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Preparation of 4,6-Disubstituted α-Pyrones by Oxidative N-Heterocyclic Carbene Catalysis

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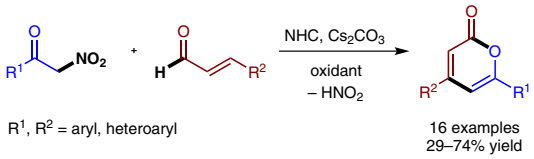
Dedicated to Prof. Dieter Enders, a pioneer and driving force in carbene catalysis, on the occasion of his 70th birthday



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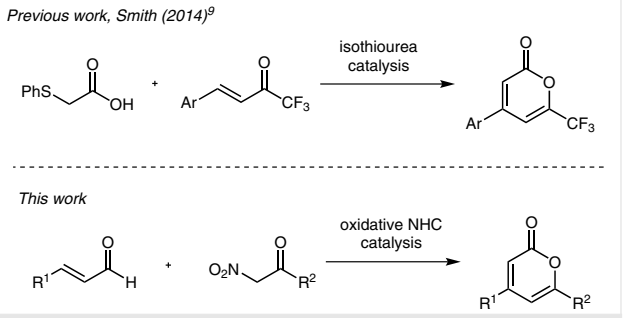
Abstract An efficient synthesis of 4,6-disubstituted α-pyrones employing redox activation of enals using N-heterocyclic carbene catalysis is reported. The strategy uses aroyl-substituted nitromethanes and enals as substrates and reactions proceed through an addition–elimination–lactonization sequence. On one hand the nitro group in the starting ketone stabilizes the enolate and on the other hand it also acts as an ionic leaving group. Products are obtained in moderate to good yields.

Key words α-pyrone, N-heterocyclic carbine, oxidative organocatalysis, NHC catalysis, elimination, lactonization

α-Pyrones[1] belong to an important class of unsaturated six-membered heterocycles present in many natural products that show biological activity such as antimicrobial,[2a] antifungal,[2b,c] anti-HIV,[2d] and phytotoxic effects.[2e] Due to their interesting biological activity and due to their valuable reactivity caused by the conjugated diene and lactone functionalities, α-pyrones have drawn great attention in synthesis.[3] It is therefore not surprising that many methods for the preparation of substituted α-pyrones have been disclosed.[4] Despite great achievements in this area considering the traditional methods and also modern transition-metal-based processes, the development of novel approaches towards α-pyrones is still of importance.

Over the past decade, N-heterocyclic carbene catalyzed redox activation of enals for the synthesis of complex heterocycles has become increasingly more attractive.[5,6] In 2010, our group[8a] demonstrated an organocascade where 1,3-diketones and in situ generated α,β-unsaturated acyl azolium ions react to give dihydropyranones.[7,8] Moreover, Lupton and co-workers have studied the NHC-catalyzed generation of α,β-unsaturated acyl azolium ions from the corresponding acyl fluorides or acyl esters and have investigated their reactivity towards C–C bond formation.[8c] Later, our group and other research groups further developed the chemistry of in situ generated α,β-unsaturated acyl azolium ions for the preparation of various important heterocycles.[8] However, the synthesis of substituted α-pyrones using N-heterocyclic carbene catalysis still remains unexplored. In 2014, Smith et al. demonstrated the synthesis of substituted α-pyrones from (phenylthio)acetic acid and trifluoromethyl enones via an isothiourea-catalyzed Michael addition–lactonization–thiol elimination process (Scheme 1).[9] However, this method is restricted to trifluoromethyl-substituted enones where only the 4-aryl substituent can be varied at the pyrone ring. Herein we report an organocascade for the preparation of 4,6-disubstituted α-pyrones starting from easily accessible aroyl-substituted nitromethanes and enals by oxidative N-heterocyclic carbene catalysis. We will show that 4,6-disubstituted α-pyrones bearing two different substituents at the pyrone ring can be readily accessed via a Michael addition–elimination–lactonization sequence (Scheme 1). Notable, only few organocatalytic methods have been reported for the synthesis of substituted α-pyrones to date.[9,10]



Scheme 1 Preparation of α-pyrones using organocatalysis

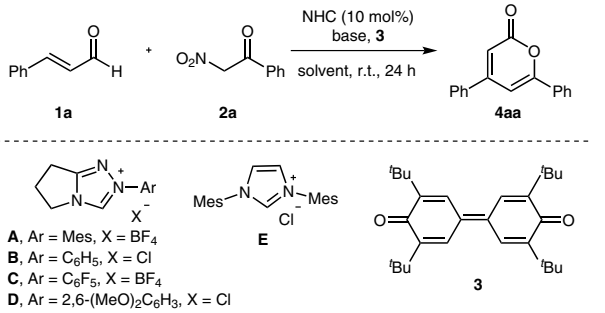
We began our investigations using *trans*-cinnamaldehyde (**1a**) and benzoylnitromethane (**2a**) as model substrates. Diphenoquinone[11] **3** was chosen as an oxidant. We delightfully found that with triazolium salt **A**[12a] as NHC precatalyst (10 mol%) and DBU (1.2 equiv) as a base in THF at room temperature, the targeted α-pyrone **4aa** was formed in 15% yield (Table 1, entry 1). Upon switching to NHC precatalysts **B**[12b] and **C**,[12b] only a trace amount of the desired pyrone **4aa** was identified (Table 1, entries 2 and 3). With Cs_2CO_3 (2.0 equiv) as the base the yield slightly improved (20%) (Table 1, entry 4) and a worse result was achieved with precatalysts **D**[12c] and **E** keeping Cs_2CO_3 as the base (Table 1, entries 5 and 6). By using 2.0 equivalents of benzoylnitromethane **2a**, the yield increased from 20% to 40% (Table 1, entry 7). Decreasing the amount of Cs_2CO_3 from 2.0 to 1.2 equivalents led to a further increase of the yield to 69% (Table 1, entry 8). Notable, a catalytic amount of Cs_2CO_3 provided only a trace amount of the targeted product (Table 1, entry 9). Other solvents such as CH_2Cl_2, toluene, MeCN, EtOAc, 1,2-dichloroethane, and DMF were tested, however, in all cases a worse result was achieved (Table 1, entries 10–15).

With optimized reaction conditions in hand, we started to explore the generality and scope of our cascade (Scheme 2). Cinnamaldehyde derivatives bearing methyl, methoxy, and dimethylamino substituents at the *para* position of the aryl ring were tested in the reaction with nitro ketone **2a**. In all three cases the targeted products **4ba–da** were obtained. Whereas the methyl congener (see **4ba**) provided the same yield as the parent cinnamaldehyde, the electron-rich methoxy- and dimethylamino-substituted enals afforded the pyrones **4ca** and **4da** in lower yields. Surprisingly, with electron-poorer cinnamaldehyde derivatives bearing a bromo, fluoro, or nitro substituent at the *para*-position, α-pyrone formation was not observed. Hence, the reaction seems to show very strong effects on electronics with best results being obtained for alkyl-substituted enals. Along these lines, we found that a methyl group at the *meta*-position of the arene ring of the enal is well tolerated to give pyrone **4ea** in 69% isolated yield. Electronic effects at the *meta*-positions are not that pronounced and for both, the *meta*-methoxy (see **4fa**, 57%) and also the *meta*-chloro derivative (see **4ga**, 67%) the α-pyrone products were isolated in good yields. The 2-furylenal **1h** also gave the desired pyrone **4ha** in 50% isolated yield.

We further tested the scope by varying the α-nitro ketone component keeping cinnamaldehyde as the reaction partner. With the tolyl ketone a slightly lower yield of the desired product **4ab** was obtained as compared to the formation of pyrone **4aa**. As for the enal component, electronic effects strongly influence reaction outcome. With *p*-methoxyphenyl nitromethyl ketone **2c** the yield significantly decreased and **4ac** was isolated in 29% yield. However, with *para*-bromo-substituted ketone **2d**, the pyrone **4ad** was obtained in 52% yield. Hence, an electron-withdrawing group seems to increase reaction efficiency. Indeed, with the chloro and fluoro derivatives yield further improved and the pyrones **4ae** and **4af** were obtained in 67% and 64% yields, respectively. It was interesting to see that with the *meta*-substituted halo-substituted congeners (**2g** and **2h**) the yield could be further improved (**4ag**: 68%; **4ah**: 74%). We were also pleased to find that the 2-naphthyl ketone worked as a substrate providing the pyrone **4ai** in 56% yield. We also tested crotonaldehyde as a non-aromatic enal in the reaction with **2a** under the optimized reaction conditions, but unfortunately only a trace amount of the desired product was formed that was not isolated.

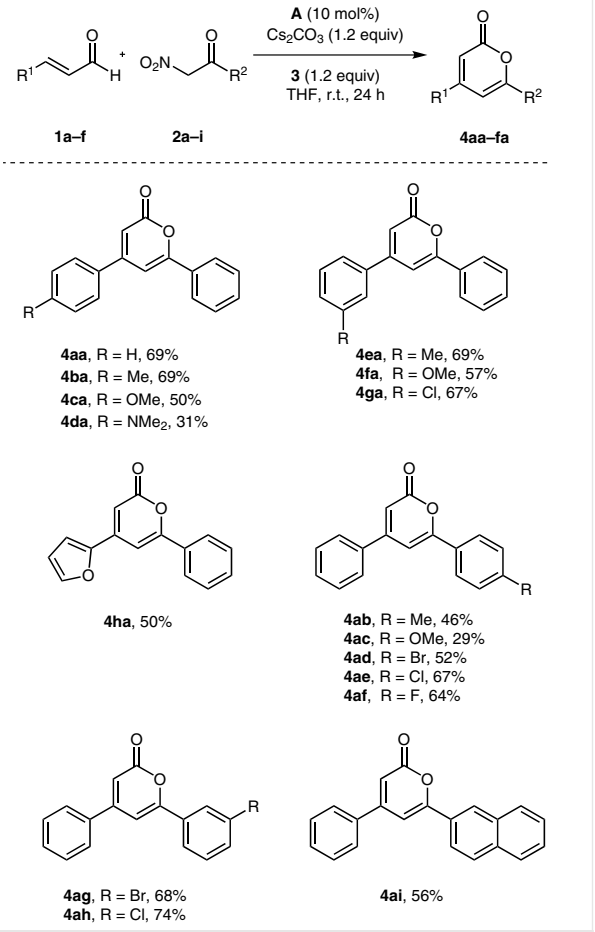
Our suggested reaction mechanism for the formation of the α-pyrones **4** is depicted in Scheme 3. Carbene **A′**, generated by deprotonation of precatalyst **A**, reacts with enal **1** to provide the corresponding Breslow intermediate which is immediately oxidized in situ by **3** to give acyl azolium ion **5**.

Table 1 Reaction Optimization[a]

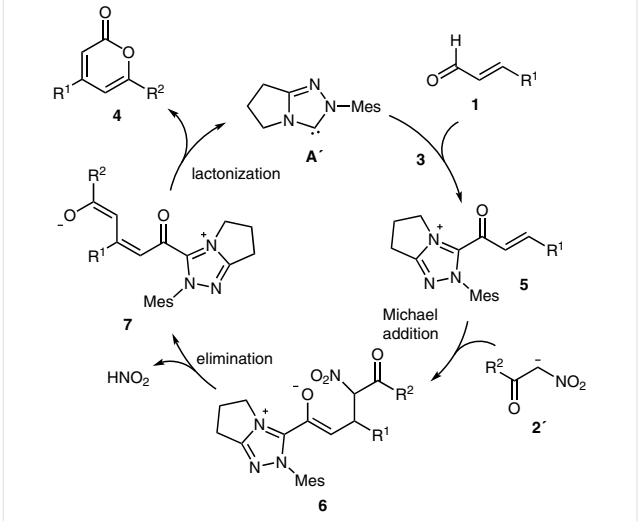


Entry	Catalyst	Base (equiv)	Solvent	Yield (%)[b]
1	**A**	DBU (1.2)	THF	15
2	**B**	DBU (1.2)	THF	trace
3	**C**	DBU (1.2)	THF	trace
4	**A**	Cs_2CO_3 (2.0)	THF	20
5	**D**	Cs_2CO_3 (2.0)	THF	15
6	**E**	Cs_2CO_3 (2.0)	THF	15
7[c]	**A**	Cs_2CO_3 (2.0)	THF	40
8[c,d]	**A**	Cs_2CO_3 (1.2)	THF	69
9[c]	**A**	Cs_2CO_3 (0.2)	THF	trace
10[c]	**A**	Cs_2CO_3 (1.2)	CH_2Cl_2	15
11[c]	**A**	Cs_2CO_3 (1.2)	toluene	20
12[c]	**A**	Cs_2CO_3 (1.2)	MeCN	15
13[c]	**A**	Cs_2CO_3 (1.2)	EtOAc	11
14[c]	**A**	Cs_2CO_3 (1.2)	DCE	22
15[c]	**A**	Cs_2CO_3 (1.2)	DMF	<5

[a] All reactions were carried on a 0.1 mmol scale for 24 h.
[b] Determined by ^1H NMR spectroscopy.
[c] **2a** (2.0 equiv) was used.
[d] Yield of the isolated product.



Scheme 2 Scope of the reaction



Scheme 3 Plausible mechanism

Conjugative addition of deprotonated **2′** to the acyl azolium ion **5**[8f] provides the enolate **6** which then undergoes HNO_2 elimination affording enolate **7**. Lactonization eventually provides the product α-pyrone **4** thereby regenerating the NHC catalyst **A′**.[13]

In summary, a novel method for the preparation of 4,6-disubstituted α-pyrones from commercially available enals and readily accessible aroyl-substituted nitromethanes via oxidative N-heterocyclic carbene catalyzed addition–elimination–lactonization has been introduced. Reactions reported are experimentally easy to perform by simply mixing precatalyst, substrates and reagents at ambient temperature providing the α-pyrones in moderate to good yields.

All reactions involving air- or moisture-sensitive reagents or intermediates were carried out in heat gun dried glassware under an argon atmosphere. THF was freshly distilled from potassium under argon. CH_2Cl_2 was freshly distilled from P_2O_5. MeCN was freshly distilled over CaH_2. DCE was freshly distilled over CaH_2. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros Organics, or Alfa Aesar. All α,β-unsaturated aldehydes were either distilled or freshly prepared prior to use. Catalysts **A**,[12a] **B**,[12b] and oxidant **3**[11] were prepared according to known literature procedures.

^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300, Bruker AV 300, or Bruker AV 400 at 300 K or a Varian 600 UNITY plus spectrometer at 299 K, relative to TMS [$\delta(^1H) = 0.0$, $\delta(^{13}C) = 0.0$]. The solvents residual proton resonance and the respective carbon resonance [$CHCl_3$, $\delta(^1H) = 7.26$, $\delta(^{13}C) = 77.0$] were used for calibration. TLC: Merck silica gel 60 F 254 plates; detection with UV light or by dipping into a solution of $KMnO_4$ [1.5 g; H_2O (400 mL), $NaHCO_3$ (5 g)] or a solution of $Ce(SO_4)_2 \cdot x\ H_2O$ (10 g), phosphomolybdic acid hydrate (25 g), and concd H_2SO_4 (60 mL) in H_2O (940 mL), followed by heating. Flash column chromatography (FC): Merck or Acros Organics silica gel 60 (40–63 µm) at approx 0.4 bar. IR spectra were recorded on a Digilab Varian 3100 FT-IR Excalibur Series. HRMS ESI (*m*/*z*) spectra were recorded on a Bruker MicroTof or an Orbitrap LTQ XL(Nanospray) of Thermo Scientific.

α-Pyrones 4aa–4ah; General Procedure

To a heat gun dried Schlenk tube under an argon atmosphere, azolium salt **A** (3.0 mg, 10 µmol), **3** (49 mg, 0.12 mmol, 1.2 equiv), Cs_2CO_3 (39 mg, 0.12 mmol, 1.2 equiv), **2a–i** (0.2 mmol, 2 equiv), and THF (1 mL) were added and the resulting solution was stirred for 5 min at rt. Then the enal **1a–h** (0.1 mmol, 1.0 equiv) was added and stirring was continued for 12 h at rt. After completion of the reaction (TLC monitoring), the crude mixture was directly subjected to flash column chromatography (pentane/EtOAc).

4,6-Diphenyl-2*H*-pyran-2-one (4aa)

According to GP with **2a** (34 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 7:1) afforded α-pyrone **4aa** (17 mg, 69%) as a white solid; mp 136 °C.

FTIR (neat): 2253, 1708, 1629, 1539, 1495, 1078, 903, 722, 649 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.94–7.87 (m, 2 H), 7.69–7.61 (m, 2 H), 7.54–7.45 (m, 6 H), 6.97 (d, *J* = 1.5 Hz, 1 H), 6.48 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 160.6, 155.7, 136.2, 131.7, 131.1, 130.8, 129.4 (× 2), 129.1 (× 2), 126.9 (× 2), 125.9 (× 2), 109.4, 101.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{12}NaO_2$: 271.0735; found: 271.0730.

6-Phenyl-4-(*p*-tolyl)-2*H*-pyran-2-one (4ba)

According to GP with **2a** (34 mg, 0.20 mmol, 2.0 equiv) and *trans*-4-methylcinnamaldehyde (**1b**, 15 mg, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ba** (18 mg, 69%) as a white solid; mp 134 °C.

FTIR (neat): 2253, 2219, 1714, 1628, 1573, 1495, 903, 723, 649 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.84 (m, 2 H), 7.61–7.52 (m, 2 H), 7.50–7.44 (m, 3 H), 7.31 (d, *J* = 7.9 Hz, 2 H), 6.96 (d, *J* = 1.5 Hz, 1 H), 6.46 (d, *J* = 1.5 Hz, 1 H), 2.43 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 160.4, 155.5, 141.3, 133.2, 131.8 (× 2), 131.0 (× 2), 130.1 (× 2), 129.1 (× 2), 126.8, 125.9, 108.7, 101.4, 21.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{14}NaO_2$: 285.0891; found: 285.0886.

4-(4-Methoxyphenyl)-6-phenyl-2*H*-pyran-2-one (4ca)

According to GP with **2a** (34 mg, 0.20 mmol, 2.0 equiv) and *trans*-4-methoxycinnamaldehyde (**1c**, 17 mg, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ca** (14 mg, 50%) as a yellowish solid; mp 124 °C.

FTIR (neat): 2254, 2287, 1720, 1626, 1538, 1462, 903, 722, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93–7.86 (m, 2 H), 7.69–7.59 (m, 2 H), 7.54–7.39 (m, 3 H), 7.07–6.99 (m, 2 H), 6.96 (d, *J* = 1.5 Hz, 1 H), 6.43 (d, *J* = 1.6 Hz, 1 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 162.0, 160.3, 155.0, 131.9, 131.0, 129.1 (× 2), 128.4 (× 2), 128.2, 125.9 (× 2), 114.8 (× 2), 107.8, 101.2, 55.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{14}NaO_3$: 301.0841; found: 301.0835.

4-[4-(Dimethylamino)phenyl]-6-phenyl-2*H*-pyran-2-one (4da)

According to GP with **2a** (34 mg, 0.20 mmol, 2.0 equiv) and *trans*-4-(dimethylamino)cinnamaldehyde (**1d**, 18 mg, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 5:1) afforded α-pyrone **4da** (9 mg, 31%) as a yellow solid; mp 145 °C.

FTIR (neat): 2185, 2043, 1710, 1606, 1522, 1202, 903, 722, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98–7.85 (m, 2 H), 7.67–7.55 (m, 2 H), 7.53–7.41 (m, 3 H), 7.00 (d, *J* = 1.6 Hz, 1 H), 6.84–6.73 (m, 2 H), 6.41 (d, *J* = 1.6 Hz, 1 H), 3.06 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.5, 159.8, 154.9, 152.2, 132.2, 130.7, 129.0 (× 2), 128.1 (× 2), 125.9 (× 2), 122.5, 112.3 (× 2), 105.4, 101.0, 40.3 (× 2).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{17}NNaO_2$: 314.1157; found: 314.1151.

6-Phenyl-4-(*m*-tolyl)-2*H*-pyran-2-one (4ea)

According to GP with **2a** (34 mg, 0.20 mmol, 2.0 equiv) and *trans*-3-methylcinnamaldehyde (**1e**, 15 mg, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ea** (18 mg, 69%) as a sticky oil.

FTIR (neat): 2253, 2217, 1714, 1630, 1590, 1495, 903, 723, 649 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01–7.84 (m, 2 H), 7.70–7.27 (m, 7 H), 6.95 (d, *J* = 1.5 Hz, 1 H), 6.46 (d, *J* = 1.5 Hz, 1 H), 2.45 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 160.3, 155.7, 139.0, 136.1, 131.6, 131.4, 130.9, 129.1, 128.9 (× 2), 127.4, 125.8 (× 2), 123.9, 109.2, 101.5, 21.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{14}NaO_2$: 285.0891; found: 285.0886.

4-(3-Methoxyphenyl)-6-phenyl-2*H*-pyran-2-one (4fa)

According to GP with **2a** (34 mg, 0.20 mmol, 2.0 equiv) and *trans*-3-methoxycinnamaldehyde (**1f**, 17 mg, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4fa** (16 mg, 57%) as a yellowish solid; mp 116 °C.

FTIR (neat): 2253, 1714, 1629, 1537, 1495, 904, 726, 649 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.83 (m, 2 H), 7.56–7.36 (m, 4 H), 7.22 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1 H), 7.15 (t, *J* = 2.1 Hz, 1 H), 7.05 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1 H), 6.94 (d, *J* = 1.5 Hz, 1 H), 6.46 (d, *J* = 1.5 Hz, 1 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 160.5, 160.3, 155.7, 137.7, 131.7, 131.1, 130.5, 129.1 (× 2), 125.9 (× 2), 119.2, 116.1, 112.6, 109.6, 101.6, 55.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{14}NaO_3$: 301.0841; found: 301.0835.

4-(3-Chlorophenyl)-6-phenyl-2*H*-pyran-2-one (4ga)

According to GP with **2a** (34 mg, 0.20 mmol, 2.0 equiv) and *trans*-3-chlorocinnamaldehyde (**1g**, 17 mg, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ga** (19 mg, 67%) as a yellowish solid; mp 139 °C.

FTIR (neat): 2254, 1705, 1629, 1537, 1495, 1079, 903, 723, 649 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.84 (m, 2 H), 7.65–7.56 (m, 1 H), 7.57–7.38 (m, 6 H), 6.89 (d, *J* = 1.5 Hz, 1 H), 6.43 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 160.9, 154.3, 138.1, 135.5, 131.5, 131.2, 130.7, 130.7, 129.1 (× 2), 127.0, 125.9 (× 2), 125.0, 109.9, 101.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{11}ClNaO_2$: 305.0345; found: 305.0340.

4-(Furan-2-yl)-6-phenyl-2*H*-pyran-2-one (4ha)

According to GP with **2a** (34 mg, 0.20 mmol, 2.0 equiv) and *trans*-3-(furan-2-yl)acrylaldehyde (**1h**, 13 mg, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 7:1) afforded α-pyrone **4ha** (16 mg, 50%) as a white solid; mp 139 °C.

FTIR (neat): 2256, 1708, 1633, 1534, 1167, 903, 723, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.85 (m, 2 H), 7.63 (d, *J* = 1.8 Hz, 1 H), 7.48–7.44 (m, 3 H), 7.00 (d, *J* = 3.5 Hz, 1 H), 6.93 (d, *J* = 1.4 Hz, 1 H), 6.59 (dd, *J* = 3.5, 1.8 Hz, 1 H), 6.50 (d, *J* = 1.3 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 160.7, 149.8, 145.9, 143.5, 131.7, 131.0, 129.1 (× 2), 125.9 (× 2), 112.8, 112.8, 104.4, 98.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{10}NaO_3$: 261.0528; found: 261.0522.

4-Phenyl-6-(*p*-tolyl)-2*H*-pyran-2-one (4ab)

According to GP with **2b** (36 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ab** (12 mg, 46%) as a yellowish solid; mp 113 °C.

FTIR (neat): 2254, 2166, 1710, 1626, 1509, 1388, 903, 721, 649 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.3 Hz, 2 H), 7.68–7.62 (m, 2 H), 7.54–7.49 (m, 3 H), 7.28 (d, *J* = 8.6 Hz, 2 H), 6.92 (d, *J* = 1.5 Hz, 1 H), 6.44 (d, *J* = 1.5 Hz, 1 H), 2.42 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 160.8, 155.9, 141.6, 136.4, 130.7, 129.8 (× 2), 129.4 (× 2), 129.0, 126.9 (× 2), 125.9 (× 2), 109.0, 100.9, 21.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{14}NaO_2$: 285.0891; found: 285.0886.

6-(4-Methoxyphenyl)-4-phenyl-2*H*-pyran-2-one (4ac)

According to GP with **2c** (39 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 5:1) afforded α-pyrone **4ac** (8 mg, 29%) as a yellowish solid; mp 115 °C.

FTIR (neat): 2254, 1715, 1608, 1508, 1464, 1257, 903, 722, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.82 (m, 2 H), 7.67–7.60 (m, 2 H), 7.55–7.47 (m, 3 H), 7.04–6.93 (m, 2 H), 6.85 (d, *J* = 1.5 Hz, 1 H), 6.41 (d, *J* = 1.5 Hz, 1 H), 3.88 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 162.0, 160.7, 156.1, 136.5, 130.7, 129.3 (× 2), 127.6 (× 2), 126.9 (× 2), 124.3, 114.6 (× 2), 108.3, 100.1, 55.6.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{14}NaO_3$: 301.0841; found: 301.0835.

6-(4-Bromophenyl)-4-phenyl-2*H*-pyran-2-one (4ad)

According to GP with **2d** (49 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ad** (17 mg, 52%) as a yellowish solid; mp 173 °C.

FTIR (neat): 2255, 2210, 1724, 1630, 1538, 1486, 903, 723, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82–7.72 (m, 2 H), 7.68–7.58 (m, 4 H), 7.56–7.49 (m, 3 H), 6.94 (d, *J* = 1.5 Hz, 1 H), 6.48 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4, 159.4, 155.6, 136.0, 132.4 (× 2), 130.9, 130.6, 129.4 (× 2), 127.3 (× 2), 126.9 (× 2), 125.6, 109.8, 101.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{11}BrNaO_2$: 348.9840; found: 348.9835.

6-(4-Chlorophenyl)-4-phenyl-2*H*-pyran-2-one (4ae)

According to GP with **2e** (40 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ae** (19 mg, 67%) as a white solid; mp 170 °C.

FTIR (neat): 2254, 1719, 1628, 1540, 1491, 1094, 903, 723, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90–7.78 (m, 2 H), 7.68–7.60 (m, 2 H), 7.57–7.46 (m, 3 H), 7.48–7.43 (m, 2 H), 6.94 (d, *J* = 1.5 Hz, 1 H), 6.48 (d, *J* = 1.4 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.4, 159.4, 155.6, 137.2, 136.1, 130.9, 130.2, 129.4 (× 4), 127.1 (× 2), 126.9 (× 2), 109.7, 101.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{11}ClNaO_2$: 305.0345; found: 305.0340.

6-(4-Fluorophenyl)-4-phenyl-2*H*-pyran-2-one (4af)

According to GP with **2f** (37 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4af** (17 mg, 64%) as a white solid; mp 146 °C.

FTIR (neat): 2188, 1718, 1678, 1507, 1160, 903, 721, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96–7.86 (m, 2 H), 7.68–7.61 (m, 2 H), 7.55–7.49 (m, 3 H), 7.22–7.13 (m, 2 H), 6.90 (d, *J* = 1.5 Hz, 1 H), 6.47 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 162.8, 162.6, 159.6, 155.8, 136.2, 130.9, 129.4, 128.1, 128.0, 126.9, 116.5, 116.2, 109.3, 101.3, 101.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{11}FNaO_2$: 289.0641; found: 289.0635.

6-(3-Bromophenyl)-4-phenyl-2*H*-pyran-2-one (4ag)

According to GP with **2g** (49 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ag** (22 mg, 68%) as a yellowish solid; mp 155 °C.

FTIR (neat): 2253, 2163, 1721, 1629, 1539, 1472, 903, 722, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.03 (t, *J* = 1.8 Hz, 1 H), 7.82 (dt, *J* = 7.9, 1.3 Hz, 1 H), 7.66–7.57 (m, 3 H), 7.55–7.48 (m, 3 H), 7.35 (t, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 1.5 Hz, 1 H), 6.49 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 158.8, 155.5, 135.9, 133.9, 133.6, 131.0, 130.6, 129.4 (× 2), 128.8, 126.8 (× 2), 124.4, 123.3, 110.1, 102.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{11}BrNaO_2$: 348.9840; found: 348.9835.

6-(3-Chlorophenyl)-4-phenyl-2*H*-pyran-2-one (4ah)

According to GP with **2h** (40 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ah** (21 mg, 74%) as a white solid; mp 159 °C.

FTIR (neat): 2256, 1694, 1628, 1536, 1428, 905, 762, 677 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88 (t, *J* = 1.9 Hz, 1 H), 7.78 (dt, *J* = 6.7, 1.9 Hz, 1 H), 7.68–7.61 (m, 2 H), 7.55–7.50 (m, 3 H), 7.47–7.36 (m, 2 H), 6.96 (d, *J* = 1.5 Hz, 1 H), 6.50 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 158.9, 155.5, 135.9, 135.4, 133.4, 131.0, 131.0, 130.4, 129.4 (× 2), 126.9 (× 2), 126.0, 124.0, 110.1, 102.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{11}ClNaO_2$: 305.0345; found: 305.0340.

6-(Naphthalen-2-yl)-4-phenyl-2*H*-pyran-2-one (4ai)

According to GP with **2i** (43 mg, 0.20 mmol, 2.0 equiv) and *trans*-cinnamaldehyde (**1a**, 13.2 µL, 0.10 mmol, 1.0 equiv). FC (silica gel, pentane/EtOAc 10:1) afforded α-pyrone **4ai** (17 mg, 56%) as a yellowish solid; mp 148 °C.

FTIR (neat): 2252, 2159, 2067, 1725, 1624, 1533, 903, 722, 650 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (br s, 1 H), 8.03–7.80 (m, 4 H), 7.79–7.62 (m, 2 H), 7.64–7.46 (m, 5 H), 7.09 (d, *J* = 1.5 Hz, 1 H), 6.51 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.8, 160.5, 155.8, 136.3, 134.5, 133.2, 130.8, 129.4, 129.3, 129.2, 128.9, 128.7, 127.9, 127.2, 126.9, 126.9, 126.5, 122.3, 109.5, 101.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{14}NaO_2$: 321.0891; found: 321.0886.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588336.

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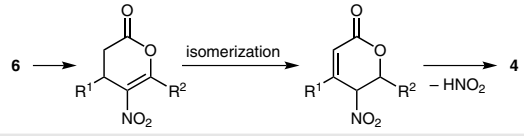
(13) It is also possible that the intermediate **6** may undergo intramolecular proton transfer to give a ketone enolate which then lactonizes to the corresponding dihydropyranone. Subsequent double bond isomerization and HNO_2 elimination will afford α-pyrone **4** (Scheme 4). We thank a reviewer for this valuable suggestion.



Scheme 4