Tetrahedron Letters 55 (2014) 3750–3752

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Simple and convenient synthesis of fluoroalkenes via direct coupling of alcohols, alkynes and fluoroboric acid under metal-free conditions

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ARTICLE INFO

Article history:
Received 10 February 2014
Revised 8 May 2014
Accepted 15 May 2014
Available online 21 May 2014

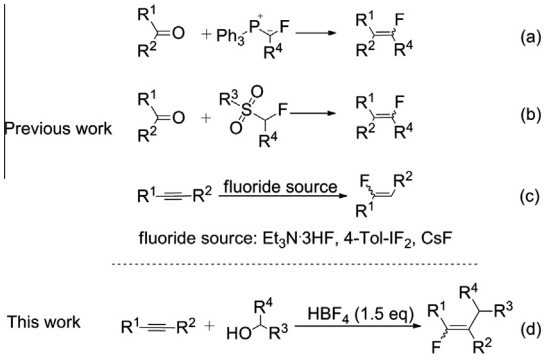
Keywords:
Fluoroalkenes
Alkynes
Alcohols
Fluoroboric acid
Metal-free

ABSTRACT

A novel and convenient method for the synthesis of fluoroalkenes from alkynes, alcohols and fluoroboric acid has been developed under mild conditions. The present protocol provides an attractive approach to access various fluoroalkenes from simple and commercially available starting materials without any metal catalyst, ligand or additive.

Organofluorine compounds play a significant role in pharmaceutical, agrochemical and material sciences, because the introduction of fluorine atom into organic compounds can significantly change their physicochemical properties.[1] Among the various fluorinated motifs, fluoroalkenes have attracted special attention because of their pharmacological properties such as anti-diabetic,[2] antiviral,[3] antibacterial[4] and anticancer[5] activity. For example, (2*S*,3*S*)-3-(3-(2-chloro-4-(ethoxysulfinyl)phenyl)-1,2,4-oxadiazol-5-yl)-1-cyclopentylidene-1-fluorobutan-2-aminium[2a] shows inhibitory activity of dipeptidylpeptidase IV (DPP-4) and (2*E*,4*E*,6*E*)-6-fluoro-7-(5,5,8,8-tetramethyl-3-propoxy-5,6,7,8-tetrahydronaphthalen-2-yl)octa-2,4,6-trienoic acid[2b] can activate retinoid X receptor, both of which have potential therapeutic application in type 2 diabetes; *N*-((*Z*)-7-fluoro-8-mercaptooct-6-enyl)benzamide[5] can be used as a potent inhibitor of histone deacetylases.

In light of the importance of fluoroalkenes, many efforts have been devoted towards the synthesis of these moieties.[6–11] Generally, the strategies for the preparation of fluoroalkenes are mostly based on Wittig reaction (Scheme 1(a))[6] and Julia olefination (Scheme 1(b)),[7] in which the preformed fluorinated phosphonium salts and fluorinated sulfones are used as fluoride sources. Recently, the direct fluorination of alkynes with $Et_3N{\cdot}3HF$, 4-Tol-IF_2, CsF or other fluoride sources[11] has become a powerful tool for the construction of fluoroalkenes (Scheme 1(c)). Nevertheless, most of these methods suffer from limitations such as costliness, requiring metal catalysts or unavailability of starting materials. Therefore, there is still a great demand for the development of more convenient and efficient methodologies to access fluoroalkenes. Here, we wish to report a simple and convenient method for the synthesis of various fluoroalkenes from alkynes, alcohols and fluoroboric acid under mild and metal-free conditions (Scheme 1(d)).



Scheme 1. Methods for the preparation of fluoroalkenes.

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http://dx.doi.org/10.1016/j.tetlet.2014.05.069
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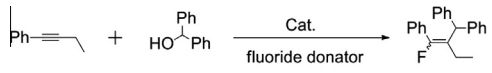
Table 1
Screening of the reaction conditions[a]



1a 2a 3a

Entry	Catalyst	Fluoride donator	Solvent	Yield[b] (%)
1	FeF_3	TBAF, NFSI, selectfluor, KF, CsF, LiF, TEA·3HF	DBE	0
2	FeF_3	HF	DBE	35
3	FeF_3	HBF_4	DBE	58
4	InF_3	HBF_4	DBE	60
5	$Cu(OTf)_2$	HBF_4	DBE	56
6	$Sc(OTf)_3$	HBF_4	DBE	56
7	$Pd(OAc)_2$	HBF_4	DBE	51
8	$AgNO_3$	HBF_4	DBE	51
9	None	HBF_4	DBE	63
10	None	HBF_4	DBE	44[c]
11	None	HBF_4	DBE	66[d]
12	None	HBF_4	DBE	59[e]
13	None	HBF_4	DBE	66[f]
14	None	HBF_4	DBE	18[g]
15	None	HBF_4	DBE	8[h]
16	None	HBF_4	DCE	59
17	None	HBF_4	DME	0
18	None	HBF_4	THF	0
19	None	HBF_4	CH_3CN	0
20	None	HBF_4	Cyclohexane	18

TBAF = tetra-*n*-butyl ammonium fluoride, NFSI = N-fluorobisbenzenesulfonimide, selectfluor = *N*-fluoro-*N*′-(chloromethyl)-triethylenediamine bis(tetrafluoroborate), TEA·3HF = triethylamine trihydrofluoride.

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), catalyst (5 mol %), fluoride donator (0.75 mmol), solvent (2 mL), 10 h, 55 °C.

[b] Isolated yields of the *E*:*Z* mixtures.

[c] HBF_4 (0.5 mmol).

[d] HBF_4 (1.0 mmol).

[e] Activated molecular sieves (4 Å) (500 mg).

[f] Anhydrous $MgSO_4$ (5.0 mmol).

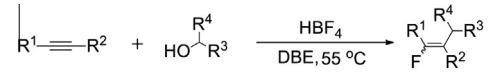
[g] 2,6-Lutidine (0.5 mmol).

[h] 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.5 mmol).

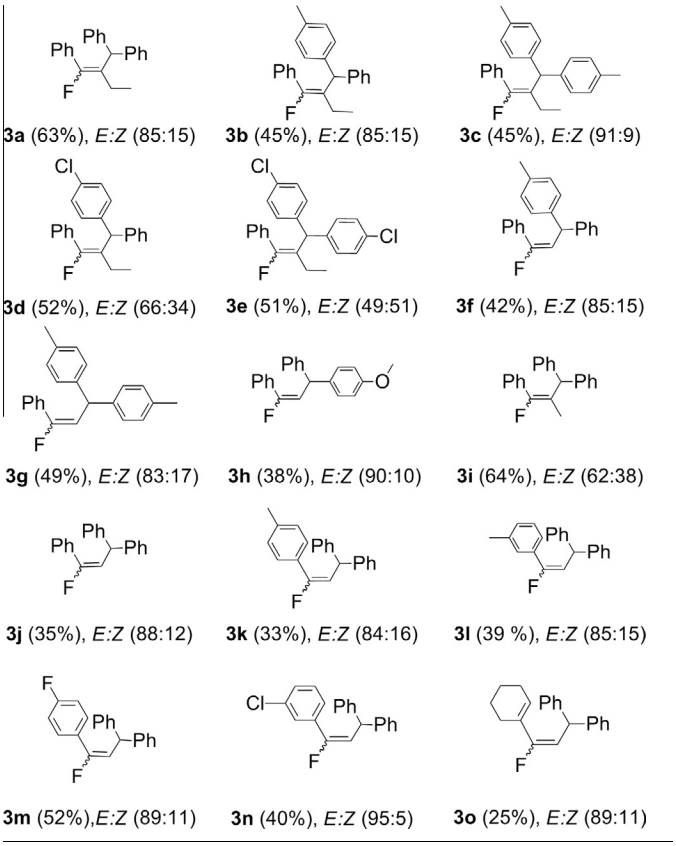
Initially, the activities of various fluoride sources were examined by using a model reaction of 1-phenyl-1-dutyne **1a** and diphenylmethanol **2a** with catalytic amount of FeF_3 in 1,2-dibromoethane (DBE) at 55 °C (Table 1, entries 1–3). Among these fluoride sources screened, only HBF_4 and HF were able to afford the desired product **3a** in 58% and 35% yields, respectively. Further investigation showed that the employment of other metal catalysts such as InF_3, $Cu(OTf)_2$, $Pd(OAc)_2$, $Sc(OTf)_3$ and $AgNO_3$ failed to improve the reaction efficiency (Table 1, entries 4–8). A 63% yield of **3a** was obtained when HBF_4 (1.5 equiv) was solely used and an increase of the amount of HBF_4 (2 equiv) or addition of desiccating agents did not obviously improve the reaction (Table 1, entries 9–13). However, the yield was sharply decreased in the presence of bulky bases, indicated that proton acid might be critical to this transformation (Table 1, entries 14–15). The screening of a range of solvents showed the reactions performed in halogenated solvents such as DBE and 1,2-dichloroethane (DCE) were significantly better than those in non-halogenated solvents THF, DME, CH_3CN and cyclohexane, and DBE was found to be the optimal reaction medium (Table 1, entry 9 and entries 16–20).

With the optimal reaction conditions in hand, the scope and limitations of the reaction were investigated and the results are shown in Table 2. In general, benzhydrol and its derivatives with electron-donating or electron-withdrawing groups on the aryl rings were all suitable for this transformation, and the corresponding products were obtained in good yields (**3a**–**3h**). With respect to alkynes, both aliphatic and aromatic alkynes were tolerable as the

Table 2
Results for the reaction of alkynes with various alcohols[a,b]

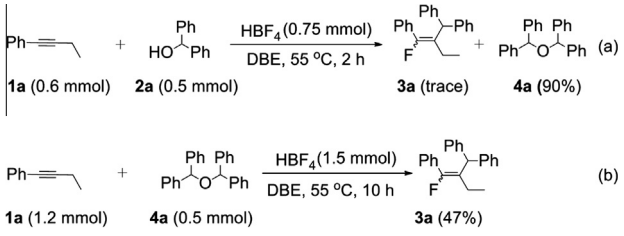


1 2 3

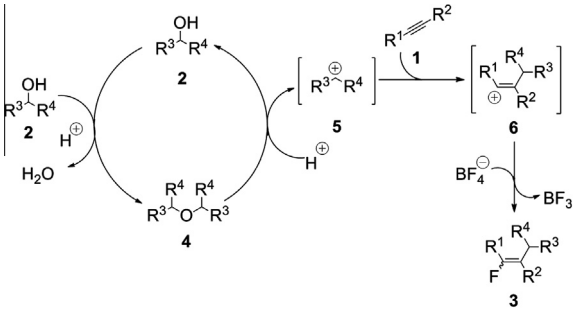


[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), HBF_4 (0.75 mmol), DBE (2 mL), 55 °C, air, 8–10 h.

[b] Isolated yields of the *E*:*Z* mixtures; the *E*:*Z* ratio was determined by ^1H NMR.



Scheme 2. Control experiments.



Scheme 3. Postulated reaction pathway.

coupling partners (**3i**–**3o**). Notably, internal aromatic alkynes (**3a**, **3i**) were more reactive than terminal alkynes (**3j**–**3o**) in the present reaction system when benzhydrol was used. The configuration of *E*-**3j** was confirmed by X-ray crystallographic analysis.[12]

In order to obtain clear mechanistic insights into this reaction, several control experiments were performed. When 1-phenyl-1-dutyne **1a** and diphenylmethanol **2a** were subjected to the standard conditions for 2 h, a trace amount of **3a** and 90% yield of dimeric ether **4a** were obtained (Scheme 2(a)). Furthermore, a 47% yield of the desired product **3a** could be obtained when the reaction of **4a** and **1a** was conducted under the standard conditions for 10 h (Scheme 2(b)). The above results suggested that dimeric ether **4** might be an intermediate in this reaction system.

Based on the above results and previous studies,[13] a postulated reaction pathway of this reaction is illustrated in Scheme 3. Firstly, alcohol **2** was activated by proton acid and attacked by another alcohol to form the dimeric ether **4**. Subsequently, the ether might combine with hydrogen ion to generate alcohol **2** and carbocation intermediate **5**, the latter then attacked alkyne **1** to form a vinyl cation **6**. Finally, the vinyl cation **6** was fluorinated by BF_4^- to deliver the desired product **3**.

In summary, we have developed a simple and convenient method for the synthesis of monofluoroalkenes from alkynes, alcohols and fluoroboric acid. The present protocol, which utilizes simple and commercially available starting materials and metal-catalyst-free conditions, provides an attractive approach to various fluoroalkenes. Further studies on the scope and application of this reaction are underway.

Acknowledgment

We thank the National Natural Science Foundation of China (21172213) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.05.069.

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12. The structure of *E*-**3j** was confirmed by X-ray crystallography. Deposit number of this compound from Crystallographic Data Centre is 921081. Copies of the data can be obtained free of charge on application to CCDC, 12, Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.
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