ORGANIC LETTERS

2006
Vol. 8, No. 14
3053−3056

Synthesis of 2-Substitued 3-Aroylindenes via Palladium-Catalyzed Carbonylative Cyclization of Diethyl 2-(2-(1-Alkynyl)phenyl)malonates with Aryl Halides

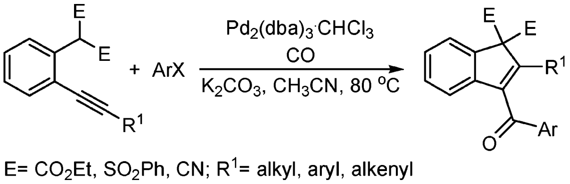
Xin-Hua Duan,[†] Li–Na Guo,[†] Hai-Peng Bi,[†] Xue-Yuan Liu,[†] and Yong-Min Liang*[,†,‡]

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. China, 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 April 27, 2006

ABSTRACT



The palladium-catalyzed reaction of readily accessible diethyl 2-(2-(1-alkynyl)phenyl)malonates with aryl halides under a balloon pressure of CO produced 2-substitued 3-aroylindenes in good yields. The reaction is believed to proceed via cyclization of the alkyne containing a proximate nucleophilic center promoted by an acylpalladium complex.

The transition metal-catalyzed cyclization of alkynes has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles.[1] Among them, the palladium-catalyzed carbonylative cyclization of alkynes bearing proximate nucleophilic centers with use of unsaturated organic halides/triflates in the presence of carbon monoxide has also been shown to be extremely effective for the synthesis of ketone-containing isoquinolines,[2] indoles,[3] and benzofurans.[4] Such reactions could generate one carbon−heteroatom bond and two carbon−carbon bonds in a single synthetic operation. However, the corresponding reactions with carbon nucleophiles to give three carbon−carbon bonded species are rare.

Very recently, we described a convenient approach to the synthesis of 2,3-disubstituted indenes from diethyl 2-(2-(1-alkynyl)phenyl)malonates and a wide variety of organic halides (Scheme 1).[5] Our continuing interest in the synthesis of indenes derivatives by this chemistry as well as the valuable biological activity[6] exhibited by some substituted indenes (their metallocene complexes may also be utilized to catalyze olefin polymerization)[7] led us to investigate the extension of the methodology to the synthesis of substituted

---

* Address correspondence to this author. Fax: +86-931-8912582. Phone: +86-931-8912593.

[†] Lanzhou University.

[‡] Chinese Academy of Science.

(1) For some recent reviews, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(2) (a) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042.

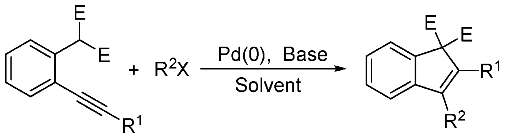
(3) (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. *Eur. J. Org. Chem.* **1999**, 1137. (b) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620. (c) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437.

(4) (a) Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org.* Chem. **1996**, *61*, 9280. (b) Hu, Y.; Zhang, Y.; Yang, Z.; Fathi, R. *J. Org. Chem.* **2002**, *67*, 2365.

(5) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org.* Chem. **2006**, *71*, 3325.

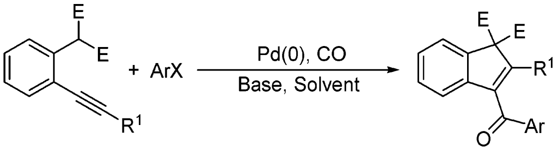
10.1021/ol061019v CCC: $33.50

Scheme 1



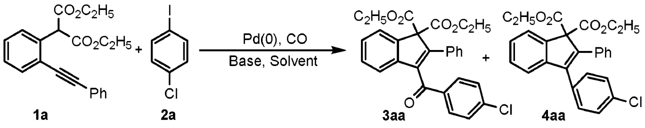
indenes. Herein, we wish to report a successful synthesis of 2-substitued 3-aroylindenes by the palladium-catalyzed carbonylative cyclization of diethyl 2-(2-(1-alkynyl)phenyl)-malonates with aryl halides in the presence of CO (Scheme 2).

Scheme 2



Initially, we started out our investigation of the reaction by using 1.0 equiv of diethyl 2-(2-(2-phenylethynyl)phenyl)-malonate (**1a**; 0.2 mmol), 1.2 equiv of 4-chloroiodobenzene under a balloon pressure of CO employing 5 mol % of Pd-$(PPh_3)_4$ and 2.0 equiv of K_2CO_3 in DMF at 100 °C for 24 h, reaction conditions that were used in our earlier palladium-catalyzed synthesis of 2,3-disubstituted indenes.[5] The desired product, diethyl 3-(4-chlorobenzoyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (**3aa**), was formed in only a 34% isolated yield, the other diethyl 3-(4-chlorophenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (**4aa**) was also isolated in 52% yield (Table 1, entry 1). 2-Phenyl 3-arylindene **4aa** was formed without incorporation of CO by a process reported previously by us.[5] Tri-*n*-butylamine and KOAc were ineffective (Table 1, entries 2 and 3). When KO*t*-Bu was used as the base, only the 2-phenyl 3-arylindene **4aa** was isolated (Table 1, entry 4).

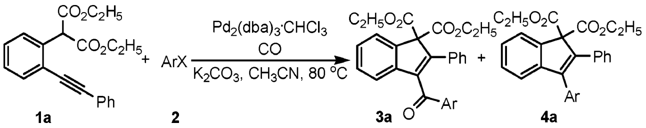
Table 1. Optimization of the Palladium-Catalyzed Carbonylative Cyclization of Diethyl 2-(2-(2-Phenylethynyl)phenyl)malonate and 4-Chloroiodobenzene[a]



entry	palladium catalysis	base	solvent	temp (°C)	isolated yield of **3aa** (%)[b]
1	$Pd(PPh_3)_4$	K_2CO_3	DMF	100	34 (52)
2	$Pd(PPh_3)_4$	$(n\text{-Bu})_3N$	DMF	100	no reaction
3	$Pd(PPh_3)_4$	KOAc	DMF	100	no reaction
4	$Pd(PPh_3)_4$	KO*t*-Bu	DMF	100	0 (65)
5	$Pd(PPh_3)_4$	K_2CO_3	DMSO	100	20 (35)
6	$Pd(PPh_3)_4$	K_2CO_3	CH_3CN	80	22 (0)
7	$Pd_2(dba)_3{\cdot}CHCl_3$	K_2CO_3	CH_3CN	80	83 (0)
8	$Pd(dba)_2$	K_2CO_3	CH_3CN	80	55 (0)
9	$Pd(OAc)_2/PPh_3$	K_2CO_3	CH_3CN	80	15 (0)

[a] Reactions were carried out on a 0.2 mmol scale in 2.0 mL of solvent under CO at 100 °C or 80 °C with 1.0 equiv of **1a**, 1.2 equiv of **2a**, 2.0 equiv of base, and 0.05 equiv of [Pd]. [b] The numbers in parentheses are the isolated yields of the corresponding 2-phenyl 3-arylindene **4aa**.

Table 2. Palladium-Catalyzed Carbonylative Cyclization of Diethyl 2-(2-(2-Phenylethynyl)phenyl)malonate with Aryl Halides[a]



entry	ArX (**2**)	time (h)	Ar (**3a**)	isolated yield (%)[b]
1	*p*-ClC_6H_4I	24	*p*-ClC_6H_4 (**3aa**)	83 (0)
2	*p*-$CH_3O_2CC_6H_4I$	24	*p*-$CH_3O_2CC_6H_4$ (**3ab**)	90 (0)
3	*p*-$NO_2C_6H_4I$	24	*p*-$NO_2C_6H_4$ (**3ac**)	75 (0)
4	*p*-$CF_3C_6H_4I$	24	*p*-$CF_3C_6H_4$ (**3ad**)	83 (0)
5	*p*-$CH_3C_6H_4I$	48	*p*-$CH_3C_6H_4$ (**3ae**)	52 (7)
6	*p*-$CH_3OC_6H_4I$	48	*p*-$CH_3OC_6H_4$ (**3af**)	42 (6)
7	PhI	24	Ph (**3ag**)	61 (0)
8	*m*-$CH_3C_6H_4I$	48	*m*-$CH_3C_6H_4$ (**3ah**)	51 (0)
9	*m*-ClC_6H_4I	24	*m*-ClC_6H_4 (**3ai**)	89 (0)
10	*m*-$NO_2C_6H_4I$	24	*m*-$NO_2C_6H_4$ (**3aj**)	85 (0)
11	*o*-$CH_3C_6H_4I$	48	*o*-$CH_3C_6H_4$ (**3ak**)	62 (0)
12	*o*-$CH_3O_2CC_6H_4I$	24	*o*-$CH_3O_2CC_6H_4$ (**3a*l***)	78 (15)
13	2-iodothiophene	48	2-thienyl (**3am**)	65 (0)
14	*p*-$NO_2C_6H_4Br$	48	*p*-$NO_2C_6H_4$ (**3ac**)	15 (22)

[a] All reactions were carried out under the optimal conditions reported in the text. [b] The numbers in parentheses are the isolated yields of the corresponding 2-phenyl 3-arylindenes **4a**.

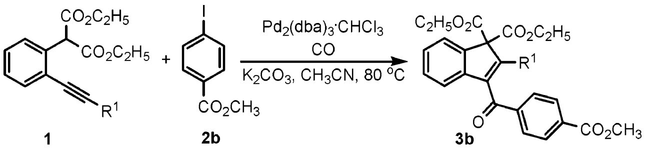
Changing the solvent from DMF to DMSO did not enhance the yield of **3aa** or the selectivity between the two indene products (Table 1, entry 5). Using acetonitrile as the solvent at 80 °C led to cleaner reaction, affording the desired product **3aa** in 22% yield with none of the side product **4aa** (Table 1, entry 6). Fortunately, the yield increased to 83% when the catalyst $Pd_2(dba)_3{\cdot}CHCl_3$ was employed instead of $Pd(PPh_3)_4$ (Table 1, entry 7). Other palladium catalysts tested, such as $Pd(dba)_2$ and $Pd(OAc)_2/PPh_3$, were less effective (Table 1, entries 8 and 9). The optimum reaction conditions thus far developed employ 1.0 equiv of **1a**, 1.2 equiv of the aryl halide, 5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, and 2.0 equiv of K_2CO_3 in CH_3CN at 80 °C under a balloon pressure of CO.

---

(6) (a) Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Tanaka, H.; Ichikawa, H.; Ono, Y.; Nakai, S. PCT Int. Appl. 9621449, 1996; *Chem. Abstr.* **1996**, *125*, 204539. (b) Mederski, W.; Dorsch, D.; Wilm, C.; Osswald, M.; Schmitges, C.-J.; Christadler, M. Ger. Offen. 19711785, 1998; *Chem. Abstr.* **1998**, *129*, 275905. (c) Dillard, R.; Hagishita, S.; Ohtani, M. PCT Int. Appl. 9603120, 1996; *Chem.* Abstr. **1996**, *125*, 341826. (d) Kouznetsov, V. V.; Puentes, C. O.; Bohorquez, A. R. R.; Zacchino, S. A.; Sortino, M.; Gupta, M.; Vazquez, Y.; Bahsas, A.; Amaro-Luis, J. *Lett. Org. Chem.* **2006**, *3*, 300.

(7) Spaleck, W.; Antberg, M.; Dolle, V.; Klein, R.; Rohmann, J.; Winter, A. *New J. Chem.* **1990**, *14*, 499.

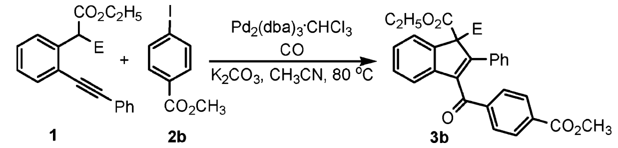
Table 3. Palladium-Catalyzed Carbonylative Cyclization of Diethyl 2-(2-(1-Alkynyl)phenyl)malonates with Methyl 4-Iodobenzoate[a]



entry	R^1	time (h)	**3b**	isolated yield (%)[b]
1	*p*-$CH_3OC_6H_4$ (**1b**)	24	**3bb**	80 (0)
2	*p*-$NO_2C_6H_4$ (**1c**)	24	**3cb**	93 (0)
3	*p*-BrC_6H_4 (**1d**)	24	**3db**	85 (0)
4	1-cyclohexenyl (**1e**)	24	**3eb**	70 (0)
5	*n*-pentyl (**1f**)	24	**3fb**	60 (0)

[a] All reactions were carried out under the optimal conditions reported in the text. [b] The numbers in parentheses are the isolated yields of the corresponding 2-substitued 3-arylindenes.

Table 4. Palladium-Catalyzed Carbonylative Cyclization of Ethyl Acetate Alkynes with Methyl 4-Iodobenzoate[a]



entry	E	time (h)	**3b**	isolated yield (%)[b]
1	SO_2Ph (**1g**)	24	**3gb**	55 (0)
2	CN (**1h**)	24	**3hb**	65 (0)

[a] All reactions were carried out under the optimal conditions reported in the text. [b] The numbers in parentheses are the isolated yields of the corresponding 2-phenyl 3-arylindenes.

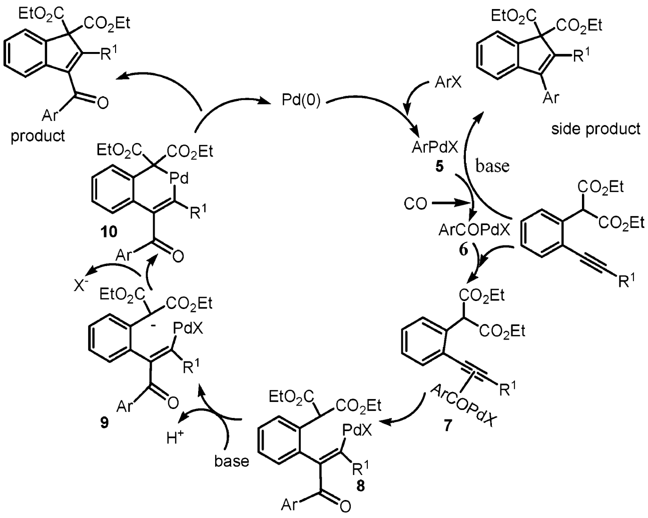
To extend the general applicability of this carbonylative cyclization reaction, the reaction of diethyl malonate alkyne **1a** with various aryl halides was carried out under the above-optimized conditions, and the results are summarized in Table 2. Aryl iodides bearing an electron-withdrawing group or an electron-donating group in the para, meta, and ortho positions afforded the corresponding multiply substituted indenes **3a** in moderate to good yields (Table 2, entries 1−6 and 8−12). Aryl iodides bearing an electron-withdrawing group in the para position usually led to good yields of the 2-phenyl 3-aroylindenes (Table 2, entries 1−4). When 4-methyliodobenzene and 4-iodoanisole were employed in the reaction with substrate **1a** (Table 2, entries 5 and 6), the corresponding products **3ae** and **3af** were isolated in 52% and 42% yields along with low yields of the side products diethyl 2-phenyl-3-*p*-tolyl-1*H*-indene-1,1-dicarboxylate (**4ae**) and diethyl 3-(4-methoxyphenyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (**4af**). Iodobenzene also afforded **3ag** in satisfactory yield (Table 2, entry 7). The reactions of **1a** and aryl iodides with an electron-withdrawing group, such as a Cl or NO_2 group in the meta position, afforded the desired products **3ai** and **3aj** in high yields (Table 2, entries 9 and 10). 3-Methyliodobenzene gave a modest yield of the indene product **3ah** (Table 2, entry 8). Aryl iodides bearing an electron-withdrawing group or an electron-donating group in the ortho position have also proven successful. For example, the reaction of 2-methyliodobenzene and methyl 2-iodobenzoate produced 62% and 78% yields of the desired products, respectively (Table 2, entries 11 and 12). In addition, the use of 2-iodothiophene also afforded the indene **3am** in 65% yield (Table 2, entry 13). In most of these reactions, only a very small amount of or no 2-phenyl-3-arylindene **4a** was isolated. Thus, these reactions exhibit good reaction selectivities. Unlike aryl iodides, aryl bromides such as 4-bromonitrobenzene gave the low yield of diethyl 3-(4-nitrobenzoyl)-2-phenyl-1*H*-indene-1,1-dicarboxylate (**3ac**) and poor selectivity (Table 2, entry 14).

We have also investigated the reactions of diethyl malonate alkynes containing different R^1 groups at the end of the triple bond with an aryl iodide. With methyl 4-iodobenzoate, diethyl malonate alkynes with an electron-withdrawing group or an electron-donating group on the benzene ring were employed in the reaction, and the corresponding products were isolated in high yields (Table 3, entries 1−3). Diethyl malonate alkyne **1e** bearing a 1-cyclohexenyl group afforded the corresponding 2-substitued 3-aroylindene **3eb** in a good yield of 70% (Table 3, entry 4). Diethyl malonate alkyne **1f** containing an *n*-pentyl group afforded the desired product **3fb** in a 60% yield (Table 3, entry 5).

Furthermore, ethyl acetate alkynes with different electron-withdrawing groups, such as ethyl 2-(2-(2-phenylethynyl)-phenyl)-2-(phenylsulfonyl)acetate (**1g**) and ethyl 2-cyano-2-(2-(2-phenylethynyl)phenyl)acetate (**1h**), have also been allowed to react with methyl 4-iodobenzoate to afford moderate yields of the desired products **3gb** and **3hb** (Table 4, entries 1 and 2).

The mechanism shown in Scheme 3 is proposed for this process. It is similar to mechanisms proposed in previously

Scheme 3



reported palladium-catalyzed syntheses of isoquinolines,[2] indoles,[3] benzofurans,[4] and furans.[8] It consists of the following key steps: (1) oxidative addition of the aryl halide to the Pd(0) catalyst, followed by CO insertion,[9] (2) coordination of the resulting acylpalladium intermediate **6** to the alkyne triple bond to form complex **7**,[2,3,4,8] (3) insertion of the alkyne in the aroyl palladium complex **7** to form a vinylic palladium intermediate, **8**, (4) generation of a carbanion by the base, (5) intramolecular nucleophilic attack of the carbanion on the vinylic palladium intermediate to afford a palladacyclic intermediate, **10**,[10] and (6) reductive elimination of the intermediate to furnish the indene and regenerate the Pd(0) catalyst. One competing process is cyclization of the starting material diethyl malonate alkynes promoted by an arylpalladium intermediate **5** to afford 2-substitued 3-arylindenes.[5]

In summary, an efficient, palladium-catalyzed synthesis of 2-substitued 3-aroylindenes has been developed. A variety of aryl iodides undergo this process, giving the desired products in moderate to good yields with good reaction selectivities. In particular, three carbon−carbon bonds are formed in a single operative step.

Acknowledgment. We thank the NSF (NSF-20021001, NSF-20572038) 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. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061019V

---

(8) Arcadi, A.; Rossi, E. *Tetrahedron Lett*. **1996**, *37*, 6811.

(9) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res*. **1977**, *10*, 434.

(10) Zhang, D.; Yum, E. K.; Liu, Z.; Larock, R. C. *Org. Lett.* **2005**, *7*, 4963.