ORGANIC LETTERS

2007
Vol. 9, No. 3
397−400

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

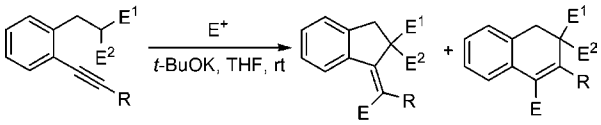
**Hai-Peng Bi,[†] Li-Na Guo,[†] Xin-Hua Duan,[†] Fa-Rong Gou,[†] Shu-Hao Huang,[†] Xue-Yuan Liu,[†] and Yong-Min Liang*[,†,‡]**

*State Key Laboratory of Applied Organic Chemistry, Lanzhou University, and State Key Laboratory of Solid Lubrication, Lanzhou Institute of Chemical Physics, Chinese Academy of Science, Lanzhou 730000, P.R. China*

*liangym@lzu.edu.cn*

**Received November 2, 2006**

## 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]

[†] Lanzhou University.
[‡] Lanzhou Institute of Chemical Physics.

(1) (a) Bew, S. P.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1996**, 1007. (b) El-Taeb, G. M. M.; Evans, A. B.; Knight, D. W.; Jones, S. *Tetrahedron Lett.* **2001**, *42*, 5945. (c) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769. (d) Liu, Y.-H.; Song, F.-J.; Cong, L. Q. *J. Org. Chem.* **2005**, *70*, 6999.

(2) (a) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2874. (b) Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 622.

(3) (a) Ren, X.-F.; Turos, E.; Lake, C. H.; Churchill, M. R. *J. Org. Chem.* **1995**, *60*, 6468. (b) Ren, X.-F.; Konaklieva, M. I.; Shi, H.; Dickey, S.; Lim, D. V.; Gonzalez, J.; Turos, E. *J. Org. Chem.* **1998**, *63*, 8898. (c) Flynn, B. L.; Flynn, G. P.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2341.

(4) (a) ten Hoedt, R. W. M.; Koten, G. V.; Noltes, J. G. *Synth. Commun.* **1977**, *7*, 61. (b) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (c) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (d) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539.

(5) (a) Peng, A. Y.; Ding, Y. X. *Org. Lett.* **2004**, *6*, 1119. (b) Peng, A. Y.; Ding, Y. X. *Tetrahedron* **2005**, *61*, 10303.

(6) (a) Banwell, M. G.; Flynn, B. L.; Wills, A. C.; Hamel, E. *Aust. J. Chem.* **1999**, *52*, 767. (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432. (c) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292.

(7) (a) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (b) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905. (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377.

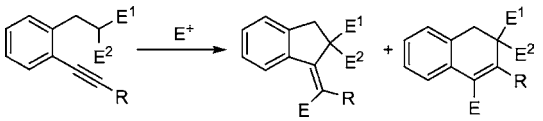
(8) (a) Djuardi, E.; McNelis, E. *Tetrahedron Lett.* **1999**, *40*, 7193. (b) Bellina, F.; Biagetti, M.; Carpita, A.; Rossi, R. *Tetrahedron* **2001**, *57*, 2857. (c) Arcadi, A.; Cacchi, S.; Giuseppe, S. D.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409. (d) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. (e) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936. (f) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677. (g) Yue, D.; Della, Ca, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581. (h) Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432. (i) Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; Gonzalez, J. M. *Chem. Commun.* **2005**, 2008.

(9) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106.

10.1021/ol062683e CCC: $37.00 
**Published on Web 01/05/2007**

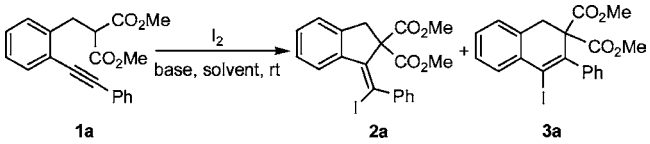
Our continuing interest was in the synthesis of indene derivatives by carboannulation.[10] This work prompted us to examine possible synthesis of indene derivatives by the electrophilic cyclization. Herein, we wish to report a successful electrophilic cyclization of acetylenic malonates and ketones for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

**Scheme 1**



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 $K_2CO_3$ 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.

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



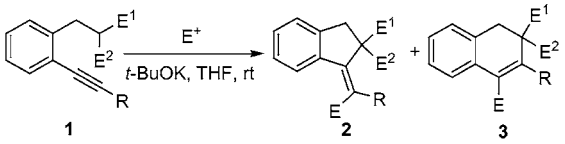
**1a** **2a** **3a**

| 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 |

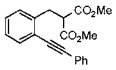
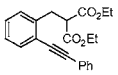
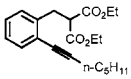
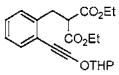
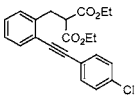
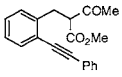
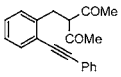
[a] All reactions were run under the following conditions, unless otherwise indicated: 0.30 mmol of **1a**, 2.0 equiv of $I_2$, and 2.0 equiv of base in 3 mL of solvent were stirred at room temperature under argon for the specified period of time. [b] The ratio was determined by $^1$H NMR analysis of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

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** | 63 | |
| | | | **3f** | 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

(10) (a) Guo, L. N.; Duan, X. H.; Bi, H. P.; Liu, X. Y.; Liang, Y. M. *J. Org. Chem.* **2006**, *71*, 3325. (b) Duan, X. H.; Guo, L. N.; Bi, H. P.; Liu, X. Y.; Liang, Y. M. *Org. Lett.* **2006**, *8*, 3053.

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]

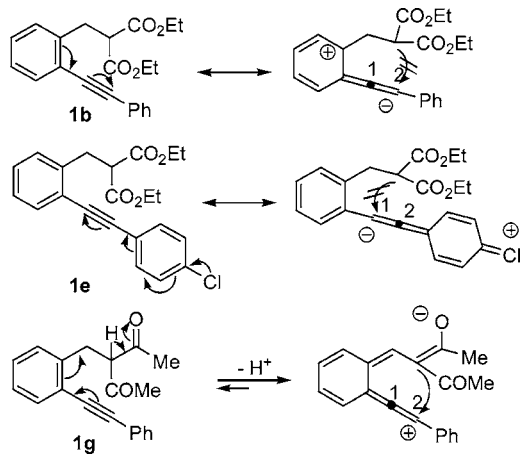



**Figure 1.** Methylene, chloric and enolization effect on the triple bond.

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, $\lambda$ = 0.71073 Å, monoclinic space group, *P*-1, $a$ = 7.615(16) Å, $b$ = 9.91(2) Å, $c$ = 12.33(2) Å, $\alpha$ = 98.11(2)°, $\beta$ = 96.80(2)°, $\gamma$ = 96.61(3)°, $V$ = 906(3) Å$^3$, Z = 2, $D_c$ = 1.642 mg/m$^3$, $\mu$ = 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$^{-3}$

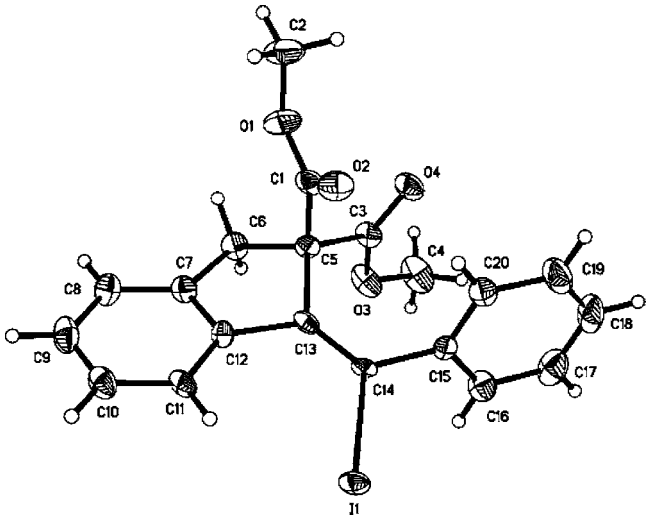
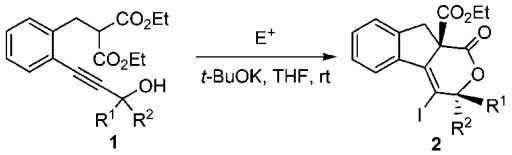



**Figure 2.** Structure of **2a**.

**Table 3.** Electrophilic Cyclization of Acetylenic Malonates[a]



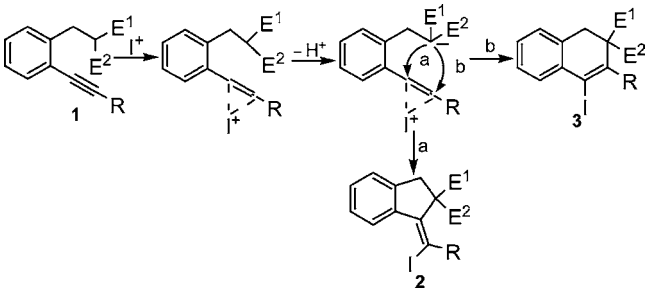

| entry | Substrate ($R^1$, $R^2$) | time (min) | product | isolated yield (%) |
|---|---|---|---|---|
| 1 | **1h** (H, H) | 30 | **2h** | 85 |
| 2 | **1h** | 20 | **2h**[b] | 80 |
| 3 | **1h** | 30 | **2h**[c] | 82 |
| 4 | **1i** (Me, H) | 30 | **2i** | 56 |
| 5 | **1j** (Ph, H) | 20 | **2j** | 55 |
| 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

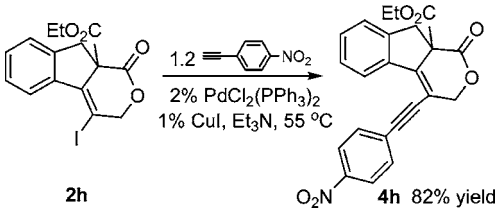
secondary alcohol **1i** led to desired product **2i** in 56% yield (entry 4). Substituted secondary alcohols **1j** and **1k**, having phenyl or *p*-tolyl substituents, produced 55% and 59% yields of the tricyclic lactones, respectively (entries 5 and 6). Similarly, diethyl 2-(2-(3-(furan-2-yl)-3-hydroxyprop-1-ynyl)benzyl)malonate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

**Acknowledgment.** We thank the NSF (NSF-20021001, NSF-20672049) and the "Hundred Scientist Program" from the Chinese Academy of Sciences for financial support.

**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.

OL062683E

(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.