Tetrahedron Letters 57 (2016) 1379–1381

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Stereoselective synthesis of iodofluoroalkenes by iodofluorination of alkynes using IF_5-pyridine-HF

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ARTICLE INFO

Article history:
Received 8 January 2016
Revised 12 February 2016
Accepted 16 February 2016
Available online 16 February 2016

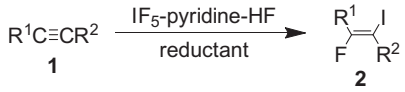
Keywords:
Iodofluorination
Iodofluoroalkene
Fluoroalkene
Stereoselective synthesis
IF_5-pyridine-HF

ABSTRACT

The iodofluorination of alkynes was carried out using IF_5-pyridine-HF and hydroquinone. The iodofluorination of an internal alkyne and a terminal alkyne proceeded stereoselectively to give the corresponding iodofluoroalkenes. An unsymmetrically substituted internal alkyne and electron deficient alkyne also afforded the corresponding iodofluoroalkenes stereoselectively. The iodofluoroalkenes thus obtained were used in the stereoselective synthesis of di- and trisubstituted fluoroalkenes.

Introduction

The iodofluorination reaction of alkynes has been conveniently used for the stereoselective synthesis of iodofluoroalkenes,[1] key intermediates for the synthesis of di- or trisubstituted fluoroalkenes.[2] Generally, iodofluorination reaction is performed using the 'IF' species generated in situ from I^+ and F^- sources, and various types of I^+ and F^- sources have been used. The conventional iodofluorination reaction has been successfully applied to internal alkyne, however, terminal alkynes afforded the expected iodofluorination products in low yields, because of the formation of by-products such as 1-iodo-1-alkyne.[1i] Therefore, more convenient and effective reagents are required for iodofluorination of alkynes. Recently, we reported a stable hypervalent iodine reagent, IF_5-pyridine-HF, and its application to fluorination reactions.[3] We also reported the iodofluorination of alkenes using the 'IF' species generated from IF_5-pyridine-HF and a reductant.[4] In this study, the iodofluorination of alkynes was investigated using IF_5-pyridine-HF and a reductant to develop a more convenient and effective method for the synthesis of iodofluoroalkenes (Scheme 1).



Scheme 1.

Results and discussion

Initially, the iodofluorination of 1-dodecyne (**1a**) with IF_5-pyridine-HF was carried out in the presence of various reductants (Table 1). When KI was used as the reductant, 1,2-diiododo-1-dodecene (**3a**) and 1-iodo-1-dodecyne (**4a**) were formed instead of the desired *trans*-1-iodo-2-fluoro-1-dodecene (**2a**). When I_2 was used as the reductant, **2a** was formed in 48% yield, however, **3a** and **4a** were also formed. On the other hand, when catechol was used as the reductant, **2a** was formed selectively in 75% yield. The best result was obtained when hydroquinone was used, and **2a** was obtained in 82% yield.

The iodofluorination of the various alkynes was carried out using IF_5-pyridine-HF and hydroquinone (Table 2). From terminal alkynes, the desired (*E*)-1-iodo-2-fluoro-1-alkenes were obtained stereo- and regioselectively (entries 1, 2, 4, 7, and 8). In the reaction with internal alkynes, both symmetrically substituted alkynes (**1c**, **e**) and unsymmetrically substituted alkynes (**1f**, **i**–**k**), gave the corresponding iodofluoroalkenes stereo- and regioselectively (entries 3, 5, 6, and 9–11). The iodofluorination of electron deficient alkynes such as **1j** and **1k** was previously unknown. Nevertheless, their iodofluorination using IF_5-pyridine-HF and hydroquinone successfully afforded the corresponding iodofluoroalkenes (**2j**) and (**2k**) stereo- and regioselectively[5] (entries 10 and 11).

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http://dx.doi.org/10.1016/j.tetlet.2016.02.063
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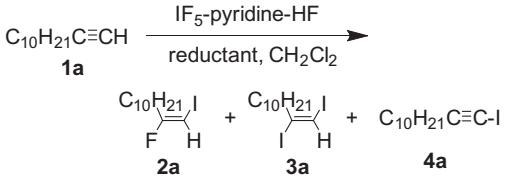
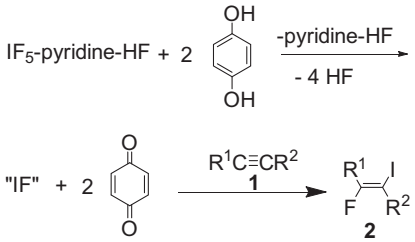
Table 1
Iodofluorination of **1a** using IF_5-pyridine-HF and various reductants[a]



Reductant	Yield of **2a**[b] (%)	Yield of **3a**[c] (%)	Yield of **4a**[c] (%)
KI	0	30	70
I_2	48	31	12
Catechol	75	0	0
Hydroquinone	82	0	0

[a] The reaction was carried out at room temperature for 12 h using 2.0 equiv of IF_5-pyridine-HF and reductant to **1a**.
[b] ^{19}F NMR yield.
[c] GC yield.

In the present reaction, IF_5-pyridine-HF was reduced by hydroquinone to give IF species which added to alkyne as shown in Scheme 2. Formation of *p*-quinone was confirmed in the reaction mixture. As the IF species is unstable in solution, it is difficult to decide the real active species which caused the selectivity of the present reaction. However, it was reported that the reactivity of the IF species is dependent on the reagents used.[7] Therefore, choice of the reducing reagent is important to realize the desired selectivity.

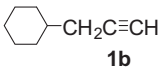
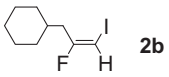


Scheme 2.

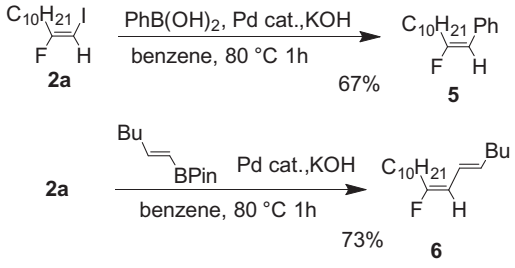
The iodofluoroalkenes thus obtained can be used for the stereoselective synthesis of di- and trisubstituted fluoroalkenes. The Suzuki–Miyaura coupling reaction of (*E*)-1-iodo-2-fluorododec-1-ene **2a** with organoboranes afforded disubstituted fluoroalkenes (**5**) and (**6**) stereoselectively[8] (Scheme 3).

Next, we attempted to synthesize trisubstituted fluoroalkene (**7**) by the cross-coupling reaction of ethyl (*E*)-2-iodo-1-fluoro-1-phenylpent-1-ene (**2f**) with phenylboronic acid.[9] However, the cross-coupling reaction of **2f** with phenylboronic acid was sluggish, and **2f** decomposed during the reaction without the formation of **7**. This problem could be overcome using phenyltriolborate (**8**)[10] instead of phenylboronic acid, and the desired **7** was obtained in 92% yield. Moreover, trisubstituted fluoroalkenes having three different substituents were also synthesized. Thus, the Sonogashira reaction of **2f** with 1-hexyne, and Suzuki–Miyaura coupling of **2j** with **8** afforded the corresponding trisubstituted fluoroalkenes (**9**) and (**10**) stereoselectively (Scheme 4).

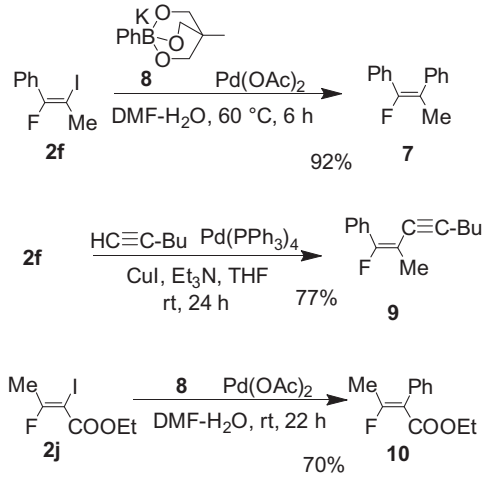
Table 2
Iodofluorination reaction of alkynes using IF_5-pyridine-HF and hydroquinone[a]

Entry	Alkyne	Reaction time (h)	Product	Yield[b] (%)
1	$C_{10}H_{21}C{\equiv}CH$ **1a**	12	$C_{10}H_{21}$ I F H **2a**	65 (82)
2	 **1b**	20	 **2b**	(67)
3	$PrC{\equiv}CPr$ **1c**	15	Pr I F Pr **2c**	71 (87)
4	$PhC{\equiv}CH$ **1d**	11	Ph I F H **2d**	(68)
5	$PhC{\equiv}CPh$ **1e**	15	Ph I F Ph **2e**	72 (90)
6	$PhC{\equiv}CMe$ **1f**	12	Ph I F Me **2f**	71 (99)
7	$AcO{-}(CH_2)_9C{\equiv}CH$ **1g**	19	$AcO{-}(CH_2)_9$ I F H **2g**	60 (73)
8	$i\text{-}PrOOC{-}(CH_2)_8C{\equiv}CH$ **1h**	20	$i\text{-}PrOOC(CH_2)_8$ I F H **2h**	60 (72)
9[c]	$PhSC{\equiv}CMe$ **1i**	14	PhS I F Me **2i**	(65)
10[d]	$MeC{\equiv}C\text{-}COOEt$ **1j**	24	Me I F COOEt **2j**	67 (78)
11	$PhC{\equiv}C\text{-}C(=O)\text{-}Me$ **1k**	17	Ph I F COMe **2k**	81 (87)

[a] If otherwise not mentioned, the reaction was carried out at room temperature in CH_2Cl_2 using 2 equiv of IF_5-pyridine-HF and hydroquinone.
[b] Isolated yield based on alkyne used. In parentheses, ^{19}F NMR yield.
[c] 1.2 equiv of IF_5-pyridine-HF and hydroquinone were used.
[d] The reaction was carried out in $(CH_2Cl)_2$ at 60 °C using 4 equiv of IF_5-pyridine-HF and hydroquinone.



Scheme 3.



Scheme 4.

Acknowledgments

We are grateful to prof. Yasunori Yamamoto (Hokkaido University) for his helpful advice on the Suzuki–Miyaura coupling using triolborate, and Daikin industries, Ltd for their donation of IF_5.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.063.

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5. *Typical procedure:* To a CH_2Cl_2 solution (5 mL) of IF_5-pyridine-HF (321 mg, 1 mmol) and 1-dodecyne (83 mg, 0.5 mmol) in a Teflon™ vessel was added hydroquinone (110 mg, 1 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min and at room temperature overnight. The solid materials was removed by filtration through a celite, and the filtrate was washed with aqueous $NaHCO_3$, and aqueous $Na_2S_2O_3$, successively. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel, hexane) gave **2a** in 65% yield (101 mg, 0.33 mmol). ^{19}F NMR yield was obtained using fluorobenzene as an internal standard. IR (neat) 2925, 1651, 1086 cm^{-1}; ^1H NMR (400 MHz) δ 5.66 (d, J = 17.6 Hz, 1H), 2.54–2.45 (m, 2H), 1.57–1.54 (m, 2H), 1.27 (br s, 14H), 0.88 (t, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz) δ −82.15 to 82.32 (m, 1F) [lit.[6] −82.25 (dt, J = 23.0, J = 17.7 Hz, 1F)]; ^{13}C NMR (100 MHz) δ 164.6 (d, $^1J_{C-F}$ = 265.4 Hz), 55.0 (d, $^2J_{C-F}$ = 40.2 Hz), 32.2, 31.3 (d, $^2J_{C-F}$ = 25.8 Hz), 30.0, 29.9, 29.7, 29.6, 29.1, 26.1, 23.0, 14.5.
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