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Fluorocyclization of *N*-Propargylamides to Oxazoles by Electrochemically Generated $ArIF_2$

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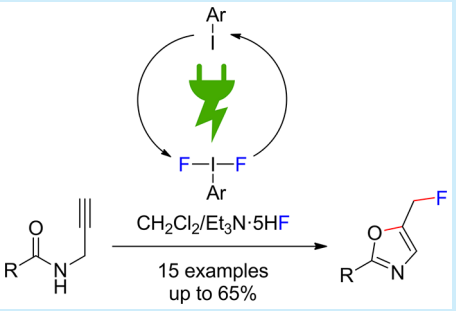
Supporting Information

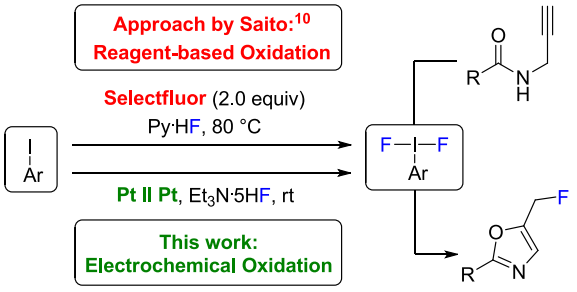
ABSTRACT: A sustainable synthesis of 5-fluoromethyl-2-oxazoles by use of electrochemistry has been demonstrated. Hypervalent $ArIF_2$ is generated by direct electrochemical oxidation of iodoarene ArI in $Et_3N{\cdot}5HF$ and mediates the fluorocyclization of *N*-propargylamides to 5-fluoromethyl-2-oxazoles. The stoichiometry in ArI turned out to be a key parameter in controlling the product selectivity. This electrochemical protocol provides access to fluorinated oxazoles starting from simply available *N*-propargylamides with yields up to 65% and offers a green alternative over conventional reagent-based approaches.



Oxazoles and oxazolines occur ubiquitously in structurally diverse natural products and pharmaceutically active ingredients.[1] For this reason, oxazoles are an important scaffold in medicinal chemistry. Drugs based on oxazoles have a wide range of biological activities.[2] Additionally, oxazole derivatives are important intermediates in organic synthesis and ligands for metal catalysis.[3] Thus, the development of efficient synthetic methodologies to oxazoles is very desirable. Various strategies for the construction of oxazoles, particularly cyclization reactions of *N*-propargylamides, have been developed either by metal-catalyzed[4] or iodine-mediated[5] activation of the triple bond. However, concerning bioactive compounds the substitution of hydrogen by fluorine such as in methyl groups as a bioisostere has been become a standard tool in molecular editing of drugs.[6] The incorporation of fluorine can modulate the metabolism of a drug and increase its potency. Thus, the deoxyfluorination reaction is a widely used approach to heterocycles containing a fluoromethyl group.[7] Typically used reagents are SF_4, XeF_2, Selectfluor, $(PhSO_2)_2NF$, or Et_2NSF_3 (DAST).[8] These reagents prove to be very powerful but have severe drawbacks: They are truly hazardous, difficult to handle, and mostly expensive. Comparatively, the use of hypervalent iodine reagents in fluorocyclization reactions provides a less dangerous and efficient path to fluorinated heterocycles.[9] Saito[10] and Gilmour[11] established straightforward strategies to fluorinated oxazoles and oxazolines by fluorocyclization of the respective *N*-allyl- or *N*-propargylamides mediated by hypervalent difluoroiodoarene $ArIF_2$ (Scheme 1). This way, the fluorocyclization provides the synthesis of the heterocycle and the fluorination in only one step. Still, these methods involve excess Selectfluor as terminal oxidant for the generation of $ArIF_2$. The use of reagent-based oxidizers leads to low atom economy and production of a lot of reagent waste.

In contrast, the electrochemical generation of iodine(III) species is an attractive alternative because electric current is used as a green oxidant and unstable intermediates are generated in situ.[12] This way, iodoarene ArI is directly oxidized to the hypervalent $ArIF_2$ at the anode.[13] Electrochemical reactions have many advantages over traditional, reagent-based syntheses. By means of the electroorganic synthesis, toxic and expensive chemical oxidizers can be replaced by electric current as an inexpensive, renewable, and inherently safe reagent.[14] It is a powerful tool to increase atom economy by reducing the amount of reagent waste on the side of oxidant using traceless electric current. Thus, organic electrochemistry attracted much attention as a green synthetic approach.[15] Recently, we demonstrated the electrochemical synthesis of 5-fluoromethyl-2-oxazolines.[16] However, an electrochemical approach to fluorinated 2-oxazoles is not described yet in the literature. Here, we present the synthesis of 5-fluoromethyl-2-oxazoles via fluorocyclization of *N*-propargylamides by electrochemically generated $ArIF_2$ for the first time (see the postulated mechanism in the Supporting Information). The electrolysis was conducted

Scheme 1. Conventionally vs Electrochemically Generated $ArIF_2$ for Fluorocyclization of *N*-Propargylamides



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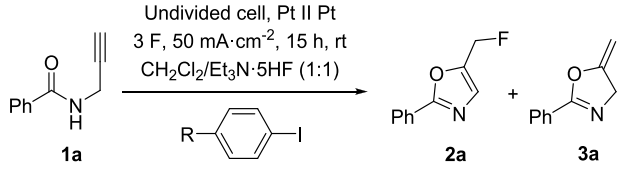
in an undivided cell equipped with a simple two-electrode arrangement using constant current conditions. The electrolytic reactions were performed at platinum electrodes in a mixture (1:1) of dichloromethane and triethylamine pentahydrofluoride ($Et_3N{\cdot}5HF$) with a substrate concentration of 0.1 mol·L^{-1} and stoichiometrically added PhI. Evaluation of the reaction conditions was conducted within screening experiments in small Teflon cells.[17] Thus, *N*-propargylbenzamide (**1a**) served as test substrate and the conversion to 5-fluoromethyl-2-phenyloxazole (**2a**) as a benchmark reaction for the parameter screening (Table 1). For optimization experiments the yield was determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

Table 1. Parameter Screening for Optimizing the Electrochemical Fluorocyclization of Substrate 1a to Oxazole 2a[a]



entry	iodoarene (R =)	iodoarene (equiv)	**2a**[b] (%)	**3a**[b] (%)
1	H	1.0	32	16
2[c]	H	1.0	0	0
3[d]	H	1.0	6	33
4[e]			0	7
5	H	2.0	51	3
6[f]	H	2.0	41	4
7	COMe	2.0	16	30
8	*t*-Bu	2.0	54	0
9	**Me**	**2.0**	**55 (53)**[g]	**0**
10[h]	Me	2.0	30	0
11[i]	Me	2.0	55	0
12[j]	H	2.0	45	0

[a]Standard reaction conditions: undivided cell, Pt electrodes, *N*-propargylbenzamide (0.5 mmol), CH_2Cl_2 (2.5 mL), $Et_3N{\cdot}5HF$ (2.5 mL), 3 F, 50 mA·cm^{-2}, 15 h, rt. [b]Determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard. [c]$CH_2Cl_2/Et_3N{\cdot}3HF$ (1:1). [d]CH_2Cl_2/Py·9HF (1:1). [e]No mediator. [f]4 F. [g]Isolated yield. [h]BDD as anode. [i]Glassy carbon as anode. [j]Ex-cell experiment.

The control experiment without current flow (0 F, no conversion of starting material) indicated, that the anodic oxidation of the iodoarene based mediator is crucial for the conversion of **1a**. Under standard reaction conditions with iodobenzene (1.0 equiv), applied charge of 3 F, current density of 50 mA·cm^{-2}, and reaction time (electrolysis + additional stirring time) of 15 h in $CH_2Cl_2/Et_3N{\cdot}5HF$ (1:1), the desired product **2a** was obtained in 32% yield (Table 1, entry 1). The reaction time exceeded the electrolysis time since after electrolysis starting material **1a** was not fully converted. Prolonging the stirring time increased the yield of **2a** but with more than 15 h no further improvement was observed. Thus, the fluorocyclization of **1a** takes longer than the anodic generation of $ArIF_2$. The nonfluorinated methylene oxazoline **3a** was identified as a byproduct. Therefore, we initially explored the electrolyte system with different ratios and amine−HF sources. Neither with higher amounts of $Et_3N{\cdot}5HF$ ($CH_2Cl_2/Et_3N{\cdot}5HF$, 1:3) nor with lower amounts (3:1) could the yield of **2a** be increased. In $Et_3N{\cdot}3HF$, no conversion of starting material was observed (Table 1, entry 2). The use of Py·9HF had an adverse effect on the formation of **2a** but promoted the side reaction to byproduct **3a** (Table 1, entry 3). In the absence of PhI no formation of oxazole **2a** was observed (Table 1, entry 4), which confirms the unique role of the iodoarene mediator. Nevertheless, small amounts of byproduct **3a** were obtained. Consequently, the side reaction seemed to be independent of the mediator. As the reaction was conducted with 2.0 equiv of iodobenzene, the yield of oxazole **2a** increased substantially (51%), while the formation of byproduct **3a** was almost fully suppressed (Table 1, entry 5). The stoichiometry in iodobenzene turned out to be a key parameter controlling the product selectivity. Thus, we further investigated the effect of the PhI stoichiometry on this electrochemical reaction (Figure 1).

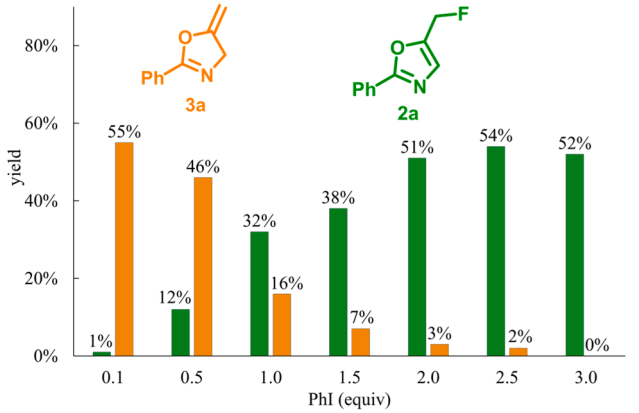


Figure 1. Product selectivity by PhI stoichiometry: fluoromethyl oxazole **2a** vs methylene oxazoline **3a**.

Under otherwise identical conditions, we studied the product formation with different equivalents of iodobenzene (0.1−3.0 equiv). Below stoichiometric amount of PhI a clear trend toward the methylene oxazoline **3a** could be observed. With 0.1 equiv of PhI, **3a** was obtained in 55%, whereas fluoromethyl oxazole **2a** was found in traces only. Although in the control experiment without iodobenzene (Table 1, entry 4) little formation of the methylene oxazoline **3a** was observed, catalytic amounts of PhI seem to prevent electrochemical degradation and allow **3a** to accumulate. In contrast, overstoichiometric amounts of PhI promote the formation of oxazole **2a** and repress the side reaction progressively. Yet, more than 2.0 equiv of PhI did not ameliorate the yield of **2a**. Based on these findings, the following experiments were conducted with 2.0 equiv of iodobenzene. The ratios of product to side product dependent on the PhI stoichiometry were further explored with electronic substitution on the aryl moiety (see the Supporting Information).

In final optimization experiments, different current densities and applied charge as well as different iodoarene mediators and anode materials were tested. Both lower (10 mA/cm^2) and higher (60 mA/cm^2) current density decreased the yield of **2a** (40% and 44%). A higher amount of applied charge also caused lower yield (Table 1, entry 6). Using 4-acetylphenyl iodide as mediator diminished the yield of **2a** and led to more byproduct **3a** (Table 1, entry 7). The 4-*tert*-butyl- and 4-methyl-substituted mediators were more efficient (Table 1, entries 8 and 9) due to lower oxidation potential. The yield dropped with boron-doped diamond (BDD) as anode material[18] (Table 1, entry 10). However, glassy carbon[19] achieved a good yield (Table 1, entry 11) but did not surpass previous observations. Concerning the

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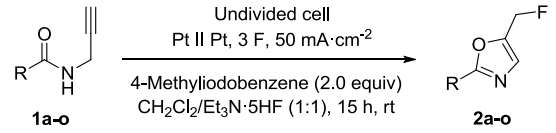
mass balance, just 55% of the starting material **1a** was converted to product **2a**. Apart from uncharacterized byproducts the electrochemical degradation and oligomerization of substrate was the dominant side reaction. Therefore, the ex-cell procedure, whereby substrate is added after anodic generation of $ArIF_2$, proved to be a powerful tool for indirect electrolysis in order to avoid such side reactions.[16] The ex-cell experiment afforded a slightly lower yield of product **2a** (Table 1, entry 12 vs 5), but 35% of **1a** was recovered (82% brsm). Within the in-cell experiment no starting material was recovered, but higher yield of **2a** was obtained due to in situ generation of unstable $ArIF_2$.

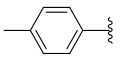
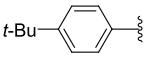
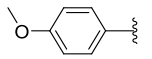
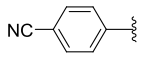
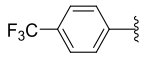
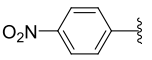
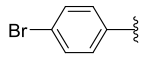
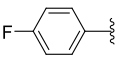
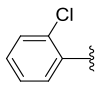
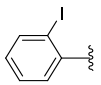
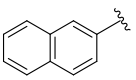
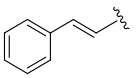
Still, the optimized reaction conditions in Table 1, entry 9, exceeded the conventional approach by Saito.[10] With the developed method, we explored the scope of the electrochemical fluorocyclization of *N*-propargylamides varying the substitution pattern at the aryl moiety (Table 2). The unsubstituted substrate **1a** gave 5-fluoromethyl-2-phenyloxazole (**2a**) in 53% yield (Table 2, entry 1). The electrosynthesis of compound **2a** was also conducted on a 2.5 mmol scale with 49% isolated yield. In comparison to the unsubstituted scaffold **2a**, the methyl- and *tert*-butyl-substituted derivatives **2b** and **2c** were obtained in lower yields (Table 2, entries 2 and 3). As the electron-rich aryl moiety led to lower yields (**2d** vs **2a**), electron-poor derivatives afforded the respective oxazoles in higher yields (**2e** vs **2a** and **2f** vs **2b**). Although methoxy derivative **2d** was obtained in only 37% yield, with the conventional method that transformation of **1d** was not even possible.[10] The nitro-substituted substrate **1g** gave 47% of product **2g**. Due to possible cathodic side reaction of the nitro group this reaction was also conducted in an ex-cell experiment. Thus, fluoromethyloxazole **2g** was obtained in 59% yield (Table 2, entry 7). Halogenated substrates **1h**−**k** with different substitution patterns and halogen atoms gave the desired products **2h**−**k** in 38−49% yields (Table 2, entries 8−11). The thienyl and furanyl oxazoles **2l** and **2m** were obtained in low yield even if performing the ex-cell procedure (Table 2, entry 12 and 13). Naphthyl oxazole **2n** was obtained in 32% (Table 2, entry 14). The cinnamamide **1o** gave styryl oxazole **2o** in 37% yield (Table 2, entry 15).

Beyond variation of the substitution pattern at the aryl moiety, also α-amide-substituted *N*-propargylbenzamides and non-aromatic derivatives were tested but did not undergo fluorocyclization. A substituent R ≠ H in the α position to the nitrogen might slow down or even inhibit isomerization to the oxazole. In the crude NMR spectra obtained from the nonaromatic derivatives mainly starting material was found. *N*-Propargylbenzamides with a substitution at the terminal position of the alkyne gave 4,5-dihydrooxazolyl ketones instead of the expected fluorinated oxazoles. Those nonsuccessful substrates are reported with more detailed data in the Supporting Information.

To conclude, the synthesis of 5-fluoromethyl-2-oxazoles by $ArIF_2$-mediated fluorocyclization of *N*-propargylamides with electric current as green oxidant has been established. This electrosynthesis provides access to fluorinated oxazoles, for example, as attractive building blocks in medicinal chemistry. The electrochemical protocol is applicable to a variety of substrates affording oxazoles involving a fluoromethyl group with yields up to 65%. In comparison to the reagent-based path,[10] this electrochemical approach permits the conversion of even electron-rich *N*-propargylamides for the first time. The simple setup using undivided cells in a two-electrode arrangement with no reagent-based oxidants needed is sustainable and inherently safe, enabling easy scale up.

Table 2. Synthesis of 5-Fluoromethyl-2-oxazole Derivatives by Electrochemical Fluorocyclization[a]



entry	2	R	yield (%)
1	2a		53
2	2b		44
3	2c		40 (39)
4	2d		37
5	2e		65
6	2f		51
7	2g		47 (59)
8	2h		49
9	2i		37 (42)
10	2j		38 (45)
11	2k		29 (38)
12	2l		21 (17)
13	2m		0 (14)
14	2n		28 (32)
15	2o		20 (37)

[a]Standard reaction conditions: undivided cell, Pt electrodes, *N*-propargylbenzamide (0.5 mmol), 4-methyliodobenzene (2.0 equiv), CH_2Cl_2 (2.5 mL), $Et_3N{\cdot}5HF$ (2.5 mL), 3 F, 50 mA·cm^{-2}, 15 h, rt. Isolated yields, ex-cell studies in parentheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02884.

General experimental procedure, synthetic details, and characterization including NMR and MS spectra for all products, byproducts. and precursors (PDF)

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Notes

The authors declare no competing financial interest.

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