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Stereoselective synthesis of (*Z*)-3-ylidenephthalides via $AlCl_3$-mediated cyclization with 2-acylbenzoic acids

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ABSTRACT

An efficient method for the synthesis of (*Z*)-3-ylidenephthalides is reported in moderate to high yield with $AlCl_3$ as catalyst. Different substrates of the 2-acylbenzoic acids are well performed in the *Z*/*E* selectivity. This method is highlighted by the gram-scale synthesis of the natural product (*Z*)-3-butylidene-5-hydroxyphthalide with anti-inflammatory activity.

Introduction

The (*Z*)-3-ylidenephthalide moiety is an important structure group of both naturally occurring products [1] and synthetic products [2] exhibiting a wide range of biological activities (Fig. 1). For examples, the natural product (*Z*)-3-butylidene-5-hydroxyphthalide (**3a**) possesses anti-inflammatory activity [3]. The Chinese angelica ingredient (*Z*)-3-butylidenephthalide (**2b**) possesses anti-diabetic [4] and anti-coagulant effects [5], and (*Z*)-3-(2-chlorobenzylidene)phthalide exhibits anti-HIV activity [2c]. In addition, (*Z*)-3-ylidenephthalides have been exploited as a versatile building block that can easily transform into other biologically heterocyclic compounds [6].

Many methods have been developed for the synthesis of (*Z*)-3-ylidenephthalides, such as (a) the modified Perkin or Julia reaction on anhydrides; [7] (b) the cyclization of 2-alkenyl or 2-allyl benzoic acid derivatives; [8] (c) transition-metal-catalysed coupling–cyclization reactions of 2-halobenzoic acids with alkynes; [9] (d) oxidative cyclization of 2-alkynylbenzaldehydes; [10] (e) Pd-catalysed CO insertion-cyclization reactions of 2-halo or 2-triflyloxyacetophenones; [11] (f) Rh- or Pd-catalysed oxidative coupling of benzoic acids with terminal alkynes or alkenes; [12] (g)

Au-catalysed tandem cyclization and hydrolysis of 2-alkynyl-*N*-methoxylbenzamides [13]. While each of these methods represents an important advance towards the synthesis of (*Z*)-3-ylidenephthalides, they still have limitations such as harsh reaction conditions, generation of side products and high toxicity of reagents. Although Takaishi and co-workers have reported the synthesis of 3-phenacylidenephthalides by treating 2-(3-oxo-3-phenylpropanoyl)benzoic acid with $SOCl_2$ (Scheme 1a) [14], it was limited by the poor stereoselectivity of the *Z*- and *E*-isomers. In 2014, Xue and co-workers reported the TSTU-mediated intramolecular cyclization of 2-acylbenzoic acids (Scheme 1b) [15]. However, the high price of the coupling reagent restricts the amplification of this method. Therefore, the development of an economical and efficient protocol for the stereoselective synthesis of (*Z*)-3-ylidenephthalides is still highly desirable. In this paper, we describe the $AlCl_3$-mediated stereoselective cyclization of 2-acylbenzoic acids for the preparation of the (*Z*)-3-ylidenephthalides with satisfactory yield and a broad substrate scope.

Results and discussion

The substrate 4-methoxy-2-pentanoylbenzoic acid (**1a**) was selected as model for the development of catalyst system. We found **1a** and its cyclized isomer **1a'**was a mixture (1a:1a′ = 1:2.5) after isolated by column chromatograph, which was presented in the NMR spectrum. Considering the cyclized isomer **1a**' may undergo the elimination process and transform into the 3-ylidenephthalide under acidic conditions, we screened various organic and lewis acids. As shown in Table 1, sulfinylchloride and *p*-toluensulfonic acid both generated the (*Z*)-3-butylidene-5-methoxyphthalide **2a** with relatively low *Z*/*E* stereoselectivity (en-

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0040-4039/

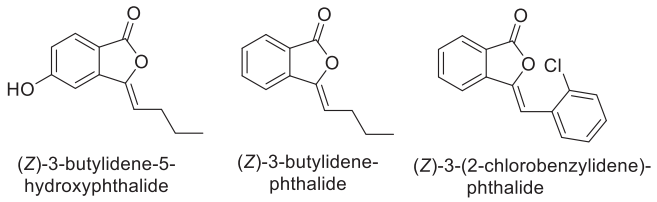
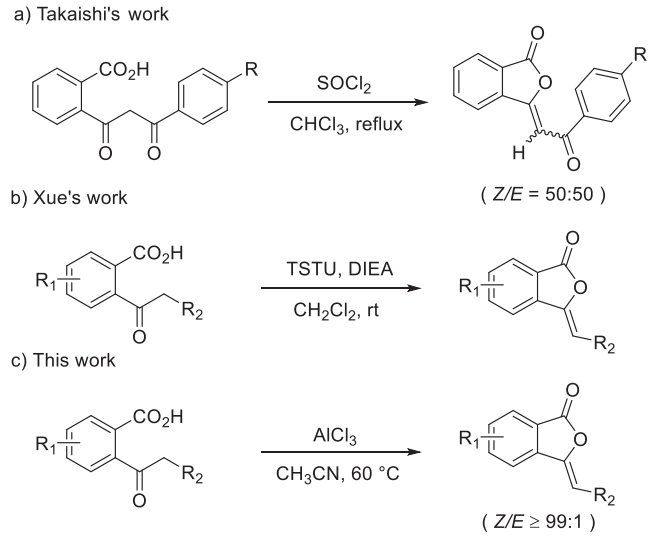


Fig. 1. Examples of (*Z*)-3-ylidenephthalides with biological activity.



Scheme 1. Synthetic methods of (*Z*)-3-ylidenephthalides from 2-acylbenzoic acids.

tries 1 and 2). Gratifyingly, we observed an excellent stereoselectivity in the presence of $AlCl_3$ with a 75% yield (entry 3). The product **2a** was not detected when we used $FeCl_3$ or $ZnCl_2$ as catalysts (entries 4 and 5). Subsequently, when screening different amounts of $AlCl_3$ as catalyst, we found reducing the amount of $AlCl_3$ would decrease the yield, and a further increase in $AlCl_3$ did not improve the yield (entries 6 and 7). Lowering the reaction to room temperature or raising it to 80 °C had no improvement on the reaction outcome (entries 8 and 9). Notably, extending the reaction time to 10 h gave a satisfactory yield, of which the isolated yield was improved to 91% (entry 10). Finally, the yield did not increase when the solvent was switched to $CHCl_3$, Acetone and EtOH (entries 11–13). After a serious of screening experiments, the optimal reaction condition was set as $AlCl_3$ (1.0 equiv) in CH_3CN at 60 °C for 10 h.

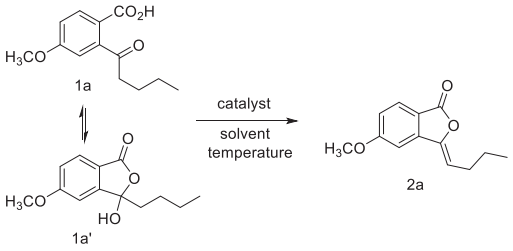
Having developed the optimized conditions for the reaction, we then investigated a series of alternative substrates. As can be seen from the examples in Table 2, substrates with both electron-donating and electron-withdrawing substituents on the aryl ring could generate corresponding (*Z*)-3-ylidenephthalides in good to high yield with excellent stereoselectivity (**2b** – **2g**, entries 2–6). Subsequently, we turned our sight into the different 2-acyl-substitutents. Gratifyingly, different 2-alkyl-acyl substrates, including alkyl groups with the steric hindrance, afforded the desired products in 60%–86% yields (**2h** – **2k**, entries 7–10). The 2-phenylacetyl (**1l** and **1m**) and 2-phenylpropanoyl (**1n** and **1o**) substrates were also tested to generate corresponding products in 58%-85% yields (entries 11–14).

The configuration of the double bond was demonstrated by the ROESY experiments exampled by the products **2a** and **2b**. ROESY correlation of H-4 with H-10 was observed, revealing the double bond was *Z*-configuration (Figure 2).

Although the precise mechanism of this reaction could not be fully illuminated, a possible reaction process is shown in Scheme 2. The complex **A, B** or **C** is formed *via* $AlCl_3$-assisted activation of the hydroxyl group of compound **a'**, [16] which is assumed to be attacked by Cl^- at Ha to give compound **b**. The Ha is less hindered than Hb, which may contribute to the high stereoselectivity of the reaction (more details see supporting information).

To further investigate the utility of the $AlCl_3$-mediated steroeselective synthesis of (*Z*)-3-ylidenephthalides in preparative organic

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst (equiv)	solvent	Temp.(°C)	Time (h)	Yield[b] (%)	*Z*/*E* Ratio[b]
1	$SOCl_2$ (1.0)	CH_3CN	60	5	85	89:11
2	p-TsOH (1.0)	CH_3CN	60	5	70	80:20
3	$AlCl_3$ (1.0)	CH_3CN	60	5	75	>99:1
4	$FeCl_3$ (1.0)	CH_3CN	60	5	N.D.	–
5	$ZnCl_2$ (1.0)	CH_3CN	60	5	N.D.	–
6	$AlCl_3$ (0.5)	CH_3CN	60	5	46	>99:1
7	$AlCl_3$ (2.0)	CH_3CN	60	5	76	>99:1
8	$AlCl_3$ (1.0)	CH_3CN	25	5	37	>99:1
9	$AlCl_3$ (1.0)	CH_3CN	80	5	76	>99:1
10	$AlCl_3$ (1.0)	CH_3CN	60	10	95 (91[c])	>99:1
11	$AlCl_3$ (1.0)	$CHCl_3$	60	10	N.D.	–
12	$AlCl_3$ (1.0)	Acetone	60	10	N.D.	–
13	$AlCl_3$ (1.0)	EtOH	60	10	30	>99:1

[a] Reaction conditions: 1a (0.5 mmol), catalyst in 2.0 mL of solvent under air.
[b] The yield and *Z*/*E* ratio were determined by ^1H NMR, phloroglucinol as the internal standard. N.D. = Not detected
[c] Isolated yields.

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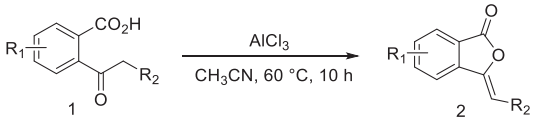
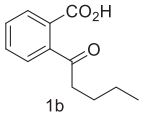
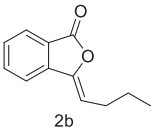
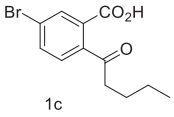
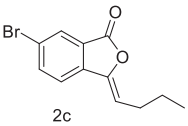
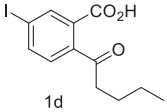
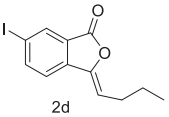
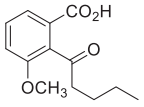
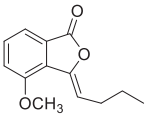
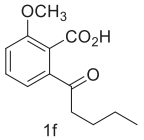
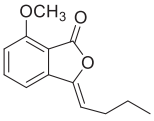
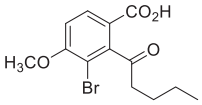
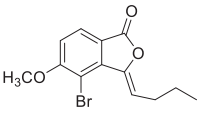
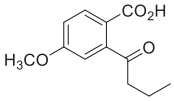
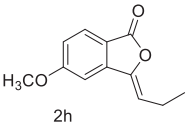
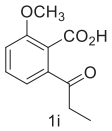
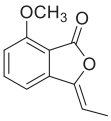
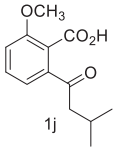
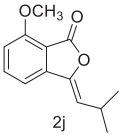
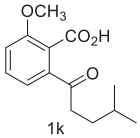
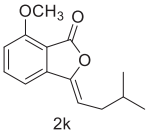
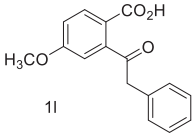
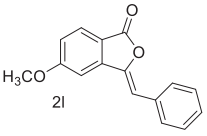
Table 2
Scope of the cyclization of 2-acylbenzoic acids.[a]



Entry	Substrate	product	yield[b]	*Z*/*E*[c] ratio
1	 1b	 2b	90	>99:1
2	 1c	 2c	83	96:4
3	 1d	 2d	80	99:1
4	 1e	 2e	82	>99:1
5	 1f	 2f	70	>99:1
6	 1g	 2g	95	>99:1
7	 1h	 2h	86	>99:1
8	 1i	 2i	76	>99:1
9	 1j	 2j	60	>99:1
10	 1k	 2k	85	>99:1
11	 1l	 2l	78	>99:1

(*continued on next page*)

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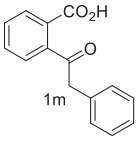
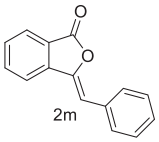
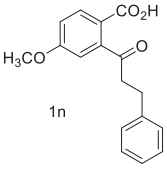
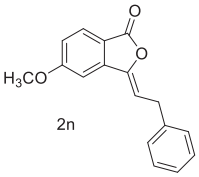
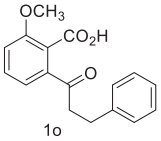
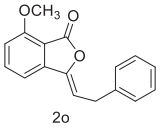
Table 2 (*continued*)

Entry	Substrate	product	yield[b]	*Z*/*E*[c] ratio
12	 1m	 2m	58	>99:1
13	 1n	 2n	78	>99:1
14	 1o	 2o	85	>99:1

[a] Reaction conditions: 2-acylbenzoic acids (1.0 mmol), $AlCl_3$ (1.0 mmol), 4.0 mL acetonitrile under air at 60 °C for 10 h.
[b] Isolated yields.
[c] The *Z*/*E* ratio were determined by ^1H NMR.

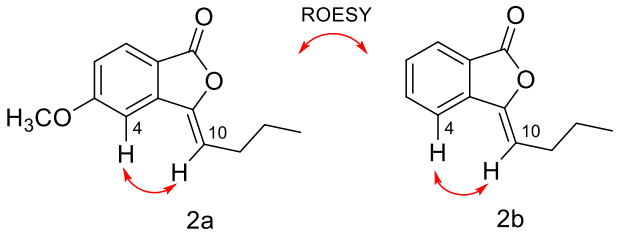
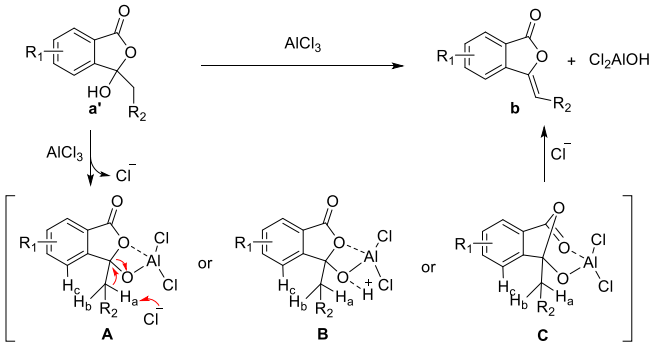
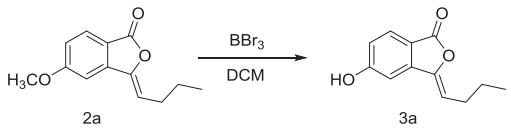


Fig. 2. ROESY experiments for the conformation of the *Z*-configuration.



Scheme 2. Proposed mechanism for the reaction pathway.

synthesize, a gram-scale reaction was conducted. A total of 4.72 g 4-methoxy-2-pentanoylbenzoic acid **1a** (20 mmol) was treated with 2.66 g $AlCl_3$ (20 mmol) under optimized reaction condition to yield 3.8 g of product **2a** (88%). With the product **2a** in hand, we next treated 2.18 g of **2a** with BBr_3 to afford (*Z*)-3-butylidene-5-hydroxyphthalide (1.9 g, 93%) as shown in scheme 3.



Scheme 3. Gram-scale synthesis of (*Z*)-3-butylidene-5-hydroxyphthalide.

In conclusion, we have developed the stereoselective synthesis of (*Z*)-3-ylidenephthalides via $AlCl_3$-mediated cyclization with 2-acylbenzoic acids. Various substrates have been investigated to generate their corresponding (*Z*)-3-ylidenephthalides in good to excellent yields under mild conditions with high stereoselectivity. This method was also applied to gram-scale preparation of (*Z*)-3-butylidene-5-hydroxyphthalide with anti-inflammatory activity.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.151734.

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