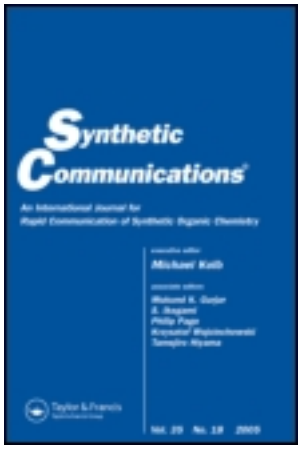

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Facile Metal-Free Synthesis of 3-Aryl-4-Substituted Coumarins from O-Hydroxy Carbonyl Compounds

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FACILE METAL-FREE SYNTHESIS OF 3-ARYL-4-SUBSTITUTED COUMARINS FROM *O*-HYDROXY CARBONYL COMPOUNDS

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The intramolecular cyclization of the esters of salicylaldehyde, O-hydroxyacetophenones, methyl salicylate, and 2′-hydroxy chalcones by potassium hydroxide in pyridine leads to a short and convenient synthesis of 3,4-disubstituted coumarins. Twenty 3-phenyl coumarins were synthesized in 80–90% yields. No other by-product, such as 2-benzylchromone or β-diketones, was observed the reactions. The mild reaction condition involves the removal of more acidic benzylic proton, which leads to a relatively cheap, nontoxic, metal-free method for the synthesis of 3-aryl-4-substituted coumarins.

Keywords: Acylation; Dickmann-type cyclization; 4-hydroxy coumarin; *O*-hydroxyacetophenone; 2-phenylacetoxyester

Coumarins have been attractive research candidates because of their applications as additives in food, perfumes, and cosmetics; anthelmintics; hypnotics; insecticides;[1–3] anticoagulants;[4] anti-HIV agents;[5,6] optical brightners;[7] and dispersed fluorescent and laser dyes.[8,9] Most reports dealing with coumarin synthesis use Pechmann,[10] Perkin,[11] Knoevenagal,[12] Reformatsky,[13] and Wittig reactions[14,15] or flash vacuum pyrolysis.[16] Different types of catalysts, namely, hetreopolyacids,[17] nano-sized sulfated tin oxide (STO)/Al-P,[18] oxalic acid,[19] $ZnCl_2$,[20] *para* toluene sulfonic acid (pTSA),[21] $Pd(OAc)_2$,[22] lithium diisopropylamide (LDA),[23] $HClO_4 \cdot SiO_2$,[24] Al-MCM-41,[25] $TiCl_4$,[26] $Bi(NO_3)_3 \cdot 5H_2O$,[27] ionic liquids,[28] $Sm(NO_3)_3 \cdot 6H_2O$,[29] Grubb's catalyst,[30] and $Zn(I_2)$,[31] have been explored to produce coumarins. Almost all methods suffer drawbacks such as use of active phenols, corrosive problems, several hours of heating above 150°C, multistep reactions, undesired by-products, expensive catalysts, and environmental pollution.

Perhaps the most direct method known for 3-aryl coumarin synthesis is Perkin condensation,[11] which suffers from tedious workup, unsatisfactory yields, harsh conditions, and corrosive condensing agent ($PhPOCl_2/Et_3N$). Deshmukh[32] has used aryl acetothiomorpholide for condensation with 2-hydroxybenzaldehyde in the presence of $POCl_3$ to give 3-phenyl coumarins in 30–49% yields. Reaction of

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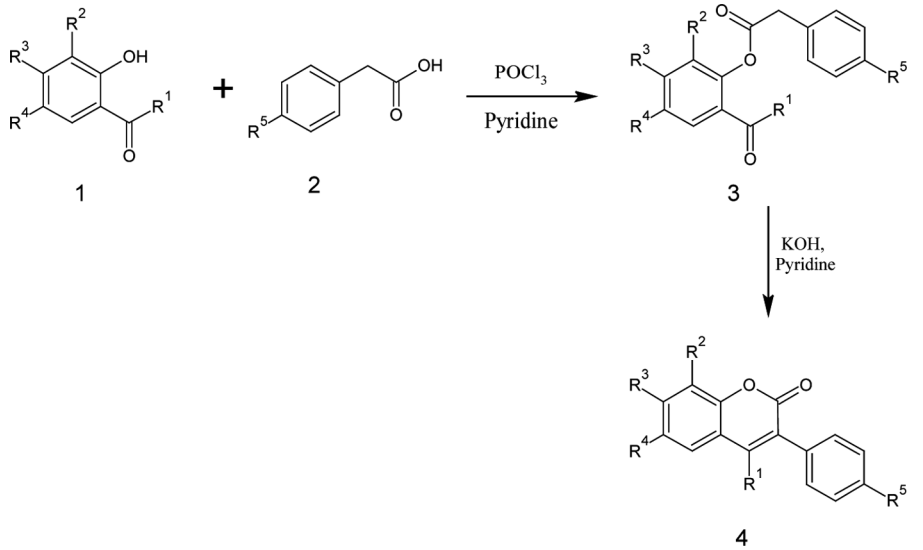
2-hydroxy benzaldehyde with phenyl acetic anhydride in the presence of dry benzene and triethyl benzyl ammonium chloride (TEBA) as a phase-transfer catalyst has also been reported to give 3-phenyl coumarin in 50–95% yield.[33] Kamat and coworkers[34] reported thermal condensation of 2′-hydroxy acetophenones with phenyl acetic acid in refluxing boiling diphenyl ether gives 4-methyl-3-phenyl coumarins in 45–89% yield; however, the reaction time was too long (10 to 37 h). Mukaiyama's esterification protocol as reported by Mashruqui and coworkers[35] uses 2-chloro-1-methyl pyridinium iodide-triethyl amine reagent to provide rapid access to 3-substituted coumarins in satisfactory yields but needs inert reaction conditions and freshly prepared catalyst. Recently, Dittmer and coworkers[36] have reported the synthesis of 3-phenylcoumarins by the use of sodium telluride with 10% yield, but the method requires costly catalyst, tedious workup, and low reaction temperature (−20°C).

Herein, we report a facile two-step methodology for synthesis of 3-aryl-4-hydroxycoumarins, 3-aryl-4-methyl coumarin, and 3-aryl coumarin by acetylation of appropriately substituted 2-hydroxycarbonyl compounds with aryl acetic acid and subsequent Dickmann-type cyclization of aryl acetoxy ester with a base to give the corresponding 3-aryl-4-substituted coumarins.

The synthesis of 3-phenyl coumarins is shown in Scheme 1. The reaction of salicylaldehyde **1a–c** with aryl acetic acid in the presence of phosphoryl chloride in pyridine afforded the ester 2-arylacetoxy salicylaldehyde in 82–88% yields. These esters were stirred with the pulverized potassium hydroxide in pyridine to afford the 3-phenyl coumarin **4a–c** (80–90% yield). Similarly, 2′-hydroxy acetophenones **1d–j** were acylated with phenyl acetic acid using phosphoryl chloride in pyridine to give ester **3d–j**, which on reaction with pulverized potassium hydroxide in pyridine, gave 3-phenyl-4-methyl coumarins **4d–j** (85–98% yield).

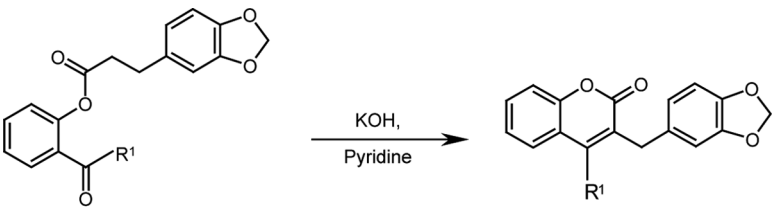


Scheme 1. Methodology used for synthesis of 3-phenyl coumarins.

A literature survey has revealed that the benzoyl derivatives of 2′-hydroxy acetophenones on subjecting to Baker–Venkatraman transformation in pulverized potassium hydroxide in pyridine gave β-diketones, which could be further cyclized to flavones or chromones under acidic workup.[37] In the esters **3**, the acidity of benzylic protons is greater than acetyl protons. Thus, the carbanion generated at benzylic carbon atom, and it undergoes Dickmann-type cyclization rather than rearrangement of aryl acetyl groups to acetyl anion as in Baker–Venkatraman rearrangement.

The extension of this reaction using ester of o-hydroxy aryl carboxylic acids with view toward developing a method for the synthesis of 4-hydroxy-3-phenyl coumarins has also been examined. Methyl salicylate **1k–l** on acylation with phenyl acetic acid in the presence of phosphoryl chloride gave ester **3k–l**, which on reaction with pulverized potassium hydroxide in pyridine gave 4-hydroxy-3-phenyl coumarins. For the synthesis of 3-benzyl-4-hydroxy coumarins, α,β-dihydro cinnamic acid was used as acylating agent for acylation of methyl salicylate. The esters were similarly treated to give 3-benzyl-4-hydroxy coumarin. Similarly, 3-benzyl coumarin was prepared from salicaldehyde (Scheme 2). 3-Phenyl-4-styrylcoumarins **4m–p** were synthesized in two steps from 2′-hydroxy chalcones **1m–p** by acylation with phenyl acetic acid and Dickmann-type cyclization using a base. Results of the formation of esters and coumarins are given in Table 1. The preparation of 4-styryl coumarins is reported from 4-acetic acid coumarin by condensation with aryl aldehyde in pyridine at 130°C and from 2′-hydroxy chalcones on condensation with Wittig reagent $Ph_3P{=}CHCOOEt$.[38] The behavior of esters **3a–c** toward Dickmann-type cyclization was also studied. Thus, the ester **3a–c** was reacted with potassium carbonate in dimethylformamide (DMF) or triethyl amine in DMF. The results of formation of coumarin are recorded in Table 2. These results suggested that the Dickmann-type cyclization in pulverized potassium hydroxide gives better results than other two conditions.

Alternatively, 3-phenylcoumarins were prepared in one step by reaction of salicaldehyde with phenyl acetyl chloride in the presence of potassium carbonate in DMF (Scheme 3). On acidic workup, it affords 3-phenylcoumarins in moderate yield. Since we need to prepare phenyl acetyl chloride from phenyl acetic acid, we did not observe any added advantage over the previous method, and there is difficulty preparing substituted phenyl acetic chloride because of their short life.



Scheme 2. Methodology used for synthesis of 3-benzyl coumarin from salicaldehyde.

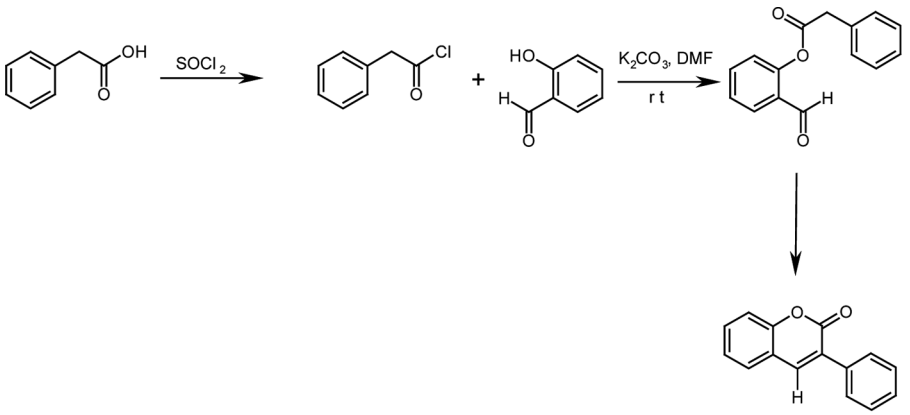
Table 1. Synthesis of aryl acetoxy esters and corresponding 3-aryl-4-substitutedcoumarin

						Ester (3)		Coumarin (4)	
Entry	R^1	R^2	R^3	R^4	R^5	M. P. (°C)	Yield %	M. P. (°C)	Yield %
a	H	H	H	H	H	59	82	132	80
b	H	H	$-OCH_3$	H	H	33	83	120	88
c	H	H	H	H	$-OCH_3$	55–56	88	140	89
d	$-CH_3$	H	H	H	H	43	90	156	90
e	$-CH_3$	H	H	$-CH_3$	H	63	89	168	92
f	$-CH_3$	H	$-CH_3$	H	H	42	92	142	90
g	$-CH_3$	$-CH_3$	H	H	H	45	78	148	88
h	$-CH_3$	H	H	Cl	H	58	94	192	98
i	$-CH_3$	H	Cl	H	H	52	92	178	96
j	$-CH_3$	Cl	H	H	H	48	82	182	92
k[a]	$-OCH_3$	H	H	H	H	70–71	94	137	90
l[a]	$-OCH_3$	H	$-OCH_3$	H	H	78	91	81–82	85
m	$-CH=CH-Ar$	H	H	Cl	$-OCH_3$	88	84	192	86
n	$-CH=CH-Ar$	H	H	$-CH_3$	Cl	95	87	181	88
o	$-CH=CH-Ar$	H	H	Cl	H	98	92	178	83
p	$-CH=CH-Ar$	H	$-CH_3$	H	$-OCH_3$	40	90	185	75

[a]In Coumarin R^1 is –OH.

Table 2. Synthesis of coumarin under different reaction conditions

Coumarin	Pyridine/KOH	K_2CO_3/DMF	K_2CO_3/NEt_3
a	92	43	48
b	81	45	43
c	80	43	44



Scheme 3. One-step synthesis of 3-phenyl coumarins from phenyl acetyl chloride.

Attempt to prepare 3-alkyl substituted coumarin by using acetic acid, propionic acid, and n-butyric acid as acylating agents were unsuccessful. These acids, on reaction with 2′-hydroxy-5-methyl acetophenones in pyridine, give a corresponding ester in poor yields. These esters did not undergo Dickmann-type cyclization by using potassium hydroxide in pyridine to afford 3-substituted coumarin. Instead, most of the time, starting material was recovered.

The present method offer several advantages: relatively cheap and readily available starting materials are used, formation of enolate is fast, the reaction completes within 10–30 min at room temperature, and it is a metal-free reaction with good atom economy.

EXPERIMENTAL

2-Hydroxy phenyl carbonyl compound **1** (0.01 mol) and phenyl acetic acid (0.012 mol) in pyridine were stirred, and a solution of phosphoryl chloride (0.02 mol) in ether was added to it over 30 min. The reaction mixture was stirred for 1 h and diluted with ice-cold HCl. The solid product thus formed was isolated and washed with cold water, 10% $NaHCO_3$, and again with water and then crystallized by ethanol. The solution of ester **3** in pyridine was added to pulverized potassium hydroxide (KOH) in pyridine in 30 min. The reaction mixture was stirred for 30–60 min and then diluted with HCl. The solid product obtained was washed with water, dried, and crystallized by ethanol.

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