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Tandem Michael Addition/Cyclization Reaction of 2,3-Allenoates with Organozincs: Facile Synthesis of Isocoumarins

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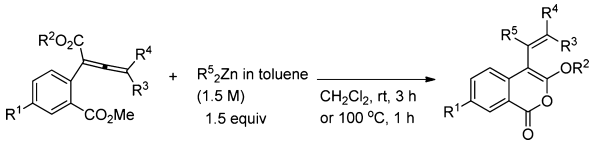
ABSTRACT



A series of isocoumarin derivatives have been synthesized via the reaction of 2-(*o*-(methoxycarbonyl)phenyl)-2,3-allenoates with organozincs in CH_2Cl_2 at room temperature (for dialkylzinc) or 100 °C (for Ph_2Zn) through a tandem Michael addition/intramolecular cyclization process.

Isocoumarins have attracted the attention of synthetic and medicinal chemists due to their diverse biological activities, including antifungal, antitumor, antiallergic, antimicrobial, anti-inflammatory, antidiabetic, phytotoxic, and immunomodulatory activities.[1] The isocoumarin framework also represents one of the privileged structures for the development of natural product-inspired compounds of potential biological interest. Selected biologically active isocoumarins are shown in Figure 1.[2−4] Besides, there are many natural products, such as phelligridin D, brevifolin, sescandelin B, dioscorone A, etc. containing isocoumarins (Figure 1).[5] Therefore, isocoumarins are attractive targets

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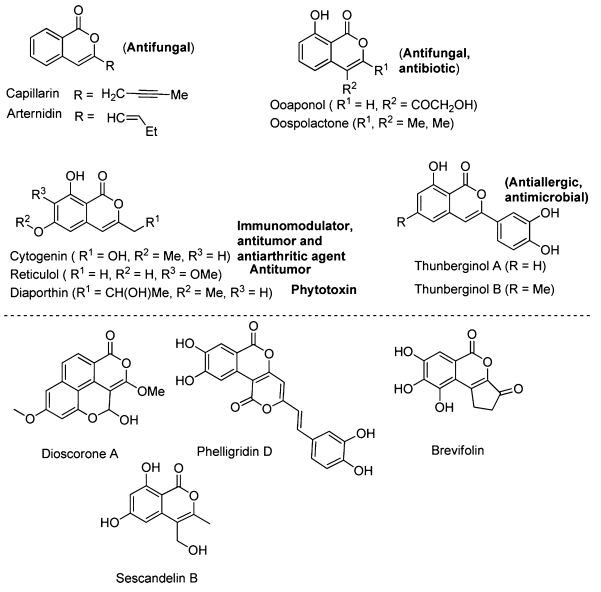


Figure 1. Some biologically active compounds and natural products containing an isocoumarin unit.

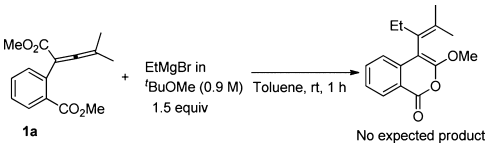
for organic synthesis. Although there are a number of reports on the preparation of isocoumarins,[6−8] there remain some limitations such as low yields, poor regioselectivity, and harsh reaction conditions in some cases. Thus, a simple, mild, efficient, regiocontrolled, and diverse preparation of isocoumarin skeletons with a specific substitution pattern is still highly desirable.

On the other hand, allenes are playing a more and more important role in modern synthetic chemistry.[9] Because of their unique structures, allenes show different reactivity compared with the corresponding alkenyl and alkynyl compounds. Recently, we have developed Michael additions of 2,3-allenoates with organomagesiums or organozincs affording various novel products, and the key intermediate is the conjugate addition dienolate.[10,11] We envisioned the sequential reaction of 2-(*o*-(methoxycarbonyl)phenyl)-2,3-allenoate with organometallic reagents may provide a novel approach to the isocoumarin skeleton (Scheme 1). However, the subtle reactivity of the two ester groups in the substrate may be a problem for this transformation. Herein, we are pleased to disclose our recent realization of this transformation using organozincs.

Scheme 1. Allene Approach to Isocoumarins

At first, we treated 2-(*o*-(methoxycarbonyl)phenyl)-2,3-allenoate **1a** with ethyl magnesium bromide in toluene at room temperature; however, the expected product was not observed mainly due to the lack of selectivity caused by the high reactivity of the Grignard reagent (Scheme 2).

Scheme 2. Initial Experiment



Next, we treated 2-(*o*-(methoxycarbonyl)phenyl)-2,3-allenoate **1a** with diethyl zinc **2a** in toluene at 100 °C[10a] (entry 1, Table 1), and interestingly the isocoumarin **3a** was formed as the sole product in 76% yield as judged by ^{1}H NMR analysis, which indicates that the organozincs undergo exclusively 1,4-conjugated addition first. The reaction could also proceed smoothly at room temperature (entry 2, Table 1). A study on solvent effects revealed that polar solvents, such as DMF and DMSO, are inferior to nonpolar solvents. CH_2Cl_2 affords the best result (entries 3−10, Table 1). Thus, we defined the reaction of

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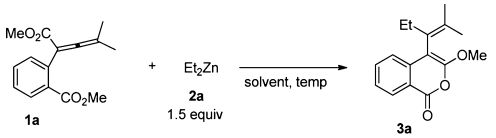
2-(*o*-(methoxycarbonyl)phenyl)-2,3-allenoate **1a** with 1.5 equiv of diethyl zinc in CH_2Cl_2 at room temperature for 3 h as the standard reaction conditions (entry 10, Table 1).

Table 1. Optimization of the Reaction Conditions[a]

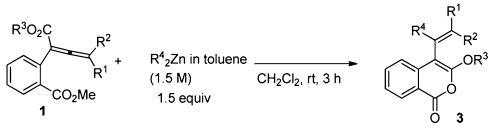


entry	solvent	temp (°C)	time (h)	yield of **3a** (%)[b]	recovery of **1a** (%)[b]
1[c]	toluene	100	0.75	76	0
2	toluene	rt	1	73	0
3	THF	rt	10.5	75	14
4	1,4-dioxane	rt	10	67	0
5	Et_2O	rt	10	64	23
6	^{t}BuOMe	rt	2	80	0
7	DMF	rt	22	–	66
8	DMSO	rt	22	–	72
9	CH_3CN	rt	5	58	0
10	CH_2Cl_2	rt	3	81	0

[a] The reaction was carried out using **1a** (0.1 mmol) in the indicated solvent (1.25 mL) in a dry Schlenk tube. [b] The yields were determined by ^{1}H NMR using mesitylene as the internal standard. [c] The reaction was carried out using **1a** (0.2 mmol) in 2.5 mL of toluene.

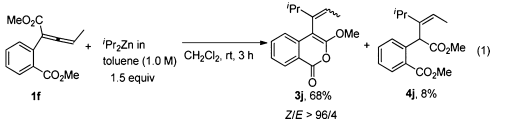
The scope of this transformation was investigated under the standard conditions (Table 2). The reaction of fully substituted 2,3-allenoates with different organozincs afforded the corresponding isocoumarins in moderate to good yields (**3a**–**3j**). The R^4 in organozinc may be alkyl (Et, *i*-Pr, *n*-Bu) or Ph (**3a**–**3d**). It should be noted that the reaction of **1a** with Ph_2Zn needs to be conducted at an elevated temperature of 100 °C mainly due to the relatively lower reactivity of diaryl zinc. R^1, R^2 may be a cycloalkyl or *n*-alkyl group (**3e**–**3g**). Ethyl allenoate **1e** also reacted smoothly with diethyl zinc affording the corresponding product **3h** in 70% yield. When trisubstituted allenoate **1f** was used as the substrate, the *Z*/*E* selectivity of the product was moderate (4.3/1). However, with a bulky dialkylzinc reagent (i.e., ^{i}Pr$_2$Zn), the *Z*/*E* selectivity of the isocoumarin product is > 96/4, while the Michael adduct **4j** was isolated in 8% yield as the side product. The substituent on the benzene ring may be an alkyl or a halide, affording the corresponding isocoumarins **3k**–**3m** in good yields (Scheme 3).

Table 2. Substrate Scope[a]

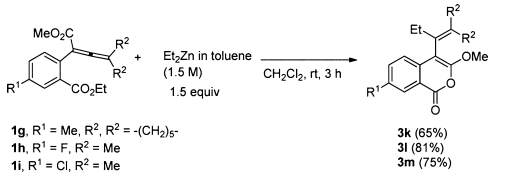


entry	R^1	R^2	R^3	R^4	yield of **3** (%)
1	Me	Me	Me (**1a**)	Et	81(**3a**)
2	Me	Me	Me (**1a**)	Et	76 (**3a**)[b]
3	Me	Me	Me (**1a**)	*i*-Pr	84 (**3b**)
4	Me	Me	Me (**1a**)	*n*-Bu	82 (**3c**)
5	Me	Me	Me (**1a**)	Ph	58 (**3d**)[c]
6	-$(CH_2)_5$-		Me (**1b**)	Et	81 (**3e**)
7	-$(CH_2)_4$-		Me (**1c**)	Et	80 (**3f**)
8	Et	Et	Me (**1d**)	Et	82 (**3g**)[d]
9	Me	Me	Et (**1e**)	Et	70 (**3h**)
10	Me	H	Me (**1f**)	Et	82 (**3i**)[e]

[a] The reaction was conducted with 1.0 mmol of 2,3-allenoates, 4 mL of toluene, and 1.5 equiv of $R^5{}_2Zn$ (1.5 M solution in toluene for Et_2Zn, 1.0 M solution in toluene for *i*-Pr_2Zn, 1.0 M solution in heptanes for *n*-Bu_2Zn, or pure Ph_2Zn). [b] The reaction was conducted with 5 mmol of **1a** for 12.5 h affording a gram scale of product. [c] The reaction was conducted in toluene under 100 °C for 1 h. [d] The reaction was conducted for 10 h. [e] The *Z*/*E* ratio was 4.3/1 by crude ^{1}H NMR analysis.



Scheme 3. Further Substrate Scope on the Benzene Ring



The structure of the products was further confirmed by the X-ray single-crystal diffraction analysis of **3d** (Figure 2).[12] In addition, the reaction could be easily conducted affording product **3a** on gram scale in a similar yield (entry 2 vs 1, Table 2).

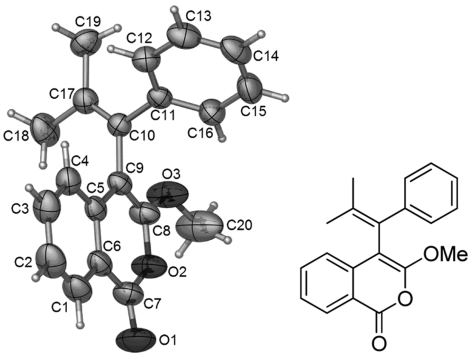
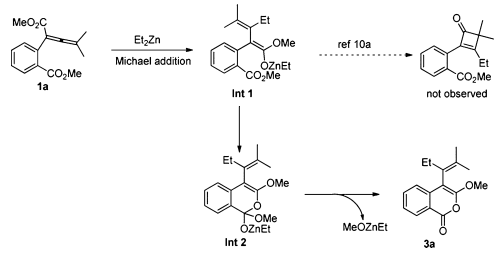


Figure 2. ORTEP of **3d**.

(12) Crystal data for **3d**: $C_{20}H_{18}O_3$, MW = 306.34, monoclinic; space group *p*2(1)/*c*, final *R* indices [$I > 2\sigma(I)$], *R*1 = 0.0374, *wR*2 = 0.0934; *R* indices (all data) *R*1 = 0.0638, *wR*2 = 0.1216, *a* = 13.1393(16) Å, *b* = 9.7705(12) Å, *c* = 27.212(3) Å, α = 90.00°, β = 110.152(5)°, γ = 90.00°, *V* = 3279.5(7) Å^3, *T* = 296(2) K, *Z* = 8, Reflections collected/unique 37301/5790 [*R*(int) = 0.0352], number of observations [$> 2\sigma(I)$] 4152, parameters: 421. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 940122.

A possible reaction mechanism was proposed as shown in Scheme 4. At first, the conjugate addition with 2-(*o*-(methoxycarbonyl)phenyl)-2,3-allenoate **1a** would form 1,3-dienolate intermediate **Int 1**. It is interesting to note that **Int 1** did not undergo the intramolecular reaction with the CO_2Me group in the allenic moiety affording a cyclobutenone, which was observed in our previous report.[10a] Instead, the subsequent intramolecular addition of zinc dienolate to aryl ester functionality leads to the formation of **Int 2**. Subsequent 1,2-elimination of MeOZnEt furnishes the isocoumarin **3a**.

Scheme 4. Possible Mechanism of the Tandem Michael Addition/Cyclization Reaction of **1a** with Organozincs



In summary, we have developed an efficient and novel method for the synthesis of isocoumarin derivatives from 2-(*o*-(methoxycarbonyl)phenyl)-2,3-alenoates and organozincs at room temperature (for dialkylzinc) or 100 °C (for Ph_2Zn). This method allows the introduction of an alkoxy group in the heterocyclic portion of the isocoumarin ring. Because of the potential of the isocoumarin products[1] and the ready availability of the starting materials,[13] this method would be useful in organic synthesis and medicinal chemistry. Further studies in this area are being actively conducted in our laboratory.

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Supporting Information Available. Detailed experimental procedures and characterization data for all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.