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A facile base-promoted domino Michael/O-alkylation reaction for the construction of succinimide-substituted 3(2*H*)-furanones

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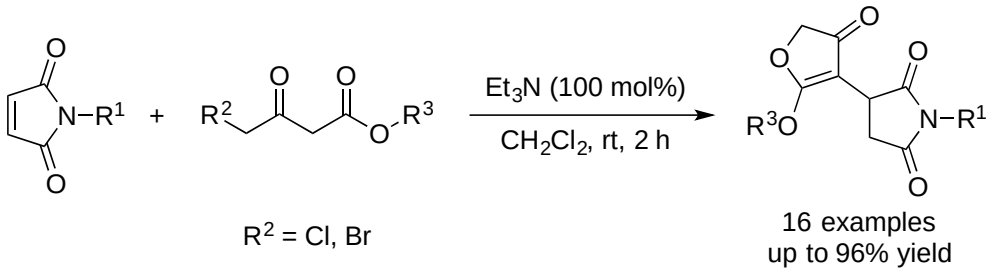
Abstract

A novel base-promoted domino Michael/O-alkylation reaction of maleimides with γ-halogenated-β-ketoesters is described. A variety of new succinimide-substituted 3(2*H*)-furanones were obtained in excellent yields (up to 96%) under simple and mild conditions. The structure of the new compound **3a** was determined by single-crystal X-ray analysis and a reaction pathway is proposed.



Keywords: Succinimide-substituted 3(2*H*)-furanones, Michael/O-alkylation, domino reaction, maleimides, γ-halogenated-β-ketoesters

Introduction

3(2*H*)-Furanones are core structural motifs that are widely present in many natural products and pharmaceutically important compounds. Substituted 3(2*H*)-furanones show a wide range of biological activities such as anti-inflammatory, antiallergic, antitumor and anti-ulcer activities (examples in Figure 1).[1-4] The significance of these molecules has led to a variety of approaches for the synthesis of substituted 3(2*H*)-furanones, including acid-catalyzed cyclization-dehydration,[5,6] transformations from furans,[7,8] alkynes[9-15] and allenes.[16] However, most of these routes require the use of specific substrates and reaction conditions are often harsh. Domino reactions are one of the most efficient strategies for the synthesis of complex molecular structures from simple materials in a single step.[17-20] Recently, γ-halogenated-β-ketoesters, which are commercially available, were used to construct substituted 3(2*H*)-furanones via domino reactions with activated alkenes[21-23] and imines.[24-26] This synthetic strategy is efficient and mild. However the activated alkenes were limited only to chain structures such as chain nitroalkenes[21,22] and chain α,β-unsaturated esters.[23] Thus it was important to discover whether other diverse activated alkenes, such as cyclic alkenes, would react with γ-halogenated-β-ketoesters to construct diverse substituted 3(2*H*)-furanones.

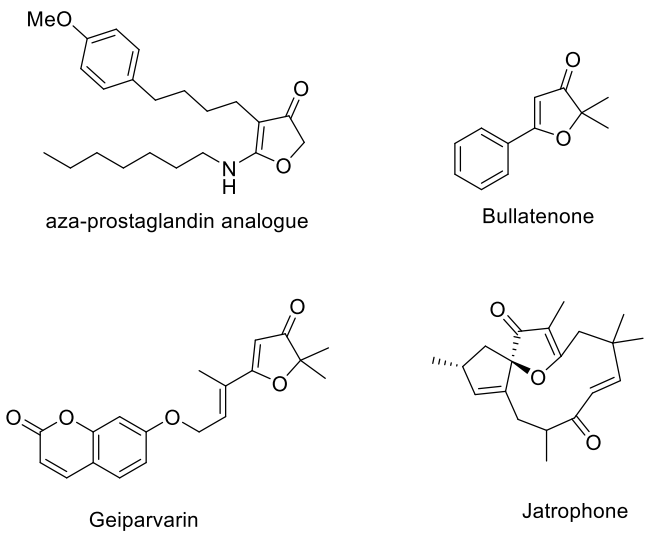
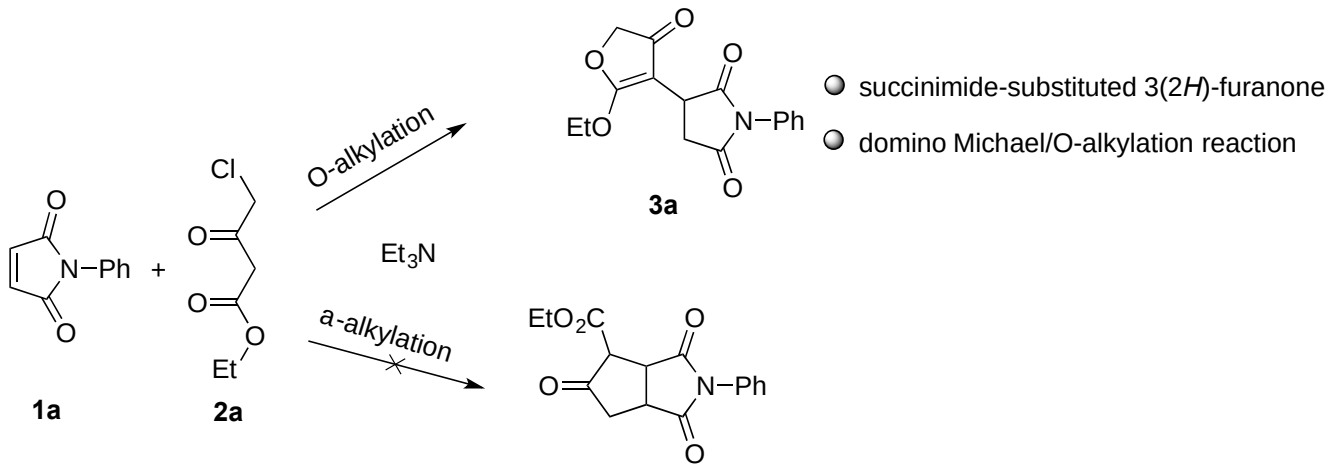


Figure 1. Bioactive products with a 3(2*H*)-furanone subunit.

Maleimides are an important class of activated cyclic alkenes. They have been extensively applied in organic synthesis to construct substituted succinimides and functionalized pyrrolidines, which are core structural units found in natural products and clinical drug candidates.[27-31] To date, there has been no report of the reaction of γ-halogenated-β-ketoesters with maleimides, which could afford a new class of products combining a biologically significant succinimide with a 3(2*H*)-furanone. These fused products might show higher or new biological activities. As a part of our continuing interest in the construction of complex and novel drug candidates,[32-36] herein, we report the first domino Michael/O-alkylation reaction of γ-halogenated-β-ketoesters with maleimides to access a new range of succinimide-substituted 3(2*H*)-furanones. According to the literature, γ-halogenated-β-ketoesters react with α,β-unsaturated aldehydes to afford cyclopentanone products via Michael/α-alkylation.[37] These reports show variable chemical reactivities of γ-halogenated-β-

ketoesters with activated alkenes. Our preliminary studies involved maleimide **1a** and ethyl 4-chloro-acetoacetate **2a** as substrates, these were allowed to react in dichloromethane at room temperature in the presence of 100 mol% Et_3N. The reaction worked well and gave succinimide-substituted 3(2*H*)-furanone **3a** via a domino Michael/O-alkylation process – not a Michael/α-alkylation process (Scheme 1).



Scheme 1. Domino Michael/O-alkylation reaction of **1a** and **2a**.

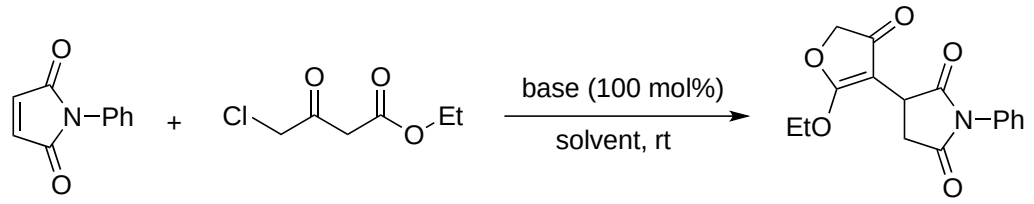
Results and Discussion

To evaluate the role of the base in this system, the reaction of *N*-phenylmaleimide **1a** with ethyl 4-chloro-acetoacetate **2a** was used as a model reaction, and a series of bases were investigated in dichloromethane at room temperature, and the results were shown in Table 1. Weak bases such as Na_2CO_3 and $NaHCO_3$ decreased the reaction rate and afforded poor yields after reaction for 24 h (Table 1, entries 2 and 3). Strong base DABCO also afforded a poor yield because impurities were produced (Table 1, entry 5). Et_3N gave the highest yield and was chosen as the most suitable base (92% yield, Table 1, entry 1). Next, the reaction was conducted in various solvents (Table 1, entries 7-14). Among them, MeOH afforded a poor yield because impurities were produced (Table 1, entry 13), *n*-hexane afforded only a trace of product because of poor solubility (Table 1, entry 14). Other solvents afforded **3a** in moderate to good yields (80-90% yield, Table 1, entries 7-12). Dichloromethane gave the highest yield and was selected as the most suitable reaction media for further optimization (Table 1, entry 1).

Increasing or decreasing the amount of Et_3N gave a lower yield (Table 2, entries 2-4 vs. 1) so having identified 100 mol% Et_3N as the optimal loading for the reaction, we next examined the effect of the reaction temperature (Table 2, entries 5 and 6). A screening of different reaction temperatures showed that the reaction gave the best results at room temperature (Table 2, entry 1). Decreasing reaction temperature slowed down the reaction rate thus decreased the yield (Table 2, entry 5). Increasing the reaction temperature also decreased the yield because impurities were produced (Table 2, entry 6). Finally, the substrate concentration was examined (Table 2, entries 7 and 8). It was found that increasing the substrate concentration slightly decreased the yield (Table 2, entry 7), lowering the substrate concentration decreased the reaction rate and gave lower yield (82% yield, Table 2, entry 8), 0.2 M was the optimal substrate

concentration. Consequently, the following reaction conditions are recommended: 100 mol% Et_3N with 0.2 M substrate in CH_2Cl_2 at room temperature (Table 2, entry 1).

Table 1. Optimization of reaction conditions[a]

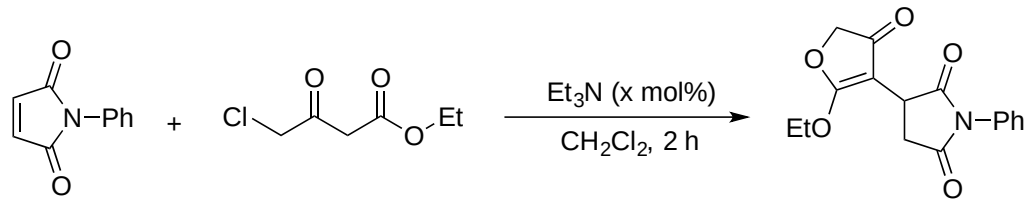


1a **2a** **3a**

Entry	Solvent	Base	Time/h	Yield[b]/%
1	CH_2Cl_2	Et_3N	2	92
2	CH_2Cl_2	$NaHCO_3$	24	trace
3	CH_2Cl_2	Na_2CO_3	24	56
4	CH_2Cl_2	NaOH	2	88
5	CH_2Cl_2	DABCO	2	21
6	CH_2Cl_2	DBU	2	90
7	Et_2O	Et_3N	2	80
8	THF	Et_3N	2	85
9	toluene	Et_3N	2	82
10	EtOAc	Et_3N	2	80
11	CH_3CN	Et_3N	2	90
12	DMF	Et_3N	2	87
13	MeOH	Et_3N	2	18
14	*n*-hexane	Et_3N	2	trace

[a]Unless otherwise noted, reactions were conducted with 0.2 mmol **1a**, 0.2 mmol **2a**, 100 mol % base, in 1.0 mL solvent at room temperature. [b]Isolated yields.

Table 2. Optimization of reaction conditions[a]



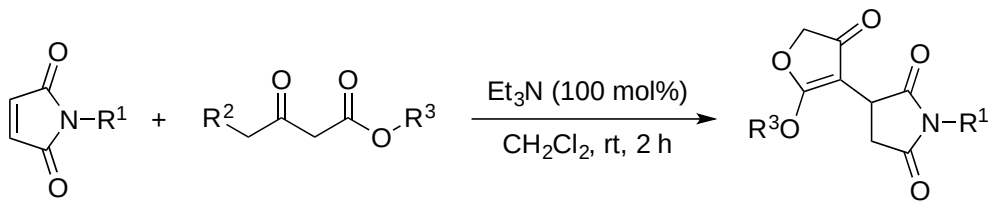
1a **2a** **3a**

Entry	x	*T*/ °C	Yield[b]/%
1	100	25	92
2	200	25	92
3	300	25	90
4	50	25	69
5	100	0	70
6	100	40	91
7[c]	100	25	89
8[d]	100	25	82

[a]Unless otherwise noted, reactions were conducted with 0.2 mmol **1a**, 0.2 mmol **2a**, x mol% base, in 1.0 mL CH_2Cl_2. [b]Isolated yields. [c]0.5 mL CH_2Cl_2 was used. [d]2.0 mL CH_2Cl_2 was used.

Under the optimal reaction conditions, the generality of this protocol was studied (Table 3). Firstly, a wide range of maleimides **1a-n** was studied (Table 3, entries 1-14). The maleimides included those bearing electron-withdrawing and electron-donating substituents on the aryl ring, as well as *N*-alkyl maleimides. All gave good yields (85-96%). The electronic properties and position of the substituents on the *N*-aryl maleimides phenyl ring affected the yield slightly (Table 3, entries 1-9). The *N*-aryl maleimide with a strong electron-withdrawing nitro group, **1g**, gave a slightly lower yield (Table 3, entry 7). Maleimide **1m** also gave a slightly lower yield due to the larger steric hindrance (Table 3, entry 13). In addition, methyl 4-chloroacetoacetate **2b** and ethyl 4-bromoacetoacetate **2c** were also tested, both provided excellent yields (Table 3, entries 15 and 16). The structure of **3a** was determined by an X-ray analysis of a single crystal (Figure 2).[38]

Table 3. Scope of substrates[a]



1a-n **2a-c** **3a-o**

Entry	**1**/R^1	**2**/R^2, R^3	**3**	Yield[b]/%
1	**1a**/C_6H_5	**2a**/Cl, Et	**3a**	92
2	**1b**/4-$CH_3C_6H_4$	**2a**/Cl, Et	**3b**	95
3	**1c**/4-$CH_3OC_6H_4$	**2a**/Cl, Et	**3c**	93
4	**1d**/4-FC_6H_4	**2a**/Cl, Et	**3d**	95
5	**1e**/4-ClC_6H_4	**2a**/Cl, Et	**3e**	93
6	**1f**/4-BrC_6H_4	**2a**/Cl, Et	**3f**	92
7	**1g**/3-$NO_2C_6H_4$	**2a**/Cl, Et	**3g**	85
8	**1h**/3-FC_6H_4	**2a**/Cl, Et	**3h**	87
9	**1i**/2-MeC_6H_4	**2a**/Cl, Et	**3i**	91
10	**1j**/CH_3	**2a**/Cl, Et	**3j**	96
11	**1k**/cyclohexyl	**2a**/Cl, Et	**3k**	92
12	**1l**/Bn	**2a**/Cl, Et	**3l**	90
13	**1m**/$CHPh_2$	**2a**/Cl, Et	**3m**	88
14	**1n**/1-naphthyl	**2a**/Cl, Et	**3n**	92
15	**1a**/C_6H_5	**2b**/Cl, Me	**3o**	94
16	**1a**/C_6H_5	**2c**/Br, Et	**3a**	96

[a]Unless otherwise noted, reactions were conducted with 0.2 mmol **1**, 0.2 mmol **2**, 100 mol % Et_3N, in 1.0 mL CH_2Cl_2 at room temperature. [b]Isolated yield.

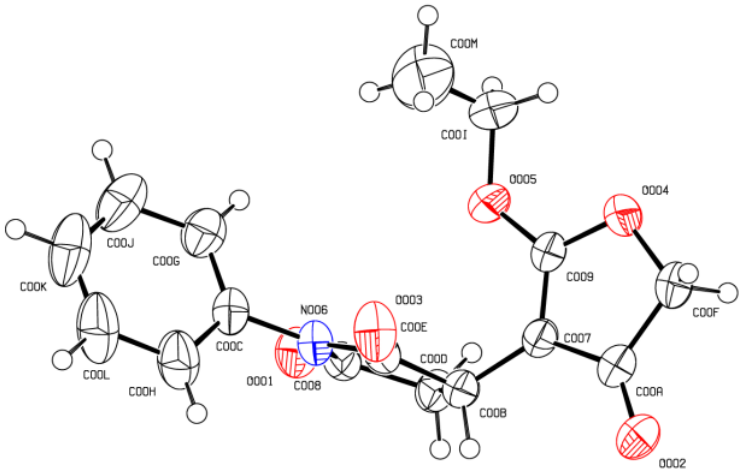
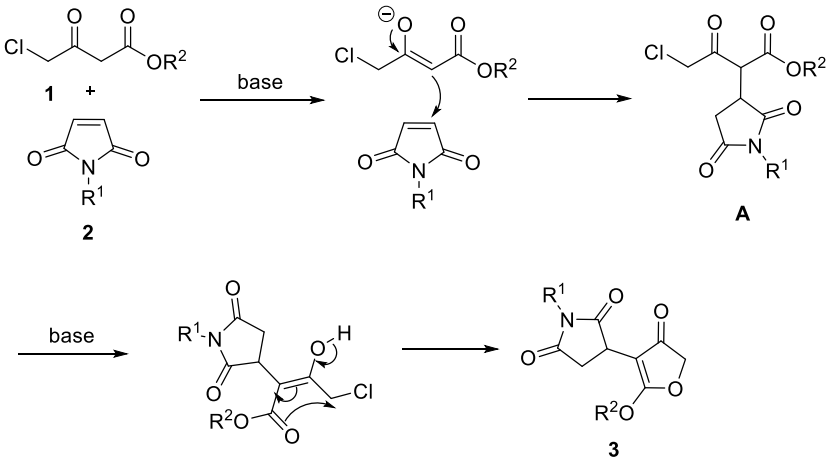


Figure 2. ORTEP representation of the X-ray crystal structure of product **3a** (thermal ellipsoids set to 30% probability level).

Based on the experimental results and the observed structure of **3a**, a proposed reaction pathway for the base-promoted domino Michael/O-alkylation reaction of maleimides **1** and γ-halogenated-β-ketoesters **2** is shown in Scheme 2.[23] First, the base deprotonates the β-ketoester to form an enolate, then nucleophilic conjugate addition to the maleimides by the enolate generates an intermediate Michael adduct **A**. Next, in the presence of base, adduct **A** forms an enolate which undergoes an intramolecular O-alkylation process to form the product **3**.



Scheme 2. Proposed pathway for the base-promoted domino Michael/O-alkylation reaction.

Conclusions

We have demonstrated a facile base-promoted domino Michael/O-alkylation reaction of maleimides and γ-halogenated-β-ketoesters. The reaction conditions are simple and mild. With this protocol, a wide range of

new succinimide-substituted 3(2*H*)-furanones were smoothly obtained in good yields (up to 96%). Further, expansion of these new succinimide-substituted 3(2*H*)-furanones to access products with known biological activities or new biologically significant molecules and testing their pharmacological activities are ongoing in our laboratory.

Experimental Section

General. *N*-Substituted maleimides **1** were prepared according to the literature method or similarly.[39] γ-Halogenated-β-ketoesters **2** were purchased from commercial suppliers and used without further purification. Commercial grade solvents were dried and purified by standard procedures as specified in Purification of Laboratory Chemicals, 4th Ed (Armarego, W. L. F.; Perrin, D. D. Butterworth Heinemann: 1997). All melting points were measured on a SGWX-4 micro melting point apparatus. ^{1}H NMR spectra were recorded at 600 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Spectra are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR spectra were collected at 150 MHz with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as internal standard ($CDCl_3$, δ = 77.0). Mass spectra were recorded on Bruker micrOTOF-QⅡ mass spectrometer. Reactions were monitored by TLC and visualized with ultraviolet light.

General procedure for the domino Michael/O-alkylation reaction. A solution of maleimide **1** (0.20 mmol, 1 equiv), γ-halogenated-β-ketoester **2** (0.20 mmol, 1 equiv) in CH_2Cl_2 (1.0 mL) was stirred at rt and Et_3N (0.20 mmol, 100 mol %) was added at the same temperature. The reaction mixture was stirred at rt for 2 h and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (eluent PE:EtOAc = 2:1) to afford pure products **3**.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-phenylpyrrolidine-2,5-dione (3a). White solid; 92% yield; mp 112.5-113.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.32 (t, *J* 7.14 Hz, 3H), 2.82 (dd, *J* 5.58, 18.18 Hz, 1H), 3.01 (dd, *J* 9.84, 18.18 Hz, 1H), 3.74-3.77 (m, 1H), 4.37-4.40 (m, 2H), 4.53 (s, 2H), 7.23 (d, *J* 7.50 Hz, 2H), 7.30 (t, *J* 7.50 Hz, 1H), 7.38 (t, *J* 7.80 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 33.2, 34.4, 66.4, 75.2, 90.8, 126.6, 128.5, 129.0, 132.3, 175.3, 176.3, 181.1, 194.1; HRMS (ESI) Calcd. for $C_{16}H_{15}NNaO_5$ $[M+Na]^+$: 324.0848; Found: 324.0842. 38. See supporting information file 2 for crystallographic data; the CCDC number is 1476572.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-(p-tolyl)pyrrolidine-2,5-dione (3b). White solid; 95% yield; mp 161.2-162.2 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.31 (t, *J* 7.14 Hz, 3H), 2.28 (s, 3H), 2.80 (dd, *J* 5.52, 18.12 Hz, 1H), 2.99 (dd, *J* 9.84, 18.12Hz, 1H), 3.72-3.75 (m, 1H), 4.35-4.39 (m, 2H), 4.52 (s, 2H), 7.10 (d, *J* 8.28 Hz, 2H), 7.17 (d, *J* 8.16 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 21.2, 33.2, 34.4, 66.8, 75.2, 90.9, 126.4, 129.6, 129.9, 138.5, 175.4, 176.4, 181.1, 194.0; HRMS (ESI) Calcd. for $C_{17}H_{17}NNaO_5$ $[M+Na]^+$: 338.1004; Found: 338.0999.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-(4-methoxyphenyl)pyrrolidine-2,5-dione (3c). White solid; 93% yield; mp 161.5-162.8 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.32 (t, *J* 7.08 Hz, 3H), 2.78 (dd, *J* 5.46, 18.12 Hz, 1H), 2.98 (dd, *J* 9.84, 18.18 Hz, 1H), 3.71 (m, 4H), 4.36-4.40 (m, 2H), 4.52 (s, 2H), 6.88 (d, *J* 8.76 Hz, 2H), 7.13 (d, *J* 8.76 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.6, 32.1, 33.3, 54.4, 65.8, 74.2, 89.9, 113.3, 123.8, 126.6, 126.8, 158.4, 174.5, 180.1, 193.1; HRMS (ESI) Calcd. for $C_{17}H_{17}NNaO_5$ $[M+Na]^+$: 354.0954; Found: 354.0948.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-(4-fluorophenyl)pyrrolidine-2,5-dione (3d). White solid; 95% yield; mp 192.0-193.0°C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.32 (t, *J* 7.14 Hz, 3H), 2.80 (dd, *J* 5.34, 18.18 Hz, 1H), 2.99 (dd, *J* 9.78, 18.18 Hz, 1H), 3.72-3.74(m, 1H), 4.37-4.41(m, 2H), 4.53 (s, 2H), 7.06 (t, *J* 8.40 Hz, 2H), 7.21-7.23 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 33.2, 34.4, 66.9, 75.2, 90.8, 115.9, 116.1, 128.1, 128.5, 161.3, 175.2, 181.2, 194.1; HRMS (ESI) Calcd. for $C_{16}H_{14}FNNaO_5$ [M+Na]$^+$: 342.0754; Found: 342.0748.

1-(4-Chlorophenyl)-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)pyrrolidine-2,5-dione (3e). White solid; 93% yield; mp 171.2-172.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.33 (t, *J* 7.08 Hz, 3H), 2.82 (dd, *J* 5.46, 18.18 Hz, 1H), 3.01 (dd, *J* 9.78, 18.12 Hz, 1H), 3.72-3.75 (m, 1H), 4.37-4.41 (m, 2H), 4.54 (s, 2H), 7.20 (d, *J* 8.52 Hz, 2H), 7.34 (d, *J* 8.58 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 33.3, 34.4, 66.9, 75.2, 90.7, 127.9, 129.2, 130.7, 134.3, 174.9, 176.1, 181.2, 194.0; HRMS (ESI) Calcd. for $C_{16}H_{14}NNaO_5$ [M+Na]$^+$: 358.0458; Found: 358.0453.

1-(4-Bromophenyl)-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)pyrrolidine-2,5-dione (3f). White solid; 92% yield; mp 172.5-173.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.35 (t, *J* 7.14 Hz, 3H), 2.85 (dd, *J* 5.52, 18.18 Hz, 1H), 3.01 (dd, *J* 9.84, 18.18 Hz, 1H), 3.74 (dd, *J* 5.52, 9.78 Hz, 1H), 4.40-4.43 (m, 2H), 4.55 (s, 2H), 7.15 (d, *J* 8.58 Hz, 2H), 7.51 (d, *J* 8.64 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.0, 32.7, 33.7, 66.3, 74.6, 90.0, 121.7, 127.5, 130.5, 131.6, 174.2, 175.3, 180.5, 193.4; HRMS (ESI) Calcd. for $C_{16}H_{14}NNaO_5$ [M+Na]$^+$: 401.9953; Found: 401.9948.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-(3-nitrophenyl)pyrrolidine-2,5-dione (3g). White solid; 85% yield; mp 168.2-169.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.39 (t, *J* 7.14 Hz, 3H), 2.92 (dd, *J* 5.46, 18.24 Hz, 1H), 3.09 (dd, *J* 9.78, 18.24 Hz, 1H), 3.79-3.82 (m, 1H), 4.44-4.48 (m, 2H), 4.59 (s, 2H), 7.59 (t, *J* 8.16 Hz, 1H), 7.68-7.69 (m, 1H), 8.18-8.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.9, 32.6, 33.6, 66.3, 74.5, 89.7, 121.1, 122.4, 129.1, 131.8, 132.4, 147.6, 173.6, 174.9, 180.4, 193.2; HRMS (ESI) Calcd. for $C_{16}H_{14}N_2NaO_7$ [M+Na]$^+$: 369.0699; Found: 369.0694.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-(3-fluorophenyl)pyrrolidine-2,5-dione (3h). White solid; 87% yield; mp 192.2-193.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.34 (t, *J* 7.08 Hz, 3H), 2.83 (dd, *J* 5.52, 18.18 Hz, 1H), 3.01 (dd, *J* 9.78, 18.12 Hz, 1H), 3.74-3.76 (m, 1H), 4.39-4.42 (m, 2H), 4.55 (s, 2H), 7.02 (t, *J* 8.40 Hz, 2H), 7.07 (d, *J* 8.04 Hz, 1H), 7.33-7.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 33.3, 34.3, 66.6, 74.9, 90.3, 114.0, 114.1, 115.1, 121.9, 129.8, 133.4, 163.2, 174.7, 181.2, 193.7; HRMS (ESI) Calcd. for $C_{16}H_{14}NNaO_5$ [M+Na]$^+$: 342.0754; Found: 342.0748.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-(o-tolyl)pyrrolidine-2,5-dione (3i). White solid; 91% yield; mp 141.0-142.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.33 (t, *J* 7.08 Hz, 3H), 2.17 (s, 3H), 2.91(dd, *J* 6.30, 18.06 Hz, 1H), 3.06 (dd, *J* 9.84, 18.18 Hz, 1H), 3.77-3.81 (m, 1H), 4.37-4.41 (m, 2H), 4.53 (s, 2H), 6.98 (d, *J* 7.68 Hz, 1H), 7.17-7.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.7, 17.6, 33.4, 34.1, 66.8, 75.2, 90.3, 126.7, 127.9, 129.4, 131.1, 131.3, 136.4, 175.2, 176.2, 181.2, 194.1; HRMS (ESI) Calcd. for $C_{17}H_{17}NNaO_5$ [M+Na]$^+$: 338.1004; Found: 338.0999.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-methylpyrrolidine-2,5-dione (3j). White solid; 96% yield; mp 103.5-104.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.35 (t, *J* 7.14 Hz, 3H), 2.71(dd, *J* 5.64, 17.94 Hz, 1H), 2.83 (dd, *J* 9.54, 17.94 Hz, 1H), 2.96 (s, 3H), 3.61 (dd, *J* 5.64, 9.48 Hz, 1H), 4.39-4.43 (m, 2H), 4.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 25.0, 33.1, 34.0, 66.8, 75.0, 90.4, 176.1, 177.3, 181.2, 194.0; HRMS (ESI) Calcd. for $C_{11}H_{13}NNaO_5$ [M+Na]$^+$: 262.0691; Found: 262.0686.

1-Cyclohexyl-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)pyrrolidine-2,5-dione (3k). White solid; 92% yield; mp 115.2-116.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.13-1.27 (m, 4H), 1.34 (t, *J* 7.08 Hz, 3H), 1.55-1.59 (m, 2H), 1.75 (d, *J* 12.72 Hz, 2H), 2.06-2.12 (m, 2H), 2.60 (dd, *J* 5.58, 18.00 Hz, 1H), 2.81 (dd, *J* 9.72, 17.94 Hz, 1H), 3.52-3.54(m, 1H), 3.93 (t, *J* 12.30 Hz, 1H), 4.38-4.42(m, 2H), 4.53 (s, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 25.0, 25.8, 28.6,

32.6, 34.1, 52.0, 66.7, 75.1, 91.0, 176.3, 177.2, 181.1, 194.1; HRMS (ESI) Calcd. for $C_{16}H_{21}NNaO_5$ $[M+Na]^+$: 330.1317; Found: 330.1312.

1-Benzyl-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)pyrrolidine-2,5-dione (3l). White solid; 90% yield; mp 118.0-119.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.20 (t, *J* 7.14 Hz, 3H), 2.68 (dd, *J* 5.70, 18.06 Hz, 1H), 2.85 (dd, *J* 9.66, 18.06 Hz, 1H), 3.61-3.63 (m, 1H), 4.27-4.29 (m, 2H), 4.52 (s, 2H), 4.58-4.64 (m, 2H), 7.17 (t, *J* 7.38 Hz, 1H), 7.22 (t, *J* 7.62 Hz, 2H), 7.31 (d, *J* 7.32 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.7, 32.1, 33.3, 41.7, 65.9, 74.4, 89.6, 126.8, 127.6, 127.7, 134.9, 174.9, 176.0, 180.2, 193.1; HRMS (ESI) Calcd. for $C_{17}H_{17}NNaO_5$ $[M+Na]^+$: 338.1004; Found: 338.0999.

1-Benzhydryl-3-(2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl)pyrrolidine-2,5-dione (3m). White solid; 88% yield; mp 120.5-121.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.23 (t, *J* 7.08 Hz, 3H), 2.74 (dd, *J* 6.00, 18.12 Hz, 1H), 2.84 (dd, *J* 9.78, 18.12 Hz, 1H), 3.58-3.61 (m, 1H), 4.28-4.32 (m, 2H), 4.51 (s, 2H), 6.51 (s, 1H), 7.18-7.19 (m, 2H), 7.20-7.25 (m, 5H), 7.28 (t, *J* 7.74 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 32.9, 34.0, 58.6, 66.8, 75.2, 90.6, 127.6, 128.3, 128.7, 137.7, 175.6, 176.8, 181.2, 194.1; HRMS (ESI) Calcd. for $C_{23}H_{21}NNaO_5$ $[M+Na]^+$: 414.1317; Found: 414.1312.

3-(2-Ethoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-(naphthalen-1-yl)pyrrolidine-2,5-dione (3n). White solid; 92% yield; mp 122.5-123.5 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.26 (t, *J* 7.08 Hz, 3H), 2.91 (dd, *J* 5.40, 18.24 Hz, 1H), 3.17 (dd, *J* 9.9, 18.24 Hz, 1H), 3.82-3.83 (m, 1H), 4.29-4.32 (m, 2H), 4.52 (s, 2H), 7.21 (d, *J* 7.20 Hz, 1H), 7.37-7.48 (m, 3H), 7.79-7.83 (m, 2H), 7.90 (d, *J* 8.40 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.6, 33.7, 34.5, 66.7, 75.2, 90.6, 122.0, 122.9, 125.2, 126.1, 126.6, 127.2, 128.3, 129.5, 129.9, 134.3, 175.7, 176.8, 181.3, 194.4; HRMS (ESI) Calcd. for $C_{20}H_{17}NNaO_5$ $[M+Na]^+$: 374.1004; Found: 374.0999.

3-(2-Methoxy-4-oxo-4,5-dihydrofuran-3-yl)-1-phenylpyrrolidine-2,5-dione (3o). White solid; 94% yield; mp 88.7-89.8 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.85 (dd, *J* 5.64, 18.12 Hz, 1H), 3.01 (dd, *J* 9.84, 18.12 Hz, 1H), 3.73-3.76 (m, 1H), 4.01 (s, 3H), 4.56 (s, 2H), 7.24 (d, *J* 7.62 Hz, 2H), 7.31 (t, *J* 7.44 Hz, 1H), 7.39 (t, *J* 7.80 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 32.5, 33.5, 56.0, 74.5, 90.0, 125.8, 127.8, 128.3, 131.4, 174.4, 175.4, 180.6, 193.3; HRMS (ESI) Calcd. for $C_{15}H_{13}NNaO_5$ $[M+Na]^+$: 310.0691; Found: 310.0686.

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Supplementary Material

Supporting Information:
Spectra of all compounds, crystallographic data of **3a**.

References

1. Sakamoto, H. T.; Flausino, D.; Castellano, E. E.; Stark, C. B. W.; Gates, P. J.; Lopes, N. P. *J. Nat. Prod.* **2003**, *66*, 693-695. http://dx.doi.org/10.1021/np020314v
2. Shin, S. S.; Byun, Y.; Lim, K. M.; Choi, J. K.; Lee, K.-W.; Moh, J. H.; Kim, J. K.; Jeong, Y. S.; Kim, J. Y.; Choi, Y. H.; Koh, H.-J.; Park, Y.-H.; Oh, Y. I.; Noh, M.-S.; Chung, S. *J. Med. Chem.* **2004**, *47*, 792-804. http://dx.doi.org/10.1021/jm020545z
3. Pashkovskii, F. S.; Shchukina, E. M.; Gribovskii, M. G.; Lakhvich, F. A. *Russ. J. Org. Chem.* **2006**, *42*, 527-540. http://dx.doi.org/10.1134/S1070428006040087
4. Shamshina, J. L.; Snowden, T. S. *Tetrahedron Lett*. **2007**, *48*, 3767–3769. http://dx.doi.org/10.1016/j.tetlet.2007.03.166
5. Jerris, P. J.; Smith III, A. B. *J. Org. Chem.* **1981**, *46*, 577–585. http://dx.doi.org/10.1021/jo00316a018
6. Smith III, A. B.; Levenberg, P. A.; Jerris, P. J.; Scarborough Jr., R. M.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501–1513. http://dx.doi.org/10.1021/ja00396a034
7. Antonioletti, R.; Bonadies, F.; Prencipe, T.; Scettri, A. *J. Chem. Soc., Chem. Commun.* **1988**, 850. http://dx.doi.org/10.1039/c39880000850
8. Winkler, J. D.; Oh, K.; Asselin, S. M. *Org. Lett.* **2005**, *7*, 387–389. http://dx.doi.org/10.1021/ol047810q
9. Liu, Y.; Liu, M.; Guo, S.; Tu, H.; Zhou, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 3445–3448. http://dx.doi.org/10.1021/ol061059z
10. Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 5878–5880. http://dx.doi.org/10.1002/anie.200601836
11. Silva, F.; Reiter, M.; Mills-Webb, R.; Sawicki, M.; Klär, D.; Bensel, N.;Wagner, A.; Gouverneur, V. *J. Org. Chem.* **2006**, *71*, 8390–8394. http://dx.doi.org/10.1021/jo061292a
12. Crone, B.; Kirsch, S. F. *J. Org. Chem.* **2007**, *72*, 5435–5438. http://dx.doi.org/10.1021/jo070695n
13. Marson, C. M.; Edaan, E.; Morrell, J. M.; Coles, S. J.; Hursthouse, M. B.; Davies, D. T. *Chem. Commun.* **2007**, 2494–2496. http://dx.doi.org/10.1039/b701548h
14. Bunnelle, E. M.; Smith, C. R.; Lee, S. K.; Singaram, S. W.; Rhodes, A. J.; Sarpong, R. *Tetrahedron.* **2008**, *64*, 7008-7014. http://dx.doi.org/10.1016/j.tet.2008.02.103
15. Egi, M.; Azechi, K.; Saneto, M.; Shimizu, K.; Akai, S. *J. Org. Chem.* **2010**, *75*, 2123–2126. http://dx.doi.org/10.1021/jo100048j
16. Poonoth, M; Krause, N. *J. Org. Chem.* **2011**, *76*, 1934–1936. http://dx.doi.org/10.1021/jo102416e
17. Izquierdo, J.; Pericàs, M. A. *ACS Catal.* **2016**, *6*, 348–356.

http://dx.doi.org/10.1021/acscatal.5b02121
18. Pellissier, H. *Adv. Synth. Catal.* **2016**, *358*, 2194-2259. http://dx.doi.org/10.1002/adsc.201600462
19. Zhao, K.; Zhi, Y.; Shu, T.; Valkonen, A.; Rissanen, Kari P.; Enders, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 12104-12108. http://dx.doi.org/10.1002/anie.201606947
20. Diez, E. S.; Vesga, D. L.; Reyes, E.; Uria, U.; Carrillo, L.; Vicario, J. L. *Org. Lett.* **2016**, 18, 1270–1273. http://dx.doi.org/10.1021/acs.orglett.6b00173
21. Dou, X.-W.; Han, X.-Y.; Lu, Y.-X. *Chem.-Eur.J.* **2012**, *18*, 85-89. http://dx.doi.org/10.1002/chem.201102796
22. Yan, Y.-Y.; Lu, R.-J.; Wang, J.-J.; Xuan, Y.-N.; Yan, M. *Tetrahedron* **2012**, *68*, 6123-6130. http://dx.doi.org/10.1016/j.tet.2012.05.082
23. John, J.; Hopf, H. *Eur. J. Org. Chem.* **2013**, 841-845. http://dx.doi.org/10.1002/ejoc.201201253
24. Luo, N.-H.; Sun, X.; Yan, Y.-Y.; Nie, S.-Z.; Yan, M. *Tetrahedron: Asymmetry* **2011**, *22*, 1536-1541. http://dx.doi.org/10.1016/j.tetasy.2011.08.022
25. John, J.; Târcoveanu, E.; Jones, P. G.; Hopf, H. *Beilstein J. Org. Chem.* **2014**, *10*, 1462–1470. http://dx.doi.org/10.3762/bjoc.10.150
26. Wang, X.-B.; Li, T.-Z.; Sha, F.; Wu, X.-Y. *Eur. J. Org. Chem.* **2014**, 739-744. http://dx.doi.org/10.1002/ejoc.201301350
27. Zou, C. C.; Zeng, C. K.; Liu, Z.; Lu, M.; Sun, X. H.; Ye, J. X. *Angew. Chem. Int. Ed.* **2016**, *55*, 14257-14261. http://dx.doi.org/10.1002/anie.201605790
28. Morita, T.; Akita, M.; Satoh, T.; Kakiuchi,F.; Miura, M. *Org. Lett.* **2016**, *18*, 4598-4601. http://dx.doi.org/10.1021/acs.orglett.6b02244
29. Kalia, D.; Malekar, P. V.; Parthasarathy, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 1432-1435. http://dx.doi.org/10.1002/anie.201508118
30. Qiu, S.; Lee, R.; Zhu, B.; Coote, M.L.; Zhao, X. W.; Jiang, Z. Y. *J. Org. Chem.* **2016**, *81*, 8061-8069. http://dx.doi.org/10.1021/acs.joc.6b01451
31. Yoshimura1, A.; Nguyen, K. C.; Rohde, G. T.; Saito, A.; Yusubov, M. S.; Zhdankin, V. V. *Adv.Synth.Catal.* 2016, 358, 2340-2344. http://dx.doi.org/10.1002/adsc.201600331
32. Zhou, J.; Wang, Q.-L.; Peng, L.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun*. **2014**, *50*, 14601-14605. http://dx.doi.org/10.1039/c4cc05207b
33. Zhou, J.; Jia, L.-N.; Wang, Q.-L.; Peng, L.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Tetrahedron* **2014**, *70*, 8665-8671. http://dx.doi.org/10.1016/j.tet.2014.09.040
34. Zhou, J.; Jia, L.-N.; Peng, L.; Wang, Q.-L.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Tetrahedron* **2014**, *70*, 3478-3484. http://dx.doi.org/10.1016/j.tet.2014.03.065
35. Wang, Q.-L.; Cai, T.; Zhou, J.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun*. **2015**, *51*, 10726-10729. http://dx.doi.org/10.1039/C5CC03793J
36. Guo, Y.-L.; Jia, L.-N.; Peng, L.; Qi, L.-W.; Zhou, J.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *RSC Adv*. **2013**, *3*, 16973-16976. http://dx.doi.org/10.1039/c3ra43344g

37. Rios, R.; Vesely, J.; Sundén, H.; Ibrahem, I.; Zhao, G. L.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 5835-5839.
http://dx.doi.org/10.1016/j.tetlet.2007.06.070
38. The CCDC number is 1476572.
39. Cava, M. P.; Deana, A. A.; Muth, K.; Mitchell, M. J. *Org. Synth.* **1961**, *41*, 93-93.
http://dx.doi.org/10.1002/0471264180.os041.24

