



# Synthesis of fluorinated triazole and isoxazole derivatives by electrochemical fluorination



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## ARTICLE INFO

### Article history:

Received 12 March 2016  
Received in revised form 5 July 2016  
Accepted 5 July 2016  
Available online 6 July 2016

### Keywords:

Electrochemical fluorination  
 $\alpha$ -Fluoroacethylene  
Triazole  
Isoxazole  
Click chemistry

## ABSTRACT

Partially fluorinated triazole derivatives were synthesized through anodic fluorination of alkynes having arylthio group and following Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) with benzyl azide. The other route toward the fluorinated triazoles, namely the anodic fluorination of triazole derivatives once prepared by advanced CuAAC of the alkyne and azide above was also investigated. It was shown that these two routes are mutually complementary methodology for the synthesis of new mono- and difluoromethyltriazole derivatives. Furthermore, Cu(I)-catalyzed isoxazole synthesis from fluorinated alkynes and imidoyl chloride was demonstrated.

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## 1. Introduction

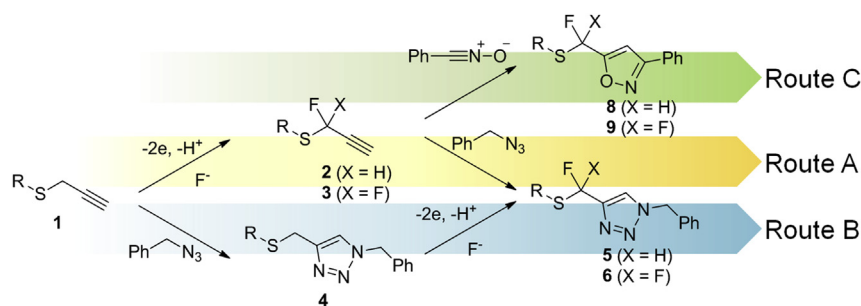
Organofluorine compounds are highly useful in various fields such as pharmaceutical chemistry and material science due to their unique chemical, physical, and biological properties.<sup>1</sup> Since almost all organofluorine compounds are not naturally occurring, they must be synthesized according to appropriate molecular design. Recent development of synthetic technique of organofluorine compounds is very noticeable. Among them, the anodic partial fluorination proceeds through electrochemical oxidation of organic compounds and following fluorination with fluoride ion used as a supporting electrolyte. This electrochemical method does not require any hazardous reagents, it is therefore regarded as a green method.<sup>2</sup> We have demonstrated the synthesis of partially fluorinated compounds having various functional groups for bioactive applications and synthetic building blocks so far.<sup>3</sup> Previously, we reported the first electrochemical synthesis of a series of fluorinated terminal alkynes,<sup>4</sup> which are potentially applicable as synthetic building blocks in organic synthesis. One promising reaction using terminal alkyne is Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC). This so-called click chemistry can produce a 1,4-disubstituted triazole derivative in excellent yield without byproduct under mild conditions.<sup>5</sup> For example, Jørgensen and his co-workers reported the synthesis of fluorinated triazoles by CuAAC of propargyl fluoride and azide derivative.<sup>6</sup> Recently,

Médebielle and his co-workers reported the synthesis and antiviral properties of difluoromethylbenzoxazole pyrimidine thioether derivatives as non-nucleoside HIV-1 reverse transcriptase inhibitors.<sup>7</sup> In consideration to these facts, the combination of anodic fluorination and CuAAC is of interest to develop versatile organofluorine compounds having a triazole moiety. Our goal in this study is to prepare a variety of fluorinated triazole derivatives from terminal alkyne having arylthio group and benzyl azide through two pathways, i.e., anodic fluorination of alkynes, followed by CuAAC (Route A) and anodic fluorination of triazoles once prepared by CuAAC (Route B) as shown in [Scheme 1](#). In addition, another kind of click chemistry, the Cu(I)-catalyzed isoxazole synthesis<sup>8</sup> was also investigated using fluorinated alkynes (Route C).

## 2. Results and discussion

According to [Scheme 1](#), Route A, the electrochemical partial fluorination of alkyne derivative **1** was carried out under optimized conditions with a passage of constant current between Pt anode and Pt cathode ([Table 1](#)).<sup>4</sup> The fluorination of the starting materials takes place through the anodic oxidation at the arylthio group, followed by deprotonation and subsequent fluorination at its  $\alpha$ -position. In general, sulfides having an electron-withdrawing group undergo selective anodic fluorination with good efficiencies due to the stabilization of once fluorinated products.<sup>9</sup> We reported previously that an acetylene moiety attached to the  $\alpha$ -carbon can act as an electron-withdrawing group such as esters and nitriles evidenced by electrochemical measurements.<sup>4</sup> In the case of

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**Scheme 1.** Routes toward triazoles and isoxazoles with fluoromethylsulfonyl group.

fluorination of **1a** and **1b**, mono-fluorinated products (**2a** and **2b**) and di-fluorinated products (**3a** and **3b**) were obtained selectively depending on the supporting HF salt used and electricity. The free triethylamine contained in  $Et_3N-3HF$  effectively acted as a base at the deprotonation step for difluorination even though the sacrificial

oxidation of triethylamine itself also occurred. Other mono-fluorinated products (**2c–2g**) were also successfully obtained under optimal conditions including the choice of supporting HF salts. These fluorinated alkynes were readily available for CuAAC. As indicated in our previous study, mono-fluorinated products **2a** and

**Table 1**  
Electrochemical fluorination of alkyne derivative 1

Entry	Alkyne 1	Supporting salt	Electricity (F/mol)	Product	Yield (%) <sup>a</sup>
1		$Et_3N-5HF$	4.0		77 <sup>b,c</sup>
2		$Et_3N-3HF$	8.0		70 <sup>c</sup>
3		$Et_3N-5HF$	4.0		35
4		$Et_3N-3HF$	8.0		66 <sup>c</sup>
5		$Et_3N-3HF$	12.0		55 <sup>d</sup>
6		$Et_4NF-3HF$	10.0		20 <sup>d</sup>
7		$Et_3N-3HF$	12.0		30 <sup>d</sup>
8		$Et_4NF-4HF$	7.0		38
9		$Et_4NF-4HF$	8.0		42

<sup>a</sup> Isolated yield.

<sup>b</sup> Determined by  $^{19}F$  NMR.

<sup>c</sup> Ref. 4a.

<sup>d</sup> Ref. 4b.

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