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Note

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Metal-Free α-Hydroxylation of α-Unsubstituted β-Oxoesters and β-Oxoamides

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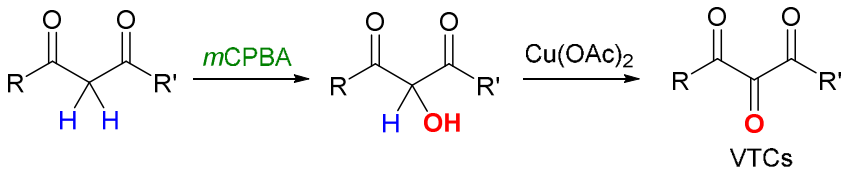
Abstract:

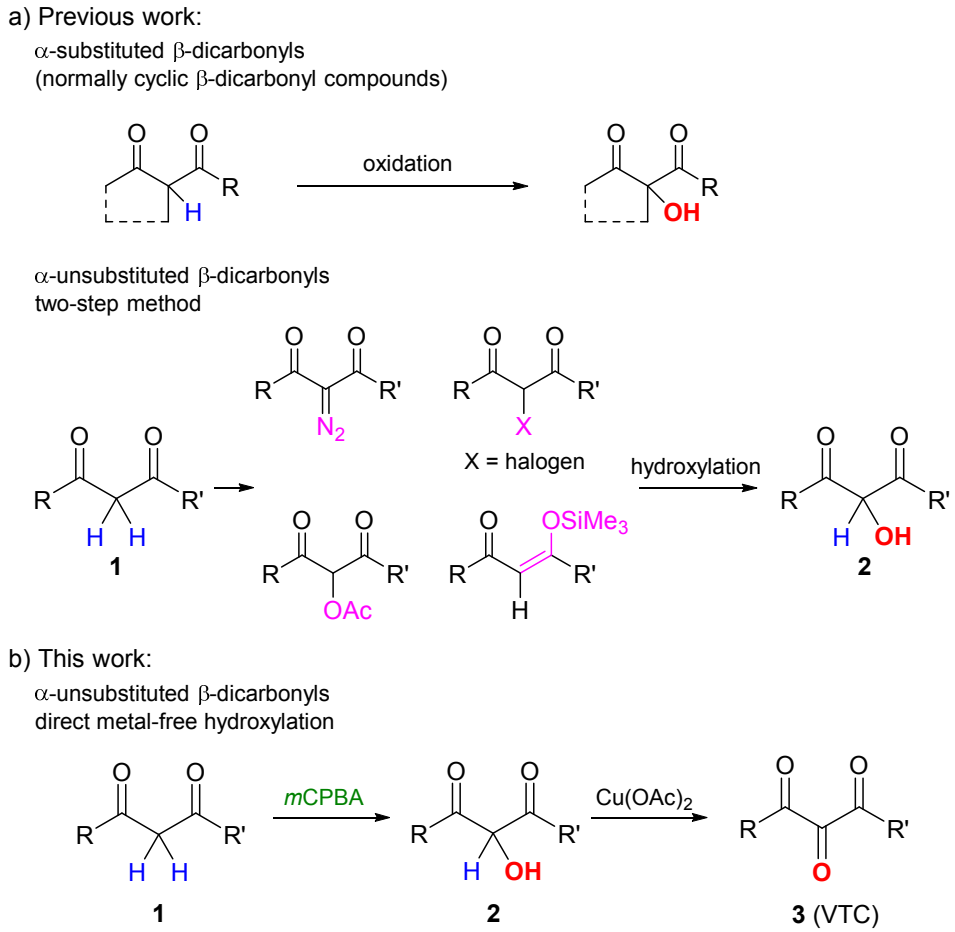


α-unsubstituted β-dicarbonyls
direct metal-free oxidation

A direct metal-free α-hydroxylation of α-unsubstituted β-oxoesters and β-oxoamides was developed using *m*-chloroperbenzoic acid as the oxidant. This transformation enabled straightforward metal-free access to important α-hydroxy-β-dicarbonyl moieties under mild reaction conditions. Furthermore, the hydroxylated products were readily converted into vicinal tricarbonyl compounds, which are useful synthetic precursors of numerous biological targets.

The α-oxidation of β-dicarbonyl compounds, leading to both α-hydroxy and α-oxo derivatives, is an important chemical transformation in synthetic chemistry and pharmaceutical science.[1] α-Hydroxy-β-dicarbonyl moieties are often found in antibiotics such as Kjellmanianone[2] and Hamigeran A,[3] as well as in key intermediates such as those for the synthesis of olmesartan,[4] dihydroimidazoquinoline, a known thrombin-activatable fibrinolysis inhibitor (TAFIa),[5] and vitamin B6.[6] Recent oxidative synthetic efforts have employed hydroperoxides,[7] dimethyldioxirane,[8] molecular oxygen,[9] and oxaziridines[10] as oxidants. However, there is no report for the direct α-hydroxylation of α-unsubstituted β-dicarbonyl compounds **1** except for only a few examples using limited substrates and metal salts as oxidant.[11] This is probably because the enolizable α-hydroxy-β-dicarbonyl compounds **2** cause further oxidation under such conditions. It appears that an additional α-substituent is required to avoid undesirable side reactions such as Baeyer-Villiger type oxidation and C-C bond cleavage.[12] Indirect methods to generate enolizable α-hydroxy-β-dicarbonyl compounds **2** require modifications of the α-carbon, such as halogenation,[13] acetylation,[14] and diazotization[5,15] or conversion to silyl enol ethers[16] before the α-hydroxylation step (Scheme 1, (a)). These two-step methods suffer from drawbacks such as somewhat complicated experimental manipulations and low efficiency. α-Hydroxylated β-dicarbonyl compounds are unstable under oxidative reaction conditions and hence decompose or undergo further oxidation to give α,β-dioxocarbonyl compounds compounds, the so-called vicinal tricarbonyls **3** (VTCs).[17] Although the direct synthesis of VTCs from **1** has been recently reported,[18,19] the VTCs were

obtained via a single-electron transfer process, which does not involve the formation of **2** as an intermediate. These circumstances prompted us to study the direct metal-free hydroxylation of **1**.

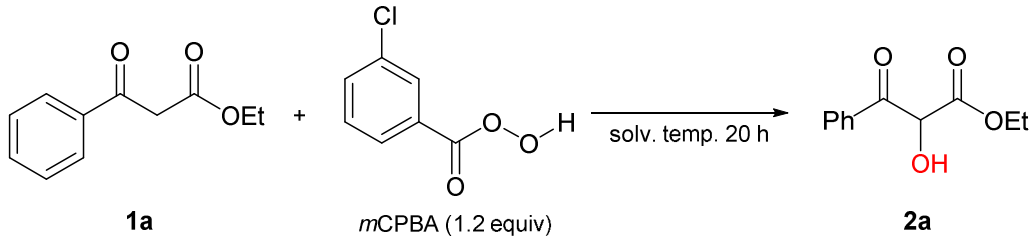


Scheme 1. α-Hydroxylation of β-dicarbonyl compounds **1** and further oxidation to give VTC **3**.

Taking into account the instability of α-hydroxy-β-dicarbonyl compounds, we employed ethyl benzoylacetate (**1a**) as the substrate for easy handling of the product (Table 1). We also employed electrophilic *m*-chloroperbenzoic acid (*m*CPBA) as the oxidant. When the reactions were conducted in alcohols at ambient temperature, complicated reaction mixtures were obtained and the desired α-hydroxylated product **2a** was formed in very low yields (Table 1, entries 1 and 2). Aprotic solvents were found to be more effective, and **2a** was obtained in moderate yields (entries 3–5).

Among the examined aprotic solvents, toluene was chosen to further optimize the reaction conditions because of its low price and low toxicity. Raising the reaction temperature to 60 °C led to almost quantitative conversion (entry 6). Whereas no reaction occurred under the same reaction conditions using other oxidants, such as *t*-BuOOH, $Na_2BO_3 \cdot 4H_2O$, H_2O_2, and H_2O_2 in AcOH. The oxidation of **1a** by *m*CPBA could be used in large scale reaction to afford **2a** in a similar yield (entry 7).

Table 1. Optimization of reaction conditions.[a]



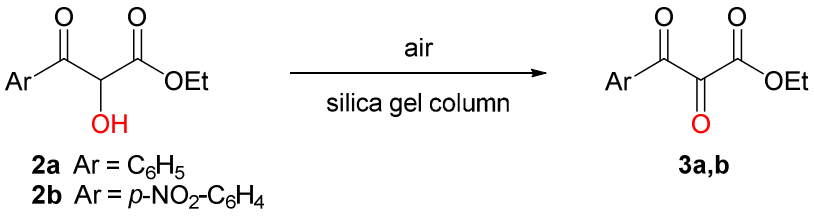
1a *m*CPBA (1.2 equiv) **2a**

Entry	Solvent	Temp. (°C)	**2a** (%)[b]
1	MeOH	rt	8
2	EtOH	rt	3
3[c]	$CHCl_3$	rt	53
4[c]	MeCN	rt	50
5[c]	PhMe	rt	53
6[c]	PhMe	60	96 (83)
7[d]	PhMe	60	90 (81)

[a]Reaction conditions: **1a** (0.2 mmol), mCPBA (65 wt%, 0.24 mmol), solvent (2 mL). [b]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard; the value in parenthesis is the isolated yield. [c]Each reactions were performed at least three times and data presented are of one representative experiment (the range of yields are 53–47% in $CHCl_3$, 50–39% in MeCN, and 53–51% in PhMe). [d]The reaction was conducted using 1.0 g (5.0 mmol) of **1a**.

Despite the presence of the benzoyl group, the α-hydroxylated product **2a** was found to be unstable toward air oxidation, and small amounts of **3a** were detected after purification by silica gel

column chromatography that had run over several hours. Hence, we concluded that the purification of **2a** should be completed within one hour (Scheme 2).



2a Ar = C_6H_5
2b Ar = *p*-NO_2-C_6H_4

3a,b

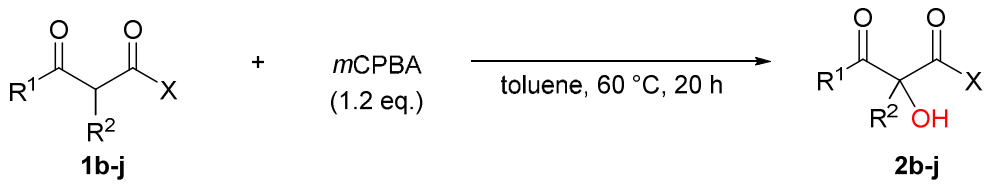
Scheme 2. Further oxidation of α-hydroxy-β-oxoester **2**.

With the optimized reaction conditions, the substrate scope was then investigated (Table 2). The electronic nature of the substituents on the phenyl ring did not reveal significant influence on the reactivity, and benzoylacetates **1b** and **1c** were efficiently α-hydroxylated (entries 1 and 2). On the other hand, the substituent obviously influence on the stability of the hydroxylated product and isolated yields somewhat varied. α-Hydroxylated *p*-nitrobenzoylacetate **2b** was found to be less stable than **2a**, and 15% of **3b** was obtained despite rapid purification by silica gel column chromatography. Furthermore, α-hydroxylated aliphatic β-oxoester **2d** revealed lower stability than **2a-c** and easily decompose to volatile and hardly isolable compound. The introduction of a longer alkyl chain or a bulkier group on the substrate led to less volatile compounds, and hydroxylated products **2e** and **2f** were isolated in 67% and 78% yields, respectively (entries 4 and 5). As anticipated, the sterically restricted cyclic β-oxoester **1g**, α-substituted oxoester, was efficiently transformed to **2g**, which is rather stable because it does not form enol form, and the isolation

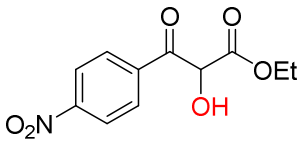
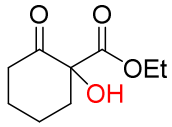
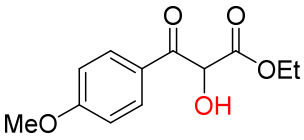
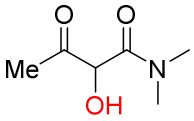
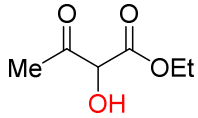
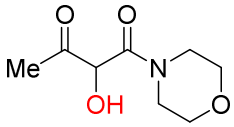
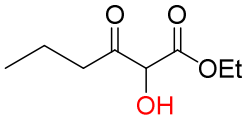
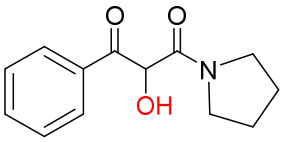
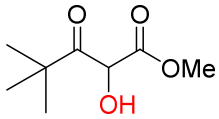
proceeded smoothly (entry 6). However, hydroxylated products were not obtained in the case of 2,4-pentanedione, 1,3-diphenyl-1,3-propanedione, and diethyl malonate.[20]

Notably, oxidation of β-oxoamides **1h–j** afforded the corresponding α-hydroxylated products **2h–j** in only moderate yields (entries 7 and 8). Lowering the reaction temperature (0 ℃) was found to slightly increase the yield of the products. In the case of benzoyl acetamide **1j**, the α-hydroxylated product **2j** was isolated in 64% yield without significant loss (entry 11).

Table 2. Reaction of β-dicarbonyls to give α-hydroxy-β-dicarbonyls.[a]



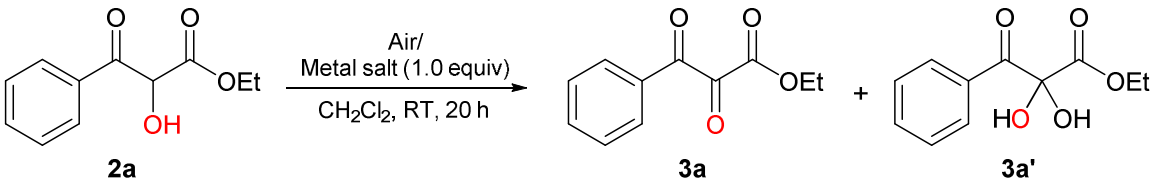
1b-j **2b-j**

Entry	Products **2**	Yield (%)[b]	Entry	Products **2**	Yield (%)[b]
1	 **2b**	90 (72)[c]	6	 **2g**	96 (95)
2	 **2c**	97 (90)	7	 **2h**	20 40 (32)[d]
3	 **2d**	0	8	 **2i**	33 51 (38)[d]
4	 **2e**	88 (67)	9	 **2j**	69 (64)[d]
5	 **2f**	95 (78)			

[a]All reactions except for **2d** were performed at least three times and data presented are of one representative experiment [b]Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard; values in parenthesis is the yield of the isolated product. [c]**3b** was isolated in 15% yield. [d]At 0 °C.

Next, we investigated the oxidation of α-hydroxy-β-dicarbonyl compounds **2** to yield VTCs **3**, which are widely used for syntheses of polyfunctionalyzed compounds[17] (Table 3). As shown in Scheme 2, silica gel aided the air oxidation to afford a mixture of VTC **3a** and its hydrate form **3a'**, though in only moderate yield (entry 1). Hence, acceleration by several metal salts was evaluated (entries 2–6), and $Cu(OAc)_2$ was identified as the most effective oxidant, to afford **3a** in 92% yield (entry 6). While the oxidation similarly proceeded 50 mol% and 20 mol% of $Cu(OAc)_2$ under air (entries 7 and 8), the efficiency of the reaction considerably decreased under argon (entry 9), which indicated the O_2 is relevant oxidant in this oxidation reaction.[21] To examine the reaction scope, compounds **2** were submitted to the latter oxidation conditions (Table 4). This method was applicable not only to hydroxylated-aromatic oxoesters **2b** and **2c** but also to aliphatic ones **2e** and **2f**, and the corresponding VTCs were furnished in high yields. α-Hydroxy-β-oxoamide **2j** was also oxidized, though the yield of **3j** was only moderate.

Table 3. Oxidation of α-hydroxy-β-oxoester **2a**.

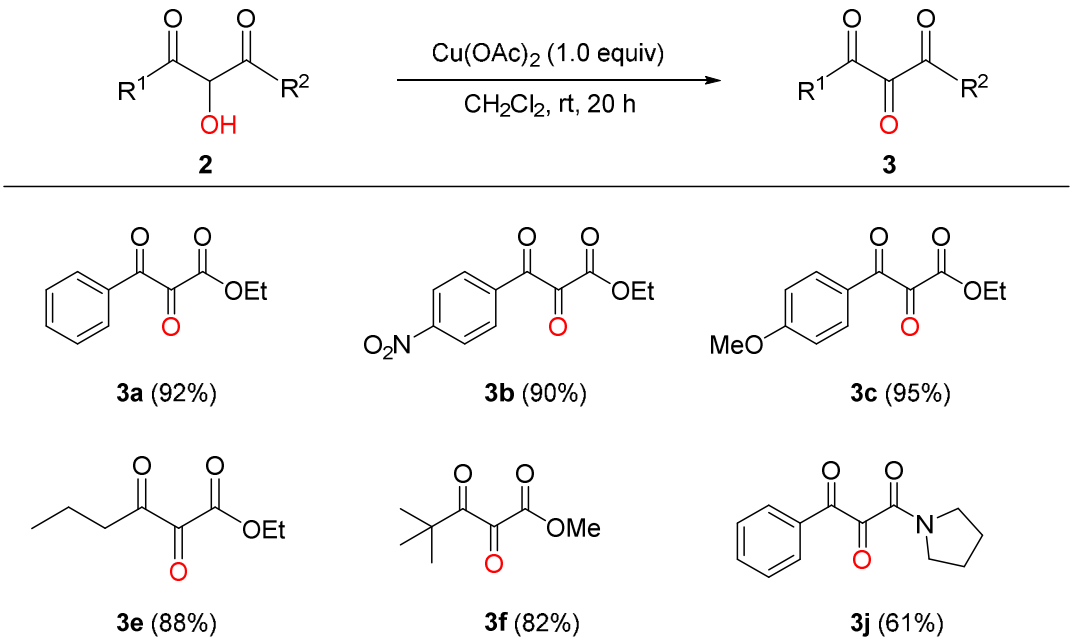


2a **3a** **3a'**

Entry	Metal salt	Yield (%)[a]
1	SiO_2[b]	56
2	Ag_2O	trace
3	AgOAc	trace
4	MnO_2	11
5	$FeCl_3$	45
6	$Cu(OAc)_2$	92
7[c]	$Cu(OAc)_2$	90
8[d]	$Cu(OAc)_2$	79
9[c,e]	$Cu(OAc)_2$	42

[a]Isolated yield. Total yield of VTCs **3a** and its hydrate form **3a'**. [b]α-Hydroxy β-oxoester **2a** was stirred with 0.5 g of silica gel at rt for 20 h. [c]50 mol% of $Cu(OAc)_2$ was used. [d]20 mol% of $Cu(OAc)_2$ was used. [d]Under argon.

Table 4. Scope of oxidation of α-hydroxy-β-dicarbonyl compounds **2**.



The direct metal-free α-oxidation of α-unsubstituted β-dicarbonyl compounds **1** was successfully achieved under mild conditions using *m*CPBA as the oxidant. This protocol constitutes a new and straightforward route to α-hydroxylated β-oxoesters and β-oxoamides. Further advantages of this method include ready availability of the substrates and high atom economy. Moreover, since the α-hydroxy-β-dicarbonyl products **2** can be efficiently converted into VTCs using $Cu(OAc)_2$ under mild conditions, this protocol represents a useful tool for the synthesis of polyfunctionalized compounds, including α-hydroxy-β-dicarbonyls and VTCs, which are useful structural units in organic and medicinal chemistry.

Experimental Section

General Procedure of α-hydroxylation

To a solution of β-dicarbonyl compounds **1** (0.20 mmol) in toluene (2 mL) *m*CPBA (65 wt%, 64.0 mg, 0.24 mmol) was added and the resultant solution was stirred for 20 h at 60 °C. The reaction mixture was washed with sat. $NaHCO_3$ aq. to remove *m*-chlorobenzoic acid, and then extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layer were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The yield of product **2** was calculated by ^1H NMR integration of the crude product using 1,1,2,2-tetrachloroethane as an internal standard. Further purification was achieved by flash column chromatography on silica gel (hexane/EtOAc = 4/1).

In the case of large-scale reaction, lowering the product yield was observed due to the phase separation by the measurable amount of water. In such case, *m*CPBA was dissolved in toluene and dried over $MgSO_4$ after separation with aqueous layer.

Transformation of 2 to VTC

To a solution of α-hydroxy-β-dicarbonyl compounds **2** (0.20 mmol) in CH_2Cl_2 (2 mL) was added $Cu(OAc)_2$ (0.20 mmol) and the resultant mixture was stirred for 20 h at rt. The reaction mixture was passed through a silica gel short column using Et_2O as an eluent to give the corresponding α,β-oxoester and α,β-oxoamide products **3**.

Spectra Data of the Products

Ethyl 2-hydroxy-3-oxo-3-phenylpropanoate (2a):[22] (34.6 mg, 83%); yellow oil. R_f = 0.37 (silica gel, hexane/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2, Hz, 3H), 4.29 (q, *J* = 7.2, Hz, 2H), 4.3 (br s, 1H), 5.60 (s, 1H), 7.48–7.53 (m, 2H), 7.63 (t, *J* = 8.0, Hz, 1H), 8.0 (d, *J* = 8.2, Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 58.1 (CH), 63.2 (CH_2), 128.9 (CH), 129.3 (CH), 133.5 (C), 134.3 (CH), 165.3 (C), 188.2 (C).

Ethyl 2-hydroxy-3-oxo-3-(4-nitrophenyl)propanoate (2b):[23] (36.5 mg, 72%); yellow oil, R_f = 0.83 (silica gel, hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 5.18 (br s, 1H), 5.57 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 2H), 8.35 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 62.9 (CH_2), 75.0 (CH), 123.9 (CH), 130.6 (CH), 137.9 (C), 151.1 (C), 168.2 (C), 192.9 (C).

Ethyl 2-hydroxy-3-oxo-3-(4-methoxyphenyl)propanoate (2c): (42.9 mg, 90%); yellow oil, R_f = 0.31 (silica gel, hexane/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 6.8 Hz, 3H), 3.89 (s, 3H) 4.18 (q, *J* = 6.8 Hz, 2H), 4.35 (br s, 1H), 5.54 (br s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 8.08 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 55.6 (CH_3), 62.2 (CH_2), 74.3 (CH), 114.1 (CH), 126.0 (C), 132.0 (CH), 164.8 (C), 168.9 (C), 192.0 (C); ATR-FTIR (cm^{-1}): 3411 (br), 2932 (w), 2648 (w), 2560 (w), 1733 (s), 1682 (s), 1429 (w), 1354 (w), 1225 (m), 1080 (m), 993 (w), 956 (w), 883 (w). HRMS (CI+) m/z calcd. for $C_{12}H_{15}O_5$: 239.0919 $(M + H)^+$, found 239.0921.

Ethyl 2-hydroxy-3-oxohexanoate (2e): (23.3 mg, 67%); yellow oil. R_f = 0.31 (silica gel, hexane/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.6 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.67 (tq, *J* = 7.2, 7.6 Hz, 2H) 2.56–2.72 (m, 2H), 3.71 (br s, 1H), 4.29 (q, *J* = 7.0 Hz, 3H), 4.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5 (CH_3), 14.0 (CH_3), 16.9 (CH_2), 40.5 (CH_2), 62.4 (CH_2), 77.8 (CH), 168.4 (C), 204.4 (C); ATR-FTIR (cm^{-1}): 3248 (br), 2965 (w), 1748 (s), 1732 (s), 1260 (m), 1152 (w), 1016 (m). HRMS (CI+) m/z calcd. for $C_8H_{15}O_4$: 175.0970 $(M + H)^+$, found 175.0969.

Methyl 2-hydroxy-4,4-dimethyl-3-oxopentanoate (2f); (27.2 mg, 78%); yellow oil. R_f = 0.33 (silica gel, hexane/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H), 3.79 (s, 3H), 3.95 (d, *J* = 6.8 Hz, 1H), 5.05 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3 (CH_3), 43.8 (C), 52.8 (CH_3), 72.8 (CH), 169.4 (C), 209.6 (C); ATR-FTIR (cm^{-1}): 3329 (br), 2961 (w), 1748 (s), 1714 (s) 1256 (m), 1155 (w), 1016 (m). HRMS (CI+) m/z calcd. for $C_8H_{15}O_4$: 175.0970 $(M + H)^+$, found 175.0968.

Ethyl 1-hydroxy-2-oxocyclohexane-1-carboxylate (2g):[11a] (35.4 mg, 95%); brown oil. R_f = 0.39 (silica gel, hexane/EtOAc, 4:1); ^{1}H NMR ($CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3H), 1.63–1.77 (m, 2H), 1.80–1.92 (m, 2H), 2.01–2.10 (m, 1H), 2.53–2.72 (m 3H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.31 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 22.0 (CH_2), 27.1 (CH_2), 37.7 (CH_2), 38.9 (CH_2), 62.1(CH_2), 80.7 (C), 170.1 (C), 207.3 (C).

2-Hydroxy-N,N-dimethyl-3-oxobutanamide (2h): (9.3 mg, 32%; reaction was conducted at 0 °C); yellow oil. R_f = 0.23 (silica gel, hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.03 (s, 3H), 3.10 (s, 3H), 4.31 (br s, 1H), 4.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3 (CH_3), 36.5 (CH_3), 37.1 (CH_3), 76.2 (CH), 167.8 (C), 206.4 (C); ATR-FTIR (cm^{-1}): 3115 (br), 2960 (w), 2354 (w), 1717 (s), 1646 (s), 1472 (w), 1456 (w), 1371 (w), 1339 (w),1250 (m), 1153 (w), 1107 (w), 1016 (m), 943 (w), 914 (w). HRMS (CI+) m/z calcd. for $C_6H_{12}NO_3$: 146.0817 $(M + H)^+$, found 146.0818.

2-Hydroxy-1-morpholinobutane-1,3-dione (2i): (14.2 mg, 38%; reaction was conducted at 0 °C); yellow oil, R_f = 0.41 (silica gel, hexane/EtOAc, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.49–3.67 (m, 4H), 3.70–3.78 (m, 4H), 4.58 (d, *J* = 6.8 Hz, 1 H), 4.79 (d, *J* = 6.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (CH_3), 43.6 (CH_2), 46.1 (CH_2), 66.4 (CH_2), 66.5 (CH_2), 76.0 (CH), 166.5 (C), 206.8 (C); ATR-FTIR (cm^{-1}): 3204 (br), 2966 (w), 1731 (s), 1635 (s), 1506 (w), 1470 (w), 1443 (w), 1410 (w), 1371 (w), 1329 (w), 1246 8m), 1152 (w), 1105 (w), 1078 (w), 1009 (m), 941 (w), 912 (w). HRMS (CI+) m/z calcd. for $C_8H_{14}NO_4$: 188.0923 $(M + H)^+$, found 188.0924.

2-Hydroxy-1-phenyl-3-(pyrrolidin-1-yl)propane-1,3-dione (2j): (29.9 mg, 64%; reaction was conducted at 0 °C); yelow oil, R_f = 0.12 (silica gel, hexane/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84–1.97 (m, 4H), 3.32–3.40 (m, 1H), 3.45–3.49 (m, 1H), 3.54–3.58 (m, 2H), 4.63 (br s, 1H), 5.32 (s, 1H), 7.45–7.51 (m, 2 H) , 7.56 (t, *J* = 7.6 Hz, 1 H) , 8.07 (d, *J* = 7.2 Hz, 2 H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 23.8 (CH_2), 26.0 (CH_2), 46.1 (CH_2), 46.8 (CH_2), 75.5 (CH), 128.7 (CH), 129.3 (CH), 133.9 (CH), 134.3 (C), 133.8 (C), 195.1 (C); ATR-FTIR (cm^{-1}): 3184 (br), 2963 (w), 1683 (s), 1635 (s), 1470 (w), 1439 (w), 1371 (w), 1344 (w), 1244 (m), 1153 (w), 1098 (w), 1080 (w), 1013 (m), 941 (w), 912 (w). HRMS (CI+) m/z calcd. for $C_{13}H_{16}NO_3$: 234.1130 $(M + H)^+$, found 234.1127.

Ethyl 2,3-dioxo-3-phenylpropanoate (3a):[23,24] (40.0 mg, 92%); yellow oil, R_f = 0.59 (silica gel, hexane/EtOAc, 4:1); Mixture of ketone and corresponding hydrated form in ratio 1:1.6. Ketone: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 7.45–7.56 (m, 2H), 7.63–7.68 (m, 1H), 7.98–8.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 63.3 (CH_2), 129.1 (CH), 130.0 (CH), 131.3 (C), 135.5 (CH), 136.2 (C), 183.7 (C), 190.2 (C); Hydrate: ^{1}H NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.2 Hz, 3 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 5.23 (br s, 2H), 7.47–7.56 (m, 2H), 7.64–7.72 (m, 1H), 8.10–8.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3), 62.3 (CH_2), 91.8 (C), 128.8 (CH), 130.4 (CH), 131.4 (C), 134.6 (CH), 168.5 (C), 193.9 (C).

Ethyl 3-(4-nitrophenyl)-2,3-dioxopropanoate (3b):[25] (51.2 mg, 95%); yellow oil. R_f = 0.61 (silica gel, hexane/EtOAc, 1:1); Isolated as a hydrated form. Hydrate ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 5.30 (br s, 2H), 8.27 (d, *J* = 8.8 Hz, 2H), 8.32 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7 (CH_3), 63.5 (CH_2), 92.1 (C), 123.8 (CH), 131.2 (CH), 136.2 (C), 151.0 (C), 169.1 (C), 190.7 (C).

Ethyl 3-(4-methoxyphenyl)-2,3-dioxopropanoate (3c):[25] (44.7 mg, 90%); yellow oil, R_f = 0.14 (silica gel, hexane/EtOAc, 4:1); Mixture of ketone and corresponding hydrated form in ratio 1:2. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, *J* = 7.2 Hz, 3 H), 3.91 (s, 3 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3), 56.0 (CH_3), 63.4 (CH_2), 114.8 (CH), 124.9 (C), 132.9 (CH), 161.2 (C), 165.8 (C), 184.2 (C), 188.5 (C); Hydrate: ^{1}H NMR (400 MHz, CDCl3) δ 1.11 (t, *J* = 7.2 Hz, 3 H), 3.88 (s, 3 H), 4.22 (q, *J* = 7.2 Hz, 2 H), 5.35 (br s, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 M Hz, $CDCl_3$) δ 14.0 (CH_3), 55.8 (CH_3), 63.3 (CH_2), 91.8 (C), 114.3 (CH), 124.4 (C), 133.0 (CH), 165.0 (C), 170.5 (C), 190.1 (C).

Methyl 2,3-dioxohexanoate (3e):[26] (31 mg, 88%); yellow oil, R_f = 0.26 (silica gel, hexane/EtOAc, 4:1); Mixture of ketone and corresponding hydrated form in ratio 1:10. Hydrate: ^{1}H NMR (400 MHz, CDCl3) δ 1.25 (s, 9H), 3.84 (s, 3H), 5.08 (br s, 2H); ^{13}C NMR (100 M Hz, $CDCl_3$) δ 13.5 (CH_3), 14.0 (CH_3), 16.9 (CH_2), 40.5 (CH_2), 62.4 (CH_2), 77.8 (CH), 168.4 (C), 204.4 (C).

Methyl 4,4-dimethyl-2,3-dioxopentanoate (3f):[27] (29.1 mg, 82%); yellow oil, R_f = 0.41 (silica gel, hexane/EtOAc, 4:1); Mixture of ketone and corresponding hydrated form in ratio 2.6:1. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 9H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5 (CH_3), 42.7 (C), 53.3 (CH_3), 161.0 (C), 183.9 (C), 206.2 (C); Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25

(s, 9H), 3.84 (s, 3H), 5.08 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.2 (CH_3), 43.1 (C), 53.5 (CH_3), 92.0 (CH), 169.9 (C), 208.1 (C).

1-Phenyl-3-(pyrrolidin-1-yl)propane-1,2,3-trione (3j): (29.0 mg, 61%); yellow oil, R_f = 0.30 (silica gel, hexane/EtOAc, 4:1); Mixture of ketone and corresponding hydrated form in ratio 2.2:1. Ketone: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93–1.97 (m, 2H), 1.99–2.04 (m, 2H), 3.58–3.62 (m, 2H), 3.61–3.78 (m, 2H), 7.52 (dd, *J* = 7.2, 8.0 Hz, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8 (CH_2), 26.1 (CH_2), 46.1 (CH_2), 46.9 (CH_2), 128.9 (CH), 130.1 (CH), 132.2 (C), 135.1 (CH), 162.1 (C), 186.9 (C), 193.2 (C); Hydrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.74–1.78 (m, 4H), 3.16–3.19 (m, 2H), 3.52–3.54 (m, 2H), 7.44 (dd, *J* = 7.2, 8.0 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 M Hz, $CDCl_3$) δ 23.5 (CH_2), 26.0 (CH_2), 46.3 (CH_2), 47.7 (CH_2), 91.5 (C), 128.9 (CH), 130.1 (CH), 131.7 (C), 134.7 (CH), 166.8 (C), 193.9 (C); ATR-FTIR (cm^{-1}): 3141 (br), 2971 (w), 1682 (s), 1651 (s), 1645 (s), 1637 (s), 1456 (w), 1396 (w), 1215 (m), 1107 (m), 1061 (m), 982 (w). HRMS (CI+) m/z calcd. for $C_{13}H_{14}NO_3$: 232.0974 $(M + H)^+$, found 232.0975.

Associated Content

Supporting Information

^{1}H, ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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