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Halocyclization of *o*-(alkynyl)styrenes. Synthesis of 3-halo-1*H*-indenes†

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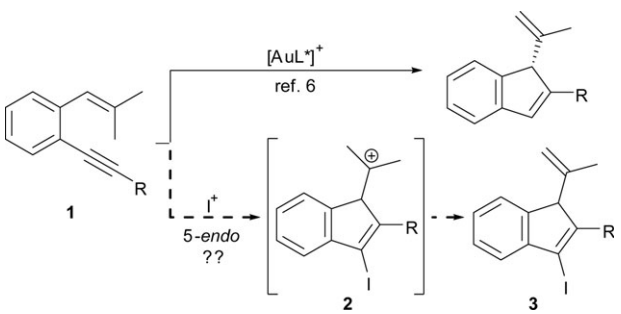
***o*-(Alkynyl)styrenes undergo halocarbocyclization processes *via* a 5-*endo-dig* ring closure. By this strategy an efficient synthesis of 3-halo-1*H*-indene derivatives has been developed.**

The electrophilic cyclization of heteroatomic nucleophiles with alkynes, mainly with iodine-containing electrophiles, is a useful method for the synthesis of functionalized heterocyclic compounds.[1] However, the analogous carbocyclization reactions, *i.e.* the internal nucleophile is a carbon-based moiety, have been much less developed. Few examples have been reported involving the use of arenes[2] and malonates[3] as nucleophilic partners. Remarkably, the use of olefins[4] for triggering this type of cyclization reactions has remained unknown until very recently, when Kirsch and co-workers have established that 1,5-enynes can undergo an iodonium-induced carbocyclization *via* 6-*endo-dig* processes.[5] On the other hand, we have recently described the (enantioselective) synthesis of 1*H*-indene derivatives by an unprecedented gold(I)-catalyzed 5-*endo-dig* cyclization of *ortho*-(alkynyl)-styrenes **1**.[6] In this context, and considering that the presence of an halogen atom at the C-3 position of the final indene derivative could be of interest for further functionalization, we wondered about the feasibility of synthesizing 3-halo-1*H*-indenes[7] from the same *o*-(alkynyl)styrenes **1** as proposed in Scheme 1.

Gratifyingly, we found that 3-iodoindene **3a** (R = Ph) was selectively formed and isolated in high yield when **1a** (R = Ph) was treated with an excess of NIS in CH_2Cl_2 at room temperature for 24 h, in the absence of any catalyst. This result shows



Scheme 1 Our proposal for the synthesis of 3-iodoindenes.

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that a direct halocyclization has occurred, probably through the formation of a stabilized carbocation **2** that undergoes proton elimination to afford the functionalized indene moiety (Scheme 1). It should be noted that in contrast to those examples recently reported by Kirsch and co-workers that proceed through a 6-*endo* cyclization process,[5] our reaction implies an unprecedented 5-*endo* halocyclization reaction of an enyne derivative.[8] The stability of the tertiary carbocation intermediate **2** could be the key for the success of the proposed 5-*endo* cyclization.

As shown in Table 1, a variety of *o*-(alkynyl)styrenes **1** are useful substrates for this iodocyclization. Reactions were performed at reflux in few hours under an air atmosphere.[9] Different substituents at the alkyne (R^1), including functionalized-aromatic, heteroaromatic, (functionalized)-alkyl, and hetero-atomic ones, are well tolerated (Table 1, entries 1–6). Regarding the alkene, besides two methyl groups, R^2 and R^3 could be part of a cyclic alkyl moiety (Table 1, entries 8 and 9) as well as two different groups such as methyl and phenyl (Table 1, entries 7 and 14). However, terminal alkynes (R^1 = H) proved to be unreactive under the reaction conditions, whereas substrates lacking a substituent at the β-position of the styrene moiety (R^2 = H) gave rise to a complex mixture of products.[10] In addition, substrates bearing electron-withdrawing as well as electron-donating groups at the benzenoid moiety efficiently underwent the iodocyclization reaction (Table 1, entries 10–14).

The possibility of using molecular iodine as the electrophilic reagent was also demonstrated by the isolation of iodoindenes **3b** and **3l**, from treatment of substrates **1b** and **1l** with I_2 and base instead of NIS (Table 1, entries 2 and 12). However, the yields were slightly lower and, moreover, in some cases, such as the reaction of **1a**, some side-products were formed along with the desired compound.

Interestingly, the same halocyclization reaction was observed when NBS was used. In this case, 3-bromo-1*H*-indenes **4a** and **4j** were isolated in good yields (Scheme 2).

We next decided to check the possibility of introducing further functionality on the C-1 substituent of the indene by performing the iodocyclization in the presence of external oxygen nucleophiles. After some optimization, we found that although the competitive elimination reaction that affords iodoindenes **3** could not be completely suppressed, 1-alkoxy-substituted 3-iodo-1*H*-indene derivatives **5** could be isolated in useful yields and in pure form by using a large excess of MeOH (Table 2). In these cases, reactions are faster and could be performed at room temperature in 1–4 h. Better selectivities to **5** and therefore yields were obtained with substrates such as **1j** and **1k** bearing electron-withdrawing substituents at the aromatic nucleus (see entries 5 and 6 *vs.* 1), and with **1g**

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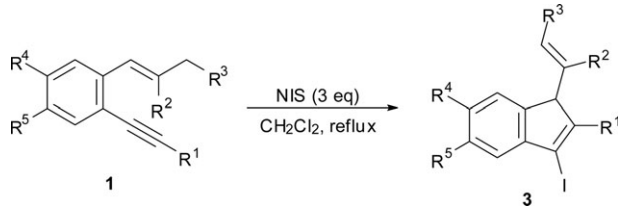
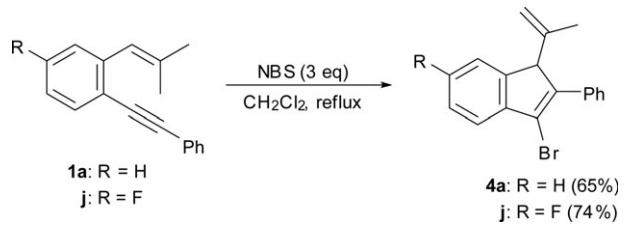
Table 1 Synthesis of 3-iodo-1*H*-indenes **3** by iodocyclization of *o*-(alkynyl)styrenes **1**



1 **3**

Entry	1	R^1	R^2	R^3	R^4	R^5	*t*/h	3	Yield[a] (%)
1	**1a**	Ph	Me	H	H	H	3	**3a**	85
2	**1b**	4-$MeOC_6H_4$	Me	H	H	H	1	**3b**	92(71)[c]
3	**1c**	3-Th[b]	Me	H	H	H	2.5	**3c**	87
4	**1d**	*n*Bu	Me	H	H	H	2	**3d**	81
5	**1e**	$(CH_2)_3CN$	Me	H	H	H	15	**3e**	71
6	**1f**	SPh	Me	H	H	H	1	**3f**	80
7	**1g**	Ph	Ph	H	H	H	4.5	**3g**	81
8	**1h**	Ph	$-(CH_2)_3-$		H	H	2	**3h**	71
9	**1i**	Ph	$-(CH_2)_4-$		H	H	3	**3i**	88
10	**1j**	Ph	Me	H	F	H	15	**3j**	79
11	**1k**	Ph	Me	H	Br	H	7	**3k**	84
12	**1l**	Ph	Me	H	$-OCH_2O-$		1	**3l**	78(67)[c]
13	**1m**	*n*Bu	Me	H	Br	H	16	**3m**	82
14	**1n**	*n*Bu	Ph	H	Br	H	36	**3n**	55[d]

[a] Isolated yield after column chromatography referred to starting material **1**. [b] 3-Thienyl. [c] Carried out with I_2/K_3PO_4 (3 equiv.) at rt. [d] ~80% conversion.



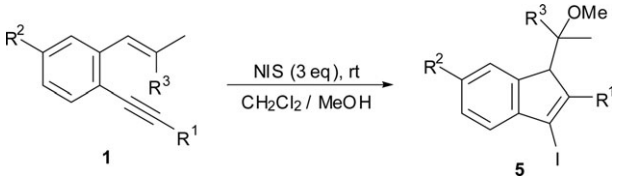
Scheme 2 Bromonium-mediated synthesis of 3-bromo-1*H*-indenes **4**.

(entry 4) that possess a phenyl group at the alkene. In addition, we have also demonstrated that I_2/K_3PO_4 could be used as iodonium source in the alkoxyiodocyclization reaction of **1a** (Table 2, entry 1), although with slightly lower selectivity.

Having in mind that 2,3-diarylindenes are known to possess biological activity,[11] we decided to employ the synthesized 3-haloindenes as precursors for the introduction of an aromatic substituent at the C-3 of the indene moiety by Pd-catalyzed cross-coupling reactions. In this way, 2,3-diarylindene derivatives **6** were obtained in high yield from **3a** and **3b** through a Suzuki coupling[12] with phenylboronic acid and $Pd(OAc)_2$/SPhos as catalytic system (Scheme 3). Interestingly, when bromoindene **4a** underwent a Stille coupling[13] with 2-(tributylstannyl)furan, the functionalized benzofulvene[14] derivative **7** was obtained, in which further isomerization of the propenyl group at the C-1 position of the indene scaffold has occurred (Scheme 3).

In summary, we have reported the direct halocyclization of *o*-(alkynyl)styrenes to give 3-halo-1*H*-indene derivatives in good to high yields under mild conditions. These results together with those recently reported by Kirsch and coworkers

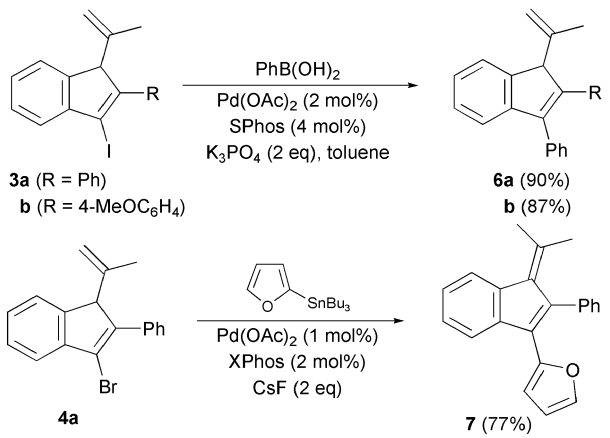
Table 2 Alkoxyiodocyclization of *o*-(alkynyl)styrenes **1**



1 **5**

Entry	1	R^1	R^2	R^3	*t*/h	5	Yield[a] (%)
1	**1a**	Ph	H	H	2	**5a**	66(58)[b]
2	**1b**	4-$MeOC_6H_4$	H	H	1	**5b**	70
3	**1f**	SPh	H	H	1	**5f**	58
4	**1g**[c]	Ph	H	Ph	3	**5g**	81[d]
5	**1j**	Ph	F	H	2	**5j**	78
6	**1k**	Ph	Br	H	4	**5k**	72

[a] Isolated yield after column chromatography referred to starting material **1**. [b] Carried out with I_2/K_3PO_4 as electrophilic source. [c] Used as a *ca.* 2 : 1 mixture of geometrical isomers. [d] Obtained as a *ca.* 2 : 1 mixture of diastereoisomers.



Scheme 3 Synthetic applications of 3-haloindenes **3** and **4**.

represent the first examples of electrophilic cyclizations of alkynes promoted by halonium ions where the nucleophilic counterpart is an alkene. In particular, our results represent the first examples of this type of halocyclization *via* a 5-*endo-dig* ring closure mechanism. The presence of a halogen in the final products allows further functionalization at the C-3 position of the indene through conventional palladium-catalyzed cross-coupling reactions. Current efforts in our lab are devoted to the development of an enantioselective version of this reaction and further applications of the obtained haloindenes in the synthesis of complex molecules.

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8 The first examples of iodonium-promoted 5-*endo-dig* carbocyclization of active methylene substrates onto alkynes have been described by Barluenga, González and co-workers in an elegant variant of the Conia-ene reaction, see ref. 3*b*.

9 Reactions also occur at room temperature, although longer reaction times are required.

10 However, α-methyl-2-phenylethynylstyrene gives rise to a 1-iodonaphthalene derivative through a 6-*endo* ring closure. See ref. 5.

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