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Direct ring fluorination of 3-substituted 5-(1,3-dioxane) acetal isoxazoles: application to the formal synthesis of a bioactive fluorinated isoxazole

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7 Fluorination directe d'isoxazoles 5-(1,3-dioxane) acétal
8 3-substitués : application à la synthèse formelle d'un
9 isoxazole fluoré d'intérêt biologique

10 *Direct ring fluorination of 3-substituted 5-(1,3-dioxane)*
11 *acetal isoxazoles: application to the formal synthesis of*
12 *a bioactive fluorinated isoxazole*

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23
24
25 **Résumé.**

26 L'accès à une nouvelle variété d'isoxazoles 4-fluorés portant un groupe aryle ou alkyle en
27 position C-3 et un fragment acétal en position C-5 a été réalisé par une fluoration directe à
28 l'aide de NFSI, avec des rendements allant jusqu'à 75 %. Cette méthodologie a été transposée
29 à l'échelle du gramme et a été appliquée à la synthèse formelle d'un composé bioactif qui
30 augmente l'activité CFTR.

31 **Abstract.**

32 The access to a novel variety of 4-fluorinated isoxazoles bearing an aryl or alkyl group in C-
33 3 position and an acetal fragment in C-5 position has been achieved through a direct
34 fluorination using NFSI with yields up to 75%. This method was transposed to gram-scale
35 and has been applied to the formal synthesis of a bioactive compound that increases CFTR
36 activity.

37 **Mots-clés.**

38 Fluorination / Isoxazole / Hétérocycles

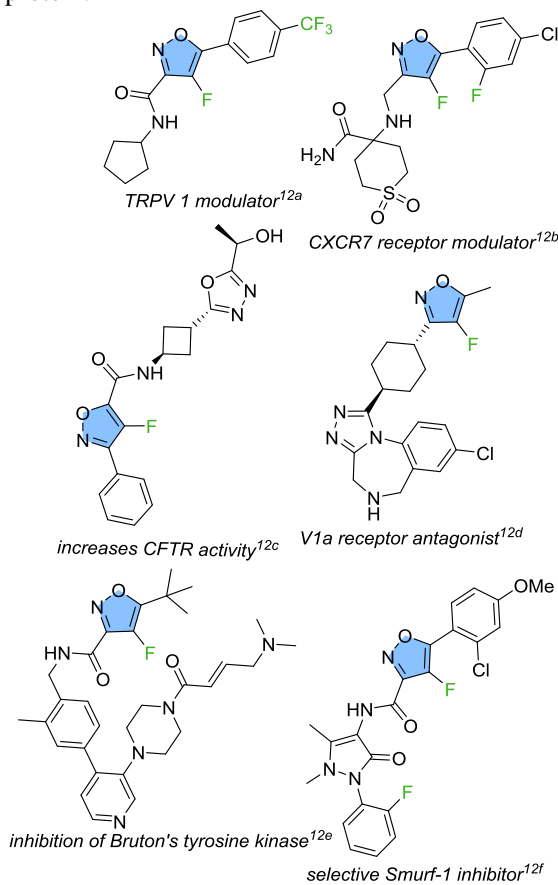
39 **Keywords.**

40 Fluorination / isoxazole / Heterocycles

1 I. Introduction:

2 Heterocyclic scaffolds represent the largest
3 family of organic compounds and have a role in
4 many fields of sciences such as medicinal
5 chemistry,¹ biochemistry² or agrochemistry.³
6 More specifically, the isoxazole skeleton is a very
7 important motif found in natural products or
8 synthetic products such as antibiotics,⁴
9 analgesics,⁵ antirheumatic,⁶ anti-inflammatory⁷ or
10 antidepressant compounds.⁸

11
12 Furthermore, the interest of fluorine and its
13 methods of introduction are still gaining
14 increasing interest as fluorination of an organic
15 molecule significantly impacts its biological
16 characteristics. In spite of the significant
17 fascination with fluorine, the challenge of
18 integrating this element into essential building
19 blocks has postponed the examination and
20 comprehension of its impacts as well as its
21 utilization. Nonetheless, notable advancement has
22 been achieved in the field over the previous
23 decade. Considering the size of the fluorine atom
24 and its electronegativity, the incorporation of a
25 fluorine or a trifluoromethyl group profoundly
26 modifies both the pharmacodynamics and
27 pharmacokinetics of the compound such as lipid
28 solubility, metabolic stability or acidity.⁹
29 Moreover, it can increase the potency of a
30 substance's engagements with a specific target
31 protein.

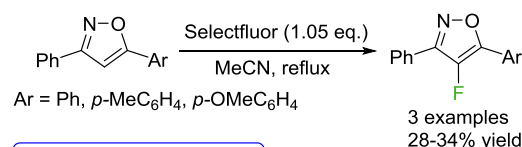


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33 Figure 1: examples of bioactive molecules containing a 4-

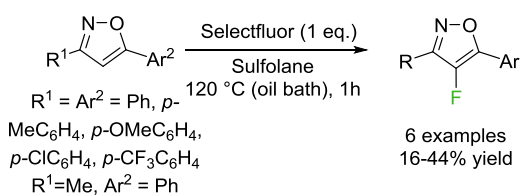
34 fluorinated isoxazole core.
35 Roughly 30% of all agrochemicals and 20% of all
36 pharmaceuticals encompass fluorine¹⁰ within their
37 structures.

38
39 With the aim of continuing our investigations into
40 the synthesis of fluorinated carbocycles and
41 heterocycles,¹¹ we envisaged to focus on a
42 synthetic pathway for the fluorination of an
43 isoxazole functionalized in C-5 by an acetal
44 fragment, an area that has been relatively
45 overlooked in existing literature despite numerous
46 molecules of interest featuring this motif (Figure
47 1).¹² The synthesis of 4-fluorinated 3,5-
48 disubstituted isoxazole was reported by either
49 condensation of 2-fluoro-1,3-diketone¹³ or gold-
50 catalysed cascade cyclisation-fluorination of
51 2-alkyne *O*-methyl oximes¹⁴ but only one
52 method for the direct fluorination in this position
53 was reported relying on the use of Selectfluor as the
54 fluorinating agent and delivering the desired
55 products in moderate chemical yields ranging from
56 16% to 44% (Figure 2).¹⁵ Furthermore, the products
57 generated during the reaction cannot undergo
58 additional post-functionalization. In this context,
59 the direct fluorination in the C-4 position of the 3,5-
60 disubstituted isoxazole core as a late-stage
61 functionalization was explored. With the
62 substitution of an acetal group at the C-5 position,
63 the resulting fluoroisoxazoles can undergo
64 deprotection, opening-up numerous possibilities for
65 additional functionalization.

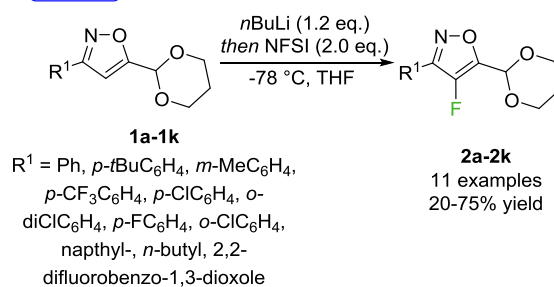
66 C. E. Stephens et al.



K. Sato, G. Sandford et al.



Our work



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69 Figure 2: synthesis of 4-fluorinated 3,5-disubstituted
70 isoxazoles via direct fluorination.

71

II. Results and discussion

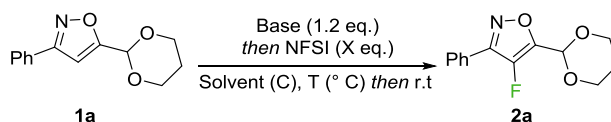
A range of 3,5-disubstituted isoxazoles **1a-1k** were prepared from diversely substituted chloroximes and bromovinyl acetals, according to a three-step procedure developed previously.¹⁶ Having those substrates in hand, our study started with a series of optimisation experiments on 5-(1,3-dioxan-2-yl)-3-phenylisoxazole **1a** (Table 1). The first experiment required 3.5 equivalents of base and NFSI to afford the fluorinated isoxazole **2a** in 47% yield for a conversion of 63% (Table 1, entry 1) at -78 °C. Other commercially available electrophilic fluorinated agent such as Selectfluor or *N*-fluoropyridinium triflate were tested but no conversion was observed under these conditions. Reducing the quantity of base and fluorinating agent to 1.2 and 2.0 equivalents respectively led to better conversions (72-74%) and higher yields (60-62%) (entries 2-3). Subsequently, the impact of the starting material's concentration in THF on the

reaction outcome was examined. The concentration was gradually increased step by step from 0.1 mol/L to 1.0 mol/L (entries 4-9), leading to an optimised yield of 75% at 0.4 mol/L (entry 6). In fact, for a concentration higher than 0.6 mol/L, the reaction medium reaches such a viscosity that stirring stops after addition of the electrophile.

Carrying out the reaction at -40 °C to achieve a full conversion led to complete degradation of the starting material (entry 10). Afterwards, other solvents were tested such as Et₂O or 2-MeTHF, but lower conversions were observed (20% and 58% respectively, entries 11 and 12). Finally, the influence of the base was studied. The starting material was fully recovered when treated with LiHMDS at -78 °C and 0 °C or with NaH at 0 °C (entries 13, 14 and 17). Unfortunately, LiTMP led to a complete degradation of the isoxazole (entry 15). Using LDA gave an encouraging result of 81% conversion and 67% yield but was still inferior to *n*BuLi (entries 16 vs 6).

Table I : optimisation of the reaction conditions^a

Entry	Base	Solvent	X (eq.)	C (mol/L)	T (°C)	t (h)	Conversion ^b (%)	Yield ^c (%)
1	<i>n</i> BuLi	THF	3.5 ^d	0.05	-78	20	63	47
2	<i>n</i> BuLi	THF	2.5 ^e	0.05	-78	20	72	62
3	<i>n</i> BuLi	THF	2.0	0.05	-78	2	74	60
4	<i>n</i> BuLi	THF	2.0	0.1	-78	2	78	61



5	<i>n</i> BuLi	THF	2.0	0.2	-78	2	82	73
6	<i>n</i> BuLi	THF	2.0	0.4	-78	1	85	75
7	<i>n</i> BuLi	THF	2.0	0.6	-78	0.5	89	71
8	<i>n</i> BuLi	THF	2.0	0.8	-78	0.5	91	70
9	<i>n</i> BuLi	THF	2.0	1.0	-78	0.5	90	70
10	<i>n</i> BuLi	THF	2.0	0.2	-40	1	100	0 ^f
11	<i>n</i> BuLi	Et ₂ O	2.0	0.2	-78	3	20	nd
12	<i>n</i> BuLi	MeTHF	2.0	0.2	-78	1	58	nd
13	LiHMDS	THF	2.0	0.4	-78	0.5	0	nd
14	LiHMDS	THF	2.0	0.4	0	0.5	0	nd
15	LiTMP	THF	2.0	0.3	-78	0.5	100	0 ^f
16	LDA	THF	2.0	0.1	-78	1.5	81	67
17	NaH	THF	2.0	0.1	0	2	0	nd

^a Reaction conditions: (**1a**, 0.43 mmol, 1.0 eq.), *n*BuLi (0.52 mmol, 1.2 eq.), NFSI (0.86 mmol, 2.0 eq.), THF (0.4 M, 1.1 mL), -78 °C to r.t., under argon.

^b After NMR ¹H analysis of the crude reaction mixture.

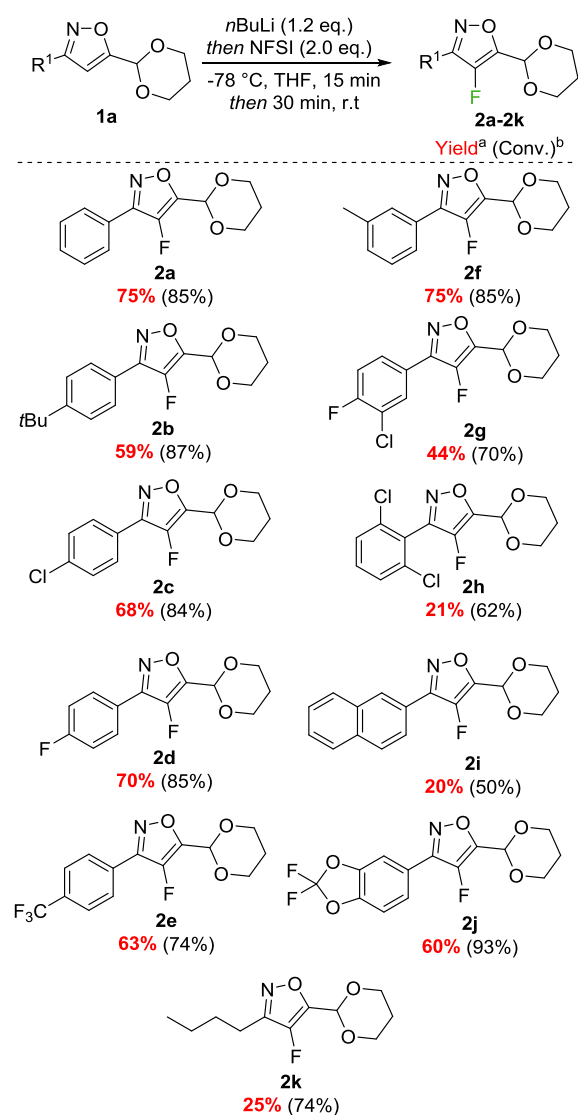
^c After isolation by column chromatography.

^d 3.5 eq. of base were used.

^e 1.5 eq. of base were used.

^f Only degradation was observed.

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5 Having these optimised conditions in hand, we
6 further explored the scope and limitations of the
7 reaction with the 3,5-disubstituted isoxazole
8 previously synthesized. This process allowed to
9 obtain the corresponding fluorinated isoxazoles
10 bearing various electron-donating or withdrawing
11 substituents in the *para*- position of the aryl ring
12 such as *t*butyl- **2b**, chlorine **2c**, fluorine **2d** or
13 trifluoromethyl **2e** groups in 59-70% yields and
14 compounds **2g** and **2h** having a 3-chloro-4-
15 fluorophenyl or a 2,6-dichlorophenyl substituent
16 were obtained in 44% and 21% yield, respectively
17 (Figure 3). Having a methyl in *meta*-position (**1f**)
18 led to 75% isolated yield of the corresponding
19 fluorinated product **2f**. To extend the feasibility of
20 our process, a bulky group such as a naphthyl- or a
21 2,2-difluorobenzodioxole was also investigated and
22 yielded the products **2i** in 20% and **2j** in 60%
23 respectively. The reaction was also suitable for
24 isoxazoles bearing a non-aromatic substituent at the
25 C-3 position and compound **2k** bearing a *n*butyl
26 chain was synthesized in 25% yield.

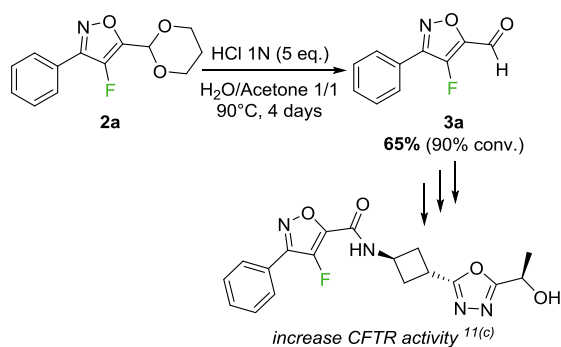


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^a after isolation by column chromatography ^b after ¹H NMR analysis of the crude reaction mixture.

1 Figure 3: scope of the fluorination
 2 Furthermore, our goal was to obtain a range of
 3 fluorinated isoxazoles that could be subsequently
 4 modified after deprotection of the acetal fragment
 5 in the C-5 position. In this context, the acetal was
 6 deprotected in acidic media (HCl 1N, 5 eq.), in a
 7 mixture of water/acetone (1/1) for 4 days at 90 °C
 8 affording the corresponding aldehyde **3a** in 65%
 9 yield (Figure 4).

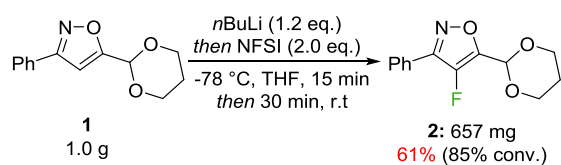
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 13 Figure 4: formal synthesis of a bioactive compound
 14 that increases CFTR activity.

15
 16 Product **3a** is an intermediate in the preparation of a
 17 bioactive compound that increases CFTR (cystic
 18 fibrosis transmembrane conductance regulator)
 19 activity.^{11c} Cystic fibrosis is a result of genetic
 20 mutations in the CFTR gene, responsible for
 21 encoding a chloride channel that spans multiple cell
 22 membranes in epithelial tissues. The loss of a
 23 functional CFTR channel leads to a reduced lung
 24 function and increases mucus viscosity resulting in
 25 chronic infection and inflammation.¹⁷ Besides
 26 respiratory impairment, CFTR also affects the
 27 regular operation of additional organs such as the
 28 pancreas, intestine, or gall bladder.

29



30
 31 Figure 5: scale-up experiment of the fluorination
 32 reaction

33
 34 The effectiveness of this fluorination process was
 35 supported by a scale-up experiment conducted
 36 under the defined standard conditions using 5-(1,3-
 37 dioxan-2-yl)-3-phenylisoxazole **1a** (Figure 5) to
 38 obtain the desired fluorinated product **2a** in 61%
 39 yield.

40

41 III. Conclusion

42

43 In conclusion, we succeeded in synthesizing a range
 44 of new 4-fluorinated 3,5-disubstituted isoxazoles
 45 bearing various substituents on the aromatic ring at
 46 the C-3 position in 20-75% yield. This process was

47 also tolerant to bulkier substituents such as a
 48 naphthyl- or a difluorodioxobenzene- and even a
 49 non-aromatic substituent such as a *n*butyl-
 50 fragment. The objective of this project was also to
 51 obtain a substrate that could be subsequently
 52 functionalized. This was achieved through the
 53 deprotection of the acetal, resulting in a much more
 54 advantageous aldehyde for subsequent synthetic
 55 processes. The usefulness of this method was
 56 demonstrated through the formal synthesis of a
 57 bioactive compound that increases CFTR activity.

58 IV. Acknowledgements

59

60
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67

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73 V. References

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