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Room-Temperature Metal-Free Electrophilic *5-endo*-Selective Iodocarbocyclization of 1,5-Enynes

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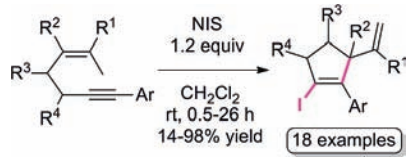
ABSTRACT



A highly efficient NIS-promoted iodocarbocyclization reaction of various functionalized 1,5-enynes is described via a 5-*endo* diastereoselective process. The cyclizations are conducted in the presence of 1.2 equiv of *N*-iodosuccinimide in dichloromethane at room temperature. The reaction conditions are compatible with several functional groups and lead to original iodo-functionalized carbocycles in good to excellent yields.

Electrophilic iodocyclization of alkynes represents a useful methodology for the synthesis of a variety of carbo- and heterocycles.[1] Although a broad scope of oxygen, nitrogen, sulfur, or selenium nucleophiles has been used with success, much fewer studies have been reported with carbon nucleophiles. The first seminal contribution in 1988 by Barluenga et al. reported a unique example of intramolecular iodoarylation of alkynes in the presence of bis(pyridine)-iodonium tetrafluoroborate.[2] Since then, several groups have studied the iodocarbocyclization reactions employing carbon nucleophiles such as aromatic rings[3] or enol and enolates.[4] At the initial stage of our study, we wondered if alkenes may act as nucleophiles toward iodonium-activated alkynes. We anticipated that 1,*n*-enynes might be good candidates for such investigations, considering their fascinating reactivity[5] and the recent theoretical investigations highlighting the analogy between halonium chemistry and π-Lewis acid catalysis.[6] In the course of our investigations, Shin, Kirsch, and co-workers independently described the iodocarbocyclization of 1,5-enynes in the presence of IBr and NIS (Scheme 1).[7]

(1) (a) Larock, R. C. In *Acetylene Chemistry. Chemistry, Biology and Material Science*; Diederich, F., Stang, P. J., Tykwinsky, R. R., Eds; Wiley-VCH: New York, 2005; Chapter 2, pp51−99. (b) Rodriguez, J.; Dulcere, J.-P. *Synthesis* **1993**, 1177. (c) Togo, H.; Iida, S. *Synlett* **2006**, 2159. (d) Mehta, S.; Waldo, J. P.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 1141.

(2) Barluenga, J.; González, J. M.; Campos, J. M.; Asensio, G. *Angew. Chem., Int. Ed.* **1988**, *27*, 1546.

(3) For selected references, see: (a) Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 12230. (b) Barluenga, J.; Trincado, M.; Marco-Arias, M.; Ballesteros, A.; Rubio, E.; González, J. M. *Chem. Commun.* **2005**, 2008. (c) Zhang, X.; Sarkar, S.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 236. (d) Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 1437. (e) Tang, B.-X.; Tang, D.-J.; Tang, S.; Yu, Q.-F.; Zhang, Y.-H.; Liang, Y.; Zhong, P.; Li, J.-H. *Org. Lett.* **2008**, *10*, 1063. (f) Rahman, M. A.; Kitamura, T. *Tetrahedron Lett.* **2009**, *50*, 4759.

(4) (a) Kitagawa, O.; Inoue, T.; Hirano, K.; Taguchi, T. *J. Org. Chem.* **1993**, *58*, 3106. (b) Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397. (c) Barluenga, J.; Palomas, D.; Rubio, E.; González, J. M. *Org. Lett.* **2007**, *9*, 2823. (d) Ali, Z.; Wirth, T. *Org. Lett.* **2009**, *11*, 229.

(5) (a) Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, *35*, 6075. (b) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371. (c) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (e) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *45*, 7427. (f) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

(6) For a recent review and seminal examples: Yamamoto, Y.; Gridnev, I. D.; Patil, N. T.; Jin, T. *Chem. Commun.* **2009**, 5075.

(7) For recent examples of iodonium-mediated *6-endo-dig* cycloisomerization of 1,5-enynes, see: (a) Lim, C.; Rao, S.; Shin, S. *Synlett* **2010**, 368. (b) Crone, B.; Kirsch, S. F.; Umland, K.-D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4661.

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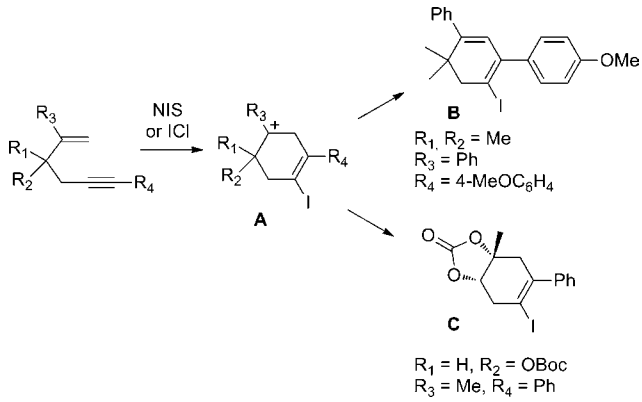
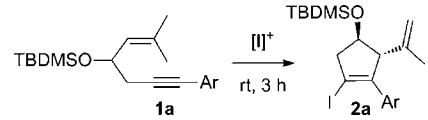
Scheme 1. Examples of Iodocyclization Reactions



In both cases, a 6-*endo* mode of cyclization is observed. Upon addition of the alkene function, the carbocation **A** formed either reacts by elimination to give the 1,3-diene **B** or is trapped by nucleophilic attack of a carbonate to give the corresponding bicyclic heterocycle **C**. Targeting the rare 5-*endo* mode of cyclizations[8] and considering the regioselectivity observed in carbophilic Lewis acid-catalyzed cycloisomerization of 1,5-enynes,[9,5] we anticipated that the introduction of carbocation-stabilizing substituents at the alkenyl terminal position would promote the desired cyclization and, hence, lead to the formation of a cyclopentenyl structure. We wish therefore to report our preliminary investigations allowing the synthesis of iodo-functionalized cyclopentenes under mild conditions. The iodocyclization of 1,5-enyne **1a** was conducted in various solvents and in the presence of electrophilic iodine sources (Table 1). We were delighted to find that the iodocyclopentene **2a** was obtained selectively at room temperature in the presence of 1.1 equiv of *N*-iodosuccinimide in dichloromethane (entry 6). No conversion was observed in toluene, whereas lower reactivities were detected in ethyl acetate or tetrahydrofuran (entries 1−3). When the reaction was conducted in acetonitrile (entry 4), the iodo derivative **2a** was isolated in only 6% yield, whereas compound **3** was obtained in 42% yield.

The formation of amide **3** resulted from a domino iodocyclization/Ritter reaction.[10] A similar side reaction was observed in MeOH (entry 5). Indeed, a methoxyiodocarbocyclization reaction allowed the formation of the ether **4** in 22% yield, along with formation of product **2a** in 19% isolated yield (entry 5). The influence of other iodonium sources was then investigated: iodine, iodochloride, and bis(pyridine) iodonium tetrafluoroborate (entries 7−9) allowed the consumption of starting material but afforded mainly degradation products or very low yield of the desired product.[11] In the latter case, the fluoro compound **5** was also isolated in 37% yield. The reaction was found to be totally diastereoselective, which was demonstrated by high-field NOESY ^{1}H NMR experiment on the acetate-protected bicyclic analogue of **2b** (see Supporting Information).

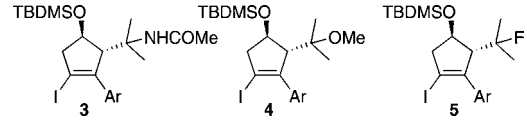
Table 1. Optimization of the Reaction Conditions on **1a**



1a **2a**

entry	[I]$^+$ source 1.1 equiv	solvent	convn (yield %)[a]
1	NIS	toluene	0
2	NIS	AcOEt	42
3	NIS	THF	75
4	NIS	CH_3CN	100 (6)
5	NIS	MeOH	100 (19)
6	NIS	CH_2Cl_2	100 (96)
7	I_2	CH_2Cl_2	100 (/)
8	ICl	CH_2Cl_2	100 (18)
9[b]	IPy_2BF_4/HBF_4	CH_2Cl_2	100 (8)

[a] Isolated yields, dr > 95:5. [b] Reaction performed at 0 °C.[7b]



3 **4** **5**

Remarkably, electrophilic activation by iodonium species takes place selectively at the carbon−carbon triple bond rather than at the alkenyl moiety.[12] This behavior seems to be strongly affected by the spatial positioning of the alkene nucleophile during the cyclization event (Scheme 2). Indeed, treatment of enyne **6** that does not possess a substituent on the 4-position of the enyne with *N*-iodosuccinimide in dichloromethane led to the formation of product **7** in moderate yield. Moreover, in the presence of an external nucleophile, the activation of the substrate took place chemoselectively at the alkenyl unsaturation. The reaction allowed the formation of **8** that results from the iodoetherification of the carbon−carbon bond of higher electronic density, in quantitative yield.

Having in hand an optimized system, the iodocarbocyclization was then applied to several 1,5-enynes (Table 2

(8) For a recent paper, which appeared during the submission process: Sanz, R.; Martinez, A.; Garcia-Garcia, P.; Fernandez-Rodriguez, M. A.; Rashid, M. A.; Rodriguez, F. *Chem. Commun.* **2010**, *46*, 7427. For a single example using Br_2, see: Schreiner, P. R.; Prall, M.; Lutz, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5757.

(9) For Hg-, Pt-, and Au-catalyzed carbocyclization of 1,5-enynes, see: (a) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Synlett* **2005**, 703. (b) Imagawa, H.; Iyenaga, T.; Nishizawa, M. *Org. Lett.* **2005**, *7*, 451. (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962. (d) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 5991. (e) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141. (f) Nelsen, D. L.; Gagné, M. R. *Organometallics* **2009**, *28*, 950. (g) Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888. (h) Martinez, A.; Garcia-Garcia, P.; Fernandez-Rodriguez, M. A.; Rodriguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633. For a W-catalyzed example of 5-*endo* cyclization, see: (i) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, K. L.; Ho Lee, P. *Org. Lett.* **2002**, *4*, 4463, and references cited therein.

(10) Uemura, S.; Fukuzawa, S.-I.; Toshimitsu, A.; Okano, M. *J. Org. Chem.* **1983**, *48*, 270.

(11) In the case of iodine and ICl, the use of an additional base, e.g., K_3PO_4,[3a] did not lead to any improvement of the yield.

(12) For the reactivity of the ene-ynamide mediated by electrophilic oxene transfer reagents, see: (a) Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2819. (b) Al-Rashid, Z. F.; Hsung, H. P. *Org. Lett.* **2008**, *10*, 661.

Scheme 2. Chemoselectivity of the NIS-Promoted Reaction of 1,5-Enyne **6**

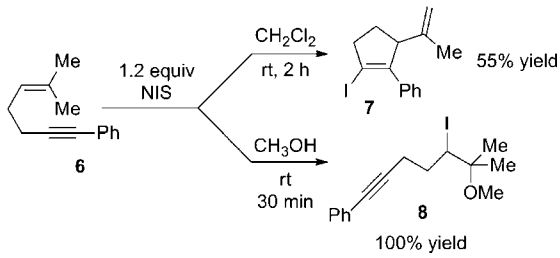
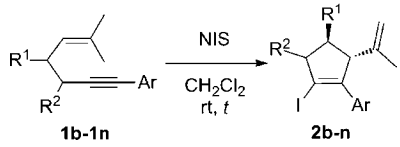


Table 2. NIS-Promoted Iodocarbocyclization of 1,5-Enynes in Dichloromethane at Room Temperature

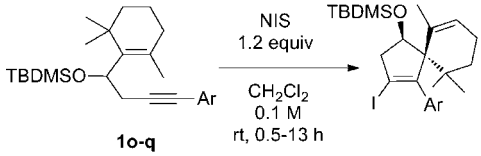


entry	1,5-enyne	R_1	R_2	Ar		time (h)	yield (%)[a]
1	**1b**	OTBDMS	H	Ph	**2b**	26	86
2	**1c**	OTBDMS	H	2-naphtyl	**2c**	9	64
3	**1d**	OTBDMS	H	2-thienyl	**2d**	3	85
4	**1e**	OTBDMS	H	2-tolyl	**2e**	5	67
5	**1f**	OBz	H	Ph	**2f**	21	98
6	**1g**	OBz	H	2-naphtyl	**2g**	27	66
7	**1h**	OBz	H	2-thienyl	**2h**	21	64
8	**1i**	OBz	H	4-$MeOC_6H_4$	**2i**	5.5	88
9	**1j**	OTES	H	Ph	**2j**	20	60
10	**1k**	OBn	H	Ph	**2k**	20	14
11[b]	**1l**	OPMB	H	Ph	**2l**	3	45[b]
12	**1m**	H	OTBDMS	Ph	**2m**	3	29[c]
13	**1n**	H	*n*-Pr	Ph	**2n**	1	41[d]

[a] Isolated yields, dr >95:5. [b] Deprotected alcohol is isolated. [c] 2:1 mixture of diastereomers. [d] 1:1 mixture of diastereomers.

and Scheme 3). Various aromatic and heteroaromatic rings (phenyl, napthyl, tolyl, and thienyl) were introduced and compatible with the reaction conditions (entries 1−4).[13] The corresponding iodocyclopentenes **2b**−**2e** were isolated in 67−86% yields. Other protected alcohols were also cleanly cyclized and functionalized, such as benzoyl or triethylsilyl-substituted 1,5-enynes. The resulting adducts **2f**−**2j** were obtained in moderate to excellent yields (entries 5−9). The benzyl or *para*-methoxybenzyl-protected 1,5-enynes allowed

Scheme 3



the formation of the desired products in low yield or as a free alcohol (entries 10 and 11).[14] The influence of the nature and position of the protected alcohol was also investigated and was found to be critical for the outcome of the reaction. In the case of enyne **1m** and **1n**, the iodocarbocyclization reactions allowed the formation of the cyclopentenyl derivatives **2m** and **2n** in modest yields (29% and 41%) and as mixtures of *syn* and *anti* diastereomers (entries 12 and 13).

The reactivities of 1,5-enynes **1o**−**1q** possessing tetrasubstituted alkenyl moieties were much more gratifying (Scheme 3), as the bicyclic iodo-functionalized derivatives were obtained in good yields. The diastereoselectivity of the process was demonstrated by NOESY experiments on **2q** and X-ray analysis of **2o** (Figure 1, see Supporting Information).[15]

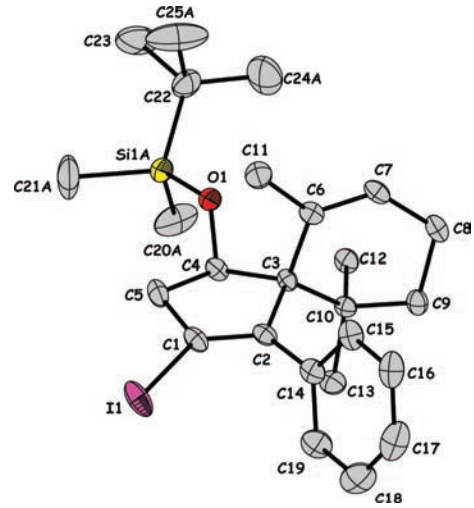


Figure 1. X-ray analysis of **2o**.

A mechanistic rationale accounting for the observed products and selectivities is proposed in Scheme 4. At the initial stage of the reaction, the iodonium ion would activate the alkynyl function through π-coordination to give intermediate **D**.

Upon nucleophilic attack of the alkenyl moiety in an *anti* fashion, an iodocyclization reaction would lead to the formation of a carbocation (intermediate E). In the absence of an external nucleophile, proton abstraction by the succinimide anion would allow the formation of the 1,3-dienic product. When an external nucleophile is present, nucleophilic attack of the carbocation would give products such as **3**, **4**, or **5**.

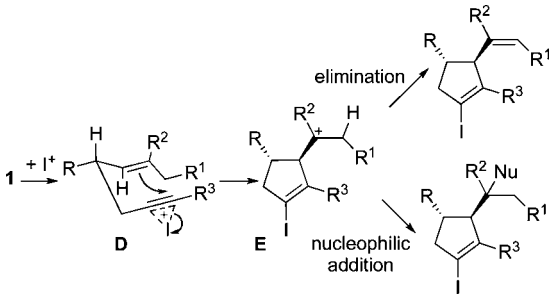
In conclusion, we have demonstrated that functionalized 1,5-enynes may be cyclized under extremely mild conditions,

(13) The reactivity of 1,5-enyne bearing an electron-deficient aryl group on the alkyne moiety was sluggish, and traces of the desired product were detected.

(14) For iodine-mediated PMB deprotection, see: Vaino, A. R.; Szarek, W. A. *Synlett* **1995**, 1157.

(15) For the iodine-mediated formation of bicyclic spiro structures, see: (a) Ref 3a. Ref 3c . (c) Okitsu, T.; Nakazawa, D.; Kobayashi, A.; Mizohata, M.; In, Y.; Ishida, T.; Wada, A. *Synlett* **2010**, 203.

Scheme 4. Mechanistic Rationale



at room temperature in the presence of NIS and without additives according to an unprecedented 5-*endo* process. The iodocarbocyclization was found to be totally diastereoselective, and the corresponding 1-iodopentenes were isolated in good to high yields. This process constitutes an easy and efficient access to highly valuable building blocks of natural products or biologically active compounds.

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Supporting Information Available: Experimental procedures, full analyses of 1,5-enynes and iodocarbocycles, and cif file for X-ray structure **2o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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