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Research Article

Barium Dichloride as a Powerful and Inexpensive Catalyst for the Pechmann Condensation without Using Solvent

Saeed Khodabakhshi

Department of Chemistry, Islamic Azad University, Gachsaran Branch, Gachsaran, Iran

Correspondence should be addressed to Saeed Khodabakhshi, saeidkhm@yahoo.com

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Various coumarin derivatives have been efficiently synthesized via barium dichloride-catalyzed Pechmann condensation reaction of various phenols and β-keto esters under solvent-free conditions. This novel and inexpensive method has advantages such as short reaction times, excellent product yields, and avoidance of organic solvents in agreement with green chemistry principles.

1. Introduction

The development of procedures to prepare heterocycles is of vital importance in synthesis of organic compounds, especially the heterocycles which can be found in naturally occurring products [1]. Coumarin derivatives possess diverse biological properties. For example, some polycyclic coumarins such as calanolides [2] isolated from *Calophyllum* genus, and others have shown potent anti-HIV activity [3]. Numerous coumarins have been also used as drug in contemporary medicine. As can be seen in Figure 1, warfarin, acenocoumarol, and phenprocoumon are vitamin K antagonists which play an anticoagulant role in the treatment of thromboembolic disorders [4].

Besides, some coumarins are used as additives in food and cosmetics [5], optical brighteners [6], and dispersed fluorescent and laser dyes [7]. Due to the above-mentioned properties of these heterocycles, their synthesis has attracted much attention of researchers. Coumarins have been synthesized by several methods. Some of them suffer from disadvantages such as harsh conditions, long reaction times, low yield of products, and use of expensive and toxic reagents or organic solvents [8–12]. In continuation of our study on catalyzed reactions [13], in this paper, a new application of barium dichloride as a Lewis acid catalyst in the synthesis of some coumarins is reported.

2. Results and Discussion

Establishing the reaction based on solvent-free conditions obviously reduces pollution and brings down handling costs due to simplification of experimental procedure, workup technique, and saving in labour [14].

In 1883, Pechmann and Duisberg found that phenols condense with β-ketonic esters in the presence of sulfuric acid, giving coumarin (benzo-2-pyrone) derivatives [15]. In fact, Pechmann condensation is a commonly method for the preparation of coumarin derivatives because it proceeds from simple precursor such as phenols and β-ketoesters. However, via the Pechmann condensation, coumarins with substitution on either pyrone or benzene ring or both are affordable in good-to-excellent yield. In this study, we found that the Pechmann cyclocondensation of phenols **1** with β-ketoesters **2** in the presence of barium dichloride as an efficient catalyst produces the substituted coumarins **3** under thermal and solvent-free conditions (Scheme 1).

In order to optimize the reaction conditions, we tested both various temperatures and amounts of the catalyst ($BaCl_2$) in the reaction of phloroglucinol (**1a**) with ethyl acetoacetate (**2a**) as a model reaction to investigate the effects of catalyst amount and temperature for the preparation of 5,7-dihydroxy-4-methylcoumarin (**3a**) (Scheme 2).

As shown in Tables 1 and 2, it can be concluded that the thermal-assisted model reaction is efficiently carried out by

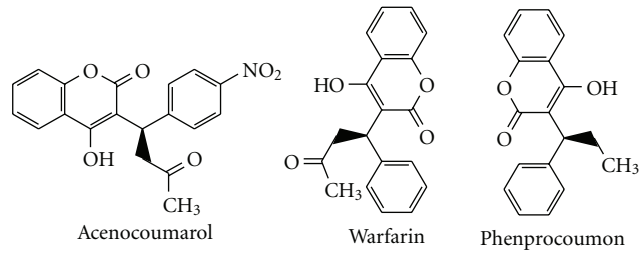
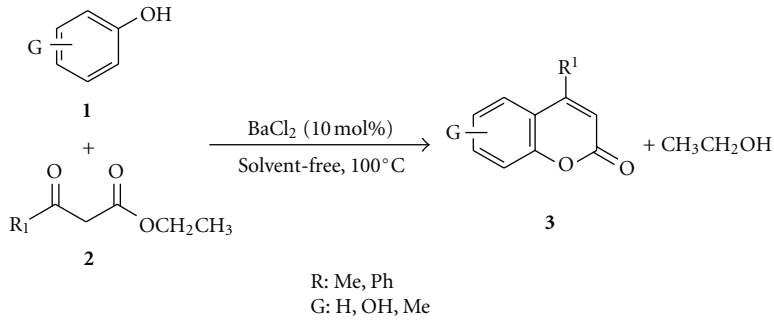
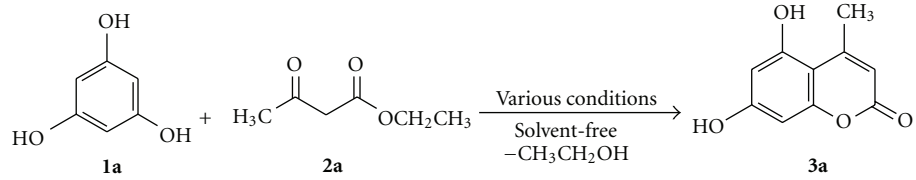


Figure 1: Chemical structure of some biologically active coumarins.



Scheme 1: The Pechmann reaction catalyzed by barium dichloride.



Scheme 2: The reaction of phloroglucinol and ethyl acetoacetate under various conditions.

Table 1: The effect of catalyst amount on the synthesis of **3a** at 100°C under solvent-free conditions.

Entry	Catalyst (mol%)	Time (min)	Yield[a] (%)
1	—	25	Trace
2	2	25	25
3	5	25	40
4	7	25	75
5	10	25	90
6	20	25	85

[a] Refers to isolated yields.

Table 2: The effect of temperature on the synthesis of **3a** using $BaCl_2$ (10 mol%) under solvent-free conditions.

Entry	Temperature (°C)	Time (min)	Yield[a] (%)
1	25	25	Trace
2	70	25	50
3	100	25	90
4	130	25	80

[a] Refers to isolated yields.

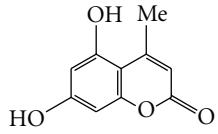
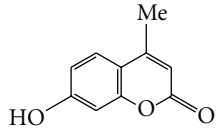
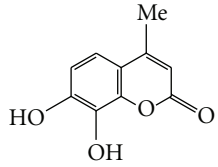
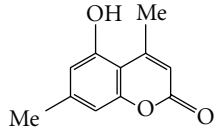
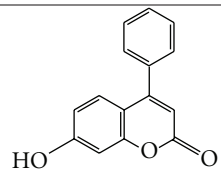
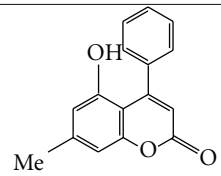
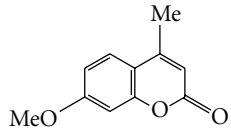
adding catalytic amounts of barium dichloride (10 mol%) in solventless conditions at 100°C. The excessive amounts of catalyst or higher temperature than 100°C cannot improve the product yield.

After optimization of the reaction conditions, as can be seen in Table 3, in order to extend the scope of this reaction, various phenols such as resorcinol, pyrogallol, and phloroglucinol were successfully used for the efficient Pechmann reaction with different β-ketoesters. A wide variety of coumarins were obtained through this method in good-to-excellent yield in short reaction times (Table 2).

The ^{1}H NMR spectrum of **3a** exhibited five sharp singlets identified as methyl (δ = 2.49 ppm), olefinic pyrone ring (δ = 5.83 ppm), two OH groups (δ = 10.28, 10.51 ppm), and protons. Two singlet signals (δ = 6.15 ppm) and (δ = 6.24 ppm) correspond to the aromatic protons of benzene ring. The proton-decoupled ^{13}C NMR spectrum of **3a** showed 10 distinct resonances in agreement with the proposed structure. A reasonable mechanism for barium-catalyzed Pechmann reaction has been proposed in Scheme 3.

In summary, the presented report demonstrates facile barium dichloride-catalyzed synthesis of coumarins via the Pechmann reactions. The important advantages of this method are the short reaction time, high yields, simple

Table 3: Synthesis of some coumarin derivatives based on Pechmann condensation using barium dichloride at 100°C under solvent-free conditions.

Entry	Product[a]	Time (min)	Yield[b] (%)	M.p. °C
3a		25	90	288–290
3b		35	85	188–190
3c		30	85	243–245
3d		30	90	244–246
3e		55	80	257–259
3f		50	85	243–245
3g		40	90	150–152

[a] Identified by comparison with authentic samples and their spectral data. [b] Refers to isolated yields.

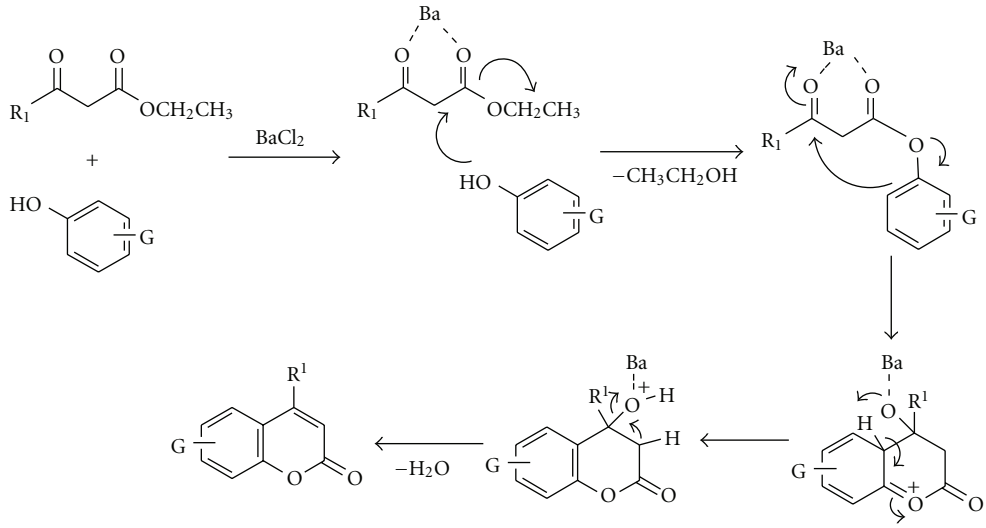
workup, the use of inexpensive and available catalyst, the nonchromatographic purification of products, that is, simple recrystallization from EtOH, and use of solvent-free conditions instead of organic solvents in accord with green chemistry criteria.

3. Experimental Section

3.1. General. The chemicals were purchased from Merck, Fluka, and Aldrich chemical companies. The reactions were monitored by TLC (silica-gel 60 F_{254}, hexane: EtOAc). IR spectra were recorded on a FT-IR Shimadzu-470 spectrometer and the ^{1}H NMR spectra were obtained on a Bruker-Instrument DPX-400 and 500 Avance 2 model.

3.2. General Procedure for the Preparation of Coumarin ***3****.* A mixture of phenol **1** (1 mmol), β-ketoesters **2** (1 mmol), and barium dichloride (10 mol%) was heated and stirred at 100°C. After completion of the reaction (controlled by TLC), the reaction mixture was cooled at room temperature and poured onto crushed ice. The solid product obtained was filtered off, washed with ice-cold water, and recrystallized from hot EtOH to obtain the pure product **3**.

Compound **3a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.51 (s, 1H), 10.28 (s, 1H), 6.24 (s, 1H), 6.15 (s, 1H), 5.83 (s, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.51, 160.55, 158.39, 155.43, 109.29, 102.55, 99.54, 94.98, 23.88. Anal. Calcd. For $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.69, H, 4.15.



Scheme 3: Suggested mechanism for the Pechmann reaction catalyzed by barium dichloride.

Compound **3b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49–7.47 (d, J = 6.8 Hz), 6.85 (d, 1H, J = 2 Hz), 6.82 (dd, 1H, J = 6.8, 2.4 Hz), 6.14 (s, 1H), 5.7 (s, 1H), 2.35 (s, 3H). Anal. Calcd. For $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 68.36, H, 4.50.

Compound **3c**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.15 (s, 1H), 9.30 (s, 1H), 7.08 (d, 1H, J = 8.8 Hz), 6.81 (d, 1H, J = 8.8 Hz), 6.10 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 160.47, 154.35, 149.81, 144.13, 143.74, 132.60, 115.88, 113.23, 112.56, 110.60, 40.42, 40.21, 40.00, 39.79, 39.58, 39.38, 39.17, 18.63. Anal. Calcd. For $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.58, H, 4.27.

Compound **3d**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H), 6.60 (d, 2H), 6.03 (s, 1H), 3.49 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 160.29, 156.90, 155.28, 155.04, 143.18, 112.37, 112.30, 108.15, 106.96, 23.91, 21.56. Anal. Calcd. For $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.71, H, 5.25.

Compound **3e**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H), 7.34 (s, 4H), 7.28, (s, 2H), 7.05 (d, 1H, J = 8.8 Hz), 6.56 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): 161.80, 160.77, 155.96, 135.52, 130.07, 129.29, 128.79, 128.54, 113.68, 111.08, 110.70. Anal. Calcd. For $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.88, H, 4.18.

Compound **3f**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H), 7.37 (m, 5H), 6.72 (s, 1H), 6.47 (s, 1H), 5.95 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): 160.09, 156.05, 155.96, 155.91, 143.93, 139.75, 128.34, 127.92, 127.75, 113.88, 112.52, 108.19, 105.44, 21.65. Anal. Calcd. For $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.25, H, 4.82.

Compound **3g**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 6.97 (s, 2H), 6.20 (s, 1H), 3.85 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.83, 160.59, 155.24, 153.86, 126.88, 113.66, 112.54, 111.58, 101.16, 56.36, 18.58. Anal. Calcd. For $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.70, H, 4.17.

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