Para-Fluorination of Anilides Using Electrochemically Generated Hypervalent Iodoarenes

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Abstract: The para-selective fluorination reaction of anilides using electrochemically generated hypervalent ArIF₂ is reported, with Et₃N·5HF serving as fluoride source and as supporting electrolyte. This electrochemical reaction is characterized by a simple set-up, easy scalability and affords a broad variety of fluorinated anilides from easily accessible anilides in good yields up to 86%.

Introduction

In the field of pharmaceuticals and agro chemicals, the installation of fluoro substituents into an aryl moiety can be used to modify its metabolic stability and therefore its bioactivity.[1] Over the recent years, more fluorine containing drugs have been approved, highlighting the importance of the substance class.[2] Therefore, acquiring elegant reaction pathways to introduce fluorine, especially late stage functionalizations, are of high interest in current research.[3]

Fluoroarenes like the anilide Picolinafen (1) and the benzoxazinone Flumioxazin (Scheme 1) are commonly used as herbicides for wheat protection.[4] One of the first known regioselective reactions for the preparation of fluorinated arenes are the Balz–Schiemann and the halogen exchange (Halex) reaction (Scheme 2).[5] While the Halex reaction of electron deficient chloroarenes is nowadays a well-established method often used in many technical processes for the synthesis of ary fluoride, the Balz–Schiemann reaction could not exceed preparations on lab scale, due to the challenging handling of diazonium salts. Other reagent-based pathways towards fluoroarenes use elemental fluorine or XeF₂, which are difficult to handle due to their high and not easy to control reactivity.[6] Alternative approaches employ metal-catalyzed reactions by using stannanes or boronic acids as leaving groups in combination with an “F⁺”-source such as Selectfluor® or 1-fluoro-2,4,6-trimethylpyridinium triflate for the installation of fluoro substituents at the arene moiety.[7] Although these methods exhibit excellent regioselectivity and yield, they suffer from the need of complex pre-functionalization and the use of leaving moieties forming toxic waste. These aspects lower the atom economy, and the use of transition metals is questionable due to sustainability and should be avoided in pharmaceutical synthesis.[8]

Another sophisticated approach for the functionalization of arenes is by the means of hypervalent iodine reagents,[9] which offer unique reactivities and safe handling at ambient temperatures.[10] They are frequently used as oxidizing reagents in a broad field of synthesis, often replacing toxic transition metals.[21] In 2015, Buckingham et al. used these I(III)-reagents for the oxidative fluorination of sulfonamides, employing PIDA as oxidizing reagent in the presence of Olah’s reagent (HF-pyridine).[12] However, a tert-butyl substituent in para-position as leaving moiety was crucial for a successful conversion. In
contrast to that, Li et al. were able to conduct a \textit{para}-selective fluorination of anilides using bis(tert-butylcarbonyloxy)-iodo-benzene (Ph(\text{OPiv})_2) in combination with HF-pyridine as fluoride source on various substrates without the use of leaving groups in good yields.\textsuperscript{[13]} Nevertheless, applying more commonly used hypervalent iodine reagents as PIFA or PIDA, a significant drop in yield was observed due to the competing acetoxylisation of the corresponding amide. Additionally, their method was limited to the fluorination of benzanilides.

In terms of sustainability, it is highly desirable to limit the use of external oxidants and reagent-based waste to a minimum. For these reasons, the use of electric current as a reactivity to valuable products, attracted a lot of attention over the past decades. Its innovative use of external oxidants and reagent-based waste to a chemically side reactions,\textsuperscript{[24]} an ex-cell approach might be an elegant way to prevent the substrate from being electrochemically depleted. Indeed, by adding the substrate after the electrolysis of the iodoarene took place, a drastic increase in yield to 86\% of 4a could be achieved (Table 2, entry 1). Consequently, the following experiments were conducted in the same ex-cell manner. Varying the amount of 4-iodotoluene to more or less than the previous used 1.5 equivalents did not result in an enhanced yield (Table 2, entries 2–3). Additionally, carbon-based electrode materials like graphite or boron-doped diamond (BDD)\textsuperscript{[20]} electrodes were investigated, but these resulted in lower yields (Table 2, entries 4–5). Therefore, platinum electrodes remained the material of choice.

### Results and Discussion

On the basis of our previously published parameters on the electrochemical formation of difluoriodotoluene for the synthesis of heterocycles,\textsuperscript{[21]} we started our optimization studies. The screening experiments were conducted in small 5 mL undivided Teflon cells using constant current conditions and platinum sheet electrodes.\textsuperscript{[32]} The conversion of pivalamide 3a as model substrate to 4-fluoropivalamide (4a) served as benchmark reaction for the optimization of the electrolysis conditions. Various parameters such as the applied charge, current density, electrode material, solvent system, fluoride sources, different protecting groups, and mediators were investigated. The yield of the optimization reactions was determined by \textsuperscript{19}F NMR using 4-fluorotoluene as internal standard (Table 1).

Variation of the fluoride source between Et\textsubscript{3}N-3HF, Et\textsubscript{3}N-5HF, and Py-9HF indicated that Et\textsubscript{3}N-5HF is the most potent system (Table 1, entries 1–3). Notably, no other than the \textit{para}-fluorinated product 4a could be detected by \textsuperscript{19}F NMR, highlighting the outstanding regioselectivity of this reaction. The necessity of the mediator could be elucidated, as an electrolysis without mediator showed only traces of 4a. In contrast to recently published results by Lennox et al., amine-5.6HF mixtures, which proved to be beneficial for iodoaryl mediated reactions\textsuperscript{[23]} gave here a lower yield (Table 1, entry 4). Next, the influence of the amount of Et\textsubscript{3}N-5HF was observed.

| Entry | Solvent/ fluoride source, R= | 4a [%]\textsuperscript{[24]} |
|-------|-----------------------------|-----------------------------|
| 1     | CH\textsubscript{3}Cl + Et\textsubscript{3}N-3HF (4:1), R=Me | 12 |
| 2     | CH\textsubscript{3}Cl + Et\textsubscript{3}N-5HF (4:1), R=Me | 19 |
| 3     | CH\textsubscript{3}Cl + Py-9HF (4:1), R=Me | 3 |
| 4     | CH\textsubscript{3}Cl + amine 5.6HF (4:1), R=Me | 13 |
| 5     | CH\textsubscript{3}CN + Et\textsubscript{3}N-5HF (2:3), R=Me | 30 |
| 6     | CH\textsubscript{3}Cl + Et\textsubscript{3}N-5HF (2:3), R=Me | 35 |
| 7     | CH\textsubscript{3}Cl + Et\textsubscript{3}N-5HF (2:3), R=Me | 45 |
| 8     | CH\textsubscript{3}Cl + Et\textsubscript{3}N-5HF (2:3), R=OMe | 10 |
| 9     | CH\textsubscript{3}Cl + Et\textsubscript{3}N-5HF (2:3), R=Bu | 43 |

[a] Electrolysis conditions: Undivided cell, Pt electrodes, pivalamide (0.5 mmol), 1.5 equiv. mediator (0.75 mmol), reaction volume: 5 mL, $j=20$ mA/cm\textsuperscript{2}, $Q=3.0$ F, r.t. [b] Quantification by \textsuperscript{19}F NMR using 4-fluorotoluene (1.0 equiv.) as internal standard. [c] Mixture of Py-9HF and Et\textsubscript{3}N-3HF.

By using a 3:2 ratio of the ionic liquid in CH\textsubscript{3}Cl, the fluorinated anilide 4a could be obtained in 45\% yield.

Since \textit{para}-unsubstituted anilides are prone to electrochemical side reactions,\textsuperscript{[24]} an ex-cell approach might be an elegant way to prevent the substrate from being electrochemically depleted. Indeed, by adding the substrate after the electrolysis of the iodoarene took place, a drastic increase in yield to 86\% of 4a could be achieved (Table 2, entry 1). Consequently, the following experiments were conducted in the same ex-cell manner. Varying the amount of 4-iodotoluene to more or less than the previous used 1.5 equivalents did not result in an enhanced yield (Table 2, entries 2–3). Additionally, carbon-based electrode materials like graphite or boron-doped diamond (BDD)\textsuperscript{[20]} electrodes were investigated, but these resulted in lower yields (Table 2, entries 4–5). Therefore, platinum electrodes remained the material of choice.

| Entry | Deviation from standard conditions\textsuperscript{[24]} | 4a [%]\textsuperscript{[24]} |
|-------|------------------------------------------------------|-----------------------------|
| 1     | none                                                 | 86 |
| 2     | 2.0 equiv. mediator                                  | 63 |
| 3     | 1.0 equiv. mediator                                  | 60 |
| 4     | Graphite electrodes                                  | 50 |
| 5     | BDD electrodes                                       | 15 |

[a] Reaction conditions: Undivided cell, Pt electrodes, 1.5 equiv. mediator (0.75 mmol), $Q=3.0$ F, $j=50$ mA/cm\textsuperscript{2}, addition of pivalamide 3a (0.5 mmol) after electrolysis, reaction volume: 5 mL, CH\textsubscript{3}Cl + Et\textsubscript{3}N-5HF (2:3), r.t. [b] Quantification by \textsuperscript{19}F NMR using 4-fluorotoluene (1.0 equiv.) as internal standard.
To validate the quantification method, the TolIF₂-mediated fluorination under optimized conditions for the test substrate 3a gave product 4a in 85% isolated yield. An electrolysis of 3a on a 2.5 mmol scale was performed with a yield of 80%, demonstrating the scalability of this conversion. Additionally, it was possible to recover up to 80% of the mediator during work-up process. With this optimized reaction protocol in hand, the scope of this reaction was explored with diverse substituents at the aryl moiety (Scheme 3). In addition to the unsubstituted aniline 3a, several substrates in ortho-position were tested. The o-toluidine-based amide 3b gave the corresponding fluorinated compound 4b in 75% yield. Choosing a sterically demanding group like 3-butyll slightly lowered the yield of 4c to 66%. For amides with a halo substituent (4d–4g) it was found that longer reaction times are required to improve the conversion. This clearly indicates the substituents’ influence on the fluorination rate. The halogen substituted substrates gave moderate yields up to 48% (4d–4g). Surprisingly, the 2-benzoyl-substituted anilide was obtained in 37% yield. In order to investigate the effect of substituents with influence on the electron density of the arene, pivalamides bearing substituents like 2-CN, 2-OMe, 2-NO₂, 2-CO₂Me were subjected to our fluorination protocol. However, only poor yields could be observed for electron-rich amides, whereas the electron-poor amides showed no conversion of the starting materials (see Supporting Information).

In contrast, anilides substituted in meta-position resulted in higher yields than their ortho-substituted analogues. The 3-methyl-pivalamide 4h could be obtained in an excellent yield of 86%. For 3-bromo- and 3-butyll equipped amides 4i and 4j better yields were achieved as well. Furthermore, pivalamides bearing multiple substituents could be successfully converted into their corresponding fluorinated counterpart (Scheme 3, 4i–4j). Even polycyclic aromatic substrates based on naphthalene and quinolone represent good substrates. The products (4o–4q) could be obtained in very good yields and no other regioisomers were detected. Only for the isoquinoline pivalamide 4r, the conversion remained low and a moderate yield of 32% could be obtained, with the amide as lactam, the same observation could be made (Scheme 3, 4s). Surprisingly, the fluorinated benzoxazinones 4t and 4u, which feature as important scaffold for herbicides, were readily formed as well.[4,27] Usually, these structures have to be formed via cyclization reactions with fluorine being introduced beforehand, underlining the broad applicability of our method.

Noteworthy, the benzoxazinone substrates can be made also by an electrochemical route,[24] there is even a report of direct electrochemical fluorination of N-unsubstituted benzoxazinones under constant potential conditions using a divided cell.[29]

A series of control experiments were conducted to gain insights into the reaction’s mechanism. Since no other than the 4-fluoro anilides were detected during optimization reactions, substrates already bearing a para-substituent (Scheme 4a: R=Me/Cl/Ph) were subjected to the fluorination conditions. For the 4-methyl substituted substrates, a benzylic derivatization might be envisioned as observed in previous studies.[10] However, no indication of such conversion was found here. Additionally, N-methylated pivalamide (3v) was tested for a possible fluorination as well. Here a drastic drop in yield to 8% was observed (Scheme 4b), indicating that the amide proton takes a crucial role in the fluorination process. Moreover, the occurrence of a radical reaction can be excluded, since the

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**Scheme 3.** Synthesis of fluorinated anilide derivatives using electrochemically generated ArIF₂. Standard reaction conditions: Undivided cell, Pt electrodes, 1.5 equiv. 4-iodotoluene (0.75 mmol), Q = 3.0 F, j = 50 mA/cm², addition of amide (0.5 mmol) after electrolysis, reaction volume: 5 mL, CH₂Cl₂ + Et₃N · 5HF (2:3), r.t. [a] Additional stirring time after addition of amide: 48 h.

**Scheme 4.** Control experiments. Reaction conditions: Undivided cell, Pt electrodes, 1.5 equiv. 4-iodotoluene (0.75 mmol), Q = 3.0 F, j = 50 mA/cm², addition of amide (0.5 mmol) after electrolysis, reaction volume: 5 mL, CH₂Cl₂ + Et₃N · 5HF (2:3), r.t. [a] Quantification by 19F NMR using 4-fluorotoluene (1.0 equiv.) as internal standard.
fluorination reaction in presence of 2.0 equivalents of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO, Scheme 4c) was not completely suppressed.

From these control experiments we propose a possible mechanism as shown in Scheme 5, which is supported by other literature findings.\textsuperscript{[9b,c,31]} The hypervalent iodine species 5a is formed by electrochemical oxidation at the platinum anode and attacked by the nucleophilic nitrogen of 3a. Hereafter, iodonium species 5b is generated, releasing HF, followed by cleavage of the N–I bond. With this step p-Tol-I (5) is released and the positive charge of nitrenium intermediate 5c is stabilized by the phenyl ring and can be trapped by nucleophlic attack with a fluoride ion at the para-position of 5d, delivering the fluorinated anilide 4a.

**Conclusion**

In summary, we established a sustainable, para-selective fluorination method of aromatic amides, using an electrochemically generated hypervalent iodine mediator. The electrochemical generation of ArIF\(_2\) is easy to conduct with an undivided two-electrode arrangement and provides a sustainable and favorable alternative to conventional synthetic protocols. The compatibility with other substrates is given due to an ex-cell approach. Beneficially, the 4-iodotoluene could be mostly recovered during the work-up protocol. A broad scope was shown and the successful fluorination of distinct heterocycles such as quinolines and benzoxazines highlights the broad applicability of this conversion. A scale-up of this electrolysis could be conducted with a similar yield, indicating the easy scalability and robust nature of this electrochemical approach.

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**Conflict of Interest**

The authors declare no conflict of interest.

**Data Availability Statement**

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** anilides · electrochemistry · electrosynthesis · fluorination · hypervalent iodine

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