Article

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Environmentally Sustainable and Chemo-selectively Favorable Synthesis of Substituted 2*H*-Pyran-2-ones in Water under MWI

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In this paper, a novel synthesis of diversely substituted 2*H*-pyran-2-ones *via* the tandem reaction of 3-hydroxyhexa-4,5-allenic esters in water under the promotion of MWI has been developed. Compared with those reactions carried out in organic solvents, water mediated synthesis of poly-substituted 2*H*-pyran-2-ones is not only environmentally sustainable, but also chemo-selectively favorable.

Keywords: 2*H*-Pyran-2-ones; Functionalized allenes; Water; Microwave irradiation; Green chemistry.

INTRODUCTION

2*H*-Pyran-2-one scaffold has attracted considerable interests since they are frequently found in a plethora of natural products.[1] Moreover, many 2*H*-pyran-2-ones exhibit a broad range of biological activities.[2] For example, 4-hydroxy-6-phenyl-3-(phenylthio)pyran-2-one (**I**, Figure 1) is an efficient HIV PR inhibitor with low micromolar affinity.[3] Phomenin (**II**) is isolated from the phytopathogenic fungus *Phoma tracheiphila,* which has remarkable phytotoxicity.[4] In another example, 6-pentyl-2-pyrone (**III**) demonstrates antimicrobial activity against *Rhizoctonia cerealis*, *Gaeumannomyces graminis* and *Botrytis cinerea*.[5] Bicyclic radicinin (**IV**) has been proved as a potential inhibitor to the germination of seeds of *Lepidum sativum*.[6] 3-Alkyl-6-chloro-2-pyrone (**V**), on the other hand, is a selective inhibitor of pancreatic cholesterol esterase.[7] The steroidal poaefusarin (**VI**) can prevent the germination of pea, beans and barley seed.[8]

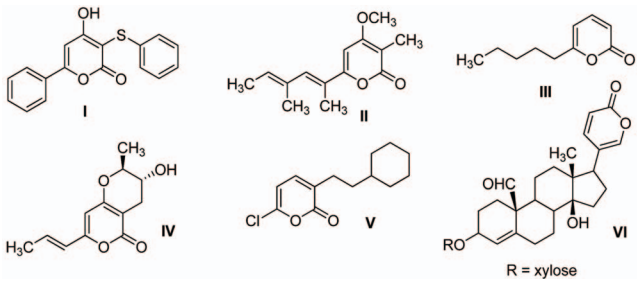

Fig. 1. 2*H*-Pyran-2-ones with remarkable biological activities.

Due to their importance, efficient methods for the preparation of 2*H*-pyran-2-ones have been extensively investigated and numerous synthetic strategies starting from different class of precursors have been established.[9-12] While these literature methods are generally efficient and reliable, some of them still suffer from difficult-to-obtain starting materials, expensive catalysts and reagents, delicate control of reaction conditions, or volatile and toxic solvents.

Nowadays, the development of environmentally friendly synthetic methods is one of the main priorities for modern chemistry. It has been well recognized that the volatile molecular organic solvents represent the biggest pollution problem in many synthetic processes. Therefore, elimination or replacement of hazardous solvents with environmentally benign ones has been intensively pursued. In this regard, water is considered as an ideal candidate since it is nontoxic, nonflammable, readily available and environmentally benign, thus providing unlimited opportunities for clean processing and pollution prevention.[13] Moreover, many organic reactions mediated by water showed unique properties compared with those carried out in hydrocarbon solvents.[14] Therefore, to develop synthetic procedures accomplished in water is an important aim for sustainable chemistry.[15]

Recently, we have developed an access toward diversely substituted 2*H*-pyran-2-ones through an acid promoted domino reaction of 3-hydroxyhexa- 4,5-allenic esters.[16] While the reaction itself is generally efficient and

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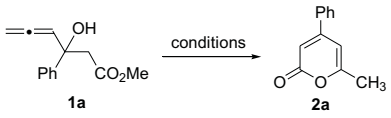
easy to perform, the solvent used therein, dichloromethane (CH_2Cl_2), is highly volatile and potentially hazardous. In addition, when the reaction was run in CH_2Cl_2, substrates with substituent on the internal position of the allene moiety afforded indenes as the major products, thus resulting in poor yields of the corresponding 2*H*-pyran-2-ones. As a continuation of our study with regard to water mediated organic reactions,[17] and considering that hydration is proposed as a key step in the formation of 2*H*-pyran-2-ones in the above described process,[16] we were curious if the selectivity for the formation of substituted 2*H*-pyran-2-ones could be improved in the presence of an excess amount of water. Herein we would like to report our preliminary results in this regard.

RESULTS AND DISCUSSION

Initially, 3-hydroxy-3-phenylhexa-4,5-dienoate (**1a**) was chosen as model substrate to study its reactivity in aqueous media. Thus, a suspension of **1a** in water in the presence of 10 mol% of H_2SO_4 was stirred at room temperature for 10 h, but the desired product, 6-methyl-4-phenyl-2*H*-pyran-2-one (**2a**), was only formed in trace amount (Table 1, entry 1). Mixed solvents did not improve the reaction obviously (entries 2-3). In further studies, we were pleased to find that the reaction could be improved significantly at increased temperatures (entries 3-7). When the reaction was run at 80 ºC for 10 h, **2a** could be obtained in a yield of 78% (entry 6). Under similar conditions, using TsOH as a catalyst gave much lower yield (entry 8). Furthermore, considering that many organic reactions progress much faster under microwave irradiation (MWI) than with conventional heating,[18] especially for reactions carried out in solvents with high dielectric constants such as water and alcohols, the reaction of **1a** in water was then run under the promotion of MWI. Inspiringly, with MWI, the period for a complete reaction shortened from 10 h to 0.5 h and the yield of **2a** amounted to 83% (entry 9). Based on the above results, the optimal conditions were identified as: treating **1a** with 10 mol% of H_2SO_4 in H_2O at 80 °C under MWI for 0.5 h. Under such conditions, **2a** was obtained in a yield of 83%.

With the optimized reaction conditions in hand, the scope of this transformation was studied. For this purpose, a series of 3-hydroxyhexa-4,5-dienoates (**2**) with different substitution patterns were treated with H_2SO_4 in water under MWI (Table 2). It turns out that this tandem reaction is not only suitable for substrates prepared from aryl substituted allenic ketones with various substituents on the aryl ring, but also compatible with substrates prepared from diaryl or alkyl, aryl disubstituted allenic ketones to give 4,6-disubstituted 2*H*-pyran-2-ones with good efficiency (Table 2, entries 1-16). Various functional groups such as methyl, methoxy, halides and cyano are well tolerated with the reaction conditions. In addition, from substrates prepared from 1,2-allenic ketones and 2-bromo-propanoate, 3,4,6-trisubstituted 2*H*-pyran-2-ones could also be obtained in good yields (Table 2, entries 17-19).

Table 1. Optimization study for the preparation of **2a** in aqueous media[a]



1a **2a**

Entry	Catalyst	Solvent	T (ºC)	t (h)	Yield (%)[b]
1	H_2SO_4	H_2O	r.t.	10	trace
2	H_2SO_4	H_2O/CH_3CN (5:1)	r.t.	10	trace
3	H_2SO_4	H_2O/THF (5:1)	r.t.	10	trace
4	H_2SO_4	H_2O	40	10	26
5	H_2SO_4	H_2O	60	10	52
6	H_2SO_4	H_2O	80	10	78
7	H_2SO_4	H_2O	100	10	78
8	TsOH	H_2O	80	10	52
9	H_2SO_4	H_2O	80	0.5	83[c]
10	H_2SO_4	H_2O	60	0.5	65[c]

[a] Reaction conditions: 0.5 mmol of **1a**, 0.05 mmol of catalyst, 5 mL of solvent; [b] Isolated yields; [c] Under MWI.

Furthermore, as mentioned previously, substrate with a substituent on the internal position of the allene moiety such as **1t** (Scheme I), afforded the corresponding 2*H*-pyran-2-one (**2t**) in low yield (25%) upon treatment with H_2SO_4 in CH_2Cl_2.[16] This is mainly due to the formation of substituted indene (**3a**, 61%). When **1t** was treated with H_2SO_4 in water under MWI, however, the formation of **3a** was suppressed and the yield of **2t** was remarkably in-

Scheme I Reaction of **1t** in different solvents

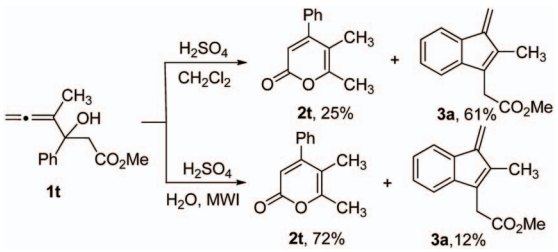
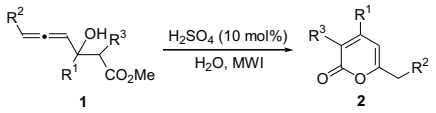


Table 2. Synthesis of 2*H*-pyran-2-ones (**2a**-**2s**) in water[a]



1 2

Entry	R^1	R^2	R^3	Product	Yield (%)[b]
1	Ph	H	H	**2a**	83
2	*p*-Cl-C_6H_4	H	H	**2b**	85
3	*p*-Br-C_6H_4	H	H	**2c**	85
4	*p*-CH_3-C_6H_4	H	H	**2d**	80
5	*p*-CH_3O-C_6H_4	H	H	**2e**	75
6	*p*-NC-C_6H_4	H	H	**2f**	88
7	*o*-F-C_6H_4	H	H	**2g**	78
8	*o*-Cl-C_6H_4	H	H	**2h**	77
9	*o*-Br-C_6H_4	H	H	**2i**	80
10	*o*-CH_3O-C_6H_4	H	H	**2j**	71
11	*m*-F-C_6H_4	H	H	**2k**	77
12	*m*-CH_3-C_6H_4	H	H	**2l**	72
13	Ph	Ph	H	**2m**	81
14	Ph	*p*-F-C_6H_4	H	**2n**	82
15	CH_3	Ph	H	**2o**	73
16	CH_3	*p*-F-C_6H_4	H	**2p**	72
17	Ph	H	CH_3	**2q**	82
18	*p*-CH_3O-C_6H_4	H	CH_3	**2r**	83
19	*p*-NC-C_6H_4	H	CH_3	**2s**	88

[a] Reaction conditions: **1** (0.5 mmol), H_2SO_4 (0.05 mmol), H_2O (5 mL), 80 ºC, MWI, 0.5 h. [b] Isolated yields.

creased from 25% to 72%. This is a promising result with regard to the much improved chemoselectivity toward the formation of 4,5,6-trisubstituted 2*H*-pyran-2-one.

The above results might be explained by a plausible mechanism shown in Scheme II.[16] Initially, acid promoted dehydration of **1t** affords 2,4,5-trienoate (**C**) *via* carbocation **A**. Subsequent hydration of **C** gives an enol (**D**). Intramolecular transesterification of **D** affords **2t**. On the other hand, the formation of **3a** is most likely through an *intramolecular* Friedel–Crafts reaction of carbocation **B**. The presence of a methyl group makes this alternative route possible since it can stabilize **B** and **E** due to the formation of a tetrasubstituted C-C double bond. When the reaction is run in CH_2Cl_2 as reported in our previous communication,[16] the relative stability of the cation intermediates (**B** and **E**) dominates the selectivity of the reaction and under this circumstance substituted indene **3a** is formed as a major product. When the reaction is run in water as described herein, on the other hand, the hydration of intemediate **C** is greatly facilited due to the presence of an excess amount of water. Therefore, the reaction mainly proceeds *via* intermediate **D**. In this case, the reaction gives substituted 2*H*-pyran-2-one (**2t**) as a major product.

Scheme II Plausible pathways for the reaction of **1t** run in different solvents

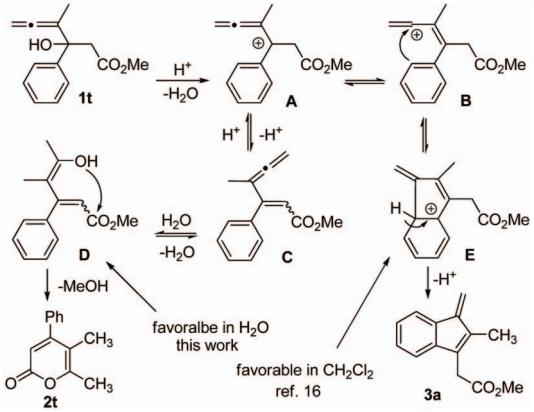
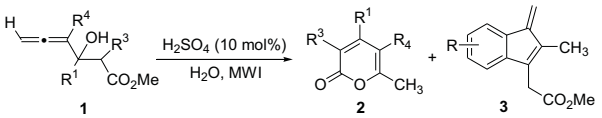


Table 3. Synthesis of diversely substituted 2*H*-pyran-2-ones (**2t**-**2ac**) in water[a]



1 2 3

Entry	R^1	R^3	R^4	Yield (%)[b]	
				2	**3**
1	Ph	H	CH_3	**2t**, 72 (25)[c]	**3a**, 12 (61)[c]
2	*p*-F-C_6H_4	H	CH_3	**2u**, 80 (22)[c]	**3b**, 9 (63)[c]
3	*p*-Cl-C_6H_4	H	CH_3	**2v**, 75 (31)[c]	**3c**, 11 (56)[c]
4	*p*-Br-C_6H_4	H	CH_3	**2w**, 78 (28)[c]	**3d**, 12 (55)[c]
5	*p*-CH_3-C_6H_4	H	CH_3	**2x**, 65 (23)[c]	**3e**, 15 (62)[c]
6	*p*-CH_3O-C_6H_4	H	CH_3	**2y**, 62 (24)[c]	**3f**, 18 (59)[c]
7	*p*-NC-C_6H_4	H	CH_3	**2z**, 82 (27)[c]	**3g**, 8 (53)[c]
8	*p*-Cl-C_6H_4	H	C_2H_5	**2aa**, 75 (27)[c]	**3h**, 13 (58)[c]
9	*p*-Br-C_6H_4	H	C_2H_5	**2ab**, 73 (25)[c]	**3i**, 10 (61)[c]
10	*p*-Cl-C_6H_4	CH_3	CH_3	**2ac**, 68 (26)[c]	**3j**, 8 (41)[c]

[a] Reaction conditions: **1** (0.5 mmol), H_2SO_4 (0.05 mmol), H_2O (5 mL), 80 ºC, MWI, 1 h. [b] Isolated yields. [c] Yields of reactions run in CH_2Cl_2.

The generality of the above process was demonstrated with a series of substrates (Table 3). This methodology allows efficient preparation of 4,5,6-tri-substituted or 3,4,5,6-tetrasubstituted 2*H*-pyran-2-ones bearing various functional groups. It is worth to be noted that in all cases 2*H*-pyran-2-ones (**2**) were obtained as major products rather than the corresponding indenes (**3**), thus resulting in a general, selective and mild synthetic protocol for synthesis of poly-substituted 2*H*-pyran-2-ones.

CONCLUSIONS

In summary, we have developed a novel synthesis of diversely substituted 2*H*-pyran-2-ones in water under MWI. Notable features of the above process include: 1) combination of water as an environmentally benign solvent for chemical transformations with the use of microwave irradiation as an efficient heating method; 2) enhanced chemoselectivity toward the formation of substituted 2*H*-pyran-2-ones in aqueous medium. With advantages such as high efficiency, favorable chemoselectivity and environmental benignancy, the synthetic method developed in this paper are expected to be used as valuable alternative protocol for the preparation of diversely substituted 2*H*-pyran-2-ones.

EXPERIMENTAL

General methods: The ^{1}H, ^{13}C NMR spectra were recorded at 400 MHz or 100 MHz, respectively. Chemical shifts were reported in ppm from tetramethylsilane (TMS) as internal standard in $CDCl_3$ solution. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets), etc. and coupling constants were given in Hz. High resolution mass spectra (HRMS) were performed on a time-of-flight (microTOF) mass spectrometer. The conversion of starting materials were monitored by thin layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm) and components were visualized by observation under UV light (254 and 365 nm). Microwave assisted reactions were performed in a commercial microwave reactor (XH-100A).

General procedure for the preparation of 2*H*-pyran-2-one (2): To a round-bottom flask containing 3-hydroxyhexa-4,5-dienoate (**1**, 0.5 mmol) in H_2O (5 mL) were added H_2SO_4 (0.05 mmol). The flask was put into the cavity of the microwave synthesis apparatus and irradiated at 300 W at 80 °C. Upon completion, it was cooled to room temperature and quenched with aqueous $NaHCO_3$. The mixture was extracted with ethyl acetate (5 mL × 3). The combined organic phases were dried, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel eluenting with ethyl acetate/hexane (1:10) to give 2*H*-pyran-2-one (**2a-2ac**, Table 2 and Table 3). From substrates **1t-1ac**, substituted indenes (**3a-3j**) were also obtained as minor products (Table 3).

6-Methyl-4-phenyl-2*H*-pyran-2-one (2a):[8] Yield (83%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 6.30 (s, 1H), 6.36 (s, 1H), 7.45-7.47 (m, 3H), 7.55-7.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2, 103.5, 108.1, 126.6, 129.1, 130.6, 135.8, 155.5, 162.1, 163.4. MS: *m/z* 187 $[MH]^+$. **4-(4-Chlorophenyl)-6-methyl-2*H*-pyran-2-one (2b):**[8] Yield (85%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 6.25 (s, 1H), 6.30 (s, 1H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2, 103.1, 108.2, 127.9, 129.4, 134.2, 136.8, 154.2, 162.5, 163.1. MS: *m/z* 221 $[MH]^+$. **4-(4-Bromophenyl)-6-methyl-2*H*-pyran-2-one (2c):**[16] Yield (85%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 6.24 (s, 1H, CH), 6.32 (s, 1H, CH), 7.42 (d, *J* = 8.0 Hz, 2H,), 7.60 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2, 103.0, 108.2, 125.1, 128.1, 132.4, 134.7, 154.3, 162.5, 163.1. MS: *m/z* 265 $[MH]^+$. **4-(4-Methylphenyl)-6-methyl-2*H*-pyran-2-one (2d):**[8] Yield (80%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 2.39 (s, 3H), 6.29 (s, 1H), 6.32 (s, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.1, 21.3, 103.3, 107.3, 126.5, 129.8, 132.8, 141.1, 155.3, 161.9, 163.5. MS: *m/z* 201 $[MH]^+$. **4-(4-Methoxyphenyl)-6-methyl-2*H*-pyran-2-one (2e):**[8] Yield (75%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.21 (s, 3H), 3.74 (s, 3H), 6.19 (s, 1H), 6.23 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 2H), 7.45 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.0, 55.4, 103.0, 106.1, 114.5, 127.5, 128.1, 154.7, 161.7, 161.8, 163.6. MS: *m/z* 217 $[MH]^+$. **4-(4-Cyanophenyl)-6-methyl-2*H*-pyran-2-one (2f):**[16] Yield (88%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3H), 6.25 (s, 1H), 6.32 (s, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2, 102.8, 109.7, 126.0, 127.4, 132.1, 132.9, 140.2, 153.5, 162.6, 163.1. MS: *m/z* 212 $[MH]^+$. **4-(2-Fluorophenyl)-6-methyl-2*H*-pyran-2-one (2g):**[16] Yield (78%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.19 (s, 3H), 6.17 (s, 1H), 6.21 (s, 1H), 7.05-7.16 (m, 2H), 7.31-7.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.9, 104.7, 111.0, 116.4, 116.6, 124.7, 124.8, 129.4, 131.9, 132.0, 151.1, 158.5, 161.0, 161.6, 162.8. MS: *m/z* 205 $[MH]^+$. **4-(2-Chlorophenyl)-6-methyl-2*H*-pyran-2-one (2h):**[16] Yield (77%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H), 6.11 (s, 1H), 6.13 (s, 1H), 7.23-7.34 (m, 3H), 7.41 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.0, 105.7, 112.0, 127.3, 129.7, 130.4, 130.6, 131.6, 135.9, 155.0, 161.4, 162.8. MS: *m/z* 221 $[MH]^+$. **4-(2-Bromophenyl)-6-methyl-2*H*-pyran-2-one (2i):**[16] Yield (80%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 3H), 6.10 (s, 1H), 6.14 (s, 1H), 7.24-7.29 (m, 2H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.0, 105.9, 112.1, 120.8, 127.8, 129.7, 130.7, 133.6, 138.1, 156.5, 161.4, 162.8. MS: *m/z* 265 $[MH]^+$. **4-(2-Methoxyphenyl)-6-methyl-2*H*-pyran-2-one (2j):**[16] Yield (71%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3H), 3.82 (s, 3H), 6.25 (s, 1H), 6.28 (s, 1H), 6.95-6.99 (m, 2H), 7.26-7.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.0, 55.5, 105.9, 111.0, 111.4, 121.0, 125.5, 129.5, 131.4, 154.5, 156.7, 160.4, 163.6. MS: *m/z* 217 $[MH]^+$. **4-(3-Fluorophenyl)-6-methyl-2*H*-pyran-2-one (2k):**[16] Yield (77%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.29 (s, 3H), 6.24 (s, 1H), 6.28 (s,

1H), 7.11-7.16 (m, 1H), 7.22 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.38-7.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.1, 103.1, 108.5, 113.5, 113.7, 117.3, 117.5, 122.3, 122.4, 130.8, 130.9, 137.9, 137.9, 154.1, 161.7, 162.5, 163.0, 164.2. MS: *m/z* 205 $[MH]^+$. **4-(3-Methylphenyl)-6-methyl-2*H*-pyran-2-one (2l):**[16] Yield (72%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.24 (s, 3H), 2.35 (s, 3H), 6.25 (s, 2H), 7.22-7.29 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.0, 21.3, 103.5, 107.8, 123.7, 127.2, 129.0, 131.3, 135.6, 138.8, 155.6, 162.0, 163.3. MS: *m/z* 201 $[MH]^+$. **6-Benzyl-4-phenyl-2*H*-pyran-2-one (2m):**[11a] Yield (81%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.86 (s, 2H), 6.22 (s, 1H), 6.35 (s, 1H), 7.26-7.38 (m, 5H), 7.44-7.55 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 40.3, 103.5, 108.6, 126.7, 127.4, 128.9, 129.1, 129.3, 130.6, 135.1, 135.7, 155.3, 163.1, 164.4. MS: *m/z* 263 $[MH]^+$. **6-(4-Fluorobenzyl)-4-phenyl-2H-pyran-2-one (2n):**[16] Yield (82%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.84 (s, 2H), 6.20 (s, 1H), 6.36 (s, 1H), 7.04 (t, J = 8.0 Hz, 2H), 7.27-7.29 (m, 2H), 7.45-7.52 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 39.4, 103.5, 108.7, 115.7, 115.9, 126.6, 129.1, 130.7, 130.75, 130.82, 135.7, 155.3, 163.0, 164.0. MS: *m/z* 281 $[MH]^+$. **6-Benzyl-4-methyl-2H-pyran-2-one (2o):**[16] Yield (73%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.05 (s, 3H), 3.74 (s, 2H), 5.72 (s, 1H), 5.92 (s, 1H), 7.24-7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 39.9, 106.4, 110.9, 127.3, 128.8, 129.2, 135.2, 156.2, 162.9, 163.4. MS: *m/z* 201 $[MH]^+$. **6-(4-Fluorobenzyl)-4-methyl-2*H*-pyran-2-one (2p):**[16] Yield (72%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.07 (s, 3H), 3.72 (s, 2H), 5.72 (s, 1H), 5.92 (s, 1H), 6.98-7.02 (m, 2H), 7.19-7.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.4, 39.0, 106.3, 111.0, 115.5, 115.8, 130.7, 130.8, 130.9, 156.1, 162.7, 163.1. MS: *m/z* 219 $[MH]^+$. **3,6-Dimethyl-4-phenyl-2H-pyran-2-one (2q):**[16] Yield (82%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.03 (s, 3H), 2.25 (s, 3H), 5.97 (s, 1H), 7.27-7.44 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 19.6, 106.6, 118.1, 127.8, 128.5, 128.7, 137.7, 152.0, 157.8, 164.8. MS: *m/z* 201 $[MH]^+$. **4-(4-Methoxyphenyl)-3,6-dimethyl-2*H*-pyran-2-one (2r):**[16] Yield (83%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.04 (s, 3H), 2.22 (s, 3H), 3.83 (s, 3H), 5.96 (s, 1H), 6.94 (d, J = 8.0 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 19.6, 55.3, 106.7, 113.9, 117.4, 129.5, 129.9, 151.7, 157.5, 159.9, 165.0. MS: *m/z* 231 $[MH]^+$. **4-(3,6-Dimethyl-2-oxo-2H-pyran-4-yl)benzonitrile (2s):**[16] Yield (88%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.01 (s, 3H), 2.27 (s, 3H), 5.91 (s, 1H, CH), 7.41 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 19.6, 105.5, 112.7, 117.5, 119.0, 128.7, 132.4, 142.2, 148.5, 158.6, 164.1. MS: *m/z* 226 $[MH]^+$. **5,6-Dimethyl-4-phenyl-2H-pyran-2-one (2t):**[11a] Yield (72%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83 (s, 3H), 2.29 (s, 3H), 6.06 (s, 1H), 7.21-7.24 (m, 2H), 7.40-7.42 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 18.1, 110.2, 112.1, 127.6, 128.5, 128.9, 158.3, 160.2, 162.6. MS: *m/z* 201 $[MH]^+$. **4-(4-Fluorophenyl)-5,6-dimethyl-2H-pyran-2-one (2u):** Yield (80%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83 (s, 3H), 2.29 (s, 3H), 6.05 (s, 1H), 7.10-7.14 (m, 2H), 7.21-7.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 18.2, 110.1, 112.4, 115.6, 115.8, 129.5, 129.6, 133.3, 133.4, 158.6, 159.2, 161.8, 162.5, 164.3. MS: *m/z* 219 $[MH]^+$. HRMS calcd for $C_{13}H_{12}FO_2$: 219.0821 [M+H], found: 219.0825. **4-(4-Chlorophenyl)-5,6-dimethyl-2*H*-pyran-2-one (2v):**[16] Yield (75%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.81 (s, 3H), 2.28 (s, 3H), 6.02 (s, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 18.1, 109.9, 112.2, 128.8, 129.0, 135.1, 135.7, 158.6, 158.9, 162.3. MS: *m/z* 235 $[MH]^+$. **4-(4-Bromophenyl)-5,6-dimethyl-2*H*-pyran-2-one (2w):**[16] Yield (78%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.82 (s, 3H), 2.29 (s, 3H), 6.03 (s, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.8, 18.2, 109.8, 112.2, 123.3, 129.3, 129.3, 131.8, 136.1, 158.7, 158.9, 162.3. MS: *m/z* 279 $[MH]^+$. **5,6-Dimethyl-4-p-tolyl-2*H*-pyran-2-one (2x):**[16] Yield (65%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83 (s, 3H), 2.27 (s, 3H), 2.37 (s, 3H), 6.03 (s, 1H), 7.12 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 18.1, 21.2, 110.3, 111.9, 127.6, 129.1, 134.4, 138.9, 158.2, 160.2, 162.7. MS: *m/z* 215 $[MH]^+$. **4-(4-Methoxyphenyl)-5,6-dimethyl-2H-pyran-2-one (2y):** Yield (62%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1. 88 (s, 3H), 2.30 (s, 3H), 3.85 (s, 3H), 6.06 (s, 1H), 6.94-6.96 (m, 2H), 7.19-7.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 18.2, 55.4, 110.4, 111.9, 113.9, 129.2, 129.6, 158.3, 159.9, 160.2, 162.9. MS: *m/z* 231 $[MH]^+$. HRMS calcd for $C_{14}H_{15}O_3$: 231.1021 [M+H], found: 231.1018. **4-(5,6-Dimethyl-2-oxo-2H-pyran-4-yl)benzonitrile (2z):**[16] Yield (82%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.80 (s, 3H), 2.30 (s, 3H), 6.04 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.7, 18.2, 109.3, 112.6, 112.9, 118.1, 128.4, 132.4, 141.8, 158.0, 159.2, 161.9. MS: *m/z* 226 $[MH]^+$. **4-(4-Chlorophenyl)-5-ethyl-6-methyl-2H-pyran-2-one (2aa):** Yield (75%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.84 (t, J = 7.2 Hz, 3H), 2.24 (q, J = 7.6 Hz, 2H), 2.30 (s, 3H), 6.00 (s, 1H), 7.16-7.19 (m, 2H), 7.39-7.41 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 17.7, 20.2, 113.0, 116.5, 128.81, 128.82, 134.9, 135.8, 158.92, 158.94, 162.3. MS: *m/z* 249 $[MH]^+$. HRMS calcd for $C_{14}H_{14}ClO_2$: 249.0682 [M+H], found: 249.0688. **4-(4-Bromophenyl)-5-ethyl-6-methyl-2H-pyran-2-one (2ab):** Yield (73%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.85 (t, J = 7.6 Hz, 3H), 2.25 (q, J = 7.6 Hz, 2H), 2.32 (s, 3H), 6.02 (s, 1H), 7.11-7.13 (m, 2H), 7.56-7.58 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 17.7, 20.2, 112.9, 116.5, 123.1, 129.1, 131.8, 136.3, 158.92, 158.94, 162.2. MS: *m/z* 293 $[MH]^+$. HRMS calcd

for $C_{14}H_{14}BrO_2$: 293.0177 [M+H], found: 293.0196. **4-(4-Chlorophenyl)-3,5,6-trimethyl-2H-pyran-2-one (2ac):**[16] Yield (68%), ^{1}H NMR (400 MHz, CDCl3) δ: 1.61 (s, 3H), 1.80 (s, 3H), 2.25 (s, 3H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 14.4, 17.7, 110.4, 119.9, 128.8, 129.1, 134.1, 135.5, 154.1, 154.4, 163.9. MS: *m/z* 249 $[MH]^+$. **Methyl 2-(2-methyl-1-methylene-1H-inden-3-yl)acetate (3a):**[16] Yield (12%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.13 (s, 3H), 3.58 (s, 2H), 3.68 (s, 3H), 5.70 (s, 1H), 6.01 (s, 1H), 7.14-7.26 (m, 3H) 7.53 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 31.6, 52.1, 110.5, 118.0, 119.2, 124.8, 128.1, 133.2, 134.9, 135.6, 143.0, 148.0, 171.0. MS: *m/z* 215 $[MH]^+$. **Methyl 2-(6-fluoro-2-methyl-1-methylene-1H-inden-3-yl) acetate (3b):** Yield (9%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.09 (s, 3H), 3.54 (s, 2H), 3.67 (s, 3H), 5.70 (s, 1H), 5.95 (s, 1H), 6.90-6.95 (m, 1H), 7.08-7.11 (m, 1H), 7.19-7.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 31.7, 52.2, 107.2, 107.5, 111.5, 114.1, 114.3, 118.7, 118.8, 132.8, 134.76, 134.80, 137.7, 137.8, 138.9, 147.3, 160.6, 163.0, 170.9. MS: *m/z* 233 $[MH]^+$. HRMS calcd for $C_{14}H_{14}FO_2$: 233.0978 [M+H], found: 233.0979. **Methyl 2-(6-chloro-2-methyl-1-methylene-1H-inden-3-yl) acetate (3c):**[16] Yield (11%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.09 (s, 3H), 3.53 (s, 2H), 3.67 (s, 3H), 5.70 (d, *J* = 2.0 Hz, 1H), 5.96 (d, *J* = 2.0 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 1H)), 7.19-7.20 (m, 1H), 7.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 31.5, 52.1, 111.8, 118.9, 119.8, 127.7, 130.8, 132.8, 135.3, 137.3, 141.4, 147.1, 170.7. MS: *m/z* 249 $[MH]^+$. **Methyl 2-(6-bromo-2-methyl-1-methylene-1H-inden-3-yl) acetate (3d):**[16] Yield (12%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.10 (s, 3H), 3.55 (s, 2H), 3.67 (s, 3H), 5.73 (s, 1H), 5.99 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 31.6, 52.2, 111.9, 118.8, 119.4, 122.6, 130.6, 132.8, 135.3, 137.6, 141.8, 147.1, 170.8. MS: *m/z* 293 $[MH]^+$. **Methyl 2-(2,6-dimethyl-1-methylene-1H-inden-3-yl)acetate (3e):**[16] Yield (15%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 2.44 (s, 3H), 3.60 (s, 2H), 3.71 (s, 3H), 5.68 (s, 1H), 6.00 (s, 1H), 7.11-7.17 (m, 2H), 7.40 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.8, 21.5, 31.7, 52.0, 109.9, 117.8, 120.3, 128.6, 133.3, 134.0, 136.0, 140.6, 148.2, 171.0. MS: *m/z* 229 $[MH]^+$. **Methyl 2-(6-methoxy-2-methyl-1-methylene-1H-inden-3-yl) acetate (3f):** Yield (18%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.08 (s, 3H), 3.54 (s, 2H), 3.67 (s, 3H), 3.83 (s, 3H), 5.64 (s, 1H), 5.95 (s, 1H), 6.75-6.78 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.9, 31.8, 52.2, 55.7, 106.8, 110.1, 112.4, 118.5, 133.1, 133.2, 136.2, 137.5, 148.0, 158.2, 171.1. MS: *m/z* 245 $[MH]^+$. HRMS calcd for $C_{15}H_{17}O_3$: 245.1177 [M+H], found: 245.1190. **Methyl 2-(6-cyano-2-methyl-1-methylene-1H-inden-3-yl) acetate (3g):**[16] Yield (8%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.15 (s, 3H), 3.57 (s, 2H), 3.67 (s, 3H), 5.84 (s, 1H), 6.08 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.70 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.1, 31.3, 52.2, 107.7, 113.7, 118.6, 119.8, 122.3, 132.4, 133.0, 136.0, 139.2, 146.2, 146.9, 170.4. MS: *m/z* 240 $[MH]^+$. **Methyl 2-(6-chloro-2-ethyl-1-methylene-1H-inden-3-yl)acetate (3h):** Yield (13%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (t, *J* = 7.6 Hz, 3H), 2.55 (q, *J* = 8.0 Hz, 2H), 3.56 (s, 2H), 3.68 (s, 3H), 5.74 (s, 1H), 6.01 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.47 (d, *J* = 1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.4, 18.1, 31.6, 52.2, 111.9, 119.2, 119.9, 127.8, 130.9, 132.2, 137.4, 141.3, 141.4, 145.7, 170.9. MS: *m/z* 263 $[MH]^+$. HRMS calcd for $C_{15}H_{16}ClO_2$: 263.0839 [M+H], found: 263.0843. **Methyl 2-(6-bromo-2-ethyl-1-methylene-1H-inden-3-yl) acetate (3i):** Yield (10%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (t, *J* = 7.6 Hz, 3H), 2.55 (q, *J* = 7.6 Hz, 2H), 3.55 (s, 2H), 3.67 (s, 3H), 5.75 (s, 1H), 6.02 (s, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.35-7.38 (m, 1H), 7.62 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 15.3, 18.0, 31.6, 52.2, 112.0, 118.9, 119.7, 122.7, 130.9, 132.3, 137.7, 141.4, 141.7, 145.7, 170.9. MS: *m/z* 307 $[MH]^+$. HRMS calcd for $C_{15}H_{16}BrO_2$: 307.0333 [M+H], found: 307.0346. **Ethyl 2-(6-chloro-2-methyl-1-methylene-1H-inden-3-yl) propanoate (3j):**[16] Yield (8%), ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.65 (t, *J* = 7.2 Hz, 3H), 1.47 (d, *J* = 7.2 Hz, 3H), 2.09 (s, 3H), 3.85-3.88 (m, 1H), 4.11-4.16 (m, 2H), 5.70 (s, 1H), 5.96 (s, 1H), 7.14-7.16 (m, 2H), 7.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.8, 14.1, 15.3, 37.4, 60.9, 111.4, 119.7, 119.8, 127.5, 130.6, 133.4, 137.8, 138.8, 140.1, 147.1, 173.7. MS: *m/z* 277 $[MH]^+$.

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