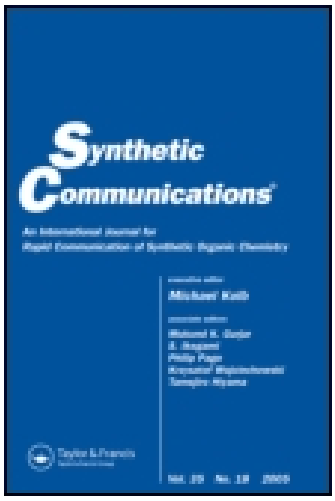

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A Single-Step Assembly of Coumarin Ring Skeleton from Oxygenated Phenols and Acetylenic Esters by Catalytic Indium Chloride in the Absence of Solvent

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A Single-Step Assembly of Coumarin Ring Skeleton from Oxygenated Phenols and Acetylenic Esters by Catalytic Indium Chloride in the Absence of Solvent

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ABSTRACT

Ring oxygenated coumarins were obtained in a single-step by condensation of appropriately substituted phenols with acetylenic esters by catalytic amounts of indium chloride in the absence of solvent.

Key Words: Coumarins; Indium chloride.

INTRODUCTION

Coumarins are ubiquitous compounds occurring naturally and they find various uses in fragrance, pharmaceutical, and agrochemical areas.[1] Several

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methods have been developed for the synthesis of coumarin skeletons.[2] Especially interesting is the recent Trost's Pd-catalyzed method for the synthesis of several oxygenated coumarins in a single-step from polyhydroxyphenols derivatives and acetylenic esters.[3] This palladium-catalyzed method constitutes an easy entry into certain coumarin structures otherwise accessible only multistep sequence. Trost et al. also evaluated other catalysts for this transformation. They also found that indium triflate was ineffective for this transformation. This prompts us to report our use of indium trichloride as an effective catalyst for this transformation.

Indium trichloride has been used as a Lewis acid catalyst in several synthetic transformations (for reviews of recent applications of $InCl_3$ see Ref.[4]). We report herein a single-step entry into coumarins using a tandem Michael addition and cyclization sequence of substituted phenols with acetylenic esters using indium chloride in catalytic ($\sim$10–12 mol%) quantities.

Thus, phloroglucinol reacts with ethyl propiolate in the presence of indium chloride (11 mol% of phloroglucinol) to give 5,7-dihydroxycoumarin (entry 2, Table 1) in 32% isolated yield (Sch. 1). Dimethylation of 5,7-dihydroxycoumarin is known to give 5,7-dimethoxycoumarin, a naturally occurring coumarin isolated from *Citrus aurantifolia* (Limettin).[5] Thus, we have a simple two-step sequence to Limettin from readily available starting materials, which was otherwise obtainable only by a lengthy route.[6] Reaction of phloroglucinol with a substituted acetylenic ester such as ethyl phenylpropiolate proceeds in better yield (55% after crystallization) to give the corresponding coumarin (entry 3, Table 1).

Another coumarin, namely 4-phenyl ayapin, is obtained under similar conditions in a single-step from Sesamol and ethyl phenylpropynoate under these indium chloride catalyzed conditions (entry 5, Table 1). Longer sequences for synthesizing ayapin related coumarins have been reported.[7]

It was found that the phenol itself failed to react with acetylenic esters by the present method. Only more reactive phenols such as hydroxy/methylene dioxy substituted phenols reacted smoothly. Also the reaction failed with phenolic substrate containing an amine function (e.g., *m*-dimethyl amino phenol).

Even though the yields are in the moderate to good range, this very simple entry into substituted coumarin skeletons should render this method worthy of further exploration and adoption.

REPRESENTATIVE EXPERIMENTAL PROCEDURE

7-Hydroxycoumarin (entry 1, Table 1): a mixture of resorcinol (0.330 g, 3 mmol), ethyl propiolate (0.400 g, 4.1 mmol), and indium chloride (0.078 g, 0.35 mmol) in a round-bottomed flask was stirred at 90°C for 2 hr. The reaction

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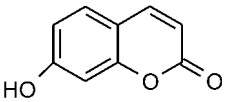
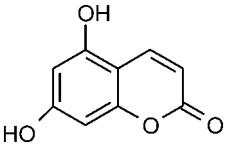
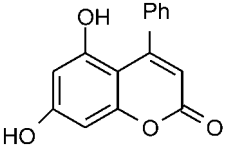
Table 1. Synthesis of substituted coumarins.

Entry	Reactants	Product	Yield[a] (%)	Melting point in °C (reported m.p. and Ref.	NMR (DMSO-d_6) (J in Hz)
1	Resorcinol (3 mmol), ethyl propiolate (4.1 mmol), $InCl_3$ (0.35 mmol)		52	230–232°C (dec) (230°C, Ref.[8])	6.21 (H_3, d, $J = 9.5$, 1H), 6.74 (H_8, d, $J = 2.4$, 1H), 6.80 (H_6, dd, $J = 8.2$, 1H), 7.52 (H_5, d, $J = 8.2$, 1H), 7.94 (H_4, d, $J = 9.5$, 1H), 10.50 (OH, br s, 1H)
2	Phloroglucinol (3.3 mmol)Ethyl propiolate (5.1 mmol), $InCl_3$ (0.36 mmol)		32	274–276 (dec) (280°C, Ref.[9])	6.02 (H_3, d, $J = 9.4$, 1H),6.18 (H_8, d, $J = 2.2$, 1H), 6.26 (H_6, d, $J = 2.2$, 1H), 7.96 (H_4, d, $J = 9.4$, 1H), 10.32 (OH, br s, 1H), 10.60 (OH, br s, 1H)
3	Phloroglucinol (3 mmol), Ethyl phenylpropiolate (4.5 mmol), $InCl_3$ (0.36 mmol)		55	236–238°C (229–230°C, Ref.[10])	5.74 (H_3, s, 1H), 6.17 (H_8, d, $J = 2.5$, 1H), 6.27 (H_6, d, $J = 2.2$, 1H), 7.25–7.45 (aromatic, m, 5H), 10.00–10.40 (br s, 2 OHs, 2H)

(*continued*)

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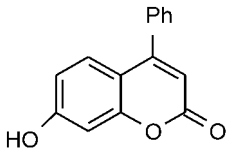
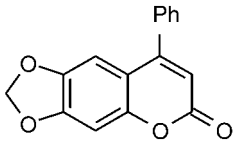
Table 1. Continued.

Entry	Reactants	Product	Yield[a] (%)	Melting point in °C (reported m.p. and Ref.	NMR (DMSO-d_6) (J in Hz)
4	Resorcinol (3 mmol), Ethyl phenylpropiolate (3.2 mmol), $InCl_3$ (0.36 mmol)		48	238–240°C (230–235°C, Ref.[10])	6.15 (H_3, s, 1H), 6.74–6.84 ($H_{6,8}$, m, 2H), 7.45–7.62 (H_5, aromatic, m, 6H), 10.60 (OH, br s, 1H)
5	Sesamol (3 mmol), Ethyl phenylpropiolate (3 mmol), $InCl_3$ (0.34 mmol)		21	140–142°C (142–143°C, Ref.[11])	6.16 (–O–CH_2–, s, 2H), 6.24 (H_3, s, 1H), 6.75 (H_8, s, 1H), 7.19 (H_5, s, 1H), 7.42–7.62 (aromatic, m, 5H)

[a]The yields reported are after crystallization except for entry 5, wherein the product was isolated by preparative TLC.

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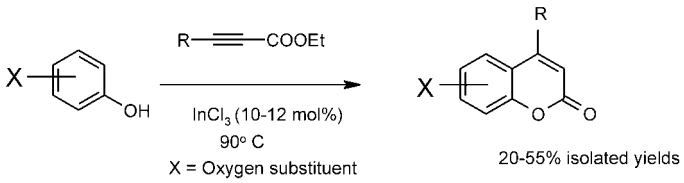

Scheme 1. $InCl_3$ catalyzed synthesis of coumarins.

mixture was allowed to cool to room temperature, diluted with 10 mL water and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous sodium sulfate; solvent removed on a rotary evaporator to give the crude product. This was dissolved in minimum amount of ethyl acetate under warm conditions and hexane was added drop-wise to induce crystallization to afford 0.256 g (52%) of the product. M.P.: 230–232°C dec (Ref.[8] 230°C).

An identical procedure was followed for 5,7-dihydroxycoumarin (entry 2, Table 1)

For the coumarins (entries 3 and 4, Table 1), the crude product was given a toluene wash (2 × 20 mL) to remove any excess unreacted acetylenic ester. The product thus obtained was triturated with ether, filtered and dried.

For the coumarin (entry 5, Table 1), the product was isolated by preparative silica gel TLC (ethyl acetate : hexane = 50 : 50).

All the reactions were run on a 3 mmol scale based on the phenolic substrates.

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