EurJOC
European Journal of Organic Chemistry

Full Paper
doi.org/10.1002/ejoc.202001071

Fluorine Chemistry

HFO-1234yf as a CF_3-Building Block: Synthesis and Chemistry of CF_3-Ynones

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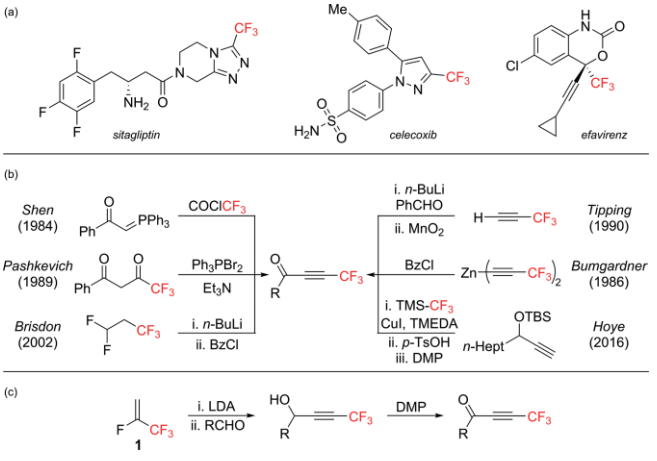
Abstract: Reaction of low cost, readily available 4th generation refrigerant gas 2,3,3,3-tetrafluoropropene (HFO-1234yf) with lithium di*iso*propylamide (LDA) leads to formation of lithium 3,3,3-trifluoropropynide, addition of which to a range of aldehydes formed CF_3-alkynyl alcohol derivatives on multigram scale, which were oxidised using Dess–Martin periodinane (DMP) to give substituted CF_3-ynones with minimal purification required. Michael-type additions of alcohol and amine nucleophiles to CF_3-ynones are rapid and selective, affording a range of CF_3-enone ethers and enaminones in excellent yields with high stereoselectivity for the *Z*-isomer. By analogous reactions with difunctional nucleophiles, a wide range of CF_3-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 trifluoromethyl group is present in several renowned blockbuster drugs (Scheme 1a). However, incorporation of the CF_3 group into organic systems relies on either inexpensive early stage processes (e.g. HF or SF_4) for the synthesis of a relatively limited range of suitable trifluoromethyl building blocks, particularly aromatic compounds bearing a CF_3 group and trifluoroacetic acid derivatives,[2] or milder, late-stage trifluoromethylating reagents (e.g. Me_3Si-CF_3, CF_3SO_2Na, CF_3-dibenzothiophenium salts or CF_3-hypervalent iodine species), the cost of which can be prohibitive on the manufacturing scale.[3] New routes to CF_3-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 ynones have received so little attention in the literature, given that ynones 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 ynones with the CF_3 group adjacent to the carbonyl ($CF_3COC{\equiv}CR$) are well known,[5] as they can be derived from trifluoroacetic acid, ynones with a terminal alkynyl CF_3 group ($RCOC{\equiv}CCF_3$) are unexpectedly rare; indeed, there have only been six reports in the literature of this class of structure (Scheme 1b).[6] CF_3-ynoates ($CF_3C{\equiv}CCO_2R$) 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.



Scheme 1. (a) Well-known heterocyclic drug molecules bearing a CF_3-group; (b) previously reported syntheses of CF_3-ynones; (c) approach in this work.

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.202001071.

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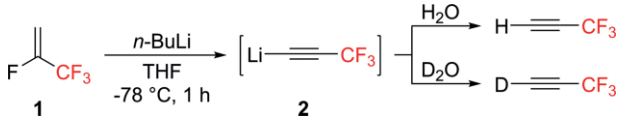
doi.org/10.1002/ejoc.202001071

In this work, we describe a new and efficient route to CF_3-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 CF_3-ynones derived from **1** can be used to access a diverse variety of both aliphatic and aromatic CF_3-containing compounds, through both intra- and intermolecular reactions with nucleophiles.

Results and Discussion

We first observed that CF_3-alkynes could be generated from **1** whilst investigating nucleophilic substitution reactions of **1**.[9a] Whilst oxygen- and sulfur-centered nucleophiles gave CF_3-enol ethers and vinyl sulfides respectively, nitrogen- and carbon-centred nucleophiles proved to be unreactive with **1** under almost all conditions. An exception was alkyl, aryl or alkynyllithium 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 ($CF_3C{\equiv}CH$) was observed by ^{19}F and ^{1}H NMR spectroscopy following quenching of the reaction mixture with H_2O (δ_H = 2.45 ppm, δ_F = −50.35 ppm; Figure S5 and S6).[10] When the reaction mixture was instead quenched with D_2O, 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 ($CF_3C{\equiv}CLi$, **2**) in situ. This method provides, therefore, a simple procedure for generating versatile synthon **2** under relatively mild conditions from a more readily available feedstock than those used previously.[11]

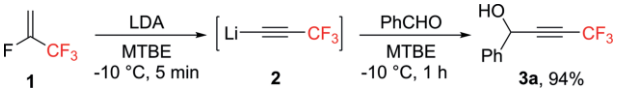


Scheme 2. Elimination of lithium fluoride from HFO-1234yf (**1**) to form lithium 3,3,3-trifluoropropynide (**2**) and subsequent reaction with water.

The possibility of using **2** derived from **1** in synthesis was then investigated, using addition to a simple electrophile, benzaldehyde, as a model reaction (Table 1), as has been previously reported with **2** derived from other sources.[12] With *n*BuLi, reaction of **2** with benzaldehyde was outcompeted by addition of Bu^- but this side reaction was successfully suppressed using lithium diisopropylamide (LDA) as the base. Whilst limited conversion was observed with lithium tetramethylpiperidide (LTMP), lithium hexamethyldisilazide (LHMDS) gave no reaction at all, which suggests that the pK_a of the protons of **1** lies somewhere between 30 and 36.[13] Both diethyl ether and THF as solvents at −78 °C gave good conversion but, at a more convenient −10 °C, THF gave much lower conversion. This corroborates literature reports that **2** is more stable in diethyl ether than THF.[6e] However, diethyl ether is an undesirable solvent for process scales due to its volatility and tendency to form peroxides. Methyl *tert*-butyl ether (MTBE), a safer and more environmentally benign alternative to diethyl ether,[14] was found to give excellent conversion. Hence, using LDA in MTBE, trifluoromethyl alcohol **3a** was obtained in excellent yield and purity without the need for column chromatography or distillation, requiring only a simple aqueous workup (Scheme 3).

Table 1. Screening of conditions for addition of **2** to benzaldehyde to form alcohol **3a**; conversion determined by ^{19}F NMR spectroscopy.

Solvent	Base	Temperature /°C	Conversion /%
Et_2O	*n*BuLi	−78	1
Et_2O	LDA	−78	82
Et_2O	LDA	−10	97
Et_2O	LTMP	−10	14
Et_2O	LHMDS	−10	0
THF	LDA	−78	82
THF	LDA	−10	13
CPME	LDA	−10	91
MTBE	LDA	−10	98
nBu_2O	LDA	−10	70



Scheme 3. Optimised synthesis of trifluoromethyl alcohol **3a**.

To gain further insight into the formation of **2** and **3a**, the reaction was monitored using in situ IR spectroscopy (Figure 1).[15] 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 CF_3-ynones as the reaction of **2** and benzoyl chloride has previously been shown to form ynone **4a**, although this required purification by distillation.[6e] 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 CF_3-ynone **4a** could not be achieved using simple work up procedures. The product **4a** can react with either iPr_2NH to give the CF_3-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 leaving 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 CF_3-ynones. Hoye et al. showed

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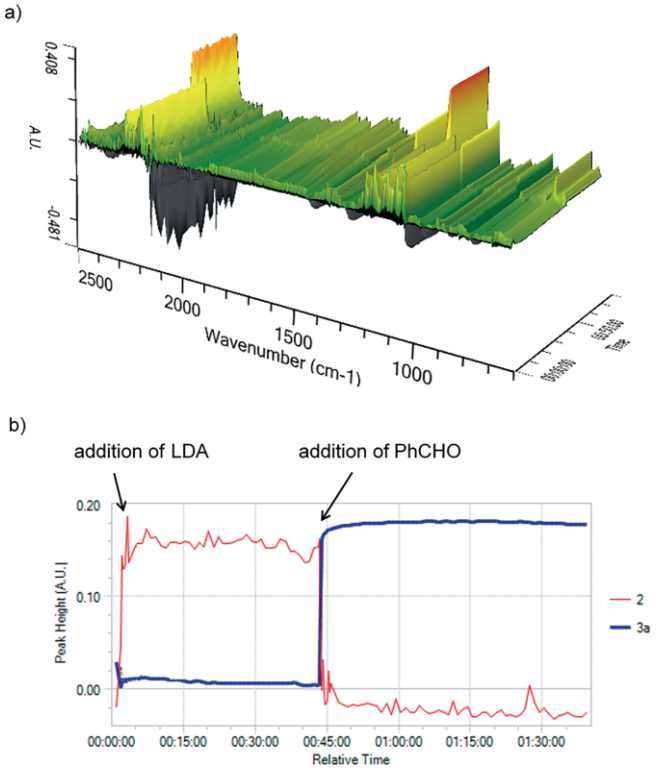
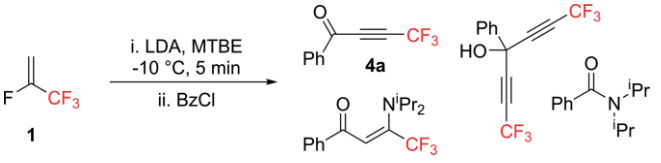


Figure 1. (a) Time-arrayed in situ IR spectra; (b) absorbance for alkynyl bonds of **2** (red, 2291 cm^{-1}) and **3a** (blue, 2284 cm^{-1}) over course of reaction.

Table 2. Substrate scope for synthesis of CF_3-ynones.

Compound	Yield / % 3a-i	Yield / % 4a-i	Compound	Yield / % 3a-i	Yield / % 4a-i
4a	94	90	**4f**	95	79
4b	94	95	**4g**	68	84
4c	82	79	**4h**	79	87
4d	86	93			
4e	75	91	**4i**	94	76

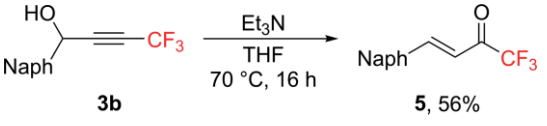
that an alkynyl CF_3-alcohol could be readily oxidised to the corresponding ynone using Dess–Martin periodinane (DMP).[6f]



Scheme 4. Attempted direct synthesis of CF_3-ynones from **1** and benzoyl chloride showing products observed under various conditions.

Applying these DMP oxidation conditions to **3a** gave CF_3-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 CF_3-alcohols **3b**–**3i** gave the corresponding previously unreported CF_3-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 CF_3-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, CF_3-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

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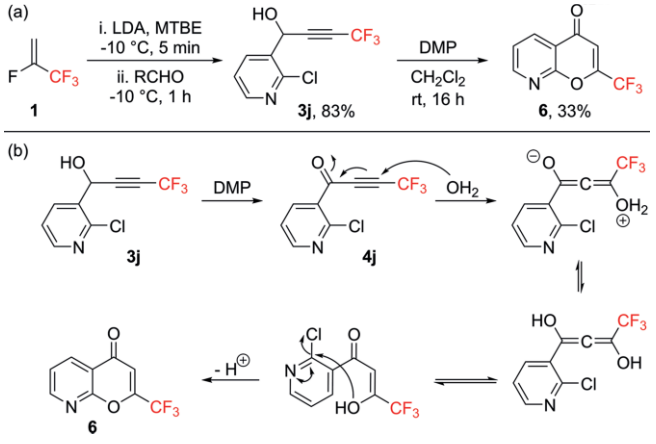
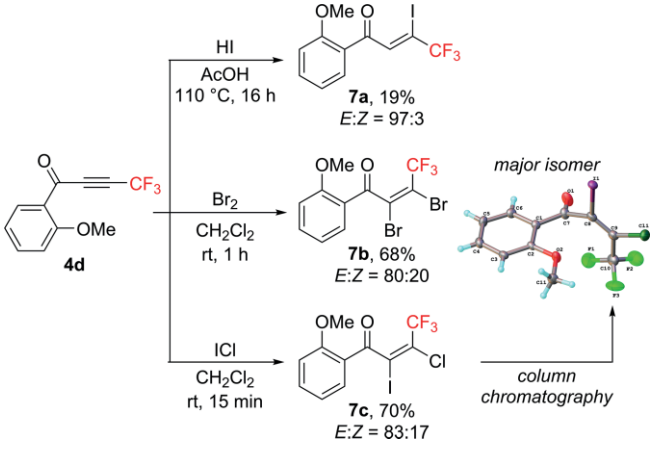
no other CF_3-derivatives are known. Indeed, azachromones appear to be an uncommon heterocyclic motif in the literature in general, although one notable example can be found in the antiallergenic drug amlexanox.[18b]



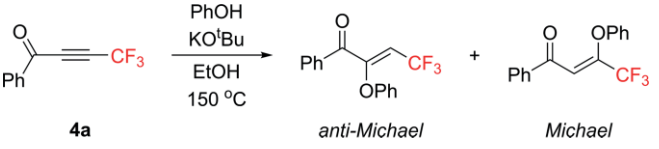
Scheme 6. (a) Synthesis of CF_3-azachromone **6**; (b) proposed mechanism for formation of **6**.

Given the cyclisation observed in the synthesis of **6**, demethylation of the related methoxy-substituted CF_3-ynone **4d** using HI was then attempted as a route to the corresponding CF_3-substituted chromones. However, this gave addition of HI across the triple bond to form enone **7a** instead (Scheme 7). The regio- and stereoselectivity appeared by NMR spectroscopy to be that arising from nucleophilic attack of iodide in a Michael-type process (see later for more details). Attempted Larock-type electrocyclization[19] of **4d** with bromine or iodine monochloride also led only to electrophilic addition, forming compounds **7b** and **7c** respectively. The major isomer of **7c** was isolated and the regio- and stereoselectivity of the electrophilic addition process confirmed crystallographically (the same selectivity was assumed for **7b**). The preference for the Z stereoisomer for **7b** and **7c** observed experimentally is supported by DFT calculations assuming thermodynamic pathways take place in these reactions (Figure S14).



Scheme 7. Electrophilic addition reactions of CF_3-ynones **4d** with structure of major isomer of **7c** as determined by X-ray crystallography.

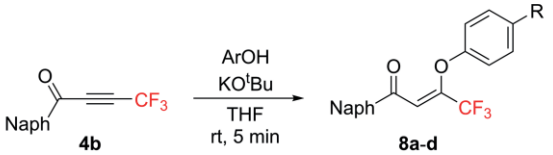
We anticipated such highly electron-poor ynones to be reactive Michael acceptors. Reactions of naphthyl CF_3-ynone **4b** with nucleophiles were explored, with **4b** used as a convenient crystalline model compound. Bumgardner et al.[6c] previously reported that reaction of **4a** with phenol and potassium *tert*-butoxide (KO*t*Bu) 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.



Scheme 8. Reported reaction of a CF_3-ynone with phenoxide.[6c]

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 KO*t*Bu 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 ^{19}F 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 thiols,[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). The reaction of **4b** with a range of other *para*-substituted phenols was then carried out to give enone ethers **8b**–**d** in 76–85 % isolated yield (Table 3). Stronger nucleophiles, such as thiophenol, aliphatic alcohols and even 4-methoxyphenol, gave intractable complex mixtures of many unidentified products under these conditions, limiting the scope of the reactions of oxygen-centred nucleophiles with CF_3-ynones.

Table 3. Reactions of CF_3-ynone **4b** with phenols.



Product	R	Yield / %	*E*:*Z*
8a	H	89	14:86
8b	NO_2	85	15:85
8c	Br	84	11:89
8d	*n*-C_5H_{11}	76	17:83

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 ^{19}F 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 that stereoselectivity is governed by thermodynamic control, with the product mixture becoming enriched in the more stable conformation.

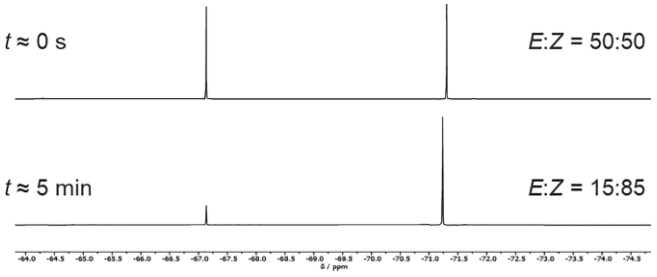


Figure 2. 19F NMR spectra from synthesis of **8b** (*E*-stereoisomer, δ_F = –67.09 ppm; *Z*-stereoisomer, δ_F = –71.13 ppm).

The effect of temperature on *E*/*Z* selectivity for the synthesis of **8a** was assessed (Figure 3). These reactions were monitored by ^{19}F NMR spectroscopy and in no case was any peak observed consistent with the anti-Michael product reported in the literature by Bumgardner et al. (δ_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 π_{CO} and π_{CF}* 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.

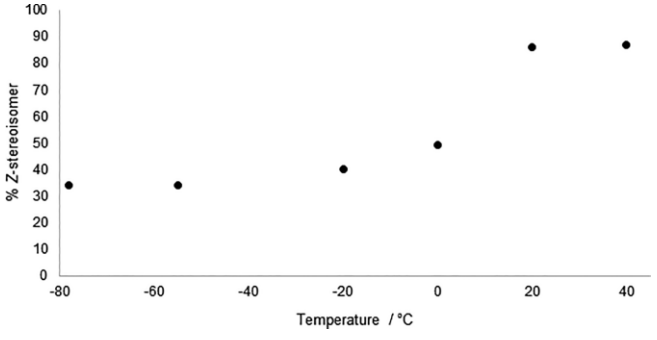
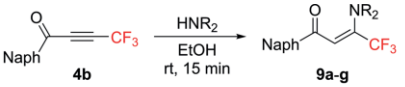


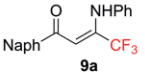
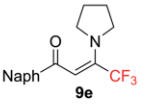
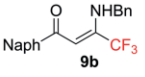
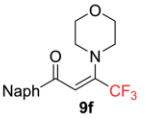
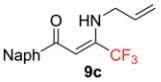
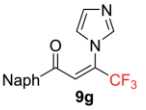
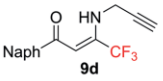
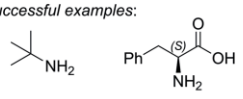
Figure 3. Selectivity for *Z*-stereoisomer in synthesis of **8a** at different temperatures as determined by ^{19}F NMR spectroscopy.

Reactions of naphthyl CF_3-ynone **4b** with a range of different amines gave rapid and clean conversion to the corresponding enaminones **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.



4b **9a-g**

Product	Yield / %	*E*:*Z*	Product	Yield / %	*E*:*Z*
 **9a**	96	0:100	 **9e**	93	1:99
 **9b**	98	0:100	 **9f**	95	2:98
 **9c**	94	0:100	 **9g**	91	29:71
 **9d**	95	0:100	*unsuccessful examples*: 		

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 π_{CC} 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 β to the carbonyl group, the reaction of CF_3-ynones with di-

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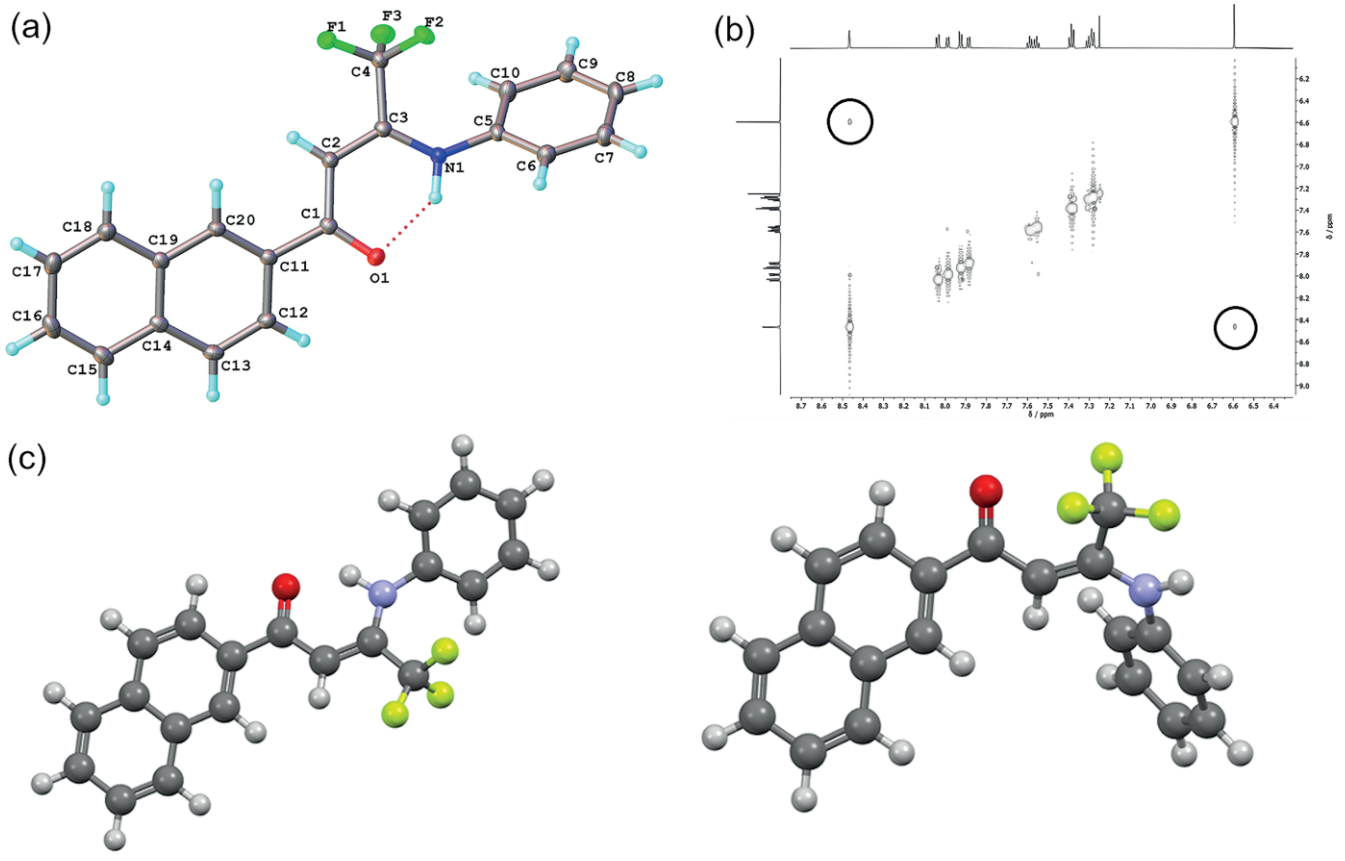
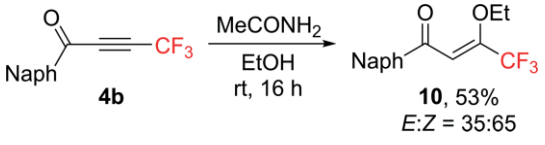


Figure 4. (a) Structure of **9a** determined by X-ray crystallography; (b) ^{1}H-^{1}H NOESY spectrum of **9a** with diagnostic through-space interaction between protons on C2 and C20 highlighted to prove regiochemistry and lack of interaction between protons on C2 and C6/10 to prove stereochemistry; (c) optimised geometries of *E*-**9a** (left) and *Z*-**9a** (right) calculated at B3LYP/6-31G.



Scheme 9. Reaction of CF_3-ynone **4b** with ethanol.

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 CF_3-ynones with the structure $CF_3COC{\equiv}CR$.[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

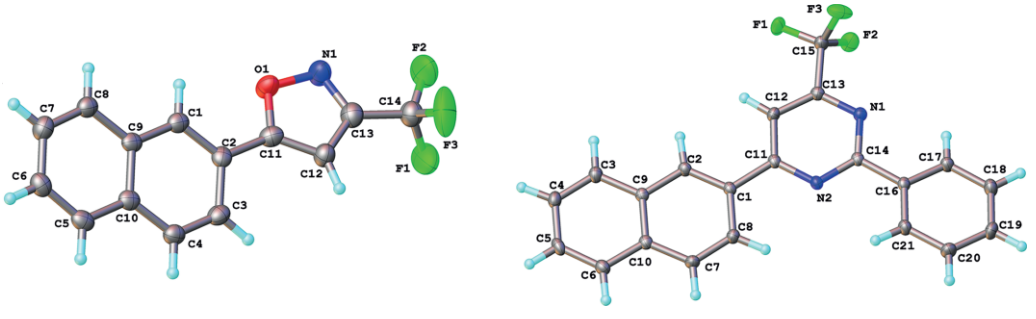


Figure 5. Molecular structures of CF_3-isoxazole **11b** (left) and CF_3-pyrimidine **11c** (right) as determined by X-ray crystallography.

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.

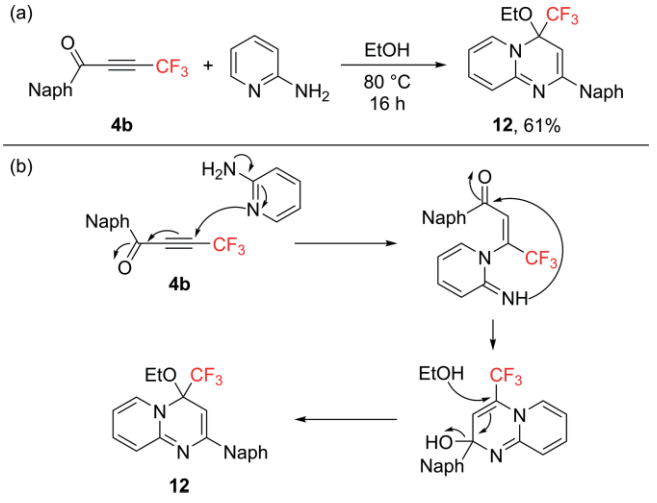
Table 5. Cyclisation reactions of CF_3-ynone **4b**.

Dinucleophile	Product	Yield / %
H_2N-NH_3Cl	**11a**	75[a]
$HO-NH_3Cl$	**11b**	76[b]
	11c	47[a]
	11d	70[c]
	11e	37[c]
	11f	67[a]

Conditions: [a] EtOH, rt, 16 h;
[b] 1 eq. K_2CO_3, 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 CF_3 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).

To demonstrate the applicability of CF_3-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



Scheme 10. (a) Reaction of CF_3-ynone **4b** with 2-aminopyridine; (b) proposed mechanism for formation of **12**.

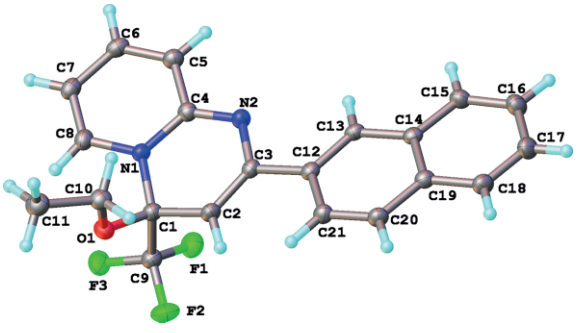
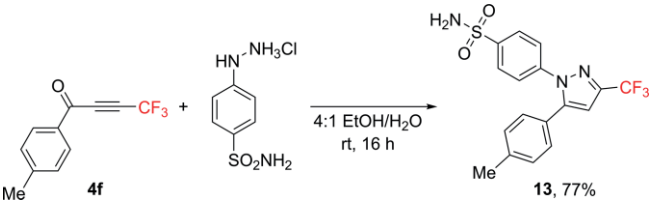


Figure 6. Molecular structures of CF_3-pyridopyrimidine **12** as determined by X-ray crystallography.

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 CF_3-ynone **4f**.

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 ($CF_3C{\equiv}CH$). With two equivalents of lithium diisopropylamide (LDA) in methyl *tert*-butyl ether, this forms the versatile synthon lithium trifluoropropynide ($CF_3C{\equiv}CLi$, **2**) in situ

by a 1,2-elimination process, which reacts with a variety of aldehydes to afford the corresponding CF_3-alcohols (**3**) in high yields on a multigram scale, rearrangement of which formed CF_3-enones (**5**). Oxidation of the CF_3-alcohols with Dess–Martin periodinane (DMP) gave CF_3-ynones ($CF_3C{\equiv}COR$, **4**) without the need for column chromatography. This methodology, therefore, gave ready access to multi-gram quantities of CF_3-ynones ($CF_3C{\equiv}COR$, **4**) from an inexpensive fluorocarbon source. Intramolecular cyclisation of these ynones gave access to CF_3-azachromones (**6**) whilst addition of various electrophiles proceeded as expected for an electrophilic addition process, giving the most thermodynamically stable stereoisomer of polyfunctional halogenated CF_3-enones (**7**). Reactions of model substrate naphthyl CF_3-ynone **4b** with various alcohols and amines as nucleophiles resulted in Michael-type reactions to form CF_3-enone esters (**8**/**10**) and CF_3-enaminones (**9**), respectively, in high yields after straightforward workups. We established that Michael addition products were obtained in reactions of CF_3-ynones ($CF_3C{\equiv}COR$, **4**) with nucleophiles rather than previously reported *anti*-Michael isomers[6c] by reversible reaction to yield the more thermodynamically stable *Z* isomers. Reactions of CF_3-ynones ($CF_3C{\equiv}COR$, **4**) with dinucleophiles gave a range of novel CF_3-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 CF_3-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 refrigerant for the synthesis of complex CF_3-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**, **11b**, **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-ol (3b): Diisopropylamine (3.5 mL, 25 mmol) was dissolved in a solution of **1** (1.43 g, 12.6 mmol) in anhydrous MTBE (100 mL) under argon. *n*-Butyllithium (2.5 M in hexanes, 10 mL, 25 mmol) was added dropwise at –10 °C and the resulting solution of lithium diisopropylamide was stirred for 5 minutes at –10 °C. 2-Naphthaldehyde (1.78 mL, 11.3 mmol) as a solution in anhydrous MTBE (20 mL) was 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 with 1 M HCl then with brine, dried with $MgSO_4$ 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. δ_H (400 MHz; $CDCl_3$) 2.46 (br s, O-H), 5.73 (1H, q, $^5J_{HF}$ 3.0, C(1)H), 7.55 (2H, m, C(4′/3′)H), 7.60 (1H, m, C(1′)H), 7.90 (4H, m (C6′-9′)H). δ_F (376 MHz; $CDCl_3$) –50.53 (d, $^5J_{HF}$ 3.0). δ_C (101 MHz; $CDCl_3$) 64.37 (d, $^4J_{CF}$ 1.3, C1), 73.86 (q, $^2J_{CF}$ 53.0, C3), 86.51 (q, $^3J_{CF}$ 6.4, C2), 114.22 (q, $^1J_{CF}$ 257.9, C4), 124.09 (s, Ar), 125.95 (s, Ar), 126.88 (s, Ar), 127.05 (s, Ar), 127.93 (s, Ar), 128.41 (s, Ar), 129.29 (s, Ar), 133.21 (s, C5′/10′), 133.67 (s, C5′/10′), 135.32 (s, C2′). IR (neat) $\tilde{\nu}_{max}$ /cm^{-1} 3324 (br, O-H), 2278 (C≡C), 2160, 2032, 1603, 1508, 1420, 1323, 1289, 1120, 1020. GC-MS (EI+) *m/z* 250 (M^+, 98 %), 232 (24, $[M - F + H]^+$), 201 (38), 183 (32), 152 (36), 129 (100, $[M - C_4H_2OF_3]^+$). HRMS (ESI+) *m/z* calcd. for $C_{14}H_9OF_3$ $[M + H]^+$ 251.0684, found 251.0683. Spectroscopic data consistent with literature reports.[24]

1-(2′-Naphthyl)-4,4,4-trifluorobut-2-yn-1-one (4b): Compound **3b** (2.00 g, 7.99 mmol) was dissolved in CH_2Cl_2 (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 $MgSO_4$ and concentrated in vacuo to give 1-(2′-naphthyl)-4,4,4-trifluorobut-2-yn-1-one, **4b** (1.89 g, 95 %), as a yellow solid, m.p. 47–48 °C. δ_H (400 MHz; $CDCl_3$) 7.67 (2H, m, ArH), 7.94 (2H, m, ArH), 8.07 (2H, m, ArH), 8.66 (1H, m, C(1′)H). δ_F (376 MHz; $CDCl_3$) –51.37 (s). δ_C (101 MHz; $CDCl_3$) 80.35 (q, $^3J_{CF}$ 6.5, C2), 87.70 (q, $^2J_{CF}$ 51.9, C3), 114.06 (q, $^1J_{CF}$ 260.1, C4), 123.32 (s, Ar), 127.66 (s, Ar), 128.21 (s, Ar), 129.37 (s, Ar), 130.18 (s, Ar), 130.28 (s, Ar), 132.41 (s, C5′/10′), 132.93 (s, C5′/10′), 134.09 (s, Ar), 136.86 (s, C2′), 175.05 (s, C1). IR (neat) $\tilde{\nu}_{max}$ /cm^{-1} 2160 (C≡C), 1648 (C=O), 1624, 1354, 1250, 1218, 1158, 1133, 1018. GC-MS (EI+) *m/z* 248 (M^+, 100 %), 220 (38), 179 (25), 170 (17), 155 (17), 127 (55). HRMS (AI+) *m/z* calcd. for $C_{14}H_7OF_3$ $[M + H]^+$ 249.0527, found 249.0513. HRMS (ESI+) *m/z* calcd. for $C_{14}H_7OF_3$ $[M + OH_3]^+$ 267.0633, found 267.0634.

3-(2′-Naphthyl)-5-(trifluoromethyl)-1*H*-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)-1*H*-pyrazole, **11a** (0.107 g, 75 %), as a yellow solid, m.p. 161–162 °C (lit. 178–179 °C from toluene).[21b] δ_H (400 MHz; $CDCl_3$) 1.69 (br s, N-H), 7.56 (2H, m, ArH), 7.66 (1H, d, $^4J_{CF}$ 1.1, C(2)H), 7.90 (3H, m, ArH), 8.03 (1H, m, ArH), 8.09 (1H, m, ArH). δ_F (376 MHz; $CDCl_3$) –74.16 (d, $^4J_{CF}$ 1.1). δ_C (101 MHz; $CDCl_3$) 120.22 (q, $^1J_{CF}$ 273.2, CF_3), 123.75 (C4), 126.51 (q, $^2J_{CF}$ 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), 131.30 (s, Ar), 133.08 (s, Ar), 135.00 (s, Ar), 157.72 (s, C3). IR (neat) $\tilde{\nu}_{max}$ /cm^{-1} 3050 (N-H), 2160, 2039, 1561, 1288, 1260, 1183, 1154, 1128, 1056. GC-MS (EI+) *m/z* 262 (M^+, 100 %), 214 (11), 165 (18), 131 (11). HRMS (AI+) *m/z* calcd. for $C_{14}H_9F_3N_2$ $[M + H]^+$ 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 joint 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

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Received: August 6, 2020