Fluorine Chemistry

HFO-1234yf as a CF₃-Building Block: Synthesis and Chemistry of CF₃-Ynones

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Abstract: Reaction of low cost, readily available 4th generation refrigerant gas 2,3,3,3-tetrafluoropropene (HFO-1234yf) with lithium disopropylamide (LDA) leads to formation of lithium 3,3,3-trifluoropropynide, addition of which to a range of aldehydes formed CF₃-alkynyl alcohol derivatives on multigram scale, which were oxidised using Dess–Martin periodinane (DMP) to give substituted CF₃-yrones with minimal purification required. Michael-type additions of alcohol and amine nucleophiles to CF₃-yrones are rapid and selective, affording a range of CF₃-enone ethers and enamrones in excellent yields with high stereoselectivity for the Z-isomer. By analogous reactions with difunctional nucleophiles, a wide range of CF₃-substituted pharmaceutically relevant heterocyclic structures can be accessed, exemplified in the simple synthesis of the anti-arthritis drug celecoxib from HFO-1234yf in just three steps.

Introduction

The introduction of fluorine atoms into therapeutic compounds is an important synthetic challenge because fluorination can impart well established beneficial effects to lipophilicity, metabolic stability, conformational preference and bioavailability.[1] In particular, the trifluromethyl group is present in several renowned blockbuster drugs (Scheme 1a). However, incorporation of the CF₃ group into organic systems relies on either inexpensive early stage processes (e.g. HF or SF₄) for the synthesis of a relatively limited range of suitable trifluoromethyl building blocks, particularly aromatic compounds bearing a CF₃ group and trifluoroacetic acid derivatives,[2] or milder, late-stage trifluoromethylating reagents (e.g. Me₃Si-CF₃, CF₃SO₂Na, CF₃-di-benzothiophenium salts or CF₃-hypervalent iodine species), the cost of which can be prohibitive on the manufacturing scale.[3]

New routes to CF₃-substituted systems from low cost building blocks under mild conditions are, therefore, highly desirable, particularly for the preparation of multi-functional derivatives bearing trifluoromethyl groups.

In this context, it is surprising that trifluoromethyl-substituted yrones have received so little attention in the literature, given that yrones are well-known to be useful starting materials in a wide range of synthetically valuable reactions,[4] such as via tandem conjugate addition of dinucleophiles, through various organocatalytic and transition-metal catalysed processes as well as cycloaddition and hydrohalogenation reactions.

Whilst yrones with the CF₃ group adjacent to the carbonyl (CF₃COC=CR) are well known,[5] as they can be derived from trifluoroacetic acid, yrones with a terminal alkynyl CF₃ group (RCOC≡CCF₃) are unexpectedly rare; indeed, there have only been six reports in the literature of this class of structure (Scheme 1b).[6] CF₃-ynoates (CF₃C≡CCO₂R) are commercially available, albeit expensive, and so their use is more widely reported in the literature but their synthesis typically requires thermolysis of the corresponding phosphoranes.[7] This procedure requires high temperatures and also evolves acetylene gas, a significant safety hazard when applied on a large scale.
In this work, we describe a new and efficient route to CF₃-ynones from 2,3,3,3-tetrafluoropropene (HFO-1234yf, 1; Scheme 1c), which is an inexpensive 4th generation refrigerant gas with low global warming potential.[8] Since HFO-1234yf is increasingly being manufactured on a very large scale for legally mandated use in automotive refrigeration systems in the EU, the chemistry of HFO-1234yf has begun to be developed in the last few years.[9] However, HFO-1234yf has not yet seen widespread use for the synthesis of more complex organic compounds and, in this paper, we show that CF₃-ynones derived from 1 can be used to access a diverse variety of both aliphatic and aromatic CF₃-containing compounds, through both intramolecular and intermolecular reactions with nucleophiles.

**Results and Discussion**

We first observed that CF₃-alkynes could be generated from 1 whilst investigating nucleophilic substitution reactions of 1.[9a] Whilst oxygen- and sulfur-centered nucleophiles gave CF₃-alkenyl ethers and vinyl sulfides respectively, nitrogen- and carbon-centered nucleophiles proved to be unreactive with 1 under almost all conditions. An exception was alkyl, aryl or alkynyl lithium reagents and lithium or sodium amides, which caused elimination of lithium fluoride rather than the initially targeted nucleophilic addition-elimination reaction (Scheme 2). Formation of 3,3,3-trifluoropropyne (CF₃C≡CH) was observed by ¹⁹F and ¹H NMR spectroscopy following quenching of the reaction mixture with H₂O (δₙH = 2.45 ppm, δₙF = –50.35 ppm; Figure S5 and S6).[10] When the reaction mixture was instead quenched with D₂O, the proton of 3,3,3-trifluoropropyne was no longer visible spectroscopically. This confirmed that, not only was elimination occurring, but also that the resulting alkyne was deprotonated by the excess organolithium reagent to form lithium 3,3,3-trifluoropropynide (CF₃C≡ClLi, 2) in situ. This method provides, therefore, a simple procedure for generating versatile synthons under relatively mild conditions from a more readily available feedstock than those used previously.[11]

![Scheme 2. Elimination of lithium fluoride from HFO-1234yf (1) to form lithium 3,3,3-trifluoropropynide (2) and subsequent reaction with water.](image)

To gain further insight into the formation of 2 and 3a, the reaction was monitored using in situ IR spectroscopy (Figure 1).[11] This revealed that both the elimination to form 2 and its subsequent addition to benzaldehyde are near instantaneous, i.e. complete within 15 seconds. There also appeared to be no significant side product formation and, indeed, isolation of 3a proved facile. The same synthetic method was applied using a range of other aldehyde substrates to give trifluoromethyl alcohols 3b–3i on multigram scale with minimal purification required in each case, affording 68–95% isolated yields (Table 2).

A model reaction of 2 with benzoyl chloride was investigated as a direct route to CF₃-ynones as the reaction of 2 and benzoyl chloride has previously been shown to form ynone 4a, although this required purification by distillation.[6c] While conversion to 4a of up to 85% was observed by NMR spectroscopy in MTBE, side product formation (Scheme 4) meant isolation of the desired CF₃-ynone 4a could not be achieved using simple work up procedures. The product 4a can react with either iPr₂NH to give the CF₃-enaminone or with additional 2 to afford the diyne alcohol, as observed by NMR and mass spectrometry (Table S1). Jeong et al. reported that reaction of 2 with Weinreb amides leads to formation of an ynone that is immediately attacked by the amine allowing group to give similar enaminones, making the ynone challenging to isolate via this method.[16]

Oxidation of alcohol 3a was instead explored as an alternative multigram scale route to CF₃-ynones. Hoye et al. showed...
Figure 1. (a) Time-arrayed in situ IR spectra; (b) absorbance for alkynyl bonds of 2 (red, 2291 cm⁻¹) and 3a (blue, 2284 cm⁻¹) over course of reaction.

Table 2. Substrate scope for synthesis of CF₃-ynones.

| Compound | Yield / % | Yield / % | Compound | Yield / % | Yield / % |
|----------|-----------|-----------|----------|-----------|-----------|
| 4a       | 94        | 90        | 4f       | 95        | 79        |
| 4b       | 94        | 95        | 4g       | 68        | 84        |
| 4c       | 82        | 79        | 4h       | 79        | 87        |
| 4d       | 86        | 93        | 4i       | 90        | 76        |
| 4e       | 75        | 91        |          | 94        | 76        |

Applying these DMP oxidation conditions to 3a gave CF₃-ynone 4a in 90 % yield and good purity after minimal purification, meaning 4a was obtained from HFO-1234yf (1) in an overall yield of 85 % over two steps. DMP mediated oxidations of CF₃-alcohols 3b–3i gave the corresponding previously unreported CF₃-ynones 4b–4i in 76–95 % isolated yield, showing good tolerance of the reaction conditions for both electron-withdrawing and donating groups on phenyl rings as well as heterocyclic and aliphatic systems (Table 2). Notably, no dehalogenation was observed with halogenated systems 4e and 4g. In each case, the reaction was kept at –10 °C for one hour after addition of the aldehyde to ensure complete consumption of the starting material. Products were isolated in good purity with only a simple aqueous workup in each case, requiring no resource intensive purification procedures. This allowed us to easily carry out these reactions on multigram scale.

Parikh-Doering oxidation of alcohol 3a with dimethyl sulfoxide, triethylamine and a sulfur trioxide-pyridine complex was also explored as an alternative method of synthesising ynone 4a but this led to formation of similar products as shown in Scheme 4 from nucleophilic attack on 4a, although the identity of the nucleophile was not clear in this case. Instead of oxidation, we found that alcohol 3b could be successfully isomerised by a Favorskii-type reaction with just triethylamine, as had been described previously by Yamazaki et al. for similar CF₃-substituted alcohols,[17] forming enone 5 (Scheme 5).

Scheme 5. Favorskii reaction of alcohol 3b to form enone 5.

Returning to the DMP oxidation reaction, one exception to the generally good functional group tolerance was observed in reactions with pyridinyl aldehydes, which were prone to hydrolysis. Reaction of 2 with 3- and 4-pyridinecarboxaldehyde gave complex mixtures of many unidentified products but 2-chloro-3-pyridinecarboxaldehyde formed alcohol 3j cleanly in good yield (Scheme 6a). However, hydrolysis then occurred in the subsequent oxidation, leading to a mixture of products. Following column chromatography, CF₃-azachromone 6 was isolated, possibly formed by attack of water on the initially targeted ynone 4j upon work-up. The resulting alcohol could then cyclise via an S_NAr reaction with the pyridinyl chloride moiety (Scheme 6b). The closest previously known analog to 6 is 5,7-dimethyl-2-trifluoromethyl-8-azachromone, which was synthesised by Sosnovskikh et al. from ethyl trifluoroacetate[18a] but
no other CF₃-derivatives are known. Indeed, azachromones appear to be an uncommon heterocyclic motif in the literature in general, although one notable example can be found in the antiallergenic drug amlexanox.\[18b\]

We anticipated such highly electron-poor ynones to be reactive Michael acceptors. Reactions of naphthyl CF₃-ynone 4b with nucleophiles were explored, with 4b used as a convenient crystalline model compound. Bumgardner et al.\[19\] previously reported that reaction of 4a with phenol and potassium tert-butoxide (KOTBu) was selective for the anti-Michael addition product at room temperature whereas, at high temperature, a mixture of anti-Michael and Michael products was obtained (Scheme 8). Similar reactivity was observed with thiophenol.

Using these literature conditions for the reaction of 4b with phenol, we found a complex mixture of products was formed. Reducing the catalytic loading of KOTBu was key to obtaining clean reactivity, with 10 mol-% giving the best results (Figure S9) and by changing solvent from ethanol to THF and reducing the reaction time from six hours to just five minutes, clean conversion to enol ether 8a was obtained (Table 3). However, 8a appeared, based on ¹H and ¹⁹F NMR coupling patterns to be exclusively the Z stereoisomer of the Michael product rather than the anti-Michael product reported in the literature. Exclusive Michael addition is consistent with other literature examples of the addition of nucleophiles to the more commonplace trifluoromethyl ynoates, including various alcohols and thiolates\[20a\], a range of different amines and phosphites\[20b–20c\] and organolithium reagents.\[20d\] Regio- and stereoselectivity was further confirmed in our case through ¹H-¹H NOE spectroscopy of 8a (Figure S7).

In the case of 4-nitrophenol, the formation of enone ether 8b was sufficiently slow that a 1:1 mixture of stereoisomers was observed by ¹⁹F NMR spectroscopy when the reagents were
Initially mixed. After 5 minutes, the $E/Z$ ratio observed in the final product (15:85) was reached (Figure 2). This reversibility suggests that stereoselectivity is governed by thermodynamic control, with the product mixture becoming enriched in the more stable conformation.

$$t = 0 \text{s} \quad E/Z = 50:50$$

$$t = 5 \text{min} \quad E/Z = 15:85$$

Figure 2. 19F NMR spectra from synthesis of $8b$ ($E$-stereoisomer, $\delta_F = -67.09$ ppm; $Z$-stereoisomer, $\delta_F = -71.13$ ppm).

The effect of temperature on $E/Z$ selectivity for the synthesis of $8a$ was assessed (Figure 3). These reactions were monitored by 19F NMR spectroscopy and in no case was any peak observed consistent with the anti-Michael product reported in the literature by Bumgardner et al. ($\delta_F = -57$ ppm).\(^{[6c]}\) It seems, therefore, that this product can only be observed in a polar protic solvent such as ethanol. At 0 °C and below, the less stable $E$ conformation of $8a$ became the major product, which corroborates the suggestion by Bumgardner et al. that the $E$ stereoisomer is kinetically favoured due to secondary orbital interactions between the $\pi_{CO}$ and $\pi_{CF_3}$ orbitals. DFT calculations reveal that the $Z$-stereoisomer of $8a$ is 0.6 kcal mol$^{-1}$ more stable than the $E$-stereoisomer (Figure S12), supporting the hypothesis that stereoselectivity is governed by thermodynamic control.

Reactions of naphthyl CF$_3$-ynone $4b$ with a range of different amines gave rapid and clean conversion to the corresponding enamiones $9a$–$g$ (Table 4). Excellent isolated yields were obtained simply by evaporation of the solvent following completion of the reaction. The use of L-phenylalanine as a nucleophile was also attempted but gave a mixture of several unidentified products, likely due to side reactions involving the carboxylic acid. A tertiary amine, tert-butylamine, was also trialled but similarly gave a mixture of products as the steric hindrance of the amine was such that the reaction slowed significantly and so the ethanol solvent could effectively compete as a nucleophile.

Table 4. Substrate scope for reaction of CF$_3$-ynone $4b$ with amines.

| Product | Yield / % | $E/Z$ | Product | Yield / % | $E/Z$ |
|---------|-----------|-------|---------|-----------|-------|
| Naph+$\text{NHPh}$ | 96 | 0.100 | Naph+$\text{NHR}$ | 93 | 1.09 |
| Naph+$\text{NHBr}$ | 98 | 0.100 | Naph+$\text{NHR}$ | 95 | 2.98 |
| Naph+$\text{NH}$ | 94 | 0.100 | Naph+$\text{NHR}$ | 91 | 29.71 |

With primary amines ($9a$–$d$), complete selectivity for the $Z$-stereoisomer was observed, as demonstrated by X-ray crystallography (Figure 4a). $^1$H–$^1$H NOE spectroscopy of $9a$ (Figure 4b) showed the same through-space correlations as for $8a$, unequivocally confirming the selectivity of the earlier enone ether syntheses (Table 3). DFT calculations show that the lowest energy conformation of the $Z$ stereoisomer of $9a$ is 6.8 kcal mol$^{-1}$ more stable than the lowest energy conformation of the $E$ stereoisomer (Figure 4c and S12), suggesting that selectivity is driven by thermodynamic control due to the favourable N–H···O hydrogen bonding interactions present in the $Z$ conformation. With secondary amines ($9e$–$g$), stereoselectivity was slightly reduced, perhaps owing to the lack of a stabilising hydrogen bonding interaction. DFT calculations on $9e$ showed that the $Z$-stereoisomer is only 3.2 kcal mol$^{-1}$ more stable (Figure S13) with undesirable steric interactions with the CF$_3$ group affecting the preferred orientation of the pyrrolidinyl plane with respect to the C=C double bond for donation of electron density from nitrogen to the $\pi_{CO}$ orbitals. Compound $9g$, containing the imidazolyl group, does not suffer these unfavourable steric interactions and so the $Z$-isomer is only more stable by 0.8 kcal mol$^{-1}$.

With the intention of using acetamide as the nucleophile to react with $4b$ in ethanol, we instead observed unexpected addition of the ethanol solvent as the nucleophile to form enone ether $10$ (Scheme 9). The role of the acetamide is unclear but it could potentially be acting as a very weak base. Unfortunately, acetamide-mediated reactions with 2-propanol and allyl alcohol using the same conditions were unsuccessful, forming intractable mixtures. Likewise, reaction of $4b$ with neat ethanol or ethanol and other bases was ineffective. This reflects the very high reactivity of CF$_3$-ynones towards nucleophilic attack.

Given that addition of amine nucleophiles occurs selectively $\beta$ to the carbonyl group, the reaction of CF$_3$-ynones with di-
nucleophiles was then explored with the aim of synthesising a range of different heterocyclic structures. Trifluoromethylated pyrazoles (11a), isoxazoles (11b), pyrimidines (11c-e), and benzodiazepines (11f) using this methodology (Table 5). The structures of isoxazole 11b and pyrimidine 11c were confirmed by X-ray crystallography (Figure 5). Notably, the synthesis of isoxazole 11b was completely regioselective, resulting from addition of the softer nitrogen nucleophilic centre to the alkyne preceding reaction of the harder oxygen site with the carbonyl. This offers selective access to the opposite isomer from that recently reported by Grygorenko from CF₃-ynones with the structure CF₃COCR.[21a] Pyrazole 11a[21b] and isoxazole 11b[21c] have been synthesised previously, the latter requiring copper catalyst and two equivalents of zinc bromide in contrast to our transition metal free approach. Together with previously unknown compounds 11c-f, these systems provide useful scaffolds for the construction of more complex compounds in, for example, pharmaceutical discovery programmes. Generally, these reactions of 4b with dinucleophiles could be carried out...
at room temperature but, in cases with poorer nucleophiles, heating and additional base was needed. For 11a and 11c, the products precipitated from the reaction mixture after stirring at ambient temperature overnight and could be simply isolated by filtration, making this method highly scalable.

**Table 5. Cyclisation reactions of CF₃-ynone 4b.**

| Dinucleophile         | Product               | Yield / % |
|-----------------------|-----------------------|-----------|
| NH₂-NH₂Cl             | 11a                   | 75[a]     |
| HO-NH₂Cl              | 11b                   | 76[b]     |
| Ph-NH₂Cl              | 11c                   | 47[c]     |
| Br-NH₂Cl              | 11d                   | 70[d]     |
| NH₂Cl                 | 11e                   | 37[e]     |
| NH₂Cl                 | 11f                   | 67[f]     |

*Conditions: [a] EtOH, rt, 16 h; [b] 1 eq. K₂CO₃, EtOH, 80 °C, 16 h; [c] EtOH, 80 °C, 16 h*

Reaction of 4b with 2-aminopyridine afforded unexpected pyrido[1,2-a]pyrimidine 12 (Scheme 10a). The pyridine nitrogen seemingly attacks first via a Michael addition adjacent to the CF₃ group, which is not unprecedented in the literature having been reported for addition of 2-aminopyridines to allenic nitriles[22a] and pentafluoropyridine,[22b–22c] after which the imine formed acts as a nucleophile to attack the carbonyl and cyclise as expected (Scheme 10b). The ethanol solvent then adds via a second Michael reaction to the electron-poor pyridopyrimidine intermediate before losing water to form 12, the structure of which was confirmed by X-ray crystallography (Figure 6).

![Figure 6. Molecular structures of CF₃-pyridopyrimidine 12 as determined by X-ray crystallography.](image)

To demonstrate the applicability of CF₃-ynones in the synthesis of valuable pharmaceuticals, the blockbuster anti-inflammatory drug celecoxib (13)[23] was prepared with 96 % regioselectivity in good yield from ynone 4f (Scheme 11). This exemplifies the potential of using a readily accessible refrigerant gas in the production of active pharmaceutical ingredients, with 13 being formed in just three steps from HFO-1234yf (1) in an overall yield of 58 % with minimal purification required at each stage.

**Scheme 11. Synthesis of celecoxib from CF₃-ynone 4f.**

![Scheme 11. Synthesis of celecoxib from CF₃-ynone 4f.](image)

**Conclusion**

In summary, the inexpensive and readily available refrigerant gas 2,3,3,3-tetrafluoropropene (HFO-1234yf, 1) has been shown for the first time to react with alkyllithium reagents or lithium amides to eliminate lithium fluoride and form 3,3,3-trifluoropropyne (CF₃C≡CH). With two equivalents of lithium diisopropylamide (LDA) in methyl tert-butyl ether, this forms the versatile synthon lithium trifluoropropanylide (CF₃C≡CLi, 2) in situ...
by a 1,2-elimination process, which reacts with a variety of aldehydes to afford the corresponding CF₃-alcohols (3) in high yields on a multigram scale, rearrangement of which formed CF₃-oxonones (5). Oxidation of the CF₃-alcohols with Dess–Martin periodinane (DMP) gave CF₃-ynones (CF₃C≡COR, 4) without the need for column chromatography. This methodology, therefore, gave ready access to multi-gram quantities of CF₃-ynones (CF₃C≡COR, 4) from an inexpensive fluorocarbon source. Intramolecular cyclisation of these ynones gave access to CF₃-azahomocycles (6) whilst addition of various electrophiles proceeded as expected for an electrophilic addition process, giving the most thermodynamically stable stereoisomer of polyfunctional halogenated CF₃-oxones (7). Reactions of model substrate naphthyl CF₃-ynone 4b with various alcohols and amines as nucleophiles resulted in Michael-type reactions to form CF₃-ynone esters (8/10) and CF₃-enaminones (9), respectively, in high yields after straightforward workups. We established that Michael addition products were obtained in reactions of CF₃-ynones (CF₃C≡COR, 4) with nucleophiles rather than previously reported anti-Michael isomers[6c] by reversible reaction to yield the more thermodynamically stable Z isomers. Reactions of CF₃-ynones (CF₃C≡COR, 4) with di nucleophiles gave a range of novel CF₃-substituted heterocycles (11/12) including pyrazoles, isoxazoles, pyrimidines and benzodiazepines, arising from initial attack of the nucleophiles at the alkyne triple bond in a similar Michael addition process. The cyclisation of CF₃-ynone 4f was successfully applied to the synthesis of the blockbuster anti-inflammatory drug celecoxib (13), in just three steps from HFO-1234yf, demonstrating the application of an industrial scale reagent for the synthesis of complex CF₃-containing systems without requiring transition metal catalysts or expensive purification methods.

**Experimental Section**

Representative examples of experimental procedures and characterisation data are given below. Full characterisation data, NMR spectra, and experimental procedures for all other compounds are given in the Supporting Information. Crystallographic data for compounds 7c, 9a, 11c and 12 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1995119–1995123.

1-(2′-Naphthyl)-4,4,4-trifluorobut-2-yn-1-one (4b): Compound 4b (0.200 g, 7.99 mmol) was dissolved in CH₂Cl₂ (100 mL) and Dess–Martin periodinane (6.78 g, 16.0 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours then a 1:1 mixture of saturated aqueous sodium thiosulfate and sodium bicarbonate was added and the resulting mixture stirred vigorously for 30 minutes. The organic layer was separated then washed with sodium thiosulfate, sodium bicarbonate then brine, dried with MgSO₄ and concentrated in vacuo to give 1-(2′-naphthyl)-4,4,4-trifluorobut-2-yn-1-one (4b) (18.9 g, 95 %), as a yellow solid, m.p. 78–80 °C. The reaction mixture was warmed to room temperature then added dropwise and the reaction was stirred at –10 °C for 1 hour. The reaction mixture was warmed to room temperature then quenched by adding saturated aqueous sodium bisulfite and stirred vigorously for 30 minutes. The aqueous layer was separated and extracted with MTBE then the combined organic extracts washed vigorously for 30 minutes. The resulting precipitate was filtered, washed with ethanolic then dried in vacuo to give 1-(2′-naphthyl)-4,4,4-trifluorobut-2-yn-1-one, 4b (1.43 g, 25 mmol) was dissolved in a solution of 1M HCl then with brine, dried with MgSO₄ and concentrated in vacuo to afford the corresponding CF₃-alcohols (4c, 1.107 g, 75 %), as a yellow solid, m.p. 161–162 °C (lit. 178–179 °C from toluene).[21b] The reaction mixture was warmed to room temperature then added dropwise and the reaction was stirred at –10 °C for 1 hour. The reaction mixture was warmed to room temperature then quenched by adding saturated aqueous sodium bisulphite and stirred vigorously for 30 minutes. The aqueous layer was separated and extracted with MTBE then the combined organic extracts washed with 1M HCl then with brine, dried with MgSO₄ and concentrated in vacuo to give 1-(2′-naphthyl)-4,4,4-trifluorobut-2-yn-1-ol, 3b (2.78 g, 94 %), as a yellow solid, m.p. 78–80 °C. δC (400 MHz; CDCl₃) 161.69 (br s, N–H), 7.56 (2H, m, ArH), 7.66 (1H, d, JCF 2.0 Hz, C(1’)-H), 7.92 (3H, m, ArH), 8.03 (1H, m, ArH), 8.09 (1H, m, ArH). δC (376 MHz; CDCl₃) –74.16 (d,4 CF 7.0), 133.67 (s, C4), 135.00 (s, C5), 135.10 (s, C6), 136.86 (s, C7), 175.05 (s, C1), IR (neat) νmax /cm–1 2160 (C≡C), 1648 (C=O), 1524, 1350, 1250, 1158, 1133, 1018. GC-MS (EI+) m/z 248 (M⁺, 100 %), 220 (38), 179 (25), 170 (17), 155 (17), 127 (55). HRMS (EI+) m/z calc. for C₁₄H₉OF₃ [M + H⁺] [M + H⁺]+ 249.0527, found 249.0513. HRMS (EI+) m/z calc. for C₁₃H₁₀OF₂ [M + H⁺] 267.0633, found 267.0634.

3-(2′-Naphthyl)-5-(trifluoromethyl)-1H-pyrazole (11a): Compound 4b (0.135 g, 0.544 mmol) and hydrazine hydrochloride (0.094 g, 1.37 mmol) were dissolved in ethanol (20 mL) and stirred at room temperature for 16 hours. The resulting precipitate was filtered, washed with ethanol then dried in vacuo to give 3-(2′-naphthyl)-5-(trifluoromethyl)-1H-pyrazole, 11a (0.107 g, 75 %), as a yellow solid, m.p. 161–162 °C (lit. 178–179 °C from toluene).[21b] δC (400 MHz; CDCl₃) 169.69 (br s, N–H), 7.56 (2H, m, ArH), 7.66 (1H, d, JCF 2.0 Hz, C(1’)-H), 7.92 (3H, m, ArH), 8.03 (1H, m, ArH), 8.09 (1H, m, ArH). δC (376 MHz; CDCl₃) –74.16 (d,4 CF 7.0). δC (101 MHz; CDCl₃) 122.02 (q, JCF 273.2, CF₃), 123.75 (C₄), 126.51 (C₂F₃, 38.2, C5), 126.96 (s, Ar), 128.00 (s, Ar), 128.04 (s, Ar), 128.11 (s, Ar), 128.99 (s, Ar), 129.13 (s, Ar), 129.17 (s, Ar), 133.08 (s, Ar), 135.00 (s, Ar), 157.72 (s, C3). IR (neat) νmax /cm–1 3050 (NH), 2160, 2039, 1561, 1288, 1260, 1183, 1154, 1128, 1056. GC-MS (EI+) m/z 262 (M⁺, 100 %), 214 (11), 165 (18), 131 (11). HRMS (EI+) m/z calc. for C₁₃H₁₀F₂N₂ [M + H⁺] 263.0796, found 263.0803. Spectroscopic data consistent with literature reports.[21b]

Crystal data and parameters of refinement are listed in Table S4. Deposition Numbers 1995119–1995123 contain the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

**Acknowledgments**

We thank GlaxoSmithKline and EPSRC for the award of an iCASE studentship to B.J. M. and Durham University MChem programme for funding to T.G.F. M.
Keywords: Fluorine · Heterocycles · HFO-1234yf · Trifluoromethyl · Ynones

[1] a) K. Müller, C. Faeh, F. Diederich, Science 2007, 317, 1881; b) S. Purser, P. R. Moore, S. Swallow, V. Gourgerneur, Chem. Soc. Rev. 2008, 37, 320; c) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, Chem. Rev. 2014, 114, 2432; d) N. A. Meanwell, J. Med. Chem. 2016, 58, 872.

[2] For an overview of CF₃ building blocks, see: a) M. Schlosser, Angew. Chem. Int. Ed. 2006, 45, 5432; Angew. Chem. 2006, 118, 5558; b) S. E. Lopez, J. Salazar, J. Fluorine Chem. 2013, 156, 73; c) A.arrisany, G. Sandford, Green Chem. 2015, 17, 2081; d) S. Caron, Organ Proc. Res. Dev. 2020, 24, 470.

[3] For recent reviews of late-stage trifluoromethylation strategies, see: a) J. Charpentier, N. Früh, A. Togni, Angew. Chem. Int. Ed. 2015, 115, 650; b) X. Yang, T. Wu, R. J. Phipps, F. D. Toste, Chem. Rev. 2015, 115, 826; c) A. Alonso, E. M. de Martignota, G. Rubiales, F. Palacios, Chem. Rev. 2015, 115, 1847; d) H.-X. Song, Q.-Y. Han, C.-L. Zhao, C.-P. Zhang, Green Chem. 2018, 20, 1662; e) X. Li, X. Shi, L. Li, D. Shi, Beilstein J. Org. Chem. 2019, 15, 2213.

[4] For previous examples of HFO-1234yf in organic synthesis, see: a) B. J. Wallington, R. Singh, Tetrahedron 2019, 54, 168; b) D. Meyer, M. El Qacemi, Org. Lett. 2020, 22, 3479.

[5] For reviews of yrones with the structure RCOCF₃, see: a) Y. Rulew, A. Romanov, RSC Adv. 2016, 6, 1984.

[6] For examples of previous preparations of 3,3,3-trifluoropropyne or lithium 3,3,3-trifluoropropynide, see: a) R. N. Haszeldine, Bull. Acad. Sci. USSR Div. Chem. Sci. 1951, 57, 165; b) W. Cen, Y. Ni, Y. Shen, J. Fluorine Chem. 1995, 73, 161; c) G. Prié, S. Richard, J.-L. Parrian, A. Duchêne, M. Abbarbi, J. Fluorine Chem. 2002, 117, 35; d) C. D. Poulter, P. L. Wiggins, T. L. Plummer, J. Org. Chem. 1981, 46, 1532.

[7] a) B. A. Chalyk, A. Khutorianskyi, A. Lysenko, Y. Fil, Y. O. Kuchkovska, K. S. Gavrilenko, I. Bakanovych, S. Y. Moroz, A. O. Gorlova, O. O. Grygorenko, J. Fluorine Chem. 2019, 84, 15212; b) G. Yang, R. G. Raptis, J. Heterocycl. Chem. 2003, 40, 659; c) X.-Z. Zhang, W.-L. Hu, S. Chen, X.-G. Hu, Org. Lett. 2018, 20, 860.

[8] a) S. R. Landor, D. D. Miller, Tetrahedron 2010, 66, 519; c) R. Ranjar-Karimi, M. Mashak- Shohtsaria, S. Hashemi-Uljerdi, R. Kia, J. Fluorine Chem. 2011, 132, 285.

[9] a) D. Rosenberg, W. Drenth, Tetrahedron 1971, 27, 3893; b) D. Meyer, M. El Qacemi, Org. Lett. 2020, 22, 3479.

[10] a) D. Rosenberg, W. Drenth, Tetrahedron 1971, 27, 3893; b) D. Meyer, M. El Qacemi, Org. Lett. 2020, 22, 3479.

[11] For examples of previous preparations of 3,3,3-trifluoropropylene or lithium 3,3,3-trifluoropropynide, see: a) R. N. Haszeldine, Nature 1950, 165, 152; b) A. L. Henne, M. Nager, J. Am. Chem. Soc. 1951, 73, 1042; c) W. C. Smith, C. W. Tulllock, E. L. Muetterties, W. R. Hasek, F. S. Fawcott, V. A. Engelhardt, D. D. Coffman, J. Am. Chem. Soc. 1959, 81, 3165; d) W. G. Finnegan, W. P. Norris, J. Org. Chem. 1963, 28, 1139; e) J. Mielcarek, J. G. Morse, K. W. Morse, J. Fluorine Chem. 1978, 12, 321; f) M. Shimizu, M. Higashi, Y. Takeda, G. Jiang, M. Murai, T. Hiyama, Synlett 2007, 7, 1163; g) A. Miyagawa, M. Naka, T. Yamazaki, T. Kawasai-Takasuka, Eur. J. Org. Chem. 2009, 4395.
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HFO-1234yf as a CF₃-Building Block: Synthesis and Chemistry of CF₃-Ynones

Reaction of the inexpensive refrigerant gas HFO-1234yf with strong base leads to elimination of HF to give an alkynide that can be trapped to form CF₃-yrones, which are highly reactive electrophiles for rapid and clean Michael-type additions. With dinucleophiles, various CF₃-heterocycles can be synthesised including the blockbuster drug celecoxib.