Electrophilic Cyclization of 1,6-Enynes

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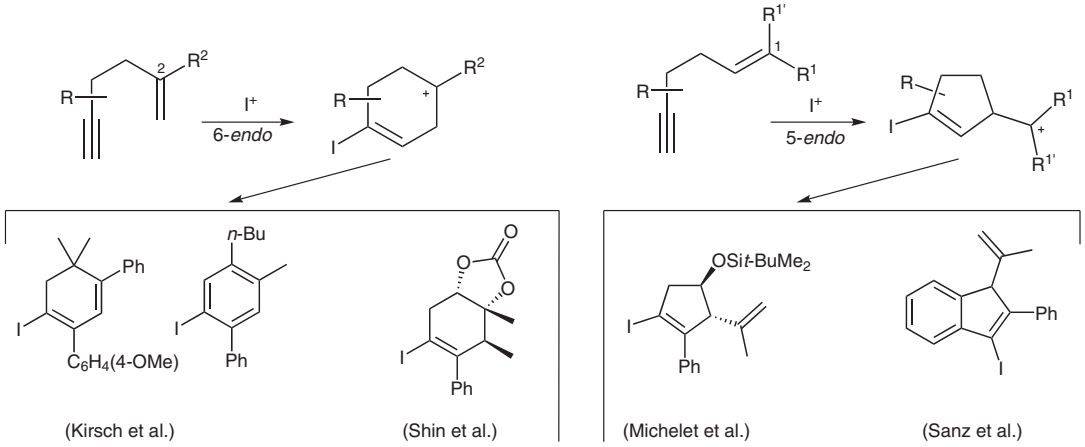
Received 25 January 2011

Abstract: The NIS-mediated iodocyclization of 1,6-enynes is described. While 1,6-enynes with a cation-stabilizing substituent at C2 position undergo 6-*exo* cyclization in poor yields, 1,6-enynes with donor substituents at C1 position favor the 5-*exo* mode of cyclization. The resulting five-membered carbocycles are obtained in moderate to good yields, thus demonstrating another facet in the iodocyclization of enynes.

Key words: enynes, cyclizations, iodine, alkynes, carbocycles

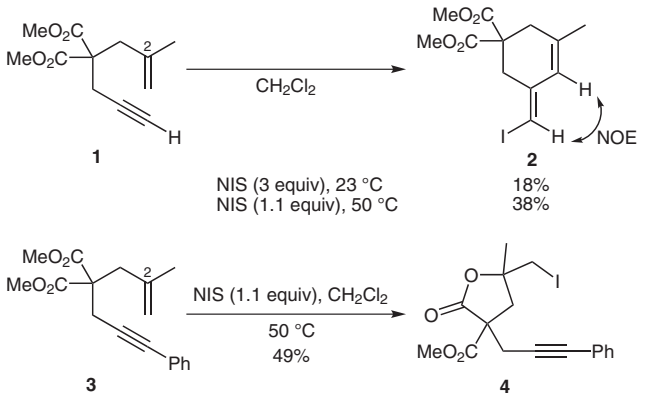
The electrophilic iodocyclization of alkynes has emerged as a powerful tool to efficiently synthesize small molecule targets. In particular, the iodonium-induced cyclization of heteroatom nucleophiles with tethered alkynes is useful to accomplish direct carbon–heteroatom bond formation for the synthesis of a variety of carbo- and heterocycles.[1,2] Despite a groundbreaking report by Barluenga et al. in 1988,[3] the analogous iodonium-induced cyclization of carbon nucleophiles remained mostly restricted to arenes[4] and malonates.[5] In 2010, we[6] and others[7] then showed how simple olefins can act as internal carbon nucleophiles in the iodocyclization of 1,5-enynes. In the presence of carbocation-stabilizing substituents at the C2 position, we[6a] and Shin[7a] et al. observed exclusive 6-*endo* cyclization converting 1,5-enynes into six-membered cyclic products of high value including highly substituted benzenes, 1,4-cyclohexadienes, and 4-fluoro cyclohexenes[8] (Scheme 1). For 1,5-enynes with carbocation-stabilizing substituents at the C1-alkenyl terminus, a 5-*endo* mode was reported as an alternative mode of cyclization.[7b,c] Here we show that 1,6-enynes are also substrates in iodonium-induced carbocyclizations yielding both six-membered and five-membered carbocycles depending on the position of cation-stabilizing substituents.

As transition-metal-catalyzed cycloisomerizations of 1,6-enynes are of exceptionally broad use to construct various carbocycles,[9,10] we expected that the corresponding iodocyclization also has the potential to deliver carbocyclic products of high complexity.[11] Due to the incorporation of I rather than H at the final product, further functionalization is made easy by use of classical cross-coupling methodologies.[12] To this end, 1,6-enyne **1** bearing a methyl donor at C2 position was treated with of *N*-iodosuccinimide (NIS) in CH_2Cl_2. The initial attempt employing three equivalents of NIS at room temperature produced only 18% of the desired six-membered ring system **2**, along with a large number of trace products not further analyzed (Scheme 2). The yield was slightly improved to 38% by using 1.1 equivalents of NIS at 50 °C in a sealed tube. As shown through NOESY studies, diene **2** was obtained as a single diastereoisomer resulting from *anti* addition onto the iodonium-activated triple bond. Other iodonium sources (e.g., I_2/K_3PO_4, IBr) did not provide better yields neither did other solvents (EtOAc, MeCN, toluene, THF, DMF). Notably, the 6-*exo* cyclization mode proved restricted to 1,6-enynes with a terminal alkyne moiety as assessed by reacting internal alkyne **3** with NIS to give lactone **4**.[13]



Scheme 1 Iodocyclization modes of 1,5-enynes

SYNLETT 2011, No. 8, pp 1151–1153
Advanced online publication: 07.04.2011
DOI: 10.1055/s-0030-1259938; Art ID: B02411ST

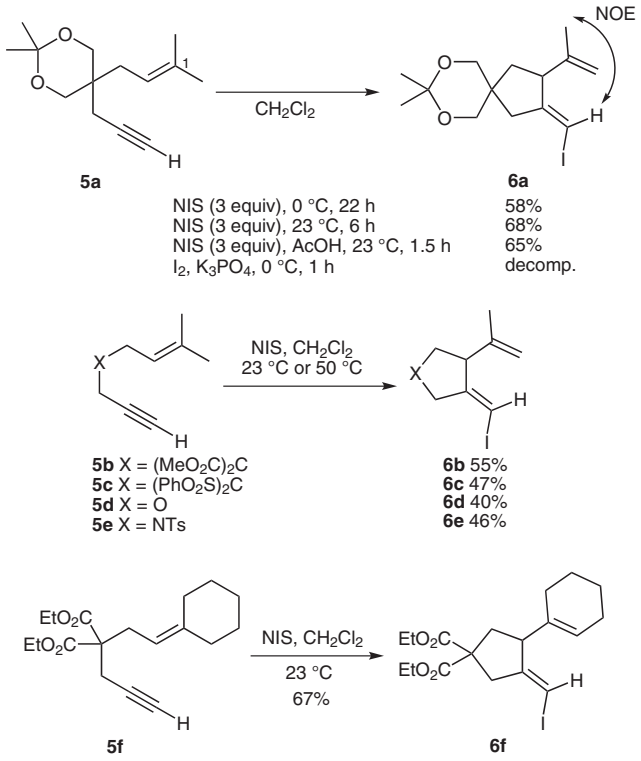


Scheme 2 6-*Exo* cyclization of 1,6-enynes

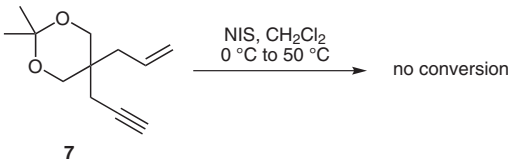
In order to investigate the alternative 5-*exo* cyclization, we sought to examine the reactivity of 1,6-enynes that possess two donor substituents at the C1-alkenyl terminus. We were pleased to find that acetonide **5a** indeed gave the expected cyclization product **6a** in up to 68% yield when employing NIS as the iodonium source in CH_2Cl_2 (Scheme 3). To rapidly convert the starting 1,6-enyne **5a**, heating to 50 °C was not required; the highest yield was obtained at room temperature after six hours. Surprisingly, significantly faster reaction times were realized when adding stoichiometric amounts of acetic acid. The origin of this effect, and why acetic acid was not incorporated under the reaction conditions,[6a,7c] is currently under investigation. Most likely, the Brønsted acid enhances the halogenating ability by activation of the succinimide carbonyl.[14] In the presence of other iodonium sources (e.g., I_2/K_3PO_4), we mostly observed rapid and complete decomposition to untraceable products.

The substrate scope was briefly examined utilizing NIS in dichloromethane at either 23 °C or at 50 °C. As shown in Scheme 3, a variety of 1,6-enynes with two substituents at C1 position underwent iodonium-induced cyclization to afford the five-membered carbocycles **6b–f** in moderate yields.[15] Notably, in all cases 5-*exo* carbocyclization occurred selectively over competing modes of cyclization. A major limitation stems again from the fact that internal alkynes do not react in the expected way.[16]

A plausible mechanism accounting for the observations reported herein is based on the intermediacy of cyclic carbocations. Accordingly, iodonium activation of the triple bond initiates the nucleophilic attack in an *anti* fashion. Since the reaction favors the carbon–carbon bond formation that, upon cyclization, leads to the more stable cationic intermediate, a substituent at C2 renders the C1 carbon of the alkene moiety more nucleophilic (6-*exo* cyclization). In sharp contrast, a disubstituted C1-alkenyl terminus generates five-membered cyclic cations via bond formation between the alkynyl C6 and the alkenyl C2 (5-*exo* cyclization). In both cases, proton abstraction (by the succinimide anion) finally delivers the diene product containing a vinyl iodide moiety. In accordance with this consideration, 1,6-enyne **7**, not bearing additional substituents at the alkene, was not converted at all when NIS was employed at various temperatures (Scheme 4).



Scheme 3 5-*Exo* cyclization of 1,6-enynes



Scheme 4 Attempted reaction of unsubstituted alkene **7**

In summary, we have investigated the reactivity of 1,6-enynes in the presence of electrophilic iodine sources. It was shown that the carbocyclization favors a pathway that proceeds through the more stabilized carbocation. A 6-*exo* process was realized in poor yields when enynes with a stabilizing substituent at the C2 position were reacted in the presence of NIS. In the case of 1,6-enynes with carbocation-stabilizing substituents at the C1-alkenyl terminus, the more rapid 5-*exo* cyclization yields the corresponding five-membered carbocycles in moderate to good yields. The transition-metal-free processes are experimentally simple to perform and demonstrate another facet of the still underdeveloped potential of electrophilic enyne cyclizations for the synthesis of diverse carbocyclic scaffolds.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This project was supported by the Deutsche Forschungsgemeinschaft (DFG), the Fonds der Chemischen Industrie (FCI), and the TUM Graduate School.

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(15) **Representative Experimental Procedure for 6f**
Enyne **5f** (32.0 mg, 105 μmol) was dissolved in CH_2Cl_2 (1 mL) and NIS (47.0 mg, 209 μmol, 2 equiv) were added. The solution was stirred at r.t. in the dark until TLC indicated full consumption of the starting material. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and a sat. aq $Na_2S_2O_3$ solution (10 mL) was added. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (pentane–Et_2O = 98:2). Carbocycle **6f** was obtained as a yellow oil (30.4 mg, 70.3 μmol, 67%); R_f = 0.18 (pentanes–EtOAc = 95:5) [UV, CAM]. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 6 H), 1.48–1.56 (m, 2 H), 1.59–1.69 (m, 2 H), 1.81–1.86 (m, 2 H), 1.98–2.05 (m, 2 H), 2.23 (t, *J* = 12.5 Hz, 1 H), 2.57 (dd, *J* = 12.8, 7.4 Hz, 1 H), 2.78 (dt, *J* = 18.1, 2.4 Hz, 1 H), 3.08 (d, *J* = 18.1 Hz, 1 H), 3.17–3.21 (m, 1 H), 4.20 (virt. pent, *J* = 6.7 Hz, 4 H), 5.53–5.57 (s, 1 H), 5.79–5.83 (m, 1 H). ^{13}C NMR (91 MHz, $CDCl_3$): δ = 14.2, 22.6, 23.1, 24.3, 25.5, 39.2, 44.9, 53.5, 58.0, 61.8, 71.9, 126.2, 135.6, 153.5, 171.3, 171.5. LRMS (EI): *m/z* (%) = 432 (5) [M^+], 387 (5), 305 (21), 231 (100), 157 (39). HRMS (EI): *m/z* calcd for $C_{18}H_{25}O_4I$ [M^+]: 432.0792; found: 432.0788.

(16) When 2,2-dimethyl-5-(3-methylbut-2-en-1-yl)-5-(3-phenylprop-2-yn-1-yl)-1,3-dioxane (as an internal alkyne derived from **5a**) was reacted with NIS in CH_2Cl_2 at r.t., the cyclization product was not observed. Instead, at least two compounds were formed that could not be unequivocally identified while, after 24 h, the bulk was unreacted starting material.