JOC*Note*

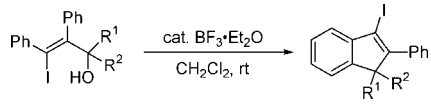
Efficient Synthesis of 3-Iodoindenes via Lewis-Acid Catalyzed Friedel−Crafts Cyclization of Iodinated Allylic Alcohols

Xiaobo Zhou, Huimin Zhang, Xin Xie, and Yanzhong Li*

Institute of Medicinal Chemistry, and Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, 3663 North Zhongshan Road, Shanghai, 200062, P. R. China

yzli@chem.ecnu.edu.cn

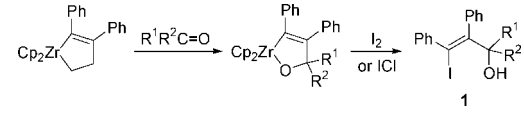
Received January 31, 2008



A convenient $BF_3 \cdot Et_2O$-catalyzed Friedel−Crafts cyclization of iodinated allylic alcohols is reported. The present reaction provides an efficient protocol to 3-iodo-1*H*-indene derivatives in good to high yields under mild conditions. Further, the iodoindene derivatives are valuable synthetic building blocks for elaboration of molecular complexity, such as in the construction of multiaryl substituted indenes by Suzuki coupling reaction.

Multisubstituted indene derivatives are very important compounds as they are useful building blocks for various biologically active molecules.[1] They can also be utilized as ligands in tailored metallocene complexes, especially for group 4 metallocenes in the catalysis of olefin polymerization.[2] Consequently, much attention has been paid to the synthesis of indene derivatives.[3] The most effective methods for their synthesis include acid-catalyzed cyclodehydration of the phenyl-substituted allylic alcohols[4] or cyclization of the phenyl-substituted alkenes,[5] the ring expansion of substituted cyclopropenes,[6] and addition of organometals to 1-indanone followed by dehydration,[7] etc. In addition to these classical methods, metal-catalyzed protocols have also been well developed in recent years, such as palladium-catalyzed carboannulation of internal alkynes with aryl halides,[8] [3 + 2] annulation of aromatic aldimines and acetylenes,[9] and cyclization of 2-alkyl-1-ethynylbenzenes via a 1,5-hydrogen shift of ruthenium−vinylidene intermediates,[10] etc. Haloindenes are important derivatives that provide further structural complexation by proceeding new C−C, C−N, or C−S bond-forming reactions. There are only limited reports for the synthesis of haloindenes, such as the bromination of indans or indenes[11] and HI-mediated cyclization of o-alkynylstyrenes,[12] etc. However, most of these methods are only effective in the formation of simple haloindenes or specific-substituted indenes, it is still difficult to synthesize haloindenes with a wide range of different substituents. In this paper, we would like to report a convenient and catalytic route for 3-iodo-1*H*-indenes through Friedel−Crafts cyclization of iodinated allylic alcohols.

SCHEME 1



1

It was known that alkynes such as diphenylacetylene undergo selective coupling with aldehydes or ketones mediated by zirconocene−ethylene complex to form five-membered oxazirconacycles.[13] Iodonolysis of this metallacycle affords the desired iodinated allylic alcohols **1**.[13f,g] Thus, a series of alcohol **1** were easily prepared in 35% ∼ 55% yields using this method. With allylic alcohol **1** in hand, we were interested in exploring the feasibility of cyclodehydration of **1** to haloindenes. We began our investigation with 3-iodo-1,2,3-triphenylprop-2-en-1-ol **1a**

(1) (a) Korach, K. S.; Metzler, M.; McLachlan, J. A. *J. Biol. Chem.* **1979**, *254*, 8963. (b) Schneider, M. R.; Ball, H. *J. Med. Chem.* **1986**, *29*, 75. (c) Senanayake, C.; Edward Roberts, F.; DiMichele, L.; Ryan, K.; Liu, J.; Fredenburgh, L.; Foster, B. *Tetrahedron Lett.* **1995**, *36*, 3993. (d) Harrowven, D. C.; Newman, N. A.; Knight, C. A. *Tetrahedron Lett.* **1998**, *39*, 6757. (e) Korte, A.; Legros, J.; Bolm, C. *Synlett* **2004**, 2397. and references therein. (f) Wang, Y.; Mo, S.-Y.; Wang, S.-J.; Li, S.; Yang, Y.-C.; Shi, J.-G. *Org. Lett.* **2005**, *7*, 1675.

(2) (a) Cadierno, V.; Diez, J.; Pilar, G. M.; Gimeno, J.; Lastra, E. *Coord. Chem. Rev.* **1999**, *193*−*19*, 147. (b) Alt, H. G.; Köppl, A. *Chem. Rev.* **2000**, *100*, 1205. (c) Zargarian, D. *Coord. Chem. Rev.* **2002**, *233*−*234*, 157. (d) Leino, R.; Lehmus, P.; Lehtonen, A. *Eur. J. Inorg. Chem.* **2004**, 3201.

(3) (a) For reviews, see: Heller, H. G. In *Rodd's Chemistry of Carbon Compounds,* 2nd ed.; Correy, S.; Ansell, M. F., Eds.; Elsevier: Amsterdam, The Netherlands, 1988; Vol. 3. (b) Okuda, J. *Top. Curr. Chem.* **1991**, *160*, 97. (c) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965.

(4) (a) Deno, N. C.; Pittman, C.; Turner, J. O. *J. Am. Chem. Soc.* **1965**, *87*, 2153. (b) Miller, W.; Pittman, C. *J. Org. Chem.* **1974**, *39*, 1955. (c) Olah, G. A.; Asensio, G.; Mayr, H. *J. Org. Chem.* **1978**, *43*, 1518. (d) Singh, G.; Ila, H.; Junjappa, H. *Synthesis* **1986**, 744. (e) Pittman, C.; Miller, W. G. *J. Am. Chem. Soc.* **1973**, *95*, 2947. (f) Gassman, P. G.; Ray, J. A.; Wenthold, P. G.; Mickelson, J. W. *J. Org. Chem.* **1991**, *56*, 5143. (g) Xi, Z.; Guo, R.; Mito, S.; Yan, H.; Kanno, K.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2003**, *68*, 1252. (h) Hu, Q.; Li, D.; Zhang, H.; Xi, Z. *Tetrahedron Lett.* **2007**, *48*, 6167.

(5) (a) Battiste, M. A.; Halton, B.; Grubbs, R. H. *Chem. Commun.* **1967**, 907. (b) Parham, W. E.; Egberg, D. C. *J. Org. Chem.* **1972**, *37*, 1545. (c) Halton, B.; Kulig, M.; Battiste, M. A.; Perreten, J.; Gibson, D. M.; Griffin, G. W. *J. Am. Chem. Soc.* **1971**, *93*, 2327. (d) Padwa, A.; Blacklock, T. J.; Getman, D.; Hatanaka, N. *J. Am. Chem. Soc.* **1977**, *99*, 2344. (e) Padwa, A.; Blacklock, T. J.; Loza, R. *J. Org. Chem.* **1982**, *47*, 3712. (f) Semmelhack, M. F.; Ho, S.; Cohen, D.; Steigerwald, M.; Lee, M. C.; Lee, G.; Gilbert, A. M.; Wulff, W. D.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7108.

(6) Yoshida, H.; Kato, M.; Ogata, T. *J. Org. Chem.* **1985**, *50*, 1145.

(7) Greifenstein, L. G.; Lambert, J. B.; Nienhuis, R. J.; Fried, H. E.; Pagani, G. A. *J. Am. Chem. Soc.* **1981**, *46*, 5125.

(8) Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2007**, *7*, 2–251.

(9) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498.

(10) Odedra, A.; Datta, S.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 3289.

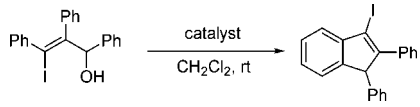
(11) (a) Tutar, A.; Cakmak, O.; Balci, M. *Tetrahedron* **2001**, *57*, 9759. (b) Lindley, W. A.; MacDowell, D. W. H. *J. Org. Chem.* **1982**, *47*, 705. (c) Ivchenko, N. B.; Ivchenko, P. V.; Nifant'ev, I. E.; Kotov, V. V. *Russ. Chem. Bull.* **2000**, *49*, 942.

(12) Saito, S.; Homma, M.; Gevorgyan, V.; Yamamoto, Y. *Chem. Lett.* **2000**, 722.

(13) (a) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (b) Copéret, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695. (c) Zhao, C.; Yu, T.; Xi, Z. *Chem. Commun.* **2002**, 142. (d) Zhao, C.; Yan, J.; Xi, Z. *J. Org. Chem.* **2003**, *68*, 4355. (e) Takahashi, T.; Xi, C.; Xi, Z.; Kageyama, M.; Fischer, R.; Nakajima, K.; Negishi, E. *J. Org. Chem.* **1998**, *63*, 6802. (f) Copéret, C.; Sugihara, T.; Wu, G.; Shimoyama, I.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 3422. (g) Guo, S.; Zhang, H.; Song, F.; Liu, Y. *Tetrahedron* **2007**, *63*, 2009.

10.1021/jo800232p CCC: $40.75
Published on Web 04/18/2008

TABLE 1. Screening of Reaction Conditions for Cyclization Reactions



entry	catalyst	mol %	time (h)	yield (%)[a]
1	HCl (3N)	10	24	–
2	HCl (concd)	50	35	41
3	H_2SO_4 (concd)	50	2	72
4	H_2SO_4 (concd)	10	24	43
5	$BF_3 \cdot Et_2O$	10	12	40
6	$BF_3 \cdot Et_2O$	20	3	75

[a] Isolated yields.

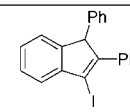
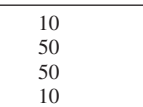
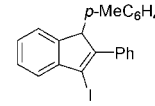
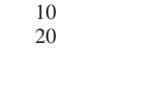
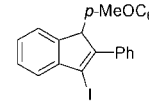
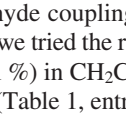
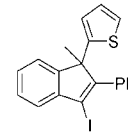
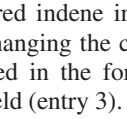
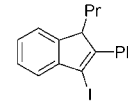
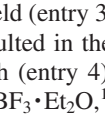
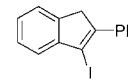
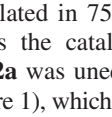
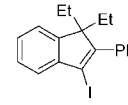
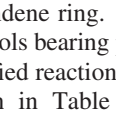
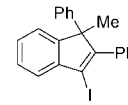
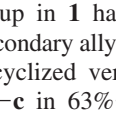
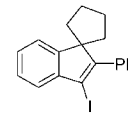
derived from alkyne−aldehyde coupling reactions. The results are shown in Table 1. First, we tried the reaction using a catalytic amount of 3 N HCl (10 mol %) in CH_2Cl_2. However, no indene products could be detected (Table 1, entry 1). Concentrated HCl (50 mol %) gave the desired indene in only 41% yield after 35 h (Table 1, entry 2). Changing the catalyst to concentrated H_2SO_4 (50 mol %) resulted in the formation of the desired 3-iodoindene **2a** in 72% yield (entry 3). Decreasing the amount of H_2SO_4 to 10 mol % resulted in the indene being formed in lower yield even after 24 h (entry 4). Interestingly, when we use a catalytic amount of $BF_3 \cdot Et_2O$,[14] the reaction completed within 3 h and **2a** was isolated in 75% yield (entry 6). Then $BF_3 \cdot Et_2O$ was selected as the catalyst for this cyclization reaction. The structure of **2a** was unequivocally confirmed by X-ray crystal analysis (Figure 1), which clearly shows that iodine substituted at C-3 of the indene ring.

A variety of allylic alcohols bearing phenyl ring moiety were then subjected to the modified reaction conditions to define the reaction scope. As shown in Table 2, the substituents on α-carbon of alcoholic group in **1** has big influence on this cyclization reaction. The secondary allylic alcohol **1a**−**c** bearing an aromatic ring at C-1 cyclized very well to generate the corresponding indenes **2a**−**c** in 63%−90% yields (Table 2, entries 1−3). A thienyl-substituted **1d** could also be applied in this reaction to form compound **2d** in 63% yield (entry 4). However, when a alkyl substituted **1e** or primary alcohol **1f** were used, the desired products of **2e** and **2f** were obtained in low yields of 31% and 15%, respectively. Reasonable yield was obtained when 2.0 equiv and 4.0 equiv of $BF_3 \cdot Et_2O$ were employed, respectively (entries 5 and 6). The results indicated that the phenyl allyl cations formed in the reactions are less stable in these cases. Interestingly, the substrates of **1g**−**I** derived from Zr-mediated alkyne−ketone coupling reactions[13g] cyclized smoothly to give **2g**−**I** in 61%−88% yields, whenever bearing phenyl or alkyl substituents (entries 7−9).

The mechanism of the formation of indene **2a** from **1a** is shown as follows (Scheme 2): First formation of an allyl cation **3** generated in situ by cleavage of the carbon−oxygen bond. **3** is in equilibrium with cation **4**, and then **4** undergoes electrocyclic ring closure to indenes **2a** by the elimination of a proton. The complete absence of indene **6** in the reaction mixture implicates that (a) the cation **3** might not exist in equilibrium with another conformer cation **5**, probably due to the steric interaction between iodo and phenyl groups; (b) cation **5** does not undergo an intramolecular Friedel−Crafts reaction.

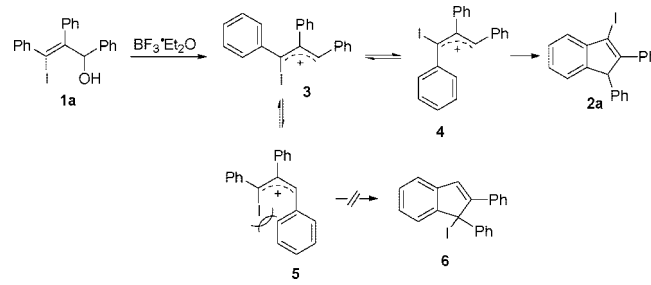
(14) (a) For the cyclodehydration of the phenyl-substituted allylic alcohols using excess amount of $BF_3 \cdot Et_2O$, see (a) ref 4d. (b) Sun, X.; Izumi, K.; Hu, C.; Lin, G. *Chin. J. Chem.* **2006**, *24*, 430.

TABLE 2. Formation of 3-Iodo-1*H*-indene Derivatives

entry	allylic alcohol	time (h)	product		yield (%)[a]
1	**1a**	3		**2a**	75
2	 **1b**	1		**2b**	90
3	 **1c**	1		**2c**	63
4	 **1d**	3		**2d**	63
5	 **1e**	12		**2e**	80[b]
6	 **1f**	12		**2f**	55[c]
7	 **1g**	3		**2g**	81
8	 **1h**	3		**2h**	61
9	 **1i**	1		**2i**	88

[a] Isolated yields. All the reactions were carried out at room temperature. [b] Reaction run using 2.0 equiv $BF_3 \cdot Et_2O$. [c] Reaction run using 4.0 equiv $BF_3 \cdot Et_2O$.

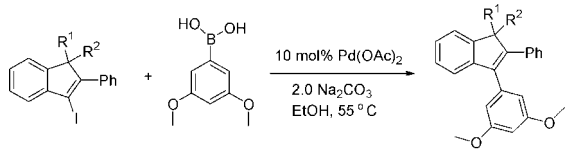
SCHEME 2



Multiaryl substituted indenes, especially 2,3-diaryl indenes have been reported to exhibit high biological activities.[15] The utility of 3-iodoindenes as useful synthetic intermediates was

(15) (a) Jordan, V. C. *Pharmacol. Rev.* **1984**, *36*, 245. (b) Hong, H. C.; Chamberlain, T. S.; Seiber, K.; Koboldt, C. M.; Isakson, P. C.; Reitz, D. B. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2377. (c) Anstead, G. M.; Peterson, C. S.; Pinney, K. G.; Wilson, S. R.; Katzenellenbogen, J. A. *J. Med. Chem.* **1990**, *33*, 2726.

SCHEME 3



7a: $R^1 = R^2 =$ Et, 68%

7b: $R^1 =$ Ph, $R^2 =$ H, 65%

investigated by Pd-catalyzed Suzuki-coupling reactions, which afforded triaryl-substituted indenes **7a** and **7b** in 68% and 65% yields, respectively (Scheme 3).

In summary, we have developed a convenient procedure for the preparation of 3-iodo-1*H*-indene derivatives in good to high yields under mild conditions. Further, the iodo derivatives are valuable synthetic intermediates for elaboration reaction, such as in the construction of multiaryl substituted indenes by Suzuki coupling reaction.

Experimental Section

A Typical Procedure for the Preparation of 3-Iodo-indenes. 3-Iodo-1,2-diphenyl-1*H*-indene (2a). To a solution of (*Z*)-3-iodo-1,2,3-triphenylprop-2-en-1-ol (**1a**) (1.0 mmol) in CH_2Cl_2 (5 mL) was added 0.2 mmol of $BF_3 \cdot Et_2O$ (27 μl) at room temperature. The reaction mixture was kept at the same temperature for 3 h. Then it was quenched with H_2O and extracted with ether (3 × 15 mL). The extract was washed with $Na_2S_2O_3$ and brine and dried over $MgSO_4$. The solvent was evaporated under vacuo and the residue was purified by flash chromatography on silica gel to provide **2a** as a light-yellow solid (296 mg, 75%). Mp 105−106 °C. ^{1}H NMR ($CDCl_3$, Me_4Si) δ 4.97 (s, 1H), 6.96−7.45 (m, 14H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ 59.7, 94.9, 122.9, 123.5, 126.7, 126.9, 127.5, 127.8, 128.00, 128.0, 128.6, 128.9, 135.8, 138.4, 145.3, 146.5, 153.6. HRMS calcd for $C_{21}H_{15}I$, 394.0219; found, 394.0219.

Acknowledgment. We are grateful to the National Natural Science Foundation of China (Grant Nos. 20442007 and 20572025) for financial support.

Supporting Information Available: Experimental details and spectroscopic characterization of all new compounds and CIF file giving crystallographic data of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800232P