Tetrahedron Letters 71 (2021) 153028

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Difluorinative-hydroxylation and C-3 functionalization (halogenation/SCN/NO) of imidazopyridine using Selectfluor as fluorine source or oxidant respectively

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ARTICLE INFO

Article history:
Received 12 January 2021
Revised 20 March 2021
Accepted 23 March 2021
Available online 26 March 2021

Keywords:
Difluorinative-hydroxylation
Fluorination
C-3 functionalization of imidazo[12-*a*] pyridines

ABSTRACT

An efficient route for the difluorinative-hydroxylation through dearomative difunctionalization of imidazopyridine using Selectfluor as fluorine source has been developed in an aqueous medium. The reaction proceeds through ionic followed by radical pathway. The products are obtained in pure form without column purification. The method was successfully applied for a gram-scale production of 3,3-difluoro-2-(4-fluorophenyl)-2,3-dihydroimidazo[1,2-*a*]pyridin-2-ol (3m). The Zolimidine drug successfully underwent difluorinative-hydroxylation in high yield. Interestingly, addition of the tetra-*n*-butyl ammonium halide or NaI or KSCN or $NaNO_2$ in the reaction provided oxidative functionalization of imidazopyridine wherein Selectfluor acted as an oxidant. The C-3 substituted (Cl, Br, I, SCN and NO) imidazo[1,2-*a*]pyridines were prepared in good yields. These two significant reactions provided wide functional group tolerance, metal/base-free, and green approach.

Introduction

Naturally occurring or synthesized fluorine containing compounds have displayed wide range of significance in medicinal chemistry, agrochemical, material science, polymer industries and positron emission tomography (PET) imaging [1]. Incorporation of fluorine atom into organic molecule augments the biological properties of parent counterparts [2]. Fluorine in bioactive compounds significantly influences the conformation, membrane permeability, pKa, metabolic stability and intrinsic potency. Hence, fluorine is often used as bioisosteric replacement for hydrogen in candidate molecule to address issues related to metabolism [3]. In past, geminal difluoro group has drawn great attention due to its presence in numerous drugs (Fig. 1) [4,5]. Additionally, presence of hydroxyl group in such difluoro-system would indeed potentiate its properties such as bioavailability and catabolic stability. One such an example is Lubiprostone (Amitiza®).

In general, Selectfluor is widely used as electrophilic fluorine source in different organic transformations [6]. On the other hand, the oxidative property of Selectfluor is used for electrophilic substitution of arenes using various nucleophiles [7a], *syn*-dichlorination of alkenes [7b], halogenation and thiocyanation of 1-arylallenes [7c], thiocyanation of indoles, pyrrole, and carbazole [7d]. Conversely, imidazopyridine scaffold is extensively found in various natural products and drugs [8]. Therefore, the manipulation of this omnipresent motif attracted much attention of organic chemists.

Along this line, many research groups have disclosed synthesis of variety of C-3 functionalized complex imidazopyridines [9]. In seminal line, Sun et al. [10] and Shinde et al. [11] reported C-3 monofluorination of imidazo[1,2-*a*] pyridines using Selectfluor as fluorine source. The direct regioselective functionalization (F, Cl, Br, I, SCN, NO) of heteroarenes using electrophile shows importance in organic synthesis [10,12]. In recent times, alternate route has been explored to generate electrophiles from nucleophiles by using oxidants. Recently, Adimurthy et al. [13] and Katrun et al. [14] developed chlorination, bromination, iodination while Hajra et al. [15] and Wang et al. [16,17] established thiocyanation on 2-aryl imidazo[1,2-*a*]pyridines. These approaches have the major drawbacks like use of photo-catalyst, longer reaction time and use of harsh condition. Noteworthy, to use these binary reactivities (fluorine donor and oxidant) of Selectfluor on single target using simple, safe, rapid, facile, sustainable and eco-friendly method is highly desirable. Herein, we report a straightforward transformation for geminal-difluoro hydroxylation in aqueous medium

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https://doi.org/10.1016/j.tetlet.2021.153028
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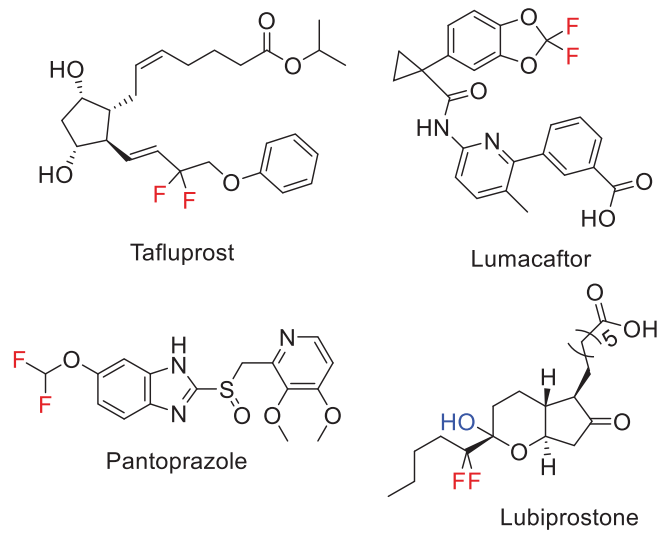


Fig. 1. Structre of the drugs containing difluoro substituent.

through dearomative difunctionalization and C-3 functionalization of imidazo[1,2-*a*]pyridines using dual reactivity of Selectfluor under simple and mild reaction condition.

Results and discussion

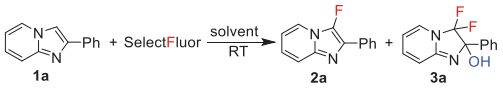
In order to identify the optimal reaction condition for difluoro-hydroxylation, we employed 2-aryl imidazo[1,2-*a*]pyridine (**1a**) and Selectfluor (1 equivalent) in dichloromethane at room temperature (entry 1, Table 1). This condition furnished monofluorinated compound **2a** in 23% yield along with unreacted **1a**. The use of other chlorinating solvents i.e. $CHCl_3$, DCE, TCE afforded **2a** in low yields and no traces of **3a** were detected (entry 2, 3 and 4). When the reaction was carried out in $CHCl_3$:H_2O (9:1, entry 5), the trace amount of **3a** was obtained along with 79% of **2a**. The similar observation was made when the reaction was performed in TCE:H_2O (9:1, entry 6). Further, we employed 2 equivalents of Selectfluor in CH_3NO_2:H_2O (9:1, entry 7) to afford 61% of required **3a** with traces of **2a**.

The reaction in CH_3CN:H_2O (9:1) resulted in 81% of **3a** exclusively. The increased yields for **2a** or **3a** in entry 5 to 8 could be attributed to the presence of protic solvent as scarce solubility of Selectfluor in aprotic solvent is reported [18]. Of note, the reaction in water afforded solely **3a** in 90% yield (entry 9, Table 1). In the crystal structure of **3a**, two molecules of **3a** exist in an asymmetric unit (Fig. 2). This crystal packing arrangement is possible due to the hydrogen bond between hydroxyl of one molecule with N1 of other molecule of **3a**. Such interactions in crystal packing have implications on solubility of these compounds and are important in drug development. After having the optimized reaction condition in hand, the substrate scope of difluorinative-hydroxylation reaction with respect to imidazo[1,2-*a*] pyridines were explored (Scheme 1).

In some reactions, CH_3CN:H_2O (2:8) was employed due to limited solubility of substrates in water. Various 2-aryl imidazo[1,2-*a*] pyridines containing both electron-donating and electron-withdrawing groups on 2-aryl ring readily furnished the corresponding products **3b**-**3h** and **3i**-**3r** in good to excellent yields. These substituents include alkyl (**3b**, **3c**, **3d**, **3e**), methoxy (**3f**), 3,4-methylenedioxy (**3g**), biphenyl (**3h**), cyano (**3i**), trifluoromethoxy (**3j**), nitro (**3k**, **3l**), fluoro (**3m**), 3,5-difluoro (**3n**), chloro (**3o**, **3p**), and bromo (**3q**, **3r**). Furthermore, different substitution on pyridine part of 2-aryl imidazo[1,2-*a*]pyridine scaffold smoothly underwent difluorinative-hydroxylation affording **3s**-**3u** in good to excellent yields. Moreover, 2-sustituted polycyclic aromatic and heteroaromatic compounds such as 2-naphthyl, 2-bromofluorenyl, and 2-thiophenyl, and 2-furyl were also compatible under the present reaction condition and furnished the products (**3v**-**3y**) in moderate yields. In addition, when the substrates with strong electron withdrawing groups like CF_3 and NO_2 on imidazo[1,2-*a*]pyridine ring were used, the reaction failed to give corresponding products. Of note, Zolimidine drug underwent difluorohydroxylation to afford **3zb** in 88% yield (Scheme 2). This protocol was successfully applied to a gram scale synthesis of **3m** (Scheme 3).

Interestingly, regioselective monofluorinated imidazo[1,2-*a*] pyridines **2a**-**2f** could be obtained when $CHCl_3$:H_2O (9:1) was used in the reaction of **1a**/**1p**/**1r**/**1i**/**1y**/**1zb** and Selectfluor (1 equivalent) in moderate to good yields (Scheme 4). The substrates containing 4-cyanophenyl and furyl on imidazo[1,2-*a*]pyridine afforded monofluorinated **2d** and **2e** respectively. Importantly, gastroprotective drug, Zolimidine (**1zb**), underwent monofluorination affording **2f** in 66% yield. Unfortunately, 3-pyridyl substituted imidazo[1,2-*a*]pyridine failed to produce **2g**. It is important to note that this protocol is much better than the Sun et al. protocol [10]. In Sun et al. protocol, the C-3 monofluorinated imidazo[1,2-*a*]pyridines were obtained using DMAP as base with 2 equivalents of Selectfluor in chloroform: water (3:1) for 14 h from imidazo[1,2-*a*]pyridines. While, in current protocol, the products are obtained in 45 min, require only 1 equivalent of Selectfluor and reaction

Table 1
Optimization of difluoro-hydroxylation of imidazo[1,2-*a*]pyridine.[a]



No.	Solvent	Selectfluor (equiv.)	Time (h)	Yield of 2a[b]	Yield of 3a[b]
1[c]	CH_2Cl_2	1	4	23	–
2[c]	$CHCl_3$	1	4	31	–
3[c]	DCE	1	4	20	–
4[c]	TCE	1	4	25	–
5	$CHCl_3$:H_2O (9:1)	1	0.45	79	trace
6	TEC:H_2O (9:1)	1	1.5	74	trace
7	CH_3NO_2:H_2O (9:1)	2	3.5	trace	61
8	CH_3CN:H_2O (9:1)	2	3	–	81
9	H_2O	2	0.45	–	90

[a] Reaction condition: **1a** (0.1 g), Selectfluor in 2 mL of solvent at room temperature. [b] isolated yields. [c] unreacted **1a** isolated. DCE = 1,2-dichloroethane, TCE = 1,1,2,2-tetrachloroethane.

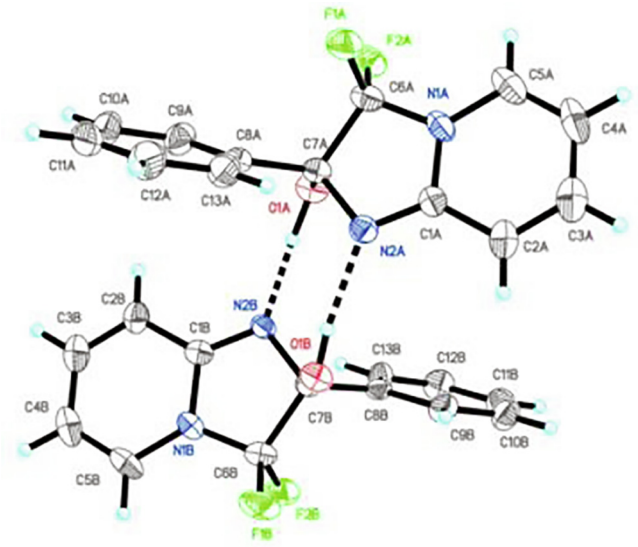
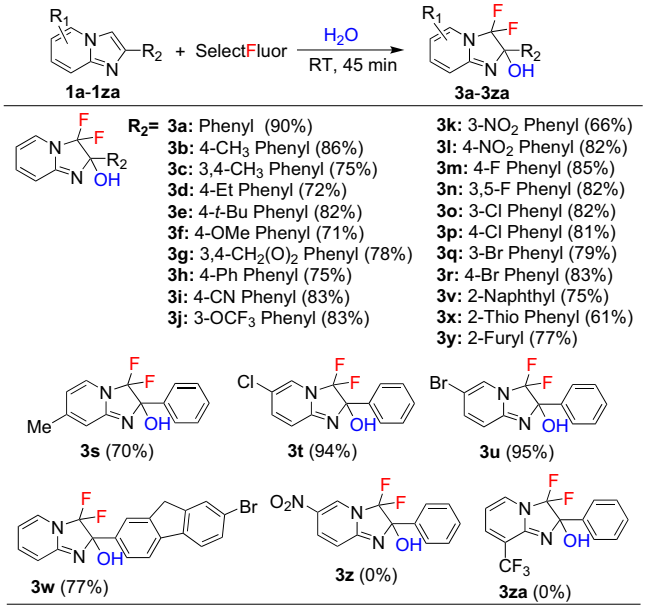
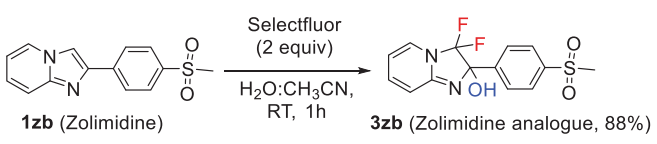


Fig. 2. A view of 3a, showing the atom-labeling Scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented by circles of arbitrary radii. The asymmetric unit contains two crystallographically independent molecules and forms a dimer by O—H. . .N hydrogen bonds (shown as dashed lines).

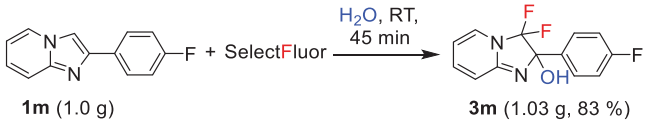


Scheme 1. Difluorinative-hydroxylation of various imidazo[1,2-*a*]pyridines*. Reaction condition: 1 (0.5 mmol), Selectfluor (1 mmol), H_2O (2 mL), RT, 45 min. Shown are the isolated yields. * indicate CH_3CN: H_2O (2:8) was used in case of 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3k, 3l, 3n, 3o, 3p, 3q, 3r and 3s instead of water.

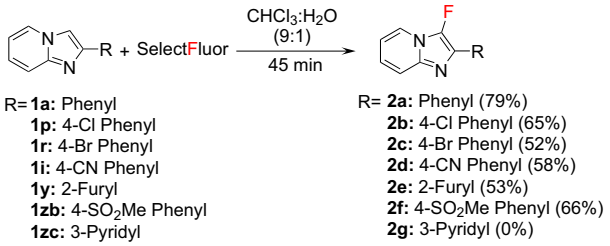


Scheme 2. Synthesis of Zolimidine analogue.

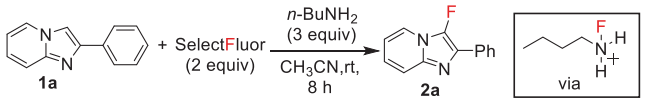
does not need DMAP. This emphasizes the significance of current protocol over Sun et al. protocol. The possible reason for this protocol being efficient is the absence of amine component in the reaction. Compound **2a** could be formed from **1a** and Selectfluor in the presence of *n*-butylamine, though with longer reaction time,



Scheme 3. Gram scale synthesis of 3m.



Scheme 4. Regioselective fluorination of imidazo[1,2-*a*]pyridines. Reaction condition: 1 (0.5 mmol), Selectfluor (0.5 mmol), $CHCl_3$:H_2O (9:1, 1 mL). Isolated yields are shown.

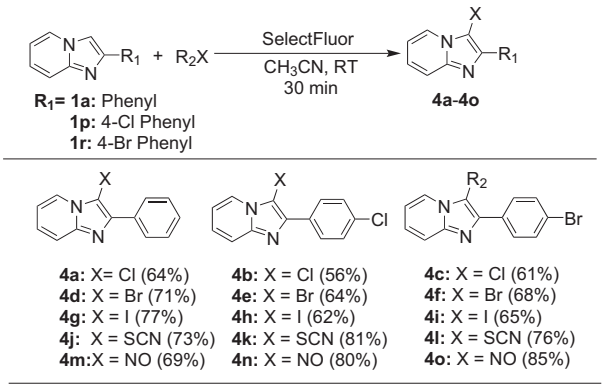


Scheme 5. Monofluorination of 1a.

likely via *n*-fluorobutan-1-aminium tetrafluoroborate (Scheme 5). The *n*-fluorosubstiuted-1-aminium tetrafluoroborate intermediate has been characterized by Chauhan et al. using NMR spectroscopy [19]. Important to note, only 40% conversion of **1a** to **2a** was observed when the reaction (Scheme 5) was conducted in $CHCl_3$:H_2O (9:1) in the presence of *n*-butylamine for 8 h. Hence, absence of nitrogen base DMAP is critical requirement for monofluorination of imidazo[1,2-*a*]pyridines.

On the other hand, functionalization (Cl, Br, I, SCN, NO) reactions on hetero arene have been scars and limited to thiocyanation using Selectfluor as an oxidant [7d]. The use of tetra-*n*-butylammonium chloride afforded 3-chloro derivatives **4a**, **4b**, **4c** with moderate yields whereas use of tetra-*n*-butylammonium bromide and sodium iodide in this protocol produced corresponding 3-bromo (**4d**, **4e**, **4f**) and 3-iodo (**4g**, **4h**, **4i**) analogues, respectively (Scheme 6). Important to note, the use of KSCN furnished 3-thiocyanate containing analogues **4j**, **4k**, **4l** in good yields. Next, the nitration with sodium nitrite in acetonitrile was attempted. In this case, the stable nitroso-compounds **4m**, **4n**, **4o** were isolated.

Based on literature precedents [20,21] & control experiments, the plausible mechanism for difluorinative-hydroxylation is proposed (Figs. 3, 4). The reaction of **1a** with 2 equivalents of Selectfluor in H_2O afforded **3a** exclusively (Scheme 1). The treatment of **1a** with 1 equivalent of Selectfluor in $CHCl_3$:H_2O (9:1) resulted in monofluorinated **2a** in 79% (Scheme 4). The presence of a radical inhibitor, TEMPO, in this reaction could not suppress the formation of monofluorinated compound **2a** (equation 1). This indicate that the monofluorination reaction proceeds through ionic mechanism. On the other hand, when **1a** was treated with Selectfluor in H_2O in the presence of TEMPO, the difluorinative-hydroxylation was inhibited. The imidazopyridine radical was trapped and detected in HRMS (equation 2). This indicate that the difluorinative-hydroxylation likely goes through the ionic mechanism followed by radical pathway. Based on these observations, it can be concluded that TEMPO is not oxidized by Selectfluor in difluorinative-hydroxyla-



Scheme 6. Functionalization of imidazo[1,2-*a*]pyridines with charged nucleophiles. Reaction condition: 1 (0.5 mmol), Selectfluor (1 mmol), R_2X = TBAC or TBAB or NaI or KSCN or $NaNO_2$ (1 mmol), CH_3CN (1 mL). Isolated yields are shown. CH_3CN:H_2O (2:8) was used in case of 4e, 4f, 4h and 4i instead of ACN. Water was used in case of 4d, 4g instead of ACN.

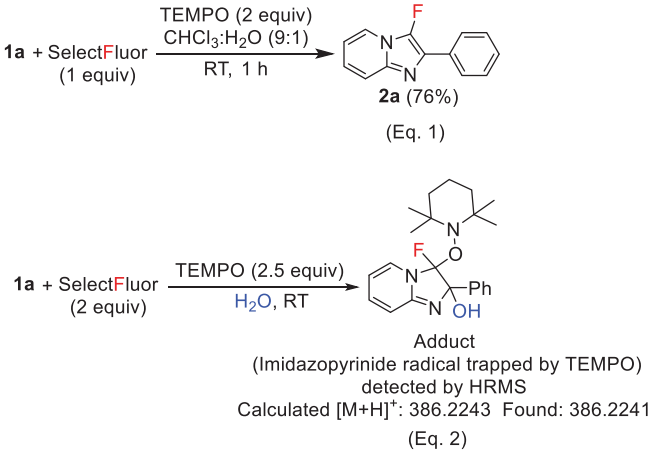


Fig. 3. Control experiments for the mechanistic insights of difluorinative-hydroxylation.

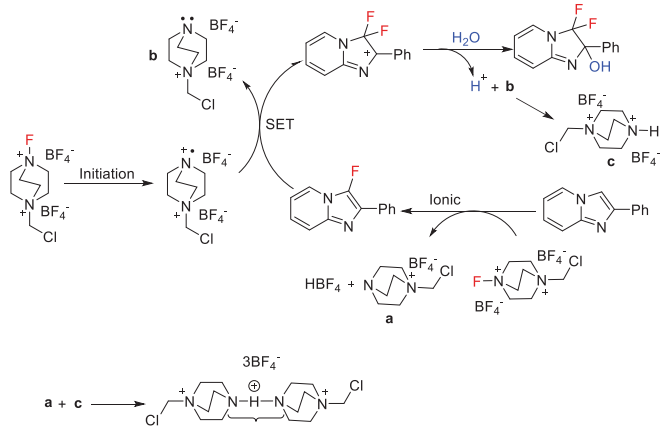


Fig. 4. Plausible mechanism for difluorinative-hydroxylation of imidazopyridine using Selectfluor.

tion. Similar observations were made by Tang et al. in the formation of aryl sulfonyl fluorides [20]. The proposed reaction mechanism for difluorinative-hydroxylation of imidazopyridine is shown in Fig. 4. In the current protocol, the initiator of the radical process is not clear. There are limited reports on fluorination using metal-free radical processes [22,23]. It is important to note that Yang et al. described the amide-assisted fluorination of anilines that does not need any metal or radical initiator [22]. The use of Selectfluor in aqueous media was enough to successfully provide the fluorination of anilines. In another example, Dan et al. reported the selective *ortho*-fluorination of pyridin-2(1*H*)-ones and 2-aminopyridines using Selectfluor in aqueous media in catalyst free system [23].

Conclusion

In summary, we developed a difluorinative-hydroxylation of imidazo[1,2-*a*]pyridines using Selectfluor in aqueous medium. The reaction proceeds through ionic followed by radical pathway. Importantly, the products are obtained in pure form without column purification. Importantly, gastroprotective drug Zolimidine successfully underwent difluorinative-hydroxylation. Further, oxidative nature of Selectfluor was explored in the presence of charged nucleophiles to furnish C-3 functionalized (Cl, Br, I, SCN, NO) imidazo[1,2-*a*]pyridines. These transformations tolerated wide functional groups, and constitute a metal/ base-free approach.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The financial support through a research grant GAP0584 from Department of Science and Technology, Government of India is acknowledged. We thank Director, CSIR-IICT (Ms. No. IICT/pubs./2019/241) for providing all the required facilities to carry out this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153028.

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