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Preparation of 5-Aryl-3-Oxo-δ-Lactones by the Potassium Carbonate-Promoted Condensation of Aromatic Aldehydes and Ethyl Acetoacetate in Ethanol

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Preparation of 5-Aryl-3-Oxo-δ-Lactones by the Potassium Carbonate–Promoted Condensation of Aromatic Aldehydes and Ethyl Acetoacetate in Ethanol

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Abstract: 5-Aryl-3-oxo-δ-lactones (6-aryl-dihydro-2H-pyran-2,4(3H)-diones) were prepared by the potassium carbonate–promoted condensation of aromatic aldehydes and ethyl acetoacetate in absolute ethanol. Benzaldehyde and substituted benzaldehydes bearing an alkoxy group (2 or 3 position), a chlorine atom (2, 3, or 4 position), a nitro group (3 or 4 position), a cyano group (4 position), or an acetyl group (4 position) react in high yields under these conditions.

Keywords: aromatic aldehyde, 6-aryl-dihydro-2H-pyran-2,4(3H)-dione, 5-aryl-3-oxo-δ-lactone, ethyl acetoacetate, potassium carbonate

While investigating conditions for Knoevenagel condensation reactions, we discovered that a side product, 5-(2-allyloxyphenyl)-3-oxo-δ-lactone (**1**), often formed when inorganic bases were used for the reaction between 2-allyloxybenzaldehyde and ethyl acetoacetate. Upon further investigation, we found that potassium carbonate in ethanol induced the condensation of 2-allyloxybenzaldehyde and ethyl acetoacetate to generate **1** in 93% isolated yield [Eq. (1)]:

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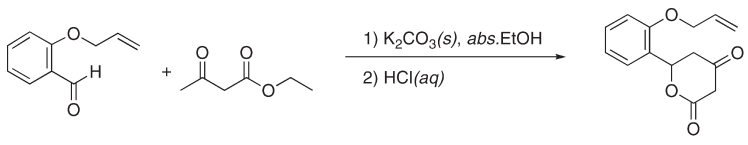


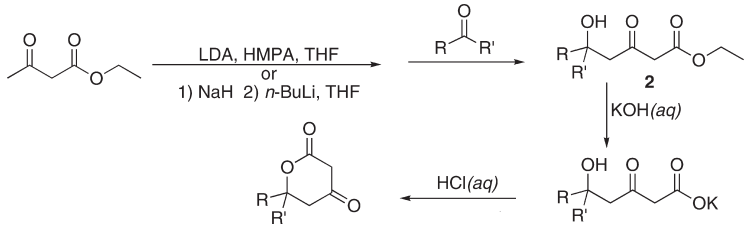
(1)

I

This result is surprising because carbonate salts have seen use as bases for Knoevenagel condensation (Eq. 1) reactions[1] and because the reaction proceeds via the addition of the less stable conjugate base of ethyl acetoacetate, which is being generated by the weak base carbonate.

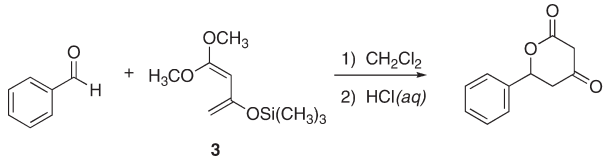
The synthesis of 5-aryl-3-oxo-δ-lactones is of interest because they exhibit a wide variety of biological activities. For example, 5-phenyl-3-oxo-δ-lactone has shown antioxidant,[2] molluscicidal,[3] and antinociceptive activity.[4] In addition, the products from the condensation of 5-phenyl-3-oxo-δ-lactone, 2,6-disubstituted anilines, and triethyl orthoformate show antifungal properties,[5] and 5-phenyl-3-oxo-δ-lactone derivatives have been shown to be effective HIV protease inhibitors.[6]

Previous syntheses of 5-substituted-3-oxo-δ-lactones most commonly involve trapping the preformed dianion of ethyl acetoacetate with an aldehyde or a ketone. Hydrolysis of the resulting hydroxyketoester (**2**) followed by treatment with hydrochloric acid then affords the desired lactone (Scheme 1).[7]



Scheme 1. Formation of 5-substitued-3-oxo-δ-lactones from the dianion of ethyl acetoacetate.

It has also been shown that hetero Diels–Alder reactions between aromatic aldehydes and diene (**3**) yield 5-aryl-3-oxo-δ-lactones after hydrolysis of the adduct [Eq. (2)].[8] However, the lengthy synthesis of diene **3**[9] has limited the use of this method.



(2)

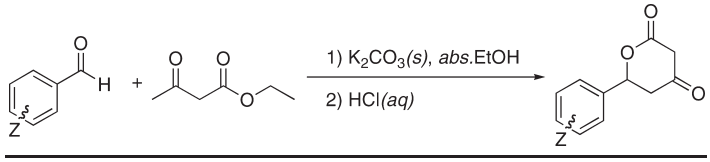
3

The procedure described herein has several advantages over the previously published methods: 1) Strong bases are not necessary for our method. 2) Highly

toxic solvents are not used in our reaction. The dianion method often employs the use of an anion stabilizers such as hexamethylphosphoramide (HMPA) along with the solvent, tetrahydrofuran (THF). 3) Our method is procedurally less complex. The dianion method requires three chemical reactions (anion addition, hydrolysis, and lactonization) to produce the desired compound, and the hetero Diels–Alder method requires the multiple-step synthesis of diene **3**. Our method requires only one reaction; the aldehyde, ethyl acetoacetate, and potassium carbonate are mixed in ethanol and stirred for 16–24 h at 45°C, followed by an acidic workup.

As shown in Table 1, aromatic aldehydes bearing an array of dissimilar electronic substituents are tolerated by these conditions. The generation of lactones from 3- or 4-nitrobenzaldehyde is especially noteworthy given that de Aguiar Amaral et al. reported difficulty with the preparation of the desired δ-lactone by the treatment of 4-nitrobenzaldehyde with the dianion of ethyl acetoacetate.[4]

Table 1. Isolated yields of 5-aryl-3-oxo-δ-lactones



Entry	Z	Isolated yield (%)
a	2-(O-$CH_2CH{=}CH_2$)	93
b	2-(MeO)	89
c	3-(MeO)	73
d	H	88
e	2-Cl	79
f	3-Cl	76
g	4-Cl	72
h	3-NO_2	65
i	4-NO_2	75
j	4-CN	56
k	4-$COCH_3$	82[a]

[a]Isolated by trituration from ether.

Although our method is easier to perform than previously published methods, it does have limitations. For example, enolizable aldehydes (i.e., heptanal), yield self-condensation (aldol) products as the major products. In addition, ketones do not react under these conditions. For example, no reaction was observed when benzophenone or 4-chloroacetophenone was used in the reaction. However, the difference in reactivity of aldehydes and ketones provides the opportunity to perform the cyclization on an aldehyde in the presence of an unprotected ketone (Table 1, entry k).

In summary, 5-aryl-3-oxo-δ-lactones can be prepared in high yields by the potassium carbonate–promoted condensation of aromatic aldehydes and ethyl actetoacetate in absolute ethanol. The presence of substituents, with varying electronic contribution, on the aromatic ring of the aldehyde is tolerated by these conditions. Although this method has some limitations, it provides a noteworthy alternative to previously published methods.

EXPERIMENTAL

Benzaldehyde, 3-methyoxybenzaldehyde, 3-nitrobenzaldehyde, 4-nitrobenzaldehyde, and 4-acetylbenzaldehyde were purchased from Aldrich Chemical Company and used without further purification. 2-Chlorobenzaldehyde, 3-chlorobenzaldehyde, 4-chlorobenzaldehyde, o-anisaldehyde, and ethyl acetoacetate were purchased from Acros Organics and used without further purification. 4-Cyanobenaldehyde was purchased from Alfa Aesar and used without further purification. 2-Allyloxybenzaldehye was prepared from salicylaldehyde.[10] Ethanol was purchased from Quantum Chemical Corporation and distilled under nitrogen from sodium. NMR spectra were collected on a JEOL Eclipse + spectrometer (300 MHz, ^{1}H). Mass spectra were collected at the University of Illinois School of Chemical Sciences Mass Spectrometry Laboratory on a VG 70-VSE 8-kV double-focusing sector mass spectrometer [electron ionization (70 eV), chemical ionization (CH_4)].

Procedure

The aldehyde (2 mmol), ethanol (2 mL, distilled from sodium), ethyl acetoacetate (2 mmol), and potassium carbonate (4 mmol) were added to a flame-dried, 15-mm × 100-mm, screw-cap centrifuge tube under nitrogen. The septa and the nitrogen-filled balloon were replaced with the centrifuge cap, and the tube was placed in an oil bath at 45°C and heated overnight (16–24 h). After cooling the tube to room temperature, the reaction mixture was transferred to a separatory funnel using 20 mL of ethyl acetate, and then 10 mL of 1 M HCl (aq.) were slowly added. The aqueous layer was extracted with two additional portions (2 × 15 mL) of ethyl acetate. The combined organic extracts were dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography.

Data

6-(2-(Allyloxy)phenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry a)

^{1}H NMR ($CDCl_3$) δ 7.49 (dd, $J = 7.7, 1.6$, 1H), 7.35 (ddd, $J = 8.2, 7.7, 1.6$, 1H), 7.06 (dt, $J = 7.4, 0.8$, 1H), 6.90 (dd, J = 8.2, 0.8 1H), 6.02 (m, 2H),

5.32 [m (two poorly resolved dq, $J = 17.3$, 1.7, and $J = 10.4$, 1.4), 2H], 4.58 [m (poorly resolved dq, $J = 5.5$, 1.4), 2H], 3.76 (d, $J = 19$, 1H), 3.52 (d, $J = 19$, 1H), 3.04 (dd, $J = 18.4$, 3.0, 1H), 2.69 (dd, $J = 18.4$, 11.3, 1H). HRMS (M + H) calcd. for $C_{14}H_{15}O_4^+$ 247.0970; found 247.0965.

6-(2-Methoxyphenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry b)

^{1}H NMR ($CDCl_3$) δ 7.49 (dd, $J = 7.4$, 1.6, 1H), 7.39 (ddd, $J = 8.3$, 7.4, 1.6, 1H), 7.07 (dt, $J = 7.4$, 1.1, 1H), 6.92 (dd, $J = 8.3$, 0.8 1H), 6.01 (dd, $J = 11.3$, 3.0, 1H), 3.83 (s, 3H), 3.75 (d, $J = 19$, 1H), 3.53 (d, $J = 19$, 1H), 3.03 (dd, $J = 18.4$, 3.0, 1H), 2.68 (dd, $J = 18.4$, 11.3, 1H). HRMS (M + H) calcd. for $C_{12}H_{13}O_4^+$ 221.0814; found 221.0812.

6-(3-Methoxyphenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry c)

^{1}H NMR ($CDCl_3$) δ 7.34 (t, $J = 7.7$, 1H), 6.93 (m, 3H), 5.68 (dd, $J = 9.6$, 3.8, 1H), 3.84 (s, 3H), 3.66 (d, $J = 19$, 1H), 3.48 (d, $J = 19$, 1H), 2.96 (dd, $J = 18.4$, 3.8, 1H), 2.87 (dd, $J = 18.4$, 9.6, 1H). HRMS (M + H) calcd. for $C_{12}H_{13}O_4^+$ 221.0814; found 221.0815.

6-(Phenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry d)

^{1}H NMR ($CDCl_3$) δ 7.42 (m, 5H), 5.71 (dd, $J = 9.6$, 4.1, 1H), 3.67 (d, $J = 19$, 1H), 3.49 (d, $J = 19$, 1H), 2.97 (dd, $J = 18.4$, 4.1, 1H), 2.89 (dd, $J = 18.4$, 9.6, 1H). HRMS (M +) calcd. for $C_{11}H_{10}O_3$ 190.0630; found 190.0632.

6-(2-Chlorophenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry e)

^{1}H NMR ($CDCl_3$) δ 7.64 (dd, $J = 7.4$, 1.9, 1H), 7.38 (m, 3H), 6.06 (dd, $J = 11.8$, 2.7, 1H), 3.81 (d, $J = 19$, 1H), 3.58 (d, $J = 19$, 1H), 3.11 (dd, $J = 18.4$, 2.7, 1H). 2.61 (dd, $J = 18.4$, 11.8, 1H). HRMS (M + H) calcd. for $C_{11}H_{10}ClO_3^+$ 225.0319; found 225.0313.

6-(3-Chlorophenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry f)

^{1}H NMR ($CDCl_3$) δ 7.43 (m, 1H), 7.38 (m, 2H), 5.67 (dd, $J = 10.7$, 3.6, 1H), 3.69 (d, $J = 19$, 1H), 3.52 (d, $J = 19$, 1H), 2.97 (dd, $J = 18.4$, 3.6, 1H), 2.83 (dd, $J = 18.4$, 10.7, 1H). HRMS (M + H) calcd. for $C_{11}H_{10}ClO_3^+$ 225.0319; found 225.0314.

6-(4-Chlorophenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry g)

^{1}H NMR ($CDCl_3$) δ 7.42 (br d, $J = 8.5$, 1H), 7.34 (br d, $J = 8.5$, 1H), 5.67 (dd, $J = 10.2$, 3.3, 1H), 3.68 (d, $J = 19$, 1H), 3.50 (d, $J = 19$, 1H), 2.95 (dd,

$J = 18.4, 3.6, 1H$), 2.82 (dd, $J = 18.4, 10.4, 1H$). HRMS (M + H) calcd. for $C_{11}H_{10}ClO_3^+$ 225.0319; found 225.0327.

6-(3-Nitrophenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry h)

^{1}H NMR (CD_3OD) δ 8.38 (br s, 1H), 8.25 (br d, $J = 8.0$, 1H), 7.90 (br d, $J = 8.0$, 1H), 7.68 (br t, $J = 8.2$), 5.66 (dd, $J = 11.5, 4.1$, 1H), 2.87 (dd, $J = 17.3, 11.5$, 1H), 2.75 (dd, $J = 17.3, 4.1$, 1H). HRMS (M + H) calcd. for $C_{11}H_{10}NO_5^+$ 236.0559; found 236.0562.

6-(4-Nitrophenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry i)

^{1}H NMR (CD_3OD) δ 8.29 (br d, $J = 8.8$, 1H), 7.74 (br d, $J = 8.8$, 1H), 5.66 (dd, $J = 11.3, 5.0$, 1H), 2.84 (dd, $J = 17.3, 11.3$, 1H), 2.74 (dd, $J = 17.3, 5.0$, 1H). HRMS (M + H) calcd. for $C_{11}H_{10}NO_5^+$ 236.0559; found 236.0553.

4-(4,6-Dioxotetrahydro-2H-pyran-2-yl)benzonitrile (Entry j)

^{1}H NMR (CD_3OD) δ 7.79 (d, $J = 8.5$, 2H), 7.67 (d, $J = 8.5$, 2H), 5.60 (dd, $J = 11.5, 4.7$, 1H), 2.82 (dd, $J = 17.3, 11.5$, 1H), 2.71 (dd, $J = 17.3, 4.7$, 1H). HRMS (M + H) calcd. for $C_{12}H_9NO_3^+$ 216.0661; found 216.0665.

6-(4-Acetylphenyl)-dihydro-2H-pyran-2,4(3H)-dione (Entry k)

^{1}H NMR (CD_3OD) δ 8.04 (d, $J = 8.2$, 2H), 7.61 (d, $J = 8.2$, 2H), 5.59 (dd, $J = 11.5, 4.4$, 1H), 2.84 (dd, $J = 17.3, 11.5$, 1H), 2.71 (dd, $J = 17.3, 4.4$, 1H). HRMS (M + H) calcd. for $C_{13}H_{13}O_4^+$ 233.0814; found 233.0820.

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