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N-Heterocyclic Carbene Catalysis

Sequential N-Heterocyclic Carbene-Catalyzed Reactions of Enals and Cyclic Aryldiene-1,3-Diones: Synthesis of Tricyclic Chromenones and Related Compounds

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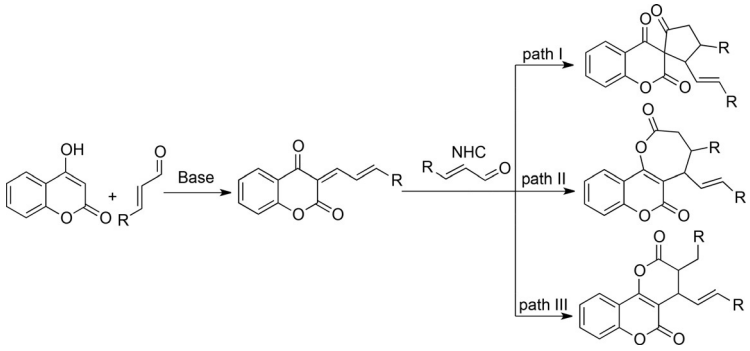
Dedicated with best wishes to Professor Gilbert Stork on the occasion of his 95th birthday

Abstract: N-Heterocyclic carbene (NHC)-catalyzed synthesis of highly functionalized pyrano[3,2-*c*]chromene-2,5-dione derivatives, pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione derivatives, and pyrano[4,3-*b*]pyran-2,5-dione derivatives with potential biological activities is reported. The reaction occurs through a Knoevenagel condensation and NHC-catalyzed enolate addition in one pot.

The renaissance of N-heterocyclic carbene (NHC)[1] catalysis actuated by the annulation of enals to aldehydes leading to γ-lactones via the intermediacy of homoenolate opened entirely new vistas in organic synthesis.[2] Recent work in this area has led to the synthesis of a wide range of compounds; these include cyclopentenes,[3,4] cyclopentanoids and spiro cyclopentanones,[5] lactams,[6] pyrazolidinones,[7] pyranones,[8] GABA (γ-aminobutyric acid) analogs/precursors,[9] γ-lactones and δ-lactones,[10] and other assorted compounds.[11] In spite of the extensive research in this area, reactions involving enals and 1,3-dicarbonyl compounds under NHC catalysis have received only scant attention; noteworthy in this context are the Diels–Alder and Stetter reactions involving enals and alkylidene diones, under NHC catalysis, reported by Chi and co-workers.[12] Although peripheral to the present work, it is worthy of mention that 1,3-diketones have been widely used in the synthesis of heterocycles by the exploitation of azolium intermediates.[13] Conspicuously, the reactivity of enals towards cyclic enediones under NHC catalysis remained uninvestigated in the context of homoenolates and enolate reactions. In view of our long-standing interest in the reactivity of enals towards a wide range of carbonyl compounds,[1m] it was decided to explore the NHC-catalyzed reaction of enals with aryldiene derivatives of cyclic 1,3-dicarbonyl compounds. A priori, it was conceptualized that 4-hydroxycoumarin on exposure to enals in the presence of base would yield the corresponding dienedione, which would predictably react with a second molecule of the enal under NHC catayasis to afford one or more of the compounds shown in Scheme 1. Coincidentally, while this work was under completion, as part of their studies on the three-component



Scheme 1. Postulated reaction sequence.

reactions of pyrazolones and enals, Enders and co-workers reported that dimedone and analogs underwent NHC-catalyzed condensation to afford 2,5-chromene diones.[14]

The selection of 4-hydroxycoumarin as the initial substrate was influenced by the fact that coumarin derivatives are known to display impressive anticoagulant, antimicrobial, anti-HIV, anticancer, anti-inflammatory, and antioxidant activities.[15] Some selected coumarin derivatives with medicinal properties are shown in Figure 1.

Not surprisingly, there have been substantial efforts toward the synthesis of complex coumarin derivatives.[16] Relevent to the present studies are NHC-catalyzed annulations of modified enals with heterocyclic C–H acid reported by Biju and co-work-

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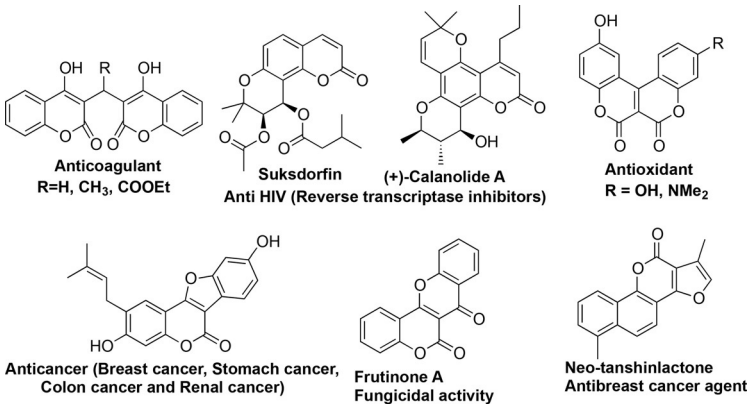


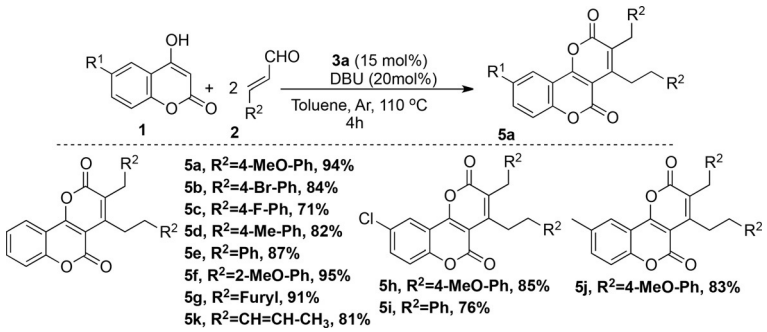
Figure 1. Biologically active coumarin derivatives.

ers,[17a] one-pot sequential Michael addition/hydroalkoxylation reactions by merging silver catalysis with primary amine catalysis reported by Enders and co-workers,[17b] and the coumarin derivative synthesis through intramolecular Michael addition of homoenolates reported by our group.[17c] It is also noteworthy that the diaryl prolinol TMS ether catalyzed reaction of enal with 2-hydroxynaphthoquinone, 4-hydroxycoumarin, and analogous compounds leading to pyranonaphthoquinones, chromenones, quinolinones, etc. has been studied in detail by Rueping and co-workers.[18]

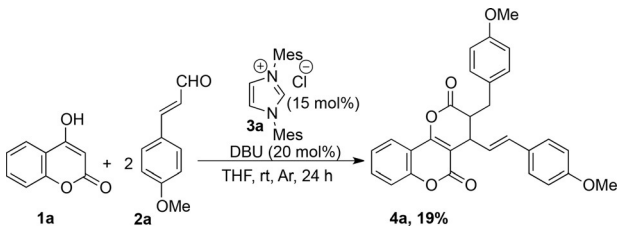
Against the backdrop of the above observations, a pilot experiment was conducted and the details are as follows. 4-Hydroxycoumarin **1a** (0.25 mmol), 4-methoxycinnamaldehyde **2a** (0.75 mmol), and imidazole-2-ylidinium chloride **3a** (15 mol%) were dissolved in THF and stirred under argon. To this mixture, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 20 mol%) was added and the stirring continued for 24 h. The reaction mixture upon column chromatography afforded the product, a white solid, and on the basis of spectroscopic data, it was assigned the structure (*E*)-3-(4-methoxybenzyl)-4-(4-methoxystyryl)-3,4-dihydropyrano[3,2-*c*]chromene-2,5-dione **4a**. The yield was only 19% and it was 1:1 mixture of diastereomers (Scheme 2).

Subsequent to the preliminary experiments, detailed optimization studies were carried out (Table 1). It was found that the IMes·HCl (IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazolium) is the only catalyst that gave the product (entry 1). Among the other solvents tested, CH_2Cl_2 as well as toluene gave the expected product **4a** in 17% yield with 1:1 diastereomeric ratio (entries 5 and 6). In the case of acetonitrile, no product was observed (entry 7). Next, we tested other bases such as NEt_3, KO*t*Bu, and K_2CO_3; however, no product was obtained (entries 8–10). Finally, the effect of temperature on the reaction was tested; in this context, we conducted an experiment in THF under reflux conditions. Interestingly, it was observed that the reaction afforded **4a** along with the isomeric product **5a** in a 1:1 ratio with an overall yield of 94%, in this case also, **4a** was found to be a 1:1 diastereomeric mixture (entry 11). When the reaction time was increased to 24 h in THF under reflux conditions, a slight improvement in the formation of product **5a** was observed (entry 12). A similar result was obtained when the reaction was conducted in toluene at 70 °C (entry 13). With a view to optimizing the yield of **5a**, the reaction was carried out in toluene heated to reflux. Gratifyingly, it was observed that the product **5a** was formed in 94% yield (entry 14). The structure of **5a** was assigned as 3-(4-methoxybenzyl)-4-(4-methoxyphenethyl)pyrano[3,2-*c*]chromene-2,5-dione on the basis of spectroscopic analyses. Conclusive evidence for the assigned structure was obtained from single-crystal X-ray analysis of an analogous compound **5f** (Figure 2).

After optimizing the reaction conditions, we studied the substrate scope of this remarkable NHC-catalyzed annulation reaction (Scheme 3). Initially, we examined the scope of enals and 4-hydroxycoumarin. It was found that the enals with various electron-withdrawing or electron-donating substituents on the 4-position of the β-aryl ring gave the annulation products, pyranochromene-2,5-diones, in good to excellent yields (**5a**–**5d**). It was found that the 2-methoxy substituent on the β-aryl ring of enal resulted in the formation of the desired product in excellent yield (**5f**). The furyl-substituted enal also furnished



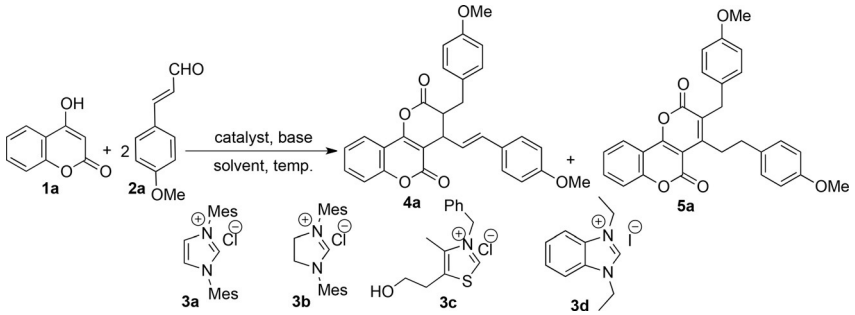
Scheme 3. Reaction of enals with 4-hydroxycoumarins. Isolated yields given.



Scheme 2. Reaction of 4-hydroxycoumarin with enal.

the annulated product in excellent yield (**5g**). Moreover, the reaction proceeded well with electron-withdrawing or electron-donating substituents on the aromatic ring of 4-hydroxycoumarin (**5h**, **5j**). In view of the pleasing results obtained with enals, it was decided to examine the reaction of a dienal **2k** with 4-hydroxycoumarin. Satisfyingly, 3-((*E*)-but-2-en-1-yl)-4-((*E*)-pent-3-en-1-yl)pyrano[3,2-*c*]chromene-2,5-dione **5k**, endowed with two alkenyl chains, was obtained in 81% yield.

Table 1. Optimization of reaction conditions.



Entry	Catalyst	Solvent, Base, *T*, *t* [h]	**4a** Yield [%]	**5a** Yield [%]
1	**3a**	THF, DBU, rt, 24	19	–
2	**3b**	THF, DBU, rt, 24	–	–
3	**3c**	THF, DBU, rt, 24	–	–
4	**3d**	THF, DBU, rt, 24	–	–
5	**3a**	CH_2Cl_2, DBU, rt, 24	17	–
6	**3a**	toluene, DBU, rt, 24	17	–
7	**3a**	CH_3CN, DBU, rt, 24	–	–
8	**3a**	THF, NEt_3, rt, 24	–	–
9	**3a**	THF, K_2CO_3, rt, 24	–	–
10	**3a**	THF, KO*t*Bu, rt, 24	–	–
11	**3a**	THF, DBU, 66 °C, 4	47	47
12	**3a**	THF, DBU, 66 °C, 24	35	55
13	**3a**	toluene, DBU, 70 °C, 24	30	60
14	**3a**	toluene, DBU, 110 °C, 4	–	94

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.75 mmol), carbene precursor (15 mol%), base (20 mol%) in 3 mL solvent. [b] Isolated yield. [c] Product **4a** forms 1:1 diastereomers in all the reactions as determined by using ^{1}H NMR spectroscopy.

with a range of enals with electron-withdrawing or electron-donating substituents in the 4-position of the β-aryl ring (**9a**–**9d**). Furyl- and thienyl-substituted enals also afforded the annulated product in good yields (**9e**, **9f**).

The proposed catalytic cycle for the NHC-catalyzed annulation reaction commences with the formation of the Breslow intermediate **II** between the free NHC **I** and one molecule of enal **2**. The Breslow intermediate **II** undergoes β-protonation to afford enol **III**. The latter undergoes Michael addition to 3-arylallylidene chroman-2,4-dione **IV**, which in turn is generated by the Knoevenagel condensation reaction of 4-hydroxycoumarin **1a** with enal **2**, leading to the intermediate **V**. The latter, on intramolecular *O*-acylation, delivers the product, dihydropyrano[3,2-*c*]chromene-2,5-dione derivative **4**, which on isomerization gives the final pyrano[3,2-*c*]chromene-2,5-dione derivative **5** (Scheme 6).

To shed some light on the mechanism of the reaction, we conducted two cross experiment by using 4-chlorocinnamaldehyde **2j** and 4-methoxycinnamaldehyde **2a** with 4-hydroxycoumarin **1a**. In this experiment, a solution of 4-hydroxycoumarin

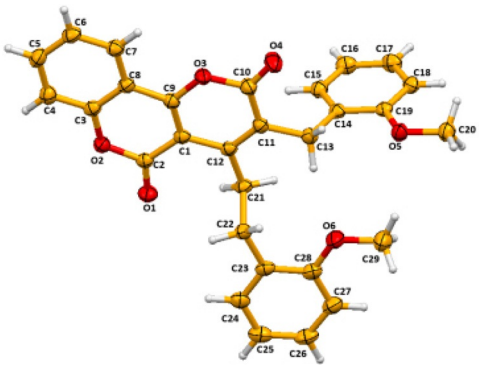
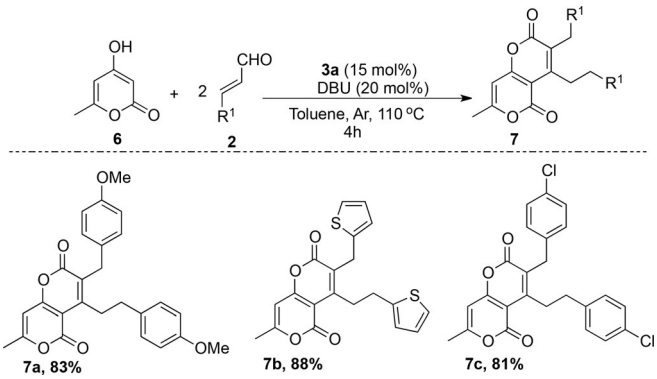


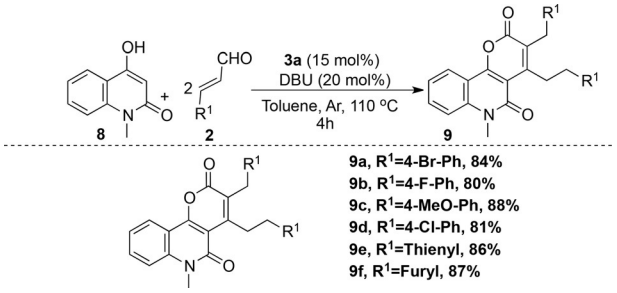
Figure 2. ORTEP diagram of **5f**.



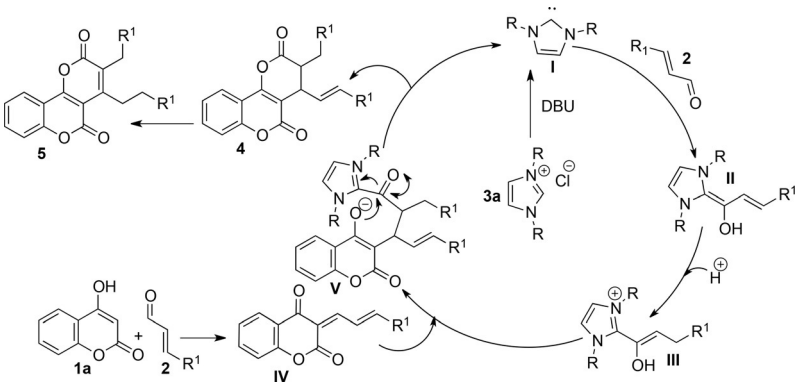
Scheme 4. Reaction of enals with 4-hydroxy-6-methyl-2*H*-pyran-2-one. Isolated yields given.

Encouraged by the success of the reactions with 4-hydroxycoumarin, it was decided to pursue the NHC-catalyzed annulation reaction of enals with 4-hydroxy-6-methyl-2*H*-pyran-2-one (Scheme 4). Gratifyingly, it was observed that the reaction proceeded efficiently with enals bearing electron-donating or electron-withdrawing substituents on the β-aryl ring (**7a**, **7c**). Furthermore, thiophene-substituted enals also afforded the annulated products in excellent yields (**7b**).

Subsequently, it was decided to examine the versatility of the enal annulation by using 4-hydroxy-1-methylquinolin-2-(1*H*)-one (Scheme 5). Interestingly, this reaction worked well

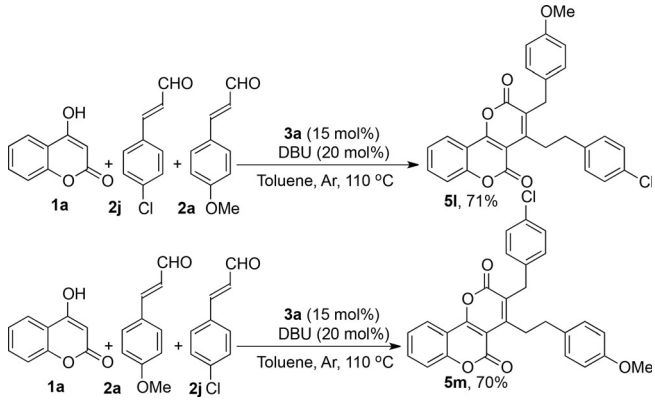


Scheme 5. Reaction of enal with 4-hydroxy-1-methylquinolin-2(1*H*)-one. Isolated yields given.



Scheme 6. Reaction mecahnism.

1a (0.25 mmol), 4-chlorocinnamaldehyde (0.375 mmol), and DBU (0.15 mmol) in toluene was stirred under reflux conditions under an argon atmosphere. After the complete consumption of 4-chlorocinnamaldehyde **2j**, monitored by TLC, 4-methoxycinnamaldehyde **2a** (0.375 mmol) and the carbene precursor (0.15 mmol) were added and the reaction was allowed to continue until 4-methoxycinnamaldehyde was completely consumed. The reaction mixture on processing gave the product **5l**, 4-(4-chlorophenethyl)-3-(4-methoxybenzyl)pyrano[3,2-*c*]chromene-2,5-dione exclusively in 71% yield. An identical experiment in which the addition of 4-methoxycinnamaldehyde **2a** and 4-chlorocinnamaldehyde **2j** was reversed gave the product **5m**, 3-(4-chlorobenzyl)-4-(4 methoxyphenethyl)pyrano[3,2-*c*]chromene-2,5-dione in 70% yield (Scheme 7). These experiments provide support for the mechanistic postulate invoked in Scheme 6.



Scheme 7. Cross experiment using different substituted cinnamaldehydes.

In conclusion, we have developed a NHC-catalyzed synthesis of highly functionalized pyrano[3,2-*c*]chromene-2,5-dione derivatives, pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione derivatives and pyrano[4,3-*b*]pyran-2,5-dione derivatives with potential biological activities. The reaction proceeds through a one-pot Knoevenagel condensation followed by a NHC-catalyzed enolate addition reaction pathway. The simple reaction conditions and the high yields of products are likely to make the reaction attractive for its application in the synthesis of a variety of natural and unnatural chromenones.

Experimental Section

Experimental procedures and characterization data including NMR spectra are included in the Supporting Information.

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Keywords: coumarin derivatives · cyclic aryldiene-1,3-diones · N-heterocyclic carbenes · organocatalysis · tricyclic chromenones

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