**K₂CO₃-PROMOTED DOMINO REACTIONS FOR SYNTHESIS OF ISOCOUMARINS UNDER MICROWAVE IRRADIATION**

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**GRAPHICAL ABSTRACT**

A small library of isocoumarin derivatives has been synthesized via K₂CO₃-catalyzed domino reactions of 2-carboxybenzaldehyde and α-bromoacetophenones under microwave irradiation (MW). This strategy offers a simple, environmentally acceptable route to synthesize isocoumarin derivatives in moderate to excellent yields. All new compounds were characterized by ¹H NMR, ¹³C NMR, infrared, and high-resolution mass spectroscopic techniques.

**Keywords** α-Bromoacetophenone; 2-carboxybenzaldehyde; domino reactions; isocoumarin; microwave irradiation

**INTRODUCTION**

Isocoumarins represent an important class of naturally occurring lactones, which are structural subunits of many natural products. For examples, Mizonu and coworkers had isolated three phenolic isocoumarin derivatives, aehlisocoumarins, from...
the underground parts of *Achlys triphylla*; Qi reported on penicimarins obtained from the sponge-derived fungus *Penicillium* sp. MWZ14-4; and Thongbai reported on gymnopalynes isolated from cultures of basidiomycete originated from the rain forest of northern Thailand (Fig. 1). These isolated products exhibit a wide range of biological activities, such as antifungal, antitumor, antiallergic, antimicrobial, anti-inflammatory, anti-diabetic, phytotoxic, and immunomodulatory activities.

Tremendous efforts have been devoted to the development of methods for efficient synthesis of isocoumarins because of their diverse biological activities. The reaction of aromatic carboxylic acids with unsaturated compounds under transition-metal catalysis to construct isocoumarins is the traditional method. Guo described the addition of *o*-halobenzoic acids to active internal alkynes in the presence of CuCl₂ to produce isocoumarins. Miura disclosed an oxidative coupling of benzoic acids and alkynes catalyzed by rhodium to synthesize isocoumarins. Lu utilized Pd(II) to catalyze oxidative coupling reaction of intramolecular benzoate containing internal alkynes for the synthesis of isocoumarins. Recently, Ma’s group prepared isocoumarin derivatives via the tandem Michael addition/intramolecular cyclization of 2-(*o*-(methoxycarbonyl)phenyl)-2,3-allenoates with organozincs. Bhakta synthesized isocoumarins by condensation of phthalaldehydic acids with *o*-bromoacetophenones in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in dry benzene. Clerici found that β-dihydroxy isobenzofuran could be converted to isocoumarin derivatives by rearrangement. Most of the reported methodologies for preparing isocoumarins possess some limitations such as poor yields or harsh reaction conditions in some cases. Microwave-assisted organic synthesis has attracted a substantial amount of attention in the past few years. The main benefits of carrying out reactions under microwave irradiation are significant rate enhancement and greater product yields that can frequently be obtained. Here we report a simple, mild, and efficient method for the preparation of isocoumarin derivatives under microwave irradiation.

**RESULTS AND DISCUSSION**

In an initial study, we investigated the domino reaction of 2-carboxybenzaldehyde 1 and *o*-bromoacetophenone in acetone under the presence of K₂CO₃ at 70°C

![Figure 1. Representative natural products containing an isocoumarin unit.](image)
for 8 h. To our delight, the domino reaction proceeded smoothly to provide the desired product 3a in 31% yield. The yield increased to 55% when the reaction was carried out at the same temperature in DMF (entry 2, Table 1). There have been reports of reactions that proceed faster in a microwave environment than under conventional conditions at the same temperature.\cite{14} When our reaction was heated by using microwave irradiation instead of conventional heating method at 70 °C in dimethylformamide (DMF) for 1 h, the yield did not improve (entry 3, Table 1). However, the reaction time under microwave irradiation condition could be shortened to 1 h in comparison to heating the mixture using oil bath. The next screening experiment focused on the ratios of 2-carboxybenzaldehyde = x-bromoacetophenone in the reaction mixture. Addition of 2-carboxybenzaldehyde in excess of 0.5 eq. increased the yield to 77%. We found that the target compound could be obtained in up to 90% yield when we added x-bromoacetophenone in excess of 1.5 eq (entry 6, Table 1).

Based on these results and our previous studies,\cite{15} a possible mechanism for the domino reaction is proposed: First, phthalaldehydic acid is deprotonated by K₂CO₃ to form carboxylic ion. Then the anion attacks x-bromoacetophenone to form the ester intermediate (II). In the presence of a base, an intramolecular S_N2 substitution takes place to form the β-hydroxy ketone (III). The product can be obtained by dehydration of the intermediate (III) at high temperature (Scheme 1).

x-Bromoacetophenone is an active reagent in this reaction, which could be attacked by carboxylic ion (I) and could also take place in other reactions. So the excess of x-bromoacetophenone is propitious to the domino reaction and the reaction time can be further shortened to 0.5 h (entry 6, Table 1).

Under the optimized reaction conditions [x-bromoacetophenone (1.5 eq), DMF, MW/100 W, 70 °C], the scope of the domino reactions of 2-carboxybenzaldehyde 1 and x-bromoacetophenone 2 was explored. The results are summarized in Scheme 1. Generally, the domino reactions between a range of readily available

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**Table 1. Optimization of the reaction conditions**

| Entry | 1/2a | Heating method | Solvent | Temp. (°C) | Time (h) | Yield (%) |
|-------|------|----------------|---------|------------|----------|-----------|
| 1     | 1:1  | Oil bath       | Acetone | 50         | 6        | 27        |
| 2     | 1:1  | Oil bath       | DMF     | 70         | 8        | 55        |
| 3     | 1:1  | MW/100 W       | Acetone | 50         | 1        | 23        |
| 4     | 1:1  | MW/100 W       | DMF     | 70         | 1        | 56        |
| 5     | 1.5:1| MW/100 W       | DMF     | 70         | 0.5      | 77        |
| 6     | 1:1.5| MW/100 W       | DMF     | 70         | 0.5      | 90        |

*Unless otherwise noted, all the reactions were performed by using 2-carboxybenzaldehyde 1 (1 mmol) and x-bromoacetophenone 2a (1 mmol) in 5 mL solvent in the presence of 2 mmol K₂CO₃.*

*Isolated yields after silica-gel flash column chromatography.*
2-carboxybenzaldehyde and substituted \(\omega\)-bromoacetophenone provided isocoumarin derivatives in moderate to excellent yields (Scheme 2). For example, \(\omega\)-bromoacetophenone 2 bearing electron-donating groups (EDG) (methoxy-, hydroxyl substituted \(\omega\)-bromoacetophenone) gave the corresponding isocoumarins 3 in better yields, whereas
ω-bromoacetophenone 2 bearing electron-withdrawing groups (EWG) (fluoro-, chloro-, nitro-substituted ω-bromoacetophenone) usually provided slightly lower yields of isocoumarins 3. This phenomenon may be explained by the fact that the electron-donating groups contribute to the formation of the carbon anion. However, when lower activity nucleophile methyl bromocrotonate reacted with 2-carboxybenzaldehyde, the isocoumarin product yield was only 26%. No product was obtained using 1-bromo-4-phenylbut-3-en-2-one as bromide in this reaction. The probable reason was that the nucleophile was very stable because of the large conjugated system.

CONCLUSION

In summary, we have developed a convenient domino reaction to synthesize various substituted isocoumarins in moderate to excellent yields from readily available starting materials. This methodology provides ready access to various multifunctional heterocycle isocumarins and quinolones.

EXPERIMENTAL

Analytical thin-layer chromatography (TLC) was carried out on precoated silica-gel plates. Column chromatography was conducted with 300- to 400-mesh silica gel. NMR spectra were recorded at 500 MHz for 1H NMR using SiMe4 as an internal standard in CDCl3 and 125 MHz for 13C NMR. Infrared (IR) data were recorded using a Nicolet Av360 instrument. Microwave irradiation was performed by single-mode microwave synthesis system (CEM Discover). Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification.

Compound 2a (299 mg, 1.5 mmol) and K2CO3 (278 mg, 2 mmol) were added to a solution of 2-carboxybenzaldehyde (150 mg, 1 mmol) in DMF (5 mL), and the mixture was stirred under microwave irradiation at 70°C until all starting material was consumed. The solid was filtered, and the filtrate was diluted with ethyl acetate and then washed with water and brine. The organic layer was dried (Na2SO4), filtered, and concentrated. The residue was purified by silica-gel flash column chromatography to afford product 3a.[12] Light yellow solid; 1H NMR (500 MHz, CDCl3) δ 8.38 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.82 (t, J = 7.5 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.65–7.63 (m, 2H), 7.53 (t, J = 7.5 Hz, 2H), 7.40 (s, 1H) ppm; 13C NMR (125 MHz, CDCl3) δ 186.6, 160.6, 150.0, 135.5, 135.2, 135.1, 133.4, 130.9, 130.0, 129.9, 128.6, 128.0, 122.6, 113.0 ppm. IR (KBr, v/cm⁻¹): 2963, 2025, 1735, 1672, 1438, 1323, 1262, 1182, 1101, 1018, 802.

Complete experimental details are available online in the Supplemental Material.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher’s website.

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