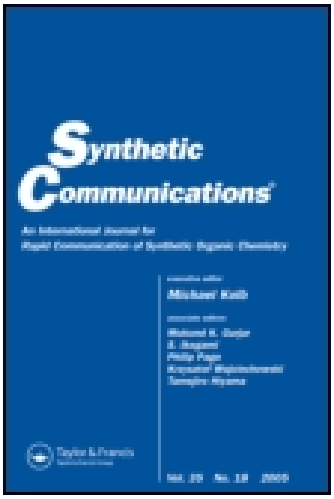

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FACILE ONE-POT METHOD FOR THE SYNTHESIS OF POLYSUBSTITUTED PHTHALIDE DERIVATIVES

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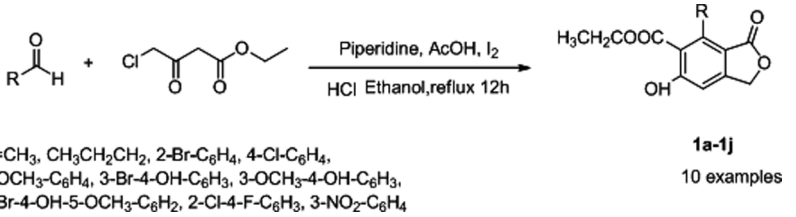
GRAPHICAL ABSTRACT



Abstract *A new three-component cyclization method is described involving two starting materials, ethyl 4-chloroacetoacetate and aldehydes, catalyzed by piperidine, acid, and iodine. Ten corresponding polysubstituted phthalides are formed with good yields (44–78%). A mechanism of the reaction is also proposed.*

Keywords Catalyst; cyclization; mechanism; phthalide

INTRODUCTION

Polysubstituted phthalides are common structural subunits in pharmaceutical and natural products that have a wide range of biological activities, including modulation of the central nervous system and protection against brain ischemia.[1–5] Moreover, they have been used as key intermediates in the synthesis of biologically active compounds such as nidulol and lactonamycin (Fig. 1).[6,7] As a result, the preparation of polysubstituted phthalides in general has been a focused area in organic synthesis.

Traditionally, synthetic methods for polysubstituted phthalide derivatives have been mainly based on benzannulation of 4-methoxycarbonylbut-2-enoate with methyl alkynoate or Diels–Alder reaction of methyl 2-(prop-1-en-2-yl)but-2-enoate

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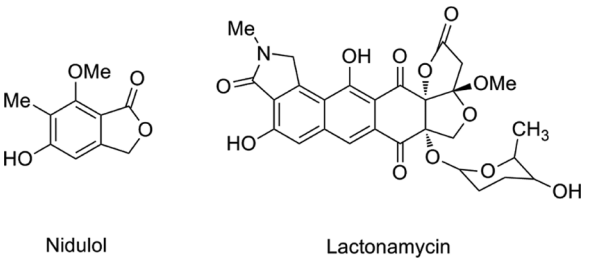
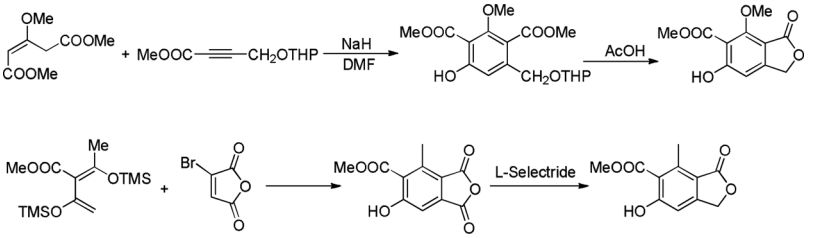
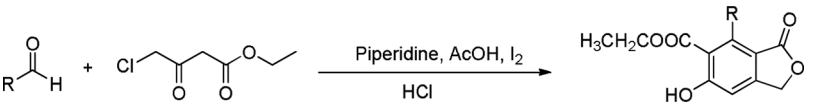


Figure 1. Structures of nidulol and lactonamycin.



Scheme 1. Traditional synthesis of phthalide derivatives.



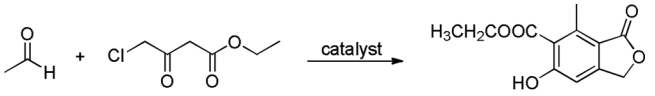
Scheme 2. Synthesis of substituted phthalide derivatives.

with furan-2,5-dione under appropriate conditions (Scheme 1).[8–12] However, these approaches have some drawbacks such as high cost and tedious procedures. Recently, methods that construct the aromatic backbone from acyclic precursors have received growing interest because of their short synthetic steps.[13–17] Herein, we describe an efficient method to synthesize polysubstituted phthalides from ethyl 4-chloroacetoacetate and aldehydes in the presence of piperidine, acid, and iodine (Scheme 2). Our method is simple and economical because no special apparatus or chemical is required. It is also devoid of any toxic by-products during the reaction.

RESULTS AND DISCUSSION

We initially conducted a preliminary study evaluating catalysis of acid and base using ethyl 4-chloroacetoacetate (2 equiv) and ethanal (1 equiv) as the starting substrates. The results are shown in Table 1. No product was found in the presence of acid or base only (Table 1, entries 1–3). Addition of catalytic amounts of both acid and base to the reaction yielded less product (Table 1, entry 4). Increasing the amounts of acid and base (1 equiv) led to more products (Table 1, entry 5), but greater

Table 1. Optimization of reaction conditions for the synthesis of **1a**



1a

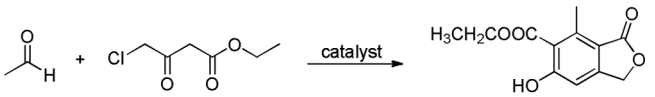
Entry	Catalyst[a]	Yield (%)[b]
1	AcOH (1 equiv)	0
2	Piperidine (1 equiv)	0
3	Triethylamine (1 equiv)	0
4	Piperidine:AcOH (1:1) (cat)	5
5	Piperidine (1 equiv), AcOH (1 equiv)	18
6	Piperidine (2 equiv), AcOH (2 equiv)	14
7	Piperidine (1 equiv), AcOH (1 equiv), HCl (cat)	39
8	Piperidine (1 equiv), AcOH (1 equiv), I_2 (1 equic), HCl (cat)[b]	63
9	Piperidine (1 equiv), AcOH (1 equiv), HCl (1 equiv)	18

[a]4-Chloroacetoacetate (2 equiv) and ethanal (1 equiv) in the presence of catalysts refluxed for 12 h in ethanol.

[b]Refers to pure products separated by chromatography.

amounts of the catalysts did not result in greater yields (Table 1, entries 6). Addition of 0.12 equiv concentrated hydrochloric acid and 1 equiv iodine gave the best result, whereas other amounts completed the reaction in poor yields (Table 1, entries 7–9). In many cases, the poor yields were a result of the formation of other by-products that could not be isolated by column chromatography.

Table 2. Optimization of reaction solvents



1a

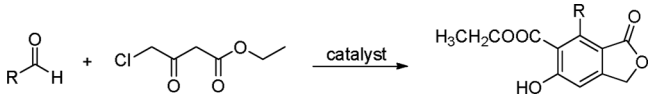
Entry	Solvent[a]	Yield (%)[b]
1	Methanol	42
2	Ethanol	63
3[c]	Ethanol	0
4	1,4-Dioxane	24
5	Acetic acid	15
6	DMF	0
7	DMSO	0

[a]4-Chloroacetoacetate (2 equiv) with ethanal (1 equiv) in the presence of piperidine (1 equiv), glacial acetic acid (1 equiv), concentrated hydrochloric acid (0.12 equiv), and iodine (1 equiv) refluxed for 12 h in different solvents (except entry 3).

[b]Refers to pure products separated by chromatography.

[c]Reacted at 40 °C in ethanol.

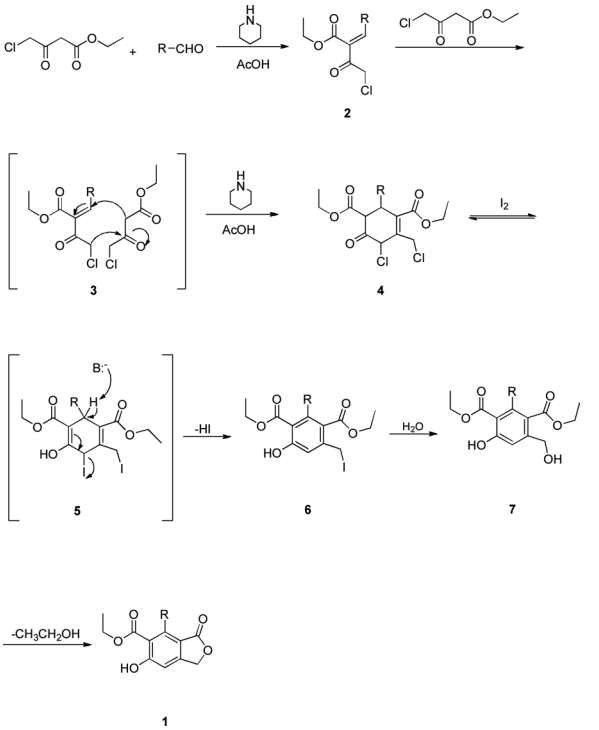
Table 3. Synthesis of substituted phthalides **1a–1j**



Entry	R	Product	Yield[a] (%)
1	CH_3	**1a**	63
2	$CH_3CH_2CH_2$	**1b**	69
3	2-Br-C_6H_4	**1c**	56
4	4-Cl-C_6H_4	**1d**	65
5	2-OCH_3-C_6H_4	**1e**	50
6	3-Br-4-OH-C_6H_3	**1f**	58
7	3-OCH_3-4-OH-C_6H_3	**1g**	44
8	3-Br-4-OH-5-OCH_3-C_6H_2	**1h**	60
9	2-Cl-4-F-C_6H_3	**1i**	60
10	3-NO_2-C_6H_4	**1j**	78

[a]Refers to pure products separated by chromatography.

We continued to investigate the effect of solvents on the reaction, such as methanol, 1,4-dioxane, acetic acid, dimethylformamide (DMF), and dimethylsulfoxide (DMSO), but the yields were found no better than the yield of ethanol (Table 2).



Scheme 3. Possible mechanism of the reaction.

To see the scope of this method, two aliphatic aldehydes and eight aromatic aldehydes were examined under the optimized conditions, and the corresponding results were summarized in Table 3. The substitutes on the aromatic aldehydes exhibited an effect on the yields of the reactions. The electron-withdrawing groups gave better yields than the electron-donating groups. For example, 3-nitrobenzaldehyde afforded the desired product **1j** as a white crystalline solid in 78% yield (Table 3, entry 10). By comparison, 2-methoxy benzaldehyde, 3-bromo-4-hydroxy-5-methoxy benzaldehyde, 3-bromo-4-hydroxybenzaldehyde, and 3-methoxy-4-hydroxybenzaldehyde gave lower yields.

To further the scope the present synthesis, a plausible mechanism of the reaction is proposed (Scheme 3). It involes the Knoevenagel reaction of aldehydes with 4-chloroacetoacetate to give a Konevenagel product **2**, which undergoes both Michael-type addition and intramolecular aldol condensation in the presence of piperidine to give a 1,3-dicarbonyl derivative **4**, which can form the enol **5** by isomerazation. It is possible to generate the stable aromatization product **6** after the dehydrohalogenation of allyl halide catalyzed by base. Then hydrolyzation of **6** give the intermediate **7.** Finally, the desired phthalide derivatives **1** is easily obtained by internal esterification in the presence of acid. In this process iodine is possible to promote elimination and hydrolyzation through an exchange of chlorine.

In summary, we have identified and studied a new and facile reaction of 4-chloroacetoacetate with aldehydes to produce corresponding substituted phthalides in moderate yields. The proposed procedure leads to building blocks, potential intermediates of organic materials, and new substituted phthalides. It holds potential for use in organic synthesis.

EXPERIMENTAL

^{1}H NMR and^{13}C NMR spectra were recorded at 400 MHz and 100 MHz on a JNM-ECA-400 instrument with tetramethylsilane (TMS) as an internal standard in the DMSO. Infrared (IR) spectra were recorded in KBr disk using a Nicolet 6700 FT-IR spectrophotometer. Electrospray ionization–mass spectrometry (ESI-MS, high resolution) was done using a Waters Xevo G2 Qtof (ESI) mass spectrometer. Melting points were determined using a RY-1 apparatus and were uncorrected.

Ethyl 4-chloroacetoacetate (2 mmol) and ethanal (1 mmol) were placed in a flask under an atmosphere of nitrogen. Piperidine (1 mmol), glacial acetic acid (1 mmol), iodine (1 mmol), concentrated hydrochloric acid (0.01 mL), and ethanol (10 mL) were added. The resulting mixture was heated at 80 °C for 12 h. After cooling to room temperature, the solvent was removed by evaporation. The residue was poured into 50 mL of water and extracted with ether. The organic layer was separated and was washed with saturated sodium chloride solution. The solvent was removed after dried over sodium sulfate and the residue was purified by column chromatography on silica gel to give the product **1a** (0.15 g, white powder) in 63% yield, mp 138.3–139.1 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm, 11.12 (s, 1H, OH), 6.91 (s, 1H, Ph-H), 5.24 (s, 2H, CH2), 4.3 (q, 2H, CH2, $J = 8$ Hz), 2.45 (s, 3H, CH3), 1.29 (t, 3H, CH3, $J = 8$ Hz); ^{13}C NMR (DMSO-d_6, 100 MHz), δ, ppm, 170.2, 166.7, 159.5, 150.9, 136.9, 124.2, 123.6, 113.3, 106.6, 68.3, 61.0, 14.0, 13.6. HRMS: calc. for C_{12} $H_{11}O_5$ 235.0612; found 235.0612.

FUNDING

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SUPPLEMENTAL MATERIAL

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

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