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Gold(I)-Catalyzed Tandem Alkoxylation/Lactonization of γ-Hydroxy-α,β-Acetylenic Esters

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Abstract: The formation of 4-alkoxy-2(5*H*)-furanones was achieved *via* tandem alkoxylation/lactonization of γ-hydroxy-α,β-acetylenic esters catalyzed by 2 mol% of [2,6-bis(diisopropylphenyl)imidazol-2-ylidine]gold bis(trifluoromethanesulfonyl)imidate [Au(IPr)(NTf_2)]. The economic and simple procedure was applied to a series of various secondary propargylic alcohols allowing for yields of desired product of up to 95%. In addition, tertiary propargylic alcohols bearing mostly cyclic substituents were converted into the corresponding spiro derivatives. Both primary and secondary alcohols reacted with propargylic alcohols at moderate temperatures (65–80 °C) in either neat reactions or using 1,2-dichloroethane as a reaction medium allowing for yields of 23–95%. In contrast to [Au(IPr)(NTf_2)], reactions with cationic complexes such as [2,6-bis(diisopropylphenyl)imidazol-2-ylidine](acetonitrile)gold tetrafluoroborate [Au(IPr)(CH_3CN)][BF_4] or (μ-hydroxy)bis{[2,6-bis(diisopropylphenyl)imidazol-2-ylidine]gold} tetrafluoroborate or bis(trifluoromethanesulfonyl)imidate – [{Au(IPr)}$_2$(μ-OH)][X] (X = BF_4, NTf_2) – mostly stop after the alkoxylation. Analysis of the intermediate proved the exclusive formation of the *E*-isomer which allows for the subsequent lactonization.

Keywords: alkoxylation; catalysis; furanones; gold; N-heterocyclic carbenes

Introduction

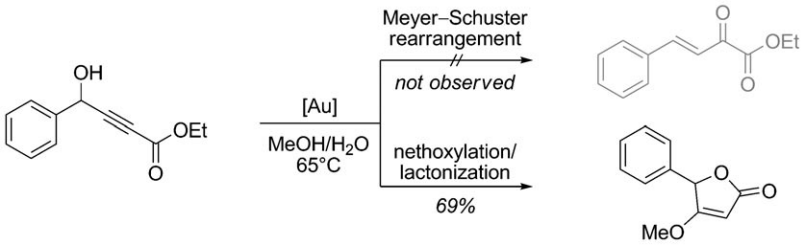
During the past decade the use of gold catalysis has developed into a research area of enormous and continuing growth.[1] In the course of explorative studies, Nolan et al. contributed, amongst others, with the gold catalyzed Meyer–Schuster rearrangement of propargylic alcohols.[2] In the context of scouting efforts in the course of this study, an unexpected reactivity for progargylic alcohols bearing ethyl esters in the acetylenic position was observed and the novel products formed using this method were identified as 4-alkoxy-2(5*H*)-furanones. Since furanones or tetronic acids are common motifs in natural products and of potential relevance in pharmaceutical applications,[3] further investigations on this reaction were undertaken (Scheme 1).

In the past, various approaches leading to furanones and tetronic acids have been devised.[3c,d,f,4] While 4-amino-2(5*H*)-furanones can be synthesized without use of a catalyst due to the basicity of the amine,[5] alcohols remain unreactive upon alkyne addition without prior activation and, to the best of our knowledge, only a few reports of methoxylated 2(5*H*)-furanones are present in the literature. These methods are in need of stoichiometric amounts of reagent or base.[3d,4e,i,6]

Teles and co-workers reported, in seminal work, the highly efficient gold-catalyzed alkoxylation of alkynes. This study indicated the significant potential of gold catalysis in this arena.[7] Here, we report the base-free gold-catalyzed formation of 4-alkoxy-2(5*H*)-furanones from a variety of propargylic alcohols using a simple and straightforward procedure.

Results and Discussion

For the present studies, IPr [IPr = 2,6-bis(disopropylphenyl)imidazol-2-ylidene] is the preferred ligand on gold for a number of reasons: [Au(IPr)Cl] (**C1**) proved an excellent choice for both the Meyer–Schus-



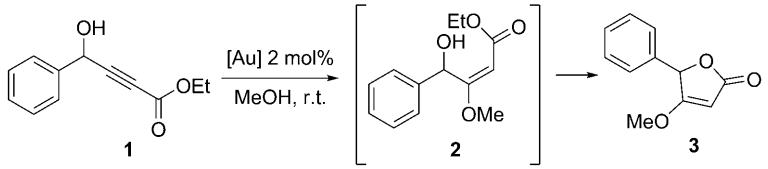
Scheme 1. 2(5*H*)-Furanone formation as observed in an earlier contribution by Nolan et al.[2]

ter rearrangement[2] as well as for the related alkyne hydration reaction[8] and it is commercially available and therefore easily accessible to synthetic chemists.[9] It was decided, however, to target the use of a well-defined catalyst and move from the two-component catalytic system [Au(IPr)Cl]/$AgSbF_6$, already shown to be active in the present targeted transformation, to single component species, such as [Au(IPr)(NTf_2)] (**C2**),[10] [Au(IPr)(CH_3CN)][BF_4] (**C3**), [{Au(IPr)}$_2$(μ-OH)][BF_4] (**C4**) and [{Au(IPr)}$_2$(μ-OH)][NTf_2] (**C5**),[11] in order to avoid the use of sensitive silver(I) salts.[12] Interestingly, results of this narrow catalyst screening revealed superior conversions with [Au(IPr)(NTf_2)]. The methoxylation of the propargylic alcohol **1a** occurred rapidly for all catalysts tested. However, the conversion of the intermediate **2a** into the 2(5*H*)-furanone **3a** was accelerated in the case of **C2** allowing for full conversion to the corresponding furanone after 3 h at room temperature. This was a rather unexpected result considering the estimated (based on NMR data) lower Lewis acidity of **C2** compared to **C3–C5** (Table 1). The increased conversion with **C5** in comparison to **C4** raises the possibility of a slight counteranion effect in the lactonization step.

Next, **C2** was tested in a substrate screening in order to evaluate the scope of the catalytic system. In order to facilitate analysis and shorten reaction times, the operational reaction temperature was raised to 65 °C and a standard reaction time of 2 h was used. As illustrated in Table 2, the catalytic system tolerated a broad spectrum of substrates and good to excellent yields were obtained. Both mesityl and naphthyl substituents on the propargylic alcohol allowed for conversion into their corresponding furanones **3b** and **3c** (Table 2, entries 2 and 3) as well as a series of substituted phenyl groups bearing both electron-withdrawing as well as electron-donating functional groups in the *para* position (Table 2, entries 4–7). It should be noted that in some cases the reaction time had to be prolonged to 12 h in order to provide complete conversion of the methoxylated intermediates. While in the case of the electron-donating *para*-phenoxy-substituted propargylic alcohol a 57% yield of **3d** could be obtained after 2 h reaction time, its electron-withdrawing nitro-substituted congener showed only ~55% NMR conversion after 2 h and required 12 h heating to finally yield 68% of the furanone **3e**. In the same manner, the halogenated substrates required prolonged reaction times (Table 2, entries 6 and 7). Encouraged by the initial results, both furan and thiophene derivatives were prepared and tested in the catalysis. The yields of their corresponding furanones **3h** and **3i** after the standard 2 h reaction time were 65 and 51%, respectively (Table 2, entries 8 and 9).

The scope was then expanded to a series of aliphatic substituents. While isobutyl- and *tert*-butyl-substituted propargylic alcohols converted in good yields into their corresponding furanones **3k** and **3l** (Table 2,

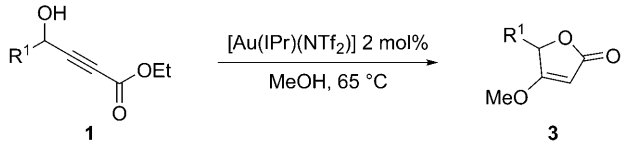
Table 1. Catalyst screening.[a]



Entry	Catalyst	$C_{Carbene}$ [ppm]	$H_{Imidazole}$ [ppm]	**2**[b]	**3**[b]
1	[Au(IPr)(NTf_2)] (**C2**)	168.9	7.33	45	55
2	[Au(IPr)(CH_3CN)][BF_4] (**C3**)	166.3	7.38	90	10
3	[{Au(IPr)}$_2$(μ-OH)][BF_4] (**C4**)	162.6	7.26	95	5
4	[{Au(IPr)}$_2$(μ-OH)][NTf_2] (**C5**)	162.9	7.25	83	17

[a] Reaction time was 3 h.
[b] Values are in %; conversions were determined by NMR.

Table 2. Scope of the Au(I)-catalyzed methoxylation/lactonization.



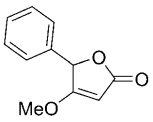
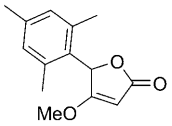
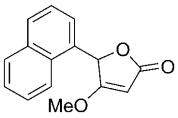
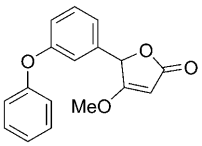
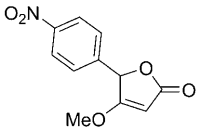
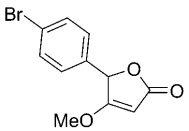
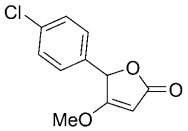
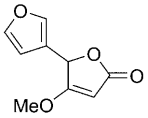
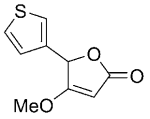
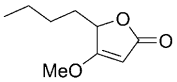
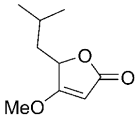
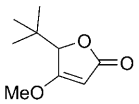
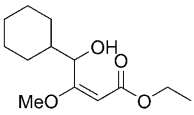
Entry	2(5*H*)-Furanone	**3**	Yield [%][a]
1		**3a**	71
2		**3b**	43
3		**3c**	95[b]
4		**3d**	57
5		**3e**	68[b]
6		**3f**	68[b]
7		**3g**	87[b]
8		**3h**	65
9		**3i**	51
10		**3j**	82
11		**3k**	71

Table 2. (Continued)

Entry	2(5*H*)-Furanone	**3**	Yield [%][a]
12		**3l**	76
13		**3m**	64[b]

[a] Isolated yields.
[b] Reaction time was prolonged to 12 h.

entries 11 and 12), surprisingly 4-cyclohexyl-4-hydroxybut-2-ynoate remained idle at the intermediate stage, even after heating for 12 h (Table 2, entry 13).

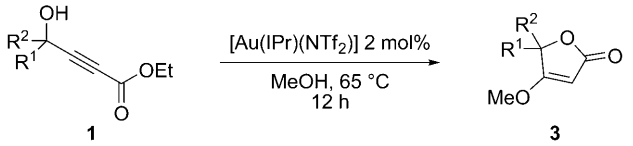
After evaluation of the scope for secondary alcohols, a series of tertiary alcohols was tested under similar reaction conditions. The reaction times were however increased to 12 h. In an initial attempt, the acyclic tertiary propargylic alcohol did convert (Table 3, entry 1) and delightfully, a 75% yield of the expected furanone **3n** was obtained.

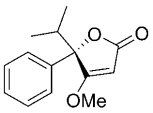
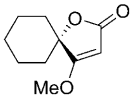
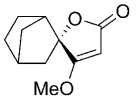
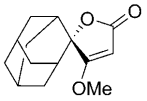
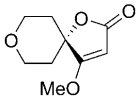
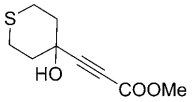
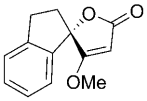
Cyclic substrates were next considered, as they would allow for rather interesting spiro compounds. As shown in Table 3, good to excellent conversions were observed for these tertiary alcohols. We began with a cyclohexyl-substituted propargylic alcohol (Table 3, entry 2), which resulted in a pleasing 82% yield. This scope was extended to the bicyclic norbonane derivative yielding an excellent 92% yield of **3p** followed by the adamantyl-substituted which afforded 61% of **3q** (Table 3, entries 3 and 4).

In a logical extension, heterocyclic substrates were tested and revealed an interesting and surprising anomaly. While the tetrahydropyran derivative converted, as expected, into the cyclized spiro-derivative in excellent 97% yield (Table 3, entry 5), the tetrahydrothiopyran derivative reacted following a completely different pathway. While the propargylic alcohol did not react at all, a transesterification of the ester moiety was observed and the methoxy ester was isolated in a 69% yield (Table 3, entry 6). It remains unclear how sulfur, which is most likely responsible, is interacting with the catalytic system to cause such a radical change in reactivity compared to its cyclohexyl and tetrahydropyran analogues.

Apart from the study of substrate scope of the present catalytic system, the tolerance for different alcohols also appeared to be of major interest since earlier reports were limited to the addition of methanol to the alkyne moiety. Therefore, a series of alcohols was tested. Taking into account the higher steric demands of most alcohols investigated, the standard reaction temperature was increased to 80 °C. Moreover, in

Table 3. Scope of the Au(I)-catalyzed methoxylation/lactonization of tertiary propargylic alcohols.



Entry	2(5*H*)-Furanone	**3**	Yield [%][a]
1		**3n**	75
2		**3o**	82
3		**3p**	92
4		**3q**	61
5		**3r**	97
6		**3s**	69
7		**3t**	53

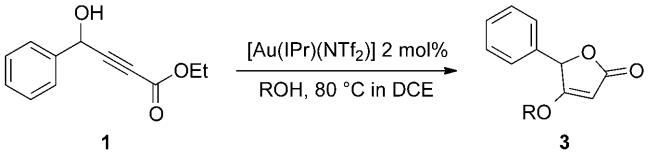
[a] Isolated yields.

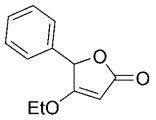
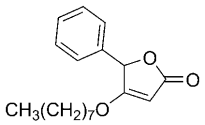
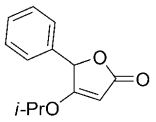
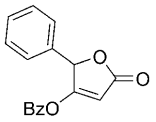
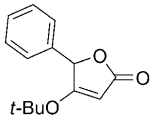
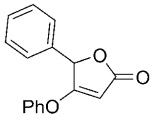
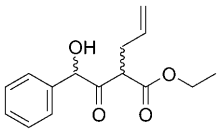
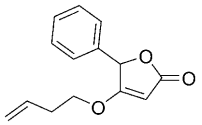
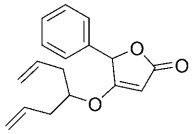
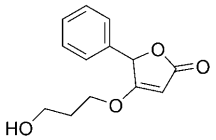
order to ensure an easy work-up, the reactions were performed either in neat conditions for alcohols such as ethanol and isopropyl alcohol or in 1,2-dichloroethane for, for example, octanol, depending on the actual boiling point, availability and toxicity of the alcohol selected.

In comparison to methanol, primary alkyl alcohols like ethanol (Table 4, entry 1) as well as octanol (Table 4, entry 2) allowed for slightly diminished but still acceptable yields of 67% for **3u** and 54% for **3v**. Moreover, a moderate yield of 48% for **3w** was also obtained using isopropyl alcohol (Table 4, entry 3) representing an example of a secondary alcohol being compatible with the methodology. Moving to benzyl alcohol, 58% of **3x** could be obtained (Table 4, entry 4). As expected, reactions with *tert*-butyl alcohol and phenol (Table 4, entries 5 and 6) failed due to their steric and electronic properties.[7,13]

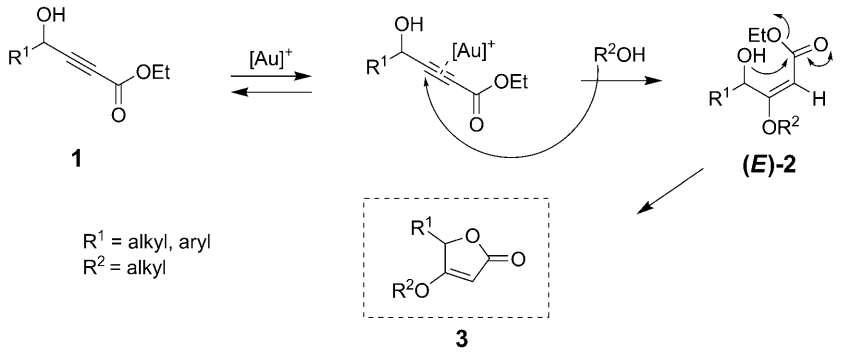
Next, a reaction with allyl alcohol was envisioned (Table 4, entry 7). The reasoning for this test was to

Table 4. Reaction of **1a** with various alcohols.



Entry	2(5*H*)-Furanone	**3**	Yield [%][a]
1		**3u**	67[b]
2		**3v**	54
3		**3w**	48[b]
4		**3x**	58
5		**3y**	nr
6		**3z**	nr
7		**3aa**	33
8		**3ab**	51[c]
9		**3ac**	23[c]
10		**3ad**	65[c]

[a] Isolated yields.
[b] Reaction performed at 65 °C using the alcohol as solvent.
[c] 12 h heating.



Scheme 2. Proposed mechanism for the gold-catalyzed furanone formation.

allow for a Claisen rearrangement following the alkoxylation/lactonization step yielding the interesting 5-phenyl-3-vinylfuran-2,4(3*H*,5*H*)-dione.[14] Unfortunately, under the given reaction conditions the Claisen rearrangement proceeded prior to lactonization yielding 33% of **3aa** (Table 4, entry 7). This reactivity pattern is attributed to a significant decrease of the activation barrier for the Claisen rearrangement by gold. The reaction usually requires heating at over 100 °C to proceed.

However, changing to homoallyl alcohol the regular alkoxylated furanone **3ab** was obtained in 51% yield (Table 4, entry 8). Reaction of a functionalized secondary alcohol was realized using 1,6-heptadien-4-ol. The yield of **3ac** was however notably diminished to 23% (Table 4, entry 9) in comparison to **3ab**. To conclude, 1,3-propanediol was subjected to this catalysis and 65% of the corresponding **3ad** was isolated (Table 4, entry 10).

In terms of mechanism, the proposal is straightforward (Scheme 2). Due to the observation of the key intermediate **2**, evaluation of the *E/Z* configuration was most important in order to distinguish between an *E/Z* isomerization of **2** allowing for full conversions or alternatively an initial *E*-selectivity of the gold-catalyzed alkoxylation. Therefore, catalyst **C4** was used to obtain **2** selectively followed by analysis using an NOE (nuclear Overhauser effect) experiment. The NOESY-NMR obtained exclusively showed NOE contacts between the methyl vinyl ether and the vinyl proton supporting a selective formation of the *E*-isomer which directly allows lactonization. As a consequence of these NOE experimental results, the initially envisioned isomerization of (possibly formed) *Z*-isomers does not need to be invoked.[2] Moreover, this would represent a rare example of *syn*-addition in gold catalysis.[15] which is however strongly related to the unique substrate properties.

Conclusions

An efficient catalytic system for the synthesis of alkoxylated furanones has been developed. With respect to the lactonization step, [Au(IPr)(NTf_2)] proved more efficient than digold or gold-nitrile complexes. The catalyst and method permit, in some instances, for the potentially useful exclusive alkoxylation without following lactonization. The new catalytic system tolerates numerous propargylic alcohols, both secondary and tertiary with various primary and secondary alcohols allowing for the assembly of a significant variety of furanones.

Experimental Section

Unless otherwise stated, manipulations were performed under air. Solvents were of *puriss* grade and used as received. NMR spectra were recorded on 400 MHz and 300 MHz spectrometers at ambient temperature in $CDCl_3$. Chemical shifts are given in parts per million (ppm) with respect to TMS.

Procedure A

In a vial, [Au(IPr)(NTf_2)] (2 mol%) was added to a solution of the corresponding propargylic alcohol (100 mg, 1 equiv.) in MeOH (2 mL). The solution was stirred for 2 h at 65 °C and the resulting mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography using a gradient of pentane/ethyl acetate.

Procedure B

Analogous to procedure A, but with 12 h heating.

Procedure C

In a vial, [Au(IPr)(NTf_2)] (8.5 mg, 2 mol%) was added to a solution of **1a** (100 mg, 0.5 mmol) and the corresponding alcohol (1.1 equiv.) in DCE (2 mL). The solution was stirred for 6 h at 80 °C and the resulting mixture was concentrated under reduced pressure. The crude product was purified by

flash column chromatography using a gradient of pentane/ethyl acetate.

Synthesis of 4-Methoxy-5-phenylfuran-2(5*H*)-one (3a)

Following procedure A, a white solid was obtained, yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.41–7.38$ (m, 3H), 7.34–7.27 (m, 2H), 5.69 (s, 1H), 5.16 (s, 1H), 3.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.7$, 172.6, 134.1, 129.5, 129.0, 126.8, 88.3, 80.4, 59.8; HR-MS: $m/z = 191.0702$, calcd. for $C_{11}H_{11}O_3$: 191.0703.

Synthesis of 5-Mesityl-4-methoxyfuran-2(5*H*)-one (3b)

Following procedure A, an off-white was obtained; yield: 43%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.85$ (br. s., 2H), 6.20 (d, $J = 1.2$ Hz, 1H), 5.25 (d, $J = 1.2$ Hz, 1H), 3.86 (s, 3H), 2.50–2.10 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.7$, 172.9, 139.2, 138.2, 131.2, 129.7, 125.8, 89.7, 77.8, 59.8, 21.0; HR-MS: $m/z = 233.1164$, calcd. for $C_{14}H_{17}O_3$: 233.1172.

Synthesis of 4-Methoxy-5-(naphthalen-1-yl)furan-2(5*H*)-one (3c)

Following procedure B, a pale yellow oil was obtained; yield: 95%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.11$ (d, $J = 7.7$ Hz, 1H), 8.01–7.89 (m, 2H), 7.70–7.45 (m, 4H), 6.57 (s, 1H), 5.33 (d, $J = 1.0$ Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 182.3$, 172.8, 133.8, 131.4, 130.0, 129.8, 128.9, 126.8, 126.1, 125.3, 124.4, 123.0, 88.9, 77.2, 59.8; HR-MS: $m/z = 263.0682$, calcd. for $C_{15}H_{12}O_3Na$: 263.0684.

Synthesis of 4-Methoxy-5-(3-phenoxyphenyl)furan-2(5*H*)-one (3d)

Following procedure A, a colourless oil was obtained; yield: 57%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35–7.30$ (m, 3H), 7.13–6.95 (m, 6H), 5.63 (s, 1H), 5.13 (d, $J = 0.8$ Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.4$, 172.4, 157.8, 156.8, 136.0, 130.3, 130.0, 123.8, 121.3, 119.5, 119.2, 117.2, 88.4, 79.9, 59.8; HR-MS: $m/z = 283.0958$, calcd. for $C_{17}H_{15}O_4$: 283.0965.

Synthesis of 5-(4-Nitrophenyl)-4-methoxyfuran-2(5*H*)-one (3e)

Following procedure B, a pale orange solid was obtained; yield: 68%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.34–8.12$ (m, 2H), 7.64–7.43 (m, 2H), 5.78 (s, 1H), 5.18 (d, $J = 1.2$ Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.7$, 171.8, 148.5, 141.2, 127.4, 124.0, 88.3, 78.7, 60.1; HR-MS: $m/z = 236.0546$, calcd. for $C_{11}H_{10}O_5N$: 236.0553.

Synthesis of 5-(4-Bromophenyl)-4-methoxyfuran-2(5*H*)-one (3f)

Following procedure B, a white solid was obtained; yield: 68%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.52–7.49$ (m, 2H), 7.20–7.17 (m, 2H), 5.63 (s, 1H), 5.15 (d, $J = 1.0$ Hz, 1H), 3.84 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 181.3$, 172.3, 133.2, 132.1, 128.3, 123.6, 88.3, 79.5, 59.9; HR-MS: $m/z = 290.9632$, calcd. for $C_{11}H_9O_3Na^{79}Br$: 290.9633.

Synthesis of 5-(4-Chlorophenyl)-4-methoxyfuran-2(5*H*)-one (3g)

Following procedure B, a white solid was obtained; yield: 87%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44–7.31$ (m, 2H), 7.33–7.30 (m, 2H), 5.72 (s, 1H), 5.22 (d, $J = 1.0$ Hz, 1H), 3.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.3$, 172.3, 135.3, 132.6, 129.1, 128.0, 88.2, 79.4, 59.9; HR-MS: $m/z = 247.0136$, calcd. for $C_{11}H_9O_3NaCl$: 247.0138.

Synthesis of 4-Methoxy-5-(furan-3-yl)furan-2(5*H*)-one (3h)

Following procedure A, a yellow oil was obtained; yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.53–7.49$ (m, 1H), 7.41 (t, $J = 1.7$ Hz, 1H), 6.34 (dd, $J = 1.7$, 0.6 Hz, 1H), 5.69 (s, 1H), 5.15 (d, $J = 1.0$ Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 181.0$, 172.2, 144.0, 141.2, 119.6, 108.2, 88.6, 73.6, 59.8; HR-MS: $m/z = 203.0317$, calcd. for $C_9H_8O_4Na$: 203.0320.

Synthesis of 4-Methoxy-5-(thiophen-3-yl)furan-2(5*H*)-one (3i)

Following the procedure A, an orange solid was obtained; yield: 51%. ^{1}H NMR ($CDCl_3$, 300 MHz,): $\delta = 7.36–7.31$ (m, 2H), 7.02 (dd, $J = 5.0$, 1.4 Hz, 1H), 5.78 (s, 1H), 5.14 (d, $J = 1.0$ Hz, 1H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 181.2$, 172.3, 134.8, 126.9, 125.3, 124.1, 88.4, 76.6, 59.8; HR-MS: $m/z = 219.0086$, calcd. for $C_9H_8O_3NaS$: 219.0092.

Synthesis of 5-Butyl-4-methoxyfuran-2(5*H*)-one (3j)

Following procedure A, a white solid was obtained; yield: 82%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.10$ (d, $J = 0.8$ Hz, 1H), 4.79 (qd, $J = 3.7$, 0.4 Hz, 1H), 3.93 (s, 3H), 1.96–1.89 (m, 1H), 1.67–1.60 (m, 1H), 1.44–1.29 (m, 4H), 0.94 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 182.6$, 172.8, 88.6, 78.9, 59.4, 31.4, 26.3, 22.3, 13.8; HR-MS: $m/z = 193.0845$, calcd. for $C_9H_{14}O_3Na$: 193.0841.

Synthesis of 5-Isobutyl-4-methoxyfuran-2(5*H*)-one (3k)

Following procedure A, a colourless oil was obtained; yield: 71%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.00$ (d, $J = 0.9$ Hz, 1H), 4.73 (ddd, $J = 9.8$, 3.1, 0.7 Hz, 1H), 3.84 (s, 3H), 1.91–1.84 (m, 1H), 1.67–1.58 (m, 1H), 1.48–1.38 (m, 1H), 0.93 (d, $J = 3.1$ Hz, 3H), 0.91 (d, $J = 3.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 183.2$, 172.8, 88.2, 77.7, 59.4, 41.2, 24.9, 23.2, 21.8; HR-MS: $m/z = 193.0841$, calcd. for $C_9H_{14}O_3Na$: 193.0841.

Synthesis of 5-(*tert*-Butyl)-4-methoxyfuran-2(5*H*)-one (3l)

Following procedure A, a white solid was obtained; yield: 76%. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.08$ (d, $J = 0.9$ Hz, 1H), 4.42 (d, $J = 0.9$ Hz, 1H), 3.85 (s, 3H), 0.99 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz): $\delta = 182.3$, 172.8, 90.0, 86.1, 59.4, 34.9, 25.4; HR-MS: $m/z = 193.0847$, calcd. for $C_9H_{14}O_3Na$: 193.0841.

Synthesis of 5-(*E*)-Ethyl 4-Cyclohexyl-4-hydroxy-3-methoxybut-2-enoate (3m)

Following procedure B, a colourless oil was obtained; yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.24$ (s, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.99 (s, 3H), 3.75 (t, $J = 6.2$ Hz, 1H), 1.88–1.50 (m, 7H), 1.27 (t, $J = 7.1$ Hz, 3H), 0.96–1.24 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 171.3$, 165.5, 96.0, 78.3, 61.7, 60.0, 42.1, 29.8, 27.9, 26.4, 26.3, 26.1, 14.4; HR-MS: $m/z = 265.1423$, calcd. for $C_{13}H_{24}O_4Na$: 265.1416.

Synthesis of 5-Isopropyl-4-methoxy-5-phenylfuran-2(5*H*)-one (3n)

Following procedure B, an off-white solid was obtained; yield: 75%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$–7.45 (m, 2H), 7.40–7.27 (m, 3H), 4.97 (s, 1H), 3.86 (s, 3H), 2.49 (spt, $J = 6.8$ Hz, 1H), 0.92 (d, $J = 6.8$ Hz, 3H), 0.81 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 183.8$, 172.4, 138.5, 128.5, 128.1, 125.2, 89.6, 87.8, 59.7, 34.5, 16.7, 16.2; HR-MS: $m/z = 233.1172$, calcd. for $C_{14}H_{17}O_3$: 233.1172.

Synthesis of 5-(4-Methoxy)-1-oxaspiro[4.5]dec-3-en-2-one (3o)

Following procedure B, a pale orange solid was obtained; yield: 82%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.95$ (s, 1H), 3.86 (s, 3H), 1.54–1.83 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 186.4$, 172.2, 87.1, 83.9, 59.4, 33.1, 24.5, 21.8; HR-MS: $m/z = 205.0835$, calcd. for $C_{10}H_{14}O_3Na$: 205.0841.

Synthesis of 3′-Methoxy-5′*H*-spiro[bicyclo[2.2.1]-heptane-2,2′-furan]-5′-one (3p)

Following procedure B, an off-white solid was obtained; yield: 92%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.89$ (s, 1H), 3.85 (s, 3H), 2.35–2.28 (m, 2H), 2.16–1.81 (m, 3H), 1.70–1.28 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 185.5$, 172.4, 89.4, 86.5, 59.6, 46.1, 40.8, 38.5, 36.5, 27.4, 23.8; HR-MS: $m/z = 195.1015$, calcd. for $C_{11}H_{15}O_3$: 195.1016.

Synthesis of 3-Methoxy-5*H*-spiro[furan-2,2′-tricyclo-[3.3.1.1^{3,7}]decan]-5-one (3q)

Following procedure B, a colourless solid was obtained; yield: 61%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.99$ (s, 1H), 3.87 (s, 3H), 2.41–2.21 (m, 4H), 2.02–1.82 (m, 4H), 1.79–1.70 (m, 4H), 1.69–1.56 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 187.3$, 171.6, 88.2, 88.0, 59.5, 37.9, 36.4, 34.6, 33.3, 26.7, 26.3; HR-MS: $m/z = 257.1155$, calcd. for $C_{14}H_{18}O_3Na$: 257.1154.

Synthesis of 3′-Methoxy-5′*H*-spiro[bicyclo[2.2.1]-heptane-2,2′-furan]-5′-one (3r)

Following procedure B, a white solid was obtained; yield: 97%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.02$ (s, 1H), 3.99–3.86 (m, 5H), 3.79 (d, $J = 2.1$ Hz, 2H), 2.16–2.05 (m, 2H), 1.56–1.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 184.7$, 171.5, 87.8, 81.1, 63.7, 59.7, 33.1; HR-MS: $m/z = 185.0803$, calcd. for $C_9H_{13}O_4$: 185.0808.

Synthesis of Methyl 3-(4-Hydroxytetrahydro-2*H*-thiopyran-4-yl)propiolate (3s)

Following procedure B, an off-white solid was obtained; yield: 69%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.77$ (s, 3H), 2.90 (s, 1H), 2.81–2.68 (m, 4H), 2.27–2.17 (m, 2H), 2.03–1.92 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 153.9$, 89.2, 77.0, 67.5, 53.1, 39.7, 25.4; HR-MS: $m/z = 201.0581$, calcd. for $C_9H_{13}O_3S$: 201.0580.

Synthesis of 3-Methoxy-2′,3′-dihydro-5*H*-spiro[furan-2,1′-inden]-5-one (3t)

Following procedure B, a pale orange solid was obtained; yield: 53%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.48$–7.35 (m, 2H), 7.35–7.28 (m, 1H), 7.24–7.10 (m, 1H), 5.27 (s, 1H), 3.93 (s, 3H), 3.35–3.20 (m, 1H), 3.18–3.04 (m, 1H), 2.77–2.61 (m, 1H), 2.59–2.47 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 182.9$, 171.8, 145.1, 138.6, 130.1, 127.2, 125.2, 123.2, 92.9, 88.3, 59.7, 35.2, 30.2; HR-MS: $m/z = 217.0861$, calcd. for $C_{13}H_{13}O_3$: 217.0859.

Synthesis of 4-Ethoxy-5-phenylfuran-2(5*H*)-one (3u)

Following procedure A but with 6 h heating in ethanol, a pale yellow solid was obtained; yield: 67%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.46$–7.28 (m, 5H), 5.67 (s, 1H), 5.12 (d, $J = 1.0$ Hz, 1H), 4.27–3.86 (m, 2H), 1.35 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.7$, 173.0, 134.3, 129.4, 128.9, 126.7, 88.2, 80.5, 69.0, 14.0; HR-MS: $m/z = 204.0783$, calcd. for $C_{12}H_{12}O_3$: 204.0781.

Synthesis of 4-(Octyloxy)-5-phenylfuran-2(5*H*)-one (3v)

Following procedure C, a colourless oil was obtained; yield: 54%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.43$–7.35 (m, 3H), 7.35–7.28 (m, 2H), 5.67 (s, 1H), 5.10 (d, $J = 1.0$ Hz, 1H), 4.03 (td, $J = 6.5$, 9.8 Hz, 1H), 3.92 (td, $J = 6.5$, 9.8 Hz, 1H), 1.78–1.62 (m, 2H), 1.40–1.12 (m, 10H), 0.87 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 180.9$, 173.0, 134.4, 129.3, 128.8, 126.6, 88.1, 80.4, 73.3, 31.8, 29.1, 29.1, 28.3, 25.6, 22.7, 14.2; HR-MS: $m/z = 288.1718$, calcd. for $C_{18}H_{24}O_3$: 288.1720.

Synthesis of 4-Isopropoxy-5-phenylfuran-2(5*H*)-one (3w)

Following procedure A but with 6 h heating in isopropyl alcohol, a pale yellow solid was obtained; yield: 48%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.44$–7.26 (m, 5H), 5.63 (s, 1H), 5.08 (d, $J = 0.9$ Hz, 1H), 4.39 (spt, $J = 6.1$ Hz, 1H), 1.35 (d, $J = 6.1$ Hz, 3H), 1.21 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 179.7$, 173.3, 134.4, 129.3, 128.8, 126.8, 88.1, 80.7, 76.9, 21.4, 21.0; HR-MS: $m/z = 218.0939$, calcd. for $C_{13}H_{14}O_3$: 218.0937.

Synthesis of 4-(Benzyloxy)-5-phenylfuran-2(5*H*)-one (3x)

Following procedure C, a pale yellow solid was obtained; yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.47$–7.28 (m, 8H), 7.25–7.13 (m, 2H), 5.73 (s, 1H), 5.20 (d, $J = 0.9$ Hz,

1H), 5.08 (d, $J=11.8$ Hz, 1H), 5.01 (d, $J=11.8$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=180.2$, 172.7, 134.1, 133.9, 129.4, 129.1, 128.9, 127.7, 126.7, 89.4, 80.5, 74.5; HR-MS: $m/z=266.0938$, calcd. for $C_{17}H_{14}O_3$: 266.0937.

Synthesis of Ethyl 2-(2-Hydroxy-2-phenylacetyl)pent-4-enoate (3aa)

Following procedure C, a pale orange oil was obtained as a mixture of isomers; yield: 33%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.45$–7.12 (m), 5.65–5.50 (m), 5.30–5.20 (m), 5.10–4.89 (m), 4.82–4.64 (m), 4.27–3.92 (m), 3.78 (q, $J=7.1$ Hz), 3.71–3.50 (m), 2.63–2.20 (m), 1.27–1.09 (m), 0.97 (t, $J=7.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=204.4$, 203.8, 168.2, 168.1, 136.7, 136.4, 133.6, 133.5, 129.1, 129.1, 129.0, 128.1, 127.9, 118.3, 117.7, 80.6, 79.8, 62.0, 61.5, 53.7, 53.3, 33.5, 31.9, 14.2, 13.9; HR-MS: $m/z=285.1096$, calcd. for $C_{15}H_{18}O_4$: 285.1103.

Synthesis of 4-(But-3-enyloxy)-5-phenylfuran-2(5*H*)-one (3ab)

Following procedure C but with 12 h heating, a pale yellow solid was obtained; yield: 51%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.46$–7.27 (m, 5H), 5.77–5.58 (m, 2H), 5.12 (d, $J=1.3$ Hz, 1H), 5.10–5.05 (m, 1H), 5.05–5.00 (m, 1H), 4.15–4.03 (m, 1H), 4.03–3.93 (m, 1H), 2.45 (tq, $J=1.3$, 6.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=180.7$, 172.8, 134.3, 132.6, 129.4, 128.9, 126.6, 118.3, 88.4, 80.4, 72.1, 32.7; HR-MS: $m/z=230.0936$, calcd. for $C_{14}H_{14}O_3$: 230.0937.

Synthesis of 4-(Hepta-1,6-dien-4-yloxy)-5-phenylfuran-2(5*H*)-one (3ac)

Following procedure C but with 12 h heating, a pale yellow oil was obtained; yield: 23%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.59$–7.28 (m, 5H), 5.96–5.77 (m, 1H), 5.73 (s, 1H), 5.61–5.36 (m, 1H), 5.32–5.11 (m, 3H), 5.06–4.83 (m, 2H), 4.44–4.03 (m, 1H), 2.60–2.47 (m, 2H), 2.46–2.24 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta=180.0$, 173.1, 134.3, 132.3, 131.8, 129.4, 128.8, 126.8, 119.1, 119.0, 88.3, 82.8, 80.6, 37.5, 37.2; HR-MS: $m/z=293.1164$, calcd. for $C_{17}H_{18}O_3Na$: 293.1154.

Synthesis of 4-(3-Hydroxypropoxy)-5-phenylfuran-2(5*H*)-one (3ad)

Following procedure C but with 12 h heating, a pale yellow solid was obtained; yield: 65%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.51$–7.15 (m, 5H), 5.66 (s, 1H), 5.14 (d, $J=1.0$ Hz, 1H), 4.30–3.97 (m, 2H), 3.76–3.43 (m, 2H), 2.17 (br. s., 1H), 1.90 (quin, $J=6.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=180.9$, 173.2, 134.1, 129.4, 128.9, 126.6, 88.4, 80.5, 70.2, 58.5, 31.1; HR-MS: $m/z=234.0884$, calcd. for $C_{13}H_{14}O_4$: 234.0887.

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