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An Expeditious Coumarin Synthesis via a “Pseudocycloaddition” Between Salicylaldehydes and Ketene

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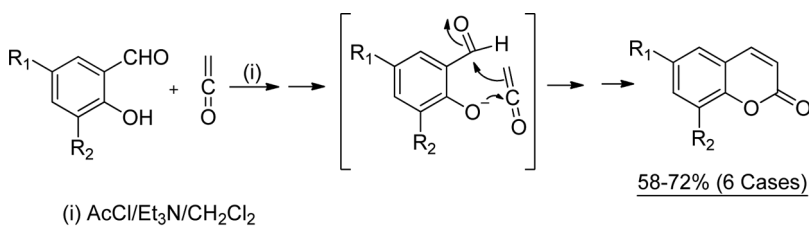
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AN EXPEDITIOUS COUMARIN SYNTHESIS VIA A “PSEUDOCYCLOADDITION” BETWEEN SALICYLALDEHYDES AND KETENE

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GRAPHICAL ABSTRACT



Abstract A variety of salicylaldehydes effected tandem nucleophilic addition onto ketene, leading to corresponding coumarins in good yields under mild conditions. This “pseudo-cycloaddition” represents a very mild variant of the historic Perkin synthesis of coumarin (which remains of key interest in both perfumery and several emerging areas).

Keywords Coumarin; Perkin synthesis; quinodimethane

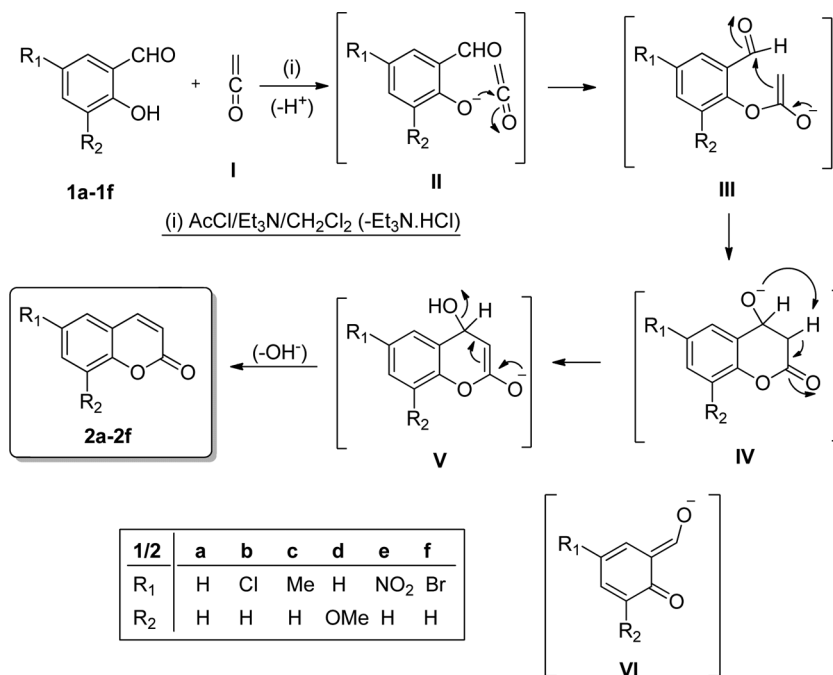
INTRODUCTION

Coumarin (**2a**, Scheme 1) is of both historic and contemporary interest.^[1] Historically, it is of interest with respect to the classical Perkin synthesis (1877),^[2] which defined one of the most important extensions of the Perkin condensation. Contemporary interest in coumarin derives from its key importance in perfumery,^[3] apart from sundry applications (in electroplating, etc.).^[4] Several modern synthetic approaches have been recently reported,^[5–7] as well as fundamental studies on the coumarin nucleus in areas as diverse as medicinal chemistry and molecular electronics.^[8,9]

The present studies were motivated by the possibility that milder versions of the original Perkin synthesis could be designed. (This typically involved refluxing salicylaldehyde and sodium acetate in acetic anhydride.) Also, the classical synthesis apparently remains mechanistically enigmatic, with several possible routes having

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Scheme 1. Synthesis of coumarins **2** from salicylaldehydes **1** and in situ-generated ketene (**I**).

been considered. These essentially differ in the order of formation of the O₁-CO and C₃-C₄ bonds and the identity of the penultimate intermediate prior to the final cyclization. It occurred to us that one of these, involving the initial formation of the O₁-CO bond followed by rapid cyclization, was susceptible to a novel approach as described here (cf. Scheme 1).

RESULTS AND DISCUSSION

Thus, the reaction of salicylaldehydes (**1**) with ketene (**I**) was envisaged to form the coumarin nucleus in **IV**, via the tandem nucleophilic addition process shown in **II–III**. The immediate product, enolate ion **III**, was expected to add rapidly to the aldehyde carbonyl group in its close proximity. Proton transfer in **IV** generates enolate **V** (likely intermolecular, although shown as intramolecular for convenience); this is followed by elimination of hydroxide ion to form coumarin (**2**). Interestingly, this one-pot procedure would represent a “pseudocycloaddition” of **I** onto **1**. [The putative *ortho*-quinodimethane tautomer **VI** of deprotonated **1** may be considered as the diene unit in this process.^[10] This analogy, however, only indicates the bonding changes, ketenes being known to undergo (2 + 2) cycloadditions preferentially.^[11,12]]

Indeed, when a mixture of **1a** (1.0 equivalent), triethylamine (3.0 equivalents), and acetyl chloride (2.0 equivalents) in dichloromethane (with added 4 Å molecular sieves) was stirred at 10 °C for 9 h, coumarin (**2a**) was formed in 72% yield (relative to **1a**). The method was extended to include a variety of substituted salicylaldehydes (**1a–1f**), the yields of the corresponding coumarins (**2a–2f**) being summarized in

Table 1. Yields (%) of the various coumarins (**2**) formed as shown in Scheme 1

2a	2b	2c	2d	2e	2f
72	64	58	70	62	67

Table 1. (The transformation was unsuccessful in the absence of the molecular sieves, which presumably traps the molecule of water that is a by-product of the process.)

It is highly likely that this reaction occurs via the reaction of **1** and ketene (**I**), which is known to be generated by the reaction of acetyl chloride and Et_3N . Ketenes are also known to add alcohols across the $\text{C}=\text{C}$ unit to form esters, whether under basic, neutral, or acidic conditions.^[11,12] The basic reaction is believed to involve nucleophilic attack of alkoxide anion at the carbonyl carbon atom leading to the enolate anion (cf. **III**). This indicates that the tandem process represented by **II** is highly likely.

When the acetate of salicylaldehyde (**1a**, the acetate is not shown) was treated with Et_3N under these conditions, it failed to form coumarin (**2a**). This strongly indicates that the formation of **2** occurs via the tandem nucleophilic addition protocol as envisaged and not via the prior formation of the acetate. [Note that Et_3N ($\text{pK}_a \sim 10$) can deprotonate **1** ($\text{pK}_a < 10$) but not an ester ($\text{pK}_a \sim 25$), thus forming **II**.^[13]

There have been a few previous reports on the synthesis of coumarins from salicylaldehydes and ketene.^[14,15] However, these employed ketene generated as a gas, in multistep reactions that generally suffered from poor yields. Recent work employs ketene dithioacetals under either electrophilic or nucleophilic activation;^[16,17] alternatively, malonic half-thioesters have been employed along with an amine catalyst.^[18] The method reported herein possesses the relative advantages of simplicity, mildness, and economy of operation.

CONCLUSIONS

We have described a novel approach to various coumarins, which remain of diverse contemporary interest. The route apparently involves a novel pseudocycloaddition via a tandem nucleophilic addition process. This employs available salicylaldehydes as substrates and is characterized by very mild reaction conditions and good overall yields.

EXPERIMENTAL

A mixture of salicylaldehyde (**1a**) (1.0 mmol), triethylamine (3.0 mmol), freshly distilled acetyl chloride (2.0 mmol) and molecular sieves (~ 0.25 g, 4 Å, as pellets) in dry CH_2Cl_2 was stirred for 9 h at 10 °C. The insolubles ($\text{Et}_3\text{N} \cdot \text{HCl}$ + molecular sieves) were filtered off, and the filtrate was worked up with ice cold water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to obtain the crude product, which was chromatographed on silica gel eluting with 20% ethyl acetate–hexane. Coumarin (**2a**) was thus obtained as a white solid in 72% yield; mp 70–73 °C (lit.^[19] 68–69 °C); ν_{max} 3058 (b, C–H), 1715 (s, CO); δ_{H} 7.26–7.72 (5 H, m, $\text{ArH} + \text{ArCH}=\text{C}$), 6.42 (1 H, d, J 9.5, $\text{ArC}=\text{CH}$).

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SUPPORTING INFORMATION

Detailed procedures and spectral characterization data for all compounds reported herein can be accessed on the publisher's website.

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