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Highly Regio- and Stereoselective Synthesis of Indene Derivatives via Electrophilic Cyclization

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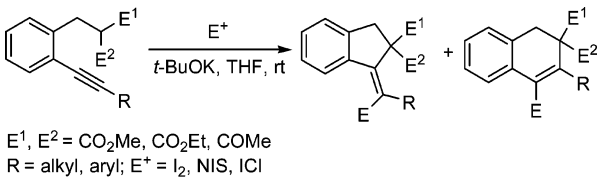
ABSTRACT



Indene or naphthalene derivatives are readily prepared in moderate to excellent yields with high regio- and stereoselectivity under very mild reaction conditions by the reaction of acetylenic malonates and ketones with I_2, ICl, or NIS. The resulting iodides can be further elaborated using palladium-catalyzed coupling reactions.

The electrophilic cyclization of heteroatomic nucleophiles such as oxygen, nitrogen, sulfur, and phosphor with tethered alkynes has proven to be an effective method of preparing a large variety of heterocyclic ring systems.[1−8] Important heterocycles such as furans,[1] pyrroles,[2] thiophenes,[3] indoles,[4] phosphaisocoumarins,[5] benzo[*b*]furans,[6] benzo[*b*]thiophenes,[7] and others[8] have been accessed using this protocol. However, only limited reports concerning electrophilic cyclization of carbon nucleophiles have been presented in the literature. In 1993, Taguchi reported an electrophilic cyclization of 4-alkynylmalonate derivatives, but the use of Ti(O*t*-Bu)$_4$ was required for the reaction to proceed.[9]

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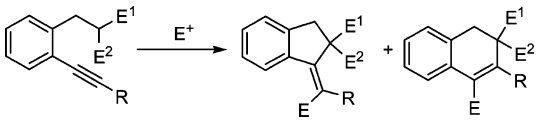
Our continuing interest was in the synthesis of indene derivatives by carboannulation.[10] This work prompted us to examine possible synthesis of indene derivatives by the electrophilic cyclization. Herein, we wish to report a successful electrophilic cyclization of acetylenic malonates and ketones for the synthesis of indene derivatives with high regio- and stereoselectivity (Scheme 1). The observed

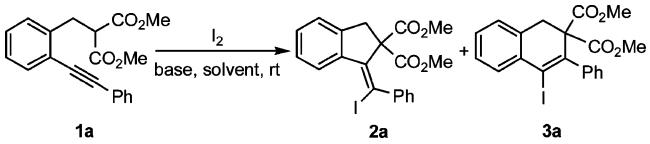
Scheme 1



selectivity is rare in electrophilic cyclization reactions.

Our initial study began with the reaction of dimethyl 2-(2-(2-phenylethynyl)benzyl)malonate (**1a**, 0.30 mmol), 2.0 equiv of *t*-BuOK, and 2.0 equiv of I_2 in THF at room temperature under argon for 20 min. The desired product (*E*)-dimethyl 1-(iodo(phenyl)methylene)-1*H*-indene-2,2(3*H*)-dicarboxylate (**2a**) was isolated in 93% yield with high regio- and stereoselectivity (Table 1, entry 1). NaOEt and K_2CO_3

Table 1. Optimization of the Electrophilic Cyclization of Dimethyl 2-(2-(2-Phenylethynyl)benzyl)malonate[a]



1a **2a** **3a**

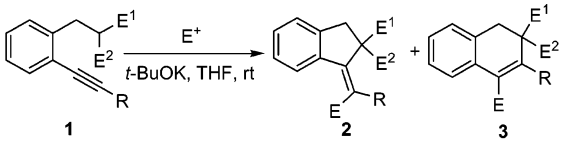
entry	base	solvent	time (min)	isolated yield (%)	ratio **2a/3a**[b]
1	*t*-BuOK	THF	20	93	>99:1
2	NaOEt	THF	30	90	>99:1
3	K_2CO_3	THF	60	nr[c]	
4	*t*-BuOK	CH_2Cl_2	45	45	>99:1
5	*t*-BuOK	MeOH	40	40	>99:1
6	*t*-BuOK	CH_3CN	45	53	>99:1

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.30 mmol of **1a**, 2.0 equiv of I_2, and 2.0 equiv of base in 3 mL of solvent were stirred at room temperature under argon for the specified period of time. [b] The ratio was determined by ^{1}H NMR analysis of the product. [c] nr = no reaction.

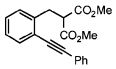
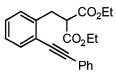
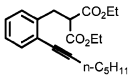
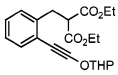
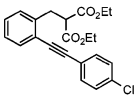
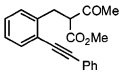
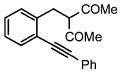
were also investigated as bases. NaOEt provided a slightly lower yield and longer reaction time than *t*-BuOK (entry 2); K_2CO_3 proved to be ineffective (entry 3). Other solvents such as CH_2Cl_2, MeOH, and CH_3CN were less effective (entries 4−6). The optimum reaction conditions thus far developed employ 1.0 equiv of **1a**, 2.0 equiv of *t*-BuOK, and 2.0 equiv of electrophile in THF at room temperature under argon.

To explore the scope of this electrophilic cyclization strategy, the reactions of **1a** with different electrophiles (I_2, ICl, and NIS) have been studied under the above optimized conditions. When using I_2, ICl, and NIS as the electrophilic reagents, only five-membered ring products have been obtained in excellent yields (Table 2, entries 1−3).

Table 2. Electrophilic Cyclization of Acetylenic Malonates and Ketones[a]



1 **2** **3**

entry	substrate	time (min)	product	isolated yield (%)	ratio of **2/3**[b]
1	 **1a**	20	**2a**	93	>99:1
2	**1a**	20	**2a**[c]	89	>99:1
3	**1a**	30	**2a**[d]	91	>99:1
4	 **1b**	35	**2b**	90	>99:1
5	 **1c**	30	**2c**	88	>99:1
6	 **1d**	30	mixture		
7	 **1e**	60	**3e**	63	<1:99
8	 **1f**	25	**2f** **3f**	63 24	
9	 **1g**	35	**3g**	90	<1:99

[a] All reactions were run under the following conditions, unless otherwise indicated: 0.30 mmol of **1**, 2.0 equiv of I_2, and 2.0 equiv of *t*-BuOK in 3 mL of THF were stirred at room temperature under argon for the specified period of time. [b] The ratio was determined by ^{1}H NMR analysis of the product. [c] The reaction was carried out using 2.0 equiv of ICl. [d] The reaction was carried out using 2.0 equiv of NIS.

Similarly, diethyl 2-(2-(2-phenylethynyl)benzyl)malonate (**1b**) gave the corresponding indene **2b** in good yield (entry 4). The reactions of diethyl malonate alkynes containing different R groups at the end of the triple bond have also been investigated. Diethyl 2-(2-(hept-1-ynyl)benzyl)malonate (**1c**) was employed in the reaction, and only the corresponding five-membered ring product was isolated in high yield (entry 5). Under similar conditions, diethyl 2-(2-(3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1- ynyl)benzyl)malonate (**1d**) produced a complex mixture of unidentified products (entry

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6). However, diethyl 2-(2-(2-(4-chlorophenyl)ethynyl)benzyl)malonate (**1e**) afforded exclusively the six-membered ring product **3e** (entry 7). We believe that the resonance and electronic effect force the carbon of the malonate group closer to C-1 or C-2 of the acetylenic malonates, resulting in five- or six-membered ring formation (Figure 1).[6c]

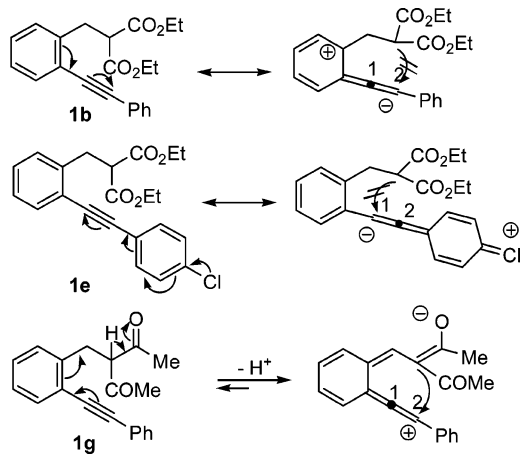


Figure 1. Methylene, chloric and enolization effect on the triple bond.

Meanwhile, acetylenes with different electron-withdrawing groups, such as methyl 2-(2-(2-phenylethynyl)benzyl)-3-oxobutanoate (**1f**), have also been used as substrate and afforded a mixture of five- and six-membered ring products. The five-membered ring product predominated (entry 8). Surprisingly, 3-(2-(2-phenylethynyl)benzyl)pentane-2,4-dione (**1g**) provided the six-membered ring product dimethyl 4-iodo-3-phenylnaphthalene-2,2(1*H*)-dicarboxylate (**3g**) as the sole product (entry 9). We think that six-membered ring formation is due to the enolization and resonance effect (Figure 1).

The molecular structure of the representative product **2a** was determined by X-ray crystallography (Figure 2).[11]

Interestingly, the reaction of substituted acetylene **1h**, which has an oxygen function at the terminal position, proceeded smoothly to give tricyclic lactone **2h** as the sole product in a short time (Table 3, entry 1). Lactonization in the reaction of **1h** must have occurred after electrophilic cyclization because in the absence of I_2 the lactone was not formed when **1h** was treated with *t*-BuOK. The reactions of **1h** with various electrophiles (ICl and NIS) have also been studied. Good yields of the expected product **2h** have been obtained, respectively (entries 2 and 3). Closely, substituted

(11) X-ray data for compound **2a**: $C_{20}H_{17}IO_4$, MW = 448.24, T = 298-(2) K, λ = 0.71073 Å, monoclinic space group, *P*-1, a = 7.615(16) Å, b = 9.91(2) Å, c = 12.33(2) Å, α = 98.11(2)°, β = 96.80(2)°, γ = 96.61(3)°, V = 906(3) Å^3, Z = 2, D_c = 1.642 mg/m^3, μ = 1.787 mm^{-1}, F(000) = 444, crystal size 0.50 × 0.45 × 0.38 mm^3, independent reflections 3045 [R (int) = 0.0485], reflections collected 4244, refinement method, full-matrix least-squares on F^2, goodness-of-fit on F^2 1.008, final R indices [$I > 2\sigma(I)$] R_1 = 0.0789, wR_2 = 0.1902, R indices (all date) R_1 = 0.0992, wR_2 = 0.2136, largest diff. peak and hole 1.840 and −2.845 e Å^{-3}

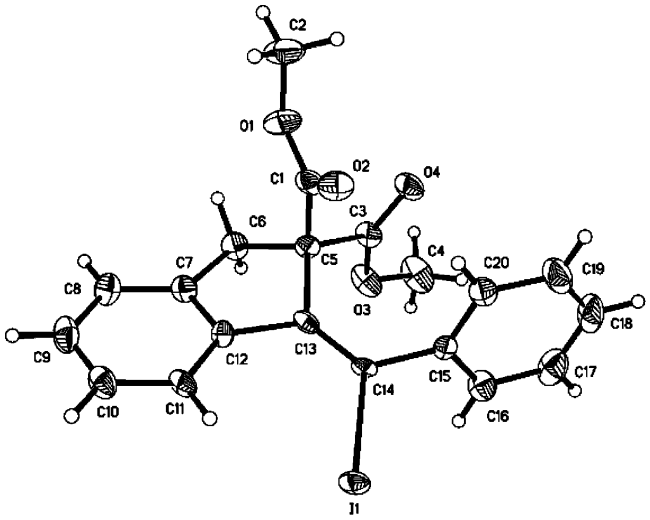
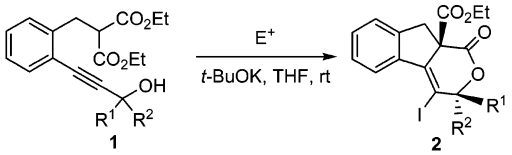


Figure 2. Structure of **2a**.

Table 3. Electrophilic Cyclization of Acetylenic Malonates[a]



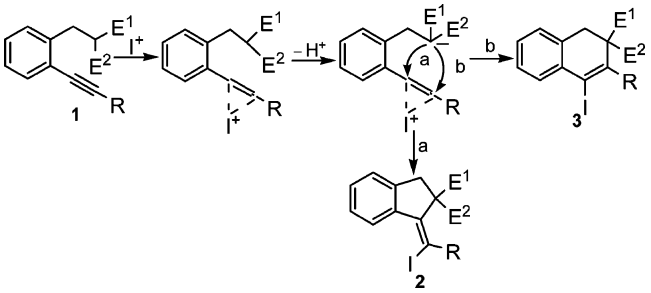
entry	Substrate (R^1, R^2)	time (min)	product	isolated yield (%)
1	**1h** (H, H)	30	**2h**	85
2	**1h**	20	**2h**[b]	80
3	**1h**	30	**2h**[c]	82
4	**1i** (Me, H)	30	**2i**	56
5	**1j** (Ph, H)	20	**2j**	55
6	**1k** (*p*-Tol, H)	40	**2k**	59
7	**1l** (furyl, H)	35	**2l**	61
8	**1m** (Me, Me)	30	**2m**	52

[a] All reactions were carried out under the optimal conditions reported in the text. [b] The reaction was carried out using 2.0 equiv of ICl. [c] The reaction was carried out using 2.0 equiv of NIS

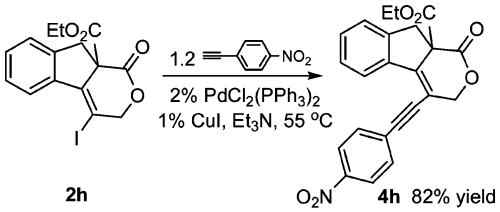
secondary alcohol **1i** led to desired product **2i** in 56% yield (entry 4). Substituted secondary alcohols **1j** and **1k**, having phenyl or *p*-tolyl substituents, produced 55% and 59% yields of the tricyclic lactones, respectively (entries 5 and 6). Similarly, diethyl 2-(2-(3-(furan-2-yl)-3-hydroxyprop-1-ynyl)benzyl)malonate (**1l**) led to desired product **2l** in 61% yield (entry 7). Fortunately, propargylic tertiary alcohol **1m** also gave the corresponding tricyclic product **2m** (entry 8).

We propose the following mechanism for this electrophilic cyclization (Scheme 2). First, the carbon−carbon triple bond of acetylenic malonates and ketones coordinates to the iodine cation generated from I_2 to generate an iodonium intermedi-

Scheme 2



Scheme 3



ate. This is followed by attack of the carbanion on the activated triple bond to afford the cyclized products.

A standard feature of this process is the fact that the indene derivatives produced by iodocyclization can be further elaborated by using various palladium-catalyzed processes. For example, the Sonagashira coupling[12] of tricyclic lactone **2h** afforded the corresponding product **4h** in 82% yield (Scheme 3).

In conclusion, an efficient, highly regio- and stereoselective synthesis of indene derivatives from acetylenic ketones and malonates by carbon nucleophiles through electrophilic cyclization under very mild reaction conditions has been developed. The resulting iodine-containing products are readily elaborated to more complex products by using known organopalladium chemistry. Further studies into the scope and limitations of the carboannulation reaction are underway.

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Supporting Information Available: Typical experimental procedure and characterization for all products, and X-ray data of **2a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For reviews, see: (a) Campbell, I. B. *The Sonogashira Cu-Pd-Catalyzed Alkyne Coupling Reaction. Organocopper Reagents*; Taylor, R. J. K., Ed.; IRL Press: Oxford, U.K., 1994; pp 217−235. (b) Sonogashira, K.; Takahashi, S. *Yuki Gosei Kagaku Kyokaishi* **1993**, *51*, 1053. (c) Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 521−549.