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Hydroalkylation leading to heterocyclic compounds. Part 1: New strategies for the synthesis of polysubstituted 2*H*-pyran-2-ones

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ABSTRACT

Polysubstituted 2*H*-pyran-2-ones and 5,6-dihydro-2*H*-pyran-2-ones were synthesized via the MCRs initiated by the hydroalkylation of alkynoates with activated methylenes. Under the optimized reaction conditions, the desired products were obtained in 47–88% isolated yields. The experimental results showed that the groups on activated methylenes act important roles in the nucleophilic attack fashion.

1. Introduction

In recent years, the rapid assembly of molecular diversity from inexpensive available starting materials via multicomponent reactions (MCRs) is an important goal of synthetic organic chemistry.[1–4] Interestingly, some of these methodologies have become completely new tools to offer small heterocyclic molecules, which are frequently found in various biologically active compounds and potentially designed medicinal agents in medicinal chemistry.[5] To date, several groups have investigated MCRs for simple and straightforward preparation of substituted heterocycles, such as 1,3-oxazinane-2,4-diones,[6] polycyclic pyrrole-2-carboxylates,[7] 3-(diarylmethylene)oxindoles,[8] and so on. Thus, the exploration of new synthetic methods and molecular diversity around heterocycles remains a major challenge in modern organic synthesis.

In the context of our longstanding interest in the alkynes chemistry,[9] we employed alkynoates for MCRs to efficiently synthesize novel six-membered heterocycles, 1,4,5,6-tetrahydropyrimidines, 2,5-dihydro-1,3-oxazin-6-ones, and 3,6-dihydro-2*H*-1,3-oxazines, which were constructed via a domino hydroamination/Mannich-type reaction/hydration–cyclization sequence (left side in Scheme 1).[10] In view of the convergent and modular nature of these transformations, our attention is directed to a new type of MCRs: hydroalkylation of alkynoates with activated methylenes to construct different types of six-membered oxygen or nitrogen-containing heterocyclic compounds (right side in Scheme 1). Among these expectantly obtained heterocycles, 2*H*-pyran-2-ones and their analogues are not only valuable materials in diverse organic synthesis,[11] but also possess a diverse range of pharmacological activity[12] and biological activity. They have been reported as plant growth inhibitors, insect antifeedants,[13] antibiotic, and antitumoral agents.[14–17] In this paper, we wish to report the synthesis of polysubstituted 2*H*-pyran-2-ones and 5,6-dihydro-2*H*-pyran-2-ones via the MCRs initiated by the hydroalkylation of alkynoates with activated methylenes.

2. Results and discussion

At the outset of this work, our preliminary investigations began with diethyl but-2-ynedioate (**1a**) with dibenzoylmethane (**2a**). Ethyl 5-benzoyl-2-oxo-6-phenyl-2*H*-pyran-4-carboxylate (**3aa**) was obtained in 87% GC yield when the reaction was carried out by the aid of a stoichiometric amount of NaOH in dioxane at 80 °C for 1 h (Table 1, entry 3). As shown in Table 1, various temperatures, alkaline additives, and solvents were examined as the potential base and solvent for the desired domino reaction. It is exciting that the chosen bases and solvents, such as sodium hydroxide (NaOH), sodium ethoxide (EtONa), potassium *tert*-butoxide (*t*-BuOK), acetonitrile (CH_3CN), toluene, and dichloromethane (CH_2Cl_2) are suitable for the reactions (Table 1, entries 1–17). NaOH proves to be the best base (Table 1, entry 4) and dioxane the best solvent (Table 1, entry 4). As a result, the best yield was obtained by the use of 0.25 mmol of **1a**, 0.25 mmol of **2a**, and 1 equiv of NaOH in dioxane (2.0 mL) at 80 °C for 2 h.

With the optimized conditions in hand, we turned our attention to examine the scope of the reactions (Table 2). When several active methylene compounds were employed, the reaction proceeded smoothly and the desired trisubstituted 2*H*-pyran-2-ones were afforded in satisfactory yields (Table 2, entries 1–4). It is delighted that some less reactive carbon electrophiles such as alkynoates **1b** and **1c** could serve as good substrates in this domino addition–cyclization reaction (Table 2, entries 5–11). For examples, the

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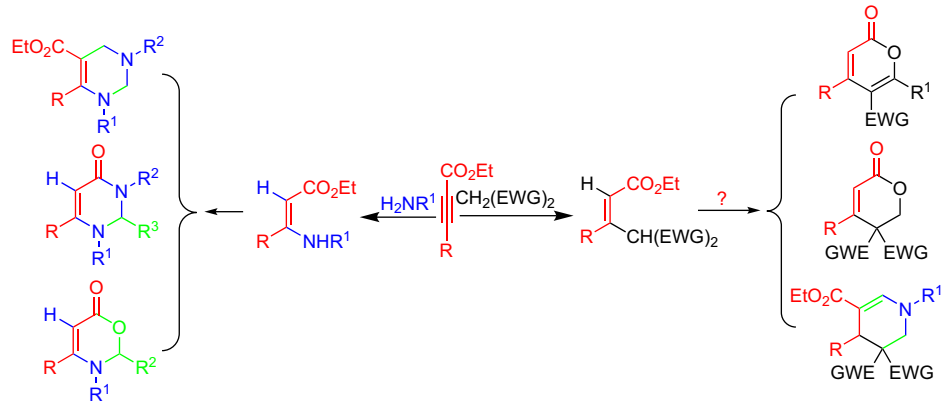
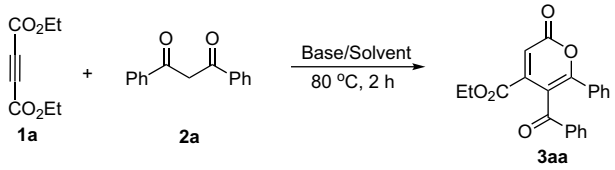


Scheme 1. Synthesis of six-membered heterocycles based on alkynoates.

Table 1
Optimization of reaction conditions[a]

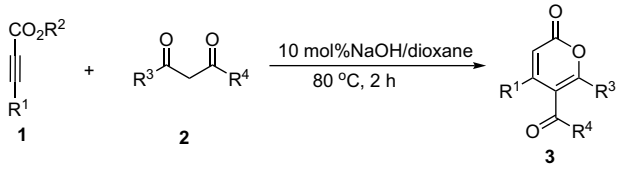


1a **2a** **3aa**

Entry	Alkaline additive	Solvent	Reaction time (h)	Yield[b] (%)
1	NaOH	Dioxane	1 (60 °C)	50
2	NaOH	Dioxane	1 (95 °C)	87
3	NaOH	Dioxane	1	87
4	NaOH	Dioxane	2	89
5	NaOH	Dioxane	3	89
6	Na_2CO_3	Dioxane	2	53
7	$NaHCO_3$	Dioxane	2	42
8	CH_3CO_2Na	Dioxane	2	59
9	EtONa	Dioxane	2	85
10	*t*-BuOK	Dioxane	2	75
11	None	Dioxane	2	39
12	NaOH	CH_3CN	2	88
13	NaOH	DMF	2	75
14	NaOH	DMSO	2	62
15	NaOH	THF	2	78
16	NaOH	CH_2Cl_2	2	86
17	NaOH	Toluene	2	84
18[c]	NaOH	Dioxane	2	88
19[d]	NaOH	Dioxane	2	87

[a] The reaction was carried out using 0.25 mmol of **1a**, 0.25 mmol of **2a**, and 1 equiv of alkaline in solvent (2.0 mL) at 80 °C for 2 h.
[b] GC yield.
[c] NaOH (10 mol %).
[d] NaOH (0.5 equiv).

Table 2
NaOH-induced domino synthesis of trisubstituted 2*H*-pyran-2-ones[a]



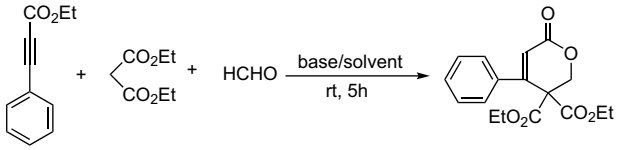
1 **2** **3**

Entry	1	2	3 (Yield %)[b]
1	**1a** (R^1=CO_2Et; R^2=Et)	**2a** (R^3=Ph; R^4=Ph)	**3aa** (85)
2	**1a**	**2b** (R^3=Ph; R^4=CH_3)	**3ab** (82)
3	**1a**	**2c** (R^3=CH_3; R^4=CH_3)	**3ac** (65)
4	**1a**	**2d** (R^3=CH_3; R^4=OEt)	**3ad** (68)
5	**1b** (R^1=Ph; R^2=Et)	**2a**	**3ba** (88)
6	**1b**	**2b**	**3bb** (83)
7	**1b**	**2c**	**3bc** (70)
8	**1b**	**2d**	**3bd** (69)
9	**1c** (R^1=*n*-C_5H_{11}; R^2=CH_3)	**2a**	**3ca** (84)
10	**1c**	**2b**	**3cb** (79)
11	**1c**	**2c**	**3cc** (59)
12	**1c**	**2d**	**3cd** (complex)

[a] All reactions were carried out using 1.0 mmol of **1** and 1.0 mmol of **2** in dioxane (2.0 mL) at 80 °C.
[b] Isolated yield.

reactions of **1b** or **1c** with **2a** afforded the corresponding products **3ba** and **3ca** with 88 and 84% isolated yields, respectively (Table 2, entries 5 and 9). It is not clear why the reaction of **1c** with **2d** generated a rather complicated mixture (Table 2, entry 12).

When ethyl 3-phenylprop-2-ynoate (**1b**) and diethyl propanedioate (**2e**) were used as the substrates, the reaction failed to afford the expected product. But it is interesting that when formaldehyde was added to the reaction mixture, another type of 2*H*-pyran-2-one analogue, diethyl 6-oxo-4-phenyl-2*H*-pyran-3,3(6*H*)-dicarboxylate (**4be**), was obtained in 82% isolated yield (Eq. 1 and Table 2, entry 6). This result showed clearly that the groups on activated methylenes could lead to different structures of 5,6-dihydro-2*H*-pyran-2-ones. When activated methylene such as dibenzoylmethane, 1-phenyl-1,3-butanedione, 2,4-pentanedione, ethyl acetoacetate was employed, the reaction only gave trisubstituted 2*H*-pyran-2-ones (**3**) even if formaldehyde was added beforehand.

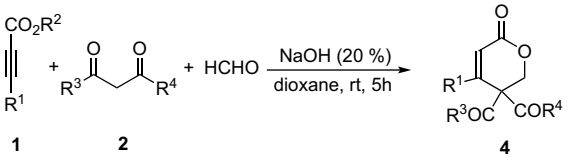


1b **2e** **4be** (1)

Representative optimization experiments were reported in Table 3. Activated methylene dibenzoylmethane could not give the 5,6-dihydro-2*H*-pyran-2-one derivatives just as shown in entries 1, 5, and 9 of Table 3. When employing diethyl propanedioate the reaction afforded the corresponding 5,6-dihydro-2*H*-pyran-2-ones with satisfactory yields (Table 3, entries 2, 6, 10, and 13). The yields were decreased to some extent along with the steric hindrance of activated methylenes (Table 3, entries 4, 8, and 12).

The proposed mechanism of these MCRs could be depicted as our hypothesis shown in Scheme 2. Our envisions all were initiated by highly active carbon anions **I** formed from activated methylenes **2** in the presence of the alkaline during the reaction, and then

Table 3
Synthesis of trisubstituted 5,6-dihydro-2*H*-pyran-2-ones[a]



1 2 4

Entry	1	2	4 (Yield %)[b]
1	**1a** (R^1=CO_2Et; R^2=Et)	**2a** (R^3=R^4=Ph)	**4aa** (trace)
2	**1a**	**2e** (R^3=R^4=OEt)	**4ae** (88)
3	**1a**	**2f**(R^3=OCH_2Ph; R^4=OEt)	**4af** (83)
4	**1a**	**2g** (R^3=R^4=OCH_2Ph)	**4ag** (78)
5	**1b** (R^1=Ph; R^2=Et)	**2a**	**4ba** (trace)
6	**1b**	**2e**	**4be** (82)
7	**1b**	**2f**	**4bf** (70)
8	**1b**	**2g**	**4bg** (50)
9	**1c** (R^1=*n*-C_5H_{11}; R^2=CH_3)	**2a**	**4ca** (trace)
10	**1c**	**2e**	**4ce** (80)
11	**1c**	**2f**	**4cf** (66)
12	**1c**	**2g**	**4cg** (47)
13	**1d** (R^1=CH_3; R^2=CH_3)	**2e**	**4de** (92)

[a] All the reactions were carried out using 1 mmol of **1**, 1 mmol of **2**, 2 mmol of formaldehyde, and 20% of NaOH in dioxane (6.0 mL) at room temperature for the desired reaction time.
[b] Isolated yield.

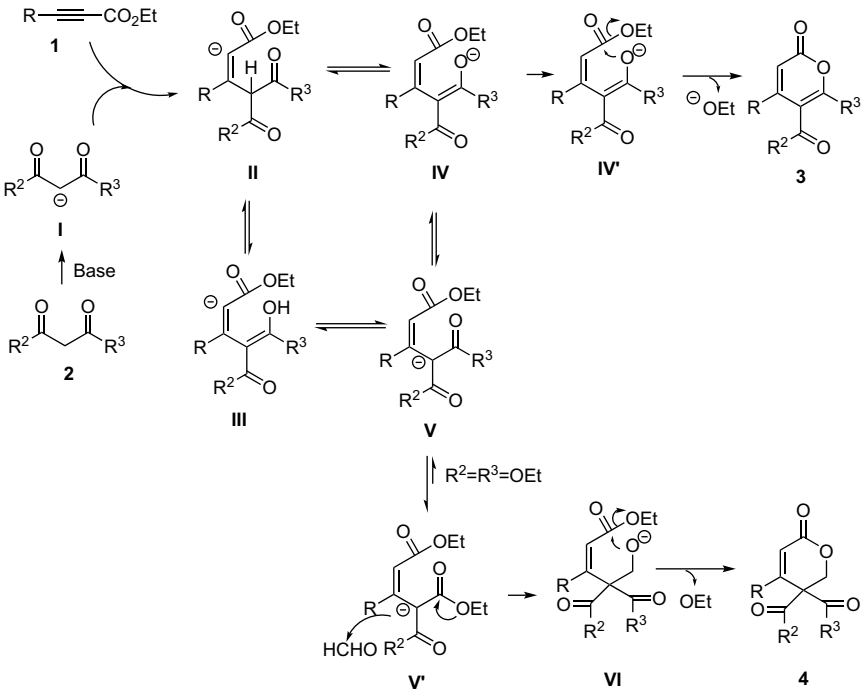
involved carbon nucleophilic attack on the carbon–carbon triple bond of alkynoates to form intermediate **II**, which the process has undergone base-induced intermolecular hydroalkylation of alkynoates. Single regioisomers shown in Tables 2 and 3 indicated that the nucleophilic attack of highly active carbon anions **I** on the carbon–carbon triple bond in alkynoates **1** played a dominant role on the regioselectivity.

Once intermediate **II** has been formed, it could exist in different resonance structures, such as **III**, **IV**, and **V**. At this stage, the presence of formaldehyde leads to two possible routes: oxygen nucleophilic attack to carbonyl carbon to form product **3** or carbon nucleophilic attack to formaldehyde to form intermediate **VI**. In comparison the results between Table 2 and Table 3, we easily found that the groups on activated methylenes act important roles in the nucleophilic attack fashion.

Table 4
Some data of 1,3-dicarbonyl compounds[18]

Entry	Compound	pK_a	Content of enol (%)
1	$CH_3COCH_2CO_2Et$	10.7	8.0
2	$CH_3COCH_2COCH_3$	9	76.4
3	$PhCOCH_2COCH_3$	9.6	89.2
4	$EtO_2CCH_2CO_2Et$	13	7.7×10^{-3}

Table 4 listed pK_a and content of enol of some dicarbonyl compounds, which could help us to explain why different results are obtained in the reaction system. The pK_a value of 1,3-dicarbonyl compounds indicated that the activated methylene C–H bond of ethyl 3-oxobutanoate, pentane-2,4-dione, and 1-phenylbutane-1,3-dione was more active than that of diethyl malonate. Due to the difference of C–H bond activity of activated methylene and the resonance phenomenon of keto–enol tautomerism in 1,3-dicarbonyl compounds, the pK_a value directly related with the enol content. For example, the enol content of 1-phenylbutane-1,3-dione reached to 89.2%, while on the other hand, the enol content of diethyl malonate was only 7.7×10^{-3}%. These data implied that the non-ester 1,3-dicarbonyl compounds were easily converted to enol resonance structures than that of ester 1,3-dicarbonyl compounds. The former favored directly oxygen nucleophilic attack to carbonyl carbon to form product **3**, and the latter favored carbon nucleophilic attack to formaldehyde to form intermediate **VI**, following intramolecular oxygen nucleophilic attack to carbonyl carbon to form product **4**. These may explain our experimental phenomenon that non- or single-ester dicarbonyl compounds react with alkynoates leading to trisubstituted 2*H*-pyran-2-ones, and diester malonate reacts with alkynoates leading to trisubstituted 5,6-dihydro-2*H*-pyran-2-ones.



Scheme 2. Proposed mechanism for the synthesis of 2*H*-pyran-2-ones and 5,6-dihydro-2*H*-pyran-2-ones.

3. Conclusion

We have disclosed highly efficient methods for the synthesis of polysubstituted 2*H*-pyran-2-ones and 5,6-dihydro-2*H*-pyran-2-ones, which were formed via domino reactions all initiated by the hydroalkylation of electron-deficient of alkynoates with activated methylenes. These reactions offered a convenient entry into several interesting heterocyclic structures, which will represent a privileged medicinal scaffold. Armed with a clear mechanistic understanding of this intriguing process, we are pursuing further studies to uncover the reaction conditions necessary for selective, high yielding synthesis of each one of these corresponding products. It is reasonable to assume that, in due course, other alkynoates, activated methylenes, aldehydes, amines or related compounds that can find application in these reactions would emerge. It is expected that this class of reactions will attract the attention of synthetic organic chemists in the near future.

4. Experimental

4.1. General

All the reactions were carried out at 80 °C in a round bottom flask equipped with magnetic stir bar for 2 h. Solvents and all reagents were used as received. ^{1}H NMR spectra was recorded in CD_3COCD_3 at 400 MHz and ^{13}C NMR spectra were recorded in CD_3COCD_3 at 100 MHz in the Guangzhou Institute of Chemistry, Chinese Academy of Sciences. Respectively, the chemical shifts (d) were referenced to TMS. GC–MS was obtained using electron ionization (EI). IR spectra were obtained as potassium bromide pellets or as liquid films between two potassium bromide pellets with a Brucker Vector 22 spectrometer. TLC was performed using commercially prepared 100–400 mesh silica gel plates (GF_{254}) and visualization was effected at 254 nm. All the other chemicals were purchased from Aldrich Chemicals.

4.2. Typical procedure for the reaction of diethyl but-2-ynedioate with dibenzoylmethane

A mixture of **1a** (170 mg, 1 mmol), **2a** (224 mg, 1 mmol), and NaOH (4 mg, 0.1 mmol) in dioxane (2 mL) was heated with stirring in a round bottom flask at 80 °C for 2 h. After cooling, the reaction was diluted with water and extracted with diethyl ether. The ether layer was washed with saturated salt water and dried with anhydrous $MgSO_4$. The resulting mixture was then analyzed by GC and GC–MS. Volatiles were removed in vacuum and the crude product was subjected to isolation by preparative TLC (GF_{254}), eluted with a 10:2 petroleum ether–diethyl ether mixture. Compound **3aa** as pale yellow solid was isolated in 296 mg (85%), after removal of the solvent.

*4.2.1. Ethyl 5-benzoyl-2-oxo-6-phenyl-2H-pyran-4-carboxylate (**3aa**)*

Pale yellow solid; IR ν_{max} (KBr): 3060, 2989, 2939, 1742, 1732, 1659, 1596, 1581, 1449, 1393, 1366, 1262, 1106, 792, 745, 697 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ ppm=1.04 (t, 3H, J=7.2 Hz), 4.10 (q, 2H, J=7.2 Hz), 6.80 (1H), 7.30–7.87 (m, 10H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=192.44, 163.51, 161.02, 159.94, 146.26, 137.17, 133.51, 131.74, 131.01, 129.25, 128.70, 128.55, 128.46, 115.75, 115.44, 62.36, 12.91; GC–MS m/z (% rel inten.): 347.87 (M^+, 43.02), 104.87 (100). Anal. Calcd for $C_{21}H_{16}O_5$: C, 72.41; H, 4.63. Found: C, 72.21; H, 4.92.

*4.2.2. Ethyl 5-acetyl-2-oxo-6-phenyl-2H-pyran-4-carboxylate (**3ab**)*

Yellow viscous oil; IR ν_{max} (KBr): 2892, 2868, 1732, 1675, 1593, 1551, 1449, 1384, 1258, 1177, 1101, 917, 862, 783, 716 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ ppm=7.93–7.52 (m, 5H), 6.65 (s, 1H), 4.01 (q, 2H, J=7.2 Hz), 2.15 (s, 3H), 1.01 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=192.7, 164.1, 163.9, 160.7, 146.1, 138.4, 134.4, 129.8, 129.7, 115.8, 115.6, 63.0, 18.9, 13.7; GC–MS m/z (% rel inten.): 285.98 (M^+, 41.13), 212.94 (100). Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.02; H, 5.28.

*4.2.3. Ethyl 5-acetyl-6-methyl-2-oxo-2H-pyran-4-carboxylate (**3ac**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 3081, 2986, 2875, 1741, 1699, 1625, 1446, 1381, 1363, 1259, 1096, 871, 807 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ ppm=6.58 (s, 1H), 4.31 (q, 2H, J=7.2 Hz), 2.39 (s, 3H), 2.29 (s, 3H), 1.32 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=198.8, 164.6, 162.9, 160.5, 145.3, 118.7, 115.5, 63.3, 31.6, 18.7, 14.0; GC–MS m/z (% rel inten.): 223.89 (M^+, 23.65), 150.97 (100). Anal. Calcd for $C_{11}H_{12}O_5$: C, 58.93; H, 5.39. Found: C, 58.82; H, 5.50.

*4.2.4. Diethyl 6-methyl-2-oxo-2H-pyran-4,5-dicarboxylate (**3ad**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 2282, 1733, 1566, 1385, 1263, 1082, 988, 859 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ ppm=1.27 (t, 3H, J=7.2 Hz), 1.31 (t, 3H, J=7.2 Hz), 4.24 (q, 2H, J=7.2 Hz), 4.31 (q, 2H, J=7.2 Hz), 2.45 (s, 3H), 6.43 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=168.1, 165.1, 164.8, 160.0, 147.4, 113.8, 109.7, 63.0, 62.4, 19.3, 14.1; GC–MS m/z (% rel inten.): 253.90 (M^+, 40.05), 180.88 (100). Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.81; H, 5.67.

*4.2.5. 5-Benzoyl-4,6-diphenyl-2H-pyran-2-one (**3ba**)*

Pale yellow needles crystals; IR ν_{max} (KBr): 3058, 1742, 1659, 1596, 1581, 1508, 1449, 1389, 1370, 1262, 1174, 1058, 856, 828, 792, 745, 697 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ ppm=7.42–8.12 (m, 10H), 4.94 (s, 1H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=196.30, 153.8, 142.9, 140.0, 138.3, 133.8, 133.5, 130.1, 129.5, 129.1, 129.0, 127.9, 123.7; GC–MS m/z (% rel inten.): 351.98 (M^+, 49.24), 104.86 (100). Anal. Calcd for $C_{24}H_{16}O_3$: C, 81.80; H, 4.58. Found: C, 81.71; H, 4.65.

*4.2.6. 5-Acetyl-4,6-diphenyl-2H-pyran-2-one (**3bb**)*

Colorless crystals; mp: 141–142 °C; IR ν_{max} (KBr): 3047, 2822, 1721, 1663, 1620, 1595, 1578, 1493, 1446, 1386, 1372, 1272, 1094, 802, 749, 693 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ ppm=7.23–7.79 (m, 10H), 6.18 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=194.6, 162.9, 161.0, 156.7, 138.4, 137.4, 134.5, 130.2, 130.1, 129.5, 129.3, 128.3, 118.4, 112.3, 18.90; GC–MS m/z (% rel inten.): 298.95 (M^+, 100). Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.86; H, 4.71.

*4.2.7. 5-Acetyl-6-methyl-4-phenyl-2H-pyran-2-one (**3bc**)*

Colorless crystals; mp: 117–118 °C; IR ν_{max} (KBr): 3066, 2923, 2821, 1739, 1696, 1601, 1577, 1494, 1448, 1380, 1259, 1054, 835, 744, 699 cm^{-1}; ^{1}H NMR (400 MHz, CD_3COCD_3): δ ppm=7.37–7.53 (m, 5H), 6.12 (s, 1H), 2.29 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=200.8, 162.8, 160.6, 155.7, 137.6, 130.8, 130.0, 128.1, 121.3, 112.2, 31.8, 18.6; GC–MS m/z (% rel inten.): 227.90 (M^+, 82.11), 184.79 (100). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.75; H, 5.12.

*4.2.8. Ethyl 6-methyl-2-oxo-4-phenyl-2H-pyran-5-carboxylate (**3bd**)*

Colorless crystals; mp: 95–96 °C; IR ν_{max} (KBr): 3032, 2985, 2938, 1741, 1718, 1618, 1578, 1494, 1447, 1381, 1265, 1084, 831,

732, 681 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.33–7.47 (m, 5H), 6.12 (s, 1H), 3.98 (q, 2H, J=7.2 Hz), 2.40 (s, 3H), 0.86 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=166.2, 165.3, 160.4, 156.4, 138.2, 130.2, 129.4, 127.5, 113.2, 112.1, 61.9, 18.9, 13.7; GC–MS m/z (% rel inten.): 257.80 (M^+, 87.89), 229.73 (100). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.79; H, 5.62.

*4.2.9. 5-Benzoyl-4-pentyl-6-phenyl-2H-pyran-2-one (**3ca**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 1725, 1667, 1380, 1084, 986, 855 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.88–7.26 (m, 10H), 6.27 (s, 1H), 2.27 (t, 2H), 1.45 (q, 2H), 1.22 (m, 4H), 0.79 (q, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=195.0, 161.0, 159.2, 138.0, 134.8, 133.2, 121.5, 130.3, 130.1, 129.6, 129.4, 129.3, 129.1, 118.5, 112.9, 33.4, 32.1, 31.8, 28.7, 22.8, 14.0; GC–MS m/z (% rel inten.): 346.04 (M^+, 24.78), 104.87 (100). Anal. Calcd for $C_{23}H_{22}O_3$: C, 79.74; H, 6.40. Found: C, 79.63; H, 6.21.

*4.2.10. 5-Acetyl-4-pentyl-6-phenyl-2H-pyran-2-one (**3cb**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 1740, 1668, 1596, 1552, 1449, 1392, 1266, 1076, 982, 912, 858, 717 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.99–7.57 (m, 5H), 6.08 (s, 1H), 2.27 (t, 2H), 1.38 (m, 2H), 1.16 (m, 2H), 0.75 (t, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ ppm=194.7, 161.3, 160.9, 158.8, 138.2, 135.2, 130.2, 130.1, 118.5, 111.6, 33.4, 31.7, 22.7, 13.0, 14.0; GC–MS m/z (% rel inten.): 284.01 (M^+, 56.77), 199.93 (100). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.22; H, 7.11.

*4.2.11. 5-Acetyl-6-methyl-4-pentyl-2H-pyran-2-one (**3cc**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 1739, 1675, 1549, 1391, 1295, 1246, 1083, 987, 860 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=5.99 (s, 1H), 2.49 (s, 3H), 2.23 (s, 3H), 2.38 (t, 2H), 1.52 (m, 2H), 1.29 (m, 4H), 0.84 (t, 3H); ^{13}C NMR (100 MHz, CD_3COCD_3) δ ppm=201.1, 160.5, 159.3, 157.4, 121.0, 110.4, 32.5, 31.7, 31.1, 27.9, 22.0, 17.9, 13.2; GC–MS m/z (% rel inten.): 222 (M^+, 8.49), 137.97 (100). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.03; H, 8.10.

4.3. Typical procedure for the reaction of ethyl 3-phenylprop-2-ynoate, diethyl propanedioate, and formaldehyde

To a stirring mixture of ethyl 3-phenylprop-2-ynoate (**1b**, 174 mg, 1 mmol) and diethyl propanedioate (**2e**, 160 mg, 1 mmol), 6 mL dioxane and NaOH (8 mg, 0.2 mmol) were added successively. The mixture was stirred under air atmosphere in a round bottom flask. The reaction was kept at air atmosphere for 4 h, after which time 35% formaldehyde (171 mg, 2 mmol) was added dropwise to the system to continue to react for 1 h. After completion of the reaction, the solvent was diluted with water and extracted with diethyl ether. The ether layer was washed with saturated salt water and dried with anhydrous $MgSO_4$. The resulting mixture was then analyzed by GC and GC–MS. Volatiles were removed under reduced pressure and the crude product was subjected to isolation by PTLC (GF_{254}), eluted with a 10:1 petroleum ether–diethyl ether mixture to afford the desired product diethyl 6-oxo-4-phenyl-2*H*-pyran-3,3(6*H*)-dicarboxylate (**4be**).

*4.3.1. Triethyl 6-oxo-2H-pyran-3,3,4(6H)-tricarboxylate (**4ae**)*

Yellow viscous oil; IR ν_{max} (KBr): 2987, 1732, 1660, 1516, 1468, 1376, 1233, 1096, 307, 859, 737 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=6.92 (s, 1H), 4.86 (s, 2H), 4.21 (m, 6H), 1.21 (m, 9H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=168.7, 166.9, 164.8, 135.8, 130.9, 72.5, 63.3, 61.9, 53.3, 14.2, 14.0; GC–MS m/z (% rel inten.): 314.28 (M^+, 1.58), 167.79 (100). Anal. Calcd for $C_{14}H_{18}O_8$: C, 53.50; H, 5.77. Found: C, 53.45; H, 5.69.

*4.3.2. 3-Benzyl 3,4-diethyl 6-oxo-2H-pyran-3,3,4(6H)-tricarboxylate (**4af**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 1731, 1640, 1371, 1237, 1090, 989 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.38–7.35 (m, 4H), 7.19–7.14 (m, 1H), 6.93 (s, 1H), 5.21 (s, 2H), 4.86 (s, 2H), 4.21–4.09 (m, 4H), 1.21 (m, 6H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=168.6, 166.9, 164.8, 136.0, 131.0, 129.3, 129.2, 129.1, 114.7, 72.5, 68.9, 63.4, 62.0, 60.6, 14.2, 14.0; GC–MS m/z (% rel inten.): 376.69 (M^+, 0.02), 91.0 (100). Anal. Calcd for $C_{19}H_{20}O_8$: C, 60.63; H, 5.36. Found: C, 60.65; H, 5.40.

*4.3.3. 3,3-Dibenzyl 4-ethyl 6-oxo-2H-pyran-3,3,4(6H)-tricarboxylate (**4ag**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 1370, 1645, 1460, 1378, 1238, 1090, 989, 741, 697 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.38–7.31 (m, 10H), 6.95 (s, 1H), 5.26–5.18 (q, 4H, J=12.4 Hz), 4.91 (s, 2H), 4.03–3.98 (q, 2H, J=7.2 Hz), 1.14 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=167.7, 165.9, 163.9, 135.2, 130.2, 128.4, 128.3, 128.2, 128.0, 126.4, 71.7, 68.1, 61.2, 59.8, 13.2; GC–MS m/z (% rel inten.): 438.38 (M^+, 0.01), 91.0 (100). Anal. Calcd for $C_{24}H_{22}O_8$: C, 65.75; H, 5.06. Found: C, 65.80; H, 5.28.

*4.3.4. Diethyl 6-oxo-4-phenyl-2H-pyran-3,3(6H)-dicarboxylate (**4be**)*

Yellow viscous oil; IR ν_{max} (KBr): 1734, 1645, 1459, 1390, 1083, 1051, 856, 771, 699 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.57–7.55 (m, 2H), 7.44–7.43 (m, 3H), 6.24 (s, 1H), 4.88 (s, 2H), 4.15 (m, 4H), 1.10 (m, 6H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=167.4, 162.4, 156.0, 136.9, 130.6, 129.2, 128.5, 119.9, 72.3, 63.6, 60.4, 14.0, 13.9; GC–MS m/z (% rel inten.): 317.91 (M^+, 59.73), 171.89 (100). Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 64.38; H, 5.79.

*4.3.5. 3-Benzyl 3-ethyl 6-oxo-4-phenyl-2H-pyran-3,3(6H)-dicarboxylate (**4bf**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 1733, 1649, 1541, 1457, 1392, 1226, 1079, 989, 844, 696 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.54–7.52 (m, 2H), 7.43–7.33 (m, 6H), 7.27–7.26 (m, 2H), 6.25 (s, 1H), 5.15 (q, 2H), 4.91 (s, 2H), 4.12 (m, 2H), 1.01 (t, 3H, J=7.2 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=267.5, 167.3, 162.4, 155.8, 136.8, 135.8, 130.7, 129.3, 129.1, 128.5, 120.0, 72.3, 68.9, 63.4, 60.5, 13.8; GC–MS m/z (% rel inten.): 380.1 (M^+, 0.24), 91.0 (100). Anal. Calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found: C, 69.58; H, 5.40.

*4.3.6. Dibenzyl 6-oxo-4-phenyl-2H-pyran-3,3(6H)-dicarboxylate (**4bg**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 1725, 1645, 1451, 1366, 1220, 1080, 988, 874, 737, 692 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.49–7.38 (m, 3H), 7.35–7.31 (m, 8H), 7.22–7.19 (m, 4H), 6.28 (s, 1H), 5.15 (q, 4H, J=12.4 Hz), 4.96 (s, 2H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=166.5, 161.7, 154.7, 135.7, 134.7, 129.9, 128.5, 128.4, 128.2, 127.5, 119.1, 71.5, 68.2, 59.6; GC–MS m/z (% rel inten.): 441.91 (M^+, 0.32), 91.0 (100). Anal. Calcd for $C_{27}H_{22}O_6$: C, 73.29; H, 5.01. Found: C, 73.30; H, 5.05.

*4.3.7. Diethyl 6-oxo-4-pentyl-2H-pyran-3,3(6H)-dicarboxylate (**4ce**)*

Pale yellow viscous oil; IR ν_{max} (KBr): 2964, 1736, 1641, 1462, 1389, 1296, 1250, 1173, 1084, 994, 861 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=5.93 (t, 1H, J=1.6 Hz), 4.72 (s, 2H), 4.30–4.25 (q, 4H, J=7.2 Hz), 2.37 (m, 2H), 1.58 (t, 2H, J=7.6 Hz), 1.34 (m, 4H), 1.28 (m, 6H), 0.91 (t, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=167.3, 162.5, 158.2, 118.1, 70.8, 63.3, 59.4, 33.8, 31.9, 26.9, 23.0, 14.2, 14.1; GC–MS m/z (% rel inten.): 311.96 (M^+,

83.06), 28.94 (100). Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74. Found: C, 61.50; H, 7.74.

4.3.8. 3-Benzyl 3-ethyl 6-oxo-4-pentyl-2H-pyran-3,3(6H)-dicarboxylate (**4cf**)

Pale yellow viscous oil; IR ν_{max} (KBr): 1735, 1643, 1516, 1481, 1390, 1250, 1171, 1083, 989, 853, 696 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.41–7.36 (m, 5H), 5.93 (t, 1H, J=1.6 Hz), 5.29 (s, 2H), 4.75 (q, 2H, J=12.4 Hz), 4.27–4.21 (m, 2H), 2.29 (m, 2H), 1.52 (m, 2H), 1.28 (m, 4H), 1.20 (t, 3H, J=7.2 Hz), 0.89 (t, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=167.3, 162.5, 158.1, 136.0, 129.4, 129.3, 128.9, 118.2, 70.8, 68.8, 63.4, 59.5, 53.8, 33.9, 31.9, 26.9, 23.0, 14.2, 14.1; GC–MS m/z (% rel inten.): 374.18 (M^+, 1.79), 91.0 (100). Anal. Calcd for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.13; H, 7.05.

4.3.9. Dibenzyl 6-oxo-4-pentyl-2H-pyran-3,3(6H)-dicarboxylate (**4cg**)

Pale yellow viscous oil; IR ν_{max} (KBr): 1731, 1643, 1460, 1384, 1230, 1082, 989, 849, 742, 694 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=7.40–7.34 (m, 10H), 5.93 (t, 1H, J=1.6 Hz), 5.27 (q, 4H, J=12.4 Hz), 4.80 (s, 2H), 2.21 (m, 2H), 1.43 (m, 2H), 1.17 (m, 4H), 0.85 (t, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=166.3, 161.8, 157.3, 135.0, 128.5, 128.4, 117.3, 69.9, 68.1, 58.8, 33.0, 30.9, 25.9, 22.0, 13.5; GC–MS m/z (% rel inten.): 435.88 (M^+, 0.03), 91.0 (100). Anal. Calcd for $C_{26}H_{28}O_6$: C, 71.54; H, 6.47. Found: C, 71.55; H, 6.47.

4.3.10. 3,3-Diethyl 4-methyl 6-oxo-2H-pyran-3,3,4(6H)-tricarboxylate (**4de**)

Yellow viscous oil; IR ν_{max} (KBr): 1738, 1646, 1516, 1439, 1373, 1338, 1241, 1096, 1012, 860 cm^{-1}; ^1H NMR (400 MHz, CD_3COCD_3): δ ppm=6.94 (s, 1H), 4.85 (s, 2H), 4.22 (m, 4H), 3.73 (s, 3H), 1.23 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, CD_3COCD_3): δ ppm=168.6, 167.0, 165.3, 136.1, 130.6, 72.5, 63.4, 60.6, 52.2, 14.0; GC–MS m/z (% rel inten.): 300.93 (M^+, 0.8), 195.74 (100). Anal. Calcd for $C_{13}H_{16}O_8$: C, 52.00; H, 5.37. Found: C, 51.98; H, 5.36.

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