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4-Picoline-catalyzed hetero-Diels–Alder type reactions: one-pot synthesis of pyrano[4,3-*c*]chromenes

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ABSTRACT

An organocatalytic hetero-Diels–Alder type reaction between α,β-unsaturated aldehydes and acetylenedicarboxylates is achieved which offers an efficient one-pot access to pyrano[4,3-*c*]chromenes from simple and readily available starting materials under mild reaction conditions.

One of the rapidly growing research areas in the field of organic synthesis is that of catalytic transformations utilizing small organic molecules called organocatalysts.[1] Although the first organocatalytic reaction was reported in the early 1970s,[2] organocatalysis was not viewed as a viable alternative to the two main classes of established catalysts (transition metal complexes and enzymes). A report, which appeared in 2000, changed completely this perception and highlighted the fascinating attributes of small organic molecules as catalysts.[3] Recently, the pyrrolidine-catalyzed synthesis of chromene-3-carbaldehyde derivatives has also been reported.[4]

The possibility of carbon–carbon bond formation by intermolecular trapping of the 1,4-zwitterionic intermediate generated from pyridine acting as an organocatalyst and dimethyl acetylenedicarboxylate (DMAD) with aldehydes, but also as a whole with carbonyl compounds, has been studied recently.[5] Mechanistically, the reaction was rationalized as involving attack of the zwitterionic intermediate on the aldehyde carbonyl, followed by a [1,3]-hydrogen shift and finally formation of (*E*)-2-aryl-but-2-enedioic esters through elimination of pyridine.

Since chromone-3-carboxaldehydes represent a very reactive system owing to the presence of an unsaturated keto function, a conjugated second carbonyl group at C-3, and above all, of an electrophilic center at C-2, which is very reactive toward Michael addition of nucleophiles, we speculated that a zwitterionic intermediate would most probably initially attack the C-2 carbon giving the reaction a different perspective.

Moreover, besides forming the basic nucleus of an entire class of natural products, that is, flavones,[6] the chromone moiety forms the important component of pharmacophores of a large number of molecules of medicinal significance[7] including anticancer agents such as psorospermin and pluramycin A.[8,9] Consequently, considerable attention is being devoted to the isolation from natural resources, and the chemistry and synthesis of chromone derivatives, as well as evaluation of their biological activity with particular focus on their potential medicinal applications.[7–11]

The reaction of chromone-3-carboxaldehyde (**1a**) and DMAD (**2a**) was selected as a model reaction. Organocatalysts were examined first and the results are summarized in Table 1. The reaction gave a poor yield of dimethyl 10-oxo-4a*H*,10*H*-pyrano[4,3-*b*]chromene-3,4-dicarboxylate (**3a**) when pyridine was used as the organocatalyst, and only traces of the product, when an electron-withdrawing substituent was introduced onto the catalyst. An analogous outcome occurred, when 2-methylpyrazine was used as the catalyst. However, the reaction proceeded smoothly with 4-methylpyridine (4-picoline) giving the pyranochromene **3a** in 42% yield. The yield was slightly improved when 100 mol % of 4-methylpyridine was used.[12]

After the reaction conditions were optimized, the generality of the reaction was investigated, and the results summarized in Table 2 show that the reaction has broad applicability.[13]

The product yield seems to be affected by the nature of the substituent at C-6 and increases when electron-donating substituents are present.

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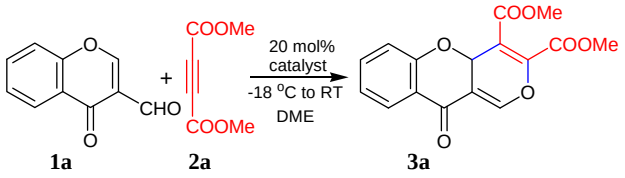
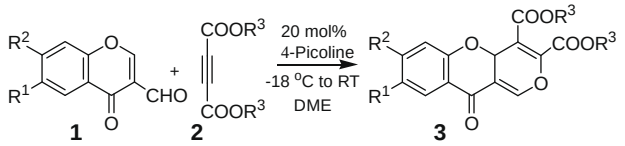
Table 1
The effect of the organocatalyst on the hetero-Diels–Alder type reaction of chromone-3-carboxaldehyde and DMAD[a]



Entry	Catalyst	Yield[b] (%)
1	Pyridine	15
2	4-Methylpyridine	42
3	4-Methylpyridine[c]	45
4	4-Chloropyridine	Trace
5	2-Methylpyrazine	Trace

[a] The reaction was performed with **1a** (1.0 mmol), **2a** (1.2 mmol), catalyst (0.2 mmol), and dimethoxyethane (10 mL) as solvent.
[b] Yield of isolated product.
[c] 100 mol % catalyst.

Table 2
Catalytic hetero-Diels–Alder type cycloadditions of chromone-3-carboxaldehydes with acetylenedicarboxylates

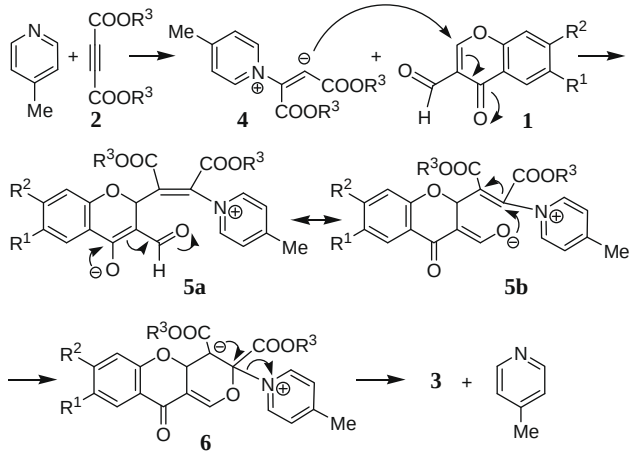


Entry		R^1	R^2		R^3	Product	Yield
1	**1a**	H	H	**2a**	Me	**3a**	42
2	**1b**	Me	H	**2a**	Me	**3b**	47
3	**1c**	$CH(Me)_2$	H	**2a**	Me	**3c**	48
4	**1d**	Cl	H	**2a**	Me	**3d**	39
5	**1e**	Cl	Me	**2a**	Me	**3e**	41
6	**1b**	Me	H	**2b**	Et	**3f**	45
7	**1c**	$CH(Me)_2$	H	**2b**	Et	**3g**	51
8	**1d**	Cl	H	**2b**	Et	**3h**	38

Another important feature of the above methodology is the fact that the chromone moiety remains intact. It should be noted that the synthetic utility of chromones is limited due to facile opening of the chromone ring[14] and strategies are being developed to circumvent this.[15] After our experimental work was completed, a publication describing the organocatalysed reaction of acetylene dicarboxylates with formyl chromones to yield pyranochromenes, by using phosphines and quinoline containing cinchona alkaloids as catalysts appeared in the literature.[16]

Mechanistically, the reaction may be rationalized as involving initial attack of the 1,4-zwitterion **4**, generated from 4-methylpyridine and acetylenedicarboxylate, on the C-2 carbon of chromone **1** to give the intermediate **5**, which after ring closure to **6** undergoes elimination of the catalyst to afford **3** (Scheme 1).

The molecular structures of all new compounds **3** were assigned on the basis of rigorous spectroscopic analysis including IR, NMR (^1H, ^{13}C, DEPT, COSY, NOESY, HETCORR, and COLOC), MS, and elemental analysis data. The assignment of **3a** is described. The elemental analysis and mass spectra established the reaction of one molecule of chromone-3-carboxaldehyde with one molecule of DMAD. Moreover, in the IR spectrum the two chromone carbonyls (1695 and 1650 cm^{-1}) were replaced by carbonyl absorptions at 1754, 1729, and 1696 cm^{-1}. The chromone aromatic moiety was easily identified from the splitting pattern of the aromatic protons.[13] Two further protons resonating at δ 5.93 and δ 7.56 with a mutual allylic coupling of 1.2 Hz were observed in the product. The proton at δ 7.56 with its carbon resonating at 144.8 ppm indicated the proximity of an oxygen and showed COLOC correlations via $^2J_{C-H}$ and $^3J_{C-H}$ with the quaternary carbons at 112.9 (C-10a), 180.9 (C-10), and at 146.3 ppm (C-3, bearing a carbomethoxy moiety) and also with the protonated carbon at 67.2 ppm (C-4a, proton at δ 5.93). These findings indicated that the carbon resonating at 144.8 ppm corresponds to the former formyl chromone carbon, the formyl oxygen forming a bond with the acetylenic moiety. Finally, the proton at δ 5.93 showed correlations via $^2J_{C-H}$ and $^3J_{C-H}$ with both former acetylenic carbons at 111.1 (C-4) and 146.3 ppm (C-3), with the quaternary carbon at 112.9 (C-10a), and also with the protonated carbon at 144.8 ppm (C-1), indicating a favorable configuration of this proton in the 4*H*-pyran ring.



Scheme 1. Proposed mechanism for the hetero-Diels–Alder type reaction.

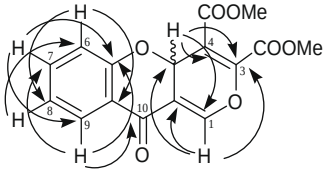


Figure 1. COLOC correlations of protons and carbons via $^2J_{CH}$ and $^3J_{CH}$ coupling in compound **3a**.

The COLOC correlations of protons and carbons via $^2J_{CH}$ and $^3J_{CH}$ coupling for compound **3a** are depicted in Figure 1.

In summary, we have reported a new and efficient methodology for an organocatalytic hetero-Diels–Alder type reaction between α,β-unsaturated aldehydes and acetylenedicarboxylates leading to a one-pot synthesis of pyrano[4,3-*c*]chromenes. Another important feature of the above methodology is the fact that the chromone moiety remains intact. The reaction is of interest since reactions involving organocatalysis have been developed rapidly in recent years.[17] In addition, Diels–Alder reactions represent a powerful organic transformation and constitute a versatile method for the synthesis of many building blocks for the total synthesis of bioactive natural products.[18] Finally, pyranochromenes belong to an important class of heterocycles, which have attracted considerable interest in organic and natural product synthesis.[19] Molecules with the pyranochromene moiety are found in Nature[20] and also exhibit a wide range of biological and pharmacological properties.[21]

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12. On using the stronger base 4-*N*,*N*-dimethylaminopyridine (DMAP) the reaction follows a different pathway, which is under further investigation.
13. In a typical experimental procedure, dimethyl acetylenedicarboxylate (0.2 mL, 1.2 mmol) was added to a stirred solution of chromone-3-carboxaldehyde (174 mg, 1 mmol) and 4-methylpyridine (0.1 mL, 0.2 mmol) in dimethoxyethane (10 mL) at −18 °C. The system was allowed to attain room temperature (~25 °C) and was stirred for 12 h in total. Distillation of the solvent in vacuo was followed by column chromatography on silica gel (ethyl acetate/hexane = 1:3) to give dimethyl 10-oxo-4a*H*,10*H*-pyrano[4,3-*b*]chromene-3,4-dicarboxylate (**3a**), 42% yield. White crystals, mp 126–128 °C (Et_2O–hexane). IR (Nujol) ν_{max}: 1754, 1729, 1696 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 3.92 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.93 (d, J = 1.2 Hz, 1H, 4a-H), 6.98 (dd, J = 8.4, 1.0 Hz, 1H, 6-H), 7.10 (ddd, J = 8.0, 7.1, 1.0 Hz, 1H, 8-H), 7.53 (ddd, J = 8.4, 7.1, 1.7 Hz, 1H, 7-H), 7.56 (d, J = 1.2 Hz, 1H, 1-H), 7.95 (dd, J = 8.0, 1.7 Hz, 1H, 9-H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.9 (OCH_3), 53.4 (OCH_3), 67.2 (C-4a), 111.1 (C-4), 112.9 (C-10a), 118.5 (C-6), 122.4 (C-8), 122.6 (C-9a), 127.4 (C-9), 136.7 (C-7), 144.8 (C-1), 146.3 (C-3), 158.9 (C-5a), 160.7 (C=O), 164.6 (C=O), 180.9 (C-10). MS (LC–MS) m/z (%): 339 (100, M^++Na). Anal. Calcd for $C_{16}H_{12}O_7$ (316.26): C, 60.76; H, 3.82. Found: C, 60.63; H, 3.88.
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