ORGANIC LETTERS

2008
Vol. 10, No. 9
1727−1730

Hexafluoroisopropanol as a Unique Solvent for Stereoselective Iododesilylation of Vinylsilanes

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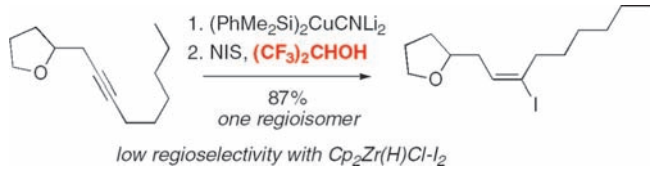
Received February 14, 2008

ABSTRACT



Stereoselective preparation of iodoalkenes from vinylsilanes is described. 1,1,1,3,3,3-Hexafluoroisopropanol serves as a unique solvent that ensures high yields and stereoselectivities in the iododesilylation of a variety of functionalized substrates.

Iodoalkenes are versatile intermediates that have found widespread use in organic synthesis. Alkynes can often serve as covenient starting materials for their preparation. Among a variety of transformations that can be employed for this purpose, hydrometalation of triple bonds followed by iodinolysis provides a direct one-step route from alkynes to iodoalkenes.[1] Hydrozirconation of alkynes followed by iodination of intermediate vinylzirconium species is an important example of this process.[2] Mildness of the reaction conditions and excellent regio- and stereocontrol with terminal alkynes make it useful for hydroiodination of triple bonds in complex substrates. Occasionally, however, difficulties in handling and storing of $HZrCp_2Cl$,[3] overhydrozirconation, and protonolysis of vinylzirconium species detract from the utility of this method. In addition, poor regioselectivity is typically observed with internal alkynes.[4]

Stannyl-[5] and silylcupration[6] followed by iododestannylation or iododesilylation provides an attractive, two-step alternative for functionalization of alkynes under mild conditions.[7] Previously, we used this approach effectively when the hydrozirconation−iodination was unproductive.[8] The advantages of silylcupration are that it does not require toxic tin reagents and the intermediate vinylsilanes are more stable and less toxic and thus more easily handled in multistep reaction sequences.

Several reagents and reaction conditions have been used for iododesilylation. These include I_2 in CH_2Cl_2,[7,9] $I_2-AgO_2CCF_3$ in CH_2Cl_2 followed by $KF{\cdot}2H_2O$, I_2/Lewis

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(2) (a) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333–340. (b) Negishi, E. In *Organometallics in Synthesis: A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley: New York, **2002**; Chapter 8, pp 925−1002. (c) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853–12910. (d) Lipshutz, B. H.; Pfeiffer, S. S.; Noson, K.; Tamioka, T. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, **2002**; Chapter 4, pp 110−148.

(3) A practical solution to this problem has been described recently. Huang, Z.; Negishi, E. *Org. Lett.* **2006**, *8*, 3675–3678.

(4) Useful level of regioselectivity is usually achieved with 2-alkynes. For examples, see ref.3

(5) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064–5073.

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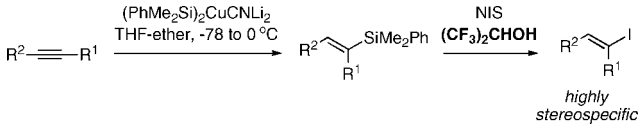
(8) (a) Lu, C.-D.; Zakarian, A *Org. Lett.* **2007**, *9*, 3161–3163. For other applications, see: (b) Coleman, R. S.; Walczak, M. C.; Campbell, E. L. *J. Am. Chem. Soc.* **2005**, *127*, 16038–16039. (c) Zakarian, A.; Batch, A.; Holton, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 7822–7824.

10.1021/ol800341z CCC: $40.75
Published on Web 04/03/2008

acid in CH_2Cl_2,[10] ICl in CCl_4 or DMF,[11] ICl or IBr in CH_2Cl_2 followed by NaOMe,[12] IPy_2BF_4 in CH_2Cl_2,[13] and *N*-iodosuccinimide (NIS) in MeCN or $ClCH_2CN-MeCN$ mixtures.[14,15] The last reagent system using NIS was developed because iododesilylation reaction of certain complex substrates with previously employed reagents was problematic, leading to poor reactivity, extensive decomposition, or low stereoselectivity.[14]

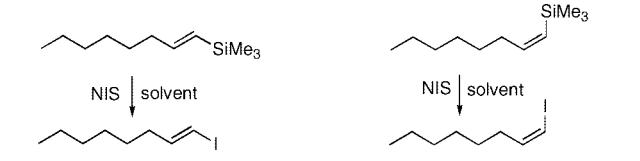
In this communication, we describe a study that demonstrates that (1) hexafluoroisopropanol (HFIP) is a uniquely suitable solvent for stereoselective iododesilylation of a variety of vinylsilanes and (2) a high regioselectivity in silylcupration of internal alkynes under Fleming's conditions can be achieved (Scheme 1).

Scheme 1



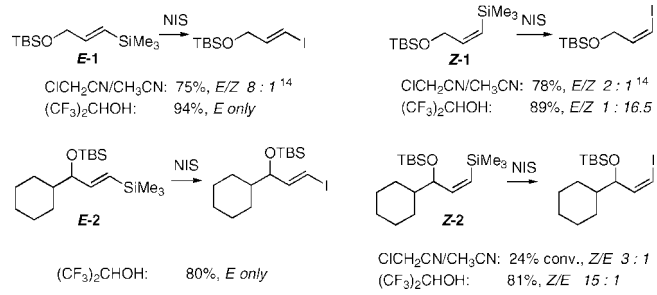
Previously, the Kishi group reported a method for a mild preparation of vinyliodides from vinylsilanes using *N*-iodosuccinimide (NIS) and a 9:1 mixture of acetonitrile and chloroacetonitrile as the solvent.[14] A high stereoselectivity was observed with many substrates, but simple vinylsilanes gave a mixture of products with modest stereocontrol. For example, (*E*)-1-trimethylsilyl-1-octene and (*Z*)-1-trimethylsilyl-1-octene provided mixtures of the corresponding (*E*)- and (*Z*)-iodoalkenes (2.8:1 and 1:1.2 ratio, respectively). We discovered that the iododesilylation with these substrates occurs with an almost complete retention of stereochemistry when $(CF_3)_2CHOH$ is employed as the solvent (Scheme 2).

Scheme 2



O-Silylated (γ-silyl)allylic alcohols are more challenging substrates. Under Kishi's conditions, the (*E*)-**1** isomer afforded the corresponding (*E*)-iodoalkene (8:1), and the (*Z*)-**1** vinylsilane also gave the (*E*)-iodoalkene with lower selectivity (2:1) (Scheme 3). With HFIP as the solvent, the

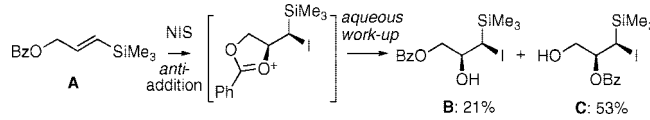
Scheme 3



iododesilylation occurs with retention of configuration for both substrates (Scheme 3). Similar results were obtained with (*E*)-**2** and (*Z*)-**2**.

In contrast to results reported by Kishi and co-workers,[14] when the TBS protecting group was replaced with the corresponding benzoate, no iodoalkene products were observed upon treatment with NIS in HFIP. As shown in Scheme 4, only regioisomeric iodohydrin products could be

Scheme 4



isolated, presumably due to benzoate participation in the electrophilic addition.[16]

During the course of our experiments, we have found that the addition of 2,6-lutidine (~1 equiv) as a buffer was beneficial in terms of yield for acid-sensitive substrates. Therefore, we have included this additive in our standard protocol in subsequent experiments.

Screening of solvents using vinylsilane **3** as the substrate revealed that hexafluoroisopropanol is uniquely suitable for stereoselective iododesilylation with NIS (Table 1). Under optimal conditions (entry 10), the *E*-isomer **4** was obtained exclusively in 90% isolated yield. The reaction can be performed at higher concentration if the cost of the solvent has to be considered. For example, at 1.0 M concentration of the substrate in HFIP, a 10:1 ratio of products was

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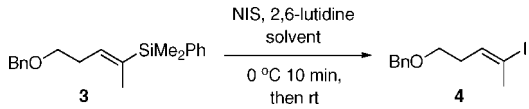
(16) (a) Similar results were obtained by Kishi with electron-rich 2,4-dimethoxy benzoates (ref,14 Table 1C, entry 10-c). (b) Relative configuration of the iodohydrin products is based on the anti-addition mechanism and is not confirmed.

Table 1. Solvent Study



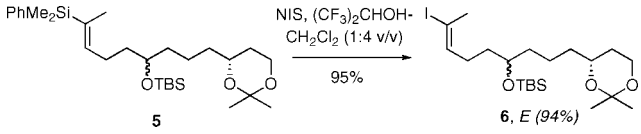
entry	solvent	reaction time	E/Z ratio[a]
1	PhMe	24 h[b]	
2	$PhCF_3$	24 h[b]	1: 2.1
3	THF	24 h[b]	1: 1.4
4	CH_2Cl_2	24 h[b]	1: 1
5	MeCN	24 h[b]	2.9: 1
6	*i*-PrOH	24 h[b]	1: 2.6
7	$ClCH_2CN$-MeCN (1:9)[c]	1.5 h	4.1: 1
8	$ClCH_2CN$-MeCN (1:9)[d]	1.5 h	4.8: 1
9	CF_3CH_2OH	3 h	5.9: 1
10	**$(CF_3)_2CHOH$ (HFIP,0.25M)**	**10 min**	***E* only**[e]
11	HFIP (0.50 M)	10 min	20: 1
12	HFIP (0.75 M)	10 min	16: 1
13	HFIP (1.0 M)	10 min	10: 1
14	HFIP (2.0 M)	10 min	2.6: 1
15	HFIP-PhMe (1:4)	10 min	2.9: 1
16	HFIP-CH_2Cl_2 (1:4)	10 min	6.5: 1
17	HFIP-MeCN (1:4)	10 min	2.1: 1
18	HFIP-CF_3CH_2OH (1:4)	10 min	6.1: 1

[a] Determined by the 300 MHz ^{1}H NMR of the crude mixture of products; see Supporting Information. [b] The reaction did not reach completion. [c] With 5 equiv of NIS. [d] With 1.2 equiv of NIS. [e] Isolated yield 90%.

obtained, favoring the retention of stereochemistry. Notably, when a 9:1 mixture of MeCN−$ClCH_2CN$ was employed, a 4.8:1 mixture of the isomers was produced.

In some cases, a mixture of HFIP and CH_2Cl_2 is acceptable as the solvent, even though with **3** the stereoselectivity is reduced (Table 1, entry 16). In this solvent mixture, iododesilylation of **5**, an intermediate in the synthesis of the BCD-bisketal of pinnatoxins,[8a] has occurred with 94% diastereoselectivity, lower than in pure HFIP but still practical for synthetic purposes (Scheme 5).

Scheme 5



The reasons for high stereoselectivity favoring the retention of configuration in hexafluoroisopropanol are not completely clear but are likely a result of high polarity and low nucleophilicity of the solvent. The low nucleophilicity should prevent solvent participation through the nuleophilic attack on the β-carbon of the putative intermediate iodonium cation (Figure 1).[16] In addition, an important observation noted in the iododesilylation reaction is the striking rate acceleration relative to other solvents. On the basis of the known strong

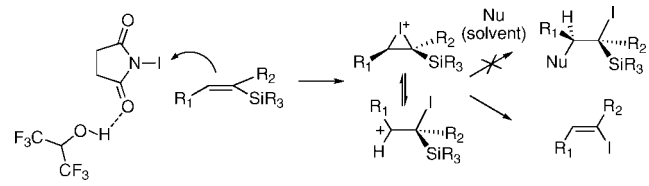
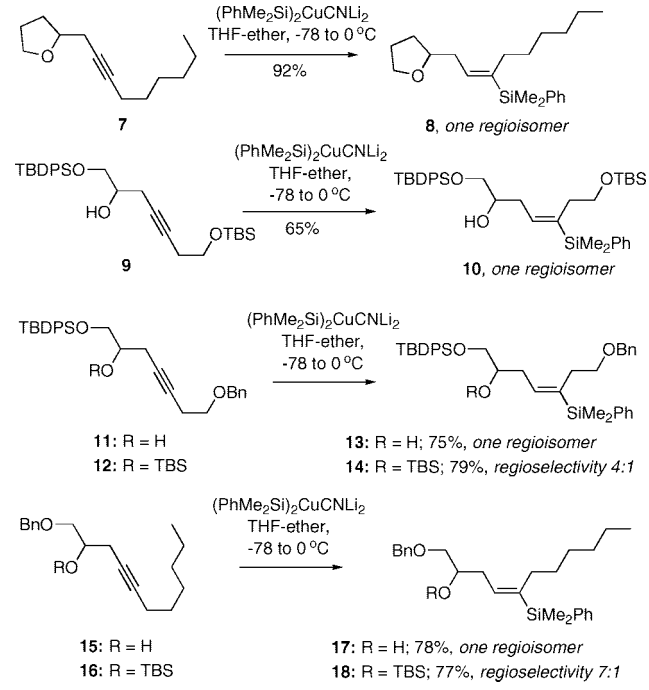


Figure 1. Proposed mechanistic model.

hydrogen-bond donating power of hexafluoroisopropanol,[17] this rate acceleration can be understood by the electrophilic activation of *N*-iodosuccinimide through hydrogen bonding.

The two-step conversion of alkynes to iodoalkenes has a significant advantage over the existing methods in some cases because high regio- and stereoselectivity can be achieved with internal alkynes *other than 2-alkynes*. For example, we have found that the silylcupration reaction is quite sensitive to branching in the homopropargylic position (Scheme 6).

Scheme 6



Silylcupration of tetrahydrofyranyl alkyne **7** was highly regioselective, affording vinylsilane **8** in high yield. Silane **8** can be iododesilylated in 95% yield to afford the corresponding iodoalkene with high diastereoselectivity.[18,19]

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(18) See Supporting Information for details.

(19) In a control experiment, hydrozirconation−iodinolysis of **7** (1.5 equiv of $HZrCp_2Cl$, PhH, 40 °C, 1 h; I_2, rt, 10 min) provided regioisomeric iodides in 75% combined isolated yield and 1.7:1 ratio, favoring the regioisomer opposite to that obtained from silylcupration−iododesilylation sequence.

Alkyne **9** provided the silylcupration product **10** with complete regiocontrol, as well.

Comparison of the results of silylcupration of substrates **11**, **12**, **15**, and **16** revealed that the free hydroxyl group has a significant directing power, presumably through coordination to the cuprate reagent. Thus, silylcupration of unprotected hydroxy alkynes **11** and **15** took place with complete regiocontrol, delivering **13** and **17**, respectively, in good yields. On the other hand, when the hydroxyl group is protected as the *tert*-butyldimethylsilyl ether, the regioselectivity is notably reduced to 4:1 for **12** and 7:1 for **16**, still favoring the same regioisomer. These results indicate that the regioselectivity is guided to some extent by coordination of the reagent to hydroxy or alkoxy groups in the substrate. Overall, practical levels of regioselectivity can be obtained with *internal* alkynes.

In conclusion, a two-step conversion of alkynes to iodoalkenes can be achieved in high yield and with high stereoselectivity via silylcupration followed by iododesilylation. This method is a practical alternative when hydrozirconation−iodination or other methods are not productive. Importantly, high regioselectivity can be achieved with a number of internal alkynes.

Acknowledgment. This research project is supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society (43838-G1), and the Department of Chemistry and Biochemistry, Florida State University. We thank Dr. Tom Gedris (FSU) for the assistance with NMR spectroscopy, and Drs. Umesh Goli and Christelle Guillo (FSU) for the assitance with high-resolution mass spectroscopy.

Supporting Information Available: Experimental procedures, copies of ^{1}H, ^{13}C NMR spectra, and selected NOE specta for compounds described in this report. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800341Z