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Iodoindenes: Synthesis and application to cross-coupling

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ABSTRACT

An expeditious synthesis of 5-, 6-, and 7-iodoindenes from the corresponding aminoindan-1-ones in more than 70% yield employing readily available precursors and ubiquitous reagents is reported. The 4-iodoindene has been prepared analogously in 40% overall yield. A three-step sequence involves diazotization-iodination of aminoindan-1-one followed by the reduction and dehydration. The iodoindenes serve as effective substrates for the regioselective Stille coupling with vinyl stannanes but isomeric mixtures are produced during Sonogashira coupling with alkynes in the presence of triethylamine.

Introduction

The haloindenes are convenient precursors in the organic and bioorganic synthesis.[1] For example, 6-bromoindene is used to prepare ethylene-bis(indenyl) ligand via Suzuki coupling.[2] The 4-, 5-, or 6-bromo(or chloro)indenes are utilized in the synthesis of inhibitors of the Na^+/H^+ exchanger[3] and histone lysine specific demethylases.[4] Moreover, 5- and 6-bromoindene are used to study the mechanism of dioxygenase-catalyzed benzylic hydroxylation of indene.[5] The 6-chloroindene serves as precursor for the synthesis of 6-chloro-*N*-hydroxy-1*H*-indene-2-carboxamide, used to study the structure–activity relationships of neurotoxin A protease inhibitors,[6] as well as fullerene-based photovoltaic acceptor materials.[7] Haloindenes are also used to synthesize halo-substituted isoquinoline derivatives.[8].

Recently, we demonstrated that pyrolysis of different bromoindenes at 1500 K produces resonance-stabilized and thermodynamically most stable 1-indenyl π radical which was found not to be an effective precursor for the further growth of polycyclic aromatic hydrocarbons (PAH)[9] through the hydrogen abstraction-acetylene (or vinylacetylene) addition.[10] Alternatively, we anticipate that pyrolysis of 5-, or 6-iodoindene isomers might lead to the formation of σ radicals localized in the phenyl ring of indene because C-I bond is weaker than C-Br bond. These 5- and 6-indenyl radicals might then act as precursors for growth of non-planar PAH molecules containing five-member rings.[11] Herein, we report a straightforward synthesis of 4-, 5-, 6-, and 7-iodoindenes isomers from readily available 7-, 6-, 5-, and 4-aminoindanones, as well as their regioselective alkenylation and further alkynylation since the enyne derivatives of indene represent potential reaction products of σ indenyl radicals with vinylacetylene and hence can serve as calibration compounds in studying the growth mechanism of PAH.

Although there are several reports for the synthesis of 5- or 6-chloro- and bromoindenes,[5-6,8a,12] there is only one method for the preparation of more reactive 5- or 6-iodoindene which requires expensive intermediates[13] and several steps.[8a] Furthermore, reported yields for 5- or 6-iodoindenes obtained by the reduction of the corresponding 5- or 6-nitroindene followed by diazotization-iodination of the resulting unstable 5- or 6-aminoindene were only 20% and 7% (see Schemes S1 and S2 in SI section).[8a] The 5-nitroindene and 6-nitroindene precursors were prepared from 1-aminoindane[14] or 5-aminoindan-1-one,[8a] respectively. Therefore, we have undertaken efforts to develop a general method for the synthesis of iodoindenes which employs iodoindan-1-ones[15] as convenient precursors and avoids the use of expensive nitroindenes, unstable aminoindenes and potentially explosive trifluoroperacetic acid.

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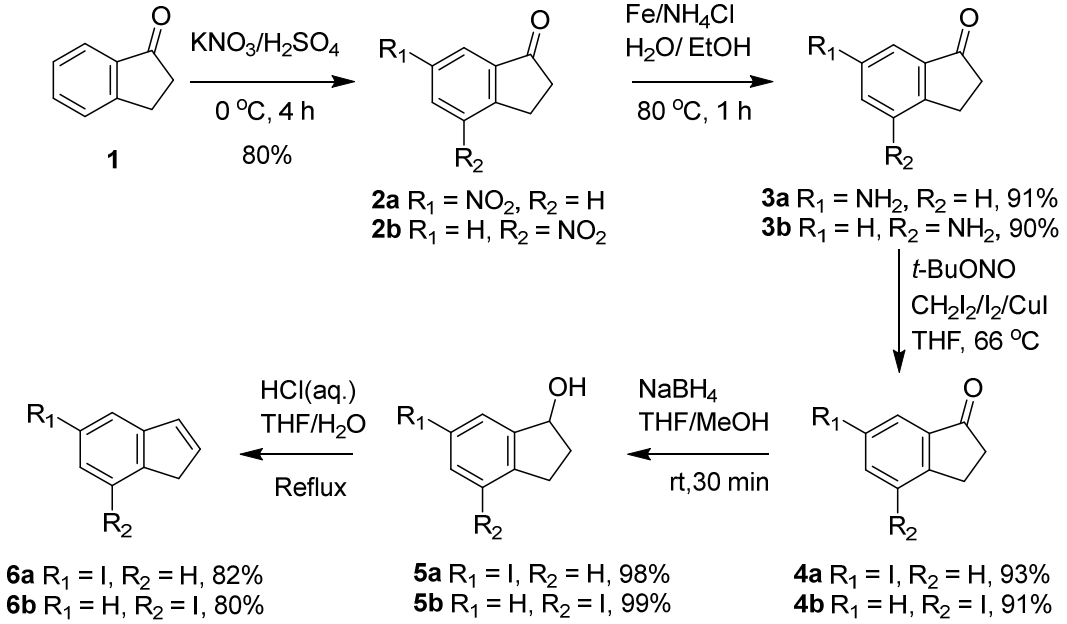
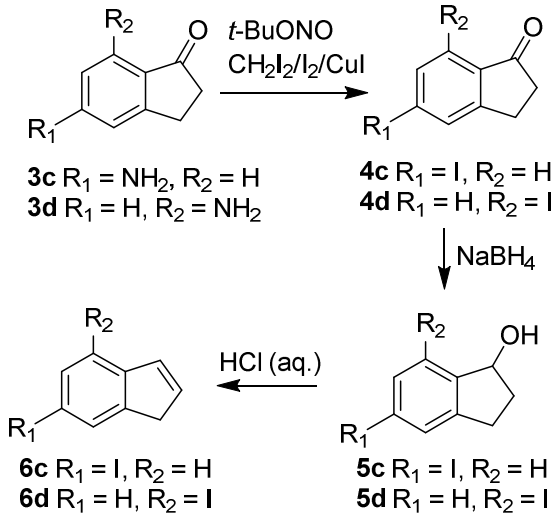


Scheme 1. Synthesis of 5-iodoindene **6a** and 7-iodoindene **6b**.

Results and discussion

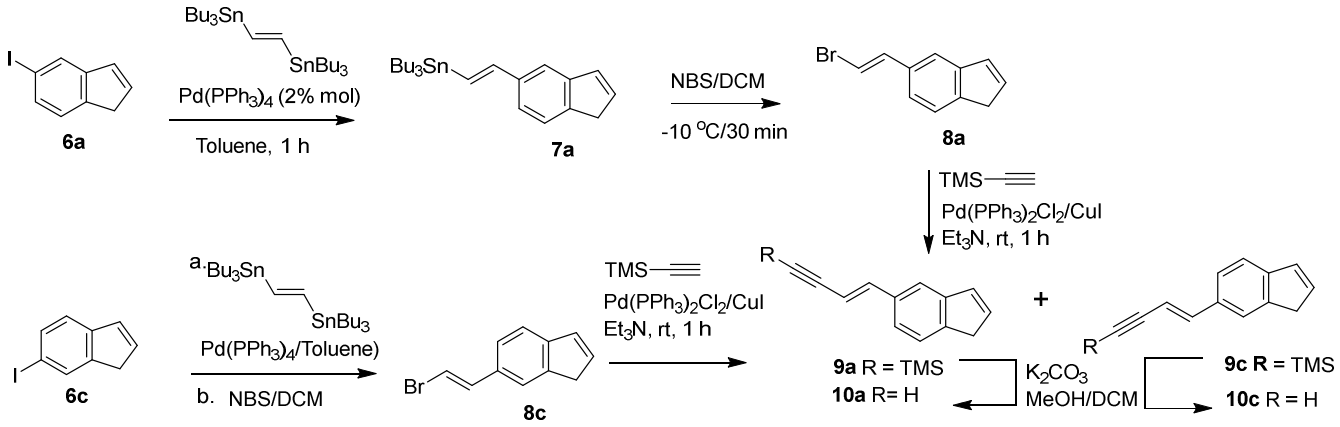
Electrophilic nitration of indan-1-one **1** with KNO_3/H_2SO_4 afforded separable mixture of 6-nitro- **2a** and 4-nitroindan-1-one **2b** (80%, 4:1 ratio; Scheme 1).[16] Selective reduction **2a** or **2b** with Fe powder/NH_4Cl [17] gave 6-amino- **3a** and 4-aminoindan-1-one **3b** in excellent yield. Subsequent, diazotization-iodination of **3a** or **3b** with *t*-BuONO[18]/CH_2I_2/I_2/CuI afforded 6-iodo- **4a** and 4-iodoindanones **4b** (>90%) in addition to diiodo substituted by-products (~4%). Reduction of **4a** or **4b** with $NaBH_4$ provided secondary alcohols **5a** and **5b** (>98%). Subsequent dehydration with aqueous HCl in THF/H_2O yielded selectively 5- and 7-iodoindenes, **6a** and **6b** (>80%). Isomerization to different indene isomers was not observed during this reaction sequence. It is noteworthy that dehydration of **5a** or **5b** with *p*-toluenesulfonic acid in refluxed toluene, used successfully for dehydration of the corresponding nitroindanoles,[8a] failed to produce expected iodoindenes. Our general method allows preparation of expensive 5-iodoindene[19] and unreported 7-iodoindene in high yields utilizing readily available and cost-effective reagents.

Subjection of the commercially available 5-aminoindan-1-one **3c** to the same sequence of diazotization-iodination followed by the reduction and dehydration yielded 6-iodoindene **6c** in 71% overall yield (Scheme 2). This represents a significant improvement to the reported five-step procedure which gave **6c** from **3c** in 3% overall yield.[8a] Our method avoids oxidation of **3c** to 5-nitroindan-1-one with trifluoroperacetic acid and does not require reduction of 6-nitroindene to unstable 6-aminoindene intermediate[8a] (Scheme S2 in SI). Analogous diazotization-iodination of 7-aminoindan-1-one **3d** gave 7-iodoindan-1-one **4d** (51%) as a major product in addition to 4-iodoindan-1-one **4b** (5.5%) and a diiodo byproduct (20%) which was tentatively assigned as 4,7-diiodoindan-1-one. Analogous treatment of **3d** with tert-butyl nitrite at ambient temperature for 8 h gave a similar distribution of products. Reduction and dehydration of **4d** afforded 4-iodoindene **6d** in 79% yield.



Scheme 2. Synthesis of 6-iodoindene **6c** and 4-iodoindene **6d**.

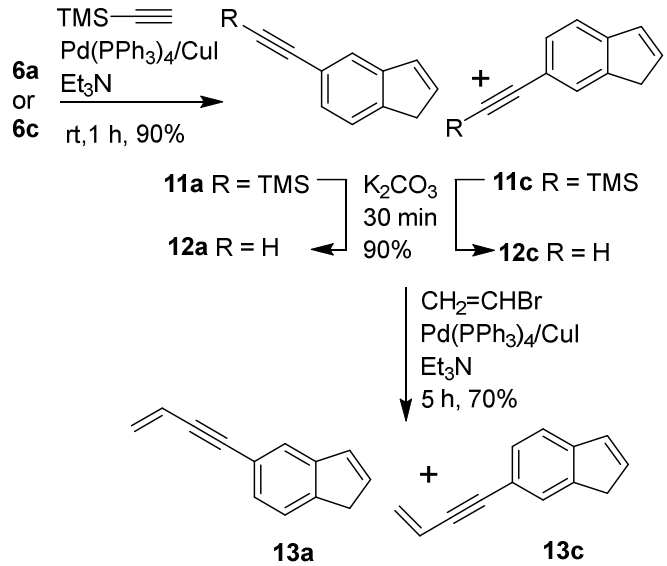
Stille coupling of **6a** with *trans*-1,2-bis(tributylstannyl)ethylene in the presence of catalytic $Pd(PPh_3)_4$ in toluene (100 °C/1 h) afforded regio- and stereoselectively the *E*-vinylstannane **7a** with no isomerization of the indene five-membered double bond (Scheme 3). Compound **7a** was directly used in the next step since attempted purification on silica gel column resulted in protiodestannylation yielding 5-vinylindene instead. Treatment of crude **7a** with NBS in DCM (-10 °C/30 min) gave 5(*E*)-(2-bromovinyl)indene **8a** (70% from **6a**) as a single product. Similarly, Stille coupling of **6c** yielded selectively 6(*E*)-(2-bromovinyl)indene **8c** also with no isomerization which would lead to **8a**. Treatment of **8a** or **8c** with



Scheme 3. Regioselective bromovinylation of iodoindenes **6a** and **6c**, and subsequent alkynylation.

trimethylsilylacetylene in the presence of catalytic $Pd(PPh_3)_2Cl_2$/CuI in Et_3N at rt gave the TMS-protected enyne as an inseparable mixture of 5-enyneindene, **9a** and 6-enyneindene, **9c** (91%; 1:1.5). Desilylation of mixture **9a** and **9c** with anhydrous K_2CO_3 in MeOH/DCM (1:1) afforded a mixture of 5- and 6-enyneindenes **10a** and **10c** (92%; 1:1.5). The ratio of enynes in mixtures **9a/9c** or **10a/10c** was assigned based on the chemical shift pattern in ^{1}H NMR and differences in the chemical shift values (e.g., H4 in **6a** (7.75 ppm) and H7 in **6c** (7.81 ppm)).

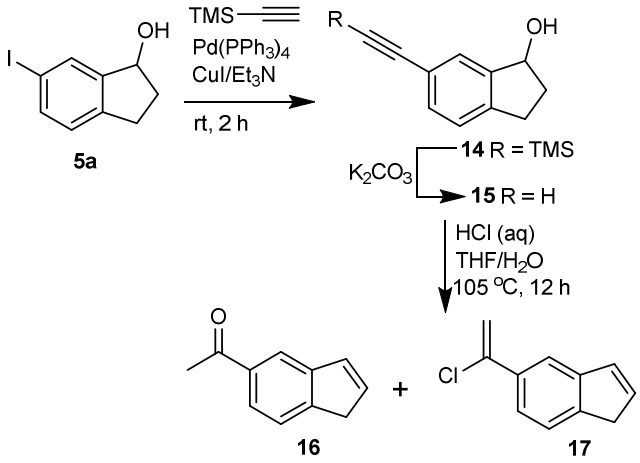
Sonogashira alkynylation of **6a** with trimethylsilylacetylene in the presence of catalytic $Pd(PPh_3)_4$/CuI in Et_3N produced 5-alkynylindene **11a** and 6-alkynylindene **11c** as 1:1.5 isomeric mixture in 90% yield (Scheme 4). Analogous treatment of **6c** gave an identical mixture of **11a** and **11c**. Attempted coupling of **6a** (or **6c**) with TMS-acetylene in the presence of 2.0 equiv. of Et_3N in dry THF resulted only in the isomerization of substrate **6a** (or **6c**) to a 1:1 mixture of **6a/6c**. Desilylation of mixture of **11a/11c** (1:1.5) with anhydrous K_2CO_3 in MeOH/DCM yielded mixture of **12a/12c** (90%; 1:1.7). Separations of either protected **11a/11c** or deprotected **12a/12c** enynes on silica gel columns were not successful because of identical mobility in several eluting systems. Pd-catalyzed coupling of **12a/12c** mixture (1:1.7) with vinylbromide (CuI/Et_3N/rt/5 h) gave mixture of 5-enyne- **13a** and 6-enyneindene **13c** (70%) in 1:1.5 ratio.



Scheme 4. Synthesis of isomeric enyneindenes via Sonogashira coupling.

Stirring of pure **6a** or **6c** in the presence of Et_3N in THF at rt for 1h resulted in the formation of 1:1 isomeric mixture of **6a/6c** (see SI section for spectra) confirming that substituted indenes are prone to base-catalyzed isomerization.[20] Moreover, when 2:1 mixture of **6a/6c** was subjected to the similar experiments a 1:1 ratio was also observed at equilibrium. These results demonstrate that the double bond in the five-member ring of the substituted indenes can shift in the presence of base leading to the observed isomers under the conditions of the coupling reactions.

To avoid isomerization of indene ring during Sonogashira coupling and in order to get regioselective access to indenyl alkynes, we attempted synthesis of single **12a** from 6-iodoindan-1-ol **5a**. Thus, coupling of **5a** with trimethylsilylacetylene provided the trimethylsilylalkyne **14** (90%) as the sole product from which the trimethylsilyl group was removed with K_2CO_3 to give 6-ethynylindan-1-ol **15**. (Scheme 5). Dehydration of either **14** or **15** with aqueous HCl led to the formation of indene products without isomerization of a double bond in cyclopentadiene ring of indene but the simultaneous addition of water or HCl to the triple bond gave acetyl **16** (80%) and 1-chlorovinyl **17** (20%) products.



Scheme 5. Regioselective synthesis of indene derivatives.

Conclusions

In summary, we have developed an expeditious synthesis of 4-, 5-, 6-, and 7-iodoindenes isomers from the corresponding aminoindan-1-ones utilizing readily available reagents. A three-step sequence involves diazotization-iodination of aminoindan-1-ones followed by the reduction and dehydration. The iodoindenes were regio- and stereoselectively converted to the corresponding (*E*)-bromovinylindenes utilizing Stille coupling with *trans*-1,2-bis(tributylstannyl)ethylene followed by bromodestannylation with NBS. Sonogashira coupling of iodoindenes with terminal alkyne in the presence of Et_3N gave isomeric ethynylindenes.

The 5- and 6-iodoindenes and their enyne derivatives may act as substrates and/or calibration compounds in studying the growth mechanism of PAH.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary Material

Experimental Section, Schemes for the reported in literature synthesis of 5- and 6-iodoindenes and NMR spectra for compounds (PDF).

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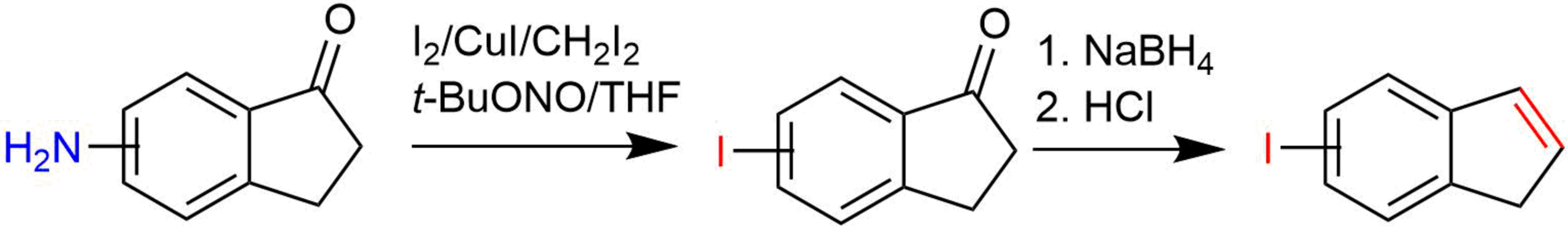

Aminoindan-1-one

Iodoindene