Utilization of fluoroform for difluoromethylation in continuous flow: a concise synthesis of α-difluoromethyl-amino acids†

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Fluoroform (CHF₃) can be considered as an ideal reagent for difluoromethylation reactions. However, due to the low reactivity of fluoroform, only very few applications have been reported so far. Herein we report a continuous flow difluoromethylation protocol on sp³ carbons employing fluoroform as a reagent. The protocol is applicable for the direct Cα-difluoromethylation of protected α-amino acids, and enables a highly efficient synthesis of the active pharmaceutical ingredient eftornithine.

The difluoromethyl group is found in an increasing array of pharmaceutical and agrochemical products.¹ Not surprisingly, therefore, significant efforts have been devoted towards the development of novel protocols for the introduction of the CHF₂-moiety into organic molecules.² In addition to well-established methods based on the deoxyfluorination of aldehydes, various methods for direct difluoromethylation have recently become available.² Among the cheapest and most versatile reagents for direct CHF₂-transfer is chlorodifluoromethane (CHF₂Cl, Freon 22). Chlorodifluoromethane is produced on a massive scale, particularly for the production of fluoropolymers, and it is available at a relatively low cost (Fig. 1). With sufficiently strong bases, CHF₂Cl can be deprotonated. The so-formed carbanion, chlorodifluoromethanide (CF₂Cl−), immediately loses chloride to generate an electrophilic singlet difluorocarbene (CF₂Cl− → CF₂ + Cl⁻). The short-lived difluorocarbene can then be trapped with a suitably reactive nucleophilic species to produce the difluoromethylated product (Fig. 1).² This reaction has been shown to proceed successfully with a range of NH-, OH- and CH-acidic compounds.² However, CHF₂Cl is a strong ozone depleting gas and it is controlled under the Montreal Protocol. As a consequence, its production and usage has become increasingly limited and expensive. A plethora of alternative difluoromethane sources have been developed in recent years, including TMSCF₂Br, (EtO)₂POCF₂Br, PhCOCF₂Cl and CHF₂OTf.² Although these reagents cover the needs of chemists for difluoromethylation on a laboratory scale, their high cost, low atom economy and limited commercial availability prohibit their usage in an industrial setting.

The most attractive CF₃- and CHF₂-source is fluoroform (CHF₃, Freon 23). Fluoroform is generated as a large-volume waste-product during the synthesis of chlorodifluoromethane (Fig. 1). It is a nontoxic and ozone-friendly gas with a boiling point of −82 °C. Since fluoroform has an extraordinary global warming potential (14 800 times higher than carbon dioxide over a 100-year period),¹ its discharge into the environment is restricted by the Kyoto Protocol. As a consequence, fluoroform needs to be destroyed or, alternatively, captured and used as a feedstock for manufacturing. The latter option, though vastly preferable, is difficult to realize due to the extraordinarily low reactivity of fluoroform. Only very recently have the first synthetically relevant transformations involving fluoroform started to emerge.⁴ Most relevant for the present work is a series of seminal publications from the laboratories of Mikami.⁵−⁷ Mikami and co-workers have shown that fluoro-

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Fig. 1 CHF₃ is a large-volume by-product in the synthesis of CHF₂Cl.
Form can be utilized for the direct difluoromethylation of a variety of substrates utilizing strong lithium bases (lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LiHMDS)).\(^5\)\(^-\)\(^7\) In addition to Mikami’s work, the difluoromethylation reactions of alkenes with CHF\(_3\) and \(\text{tBuOK}\), as well as the difluoromethylation of phenols and malonates with aqueous KOH,\(^9\) have been described by Shibata and Dolbier, respectively. The mechanism of the difluoromethylation reaction is believed to resemble that of the corresponding reaction with CHF\(_2\)Cl.\(^8\)\(^-\)\(^10\) An electrophilic singlet difluorocarbene is formed by the deprotonation of CHF\(_3\) and the subsequent rapid \(\alpha\)-elimination of fluoride. Difluorocarbene then reacts with the anion of the substrate (Fig. 1).

The main objective of the present work was to establish a scalable, continuous flow synthesis route to \(\text{C}^\alpha\)-difluoromethyl amino acids using fluoroform as the reagent (Scheme 1). \(\text{C}^\alpha\)-Difluoromethyl amino acids are potent and selective \(\alpha\)-inhibitors of their respective \(\alpha\)-amino acid decarboxylases.\(^1\)\(^1\) Representatives of this class of compounds exhibit a broad spectrum of biological activities, such as antibacterial, antihypertensive, cancerostatic, and cytotoxic activities.\(^1\)\(^1\) Currently, only \(\text{DL}-\alpha\)-difluoromethylornithine (efflorofamine), an inhibitor of ornithine decarboxylase, is in medical use (Scheme 1). Efflorofamine has been explored as an anticancer agent, and it is in clinical use for the treatment of African sleeping sickness as well as of \(\text{Pneumocystis carinii pneumonia}\), the most frequent opportunistic infection associated with acquired immunodeficiency syndrome (AIDS).\(^1\)\(^1\) It is on the World Health Organization’s Model List of Essential Medicines. Two different strategies can be employed for the generation of \(\text{C}^\alpha\)-difluoromethyl amino acids: (i) construction of the amino acids from fluorine-containing building blocks (e.g. \(\alpha\)-difluoromethyl malonates)\(^1\)\(^2\)\(^,\)\(^1\)\(^3\) or (ii) direct substitution of the \(\alpha\)-hydrogen of amino acids with a CHF\(_2\) moiety (Scheme 1).\(^1\)\(^4\) The direct \(\text{C}^\alpha\)-difluoromethylation of Schiff base-protected \(\alpha\)-amino acid methyl esters with CHF\(_3\)Cl as the reagent has been demonstrated by Bey and others.\(^1\)\(^4\) The \(\alpha\)-difluoromethylation of protected amino acids with CHF\(_3\) is currently not reported. Indeed, the protocol described herein is, to the best of our knowledge, the first example where fluoroform is utilized for the preparation of a pharmaceutical endproduct.

First preliminary batch experiments were performed with diethyl phenylmalonate (1\(a\)) as a model substrate (Table 1).

![Scheme 1](image)

**Scheme 1** Synthesis of \(\text{DL}-\text{C}^\alpha\)-difluoromethyl amino acids.

| Base (equiv.) | \(t_1\) (min) | \(T_1\) (°C) | \(t_2\) (min) | \(T_2\) (°C) | Conv\(^a\) (%) | Sel\(^a\) (%) |
|--------------|---------------|---------------|---------------|---------------|----------------|--------------|
| 1 \(\text{tBuOK}\) (3) | 5 | 25 | 60 | 25 | 28 | 0 |
| 2 \(\text{tBuOLi}\) (3) | 5 | 25 | 60 | 25 | 4 | 0 |
| 3 LDA (2) | 5 | 25 | 5 | 25 | 0 | 0 |
| 4 \(\text{nBuLi}\) (2) | 5 | 25 | 5 | 25 | 0 | 0 |
| 5 \(\text{nBuLi}\) (2) | 5 | 80 | 5 | 80 | 0 | 0 |
| 6 \text{LiHMDS} (2) | 5 | 25 | 60 | 25 | 2 | 100 |
| 7\(^c\) KOH (15) | 30 | 25 | 120 | 25 | 32\(^d\) | 0 |

\(^a\) Reaction conditions: 0.5 mmol diethyl phenylmalonate 1\(a\) in 0.5 mL THF, base, and CHF\(_3\) (balloon). \(^b\) Analyzed by HPLC-UV/VIS at 215 nm. \(^c\) Method B in ref. 9. \(^d\) 20% ethyl phenylacetate (by hydrolysis and decarboxylation).

For these reactions, malonate was dissolved in the desired solvent and a base was added. After stirring the mixture for a few minutes at the indicated temperatures (\(t_1, T_1\) in Table 1), fluoroform was slowly passed through the reaction mixture under vigorous stirring (\(t_2, T_2\) in Table 1). Using phenylmalonate 1\(a\) as a substrate, no product was formed with \(\text{nBuLi},\) LDA or \(\text{tBuOK}\) as a base (entries 1 to 5 in Table 1). Furthermore, attempts to reproduce the results reported by Dolbier and coworkers failed in our hands.\(^9\) According to Dolbier’s procedure, the phenylmalonate 1\(a\) is stirred in aqueous KOH for 30 min at room temperature. MeCN or dioxane is then added and fluoroform is bubbled through the solution.\(^9\) Our experiments under these reaction conditions did not yield any difluoromethylated product (entry 7 in Table 1). Small amounts of the desired product were formed using LiHMDS as a base (entry 6 in Table 1). Mikami and co-workers have already shown that fluoroform in combination with LiHMDS can be utilized for the direct difluoromethylation of cyclic amides, cyclic and open esters, and certain simple malonates.\(^3\) According to the authors, the reaction proceeds best with 2 equiv. of base and 5 equiv. of CHF\(_3\). Reaction times of 6 to 48 h at reaction temperatures of 0 to 25 °C were needed to provide the desired products in good yields.\(^5\)

Encouraged by this result, we were keen to develop a continuous flow protocol for this reaction. Continuous processing techniques have had a significant impact on the development of more sustainable manufacturing routes for several pharmaceuticals.\(^1\)\(^5\)\(^-\)\(^1\)\(^8\) For gas–liquid reactions, several specific advantages exist: high pressure operation and fast gas–liquid mass transfer enhance the availability of the gaseous reagent in the liquid phase.\(^1\)\(^6\)\(^,\)\(^1\)\(^7\) In addition, the gaseous reagent can be dosed into the liquid phase with precise stoichiometry using mass flow controllers.\(^1\)\(^6\)\(^,\)\(^1\)\(^7\) Our initial flow setup consisted of two continuous syringe pumps to introduce (i) a 0.5 M solution of substrate in THF (Feed A, Table 2), and (ii) a...
commercial solution of LiHMDS (Feed B, Table 2). The two feeds were mixed in a Y-shaped connector in a cooling bath. The substrate is deprotonated in a 2 mL residence loop (reactor 1), before the mixture is combined with fluoroform in a second Y-shaped connector in a second cooling bath. The flow rate of the fluoroform stream was controlled using a calibrated mass flow controller (MFC). The combined mixture then went through a second cooled residence loop (reactor 2) and left the flow system through a third residence loop at reactor (3), while the phenyl derivative 1b was used as the model substrate for the initialization of optimization. With flow rates of 300 µL min⁻¹ for Feed A, 200 µL min⁻¹ for Feed B and 8.3 mL min⁻¹ for fluoroform, a stoichiometry of 1 : 1.3 : 2.5 for substrate/LiHMDS/CHF₃ and a total residence time of ~20 min was obtained. The flow reactions clearly revealed that the conversion increased with a decrease in temperature and an increase in pressure (Table 2). Also the selectivity increased slightly with decreasing temperatures (Table 2). As already observed by Mikami and co-workers, the best results are obtained with 2 equiv. of base (see Table S1 in the ESI†). Also, for fluoroform, 2 to 3 equiv. were identified as the ideal amount.

The general reaction conditions were suitable for a variety of substrates (Fig. 2). Malonates with sterically benign alkyl groups in the α-position performed particularly well (1d to 1f in Fig. 2), while the phenyl derivative 1a resulted in low conversion. The reaction was remarkably clean, with the unreacted substrate and tris(trimethylsilyl)amine being the only contaminants in the crude mixture after washing with water. The analytically pure compounds were isolated by preparative thin-layer chromatography (TLC). The yield of diethyl methylmalonate 2e was the same as that previously reported for the batch protocol, even though the reaction time for the present procedure was significantly shorter (20 min vs. 20 h for the batch procedure). The yield of product 2e was lower than that reported for the batch procedure (39% vs. 78% according to ¹⁹F-NMR spectroscopy). The other difluoromethylated compounds prepared in this work have not been previously reported.

As mentioned in the introduction, the synthesized α-difluoromethyl malonates can be converted to the respective α-difluoromethyl amino acids in a multi-step transformation (Scheme 1). However, since a direct difluoromethylation of natural α-amino acids has clear advantages, reactions with Schiff base-protected α-amino acid methyl esters were investigated. The N-benzylidene-protected α-amino acid methyl esters were readily available from the parent amino esters using literature procedures (for experimental details, see the ESI†). Gratifyingly, subjecting the N-benzylidene-protected α-amino acid methyl esters 1g to 1k to the general reaction conditions resulted in >95% conversion to the desired product. Indeed, the reaction was remarkably clean with only one CHF₂-moiety (two doublets of doublets) detectable in

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**Table 2** Diffuoromethylation of methyl diphenylacetate 1b under flow conditions

| T (°C) | p (bar) | Conv (%) | Sel (%) |
|--------|---------|----------|--------|
| 1      | 40      | 63       | 81     |
| 2      | 25      | 65       | 80     |
| 3      | ~10     | 82       | 88     |
| 4      | ~15     | 86       | 91     |
| 5      | ~15     | 92       | 91     |

*Reaction conditions: Feed A: 0.5 M diethyl phenylmalonate 1b in THF; Feed B: 1 M LiHMDS in THF; with flow rates for Feed A/Feed B/CHF₃ = 0.30 : 0.20 : 8.3 mL min⁻¹, respectively, the following conditions were obtained: LiHMDS (1.33 equiv.); CHF₃ (2.5 equiv.). Analyzed by GC-FID. For a detailed description of the experiments, see the ESI.*

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**Fig. 2** Continuous flow C₂⁺-difluoromethylation with fluoroform.

Reaction conditions: Feed A: 0.5 M diethyl phenylmalonate 1b in THF; Feed B: 1 M LiHMDS in THF; with flow rates for Feed A/Feed B/CHF₃ = 0.30 : 0.20 : 8.3 mL min⁻¹, respectively, the following conditions were obtained: LiHMDS (1.33 equiv.); CHF₃ (2.5 equiv.). Analyzed by GC-FID. For a detailed description of the experiments, see the ESI.†
the $^{19}$F-NMR spectra of the crude reaction mixtures. Difluoromethylation on the imine carbon, a side reaction typically encountered in reactions with CHF$_2$Cl as a reagent, was not observed.\textsuperscript{14b} Due to the instability of the Schiff base to hydrolysis, isolation of the intermediate products was not attempted. Instead, the $N$-benzylidene- and the O-methyl-protecting groups were directly removed by heating the crude product in 6 N HCl in a microwave batch autoclave (150 °C for 45 min). The released benzaldehyde was removed by extracting with ether and the aqueous phase was concentrated. After 45 min). The released benzaldehyde was removed by extracting

Conclusions

A gas–liquid continuous flow difluoromethylation protocol employing fluoroform as a reagent was reported. Fluoroform, a by-product of Teflon manufacture with little current synthetic value, is the most attractive reagent for difluoromethylation reactions. The continuous flow process allows this reaction to be performed within reaction times of 20 min with 2 equiv. of base and 3 equiv. of fluoroform. Importantly, the protocol allows the direct C$_4$-difluoromethylation of protected $\alpha$-amino acids. These compounds are highly selective and potent inhibitors of pyridoxal phosphate-dependent decarboxylases. The starting materials are conveniently derived from the commercially available $\alpha$-amino acid methyl esters, and the final products are obtained in excellent purities and yields after simple hydrolysis and precipitation. The developed process appears to be especially appealing for industrial applications, where atom economy, sustainability, reagent cost and reagent availability are important factors.

Conflicts of interest

There are no conflicts to declare.

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