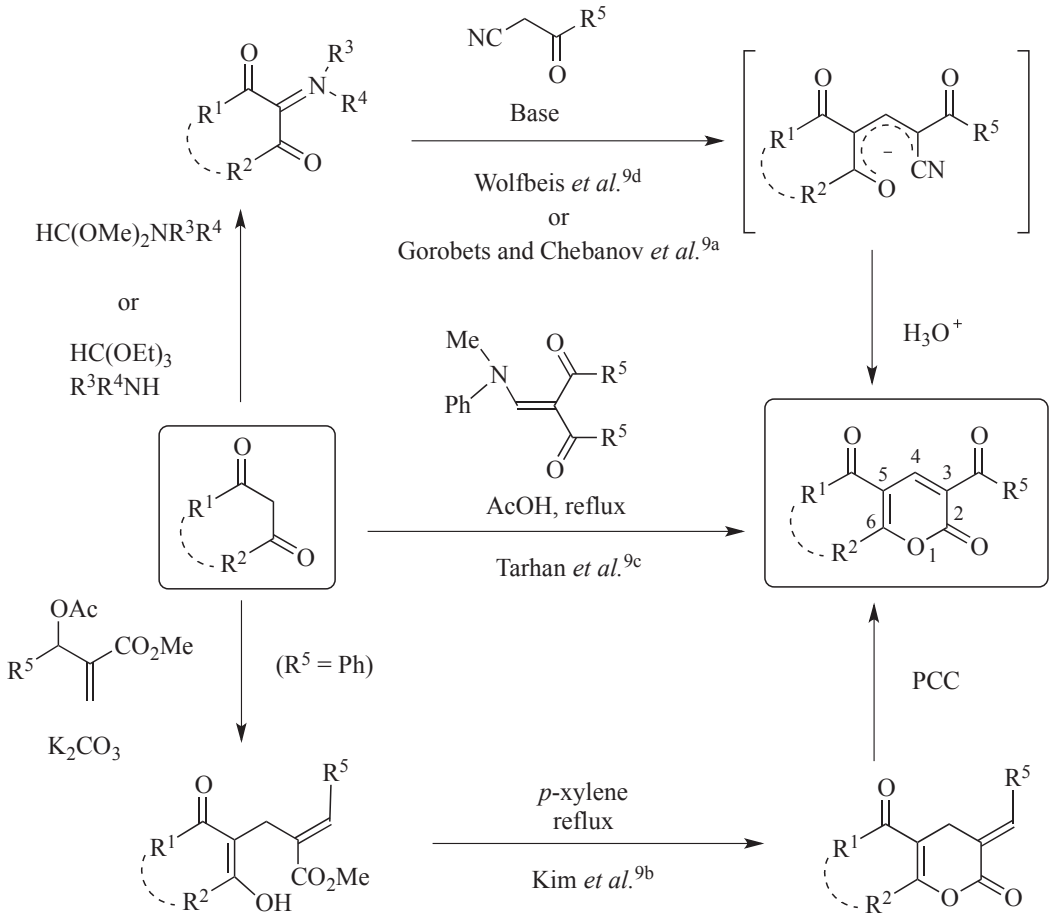
Abstract – A simple and facile procedure for the preparation of 2-oxo-2*H*-1-pyran-3-carboxylate bearing electron-withdrawing groups at the 5-position, such as the alkylcarbonyl and alkoxycarbonyl moieties, was developed. Various 1,3-dicarbonyl compounds were treated with dimethyl (methoxymethylene)malonate in the presence of Cs_2CO_3 as a base in tetrahydrofuran at room temperature. This method was particularly effective in the syntheses of bicyclic structures, such as 5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-carboxylates.

INTRODUCTION

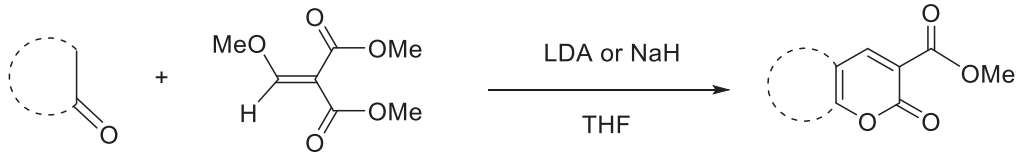
The 2*H*-1-pyran-2-one ring system is present in a number of natural products[1] and biologically active compounds, such as the nonpeptide protease inhibitor of human immunodeficiency virus-1,[2] and is also involved in the regulation of root architecture[3] and plant growth promotion,[4] in addition to exhibiting antifungal activity,[5] and antibacterial activity.[6] It is also useful as a building block in organic synthesis as a scaffold for the α,β,γ,δ-conjugated lactone group within a six membered ring.[7] We previously reported a study into 2*H*-1-pyran-2-one building blocks bearing electron-withdrawing groups at the 3,5-positions.[8] Although the preparation of these compounds from 1,3-dicarbonyl compounds has been reported by a number of groups (Scheme 1),[9] each method involves multiple steps, cumbersome procedures, or severe reaction conditions (e.g., reflux in acid). We therefore attempted the development of a novel preparation method for 2-oxo-2*H*-1-pyran-3-carboxylates bearing the electron-withdrawing group at the 5-position. In this paper, their mild and facile preparation is reported.



Scheme 1. Reported syntheses of 2*H*-1-pyran-2-ones bearing electron-withdrawing groups at the 3,5-positions

RESULTS AND DISCUSSION

To prepare the desired 2-oxo-2*H*-1-pyran-3-carboxylates bearing the electron-withdrawing group at the 5-position, the method of Boger *et al*. was employed (Scheme 2).[10]

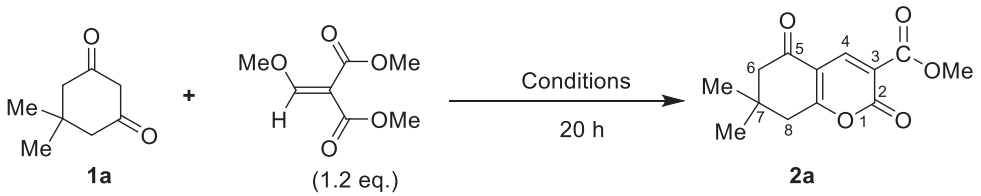


Scheme 2. Preparative method for 2-oxo-2*H*-1-pyran-3-carboxylates as reported by Boger *et al.*

Thus, the 2-oxo-2*H*-1-pyran-3-carboxylates were prepared from the corresponding ketones and dimethyl (methoxymethylene)malonate in the presence of an appropriate base. In the case of readily enolizable ketones such as 3,4-dihydronaphthalen-2(1*H*)-one, sodium hydride was used as a base, and in the case of simple ketones such as cyclohexanone, lithium diisopropylamide (LDA) was employed. We therefore assumed that 2*H*-1-pyran-2-ones bearing electron-withdrawing groups at the 3,5-positions could be

prepared from 1,3-diketones (**1**) using a weaker base than NaH in an appropriate solvent. Initially, 5,5-dimethylcyclohexane-1,3-dione (**1a**) was treated with dimethyl (methoxymethylene)malonate in acetone in the presence of K_2CO_3 as a base at room temperature for 20 h. The desired product, methyl 5,6,7,8-tetrahydro-7,7-dimethyl-2,5-dioxo-2*H*-1-benzopyran-3-carboxylate (**2a**) was obtained in 30% yield (entry 1, Table 1). The structure of **2a** was confirmed by comparison with the spectral data described in the literature.[9d] For optimization of the reaction conditions, the base, amount of base, and reaction temperature were varied. However, organic bases such as triethylamine and pyridine were found to be ineffective (entries 6 and 7). Based on the improved results obtained under the conditions of entry 5, further solvent optimization was carried out to allow the isolation of 4-hydroxy-4-methylpentan-2-one as a by-product, which was derived from the aldol reaction of the acetone, and the results are summarized in Table 1. In methanol, the formation of **2a** was not observed (entry 8). However, in dichloromethane and polar aprotic solvents, such as DMF and DMSO, **2a** was obtained in moderate to good yields (entries 9–11). More specifically, the optimal conditions were found to be 3.0 eq. Cs_2CO_3 as a base in THF as the solvent (entry 12).

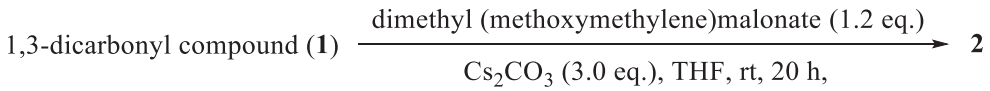
Table 1. Examination of reaction conditions for the transformation of **1a** to **2a**

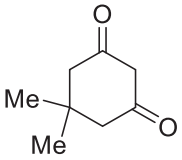
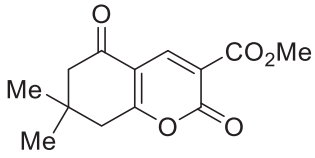
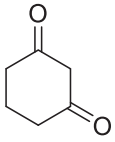
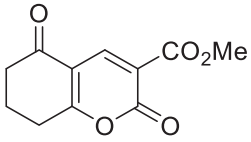
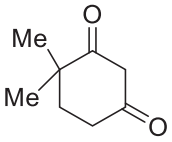
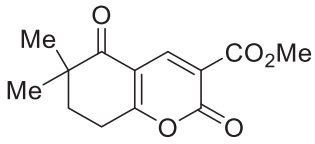
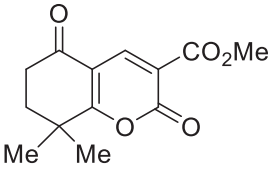
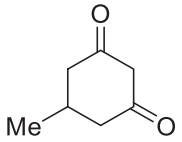
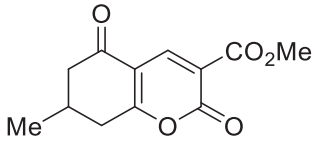
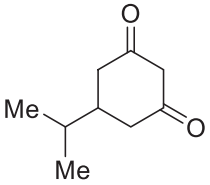
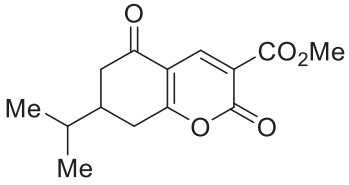
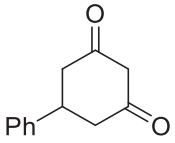
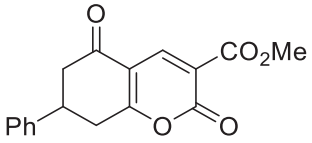
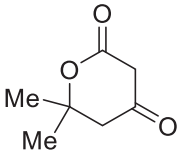
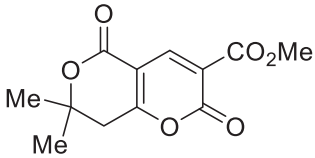
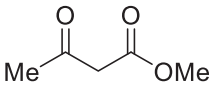
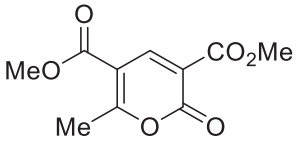


Entry	Base (eq.)	Solvent	Temperature	Yield (%)[a]
1	K_2CO_3 (1.0)	acetone	rt	30
2	K_2CO_3 (1.0)	acetone	reflux	Complex mixture
3	K_2CO_3 (0.1)	acetone	reflux	Complex mixture
4	K_2CO_3 (3.0)	acetone	rt	37
5	Cs_2CO_3 (3.0)	acetone	rt	64
6	Et_3N (3.0)	acetone	rt	No reaction
7	pyridine (3.0)	acetone	rt	No reaction
8	Cs_2CO_3 (3.0)	MeOH	rt	No reaction
9	Cs_2CO_3 (3.0)	CH_2Cl_2	rt	67
10	Cs_2CO_3 (3.0)	DMF	rt	80
11	Cs_2CO_3 (3.0)	DMSO	rt	83
12	Cs_2CO_3 (3.0)	THF	rt	93
13	Cs_2CO_3 (1.0)	THF	rt	77

[a] Isolated yield.

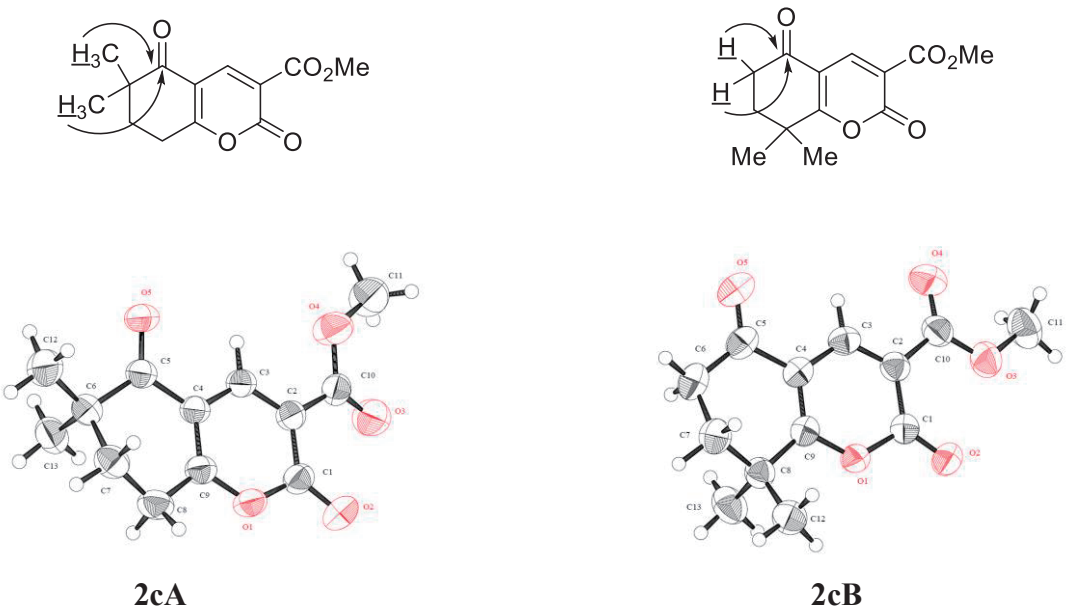
Table 2. Reaction of various 1,3-dicarbonyl compounds (**1**) with dimethyl (methoxymethylene)malonate



Entry	1,3-Dicarbonyl compound		Product		Yield (%)[a]
1	**1a**:		**2a**:		93 (43)[b]
2	**1b**:		**2b**:		51 (39)[b]
3	**1c**:		**2cA**:		28
			2cB:		17
4	**1d**:		**2d**:		64
5	**1e**:		**2e**:		76
6	**1f**:		**2f**:		58 (51)[b]
7	**1g**:		**2g**:		46
8	**1h**:		**2h**:		54[c] (68)[d]

[a]Isolated yield. [b]The number in parentheses indicates the overall yield from two steps presented in the literature.[9d] [c]As a base, *tert*-BuOK was used. [d]The number in parentheses indicates the literature yield.[9c]

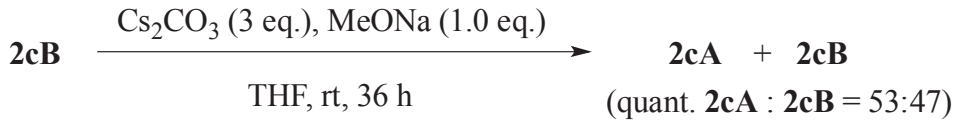
To examine the substrate scope, the reaction conditions of entry 12 were then applied to various 1,3-dicarbonyl compounds, and the results are summarized in Table 2. As presented in Table 2, the 6-membered 1,3-dioxo cyclic compounds gave their corresponding 2*H*-pyran-2-ones in moderate yields (entries 2–6). Interestingly, 4,4-dimethylcyclohexane-1,3-dione (**1c**) afforded two regioisomers, namely 5,6,7,8-tetrahydro-6,6-dimethyl-2,5-dioxo-2*H*-benzopyran-3-carboxylate (**2cA**) and 5,6,7,8-tetrahydro-8,8-dimethyl-2,5-dioxo-2*H*-benzopyran-3-carboxylate (**2cB**), in 28 and 17% yields, respectively (entry 3). The structures of **2cA** and **2cB** were determined by spectral analyses. More specifically, in the heteronuclear multiple bond coherence (HMBC) spectra, correlations between the 6-methyl hydrogen atoms and the 5-carbonyl carbon atom in **2cA**, and the 6-hydrogen atoms and 5-carbonyl carbon atom in **2cB** were observed. Finally, the structures of **2cA** and **2cB** were confirmed by X-ray crystallography (Figure 1).



2cA **2cB**

Figure 1. Selected HMBC correlations in **2cA** and **2cB**, and their obtained X-ray structures

To interpret this obtained ratio, density functional theory (DFT) calculations were then performed for **2cA** and **2cB** using the ωB97X-D/6-31G* level of theory. The results indicated that **2cA** was more stable than **2cB** by 1.66 kJ/mol, resulting in an **2cA**:**2cB** ratio of 66:34. Indeed, this ratio is almost entirely consistent with the obtained experimental yields. In addition, to confirm the presence of an equilibrium between these two compounds, **2cB** was treated using three equivalents of Cs_2CO_3 in the presence of one equivalent of sodium methoxide in THF at room temperature for 36 h. As a result, a 53:47 mixture of **2cA** and **2cB** was obtained, as estimated from the ^{1}H NMR spectrum (Scheme 3).[11]



Scheme 3. Treatment of **2cB** with Cs_2CO_3 and sodium methoxide

Furthermore, 6,6-dimethyl-4-oxo-δ-lactone (**1g**) also gave the desired product **2g** in 46% yield (entry 7), although the reaction of acyclic 3-oxo-butanoate (**1h**) with Cs_2CO_3 afforded **2h** in only 28% yield. However, when potassium *tert*-butoxide was employed as a base, the latter yield was improved to 54% (entry 8). These results therefore indicate that our method is suitable for application in the reactions of lactone and acyclic dicarbonyl compounds.

In conclusion, a simple and facile procedure for the preparation of 2-oxo-2*H*-1-pyran-3-carboxylates bearing electron-withdrawing groups such as the alkylcarbonyl and alkoxycarbonyl moieties was successfully developed. Various 1,3-dicarbonyl compounds were treated with dimethyl (methoxymethylene)malonate in the presence of Cs_2CO_3 as a base in THF at room temperature to obtain the desired products. This method therefore addresses previous issues related to preparation of the 2*H*-1-pyran-2-one ring system, which is present in a number of natural products and biologically active compounds. Studies are now ongoing in our group into the use of 2-oxo-2*H*-1-pyran-3-carboxylates bearing electron-withdrawing groups as a building blocks, and the results will be presented in due course.

EXPERIMENTAL

General: Melting points were measured with a Yanaco MP micro-melting point apparatus and uncorrected. NMR spectra were measured on JEOL AL-300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), JEOL ECS-400 (^{1}H: 400 MHz; ^{13}C: 100 MHz), and Bruker Ascend^{TM} 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometers with tetramethylsilane as the internal standard. Chemical shifts are reported in ppm. IR spectra were measured with Shimadzu FTIR-8400 spectrophotometer. A JEOL JMS-GC mate II spectrometer was used for low-resolution and high-resolution electron ionizations MS (LR-EIMS and HR-EIMS). X-ray crystal analyses were performed on Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Cu-Kα radiation at 23.0 ºC. Silica gel 60 F_{254} (Merck) for thin layer chromatography and Silica gel 60N (Kanto Chemical Co., Inc.) for column chromatography were used.

Typical Procedure for the Synthesis of Methyl 5-Acyl-2-oxo-2*H*-1-pyran-3-carboxylate (2)

The mixture of 1,3-dicarbonyl compound (**1**: 1.0 mmol), dimethyl (methoxymethylene)malonate (1.2 eq.), Cs_2CO_3 (3.0 eq.) in THF (5.0 mL) was stirred at room temperature under an N_2 atmosphere until **1** was

disappeared by TLC check (about 20-24 h). After acidification with 1N HCl aq., the mixture was extracted with EtOAc (3 times). The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, and evaporated under the reduced pressure. The residue was chromatographed on silica gel with *n*-hexane-EtOAc as eluent to give the corresponding methyl 5-acyl-2-oxo-2*H*-1-pyran-3-carboxylate (**2**).

The compounds **2a**,[9d] **2b**,[9d] **2f**,[9d] and **2h**[9c] are known.

Methyl 5,6,7,8-Tetrahydro-6,6-dimethyl-2,5-dioxo-2*H*-1-benzopyran-3-carboxylate (2cA)

Less polar compound. Colorless prisms; mp 121.5-123.0 ºC (acetone-*n*-hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (6H, s), 2.02 (2H, t, J=6.8 Hz), 2.93 (2H, t, J=6.8 Hz), 3.91 (3H, s), 8.67 (1H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 24.0, 25.5, 33.3, 40.7, 52,8, 112.5, 115.1, 146.3, 156.0, 162.9, 176.8, 197.7; IR ($CDCl_3$): 3028, 1776, 1719, 1688, 1566, 1393,1250 cm^{-1}; LR-EIMS *m/z*: 250 (M^+, 88), 219 (30), 218 (33), 194 (100), 164 (38), 163 (35); HR-EIMS calcd for $C_{13}H_{14}O_5$: 250.0841. Found: 250.0844. X-ray Crystal Data: Crystal Color, Habit; colorless, prism, Crystal Dimensions; 0.350 x 0.300 x 0.200 mm, Crystal System; monoclinic, Lattice Type; C-centered, Lattice Parameters; a = 23.9199(5) Å, b = 9.9725(2) Å, c = 10.7508(2) Å, β = 109.350(8) °, V = 2419.63(15) Å^3, Space Group; C2/c (#15), Z value; 8, D_{calc}; 1.374 g/cm^3, F_{000}; 1056.00, μ(CuKα); 8.947 cm^{-1}. Intensity Measurement: Diffractometer; R-AXIS RAPID, Radiation; CuKα (λ = 1.54187 Å), graphite monochromated, Voltage, Current; 40 kV, 100 mA, Temperature; 23.0 ºC, Detector Aperture; 460.0 x 256.0 mm, Data Images; 45 exposures, ω oscillation Range (χ=54.0, ϕ=0.0); 80.0 - 260.0°, Exposure Rate; 70.0 sec./°, ω oscillation Range (χ=54.0, ϕ=90.0); 80.0 - 260.0°, Exposure Rate; 70.0 sec./°, ω oscillation Range (χ=54.0, ϕ=180.0); 80.0 - 260.0°, Exposure Rate; 70.0 sec./°, ω oscillation Range (χ=54.0, ϕ=270.0); 80.0 - 260.0°, Exposure Rate; 70.0 sec./°, ω oscillation Range (χ=0.0, ϕ=0.0); 80.0 - 260.0°, Exposure Rate; 70.0 sec./°, Detector Position; 127.40 mm, Pixel Size; 0.100 mm, $2\theta_{max}$; 136.1°, No. of Reflections Measured; Total: 13061, Unique: 2189 (R_{int}= 0.0385), Corrections; Lorentz-polarization Absorption (trans. factors: 0.689-0.836), Secondary Extinction (coefficient: 3.16000e-003). Structure Solution and Refinement: Structure Solution; Direct Methods (SHELXT Version 2018/2), Refinement; Full-matrix least-squares on F^2, Function Minimized; Σ w (Fo^2 - Fc^2)^2, Least Squares Weights; w = 1/ [$\sigma^2(Fo^2)$ + (0.0549 · P)^2 + 0.9970 · P] where P = (Max(Fo^2,0) + 2Fc^2)/3, $2\theta_{max}$ cutoff; 136.1°, Anomalous Dispersion; All non-hydrogen atoms, No. Observations (All reflections); 2189, No. Variables; 220, Reflection/Parameter Ratio; 9.95, Residuals: R1 (I>2.00σ(I)); 0.0376, Residuals: R (All reflections); 0.0416, Residuals: wR2 (All

reflections); 0.1080, Goodness of Fit Indicator; 1.049, Max Shift/Error in Final Cycle; 0.017, Maximum peak in Final Diff. Map; 0.16 $e^-/Å^3$, Minimum peak in Final Diff. Map; -0.15 $e^-/Å^3$.

Deposition number CCDC-1981839 for **2cA**. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Selected Bond lengths (Å)					
O1-C1	1.403(2)	O1-C9	1.3463(16)	O2-C1	1.1972(17)
O3-C10	1.1901(18)	O4-C10	1.326(2)	O4-C11	1.439(3)
O5-C5	1.2154(17)	C1-C2	1.456(2)	C2-C3	1.3564(17)
C2-C10	1.479(2)	C3-C4	1.418(2)	C4-C5	1.4795(17)
C4-C9	1.362(2)	C5-C6	1.523(2)	C6-C7	1.536(2)
C6-C12	1.527(2)	C6-C13	1.538(2)	C7-C8	1.520(2)
C8-C9	1.483(3)				
Selected Bond Angles (°)					
C1-O1-C9	123.66(12)	C10-O4-C11	117.48(13)	O1-C1-O2	115.81(14)
O1-C1-C2	115.27(11)	O2-C1-C2	128.92(16)	C1-C2-C3	119.70(15)
C1-C2-C10	118.39(12)	C3-C2-C10	121.83(14)	C2-C3-C4	121.88(14)
C3-C4-C5	121.33(13)	C3-C4-C9	118.20(12)	C5-C4-C9	120.47(14)
O5-C5-C4	120.01(15)	O5-C5-C6	123.17(12)	C4-C5-C6	116.81(12)
C5-C6-C7	108.15(13)	C5-C6-C12	110.47(13)	C5-C6-C13	107.01(15)
C7-C6-C12	110.36(15)	C7-C6-C13	111.10(13)	C12-C6-C13	109.68(14)
C6-C7-C8	113.96(15)	C7-C8-C9	111.13(14)	O1-C9-C4	121.14(14)
O1-C9-C8	114.10(13)	C4-C9-C8	124.76(12)	O3-C10-O4	122.61(18)
O3-C10-C2	126.50(16)	O4-C10-C2	110.88(12)		

Methyl 5,6,7,8-Tetrahydro-8,8-dimethyl-2,5-dioxo-2*H*-1-benzopyran-3-carboxylate (2cB)

Polar compound. Colorless needles; mp 114.0-116.0 ºC (acetone-*n*-hexane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.45 (6H, s), 2.04 (2H, t, *J*=6.8 Hz), 2.65 (2H, t, *J*=6.8 Hz), 3.91 (3H, s), 8.64 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 25.7, 33.5, 34.9, 36.3, 52.8, 112.5, 114.9, 145.8, 156.0, 162.9, 183.5, 193.0; IR ($CDCl_3$): 3028, 1711, 1717, 1690, 1560, 1387, 1261 cm^{-1}; LR-EIMS *m/z*: 250 (M^+, 96), 218 (32), 207 (43), 194 (100); HR-EIMS calcd for $C_{13}H_{14}O_5$: 250.0841. Found: 250.0839. X-ray Crystal Data: Crystal Color, Habit; colorless, platelet, Crystal Dimensions; 0.500 x 0.100 x 0.020 mm, Crystal System; orthorhombic, Lattice Type; Primitive, Lattice Parameters; a = 19.2982(10) Å, b = 6.3353(3) Å, c = 19.7290(10) Å, V = 2412.0(2) $Å^3$, Space Group; Pbca (#61), Z value; 8, D_{calc}; 1.378 g/cm^3, F_{000}; 1056.00, μ(CuKα); 8.975 cm^{-1}. Intensity Measurements: Radiation; CuKα (λ = 1.54187 Å), graphite monochromated, Voltage, Current; 40 kV, 100 mA, Temperature; 23.0 ºC, Detector Aperture; 460.0 x 256.0 mm, Data Images; 45 exposures, ω oscillation Range (χ=54.0, ϕ=0.0); 80.0 - 260.0°, Exposure Rate; 240.0 sec./°, ω oscillation

Range (χ=54.0, ϕ=90.0); 80.0 - 260.0°, Exposure Rate; 240.0 sec./°, ω oscillation Range (χ=54.0, ϕ=180.0); 80.0 - 260.0°, Exposure Rate; 240.0 sec./°, ω oscillation Range (χ=54.0, ϕ=270.0); 80.0 - 260.0°, Exposure Rate; 240.0 sec./°, ω oscillation Range (χ=0.0, ϕ=0.0); 80.0 - 260.0°, Exposure Rate; 240.0 sec./°, Detector Position; 127.40 mm, Pixel Size; 0.100 mm, $2\theta_{max}$; 136.2°, No. of Reflections Measured Total: 23642, Unique; 2203 (R_{int} = 0.0356), Corrections; Lorentz-polarization Absorption (trans. factors: 0.815 - 0.982), Secondary Extinction, (coefficient: 7.80000e-004). Structure Solution and Refinement: Structure Solution; Direct Methods (SHELXT Version 2018/2), Refinement; Full-matrix least-squares on F^2, Function Minimized; Σ w $(Fo^2 - Fc^2)^2$, Least Squares Weights; $w = 1/ [\sigma^2 (Fo^2) + (0.0504 \cdot P)^2 + 0.4117 \cdot P]$ where $P = (Max(Fo^2,0) + 2Fc^2)/3$, $2\theta_{max}$ cutoff; 136.2°, Anomalous Dispersion; All non-hydrogen atoms, No. Observations (All reflections); 2203, No. Variables; 220, Reflection/Parameter Ratio; 10.01, Residuals: R1 (I>2.00σ(I)); 0.0350, Residuals: R (All reflections); 0.0456, Residuals: wR2 (All reflections); 0.0989, Goodness of Fit Indicator; 1.036, Max Shift/Error in Final Cycle; 0.005, Maximum peak in Final Diff. Map; 0.12 $e^-/Å^3$, Minimum peak in Final Diff. Map; -0.12 $e^-/Å^3$.

Deposition number CCDC-1981840 for **2cB**. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Selected Bond lengths (Å)					
O1-C1	1.4131(16)	O1-C9	1.3492(16)	O2-C1	1.1942(18)
O3-C10	1.325(2)	O3-C11	1.444(3)	O4-C10	1.207(2)
O5-C5	1.221(2)	C1-C2	1.451(2)	C2-C3	1.350(2)
C2-C10	1.480(2)	C3-C4	1.416(2)	C4-C5	1.474(2)
C4-C9	1.3544(19)	C5-C6	1.495(2)	C6-C7	1.519(3)
C7-C8	1.538(2)	C8-C9	1.503(2)	C8-C12	1.532(3)
C8-C13	1.534(3)				

Selected Bond angles (°)					
C1-O1-C9	124.04(10)	C10-O3-C11	115.60(15)	O1-C1-O2	115.01(12)
O1-C1-C2	114.61(12)	O2-C1-C2	130.35(13)	C1-C2-C3	119.38(13)
C1-C2-C10	122.49(13)	C3-C2-C10	118.04(13)	C2-C3-C4	122.84(14)
C3-C4-C5	120.95(13)	C3-C4-C9	117.97(13)	C5-C4-C9	120.87(13)
O5-C5-C4	120.94(14)	O5-C5-C6	122.54(14)	C4-C5-C6	116.49(13)
C5-C6-C7	113.19(14)	C6-C7-C8	113.50(14)	C7-C8-C9	107.99(12)
C7-C8-C12	108.68(14)	C7-C8-C13	111.49(14)	C9-C8-C12	110.15(13)
C9-C8-C13	108.55(14)	C12-C8-C13	109.96(15)	O1-C9-C4	120.70(12)
O1-C9-C8	113.08(11)	C4-C9-C8	126.19(13)	O3-C10-O4	122.89(15)
O3-C10-C2	114.57(13)	O4-C10-C2	122.52(15)		

Methyl 5,6,7,8-Tetrahydro-7-methyl-2,5-dioxo-2*H*-1-benzopyran-3-carboxylate (2d)

Colorless plates; mp 122.0-123.0 ºC (acetone-*n*-hexane); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.21 (3H, d, *J*=6.6 Hz), 2.30 (1H, dd, *J*=11.6, 16.4 Hz), 2.40-2.51 (1H, m), 2.66 (1H, dd, *J*=10.1, 18.7 Hz), 2.70 (1H, ddd, *J*=1.3, 3.9, 16.4 Hz), 2.95 (1H, ddd, *J*=1.3, 4.7, 18.7 Hz), 3.91 (3H, s), 8.64 (1H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 20.8, 27.9, 36.2, 44.6, 52,8, 113.8, 114.9, 145.3, 156.0, 162.8, 177.9, 192.9; IR ($CDCl_3$): 1780, 1719, 1690, 1564, 1394, 1265, 1244 cm^{-1}; LR-EIMS *m/z*: 236 (M^+, 100), 205 (61), 194 (31), 166 (66), 163 (35); HR-EIMS calcd for $C_{12}H_{12}O_5$: 236.0685. Found: 236.0687.

Methyl 5,6,7,8-Tetrahydro-7-isopropyl-2,5-dioxo-2*H*-1-benzopyran-3-carboxylate (2e)

Yellowish oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 (6H, d, *J*=6.8 Hz), 1.72 (1H, octet, *J*=6.8 Hz), 2.03-2.16 (1H, m), 2.30 (1H, dd, *J*=13.0, 16.4 Hz), 2.71 (1H, dd, *J*=12.1, 18.8 Hz), 2.72 (1H, ddd, *J*=1.6, 3.6, 16.4 Hz), 2.90 (1H, ddd, *J*=1.5, 4.7, 18.8 Hz), 3.91 (3H, s), 8.65 (1H, s); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 19.3, 19.4, 31.7, 32.2, 39.0, 40.6, 52.8, 113.8, 115.0, 145.3, 156.0, 162.9, 178.4, 193.2; IR ($CDCl_3$): 1776, 1719, 1688, 1566, 1393 cm^{-1}; LR-EIMS *m/z*: 264 (M^+, 100), 233 (39), 222 (49), 168 (61), 153 (81), 136 (34); HR-EIMS calcd for $C_{14}H_{16}O_5$: 264.0998. Found: 264.0995.

Methyl 7,8-Dihydro-7,7-dimethyl-2,5-dioxo-2*H*,5*H*-pyrano[4,3-*b*]pyran-3-carboxylate (2g)

Colorless solid; mp 140.0-143.0 ºC (*i*-Pr_2O); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.58 (6H, s), 3,02 (2H, s), 3.92 (3H, s), 8.65 (1H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 28.0, 38.5, 53.0, 79.9, 105.5, 115.5, 146.6, 155.4, 161.2, 162.4, 172.6; IR ($CDCl_3$): 1788, 1728, 1572, 1261 cm^{-1}; LR-EIMS *m/z*: 252 (M^+, 86), 237 (47), 194 (53), 165 (93), 164 (40), 163 (100), 59 (50); HR-EIMS calcd for $C_{12}H_{12}O_6$: 252.0634. Found: 252.0639.

Computational Methods

Using Spartan'18 software (Wavefunction, Inc. Irvine, CA), the candidate compounds of at most five hundreds from lowest-energy or <40 kJ/mol differences from lowest-energy were generated using the molecular mechanics method with the MMFF level of theory, which automatically identifies the conformational degrees of freedom (single bonds and flexible rings). The equilibrium geometries of the candidate compounds were then sequentially recalculated using the semi-empirical method with the PM3 level of theory, in addition to the Hartree-Fock method with the 6-31G* level of theory. Finally, the lowest-energy structures of **2cA** and **2cB** from some candidate compounds were obtained using the DFT method with the ωB97X-D/6-31G* level of theory.

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