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Synthesis of Indene Derivatives via Electrophilic Cyclization

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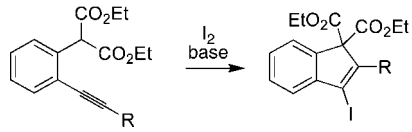
ABSTRACT



3-Iodo-*1H*-indene derivatives are synthesized by iodonium-promoted 5-*endo-dig* carbocyclization of 2-substituted ethynylmalonates. Various 2-substituted ethynylmalonates bearing aryl-, alkyl- and ether-protected propargyl alcohols were successfully converted to cyclized products. Their use in subsequent reactions as substrate and catalyst was investigated.

The indene moiety is present in a large number of drug candidates possessing interesting biological activities.[1] They are also used as ligands in metallocene complexes, especially group IV metallocene complexes used in the area of catalytic olefin polymerization.[2] Therefore, a number of synthetic approaches toward the construction of indene ring systems have been developed such as the reduction or dehydration of indanone,[3] the cyclization of substituted 1,3-butadienes in the presence of Lewis acids,[4] or the ring expansion of suitably substituted cyclopropenes.[5] A variety of transition metal complexes, e.g., Pd,[6] Ni,[7] and Co,[8] have been used to synthesize indenes via carboannulations of alkynes, but there are only limited reports for the synthesis of haloindenes, such as the bromination of indane or indene derivatives[9] and hydrogen iodide mediated cyclizations of *o*-alkynylstyrenes.[10] Roussel et al. reported the synthesis of 3-chloroindenes by trifluoromethanesulfonic acid catalyzed benzoylation of 2-methyl-2-butene.[11] Sauers et al. reported the synthesis of fluoroindenes by rearrangement of diazirines via photolysis.[12] Recently, the synthesis of 3-iodo-*1H*-indene derivatives via Lewis acid catalyzed Friedel−Crafts cyclizations of iodinated allylic alcohols was published.[13] Also stereoselective cyclizations have been developed using iodine electrophiles.[14] Several of these classical methods have some drawbacks in the preparation of indenes such as long reaction sequences, use of expensive transition metals, strong acidic conditions, and less tolerance for sensitive organic functionalities. However, haloindenes are important derivatives that provide

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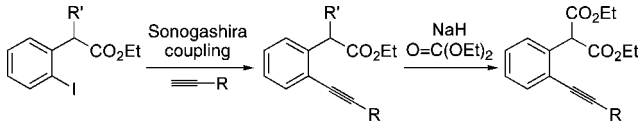
opportunity for further subsequent reactions by C−C, C−N, or C−S bond-forming reactions.

Herein, we report the synthesis of 3-iodo-*1H*-indenes through an iodocarbocyclization of 2-substituted ethynylmalonates. Liang et al. reported the synthesis of indene derivatives by an *exo*-iodocarbocyclization of 2-substituted ethynylbenzyl malonates,[15] and Barluenga et al. synthesized iodocyclopentenes from β-ketoester derivatives.[16] Taguchi et al. also have investigated iodocyclizations of malonate derivatives.[17] To the best of our knowledge, this is the first report for the synthesis of 3-iodo-*1H*-indenes by an iodonium-promoted 5-*endo-dig* carbocyclization of 2-substituted ethynylmalonates. Various heterocyclic compounds can also be accessible using 5-*endo-dig* cyclizations of suitable substrates.[18]

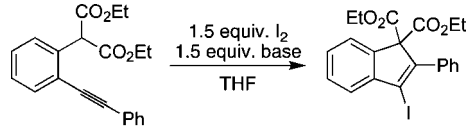
Scheme 1. Synthesis of Alkynyl Malonates **3**



The synthesis of alkynyl malonates proceeded smoothly starting either from ethyl (2-iodophenyl)acetate **1a** (R = H) or from (2-iodophenyl) propanedioic acid diethyl ester **1b** (R = CO_2Et).[19] Sonogashira coupling led to alkynes **2** and **3f** in good yields (42−76%), which were then treated (**2a**−**2e**) with sodium hydride and diethylcarbonate to obtain the starting materials **3** for the carbocyclization reactions.

To find optimal reaction conditions for the iodine-mediated carbocyclizations, several reagent combinations and reaction conditions were screened. Compound **3a** (R = Ph) was treated with NaH before iodine was added, and the reaction mixture was refluxed for 2 h (Table 1). Product **4a** was purified by column chromatography and obtained in 77% yield as a crystalline solid (entry 1). The structure of compound **4a** was confirmed by NMR spectroscopy and, additionally, through X-ray analysis.[20] Treatment of compound **3a** with iodine in the presence of pyridine led to complete recovery of starting material (entry 2). The combination of NaO*t*Bu and iodine is known to generate *tert*-butyl hypoiodite.[21] Initial addition of sodium *tert*-butoxide followed by iodine and heating to reflux resulted in 74% yield of cyclized product **4a** after purification (Table 1, entry 3). Even after several hours of stirring at room temperature (Table 1, entry 4) under otherwise similar reaction conditions, we obtained the product **4a** in 69% yield. All reaction conditions except entry 2 are almost equally effective for these carbocyclizations, resulting in clean conversion toward the cyclized product.

Table 1. Screening of Reaction Conditions for the Cyclization of **3a**

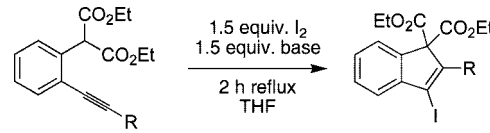


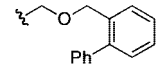
entry	base	time [h]	temp [°C]	yield **4a** [%]
1	NaH	2	65	77[a]
2	Pyridine	2	65	0
3	NaO*t*Bu	2	65	74
4	NaO*t*Bu	80	20	69

[a] 1.2 equiv of base and 1.2 equiv of iodine were used.

To investigate the scope of the reaction a variety of differently substituted alkynyl moieties with aliphatic and aromatic substituents were successfully converted to the cyclized products in good yields as shown in Table 2.

Table 2. Formation of 3-Iodo-1*H*-indene Derivatives **4**



entry	R	product	base	yield [%]
1	Ph	**4a**	NaH	77[a]
2	2-naphthyl	**4b**	NaH	71
3	3-MeOC$_6$H$_4$	**4c**	NaH	78
4	CH_2OBn	**4d**	NaH	67
5		**4e**	NaH	62
6	$(CH_2)_4CH_3$	**4f**	NaO*t*Bu	71

[a] 1.2 equiv of base and 1.2 equiv of iodine were used.

Electron-donating substituents such as a methoxy moiety in the *meta*-position (Table 2, entry 3) or propargylic ethers are tolerated under these conditions (Table 2, entries 4 and 5). The yields for the cyclization of substrates **3** having

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(20) CCDC 705766 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

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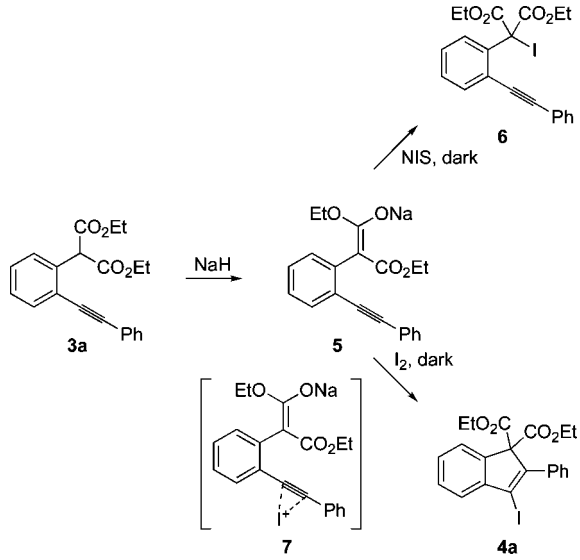
simple aromatic or aliphatic substituents (Table 2, entries 1, 2, and 6) are good as well.

Literature evidence[22] and the course of the reaction revealed that an addition of iodine to the deprotonated malonate **5** may result in the initial formation of an α-iodomalonate **6**.[23] This quite unstable compound has also been identified, but only as a mixture together with the starting material **3a**. In the presence of iodide (NaI) or by reaction with elemental iodine the formation of the cyclized product **4a** via **7** is observed.

Scheme 2. Mechanistic Considerations



Others and we have already shown that iodine derivatives can be used as catalysts for the in situ generation of hypervalent iodine compounds.[24] α-Oxytosylations of propiophenone **8** can be performed by using catalytic amounts of **4a** leading to the product **9** in 53% yield (Scheme 3). Compounds of type **4d** and **4e** have the additional benefit of

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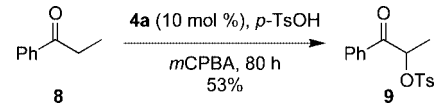
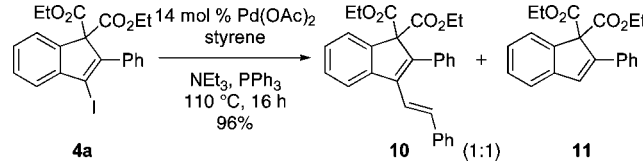
Scheme 3. Use of **4a** as Catalyst in the α-Oxytosylation of Propiophenone



bearing an oxygen close to the iodine. Attachment of a chiral moiety to the oxygen can provide fast access to enantiomerically pure catalysts for asymmetric synthesis.

To also exploit other reactions, compound **4a** was subjected to Heck reaction conditions resulting in the formation of two compounds **10** and **11**, which could not be separated through column chromatography (Scheme 4). The reaction

Scheme 4. Heck Reaction Using **4a** as Substrate



mixture was analyzed by GC-MS, and a ratio of 1:1 (**10**:**11**) was established.

In conclusion, this methodolgy offers a fast way for the facile synthesis of 3-iodo-1*H*-indene derivatives from easily accessible starting materials that can further be elaborated by other chemistries such as palladium and hypervalent iodine chemistry.

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Supporting Information Available: Experimental procedures for the synthesis of **1a,1b**, **2a**−**2e**, **3a**−**3f**, **4a**−**4f**, **9**, **10**, and **11** and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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