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A Cascade Reaction Actuated by Nucleophilic Heterocyclic Carbene Catalyzed Intramolecular Addition of Enals via Homoenolate to α,β-Unsaturated Esters: Efficient Synthesis of Coumarin Derivatives

C. R. Sinu,[†] D. V. M. Padmaja,[†] U. P. Ranjini,[†] K. C. Seetha Lakshmi,[†] Eringathodi Suresh,[‡] and Vijay Nair*,[†]

Organic Chemistry Section, National Institute for Interdisciplinary Science and Technology (CSIR), Thiruvananthapuram, India, and Analytical Science Division, Central Salt and Marine Chemicals Research Institute, Bhavnagar, 364002, India

vijaynair_2001@yahoo.com

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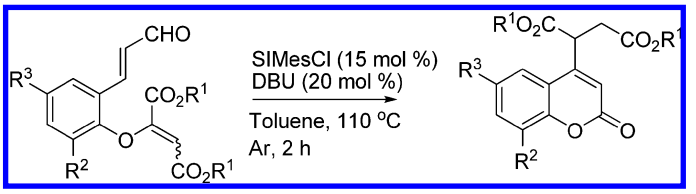
ABSTRACT



A nucleophilic heterocyclic carbene mediated intramolecular homoenolate reaction strategy for the efficient synthesis of 4-alkyl substituted coumarins is described.

In his pathbreaking work[1] in 1958, Breslow generated a nucleophilic heterocyclic carbene (NHC)[2−4] and demonstrated its use in benzoin condensation via the intermediacy of an enaminol, generally called the Breslow intermediate, which was formed by the addition of NHC to benzaldehyde. Despite this laboratory demonstration and a general awareness that a number of important chemical transformations in nature,[5] such as decarboxylation of α-ketoacids, formoin condensation etc., occur via this process, the potential utility of NHC has remained largely unexplored except for its use in catalyzing the conjugate addition of enals to activated π-systems, invented by Stetter.[6]

[†] National Institute for Interdisciplinary Science and Technology (CSIR).
[‡] Central Salt and Marine Chemicals Research Institute.

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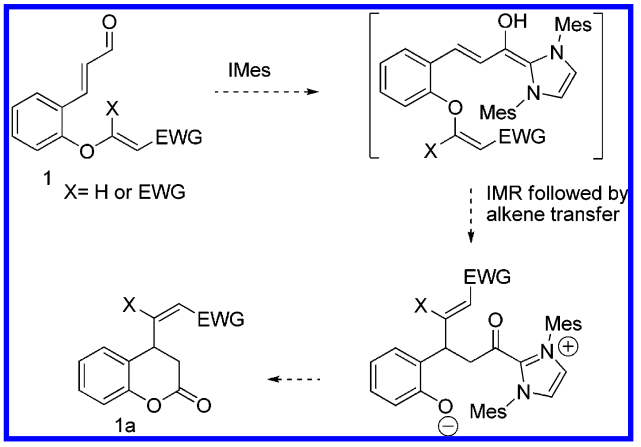
A welcome change in this situation occurred in 2004 with the demonstration that, akin to the formation of enaminol from benzaldehyde and NHC, the latter would generate a homoenolate equivalent from cinnamaldeyde by a conjugate umpolung, independently by Glorius[7] and Bode.[8] Subsequently, a number of groups, including our own, have exploited homoenolate chemistry for the synthesis of a variety of important molecular systems, such as spirolactones,[9] lactams,[10] cyclopentenes,[11] cyclopentanones[12] and other cyclopentanoids,[13] indanes,[14] GABA derivatives,[15] pyrones,[16] pyridazinones,[17] etc. Other important works focusing on the redox chemistry of homoenolates have also been reported.[18]

Despite the enormous progress in the area of NHC mediated intermolecular homoenolate chemistry,[2] there are only a few intramolecular homoenolate reactions[19] known in the literature. In view of this, intrigued by the possibility of designing an intramolecular reaction, it was conceptualized that cinnamaldehyde appended with 2-*O*-alkenoate, on treatment with NHC, was likely to undergo a cascade reaction triggered by the initial formation of homoenolate and its intramolecular Michael addition, and a series of events culminating in the formation of a coumarin derivative (Scheme 1).

Scheme 1. Conceptual Framework



Of note, coumarin derivatives[20] are important synthetic targets due to their biological properties.[21] *Inter alia*, they are known to possess potent anticoagulant,[22] antitumor,[23] vasodilatory,[24] anti-HIV,[25] and anti-inflammatory[26] properties. Some coumarin derivatives are endowed with useful fluorescent properties.[27]

Thus, from both mechanistic and synthetic standpoints the pursuit of an intramolecular homoenolate reaction shown in Scheme 1 was considered worthwhile. The results of our investigation form the subject matter of this paper.

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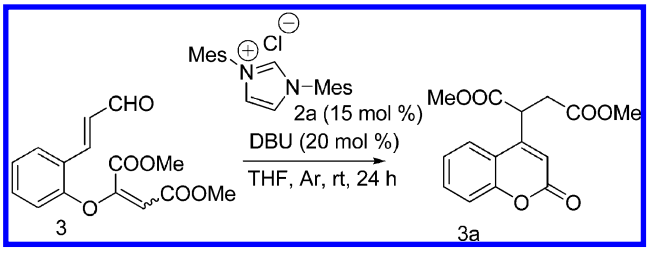
Our studies commenced by treating the 2-substituted cinnamaldehyde **3**, obtained by the reaction of 2-hydroxy cinnamaldehyde with dimethyl acetylene dicarboxylate (DMAD), with the imidazolium precatalyst and DBU in dry THF under an argon atmosphere (Scheme 2). After 24 h the solvent was removed and the crude product when subjected to column chromatography on silica gel afforded 15% of the product, 4-alkyl substituted coumarin **3a**.

Scheme 2. Proof of the Concept



The structure of the product was established by common spectroscopic techniques, and the final confirmation was obtained from single crystal X-ray analysis (Figure 1).

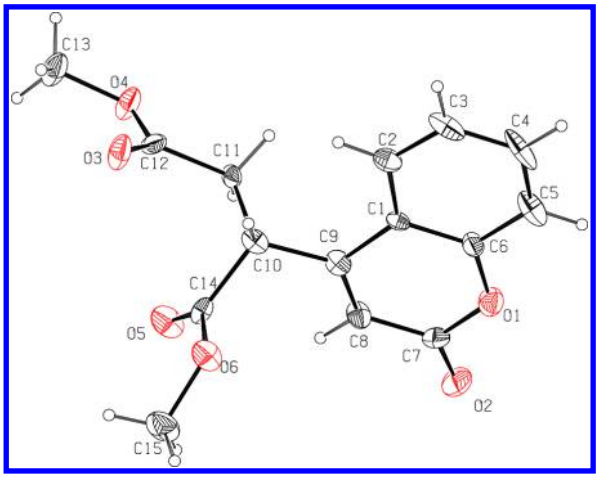


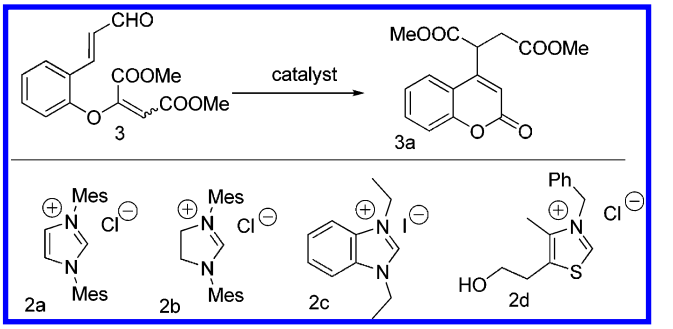
Figure 1. ORTEP diagram of **3a**.

In view of the success of the reaction, we examined the usefulness of other commonly available NHC catalysts in this reaction. A number of experiments were conducted, and the results are summarized in Table 1. Among the four catalysts investigated, imidazolinium catalyst **2b** gave the best result (Table 1, entry 7).

After having reasonably well established the optimum parameters, the reaction was extended to other substituted cinnamaldehyde derivatives, Table 2.

In order to establish advantages, if any, in subjecting the *E* and *Z* isomers separately to the cascade process, we prepared them separately. When these were subjected to the reaction conditions identical to those experienced by *E*/*Z* mixtures, the same products were obtained in comparable yields. The results are summarized in Table 3.

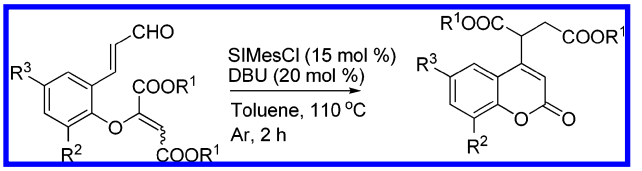
Table 1. Condition Optimization



entry	catalyst	base	solvent, temp (°C)	time (h)	yield[a] (%)
1	**2a**	DBU	THF, rt	24	15
2	**2a**	DBU	THF, 65 °C	24	45
3	**2a**	DBU	toluene, 110 °C	24	56
4	**2b**	DBU	THF, rt	24	20
5	**2b**	DBU	THF, 65 °C	24	68
6	**2b**	DBU	toluene, rt	24	48
7	**2b**	DBU	toluene, 110 °C	2	93
8	**2b**	DMAP	toluene, 110 °C	24	40
9	**2b**	K_2CO_3	toluene, rt	24	–
10	**2b**	Et_3N	toluene, rt	24	–
11	**2c**	DBU	toluene, 110 °C	24	42
12	**2d**	DBU	toluene, 110 °C	24	50
13	–	DBU	toluene, 110 °C	24	–
14	**2b**	DBU	DCM, rt	24	–

[a] Isolated yield.

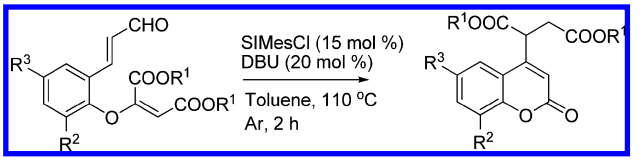
Table 2. Reaction of Mixture of *E* and *Z* Isomers



entry	*E*/*Z* isomer ratio[a]	R^1	R^2	R^3	product	yield[b] (%)
1	1:1	$-CH_3$	H	H	**3a**	93
2	0.65:1	$-CH_3$	H	Br	**4a**	78
3	0.88:1	$-CH_3$	H	$-C(CH_3)_3$	**5a**	70
4	0.65:1	$-CH_3$	H	$-CH(CH_3)_2$	**6a**	66
5	1:1	$-CH_3$	$-OCH_3$	H	**7a**	60
6	0.75:1	$-CH_3$	H	$-OCH_3$	**8a**	60
7	1:0.68	$-CH_3$	H	-Cl	**9a**	55
8	1:1	$-CH_3$	$-CH_3$	H	**10a**	47
9	1:1	$-CH_3$	H	$-CH_3$	**11a**	46
10	1:1	$-CH_3$	I	H	**12a**	46
11	0.6:1	$-CH_3$	H	$-NO_2$	**13a**	–
12	1:0.61	$-C(CH_3)_3$	H	-Br	**14a**	21
13	1:1	$-CH_2CH_3$	H	H	**15a**	81

[a] *E*/*Z* ratio calculated from ^{1}H NMR. [b] Isolated yield.

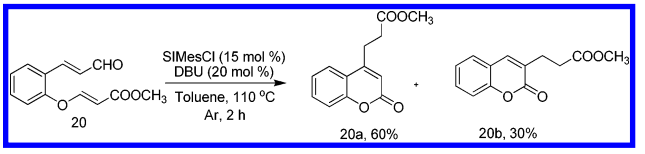
Table 3. Reaction of *E* and *Z* Isomers



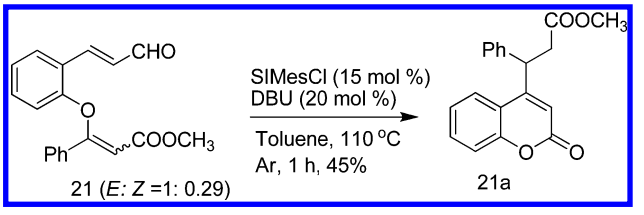
					yield (%)	
entry	R^1	R^2	R^3	product	Z^a	E^b
1	$-CH_3$	H	H	**3a**	83	66
2	$-CH_3$	$-OCH_3$	H	**7a**	63	81
3	$-CH_3$	H	-Cl	**9a**	69	60
4	$-CH_3$	H	-Br	**4a**	75	69
5	$-CH_3$	H	$-OCH_3$	**8a**	65	78
6	$-CH_2CH_3$	H	H	**15a**	68	72
7	$-CH_2CH_3$	H	-Cl	**16a**	65	58
8	$-CH_2CH_3$	H	-Br	**17a**	85	89
9	$-CH_2CH_3$	H	$-OCH_3$	**18a**	62	76
10	$-CH_2CH_3$	$-OCH_3$	H	**19a**	67	74

[a] Isolated yield from *Z* isomer. [b] Isolated yield from *E* isomer.

Scheme 3



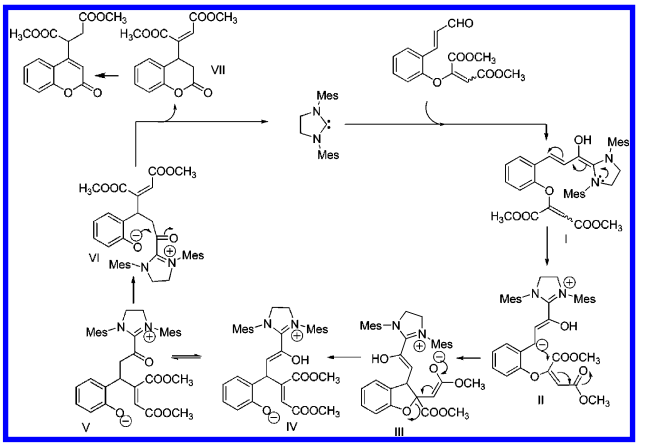
Scheme 4



In order to explore the scope of the coumarin synthesis, we conducted the reaction with substrates derived from other acetylenic esters; the results are presented in Schemes 3 and 4.

The above results suggest that 1,2-substitution of the acetylenic esters is crucial to the selective formation of the homoenolate product.

Scheme 5. Proposed Mechanism



The proposed catalytic cycle begins with the initial addition of NHC to the aldehyde leading to the generation of the homoenolate species **II** (Scheme 5). The latter is suitably positioned for a Michael addition to the olefinic ester resulting in a five-membered intermediate **III** which on fragmentation renders the phenoxide ion **IV**. The formation of this phenoxide ion may provide the driving force for this reaction. Conceivably **V** can endure σ-bond rotation and subsequent cyclization concomitant with the ejection of the catalyst to deliver **VII**; the latter on isomerization affords the final product.

In conclusion, the coumarin synthesis reported herein is noteworthy for its efficiency, novel cascading process involving an intramolecular Michael addition of homoenolate, alkene transfer via Grob type fragmentation, and intramolecular cyclization. It may also be mentioned that the coumarins obtained are endowed with a functionalized carbon chain, thus allowing their further transformation to diverse products of potential value.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.