Efficient and Atom-Economic Synthesis of α-Substituted β-Chromonyl-α,β-unsaturated Carbonyls through Molecular Rearrangement

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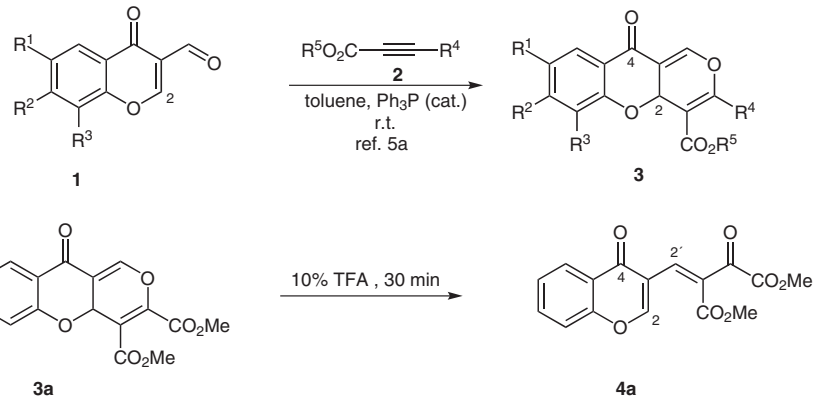
Abstract: Under mild acidic conditions [4+2] cycloadducts of 3-formylchromones and acetylenecarboxylates rearrange to yield α-substituted-β-chromonyl-α,β-unsaturated carbonyl compounds in excellent yields.

Key words: benzopyrones, rearrangements, cascade reactions, acetylenecarboxylates

Benzopyrone scaffold is one of the privileged molecular frameworks embodied by many natural products displaying diverse biological activities.[1] It had inspired chemists to generate compound libraries based on benzopyrone and related molecular architectures for medicinal chemistry and chemical biology investigations.[2] To get an easy access to a large number of diverse molecules based on benzopyrone scaffold, the substrates should be either commercially available or accessible by efficient synthetic processes. For instance, commercially available substituted 3-formylchromones[3] have been extensively employed in the synthesis of skeletally diverse compound collections.[4] In the same context, benzopyrone-substituted olefins can be regarded as important precursors for generating diverse hetero- and carbocyclic molecules.[4d] These olefins in principle can be obtained either by Wittig olefination of chromone aldehydes with phosphorus ylides or by an aldol condensation reaction with active methylene carbonyls under basic reaction conditions. However, if the availability of the desired phosphoranes for the Wittig reaction is one limitation, the facile addition of carbon nucleophile to highly electrophilic C-2 carbon of the 3-formylchromones (**1**) leading to chromone ring opening[3] makes them hard substrates for condensation reactions too. Moreover, atom-economic alternatives to aldol condensation and Wittig olefination are always desired. Recently, we discovered a novel phosphine-catalyzed [4+2]-annulation reaction between 3-formylchromones **1** and electron-deficient acetylene carboxylates **2**.[5a] However, during attempts to resolve the enantiomers of the adduct **3** using chiral HPLC, partial transformation of **3** into another compound was observed. Suspecting that the trifluoroacetic acid (TFA) present in the solvent system was responsible for this transformation, pure adduct **3a** was treated overnight with 1% TFA in dichloromethane. A simple silica gel column chromatographic purification of the crude reaction mixture yielded the dimethyl-2-oxo-3-[(4-oxo-4*H*-chromene-3-yl)methylene]succinate (**4a**) in 55% yield (Scheme 1).

Further, we observed that increasing the concentration of TFA to 10% in dichloromethane could complete the reaction in half an hour and yielding **4a** quantitatively. On the other hand catalytic amounts of the TFA could not complete the reaction even after 48 hours. Although, $BF_3 \cdot OEt_2$ completed the reaction within ten minutes with slightly reduced yield of **4a**, we preferred to use the milder reaction conditions with TFA for this transformation.[6]



Scheme 1

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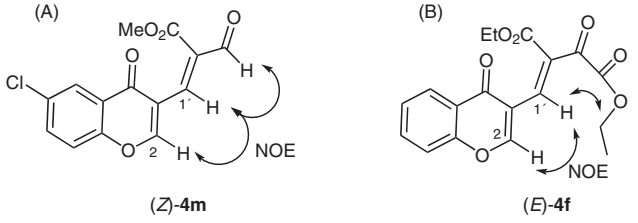
Structure of the product **4a** was corroborated by spectroscopic analysis.[7–9] Whereas the mass analysis revealed **4a** to be isomeric to the substrate, disappearance of singlet peak for C2-H of **3a** and appearance of one for an olefinic proton (in aromatic region) in ^{1}H NMR spectrum suggested the rearrangement of the adduct **3**. Further, appearance of a doublet at δ = 8.32 ppm for one proton (with long-range coupling to another proton at δ = 7.50 ppm) in the ^{1}H NMR spectrum (for C2-H of **4a**) and the appearance of C-4 at δ = 174 ppm[10] in the ^{13}C NMR spectrum indicated the intact chromone moiety with an α,β-unsaturated carbonyl branch on C-3. The ketone carbonyl of the ketoesters moiety appeared at δ = 180.8 ppm in the ^{13}C NMR spectrum confirming the structure to be **4a**.

The reaction yielded the conjugated ketoesters decorated with a substituted benzopyrone moiety in excellent yields (Table 1, entries 1–7). Interestingly, when **3h** supporting only one ester moiety was treated with TFA, conjugated aldehyde **4h** was obtained in very good yield (entry 8, Table 1).[8] Substrates **3i**–**n** yielded the corresponding β-chromonyl acrylates **4i**–**n** in acceptable yields (entries 9–14, Table 1). Further, employing the adduct **3o** supporting a phenyl group yielded the corresponding phenyl ketone **4o**[9] in good yield (entry 15, Table 1).

The NMR spectra and LC-MS analysis clearly indicated the formation of a single isomer of **4**. The configuration of the molecules **4** was elucidated with the help of 1D NOE NMR experiments. Selective irradiation of the aldehydic proton in **4m** led to enhancement of the signal for C1′-H. On irradiating the latter, a clear enhancement for the C2-H (and vice versa) was observed, thus establishing the *Z*-configuration to the molecule (Figure 1, A). Similar NOE effects were observed in the case of ketoester **4f**. While irradiation of C2-H in **4f** resulted in signal enhancement for C1′-H; the latter on irradition led to the signal enhancement for C2-H besides a weak signal enhancement for the methylene(-OCH_2Me) proton of ketoester (established by HMBC and HSQC NMR experiments, Figure 1, B). Thus, *E*-configuration was assigned to the ketoesters **4a**–**g**.

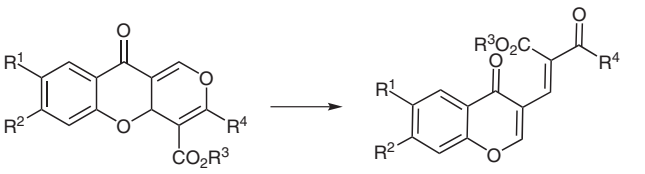


(*Z*)-**4m** (*E*)-**4f**

Figure 1

Mechanistically, we assume that the [4+2] adducts **3** act as push–pull system under acidic conditions. Facilitated by the formation of aromatic pyrilium cation, the chromone ring would open up yielding **5** which undergoes intramolecular addition of the phenol leading to cyclic allyl vinyl ether **6** formation. The latter could undergo protonation and ring opening of the dihydropyran ring forming an extended enol **7** which tautomerize to the observed product after a single-bond rotation to avoid the steric proximity of the ester functionality to the benzopyrone ring. Alternatively, the Claisen ring opening of **6** would yield the isomer of observed product **4′** which could isomerize via acid-catalyzed tautomerism to **7** before transforming to **4** (Scheme 2).[11]

Table 1 Rearrangement of the Adducts **3** to **4**[a]



3 **4**

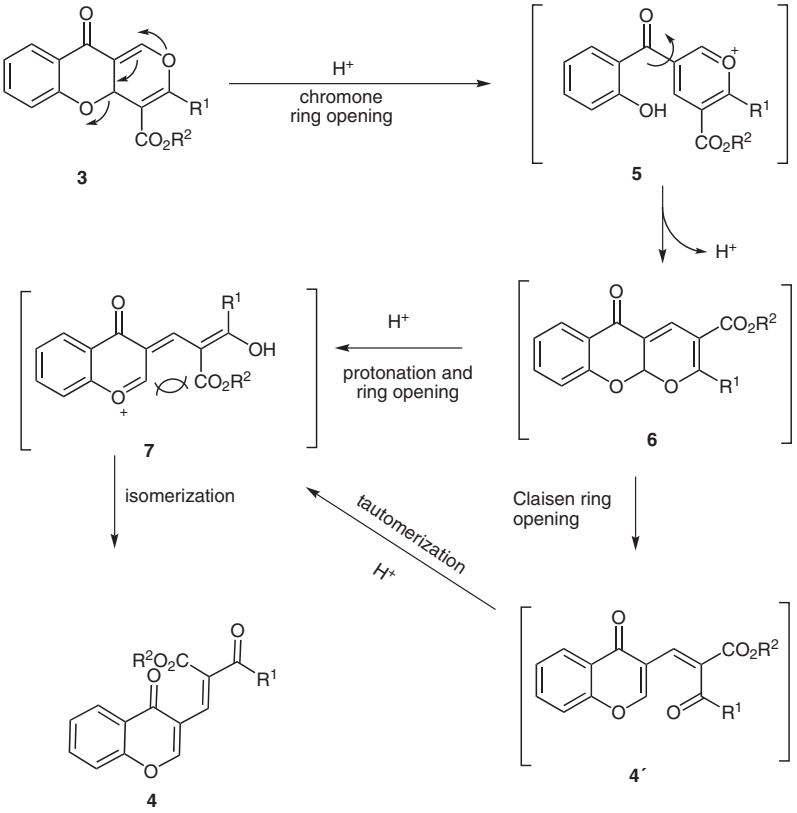
Entry	R^1	R^2	R^3	R^4	Yield of **4** (%)[b]
1	H	H	Me	CO_2Me	**4a** 99
2	Cl	H	Me	CO_2Me	**4b** 94
3	*i*-Pr	H	Me	CO_2Me	**4c** 98
4	*i*-Pr	H	Et	CO_2Et	**4d** 98
5	Me	H	Et	CO_2Et	**4e** 91
6	H	H	Et	CO_2Et	**4f** 97
7	Cl	H	Et	CO_2Et	**4g** 91
8	H	H	Me	H	**4h** 87
9	Cl	Me	Me	H	**4i** 94
10	Me	H	Me	H	**4j** 92
11	H	H	*t*-Bu	H	**4k** 98
12	*i*-Pr	H	Me	H	**4l** 88
13	Cl	H	Me	H	**4m** 82
14	Br	H	Me	H	**4n** 83
15	H	H	Et	Ph	**4o** 89

[a] Reaction conditions: 10% TFA in CH_2Cl_2, 30 min, r.t.
[b] Isolated yields after flash column chromatography.

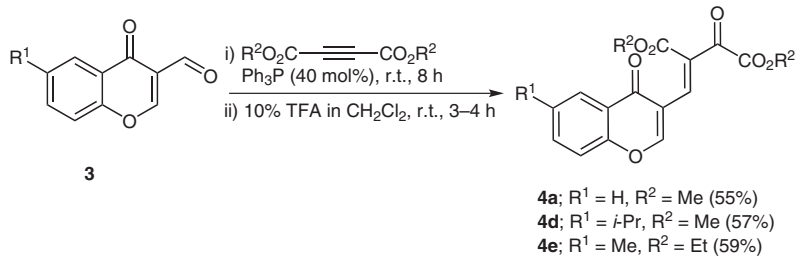
In order to make a direct access to the products **4** employing commercially available 3-formylchromones, a one-pot, two-step procedure was developed. To this end, 3-formylchromone was treated with dimethylacetylene-dicarboxylate (DMAD) and triphenylphosphine to yield the [4+2] adduct **4a**. After completion of the reaction (TLC), it was quenched by slow addition a solution of 10% TFA in dichloromethane at low temperature (0–4 °C) and stirring the solution at room temperature for three to four hours (TLC).

Although, by this method we could avoid the purification of adducts **3**, the yields of the rearrangement products **4** were clearly compromised (Scheme 3).

In summary, we have discovered a very efficient, easy, and atom-economic cascade synthesis of benzopyrone-



Scheme 2 Cascade rearrangement of adducts **3** to **4**



Scheme 3 One-pot synthesis of **4** from commercially available 3-formylchromones

substituted acrylates and oxosuccinates. The significance of this methodology could be realized from the fact that other possible routes to these molecules should be multi-step and tedious considering the reactivity of 3-formyl-chromones.[3,12] The reactive aldehyde and ketoester functionalities in the molecules **4** would always compete with substrates in alternative routes.[13] We are currently exploring the applications of these molecules in compound library syntheses which shall be reported in the near future.

Acknowledgment

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(6) **General Procedure for the Rearrangement of the Adducts 3 to 4**
TFA (1 mL in 5 mL CH_2Cl_2) was added slowly dropwise to the CH_2Cl_2 solution (5 mL) of the tricyclic benzopyrones **3** (1 mmol). The reaction mixture was stirred at r.t. for 30 min under argon. The reaction was monitored by TLC using cyclohexane–EtOAc (7:3) as eluent. After evaporation of the solvent, the crude product was purified by column chromatography on silica gel with cyclohexane–EtOAc as the eluent.

(7) **Spectroscopic Data for the Ketoester 4a**
Yellow solid; mp 177–178 °C; R_f = 0.33 (cyclohexane–EtOAc, 6:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 0.7 Hz, 1 H), 8.21–8.19 (dd, *J* = 1.6, 8.0 Hz, 1 H), 7.63 (td, *J* = 1.6, 7.8 Hz, 1 H), 7.50 (d, *J* = 0.7 Hz, 1 H), 7.49–7.47 (dd, *J* = 1.0, 7.4 Hz, 1 H), 7.43 (td, *J* = 1.0, 7.4 Hz, 1 H), 3.98 (s, 3 H), 3.82 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.8, 174.0, 164.8, 161.1, 159.6, 155.7, 134.6, 132.9, 131.6, 126.7, 126.2, 123.3, 118.3, 118.0, 53.1, 52.6. ESI-HRMS: *m/z* calcd for $C_{16}H_{13}O_7$ [M + H$^+$]: 317.06558; found: 317.06568.

(8) **Spectroscopic Data for the Aldehyde 4h**
Yellow solid; mp 120–122 °C; R_f = 0.39 (cyclohexane–EtOAc, 6:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.71 (s, 1 H, CHO), 8.66 (d, *J* = 0.8 Hz, 1 H), 8.28–8.24 (m, 2 H), 7.73 (d, *J* = 0.8 Hz, 1 H), 7.52–7.44 (m, 2 H), 3.89 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.3, 174.8, 165.6, 158.4, 155.8, 140.8, 134.5, 133.8, 126.4, 126.3, 123.6, 118.4, 118.3, 52.6. ESI-HRMS: *m/z* calcd for $C_{14}H_{11}O_5$ [M + H$^+$]: 259.06010; found: 259.06017.

(9) **Spectroscopic Data for the Phenyl Ketone 4o**
Yellow solid; mp 171–173 °C; R_f = 0.45 (cyclohexane–EtOAc, 6:4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18–8.16 (dd, *J* = 1.3, 8.4 Hz, 1 H), 8.15 (d, *J* = 1.0 Hz, 1 H), 8.05 (d, *J* = 1.0 Hz, 1 H), 7.93–7.91 (dd, *J* = 1.3, 8.4 Hz, 1 H), 7.63 (td, *J* = 7.8 Hz, 1 H), 7.55–7.35 (m, 5 H), 7.28–7.25 (m, 1 H), 4.25–4.19 (q, *J* = 7.1 Hz, 2 H), 1.17 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.5, 175.2, 164.3, 156.2, 155.8, 140.6, 136.1, 134.1, 133.8, 132.9, 129.8, 129.0, 128.7, 128.5, 126.1, 125,7, 123.5, 119.0, 118.1, 61.5, 13.9. ESI-HRMS: *m/z* calcd for $C_{21}H_{17}O_5$ [M + H$^+$]: 349.10705; found: 349.10719.

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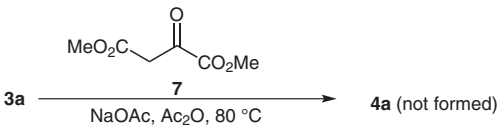
(13) An alternative synthesis of **4** by a Wittig olefination of 3-formylchromone would require the corresponding ketoester or aldehydic phosphoranes which are not commercially available and require multistep synthesis and also remain susceptible to self-olefination and polymerization reaction. The same is true for the alternative aldol condensation strategy to provide **4** by reacting chromone aldehydes with ketoester **7**. Using our previously reported methodology[14] to condense 1,3-dicarbonyls with 3-formylchromone, we could observe self-condensation products of **7** but not any formation of **4a** (Scheme 4).



Scheme 4

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