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PAPER

A novel NHC-catalyzed transformation of 2*H*-chromene-3-carboxaldehydes to 3-methyl-2*H*-chromen-2-ones†

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An unexpected transformation of 2*H*-chromene-3-carboxaldehydes to coumarin derivatives, mediated by NHC, is reported.

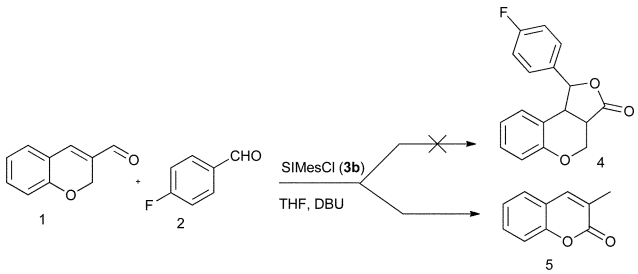
Introduction

The groundbreaking work on nucleophilic heterocyclic carbene (NHC) mediated benzoin condensation by Breslow in 1958 constitutes the first definitive example of such a catalytic transformation.[1] Inexplicably, with the exception of the Stetter reaction,[2] the unique catalytic properties of NHC remained virtually unexplored for a long time. In recent years, however consequent to the reemergence of interest in organocatalysis,[3] NHC catalyzed reactions have been attracting considerable attention. A number of novel protocols of synthetic value employing NHC catalysis, such as asymmetric benzoin condensation,[4] inter- and intra-molecular Stetter reactions,[5] redox reactions[6] and transesterification reactions,[7] have been published by different groups.

The first report on the unique NHC catalyzed generation of homoenolate by Bode and Glorius was followed by a variety of novel application of this species. Some of the key reactions involving homoenolates are the formation of γ-butyrolactones,[8,9] γ-lactams,[10] spiro-γ-lactones,[11] δ-lactones,[12] cyclopentenes,[13,14] β-lactams,[15] spirocyclopentanones,[16] and γ-amino butyric acid (GABA) derivatives.[17]

Results and discussion

In the context of our continuing interest in the chemistry of homoenolates and with a view to extending the scope of the latter, we sought to generate endocyclic homoenolates and examine their reactivity towards electrophiles. In a prototype experiment, 2*H*-chromene-3-carboxaldehyde **1** (Scheme 1) was exposed to SIMes (1,3-dimesityl imidazolinium carbene), generated from the chloride salt (**3b**) of SIMes by DBU, in the presence of 4-fluorobenzaldehyde. It was surmised that the homoenolate



Scheme 1

formed from **1** would be trapped by the latter to form a γ-lactone consistent with known homoenolate chemistry. In the event the reaction yielded none of the expected product, but surprisingly 3-methyl-2*H*-chromen-2-one (3-methyl coumarin) **5** was formed in 25% yield. Coumarin derivatives are often prepared by the application of the Knoevenagel reaction[18] or Perkin reaction[19] with salicylaldehydes. A mechanistically related process involving the latter and enals engaging NHC catalysis leading to 3-alkyl coumarins in moderate yields was reported recently.[20] Although the expected reaction did not occur, intrigued by the novelty of the reaction, we decided to pursue it in some detail. Additional incentive for our studies was accrued from the well documented and important biological properties of coumarin derivatives.[21] *Inter alia* they have been shown to possess antithrombotic,[22] vasodilatory[23] and anti-inflammatory [24] properties.

Against the backdrop presented above, an experiment was conducted in which the aldehyde **1** was exposed to the catalyst **3b**, in DCM in the absence of 4-fluorobenzaldehyde. The reaction mixture on column chromatography (95 : 5 hexane : ethyl acetate) afforded the product **5** in 30% yield. Subsequent studies aimed at catalyst screening revealed that the best result was obtained with **3b** in THF (Tables 1 and 2).

In order to explore the generality of the reaction, a number of substituted chromene aldehydes were treated with the catalyst, and the results are presented in Table 3.

All the products were characterized by spectroscopic analysis. In addition, final proof for the structure of the product

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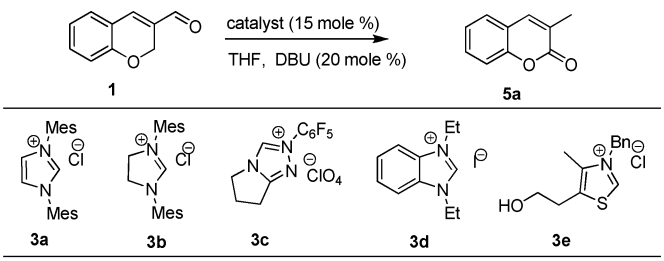
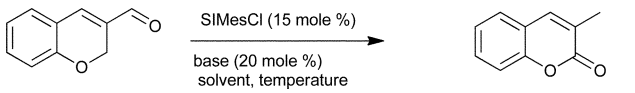
Table 1 Catalyst screening



Entry	Catalyst	Conditions	Yield (%)
1	**3a**	THF, rt, 8 h	27
2	**3b**	THF, rt, 8 h	94
3	**3c**	THF, rt, 8 h	—
4	**3d**	THF, rt, 8 h	50
5	**3e**	THF, rt, 24 h	—
6	—	THF, rt, 8 h	—

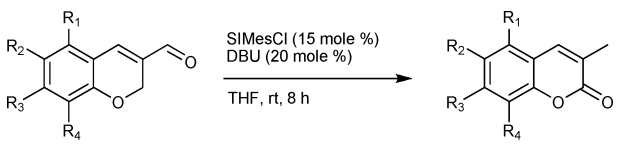
Table 2 Optimization of conditions



Entry	Base	Solvent	Temp.	Time (h)	Yield[a] (%)
1	DBU	DCM	rt	24	30
2	DBU	THF	rt	8	94
3	DBU	Toluene	rt	24	38
4	DBU	CH_3CN	rt	24	—
5	K_2CO_3	CH_3CN	82 °C	12	—
6	DMAP	THF	rt	24	—
7	K_2CO_3	THF	rt	24	—

[a] Isolated yield.

Table 3 Scope of the reaction



Entry	Product	R^1	R^2	R^3	R^4	Yield[a] (%)
1	**5a**	H	H	H	H	94
2	**5b**	H	Br	H	H	82
3	**5c**	H	Cl	H	H	80
4	**5d**	H	$(CH_3)_2CH$	H	H	70
5	**5e**	H	H	CH_3	H	65
6	**5f**	H	OCH_3	H	H	64
7	**5g**	H	CH_3	H	H	53
8	**5h**	H	H	$(CH_3)_2CH$	H	45

[a] Isolated yield.

was obtained by single crystal X-ray determination on **5g** (Fig. 1).

While the mechanistic intricacies of the transformation described here remain to be unravelled, a rationalization along the following lines may be postulated (Scheme 2).

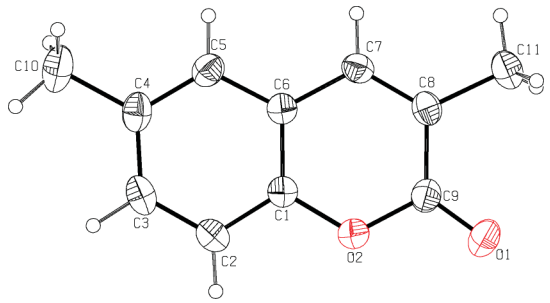
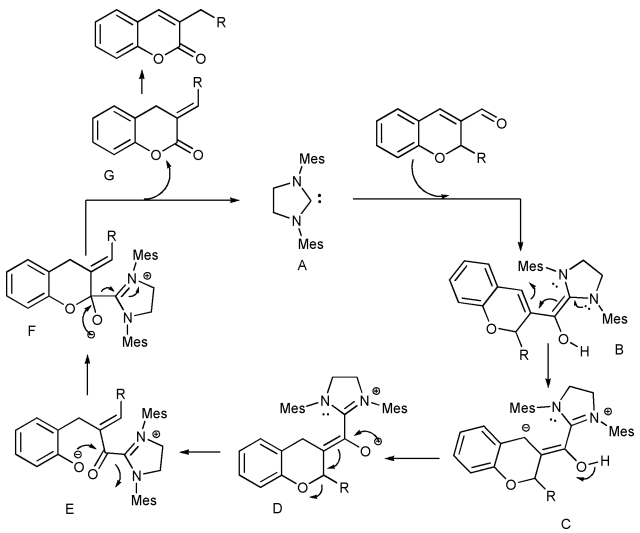


Fig. 1 Single crystal X-ray structure of **5g** (40% probability factor for the thermal ellipsoids).

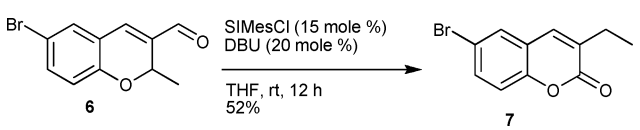


Scheme 2 Postulated catalytic cycle.

Conceivably the initially formed Breslow intermediate **B** transforms to the homoenolate equivalent **C** which on proton transfer delivers the species **D**. The latter undergoes a fragmentation, reminiscent of the Grob fragmentaion, to generate **E**; it then undergoes intramolecular acylation to afford **F**. Subsequent elimination of the carbene followed by isomerization of the enone delivers the 3-alkyl coumarin.

Notwithstanding the superficial resemblance of the key step in the cascade process to Grob fragmentation,[25] it is important to note that there are major differences between the two transformations. For instance, almost always, the scission of a C–C σ bond is a *fait accompli* in the Grob fragmentation, whereas no such thing occurs in the present process. Evidently a more detailed discussion of the cascade reaction will have to await the results of further investigations. It may be pointed out that, as far as we know, this is the first example of a cascade process of this type mediated by NHC.

As a prelude to examining the scope of the reaction and to gain some support for the mechanistic postulate we investigated the reaction with 6-bromo-2-methyl-2*H*-chromene-3-carbaldehyde (Scheme 3).



Scheme 3

Gratifyingly, in this case also, analogous product was obtained.

Conclusions

In conclusion, we have uncovered a novel NHC catalyzed rearrangement of chromene-3-carboxaldehydes to 3-methyl coumarins. It is conceivable that the process will find application to the synthesis of biologically active coumarin derivatives. Further studies are currently under way.

Experimental

General

Melting points were recorded on a Büchi melting point apparatus and are uncorrected. NMR spectra were recorded at 500 (^{1}H) and 125 (^{13}C) MHz respectively on a Bruker DPX-500 MHz NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded under EI/HRMS or FAB using a JEOL JMS 600H mass spectrometer. IR spectra were recorded on a Bruker Alpha-T FT-IR spectrophotometer. Gravity column chromatography was performed using 100–200 mesh silica gel and mixtures of petroleum ether–ethyl acetate were used for elution.

General procedure for the synthesis of 3-methyl coumarins

DBU (20 mol %) was added to a suspension of the carbene precursor 1,3-dimesityl imidazolinium chloride (SIMesCl) (15 mol %) and 2*H*-chromene-3-carboxaldehyde (0.50 mmol) in dry THF (5 mL) and the resulting solution was stirred for 8 h–12 h. After the removal of the solvent by distillation in vacuum using a rotary evaporator, the residue was subjected to chromatography on a silica gel (100–200 mesh) column using 95 : 5 petroleum ether–ethyl acetate solvent mixtures to afford the 3-alkyl coumarin derivatives.

3-Methyl-2*H*-chromen-2-one (5a). White solid. Mp: 90–92 °C [87–90 °C],[26] **IR** (film) 1709, 1638, 1447, 918 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.42 (s, 1H) 7.39–7.35 (m, 1H) 7.32 (d, 1H, J = 8 Hz) 7.2 (d, 1H, J = 8 Hz) 7.17–7.14 (m, 1H) 2.14 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 161.9, 153.3, 139.0, 130.4, 126.8, 125.9, 124.1, 119.5, 116.4, 17.2 ppm. **LRMS-FAB** calcd. for $C_{10}H_8O_2$ (M+H)$^+$: 161.06, found: 161.09.

6-Bromo-3-methyl-2*H*-chromen-2-one (5b). Yellow solid. Mp: 152–153 °C [151–152 °C],[27] IR (film) 1726, 1599, 1478, 1248, 922, 815 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.55–7.53 (m, 2H) 7.41 (s, 1H) 7.19 (d, 1H, J = 9.5 Hz) 2.23 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 161.2, 152.1, 137.6, 133.2, 129.2, 127.3, 121.1, 118.2, 116.8, 17.3 ppm. **LRMS-FAB** calcd. for $C_{10}H_7BrO_2$ (M+H)$^+$: 238.97, found 239.11.

6-Chloro-3-methyl-2*H*-chromen-2-one (5c). Yellow solid. Mp: 152–154 °C [151–152 °C],[28] IR (film) 1726, 1602, 1410, 1479, 925, 815 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.43 (s, 1H) 7.41–7.38 (m, 2H) 7.25 (s, 1H) 2.23 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 161.2, 151.6, 137.7, 130.4, 129.5, 127.4, 126.1, 120.6, 117.9, 17.3 ppm. **LRMS-FAB** calcd. for $C_{10}H_7ClO_2$ (M+H)$^+$: 195.02, found: 195.01.

6-Isopropyl-3-methyl-2*H*-chromen-2-one (5d). Colourless liquid, **IR** (film) 1724, 1619, 1428 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.48 (s, 1H) 7.32–7.29 (m, 1H) 7.22–7.20 (m, 2H) 2.98–2.93 (m, 1H) 2.20 (s, 3H) 1.27 (d, 6H, J = 7 Hz). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 162.2, 151.5, 144.8, 139.2, 128.9, 125.5, 124.1, 119.3, 116.2, 33.5, 24.1, 17.2 ppm. **LRMS-FAB** calcd. for $C_{13}H_{14}O_2$ (M+H)$^+$: 203.11, found 203.21.

3,7-Dimethyl-2*H*-chromen-2-one (5e). white solid. Mp: 104–106 °C, **IR** (film) 1710, 1623, 1437 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.69(s, 1H) 7.33(d, 1H, J = 8 Hz) 7.15 (d, 1H, J = 8 Hz) 7.11 (s, 1H) 2.52 (s, 3H) 2.24 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 161.8, 153.8, 138.9, 135.9, 130.1, 126.5, 124.6, 117.1, 114.6, 21.7, 17.2 ppm. **LRMS-FAB** calcd. for $C_{11}H_{10}O_2$ (M+H)$^+$: 175.07, found 175.20.

6-Methoxy-3-methyl-2*H*-chromen-2-one (5f). Mp 114–116 °C [112 –115 °C],[29] **IR** (film) 1704, 1630, 1538 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.45 (s, 1H) 7.23 (d, 1H, J = 9 Hz) 7.03–7.00 (m, 1H) 6.82 (s, 1H) 3.83 (s, 3H) 2.21 (s, 3H). **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 162.0, 155.9, 147.7, 138.8, 126.3, 119.9, 117.8, 117.4, 109.2, 55.6, 17.3 ppm. **LRMS-FAB** calcd. for $C_{11}H_{10}O_3$ (M+H)$^+$: 191.07, found 191.27.

3,6-Dimethyl-2*H*-chromen-2-one (5g). Mp 114–116 °C, IR (film) 1711, 1600 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.43 (s, 1H) 7.24–7.23 (m, 1H) 7.19–7.17 (m, 2H) 2.39 (s, 3H) 2.19 (s, 3H). **^{13}C NMR**($CDCl_3$, 125 MHz): δ 162.1, 151.4, 138.9, 133.7, 131.3, 126.7, 125.7, 119.3, 116.2, 20.8, 17.2 ppm. **LRMS-FAB** calcd. for $C_{11}H_{10}O_2$ (M+H)$^+$: 175.07, found 175.23.

7-Isopropyl-3-methyl-2*H*-chromen-2-one (5h). Colourless liquid **IR** (film) 1706, 1627, 1533 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.47 (s, 1H) 7.30 (d, 1H, J = 8 Hz) 7.17–7.15 (m, 1H) 7.11–7.09 (m, 1H) 3.02–2.94 (m, 1H) 2.20 (s, 3H) 1.28 (d, 6H, J = 7 Hz) **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 162.3, 152.3, 138.9, 135.3, 130.4, 126.6, 125.1, 117.5, 114.1, 34.2, 23.7, 23.6, 17.2 ppm. **LRMS-FAB** calcd. for $C_{13}H_{14}O_2$ (M+H)$^+$: 203.11, found 203.13.

6-Bromo-3-ethyl-2*H*-chromen-2-one (7). White solid. Mp: 110–112 °C, IR (film) 1719, 1628, 1599 cm^{-1}. **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.50 (d, 1H, J = 2 Hz) 7.48–7.46 (m, 1H) 7.31 (s, 1H) 7.13 (d, 1H, J = 8.5 Hz) 2.57–2.52 (m, 2H) 1.19 (t, 3H, J = 7 Hz) **^{13}C NMR** ($CDCl_3$, 125 MHz): δ 159.7, 150.9, 134.8, 132.1, 131.7, 128.4, 120.1, 117.1, 115.7, 22.9, 11.1 ppm. **LRMS-FAB** calcd. For $C_{11}H_9BrO_2$ (M+H)$^+$: 252.99, found 253.28.

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