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Construction of 2-Pyrone Skeleton via Domino Sequence between 2-Acyl-1-Chlorocyclopropanecarboxylate and Amines

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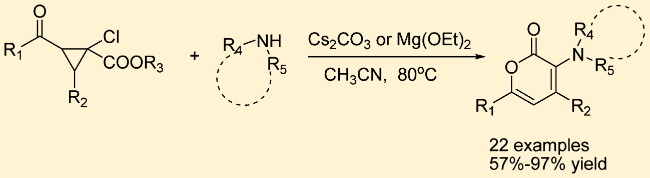
Supporting Information

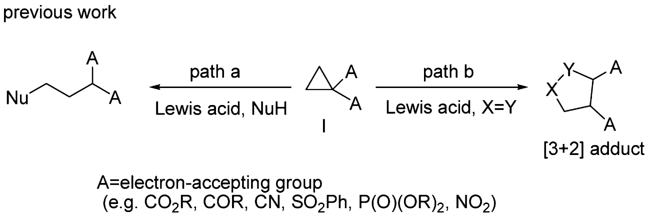
ABSTRACT: A base-promoted domino reaction of 2-acyl-1-chlorocyclopropaneformic esters with amines is described. In the presence of inorganic bases like Cs_2CO_3 or $Mg(OEt)_2$, the reaction proceeded smoothly in acetonitrile to afford 2-pyrone derivatives in modest to excellent yields (up to 97%). This reaction provides a straightforward and transition metal-free protocol to efficiently construct 2-pyrone skeleton. A possible mechanistic process involving 1,2-elimination of hydrogen chloride, aza-Michael addition, ring-opening, and intramolecular lactonization was suggested to rationalize the formation of the target 2-pyrone derivatives.



INTRODUCTION

Cyclopropanes, the smallest strained carbocycle, have been demonstrated to be useful synthetic precursors due to their rich chemical reactivity in organic chemistry.[1] The ring-opening reaction of activated cyclopropanes with a variety of nucleophiles provides a versatile access to various functionalized carbon skeletons.[2] The representative activated cyclopropanes are compounds I that bear two electron-withdrawing groups at 3-positions. In the presence of Lewis acids, the strained cyclopropane ring can be opened by direct nucleophilic attack in stereodefined S_N mode (Scheme 1, path a),[3] or through formal [3 + n] (n = 2, 3, 4) cycloaddition reaction with various dipolarophiles (Scheme 1, path b).[4] However, to our knowledge, few examples of cyclopropanes bearing electron-donating amino or alkoxy groups were reported to undergo through spontaneous ring-opening process in the absence of Lewis acid catalyst until now.[5]

Scheme 1. Reactivity of Typical Activated Cyclopropanes



Recently, we established a convenient method for generating a new kind of reactive cyclopropene intermediate II with two electron-withdrawing groups on its C═C bond.[6] In view of its structural feature, we anticipated that the electron-deficient cyclopropene II could combine with other nucleophiles to provide another type of activated cyclopropane III bearing two acceptors and one donor in structure. As depicted in Scheme 2, we wonder if this type of cyclopropane III could open spontaneously to form the intermediate IV, an apparently versatile synthon in organic synthesis. For this purpose, the reactions of 2-acyl-1-chlorocyclopropanecarboxylates with a variety of primary and secondary aliphatic amines have been performed. As a consequence, the transition metal-free reactions proceeded smoothly under mildly basic conditions to afford one of a kind unexpected products, 3-amino-2-pyrone derivatives **3**.

As is known to us, a 2-pyrone unit as a key structural motif exists in large numbers of natural products and pharmaceutically active compounds,[7] and in particular functionalized 2-pyrones, such as 3-aryl-2-pyrone derivatives, were synthesized and used as potential HIV-1 protease inhibitors and anti-inflammatory, anticancer, and antitumor agents in the past few years (Figure 1).[7,8]

These 2-pyrone derivatives were usually obtained either through traditional approaches[9] or by transition-metal catalyzed procedures.[10] These methods, however, suffer from various disadvantages, such as harsh reaction conditions, limitation of substrates, and poor chemoselectivity. Thus, there is still great demand to develop an efficient synthetic approach for various 2-pyrone derivatives from inexpensive and readily available starting materials. For this reason, our attention was focused on construction of a 2-pyrone skeleton from 2-acyl-1-chlorocyclopropanecarboxylates, and the interesting results observed in our preliminary experiments encouraged us to investigate the details for the above reaction.

RESULTS AND DISCUSSION

To begin with, the reaction of ethyl 2-benzoyl-1-chlorocyclopropanecarboxylate **1a** with pyrrolidine **2a** was performed in

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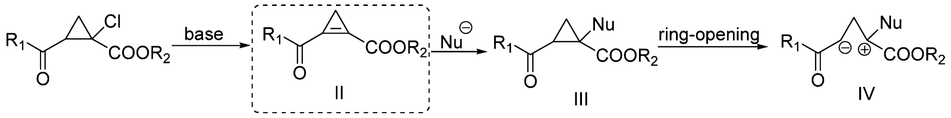
Scheme 2. Our Assumption for the Reaction



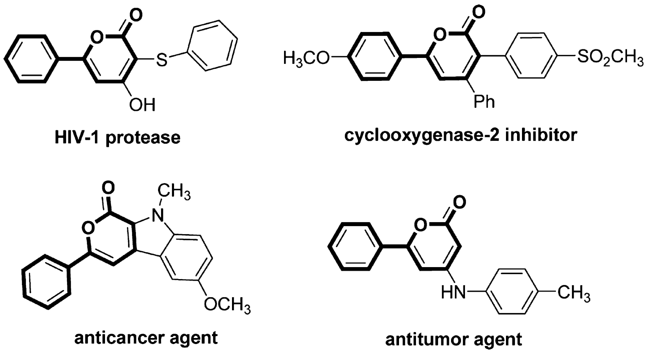
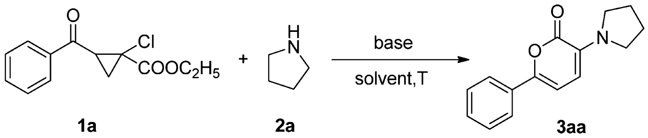


Figure 1. Some representative compounds with 2-pyrone unit.

the presence of K_2CO_3 in DMSO. The main product isolated was identified to be 2-pyrone **3aa** by spectroscopic means (Table 1, entry 1). This structural assignment was further confirmed by single-crystal X-ray diffraction analysis of its homologue **3ba** (see Supporting Information, SI). Besides **3aa**, a considerable amount of oligomers with high polarity were also detected by TLC, which might result from the cyclopropene II. In order to get the optimal reaction conditions, the effect of bases and solvents on the reaction was next assessed. All the observed results are summarized in Table 1. Apparently, the property of the various bases listed in Table 1 had an obvious influence on the reaction. Among the common inorganic bases such as K_2CO_3, Na_2CO_3 and K_3PO_4, Cs_2CO_3 gave the highest yield (77%) of the desired product **3aa**, mainly due to its good solubility in DMSO (Table 1, entries 1−4). Use of other inorganic or organic bases with high basicity like KOH and CH_3ONa led to rapid consumption of **1a** and a sharp decline in the yield of **3aa** (Table 1, entries 5−10). In addition, tertiary amines such as diisopropylethylamine (DIPEA), triethylamine (TEA), and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) can also promote the reaction, but furnished **3aa** only in 31%, 25%, and 39%, respectively (Table 1, entries 11−13). Therefore, Cs_2CO_3 as the most appropriate base was chosen to study the effect of solvent, base loading, and reaction temperature.

In view of this reaction feature, various aprotic polar solvents were mainly assessed (Table 1, entries 14−17). The reaction proceeded readily in DMF, CH_3CN, and 1,4-dioxane to give 2-pyrone **3aa**, respectively, in 37%, 77%, and 21% yields (Table 1, entries 14−16). Only a trace amount of **3aa** was detected in 1,2-dichloroethane (1,2-DCE) (Table 1, entry 17). Thus, we replaced DMSO with CH_3CN as the solvent in the following experiments to simplify the workup procedure. In addition, the loading of base was also examined. When the amount of Cs_2CO_3 was reduced from 4 equiv to 3 equiv or 2 equiv, a detectable decrease in both the reaction rate and the product

Table 1. Reaction Condition Optimization[a]



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

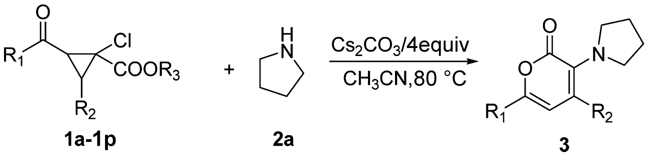
entry	base	solvent	T (°C)	time (h)[b]	conversion (%)	yield (%)[c]
1	K_2CO_3	DMSO	80	15	100	56
2	Na_2CO_3	DMSO	80	15	100	10
3	K_3PO_4	DMSO	80	10	100	27
4	Cs_2CO_3	DMSO	80	5	100	77
5	LiOH	DMSO	80	5	100	35
6	NaOH	DMSO	80	5	100	22
7	KOH	DMSO	80	5	100	12
8	$Mg(OH)_2$	DMSO	80	5	100	68
9	CH_3ONa	DMSO	80	1	100	trace
10	*t*-BuOK	DMSO	80	1	100	trace
11	DIPEA	DMSO	80	18	100	31
12	TEA	DMSO	80	18	100	25
13	DBU	DMSO	80	7	100	39
14	Cs_2CO_3	DMF	80	10	100	37
15	Cs_2CO_3	CH_3CN	80	6	100	77
16	Cs_2CO_3	1,4-Dioxane	80	12	100	21
17	Cs_2CO_3	1,2-DCE	80	12	100	trace
18[d]	Cs_2CO_3	CH_3CN	80	9	100	44
19[e]	Cs_2CO_3	CH_3CN	80	12	100	37
20	Cs_2CO_3	CH_3CN	60	16	100	41

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), and base (0.8 mmol) in solvent (2 mL) stirred at the specified temperature. [b] Determined by TLC. [c] Isolated yields based on the consumed substrate **1a**. [d] Cs_2CO_3 (0.6 mmol). [e] Cs_2CO_3 (0.4 mmol).

yield was observed (Table 1, entries 18−19). Lowering the reaction temperature from 80 to 60 °C, the above reaction was obviously decelerated, and the product yield declined to 41% (Table 1, entry 20).

Having established the optimal conditions, the substrate scope for this reaction was next investigated. A series of substrates **1** with different R_1, R_2, and R_3 groups were thus prepared according to the method reported previously.[6] As shown in Table 2, the property of R_1 group exerts a marked influence on the reaction (Table 2, entries 1−11). When R_1 is an aryl group, the reaction of substrates **1a**−**1i** proceeded smoothly to afford the corresponding 2-pyrones **3aa**−**3ia** in moderate to excellent yields (Table 2, entries 1−9), depending upon the electronic property of substituent groups on aromatic ring. In fact, electron-donating groups such as MeO and Me favored the formation of products **3ba** and **3ca** in excellent yields (Table 2, entries 2−3), whereas electron-withdrawing groups like Cl and Br decreased the yields of products **3da**, **3ea**, and **3fa** in comparison with **3aa** (Table 2, entries 4−6). Substrates **1g**−**1i** with biphenyl, 2-thienyl or 1-naphthyl groups were also tolerated in this process, affording products **3ga**−**3ia** in moderate to good yields, respectively (Table 2, entries 7−9). A significant decline in the yield was observed when R_1 is a methyl group, and only 34% yield of the desired product **3ja** was isolated (entry 10). Under the same conditions, substrate **1k** (R_1 = OMe) did not react with **2a** at all, mainly due to the hard 1,2-elimination of HCl (Table 2, entry11). In the case of **1l** (R_2 = Ph), the reaction with **2a** is rather complicated, and almost no the product **3la** was detected with the consumption of **1l** (Table 2, entry 12), indicative of the influence of steric hindrance of R_2 group. Thus, the steric effect of R_3 group on the reaction was also examined. The results listed in Table 2 (entries 13−16) clearly show that the methyl ester **1m** gave the highest yield (entry 13), and the bulky *t*-butyl ester **1n** provided the lowest yield (entry 14). These examples illustrate that the intramolecular lactonization step of forming 2-pyrone would be decelerated to some extent with the increasing size of R_3 group.

Table 2. Substrate Scope for the Reaction of 1 with 2a[a]



entry	1	R_1	R_2	R_3	product	yield (%)[b]
1	**1a**	C_6H_5	H	Et	**3aa**	77
2	**1b**	4-MeC_6H_4	H	Et	**3ba**	84
3	**1c**	4-MeOC_6H_4	H	Et	**3ca**	96
4	**1d**	4-ClC_6H_4	H	Et	**3da**	73
5	**1e**	4-BrC_6H_4	H	Et	**3ea**	62
6	**1f**	2-BrC_6H_4	H	Et	**3fa**	61
7	**1g**	4-PhC_6H_4	H	Et	**3ga**	46
8	**1h**	2-thienyl	H	Et	**3ha**	41
9	**1i**	1-naphthyl	H	Et	**3ia**	70
10	**1j**	Me	H	Et	**3ja**	34
11	**1k**	MeO	H	Et	**3ka**	
12	**1l**	C_6H_5	C_6H_5	Et	**3la**	nd
13	**1m**	C_6H_5	H	Me	**3aa**	83
14	**1n**	C_6H_5	H	*t*-Bu	**3aa**	52
15	**1o**	C_6H_5	H	$(CH_2)_2Cl$	**3aa**	63
16	**1p**	C_6H_5	H	benzyl	**3aa**	67

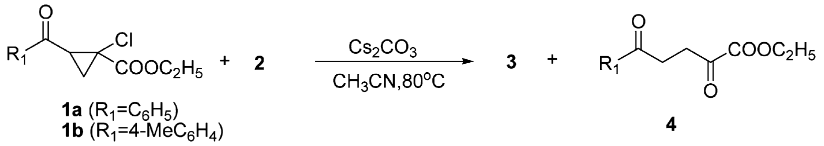
[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol) and Cs_2CO_3 (0.8 mmol) in CH_3CN (2 mL) was stirred at 80 °C. [b]Isolated by column chromatography.

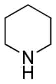
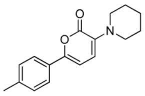
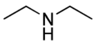
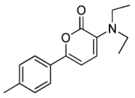
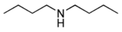
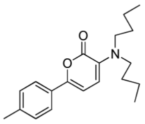
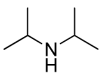
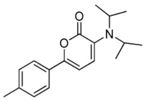
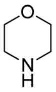
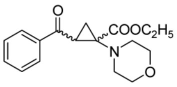
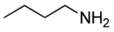
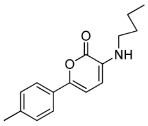
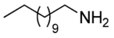
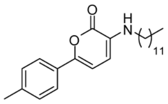
Under the optimized conditions, other aliphatic secondary amines were also utilized to test their reactions with substrates **1a** or **1b**. The results given in Table 3 clearly show the marked influence of the amine structure on the reaction. For simple secondary amines such as diethylamine, an unexpected ring-opening product, 2-ketoester **4b**, was competitively accompanied by the desired 2-pyrones (Table 3, entries 1−3). However, the use of bulkier diisopropylamine gave a complicated reaction with **1b**, and almost no 2-pyrone **3be** and 2-ketoester **4b** were detected (Table 3, entry 4). In contrast, the reaction of morpholine **2f** underwent smoothly and provided a formal substitution product **5** in the yield of 88% rather than the expected 2-pyrone (Table 3, entry 5). Furthermore, primary amines such as *n*-butylamine **2h** and lauryl amine **2i** were also assessed. In the cases, the corresponding 2-pyrones **3bh** and **3bi** were also produced, although in low yields (Table 3, entries 6−7). Apparently, the product distribution is greatly dependent upon the structure of amines.

The formation of a considerable amount of 2-ketoester **4b** made us realize the role of water existing in the reaction system. Consequently, a great deal of effort was taken to improve the yield of 2-pyrone by removal of the water. As shown in Table 4, addition of 4 Å zeolite led to an increase of **3bb** and a decrease of **4b** to some extent for its selective absorption of water (Table 4, entries 1 vs 2). This result encouraged us to examine other additives, especially common alkoxides like $LiOCH_3$, $Mg(OEt)_2$ and $Al(OPr\text{-}i)_3$, since these basic metal alkoxides could convert H_2O into alcohol under basic reaction conditions. To our delight, the relative yields of **3bb** to **4b** were somewhat elevated when 1 equiv of each of the metal alkoxides was added (Table 4, entries 3−5). In particular, addition of $Al(OPr\text{-}i)_3$ almost caused the disappearance of **4b**, and the isolated yield of **3bb** was raised to 63% (Table 4, entry 5). The same thing also happened when 4 equiv $LiOCH_3$ or $Mg(OEt)_2$ was individually used as the base, and only the expected product **3bb** was obtained in 49% and 93% yields (Table 4, entries 6−7). From the above observations, we realized that $Mg(OEt)_2$ was a more efficient promoter than Cs_2CO_3 for this domino process.

With these improved results in hand, we decided to use $Mg(OEt)_2$ as the base to probe the reactions of various substrates **1** with aliphatic amines **2**. All the results were summarized in Table 5. First, the reaction of each of **1a**, **1c**, **1d**, and **1h** with pyrrolidine **2a** was re-examined under the above conditions. In most of the cases, much higher yields of the corresponding 2-pyrones **3** were obtained in comparison with those using Cs_2CO_3 as the base (Table 5, entries 1−4). In addition, it was worth mentioning that $Mg(OEt)_2$ can promote the reaction of steric substrate **1l** with pyrrolidine **2a** efficiently, giving the expected product **3la** in 71% yield (Table 5, entry 5). Treating with simple secondary amines **2c** and **2d**, the reaction of **1b** gave the desired product **3bc** and **3bd** in high yields of 97% and 91%, respectively (Table 5, entries 6−7). Under the same conditions, however, the bulky amine **2e** and primary amine **2h** still did not give detectable amount of **3be** and **3bh** (Table 5, entries 8−9). The substituent effect of the R_1 group on the reaction was also studied by performing the reaction of two representative substrates **1c** and **1d** with **2b**. As a result, a slightly low yield was observed in the case of **1d**, consistent with the results in Table 2 (Table 5, entries 10−11). The

Table 3. Reaction of Substrates 1 with Amines 2[a]



entry	substrate **1**	substrate **2**	products		yields of 3/4(%)[b]
1	**1b**	 **2b**	 **3bb**	**4b**	33/50
2	**1b**	 **2c**	 **3bc**	**4b**	26/18
3	**1b**	 **2d**	 **3bd**	**4b**	34/10
4	**1b**	 **2e**	 **3be**	**4b**	nd
5	**1a**	 **2f**	 **5**		88
6	**1b**	 **2h**	 **3bh**		18
7	**1b**	 **2i**	 **3bi**		18

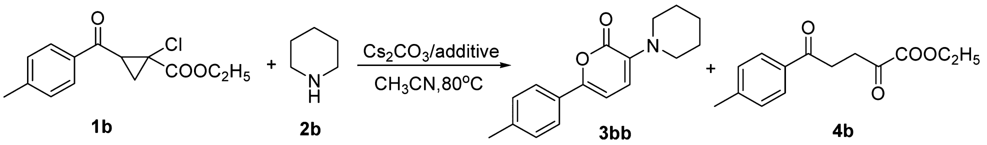
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol) and Cs_2CO_3 (0.8 mmol) in CH_3CN (2 mL) was stirred at 80 °C. [b]Isolated by column chromatography.

reaction of **1d** with the amines **2c** or **2d** also provided high yields of the 2-pyrones **3dc** or **3dd** (Table 5, entries 12−13). Therefore, we speculated that $Mg(OEt)_2$ might play dual roles during the reaction: the conversion of H_2O into $Mg(OH)_2$ and the coordination to oxygen of carbonyl group of substrate **1**, which would favor the intramolecular lactonization to form the desired 2-pyrone **3**.

To gain insight into the mechanism of this cascade reaction, some control experiments were carried out carefully (Scheme 3). First, when the reaction of **1b** with pyrrolidine was done in DMSO at room temperature in the presence of 2 equiv Cs_2CO_3, only the 2-ketoester **4b** was detected by TLC analysis. In fact, **4b** was isolated in a high yield after the reaction mixture was worked up with dilute aqueous HCl (eq a). Thus, we wonder whether the 2-ketoester **4b** was the key intermediate to form the 2-pyrone **3**. For this reason, the reaction of **4b** and pyrrolidine in DMSO was examined in the presence of 2 equiv Cs_2CO_3 at 80 °C, and a complicated reaction was observed, in which highly polar oligomers were detected by TLC (eq b). However, the expected product **3ba** was obtained in 76% yield when the mixture of **1b**, pyrrolidine and 2 equiv. Cs_2CO_3 in DMSO was stirred in advance at room temperature for 20 h, then another 2 equiv of Cs_2CO_3 was added, and the reaction mixture was heated and stirred at 80 °C for another 2 h (eq c). From the big difference observed in the above experiments, we realized that an iminium species rather than **4b** could be the key intermediate. Another evidence to support this opinion came from competition experiments of two different aliphatic amines. When the substrate **1b** was treated with **2a** in advance at room temperature in the presence of 2 equiv Cs_2CO_3, then another amine **2d** was added, and the mixture was stirred at 80 °C for 2 h, as a consequence, only **3ba** rather than **3bd** was yielded (eq d). Once addition order of **2a** and **2d** was reversed, **3bd** became the only 2-pyrone product (eq e).

On the basis of the above investigation, we proposed a possible mechanism as depicted in Scheme 4. The reaction was

Table 4. Influence of Additive on the Reaction of 1 with 2[a]



entry	additive	product yield (%)[b] 3bb	product yield (%)[b] 4b
1	none	33	50
2	4A zeolite	41	32
3	$LiOCH_3$	33	34
4	$Mg(OEt)_2$	46	26
5	$Al(OiPr)_3$	63	trace
6[c]	$LiOCH_3$	49	
7[c]	$Mg(OEt)_2$	93	

[a] Unless otherwise specified, all reactions were performed with **1b** (0.2 mmol), **2b** (0.2 mmol), additive (1 equiv), and Cs_2CO_3 (4 equiv) in 2 mL CH_3CN. [b] Isolated yields. [c] 4 equiv of $LiOCH_3$ or $Mg(OEt)_2$ was used instead of Cs_2CO_3.

initiated by a simple 1,2-elimination to offer a highly reactive cyclopropene intermediate II, then II was converted into a new type of cyclopropane III with donor−acceptor groups (D−A) via aza-Michael addition with amine. Such type of donor−acceptor (D−A) cyclopropane III would readily transform into a transient iminium intermediate IV through a spontaneous ring-opening pattern, and subsequent deprotonation and intramolecular lactonization led to the formation of the 2-pyrone finally. In the presence of water, the iminium IV would be easily converted into 2-ketoester **4** via common hydrolysis.

Considering the structure feature of the 2-pyrone derivatives, we are interested in their photophysical properties. As shown in Figure 2, **3bb** has an intense blue fluorescene in ethanol excited by 325 nm ultraviolet rays. The similar fluorescent emission for compounds **3fa**, **3bb**, and **3db** were also observed. Moreover, the fluorescence wavelength was dependent on the electronic property of substituents at 3, 6-positions of the 2-pyrone. The intense fluorescent emission of **3** may be attributed to the special coplanar structure between 2-pyrone unit, 6-aromatic nucleus and 3-pyrrolidine ring, which was confirmed from the X-ray analysis of **3ba** (see SI). From a synthetic perspective, both the 6-aryl and 3-amino groups of these 2-pyrones were amenable sites for functionalization or modification. Thus, these polycyclic compounds **3** could be used as a family of potential small-molecule fluorophores.

■ CONCLUSIONS

In summary, we have successfully developed an easily available, efficient, and direct synthetic approach to yield important 2H-pyran-2-one derivatives started from ethyl 2-acyl-1-chlorocyclopropanecarboxylates and aliphatic amines. This base-promoted domino reaction may occur via sequential 1,2-elimination, aza-Michael addition, spontaneous ring-opening, deprotonation, and intramolecular lactonization in one pot under mild transition metal-free conditions, which makes the method green and atom-economic. In view of the broad interest in 2H-pyran-2-one derivatives, this novel one-pot procedure could prove useful in synthetic and medicinal chemistry. In addition, these 2H-pyran-2-one derivatives can emit blue fluorescene. Further study on the versatile substrates for constructing diverse cyclic compounds with potential bioactivity is ongoing in our laboratory.

■ EXPERIMENTAL SECTION

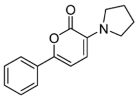
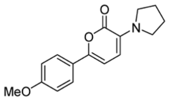
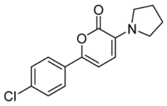
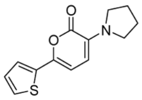
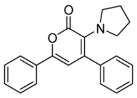
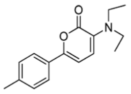
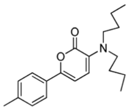
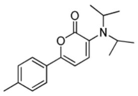
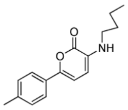
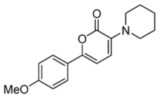
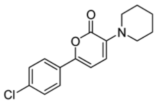
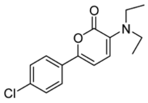
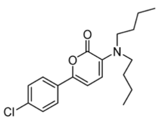
General Methods. All reagents and solvents were of commercial grade and purified prior to use when necessary. Reactions were monitored by TLC analysis using silica gel 60 Å F-254 thin layer plates. Flash column chromatography was performed on silica gel 60 Å, 10−40 μm. All ^1H NMR and ^{13}C NMR spectra were recorded on a 400 or 600 MHz spectrometer with solvent resonances as the internal standard (^1H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). The following abbreviations are used to describe peak patterns where appropriate: s = singlet, d = doublet, t = triplet q = quartet, m = multiplet, and br s = broad signal. All coupling constants (*J*) are given in Hz. IR spectra were recorded on an infrared spectrometer. Melting point was recorded on a melting point detector. HRMS was measured on a TOF-Q mass spectrometer equipped with an ESI technique.

Typical Procedure for Synthesis of 2-Benzoyl-1-chlorocyclopropanecarboxylate 1a. Terminal electron-deficient alkene (10 mmol) was added to a solution of ethyl dichloroacetate (10 mmol) and Cs_2CO_3 (11 mmol) in 20 mL DMF. The mixture was stirred at room temperature. The reaction was monitored by TLC until all the substrate terminal electron-deficient alkene disappeared. The mixture was then washed with water and extracted with CH_2Cl_2. Combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluent to afford the corresponding product **1a** in 72% yield. Unless otherwise specified, all other products **1** were synthesized according to this typical procedure.

Typical Procedure for Synthesis of 6-Phenyl-3-(pyrrolidin-1-yl)-2H-Pyran-2-one 3aa. Compounds **1a** (0.2 mmol), **2a** (0.2 mmol) and Cs_2CO_3 or $Mg(OEt)_2$ (0.8 mmol) were put into 2 mL of anhydrous CH_3CN, and the mixture was heated and stirred at 80 °C. The reaction was monitored by TLC until all the substrate **2a** disappeared. The reaction mixture was then cooled down to room temperature. The solvent was removed under reduced pressure, and the residue was washed with water and extracted with CH_2Cl_2 three times. The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluent to afford the corresponding product **3aa**. Unless otherwise specified, all other products **3** and **5** were obtained according to this typical procedure.

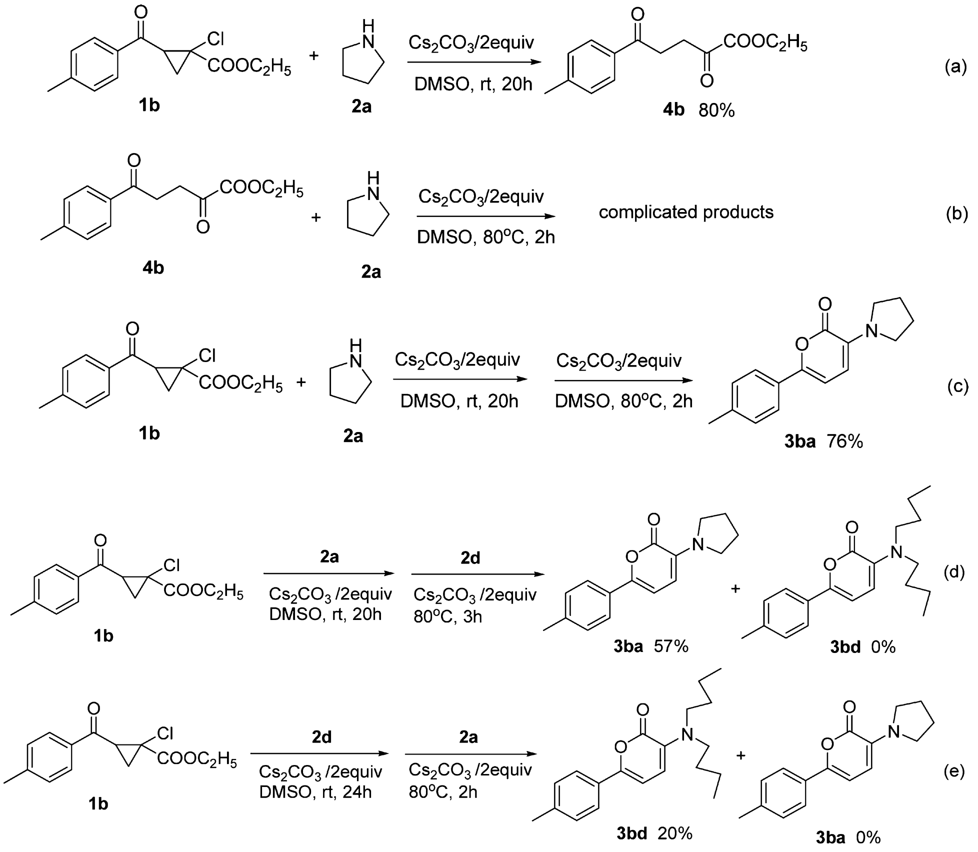
Typical Experiment Procedure for Product 4. Compounds **1a** (0.2 mmol), **2a** (0.2 mmol) and Cs_2CO_3 (0.4 mmol) were added into 2 mL of anhydrous CH_3CN, and the mixture was stirred at room temperature. The reaction was followed by TLC until all the substrate **2a** disappeared. The solvent was removed under reduced pressure, and the residue was neutralized with dilute aqueous HCl, extracted with CH_2Cl_2 three times and washed with brine. The combined organic

Table 5. Reaction of 1 with 2 Using $Mg(OEt)_2$ as the Base[a]

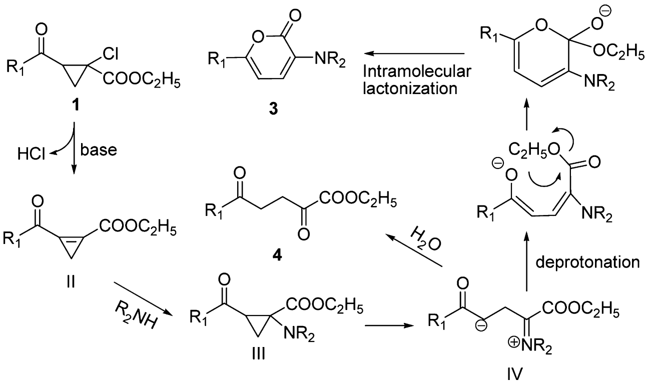
entry	substrate **1**	substrate **2**	product **3**	yield (%)[b]
1	**1a**	**2a**	 **3aa**	91(77)
2	**1c**	**2a**	 **3ca**	96(96)
3	**1d**	**2a**	 **3da**	87(73)
4	**1h**	**2a**	 **3ha**	57(41)
5	**1l**	**2a**	 **3la**	71(nd)
6	**1b**	**2c**	 **3bc**	97(26)
7	**1b**	**2d**	 **3bd**	91(34)
8	**1b**	**2e**	 **3be**	trace
9	**1b**	**2h**	 **3bh**	trace
10	**1c**	**2b**	 **3cb**	81(32)
11	**1d**	**2b**	 **3db**	73(40)
12	**1d**	**2c**	 **3dc**	81(30)
13	**1d**	**2d**	 **3dd**	80(26)

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol) and $Mg(OEt)_2$ (0.8 mmol) in CH_3CN (2 mL) was stirred at 80 °C. [b]Yields in parentheses for Cs_2CO_3.

Scheme 3. Investigation into the Reaction Mechanism



Scheme 4. Proposed Mechanism for the Domino Reaction



extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether and ethyl acetate as eluent to afford the product **4**.

6-Phenyl-3-(pyrrolidin-1-yl)-2H-pyran-2-one (***3aa***). Bright yellow solid (37 mg, 77% yield): mp 136.8−137.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 7.6 Hz, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.31 (d, J = 7.4 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 6.11 (s, 1H), 3.53 (t, J = 6.5 Hz, 4H), 1.97 (dd, J = 8.0, 5.2 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 148.9, 146.0, 134.6, 132.2, 128.7, 128.2, 123.7, 102.9, 49.8, 25.2. IR (KBr) ν 1705, 1617 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{16}NO_2$ $[M + H]^+$ 242.1181, found 242.1187.

3-(Pyrrolidin-1-yl)-6-p-tolyl-2H-pyran-2-one (***3ba***). Bright yellow solid (43 mg, 84% yield): mp 142.3−144.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.55 (d, J = 7.6 Hz, 1H), 6.09 (s, 1H), 3.51 (t, J = 6.5 Hz, 4H), 2.38 (s, 3H), 1.96 (t, J = 6.6 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 149.2, 138.2, 134.3, 129.5, 129.4, 123.7, 111.8, 102.2, 49.8, 25.2, 21.3. IR (KBr) ν 1708, 1617 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{18}NO_2$ $[M + H]^+$ 256.1338, found 256.1330.

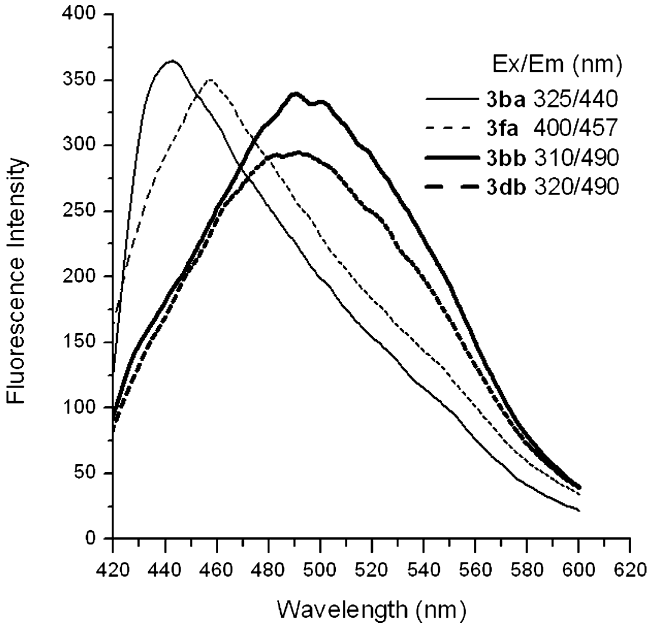


Figure 2. Fluorescence spectra of compound **3ba**, **3fa**, **3bb**, and **3db** (10 uM) in EtOH.

6-(4-Methoxyphenyl)-3-(pyrrolidin-1-yl)-2H-pyran-2-one (***3ca***). Bright yellow solid (52 mg, 96% yield): mp 144.2−145.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.47 (d, J = 7.6 Hz, 1H), 6.13 (s, 1H), 3.84 (s, 3H), 3.49 (t, J

= 6.4 Hz, 4H), 1.96 (t, J = 6.4 Hz, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.6, 154.2, 133.7, 131.48, 131.5, 125.3, 124.9, 114.2, 101.3, 55.4, 49.8, 25.2. IR (KBr) ν 1711, 1618 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{18}NO_3$ $[M + H]^+$ 272.1287, found 272.1290.

6-(4-Chlorophenyl)-3-(pyrrolidin-1-yl)-2H-pyran-2-one (**3da**). Bright yellow solid (40 mg, 73% yield): mp 158.1−161.3 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (d, J = 8.6 Hz, 2H), 7.35 (t, J = 12.7 Hz, 2H), 6.56 (d, J = 7.6 Hz, 1H), 6.11 (s, 1H), 3.52 (t, J = 6.5 Hz, 4H), 1.96 (t, J = 6.6 Hz, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.1, 147.8, 134.3, 134.2, 133.9, 130.6, 128.9, 124.9, 103.2, 50.0, 25.3. IR (KBr) ν 1714, 1615 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{15}ClNO_2$ $[M + H]^+$ 276.0791, found 276.0793.

6-(4-Bromophenyl)-3-(pyrrolidin-1-yl)-2H-pyran-2-one (**3ea**). Bright yellow solid (40 mg, 62% yield): mp 159.6−162.2 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61−7.52 (m, 2H), 7.50 (d, J = 8.7 Hz, 2H), 6.58 (d, J = 7.6 Hz, 1H), 6.08 (s, 1H), 3.53 (t, J = 6.4 Hz, 4H), 1.96 (t, J = 6.6 Hz, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.2, 147.8, 134.53, 134.50, 131.8, 131.1, 125.1, 122.1, 103.3, 49.9, 25.3. IR (KBr): ν 1699, 1618 cm^{-1}. HRMS (ESI) m/z calcd for $C_{15}H_{15}BrNO_2$ $[M + H]^+$ 320.0286, found 320.0284.

6-(2-Bromophenyl)-3-(pyrrolidin-1-yl)-2H-pyran-2-one (**3fa**). Bright yellow solid (39 mg, 61% yield): mp 112.3−114.2 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66−7.57 (m, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.18 (td, J = 7.9, 1.4 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.11 (d, J = 6.3 Hz, 1H), 3.55 (t, J = 6.5 Hz, 4H), 2.02−1.88 (m, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.6, 147.5, 134.5, 134.4, 133.9, 133.4, 130.3, 129.7, 127.7, 120.9, 108.5, 49.9, 25.3. IR (KBr) ν 1711, 1623 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{15}BrNO_2$ $[M + H]^+$ 320.0286, found 320.0289.

6-(4-Diphenyl)-3-(pyrrolidin-1-yl)-2H-pyran-2-one (**3ga**). Bright yellow solid (29 mg, 46% yield): mp 114.3−116.8 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.66 (t, J = 11.2 Hz, 4H), 7.47 (t, J = 7.5 Hz, 2H), 7.38 (t, J = 7.3 Hz, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.26 (s, 1H), 3.57 (s, 4H), 2.00 (s, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.0, 145.1, 144.4, 140.3, 137.4, 128.9, 128.6, 127.9, 127.4, 127.2, 124.8, 118.4, 104.5, 51.7, 25.4. IR (KBr) ν 1702, 1613 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{20}NO_2$ $[M + H]^+$ 318.1494, found 318.1490.

3-(Pyrrolidin-1-yl)-6-(thiophen-2-yl)-2H-pyran-2-one (**3ha**). Bright yellow solid (28 mg, 57% yield): mp 82.7−84.6 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.35 (d, J = 3.1 Hz, 1H), 7.25 (d, J = 4.8 Hz, 1H), 7.11−6.96 (m, 1H), 6.43 (d, J = 7.6 Hz, 1H), 6.09 (s, 1H), 3.52 (t, J = 6.3 Hz, 4H), 1.97 (t, J = 6.3 Hz, 4H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 158.8, 136.1, 134.6, 132.9, 128.4, 127.9, 125.1, 123.3, 102.5, 49.9, 25.2. IR (KBr) ν 1695, 1609 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{14}NO_2S$ $[M + H]^+$ 248.0745, found 248.0741.

6-(Naphthalen-4-yl)-3-(pyrrolidin-1-yl)-2H-pyran-2-one (**3ia**). Bright yellow solid (41 mg, 70% yield): mp 84.9−87.8 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.28 (t, J = 8.1 Hz, 1H), 7.93−7.80 (m, 2H), 7.66 (d, J = 7.1 Hz, 1H), 7.58−7.48 (m, 3H), 6.48 (d, J = 7.4 Hz, 1H), 6.23 (s, 1H), 3.61−3.52 (m, 4H), 2.04−1.93 (m, 4H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 159.9, 133.9, 130.7, 130.5, 129.5, 128.5, 126.8, 126.8, 126.0, 125.3, 125.1, 121.4, 108.0, 50.0, 25.3. IR (KBr) ν 1709, 1616 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{18}NO_2$ $[M + H]^+$: 292.1338, found: 292.1334.

6-Methyl-3-(pyrrolidin-1-yl)-2H-pyran-2-one (**3ja**). White solid (12 mg, 34% yield): mp 65.3−66.2 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 5.97 (s, 1H), 5.86 (d, J = 6.5 Hz, 1H), 3.40 (s, 4H), 2.18 (s, 3H), 1.94 (s, 4H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 157.2, 152.4, 133.2, 118.3, 108.1, 51.7, 25.4, 19.4. IR (KBr) ν 1711, 1638 cm^{-1}; HRMS (ESI) m/z calcd for $C_{10}H_{14}NO_2$ $[M + H]^+$ 180.1025, found 180.1019.

4,6-Diphenyl-3-(pyrrolidin-1-yl)-2H-pyran-2-one (**3la**). Bright yellow solid (45 mg, 71% yield): mp 114.8−115.7 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.77 (d, J = 7.6 Hz, 2H), 7.46−7.39 (m, 6H), 7.36 (dt, J = 14.5, 7.3 Hz, 2H), 6.64 (s, 1H), 3.19 (t, J = 6.4 Hz, 4H), 1.79−1.75 (m, 4H). ^{13}C NMR (151 MHz, CDCl3) δ 161.3, 150.6, 138.9, 136.3, 131.9, 130.7, 128.9, 128.7, 128.36, 128.30, 127.99, 124.4, 106.2, 51.2, 25.7. IR (KBr) ν 1698, 1627 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{20}NO_2$ $[M + H]^+$ 318.1494, found 318.1498.

3-(Piperidin-1-yl)-6-p-tolyl-2H-pyran-2-one (**3bb**). Yellow solid (50 mg, 93% yield): mp 102.3−105.7 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 6.58 (s, 2H), 3.12 (s, 4H), 2.39 (s, 3H), 1.77 (s, 4H), 1.63 (d, J = 5.1 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.8, 152.8, 139.4, 138.0, 129.5, 129.1, 124.5, 121.0, 101.1, 50.4, 25.7, 24.3, 21.3. IR (KBr) ν 1713, 1624 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{20}NO_2$ $[M + H]^+$ 270.1494, found 270.1491.

3-(Diethylamino)-6-p-tolyl-2H-pyran-2-one (**3bc**). Yellow liquid (50 mg, 97% yield): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (t, J = 12.0 Hz, 2H), 7.22 (d, J = 8.1 Hz, 2H), 6.59 (d, J = 7.5 Hz, 1H), 6.39 (d, J = 7.5 Hz, 1H), 3.38 (dd, J = 13.7, 6.8 Hz, 4H), 2.39 (s, 3H), 1.14 (t, J = 7.0 Hz, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 160.0, 151.5, 139.0, 134.9, 129.5, 129.1, 124.2, 119.8, 101.3, 44.3, 21.3, 12.1. IR (KBr) ν 1713, 1624 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$ 258.1494, found 258.1497.

3-(Dibutylamino)-6-p-tolyl-2H-pyran-2-one (**3bd**). Yellow liquid (57 mg, 91% yield): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 6.58 (d, J = 7.5 Hz, 1H), 6.39 (d, J = 7.5 Hz, 1H), 3.40−3.24 (m, 4H), 2.38 (s, 3H), 1.58−1.46 (m, 4H), 1.33 (tt, J = 14.6, 7.3 Hz, 4H), 0.94 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.9, 151.0, 138.8, 135.1, 129.5, 129.2, 124.1, 118.9, 101.4, 50.7, 29.3, 21.3, 20.4, 13.9. IR (KBr) ν 1714, 1624 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{28}NO_2$ $[M + H]^+$ 314.2120, found 314.2125.

3-(Butylamino)-6-p-tolyl-2H-pyran-2-one (**3bh**). White solid (10 mg, 18% yield):mp 106.2−107.3 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.61 (d, J= 8.2 Hz, 2H), 7.22 (t, J= 9.5 Hz, 2H), 6.62 (d, J= 7.5 Hz, 1H), 6.18 (d, J= 7.5 Hz, 1H), 3.11 (t, J= 7.1 Hz, 2H), 2.38 (s, 3H), 1.71−1.64 (m, 2H), 1.47 (dq, J= 14.7, 7.4 Hz, 2H), 0.99 (t, J= 7.4 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 160.4, 147.9, 138.5, 132.8, 129.4, 125.9, 123.8, 107.6, 102.3, 43.2, 30.6, 21.3, 20.3, 13.8. IR (KBr) ν 1691, 1623 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$ 258.1494, found 258.1491.

3-(Dodecylamino)-6-p-tolyl-2H-pyran-2-one (**3bi**). White solid (14 mg, 18% yield): mp 93.7−94.9 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 6.62 (d, J = 7.5 Hz, 1H), 6.08 (d, J = 7.5 Hz, 1H), 3.09 (t, J = 7.1 Hz, 2H), 2.38 (s, 3H), 1.67 (dt, J = 14.7, 7.2 Hz, 2H), 1.43 (ddd, J = 19.1, 8.8, 3.2 Hz, 4H), 1.37−1.28 (m, 14H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 160.5, 147.3, 138.3, 133.3, 129.4, 126.6, 123.7, 106.2, 102.4, 43.2, 31.9, 29.66, 29.64, 29.60, 29.56, 29.38, 29.36, 28.7, 27.2, 22.7, 21.2, 14.1. IR (KBr) ν 1705, 1629 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{36}NO_2$ $[M + H]^+$ 370.2746, found 370.2742.

6-(4-Methoxyphenyl)-3-(piperidin-1-yl)-2H-pyran-2-one (**3cb**). Yellow solid (46 mg, 81% yield): mp 128.6−130.5 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.68 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.56 (s, 1H), 6.48 (d, J = 7.5 Hz, 1H), 3.84 (s, 3H), 3.22−2.96 (m, 4H), 1.86−1.67 (m, 4H), 1.67−1.50 (m, 2H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 160.5, 159.9, 152.8, 137.5, 126.1, 124.5, 121.4, 114.2, 100.3, 55.4, 50.4, 25.6, 24.3. IR (KBr) ν 1721, 1619 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{20}NO_3$ $[M + H]^+$ 286.1443, found 286.1441.

6-(4-Chlorophenyl)-3-(piperidin-1-yl)-2H-pyran-2-one (**3db**). Yellow solid (42 mg, 73% yield): mp 94.1−96.3 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.67 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 6.59 (d, J = 6.8 Hz, 2H), 3.14 (s, 4H), 1.75 (s, 4H), 1.62 (d, J = 4.9 Hz, 2H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 159.3, 151.2, 135.1, 130.2, 129.0, 128.9, 125.7, 120.5, 102.0, 50.3, 25.5, 24.2. IR (KBr) ν 1715, 1627 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{17}ClNO_2$ $[M + H]^+$ 290.0948, found 290.0951.

6-(4-Chlorophenyl)-3-(diethylamino)-2H-pyran-2-one (**3dc**). Yellow liquid (45 mg, 81% yield): ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.66 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.01−6.13 (m, 2H), 3.48−3.34 (m, 4H), 1.21−1.13 (m, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 159.3, 140.0, 135.0, 130.2, 129.9, 129.0, 128.9, 125.5, 102.2, 22.0, 12.2. IR (KBr) ν 1714, 1624 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{17}ClNO_2$ $[M + H]^+$ 278.0948, found 278.0943.

6-(4-Chlorophenyl)-3-(dibutylamino)-2H-pyran-2-one (**3dd**). Yellow liquid (53 mg, 80% yield): ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.64 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.5 Hz, 2H), 6.59 (d, J = 7.6 Hz, 1H), 6.34 (s, 1H), 3.52−3.27 (m, 4H), 1.68−1.44 (m, 4H), 1.33 (tt, J =

20.7, 10.3 Hz, 4H), 0.93 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 159.4, 149.1, 135.6, 134.4, 130.4, 128.9, 125.2, 117.3, 102.5, 50.8, 29.3, 20.3, 13.9. IR (KBr) ν 1714, 1625 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{25}ClNO_2$ [M + H]$^+$ 334.1574, found 334.1576.

Ethyl 2,5-dioxo-5-p-tolylpentanoate (***4b***). Yellow liquid (53 mg, 80% yield): ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 5.0 Hz, 2H), 4.40 (q, *J* = 7.1, 2H), 3.40 (t, *J* = 6.2 Hz, 2H), 3.27 (t, *J* = 6.2 Hz, 2H), 2.44 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.0, 196.4, 163.9, 144.0, 134.5, 128.9, 127.9, 61.4, 37.1, 35.5, 21.1, 14.7. IR (KBr) ν 1724, 1676, 1604 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{16}O_4$ [M + H]$^+$ 249.1127, found 249.1125.

Ethyl 2-benzoyl-1-(morpholin-1-yl)cyclopropanecarboxylate (***5***). Yellow solid (53 mg, 88% yield): mp 208.9−211.3 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.41−7.29 (m, 3H), 5.22 (t, *J* = 2.7 Hz, 1H), 4.32 (q, *J* = 7.1 Hz,, 2H), 3.84−3.69 (m, 4H), 3.10 (qd, *J* = 18.0, 2.7 Hz, 2H), 2.97−2.84 (m, 2H), 2.68−2.55 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 170.3, 155.2, 130.1, 128.6, 128.3, 125.2, 101.2, 92.4, 66.7, 61.8, 46.3, 38.2, 14.2. IR (KBr) ν 1719, 1673, 1609 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{22}NO_4$ [M + H]$^+$ 304.1549, found 304.1544.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C NMR spectra for all compounds. X-ray structure of **3ba** and crystal data of **3ba** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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