

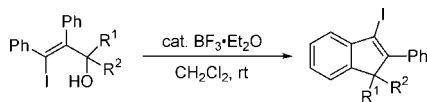
Efficient Synthesis of 3-Iodoindenes via Lewis-Acid Catalyzed Friedel–Crafts Cyclization of Iodinated Allylic Alcohols

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Received January 31, 2008

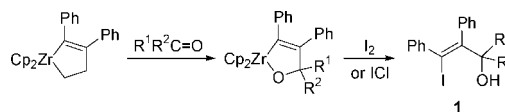


A convenient $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -catalyzed Friedel–Crafts cyclization of iodinated allylic alcohols is reported. The present reaction provides an efficient protocol to 3-iodo-1*H*-indene derivatives in good to high yields under mild conditions. Further, the iodoindene derivatives are valuable synthetic building blocks for elaboration of molecular complexity, such as in the construction of multiaryl substituted indenenes 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 alcohols⁴ 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 indenenes¹¹ 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 indenenes, 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*-indenenes through Friedel–Crafts cyclization of iodinated allylic alcohols.

SCHEME 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**

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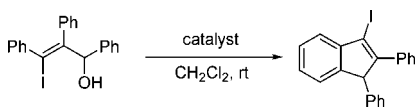
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TABLE 1. Screening of Reaction Conditions for Cyclization Reactions

				
entry	catalyst	mol %	time (h)	yield (%) ^a
1	HCl (3N)	10	24	—
2	HCl (concd)	50	35	41
3	H ₂ SO ₄ (concd)	50	2	72
4	H ₂ SO ₄ (concd)	10	24	43
5	BF ₃ ·Et ₂ O	10	12	40
6	BF ₃ ·Et ₂ O	20	3	75

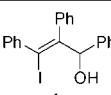
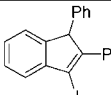
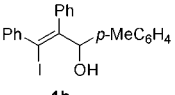
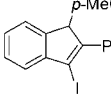
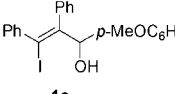
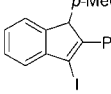
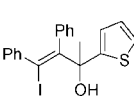
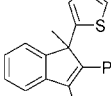
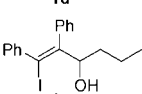
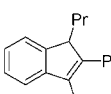
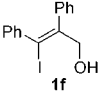
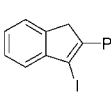
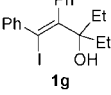
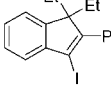
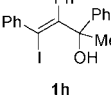
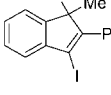
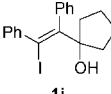
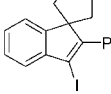
^a Isolated yields.

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 CH₂Cl₂. 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 H₂SO₄ (50 mol %) resulted in the formation of the desired 3-iodoindene **2a** in 72% yield (entry 3). Decreasing the amount of H₂SO₄ 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 BF₃·Et₂O,¹⁴ the reaction completed within 3 h and **2a** was isolated in 75% yield (entry 6). Then BF₃·Et₂O 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.

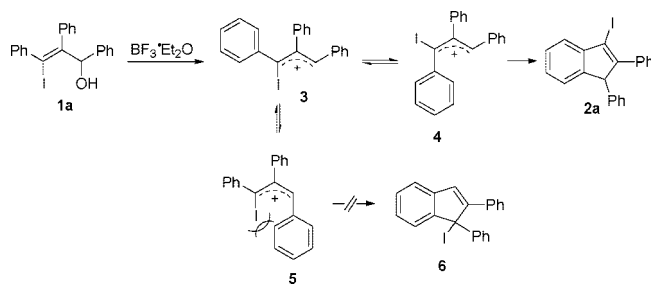
A variety of allylic alcohols bearing phenyl ring moiety were then subjected to the modified reaction conditions to define the reaction scope. As shown in Table 2, the substituents on α -carbon of alcoholic group in **1** has big influence on this cyclization reaction. The secondary allylic alcohol **1a–c** bearing an aromatic ring at C-1 cyclized very well to generate the corresponding indenenes **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 BF₃·Et₂O 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 indenenes **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.

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

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

^a Isolated yields. All the reactions were carried out at room temperature. ^b Reaction run using 2.0 equiv BF₃·Et₂O. ^c Reaction run using 4.0 equiv BF₃·Et₂O.

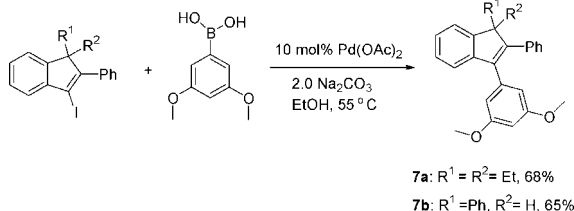
SCHEME 2

Multiarlyl substituted indenenes, especially 2,3-diaryl indenenes have been reported to exhibit high biological activities.¹⁵ The utility of 3-iodoindenenes as useful synthetic intermediates was

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SCHEME 3



investigated by Pd-catalyzed Suzuki-coupling reactions, which afforded triaryl-substituted indenenes **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 indenenes 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (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 $\text{Na}_2\text{S}_2\text{O}_3$ 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. ^1H 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 $\text{C}_{21}\text{H}_{15}\text{I}$, 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