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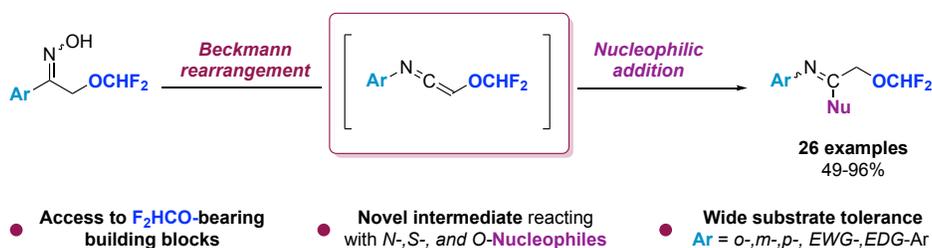
Ketenimines as intermediates to access difluoromethoxylated scaffolds

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Supporting Information Placeholder

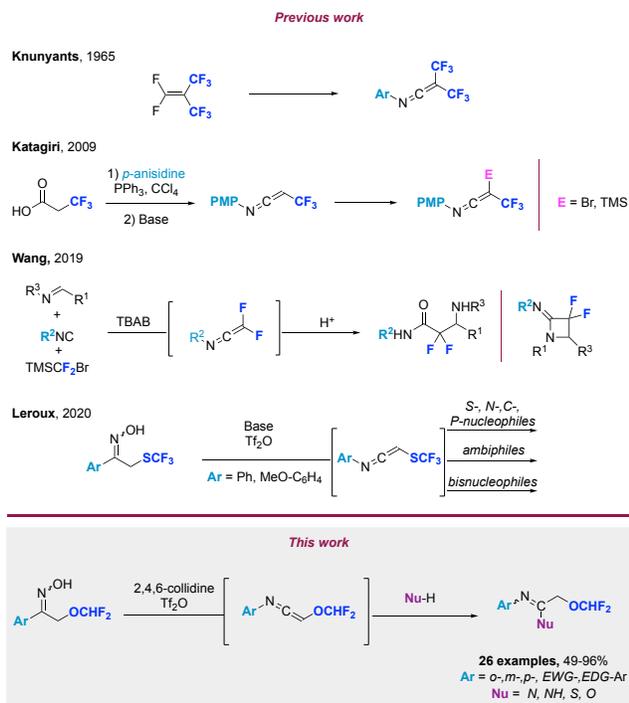
ABSTRACT: We report herein the *in situ* generation of difluoromethoxylated ketenimines. This novel intermediate is readily obtained from the corresponding oxime through a Beckmann rearrangement. The reactivity potential of this species is demonstrated as it easily undergoes addition of various nucleophiles, with a great modularity of the starting oxime. The broad applicability of this transformation leads to a chemical library of original molecules, bearing $-\text{OCHF}_2$, an Emergent Fluorinated Group (EFG).

The importance of organofluorinated compounds in medicinal chemistry or agrochemistry is nowadays undeniable, fluorine atoms being present in more than 20% of the commercial pharmaceuticals¹ and in 53% of agrochemicals². Fluorine has indeed shown its ability to modify the biological as well as physicochemical properties of molecules compared to their hydrogen-bearing analogues.^{3,4} Nevertheless, most of such compounds bear a trifluoromethyl group or a single fluorine atom.^{1,2} Thus, the demand for alternative groups —Emergent Fluorinated Groups (EFG)— in order to provide new reactivities/modes of action and thus potentially improve biological activities, is perpetually increasing.⁵ Whereas difluoromethyl and trifluoromethoxy substituents have recently gained visibility, $-\text{OCHF}_2$ is still rarely encountered. The difluoromethoxy group is yet emerging as particularly interesting, combining the previously mentioned classical properties of fluorine with unique properties due to the presence of the proton. The difluoromethoxy moiety can indeed act as a hydrogen donor through weak hydrogen bonding interactions. Furthermore, this group has the ability to modulate the lipophilicity of molecules in accordance with their environment.⁶⁻⁸ This is the result of a simple rotation of the $\text{O}-\text{CHF}_2$ bond, allowing to change the overall dipole moment of the moiety. Besides, unlike $\text{Ar}-\text{OCF}_3$ or $\text{Ar}-\text{OCH}_3$, $\text{Ar}-\text{OCHF}_2$ shows no preferential conformation of the $-\text{OCHF}_2$ bond (whether in the arene plane or orthogonal to it). An increase of the binding

affinity to active sites might thus be induced by this adaptability. The Aryl- OCHF_2 moiety is already found in a few bioactive compounds, thus highlighting its key importance in modern fluorine chemistry: potent enzyme inhibitor⁹ Roflumilast, anti-pump inhibitor Pantoprazole¹⁰ (Protonix[®]), antimicrobial agents,¹¹ or anti-HIV agents.¹²

In view of these interesting properties of the $-\text{OCHF}_2$ moiety, we felt the urge to develop a new strategy for its introduction, especially since the methods allowing access to aliphatic F_2HCO -compounds are scarce.¹³⁻²¹ As a complementary strategy with regard to the difluoromethylation of aliphatic alcohols, we chose to explore the development of a reactive F_2HCO -containing intermediate, which could be engaged in a broad array of reactions to afford a vast diversity of high value scaffolds.

Scheme 1. Reported syntheses and reactivities of fluorinated ketenimines

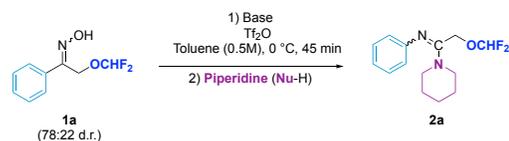


In sight of the previous research in our group on trifluoromethanesulfonylated ketenimines²² and of the known wide reactivity of ketenimines in general,^{23–28} we decided to investigate the use of F₂HCO-bearing ketenimines as key intermediates for the synthesis of valuable motifs such as amidines, imidates as well as thioimidates. The interest of the obtained scaffolds is all the more important given the presence of these structures in biologically active molecules.^{29–31} As a matter of fact, ketenimines bearing fluorinated substituents have been underinvestigated. Apart from F₃CS-substituted ketenimines, only bis(trifluoromethyl), trifluoromethyl and bis(difluoro) derivatives have been reported respectively by Knunyants^{32–38} (1965), Katagiri (2009)³⁹ and Wang (2019)⁴⁰ (Scheme 1).

In this paper we report the *in situ* synthesis of various difluoromethoxylated ketenimines, followed by their use as general tools for the introduction of the emergent -OCHF₂ moiety by submission to the nucleophilic addition of amines, thiols, as well as alcohols.

The postulated key F₂HCO-bearing ketenimine intermediate was generated *in situ* from the corresponding oxime probably through a Beckmann rearrangement. Unfortunately, unlike its trifluoromethanesulfonylated analogue²², the ketenimine intermediate could never be observed nor isolated, resulting only in the obtention of the corresponding amide upon capture of water. We subsequently decided to test the reactivity of this transient species with nucleophiles. Starting with the conditions used for the nucleophilic addition on trifluoromethanesulfonylated ketenimines—2,4,6-collidine (2.0 equiv.), Tf₂O (1.0 equiv.) in toluene—,²² various solvents, bases, as well as reactant stoichiometries were screened (Table 1). Piperidine was chosen as the nucleophile for the optimisation as it had proven to give the best results in the case of F₃CS-bearing intermediates.

Table 1. Optimization of the reaction conditions



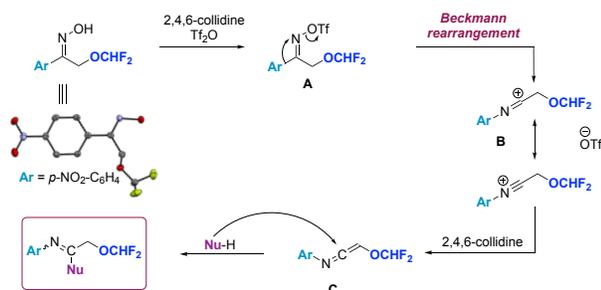
Entry	Tf ₂ O (equiv.)	NuH (equiv.)	Base (2.1 equiv.)	Yield ^a (%)
1	1.0	1.0	2,4,6-collidine	Traces
2	2.0	2.0	2,4,6-collidine	14 (11)
3	2.0	2.0	2,4,6-collidine	27 (21) ^b
4	1.5	1.5	2,4,6-collidine	25 (20)
5	1.1	1.4	2,4,6-collidine	90 (70)
6	1.0	1.1	2,4,6-collidine	67 (55)
7	1.1	1.4	2,4,6-collidine	50 (39) ^c
8	1.1	1.4	pyridine	Traces
9	1.1	1.4	2,6-lutidine	43 (34)
10	1.1	1.4	DIPEA	32 (25)

^a All yields are isolated yields after purification *via* column chromatography, starting from the 78:22 mixture of diastereomeric oximes (0.5 mmol) **1a**, and recalculated from the amount of starting active diastereomer of **1a**; in parentheses, uncorrected isolated yield (i.e. based on the starting mixture of isomers of the oxime). ^b Purified over basified silica. ^c THF was used as a solvent instead of toluene.

Regarding the stoichiometry of the different reactants involved in the reaction (Table 1, entries 1–6), it appeared that at least a small excess of triflic anhydride was necessary in order to ensure the complete conversion of the oxime. A slight excess of nucleophile compared to Tf₂O was thus required in turn, to prevent the quenching of the nucleophile by excess Tf₂O or TfOH. Similarly, 2.1 equivalents of the base were necessary to form the activated oxime **A**, then to deprotonate the nitrilium intermediate **B** involved in the Beckmann rearrangement in order to form the ketenimine **C** (see Scheme 2).^{41–43} It appeared that when THF was used as solvent instead of toluene, the yield of the reaction rapidly decreased from 90 to 50 % (Table 1, entry 7). Regarding the choice of the organic base, 2,4,6-collidine still gave the best results with the cleanest reaction mixture. Indeed, employing pyridine only resulted in the obtention of traces of product (entry 8), whereas 2,6-lutidine and DIPEA gave respectively 43% and 32% yield (entries 9 and 10) and tricky purifications. Moreover, in the case of nucleophilic addition of amines, the removal of the organic base from the reaction media was always challenging. Rewardingly, a simple washing with an aqueous solution of copper sulfate was found to be a convenient solution. The stereochemistry of the starting oxime is of key importance for this transformation. The reaction was usually performed using a 78:22 mixture of diastereoisomers of the oxime **1a**.⁴⁴ Nevertheless, when performing the addition of a nucleophile on each of the isomers separately, only the major oxime yielded the expected product. These results are consistent with a *Z* configuration of the major diastereoisomer (i.e. with the aryl group being

located *trans* to the OH one), following the described stereospecificity of the Beckmann transformation⁴⁵ under classical conditions. This assignment is supported by the similarity with the Infra-Red Spectra of oximes in which the aromatic is *trans* to the -OH, as well as the higher NMR shifts of the major oxime^{46,47} and finally by an X-Ray diffraction crystallographic structure of the nitrophenyl-substituted major isomer; accordingly, the mechanism discussed above was proposed (Scheme 2).

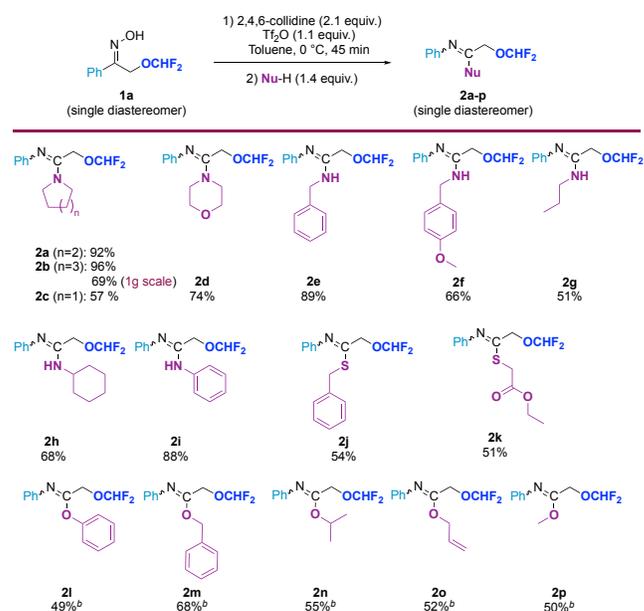
Scheme 2. Proposed mechanism^a



^a The crystallographic structure is registered under CCDC number 2201857, and is displayed with ellipsoids at the 50% probability level (see SI for details).

With the optimized conditions in hand, the nucleophilic behaviour of various secondary amines was tested yielding the corresponding amidines as single isomers in good to excellent yields (Scheme 3).⁴⁸ Endocyclic aliphatic secondary amines with 5–7-membered rings gave good yields of the desired amidines **2a–d**, especially azepane which afforded the expected product with 96% yield (**2b**). Aryl-, benzyl- or alkyl-derived primary amines were also used as potent nucleophiles with slightly lower yields (**2e–i**, 51–89%), probably due to a lower nucleophilicity. Aliphatic *n*-propylamine (**2g**) notably only gave the expected product with a yield of 51%. The reaction was also investigated using two thiols: benzyl mercaptan and mercaptoethyl acetate, yielding respectively **2j** (54%) and **2k** (51%). Surprisingly, despite the low reactivity of alcohols, their nucleophilic addition was also observed in moderate yields. As a reminder no such product had been obtained from the reaction with trifluoromethanesulfanylated ketenimines.²² Besides, the use of alkoxides formed *via* prior deprotonation with NaH allowed us to increase these yields. After apparent degradation of these products into the corresponding amides during the aqueous work-up and over silica, we decided to directly purify the crude materials by column chromatography using basified silica gel, allowing reasonable yields (**2l–p**, 49–68%).

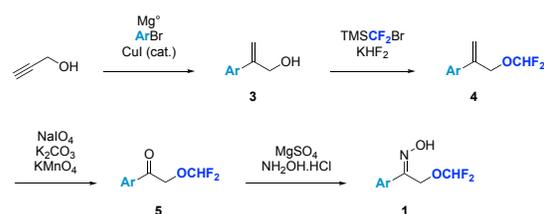
Scheme 3. Scope for the addition of nucleophiles^a



^a All reactions were carried out on the pure major isomer of the oxime; all yields are isolated yields after work-up with sat. aqueous CuSO₄ and purification via column chromatography, starting from the active diastereomer of the oxime only (0.5 mmol). ^b Alcohols were subjected to deprotonation by NaH (1.4 equiv.) in toluene before addition on the ketenimine intermediate. The crude was directly purified over basified silica gel.

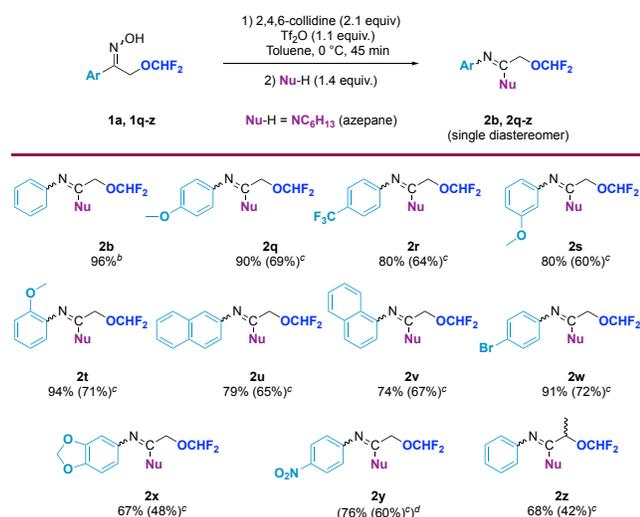
Moreover, a general route was developed to access the oximes starting from propargyl alcohol (See Scheme 4). The addition of a Grignard reagent leads to prop-2-en-1-ol **3**, which is then difluoromethylated with TMSCF₂Br. An oxidative cleavage of **4** leads to ketone **5**. The corresponding oxime is finally obtained from reaction with hydroxylamine.

Scheme 4. General route to access F₂HCO-bearing oximes.



This allowed us to vary the aromatic moiety and thus to investigate its influence on the nucleophilic addition (See Scheme 5).⁴⁸ As a matter of fact, by substituting the phenyl with either electron-withdrawing or electron-donating groups, no notable variation of the yield was observed, indicating that the Beckmann rearrangement does not seem to be influenced by the electronic character of the migrating group. Furthermore, the position of a given substituent, e.g. the methoxy group in **2q,s–t**, does not seem to impact reactivity either. The reaction also tolerated well the presence of a bromine atom in the *para* position, with 91% yield of **2w**, showing an interesting potential for post-functionalization *via* cross-coupling reactions for instance. The presence of a bulky aromatic group, such as naphthalene (**2u**, **2v**) or 1,3-benzodioxole (**2x**), seemed to decrease slightly the yields of the reaction. In addition, the transformation on an α -substituted oxime proved efficient and yielded **2z** in 68%.

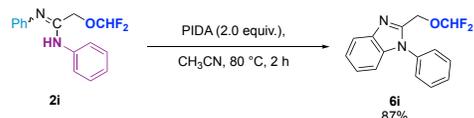
Scheme 5. Scope for the variation of the migrating group^a



^a Unless otherwise stated, all compounds were isolated after work-up with sat. aqueous CuSO₄ and purification via column chromatography, the yields are isolated yields after purification via column chromatography, starting from the mixture (d.r.=61:39 -90:10) of oximes (0.2-0.5 mmol), recalculated from the amount of starting active diastereomer of the oxime. ^b Starting from the pure active isomer of the oxime. ^c In parentheses, uncorrected yield based on the mixture of isomeric oximes. ^d Due to rapid degradation over silica, the given yields were determined by ¹⁹F-NMR using *o,o*-trifluorotoluene as an internal standard.

Furthermore, amidines being known to be suitable substrates for heterocycle synthesis,⁴⁹ we decided to investigate the versatility of our synthesized compounds. As a matter of fact, post-functionalisation of fully *N*-substituted amidines proved difficult, nevertheless the H-bearing ones offered more possibilities. In that perspective, **2i** was cyclized into **6i**—since benzimidazole is a structure of particular interest for medicinal chemistry⁵⁰⁻⁵² by treatment with PIDA.⁵³ The product was obtained in 87% yield (Scheme 6).

Scheme 6. Synthesis of benzimidazole 6i from amidine 2i



In conclusion, we have developed an efficient method to access valuable new difluoromethoxylated molecules *via* the addition of nucleophiles on F₂HCO-bearing ketenimines as intermediates. The transformation gave moderate to excellent yields with different types of nucleophiles such as amines, thiols and even alkoxides, which failed to produce the corresponding products in the case of the parent F₃CS-derived ketenimines. Besides, the migration of aryl groups, supposedly going through a Beckmann rearrangement, tolerated very well a variation of both the electrophilic and steric profile of the latter, enabling the access to functionalized molecules. The study of other versatile F₂HCO-bearing intermediates to access valuable difluoromethoxylated compounds is underway in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, characterization data, crystal data and NMR spectra for all new compounds.

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Notes

The authors declare no competing financial interests.

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