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# Difluoromethoxylated Ketones as Building Blocks for the Synthesis of Challenging OCF<sub>2</sub>H-Bearing N-Heterocycles

Anaïs Loison,<sup>[a]</sup> Gilles Hanquet,<sup>[a]</sup> Fabien Toulgoat,<sup>[b, c]</sup> Thierry Billard,<sup>[b]</sup> Armen Panossian,<sup>\*[a]</sup> and Frédéric R. Leroux<sup>\*[a]</sup>

We report herein an unprecedented synthesis of difluoromethoxylated nitrogen-containing heterocycles from the corresponding  $\alpha$ -(difluoromethoxy)ketones as versatile building blocks. Pyrazoles, isoxazoles and pyrimidines could be obtained via an enaminone intermediate, whereas in the direct reaction of  $\alpha$ -(difluoromethoxy)ketones with arylhydrazines, a Fischer indole

synthesis was achieved. All these scaffolds, which are uncommon, or even sometimes novel, due to the directly attached emerging fluorinated group (EFG) –OCF<sub>2</sub>H, might be of high potential in life sciences and appear as an interesting alternative to more and more controversial classical fluorinated groups, such as the ubiquitous trifluoromethyl group.

## Introduction

The prevalence of organofluorine compounds in pharmaceuticals<sup>[1]</sup> and agrochemicals<sup>[2]</sup>, with 18% and 16% of compounds on the market bearing fluorine, respectively, can be explained by the advantageous properties conferred by the latter, including notably significant modifications in biological behavior and physicochemical properties compared to their hydrogen-containing analogues.<sup>[3,4]</sup> Nevertheless, most compounds actually carry single fluorine atoms or trifluoromethyl groups.<sup>[1,2]</sup> In the perspective of improving the biological activities of potential active ingredients by providing new reactivities or new modes of action, the development of alternative fluorinated groups is highly necessary.<sup>[5]</sup> In addition, the bioaccumulation of fluorinated compounds in water, air

and soil, is nowadays a major concern. Indeed, while the persistence of per- and polyfluoroalkyl substances<sup>[6,7]</sup> may soon lead to restrictions by ECHA, fluorinated pesticides are also of concern as they can be metabolized into trifluoroacetic acid, whose persistent salts also lead to soil acidification.<sup>[8,9]</sup> To address these challenges, many research groups have focused on the development of new fluorinated groups.<sup>[5]</sup> Among them, great interest has been shown in the methods of introduction of –OCF<sub>3</sub>,<sup>[10]</sup> which confers to the molecules carrying it a particular conformation<sup>[11]</sup> as well as an increased lipophilicity.<sup>[12]</sup> Nevertheless, access to trifluoromethoxylated scaffolds is still not straightforward,<sup>[13]</sup> and the advantages of this emerging fluorinated group are overshadowed by concerns about its excessive lipophilicity, which impacts its solubility, as well as its potential degradation into toxic fluorophosgene.<sup>[14,15]</sup> In this respect, the difluoromethoxy group,<sup>[16]</sup> still rarely encountered, appears to be an interesting alternative. Indeed, it shares with –OCF<sub>3</sub> the modifications of properties induced by the presence of fluorine atoms, such as the impact on lipophilicity, pK<sub>a</sub> and metabolic stability. Nevertheless, the presence of a proton affects these changes in a different way<sup>[17–20]</sup> (Figure 1). First,

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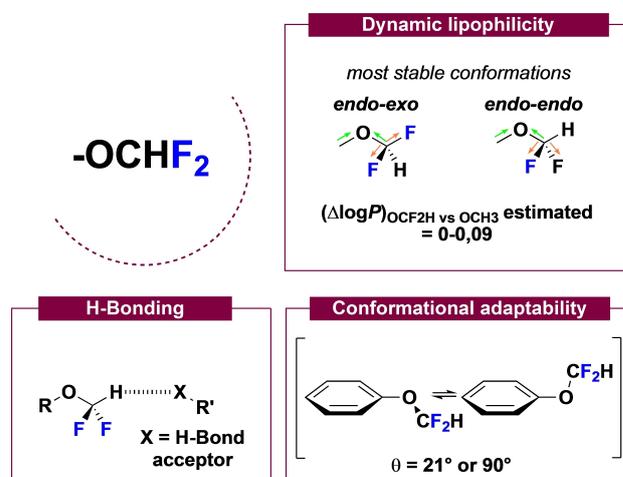


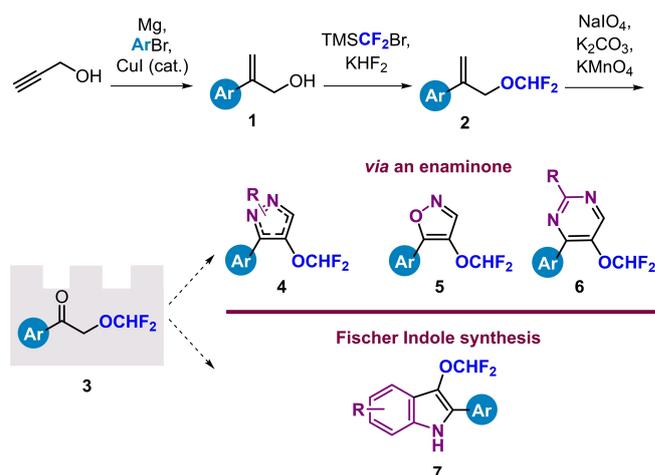
Figure 1. Specific properties of the –OCF<sub>2</sub>H group.

since the overall dipole moment of the molecule is different depending on the environment, molecules carrying a difluoromethoxy moiety possess a dynamic lipophilicity, with a general value between the ones of  $-\text{OCH}_3$  and  $-\text{OCF}_3$ . In addition, novel interactions in active protein sites can be induced by weak hydrogen-bonding, and the binding affinity could also be enhanced by the conformational adaptability of  $\text{Ar}-\text{OCF}_2\text{H}$ , as two energy minima are predicted for  $\theta$  (the dihedral angle between the planes of the COC unit and the benzene ring) =  $90^\circ$  and  $21^\circ$ . Furthermore, unlike  $-\text{CF}_3$ , it cannot be metabolized into TFA. A few bioactive compounds indeed already exhibit the  $-\text{OCF}_2\text{H}$  moiety, indicating the importance and potential of this motif in life sciences. Roflumilast,<sup>[21]</sup> a potent enzyme inhibitor, and pantoprazole<sup>[22]</sup> (Protonix<sup>®</sup>), a pump inhibitor, are striking examples. In addition, the moiety is also present in antimicrobial agents<sup>[23]</sup> or anti-HIV agents.<sup>[24]</sup>

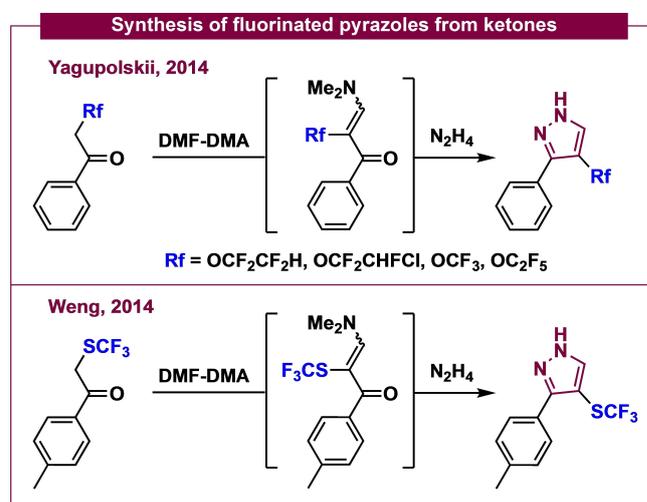
Despite their potential and the great interest in fluorinated heterocycles<sup>[25–27]</sup> – more than 85% of all biologically-active chemicals containing heterocycles –,<sup>[28]</sup> difluoromethoxylated heteroarenes are still rare, with only 4 structures reported in the Merck index.<sup>[29]</sup> In fact, even these structures are still rarely encountered; two difluoromethoxylated pyrazoles are commercially available today and show activity as herbicides: pyroxasulfone<sup>[30,31]</sup> and pyraflufen-ethyl,<sup>[32]</sup> indicating the need for easy access to such compounds. In addition, these may exhibit similar behaviour to difluoromethylated pyrazoles, whose antifungal activity is thought to be due to the H-bonding of the difluoromethylene group in succinate dehydrogenase enzymes.<sup>[33]</sup> The usual access to difluoromethoxylated heterocycles is the difluoromethylation of a pendant hydroxy group.<sup>[34,35]</sup> However, this process requires easy access to the corresponding hydroxylated heterocycles. Furthermore, the difluoromethylation of compounds is not straightforward, with the efficiency often depending on the substrate. An alternative strategy would be to construct the heterocycles from polyvalent  $\text{OCF}_2\text{H}$ -containing synthons. We have recently reported the preparation of difluoromethoxylated building-blocks via  $\text{F}_2\text{HCO}$ -containing ketenimines, formed from  $\alpha$ - $(\text{F}_2\text{HCO})$ -ketoximes, themselves obtained from  $\alpha$ - $(\text{F}_2\text{HCO})$ -ketones. In fact, the latter ketones accessed *via* the route described in Scheme 1 (steps affording compounds 1–3),<sup>[36]</sup> as such, have a strong potential as difluoromethoxylated synthons and could be readily converted into heterocycles, where the  $-\text{OCF}_2\text{H}$  group would be directly connected to the ring. Accordingly, we report herein an efficient synthesis of  $\text{OCF}_2\text{H}$ -bearing pyrazoles, isoxazoles and pyrimidines starting from  $\alpha$ -difluoromethoxylated ketones via an enaminone intermediate,<sup>[37]</sup> as well as an elegant Fischer indole synthesis using various hydrazine derivatives (Scheme 1).

## Results and Discussion

We first envisioned accessing  $\text{OCF}_2\text{H}$ -bearing pyrazoles, by condensation of hydrazine with the difluoromethoxylated enaminone, as this strategy had already been applied successfully to the synthesis of other pyrazoles bearing  $\alpha$ -fluoroether or thioether motifs (Scheme 2).<sup>[38,39]</sup> The enaminone was easily



Scheme 1. Access to difluoromethoxylated heterocycles via a key  $\alpha$ - $(\text{F}_2\text{HCO})$ -ketone as building block.



Scheme 2. Examples of fluorinated pyrazoles synthesized from the corresponding ketones via the enaminone.

obtained by reaction between the key  $\alpha$ -difluoromethoxyketone and  $N,N$ -dimethylformamide dimethylacetal (DMF-DMA).

Starting from the conditions used in the literature<sup>[38,40]</sup> for the synthesis of pyrazoles bearing poly- and perfluoroalkoxy groups (Table 1, Entry 1) we obtained 4a in a 88% yield. We then decided to perform a rapid screening of solvents, hydrazine sources, as well as acid additives (Table 1). The more common hydrazine monohydrate showed a slight improvement in yield and was therefore adopted (Entry 2). It was also found that a large excess of acid was necessary, as when only 5 equivalents were used, the yield decreased drastically to 46% (Entry 3). In addition, acetic acid showed a slightly lower efficiency (Entry 4). A range of solvents were found to be compatible with the reaction and ethanol was selected as it appeared to be the most environmentally friendly choice.

Furthermore, with the optimized conditions in hand (Entry 2, Table 1), a one-pot reaction starting from the ketone was easily set up, giving the expected pyrazole in 73% yield. The

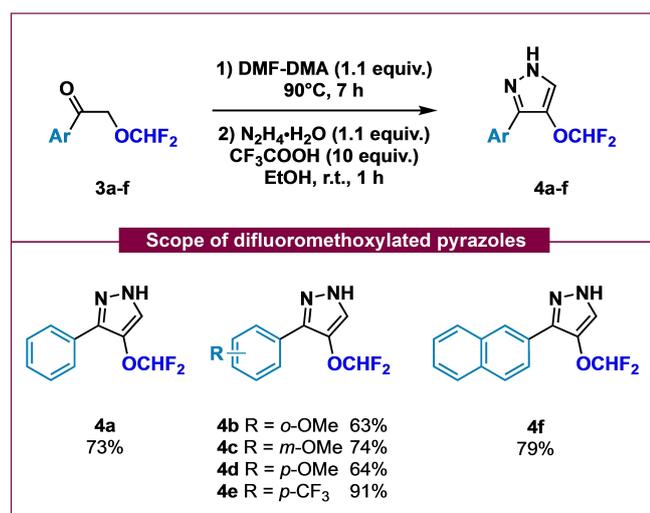
**Table 1.** Optimization of the conditions for the synthesis of OCF<sub>2</sub>H-bearing pyrazoles.

Entry	Deviation of the conditions	Yield <sup>[a]</sup>
1	None	(93) <sup>[b]</sup> 88
2	N <sub>2</sub> H <sub>4</sub> ·H <sub>2</sub> O	(94) <sup>[b]</sup> 90
3	CF <sub>3</sub> COOH (5 equiv.)	(48) <sup>[b]</sup> 46
4	CH <sub>3</sub> COOH (10 equiv.)	(83) <sup>[b]</sup> 77
5	MeOH	(quant.) <sup>[b]</sup> 88
6	THF	(90) <sup>[b]</sup> 73
7	EtOH	(quant.) <sup>[b]</sup> 92
8	EtOH, 1 h	(quant.) <sup>[b]</sup> 91
9	Acetone, 1 h	(95) <sup>[b]</sup> 80

[a] All yields are isolated yields starting from 2-(difluoromethoxy)-3-(dimethylamino)-1-phenylprop-2-en-1-one (0.12 mmol). [b] ( ) Yields determined by <sup>19</sup>F-NMR using α,α,α-trifluorotoluene as an internal standard.

reaction was found to be tolerant to electronic (H-, CF<sub>3</sub>-, MeO-, benzo) as well as steric (*o*-MeO-, benzo) variations on the aromatic part, giving the corresponding pyrazoles in good to excellent yields (63-91%) (Scheme 3).

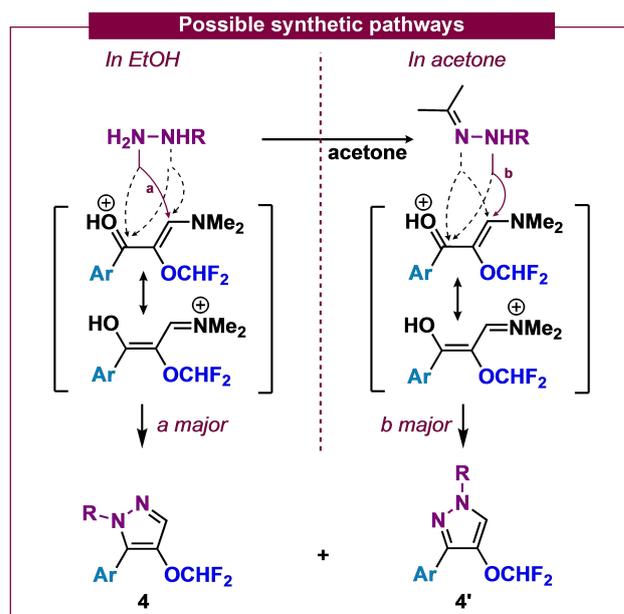
In addition, the reaction was applied to substituted hydrazines and the regioselectivity of the transformation was studied (Table 2). It appeared that under the optimized conditions (Table 1, Entry 2), using methyl hydrazine, pyrazole **4g** with the phenyl ring in position 5 was formed preferentially over its 3-Ph regioisomer **4g'** (68:32) (Table 2, Entry 1). In fact, obtaining such mixtures is not surprising as it had already been



**Scheme 3.** Synthesis of difluoromethoxylated pyrazoles. [a] All yields are isolated yields after work-up and purification via column chromatography, starting from 1-aryl-2-(difluoromethoxy)ethan-1-ones (0.3 mmol).

reported in the literature for similar reactions, due to the presence of two nucleophilic nitrogen atoms that could react on two electrophilic sites (Scheme 4).<sup>[41–43]</sup> On the other hand, when acetone was chosen as an alternative solvent, the regioselectivity was completely reversed and **4g'** was selectively obtained (> 7:93) (Entry 2). This result can be explained by the condensation of the hydrazine with acetone occurring first, enabling the formation of the corresponding hydrazone, in which only the secondary nitrogen can proceed to the nucleophilic attack (Scheme 4, *path b*). In contrast, when using HFIP as a solvent (Entry 3), only a weak conversion was observed with very little regioselectivity. This result seems surprising, as Fustero *et al.* described the regioselective formation of pyrazoles using such fluorinated solvents.<sup>[42]</sup> It is also worth mentioning that increasing the reaction temperature had no impact on yields or selectivity (Entries 4 and 5). When phenylhydrazine was used instead, as the aniline nitrogen was much less nucleophilic than the methylamine nitrogen, **4h** was obtained with an excellent regioselectivity in EtOH (Entry 6) (Scheme 4, *path a*) and **4h'** was predominant in acetone (Entry 7), in agreement with previous results. Finally, we attempted to increase the electrophilicity of the carbonyl relative to the iminium (Scheme 4) by decreasing the electron density of the aromatic moiety. This resulted in a decrease in selectivity towards **4i** vs **4i'** (57:43) (Entry 8).

With these encouraging results we considered extending the reaction to the synthesis of isoxazoles.<sup>[44–46]</sup> Unfortunately, applying our optimized conditions, but with hydroxylamine hydrochloride, only the di-oxime was obtained (Table 3, Entry 1) and when the reaction was heated at 85 °C, the main products observed were the 5-hydroxyisoxazolines resulting from failed dehydration to the desired isoxazoles (Entry 2). Despite numerous attempts to convert the former (Entries 3–5), only trace



**Scheme 4.** Potential synthetic pathways leading to the formation of 2 regioisomers.

**Table 2.** Study of the parameters impacting the regioselectivity.

Entry	Ar	R	Conditions	Yield (4) <sup>[a]</sup>	Yield (4') <sup>[a]</sup>
1	Ph	Me	EtOH, r.t.	(98) <sup>[b]</sup> 97 (4 g/4 g' = 68:32)	
2	Ph	Me	Acetone, r.t.	(99) <sup>[b]</sup> 91 (4 g/4 g' = 7:93)	
3	Ph	Me	HFIP, r.t.	(17) <sup>[b]</sup> (4 g/4 g' = 44:56)	
4	Ph	Me	EtOH, reflux	(98) <sup>[b]</sup> 96 (4 g/4 g' = 65:35)	
5	Ph	Me	Acetone, reflux	(quant) <sup>[b]</sup> 92 (4 g/4 g' = 4:96)	
6	Ph	Ph	EtOH, r.t.	4 h (92) <sup>[b]</sup> 85 <sup>[c]</sup>	4 h' (7) <sup>[b]</sup> 6 <sup>[c]</sup>
7	Ph	Ph	Acetone, r.t.	4 h (18) <sup>[b]</sup> 14 <sup>[c]</sup>	4 h' (80) <sup>[b]</sup> 72 <sup>[c]</sup>
8	4-F <sub>3</sub> C-C <sub>6</sub> H <sub>4</sub>	Me	EtOH, r.t.	90 (4 i/4 i' = 57:43)	

[a] All yields are isolated yields starting from 1-aryl-2-(difluoromethoxy)-3-(dimethylamino)prop-2-en-1-ones (0.3 mmol). [b] ( ) Yields determined by <sup>19</sup>F-NMR using  $\alpha,\alpha,\alpha$ -trifluorotoluene as an internal standard. [c] The two regioisomers were separable by column chromatography.

**Table 3.** Optimization of the conditions for the synthesis of OCF<sub>2</sub>H-bearing isoxazoles.

Entry	T [°C]	t [h]	Solvent	Step 2	Yield (5 a : 5 a') <sup>[a]</sup>
1	r.t.	1	EtOH	–	0
2	85	18	EtOH	–	Traces
3	85	18	EtOH	CF <sub>3</sub> COOH (10 equiv.)	Traces
4	85	18	EtOH	Aq. Na <sub>2</sub> CO <sub>3</sub> (2 equiv.)	Traces
5	85	18	EtOH	SOCl <sub>2</sub> (2.1 equiv.) + Pyridine ((8 equiv.), Toluene)	(30) <sup>[b]</sup> (1 : 1)
6 <sup>[c]</sup>	80	18	CH <sub>3</sub> CN	–	(93) <sup>[b]</sup> 81 (1 : 0)

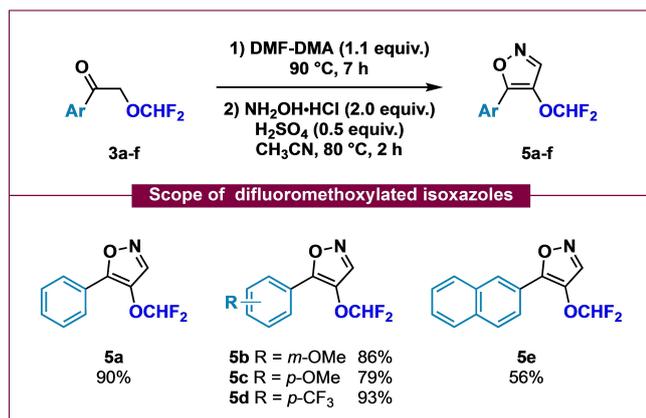
[a] All the yields are isolated yields starting from 2-(difluoromethoxy)-3-(dimethylamino)-1-phenylprop-2-en-1-one (0.3 mmol). [b] ( ) Yields determined by <sup>19</sup>F-NMR using  $\alpha,\alpha,\alpha$ -trifluorotoluene as an internal standard. [c] using NH<sub>2</sub>-OH (2.0 equiv.), conc. H<sub>2</sub>SO<sub>4</sub> (0.2 equiv.) in CH<sub>3</sub>CN at 80 °C for 2 h.

amounts of isoxazoles were present. Finally, we decided to use the conditions developed in our group for the synthesis of 5-benzylamino-isoxazolines:<sup>[41]</sup> NH<sub>2</sub>OH (2.0 equiv.), H<sub>2</sub>SO<sub>4</sub> (0.5 equiv.) in acetonitrile, but carrying out the reaction at 80 °C instead of room temperature (Entry 6). We thus directly accessed the isoxazole in the form of a single regioisomer 5a.

Using these conditions, it was possible, as in the aforementioned case of pyrazoles, to develop a one-pot process from the ketone, affording 5a–e in good to excellent yields regardless of the substitution of the aromatic moiety (Scheme 5). Only the

reaction of 2-(difluoromethoxy)-1-[4-(trifluoromethyl)phenyl]ethan-1-one 3c required a longer (18 h) heating to achieve complete dehydration of the 5-hydroxyisoxazoline, affording 5c in 93% yield.

Finally, after the condensation of hydrazines and hydroxylamine as 1,2-dinucleophiles on difluoromethoxylated enamines, we were interested in the access to difluoromethoxylated pyrimidines<sup>[47,48]</sup> from amidines as 1,3-dinucleophiles. As a starting point, we used the conditions that we had already employed in the synthesis of bis(fluoroalkyl)pyrimidines,<sup>[49]</sup> and



**Scheme 5.** Scope for the synthesis of difluoromethoxylated isoxazoles. [a] All yields are isolated yields after work-up and purification via column chromatography, starting from 1-aryl-2-(difluoromethoxy)ethan-1-ones (0.3 mmol).

we proceeded to optimize the reaction conditions (Table 4) with acetamidine hydrochloride. With acetonitrile as solvent, only low conversion was obtained, even after 24 h (Entries 1 and 2). In contrast, EtOH afforded the pyrimidine **6a** in an isolated yield of 80% after 24 h (Entry 4). In order to reduce the reaction time, microwave irradiation was attempted, but only low conversion was observed (Entry 5). Therefore, the selected parameters were the following: acetamidine hydrochloride (2.0 equiv.), Et<sub>3</sub>N (3.0 equiv.) in refluxing EtOH for 24 h.

Again, the one-pot two-step process was found to be efficient, yielding 78% of **6a**. After ensuring that the reaction was, as before, tolerant to electron-rich as well as electron-poor aromatic groups, affording **6b** (Ar = *p*-MeO-C<sub>6</sub>H<sub>4</sub>) and **6c** (Ar = *p*-CF<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>) in 76 and 71% yields respectively, we thought it would be of particular interest to study the efficiency of the

**Table 4.** Optimization of the conditions for the synthesis of OCF<sub>2</sub>H-bearing pyrimidines.

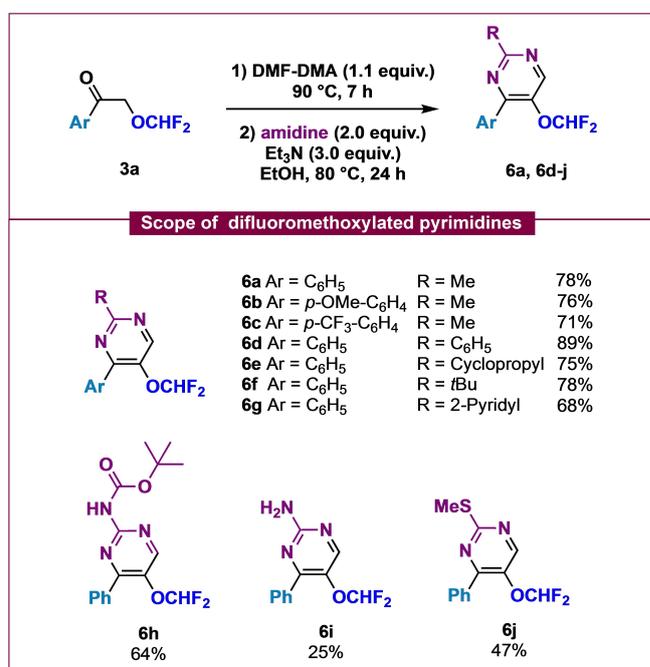
Entry	t	Solvent	Yield ( <b>6a</b> ) <sup>[a]</sup>
1	6 h	CH <sub>3</sub> CN	(10) <sup>[b]</sup>
2	24 h	CH <sub>3</sub> CN	(32) <sup>[b]</sup> 30
3	6 h	EtOH	(50) <sup>[b]</sup>
4	24 h	EtOH	(92) <sup>[b]</sup> 80
5	30 min <sup>[c]</sup>	EtOH	(9) <sup>[b]</sup>

[a] All the yields are isolated yields starting from 2-(difluoromethoxy)-3-(dimethylamino)-1-phenylprop-2-en-1-one (0.3 mmol). [b] ( ) Yields determined by <sup>19</sup>F-NMR using α,α,α-trifluorotoluene as an internal standard. [c] Microwave irradiation at 80 °C.

transformation with different types of amidines (Scheme 6). Indeed, good to excellent results (68–89%) were obtained with both aromatic and aliphatic amidines (**6a–g**). Guanidines were also employed in the reaction. While guanidine hydrochloride gave the expected product **6i** in only 25% yield, the *N*-Boc-protected version was obtained in a significantly better yield (**6h**, 64%). Another interesting example is 5-(difluoromethoxy)-2-(methanesulfanyl)-4-phenylpyrimidine **6j** which was produced in 47% yield. Unfortunately, neither free thiourea, nor any urea derivative afforded the expected products.

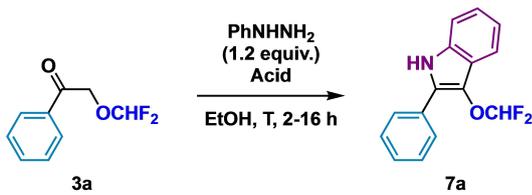
In addition to synthesizing various types of nitrogen-bearing heterocycles via an enaminone intermediate, we considered directly using our polyvalent ketone building block to access unprecedented 3-(difluoromethoxy)-1*H*-indoles via a Fischer synthesis. In fact, 2-(difluoromethoxy)-1*H*-indoles can be accessed by reacting 2-oxo-2,3-dihydro-1*H*-indoles with a difluorocarbene source, but to date, no method describes the synthesis of its positional isomer. The Fischer indole synthesis is known to require acidic conditions. Therefore, different acid sources, as well as concentrations were examined, and then the temperature and reaction time were optimized (Table 5). It was found that concentrated HCl (Entry 1) gave the best results, with H<sub>2</sub>SO<sub>4</sub> and AcOH giving lower yields (Entries 2 and 3). In addition, heating was found to be necessary, as the yield dropped to 65% when the reaction was mildly heated to 50 °C (Entry 4).

Moderate to good yields were achieved when phenylhydrazine was reacted with various ketones, with no apparent effect of the steric or electronic character of the aromatic ring of the ketone (Scheme 7, **7a–g**). The sigmatropic rearrangement



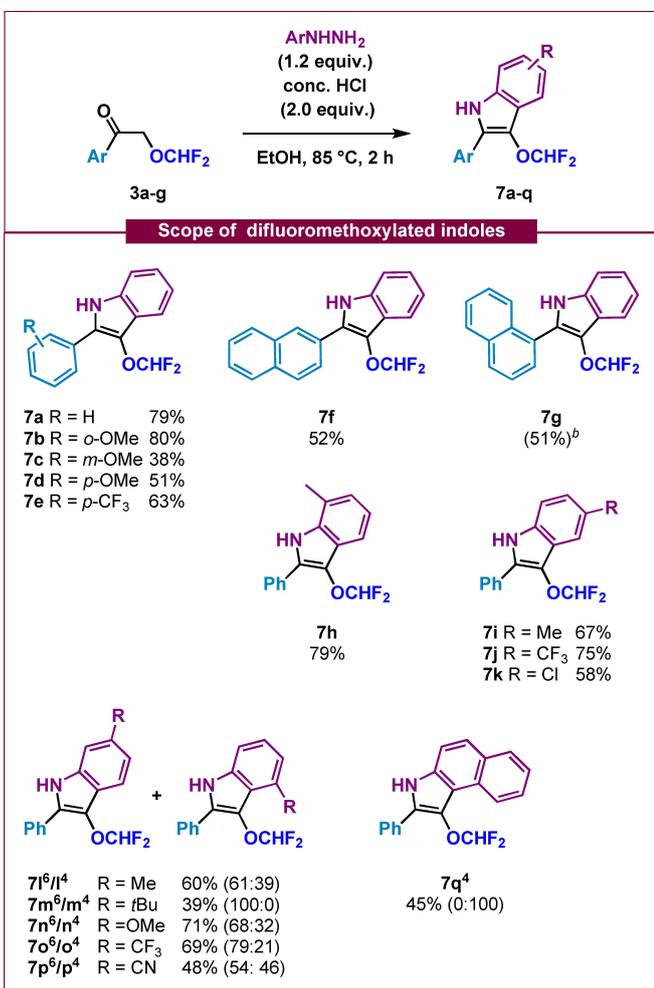
**Scheme 6.** Scope for the synthesis of difluoromethoxylated pyrimidines. [a] All yields are isolated yields after work-up and purification via column chromatography, starting from 2-(difluoromethoxy)-1-phenylethan-1-one (0.3 mmol).

**Table 5.** Optimization of the conditions for the synthesis of OCF<sub>2</sub>H-bearing indoles.



Entry	acid	T [°C]	Yield % (7) <sup>[a]</sup>
1	HCl	80	82
2	H <sub>2</sub> SO <sub>4</sub>	80	55
3	AcOH	80	Traces
4	HCl	50	65

[a] All the yields are isolated yields starting from 2-(difluoromethoxy)-1-phenylethan-1-one (0.3 mmol) and phenylhydrazine (0.36 mmol, 1.2 equiv.) in EtOH (1.7 M).



**Scheme 7.** Scope for the synthesis of difluoromethoxylated indoles. [a] All yields are isolated yields after work-up and purification via column chromatography, starting from 1-aryl-2-(difluoromethoxy)ethan-1-ones (0.3 mmol). [b] ( ) Yields determined by <sup>19</sup>F-NMR using  $\alpha,\alpha,\alpha$ -trifluorotoluene as an internal standard.

was also found to be tolerant for many hydrazine derivatives. When *ortho*- or *para*-substituted phenylhydrazines were used, the corresponding indoles were synthesized in good yields (**7h–k**, 58–79%) and only 4-methoxyphenylhydrazine failed to yield the expected product. As a matter of fact, despite full conversion of the ketone, only traces of the indole were observed, leading us to think that this particular product might be highly unstable and undergo degradation at 85 °C.

Using *meta*-substituted hydrazines, two regioisomers can be produced, namely the 4- or 6-substituted 1*H*-indoles. As described in the literature, when electron donating groups are used, 6-substituted 1*H*-indoles are mainly formed (**7l**, **7m**, **7n**) whereas this tendency decreases with electron withdrawing groups, such as a cyano one (**7p**).<sup>[50,51]</sup> Nevertheless, using 3-(trifluoromethyl)phenylhydrazine, the 6-isomer **7o** remains largely the major product, most probably due to the steric hindrance of the aryl moiety, which also appears to be an important factor. Indeed, with the large *t*Bu group, 6-*tert*-butyl-3-(difluoromethoxy)-2-phenyl-1*H*-indole **7m<sup>6</sup>** was exclusively obtained. On the other hand, obtaining **7q<sup>4</sup>** from the reaction with 2-naphthalenyldiazine cannot be rationalized by steric effects, but could be explained by the fact that the formation of this product disturbs less the aromaticity during the rearrangement.<sup>[52]</sup>

## Conclusions

In conclusion, we have developed a convenient method to access a wide variety of new nitrogen heterocycles bearing the emerging group –OCF<sub>2</sub>H. Starting from a single versatile building-block, i.e. a difluoromethoxylated ketone, we were able to prepare pyrazoles, isoxazoles, pyrimidines as well as indoles. The reactions proved to be tolerant to the electronic and steric characters of the substrates. In addition, the versatile reactivity of the ketone with a wide range of compounds, including hydrazines, hydroxylamine, and amidines allowed the creation of a library of valuable scaffolds. These results are especially important as fluorinated heterocycles predominate in bioactive compounds and unique properties could be conferred by the difluoromethoxy group, a particularly attractive alternative to the now more common but increasingly controversial fluorinated groups.

## Experimental Section

**General procedure for the synthesis of the starting difluoromethoxylated ketones, adapted from the literature:** General procedures for the synthesis of **1a–g**, **2a–g** and **3a–g** have been described in our previous publication.<sup>[36]</sup>

**General Procedure A for the one-pot synthesis of pyrazoles 4a–f:** A mixture of 1-aryl-2-(difluoromethoxy)ethan-1-one **3a–f** (1 equiv., 0.30 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.1 equiv., 44  $\mu$ L, 0.33 mmol) was heated at 90 °C for 7 h. Excess DMFDMA was removed under vacuum. The obtained residue was dissolved in EtOH (0.20 mL). Hydrazine (1.1 equiv., 0.33 mmol, 17  $\mu$ L) and CF<sub>3</sub>COOH (10 equiv., 92  $\mu$ L, 1.24 mmol) were added and the mixture

was stirred at r.t for 1 h. The solution was quenched with water and neutralized with a saturated solution of sodium bicarbonate. The product was extracted with dichloromethane (3x5 mL), then the organic layer was washed with water (3x5 mL), dried with MgSO<sub>4</sub> and the solvents removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the expected product **4a–f**.

**General Procedure B for the regioselective one-pot synthesis of pyrazoles **4g'–4i'**:** A mixture of 1-aryl-2-(difluoromethoxy)ethan-1-one **3** (1 equiv., 0.30 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.1 equiv., 44  $\mu$ L, 0.33 mmol) was heated at 90 °C for 7 h. Excess DMFDMA was removed under vacuum. The obtained residue was dissolved in acetone (0.20 mL). Hydrazine (1.1 equiv., 0.33 mmol) and CF<sub>3</sub>COOH (10 equiv., 92  $\mu$ L, 1.24 mmol) were added and the mixture was stirred at r.t for 1 h. The solution was quenched with water and neutralized with a saturated solution of sodium bicarbonate. The product was extracted with dichloromethane (3x5 mL), then the organic layer was washed with water (3x5 mL), dried with MgSO<sub>4</sub> and the solvents removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel to afford the expected product **4g'–i'**.

**General Procedure C for the one-pot synthesis of isoxazoles **5a–e**:** A mixture of 1-aryl-2-(difluoromethoxy)ethan-1-one **3a–f** (1 equiv., 0.30 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.1 equiv., 44  $\mu$ L, 0.33 mmol) was heated at 90 °C for 7 h. Excess DMFDMA was removed under vacuum. The obtained residue was dissolved in CH<sub>3</sub>CN (1 mL). Hydroxylamine hydrochloride (2.0 equiv., 42 mg, 0.60 mmol) and H<sub>2</sub>SO<sub>4</sub> (0.5 equiv., 10  $\mu$ L, 0.15 mmol) were added and the mixture was stirred at 80 °C for 2 h. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel to afford the expected product **5a–f**.

**General Procedure D for the one-pot synthesis of pyrimidines **6a–j**:** A mixture of 1-aryl-2-(difluoromethoxy)ethan-1-one **3** (1 equiv., 0.30 mmol) and *N,N*-dimethylformamide dimethyl acetal (1.1 equiv., 44  $\mu$ L, 0.33 mmol) was heated at 90 °C for 7 h. Excess DMFDMA was removed under vacuum. The obtained residue was dissolved in EtOH (0.5 mL). The selected amidine hydrochloride (2.0 equiv, 0.60 mmol) and Et<sub>3</sub>N (3.0 equiv., 0.13 mL, 0.90 mmol) were added and the mixture was stirred at 80 °C for 24 h. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel to afford the expected product **6a–j**.

**General Procedure E for the synthesis of Indoles **7a–q**:** A round-bottom flask was charged with 1-aryl-2-(difluoromethoxy)ethan-1-one (1.0 equiv., 0.30 mmol), arylhydrazine (1.2 equiv., 0.36 mmol) and concentrated HCl (12 N, 2 equiv., 50  $\mu$ L) in EtOH (0.20 mL). The resulting mixture was refluxed at 85 °C for 2 h. The crude material was purified directly by column chromatography on silica gel to afford the expected product **7a–q**.

## Supporting Information

Additional references cited within the Supporting Information.<sup>[36]</sup>

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## Conflict of Interests

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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