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COMMUNICATION

Fluorinated cyclopropanes: Synthesis and chemistry of the aryl α,β,β-trifluorocyclopropane motif

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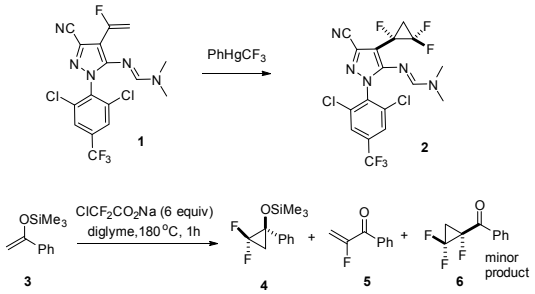
Connor J. Thomson,[a] Qingzhi Zhang,[a] Nawaf Al-Maharik,[a,b] Michael Buehl,[a] David B. Cordes,[a] Alexandra M. Z. Slawin[a] and David O'Hagan[a]*

Abstract: A general route to aryl α,β,β-trifluorocyclopropanes is reported and aryl oxidation gave the corresponding α,β,β-trifluorocyclopropane carboxylic acid. Reactions of the corresponding amides with phenol/thiophenol resulted in HF elimination and then conjugate addition. The partially fluorinated cyclopropane has a similar lipophilicity to $-CF_3$ despite three carbon atoms, and it emerges as a novel motif for drug discovery.

Around 20% of pharmaceuticals and 35% of agrochemicals contain fluorine largely from modifications for improving the pharmacokinetics of bioactive leads.[1,2] There are consequences in changing to such an electronegative atom, the most obvious of which is the introduction of polarity.[3] In the context of medicinal chemistry it is becoming recognised that polarity increases with selective fluorination (eg $-CH_2F$, $-OCH_2F$) on alkane substituents, and this is an attractive feature for lowering Log P, whereas higher levels of fluorination (eg $-CF_3$, $-OCF_3$) lead to increased lipophilicity. These observations have stimulated our interest in partially fluorinated motifs as potential starting points as library components for drug discovery.[4] We have introduced all *cis*-2,3,5,6-tetrafluorocyclohexane in this regard.[5] Also the $ArSCF_2CH_3$ and $ArOCF_2CH_3$ substituents are mixed fluorinated motifs, which are significantly less lipophilic than the corresponding $RSCF_3$ and OCF_3 groups respectively.[6] In this paper we describe a practical synthesis of 1,2,2-trifluorocyclopropanes as a partially fluorinated cyclopropane motif. Only two previous reports describe this ring system (Scheme 1). In an isolated example[7] cyclopropane **2** was prepared by difluorocarbene addition from phenyl(trifluoromethyl)mercury to generate vinyl fluoride **1**, however in general mercuric reagents are not attractive due to their toxicity. The only other reported synthesis[8] involved difluorocarbene addition to silylenol ether **3**. This gave the expected difluorocyclopropane **4** as the major product, however trifluorocyclopropane **6** emerged as a side product, which presumably arose by adventitious difluorocarbene addition to an *in-situ* formed vinylfluoride **5**. These are the only examples we are aware of for the preparation of this ring system and therefore the published routes and range of examples are extremely limited.



Scheme 1. Previous syntheses of α,β,β-trifluorocyclopropanes.

In this paper we explore the addition of difluorocarbene generated from the Ruppert-Prakash reagent[9] to vinyl fluorides and find it a straightforward method for the synthesis of α,β,β-trifluorocyclopropanes. We also look at aryl oxidation of these products to the corresponding α,β,β-trifluorocyclopropane carboxylic acid and then explore the reactivity of the corresponding amides with thiols and phenols.

The preparation of aryl α,β,β-trifluorocyclopropanes **11** required access to α-fluorostyrenes **10** as substrates. These could be prepared from styrenes **8** followed by bromofluorination[10] to generate intermediates **9**, and then hydrogen bromide elimination[11] as illustrated in Scheme 2.

[a] EaStCHEM School of Chemistry, University of St. Andrews, St. Andrews, Fife, KY16 9ST.
[b] Alistiqlal University, Jericho-Palestine.
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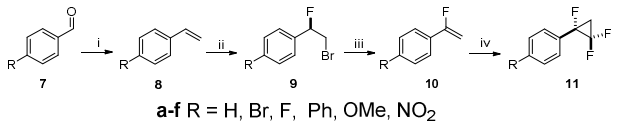
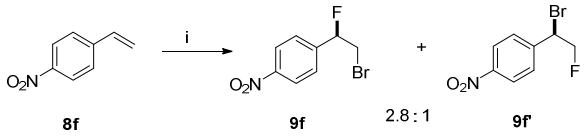


Scheme 2. i.[CH_3PPh_3]Br, nBuLi, THF, 70°C, 4 h, 32-58%; ii. NBS, $Et_3N.3HF$ or Pyr.HF, DCM, 0°C to rt, 4 h, 39-80%; iii. KO^tBu, THF, 0°C to rt, 59-82%; iv. $TMSCF_3$, NaI, THF, 55°C, 20 h, 53-93%.

Bromofluorination generated a single regioisomer of products **9** for all of the substrates explored except p-nitrostyrene (**8f**). In this case the more acidic Pyr.HF (70%) rather than $Et_3N.3HF$ was required for reaction and it gave rise to the mixture of regio-isomers **9f** and **9f'** (2.8:1.0 ratio) as illustrated in Scheme 3.



Scheme 3. Bromofluorination of p-nitrostyrene. i) NBS, HF:Pyr (70%), CH_2Cl_2, 0°C to 25°C, 4 h, 39%.

A two-step telescoped approach to α–fluorostyrene **10a** from styrene **8a** was explored and this led to a more efficient process (76% vs. 61%). In this case an increased number of equivalents of KO^tBu (8.0 vs 1.5 eq) was required to drive the dehydrobromination reaction to completion. α-Fluorostyrene **10e** was also obtained in this one-pot-two-step manner in the yield of 82%. The resultant α-fluorostyrenes were then treated with $TMSCF_3$/NaI[9] to affect their conversions to cyclopropanes **5** in modest to good isolated yields as illustrated in Figure 1. This would appear to offer a straight forward route to this rare motif.

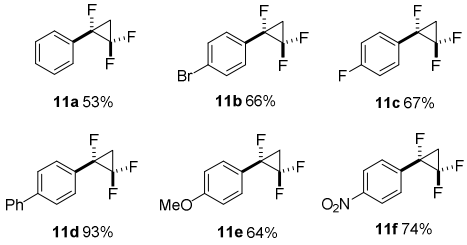
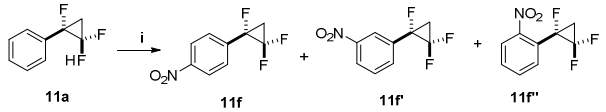
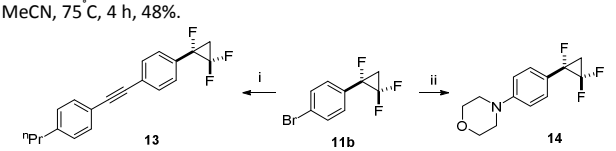


Figure 1. Aryl-1,2,2-trifluorocyclopropane products **11**. Yields represent the cyclopropanation reaction from the corresponding α-fluorostyrene **10.**

The aryl cyclopropanes **11** were explored in a range of aromatic functionalisation reactions to assess the compatibility of the partially fluorinated ring with mainstream reaction conditions. For example nitration of **11a** proceeded cleanly to give a mixture of the *o*-, *m*- and *p*- nitroaromatic products (ratio 1.2 : 1.0 : 2.1) **11f**, **11f'** and **11f"** as illustrated in Scheme 4. The *meta* product **11f'** was most readily isolated by chromatography, while the *ortho* and *para* isomers **11f** and **11f"** were recovered as a mixture. Sonogashira[12] and Buchwald-Hartwig[13] Pd-mediate cross coupling reactions were carried out on the *para*-Br arylcyclopropane **11b** (Scheme 4). A Sonogashira coupling of **11b** to 1-ethynyl-4-propylbenzene (**12**), with CuI and $Pd(PPh_3)_2Cl_2$, furnished 4,4'-substituted diphenylacetylene **13** in good (76%) yield and amination of **11b** using morpholine ($Pd_2(dba)_3$ and BINAP) gave the cross coupled product **14** in excellent yield (93%).

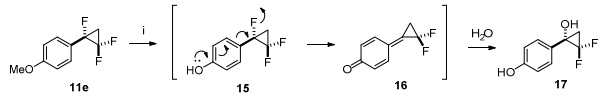


Scheme 4. Nitration of **11a** affords a mixture of isomers. i) NH_4NO_3, TFA, MeCN, 75°C, 4 h, 48%.



Scheme 5. Palladium catalysed cross-coupling reactions of **11b**. i) **12**, $PdCl_2PPh_3$, CuI, PPh_3, Et_3N, DMF, 80°C, 20h, 76%; ii) morpholine, $Pd_2(dba)_3$, BINAP, Cs_2CO_3, toluene, 80°C, 36 h, 93%.

Methyl ether cyclopropane **11e** was treated with boron tribromide[14] in an effort to prepare the corresponding phenol however this generated phenolcyclopropanol **17** in excellent yield (90%). This product appears to have arisen from a hydrolytic reaction of intermediate **16** triggered by the electronic nature of the phenol located *para* to the benzylic fluorine of the cyclopropane ring and the expulsion of hydrogen fluoride from intermediate **15**, as illustrated in Scheme 6. This may emerge as an attractive feature if incorporated into a drug scaffold as it offers the potential to release a reactive intermediate during metabolism. Such approaches have been used for the development of electrophilic cytotoxic pro-drugs which react with DNA.[15]



Scheme 6. Rational for the conversion of **11e** to **17**. i) BBr_3, DCM, rt, 1h, 90°C, 90%.

One of the most informative predictors of druggability is logP.[16] We chose to measure Log Ps of comparative phenyl derivatives by reverse phase HPLC in acetonitrile/water.[17] Trifluorocyclopropane **11a** is more polar than cyclopropylbenzene, consistent with partial fluorination which polarises the cyclopropane hydrogens (Figure 2). Notably, the trifluorocyclopropane **11a** has the same log P as trifluoromethylbenzene (logP = 3.2) suggesting that it may have use as a larger aliphatic substituent than trifluoromethyl, containing two more carbons, but without any increase in lipophilicity.

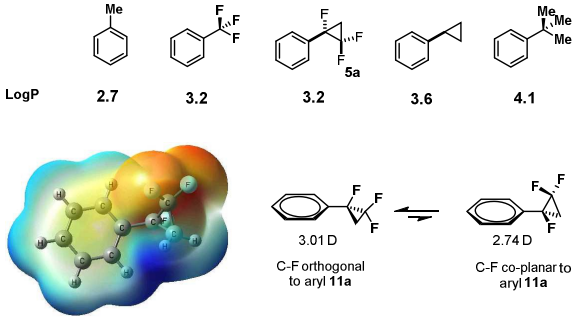


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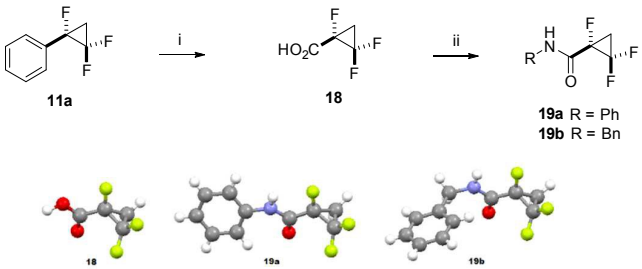
Figure 2. Comparison of experimentally derived Log P values of **11a** relative to some aryl derivatives and molecular dipole values and an ESP map of **11a**.

Conformational analysis[18] of aryl α,β,β-trifluorocyclopropane **11a** has revealed that the lowest energy conformer orients the C-F bond perpendicular to the aryl ring (Figure S3). An electrostatic surface potential map[19] of this conformer is shown in Figure 2 and Figure S4, illustrating the polar nature of the ring. Calculated molecular dipole moments demonstrated a significant polarity for the partially fluorinated cyclopropane, with the lower energy conformer (C-F orthogonal) of **11a** being the more polar (3.01 D versus 2.74 D).

Having developed a synthesis of the aryl-α,β,β-trifluorocyclopropanes we then explored aryl oxidation. Treatment of **11a** with $RuCl_3/NaIO_4$ under the phase-transfer conditions first described by Sharpless,[20] resulted in an efficient oxidation to generate the corresponding α,β,β-trifluorocyclopropane carboxylic acid **18** (Scheme 7).



Scheme 7. i) $RuCl_3$ (cat), $NaIO_4$, $CH_3CN/H_2O/CCl_4$, 90°C, 3 days, 60%; ii) $PhNH_2$ or $PhCH_2NH_2$, HOBt, EDCI, Et_3N, rt, overnight, 86% and 82%. X-Ray structures of **18**, **19a** and **19b** are inset.

This carboxylic acid could be converted to amides with amines under standard conditions, a reaction which was exemplified using aniline and benzylamine as illustrated in Scheme 7. The structures of carboxylic acid **18** and amides **19a** and **19b** were confirmed by X-ray structure analysis (Scheme 7). The α-fluorine of the cyclopropyl ring and the carbonyl oxygens point in opposite directions (F-C-C=O torsions angles of 161.0° and 167.2° for **19a** and **19b** respectively), a conformation consistent with the established preference of α-fluoroamides.[21] This was further confirmed by a DFT theory study exploring the conformation of a truncated N-methylamide **20** model. The resultant rotational energy profile, rotating around the (F)C-C(O)N bond, is shown in Figure 3, and gas phase, and a dielectric continuum to simulate a polar solvent (H_2O) are compared. There is a significant energy minimum (~5.0 kcal $mol^{-1}_{(gas)}$ or ~3.5 kcal $mol^{-1}_{(H2O)}$) in each case for the conformation with the C-F and C=O bonds oriented *anti* – parallel to each other. Together, with the X-Ray structures of **13a** and **13b** this suggests a preferred conformation for this cyclopropyl amide motif.

The reactivity of amide **19a** was explored with nucleophiles in view of the inherently polar nature of the α,β,β-trifluorocyclopropyl ring, particularly in conjugation with the amide. Treatment of **19a** with 4-bromophenol in acetonitrile and K_2CO_3 at 60°C generated a complex mixture from which phenol ether **22** was isolated and crystallised for X-ray structure determination (Scheme 8 and Figure 4). The product can be rationalised by progressing through a base induced dehydrofluorination, and then attack of *in situ* phenoxide to generate putative cyclopropene intermediate **21** shown in Scheme 8. A similar reaction with *β*-naphthiol and sodium hydride in THF was more efficient, and generated thioether **23a** in excellent yield. Reaction of 4-bromothiophenol with the amide under the same conditions led to **23b** a product that was readily crystallised. The

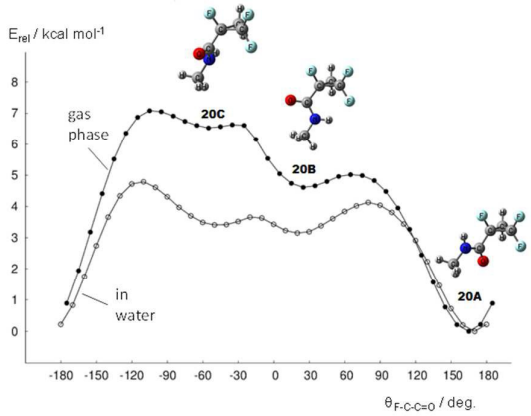
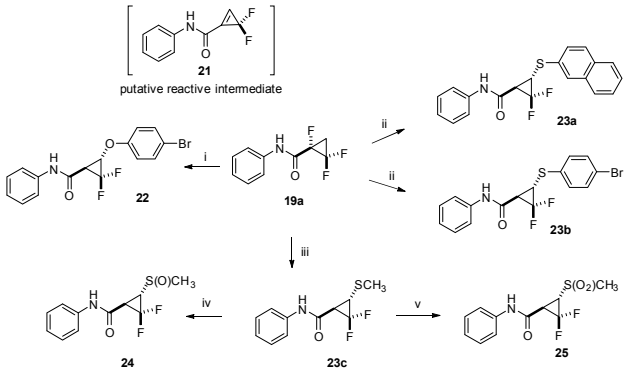


Figure 3. DFT (B3LYP/6-311+G** level), rotational energy profile of N-methyl amide model **20**. Full circles: gas phase, open circles: in a polarizable continuum (CPCM). Conformation **20A** is lowest in energy when the C-F and C=O bonds oriented anti – parallel to each other.

structure is shown in Figure 4. These adducts demonstrate a particular reactivity of the α,β,β,-trifluorocyclopropyl amide motif which has potential in the design of mechanism based (suicide) enzyme inhibitors.



Scheme 8. Reactions of amide **19a** with phenol and thiols. i) 4-bromophenol, K_2CO_3, CH_3CN, 60°C, overnight 18 h, 32%; ii) 2-naphthalenethiol or 4-bromothiophenol, NaH, THF, 0°C to rt, 16 h 72 and 65%; iii) MeSK, CH_3CN, rt, 16 h, 71%; iv) air, CH_3CN, 60°C, partial oxidation; v) mCPBA, DCM, 0°C to rt, 4h, 81%.

Several experiments were performed to try to observe cyclopropene intermediate **21** by ^{19}F-NMR, however these were unsuccessful. Treating amide **19a** with sodium hydride at 0°C to rt in THF or with K_2CO_3 at 50-60°C in acetonitrile led to a disappearance of amide **19a** (*in situ* VT-^{19}F-NMR) along with the formation of a gummy residue suggesting polymerisation.

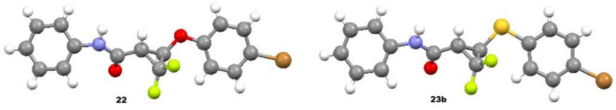


Figure 4. X-ray derived structures of **22** and **23b**

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Amide was also reacted with KSMe in acetonitrile, as both a base and a nucleophile. The resultant adduct proved labile to oxidation and generated sulfoxide **24**. Complete oxidation of this adduct with mCPBA afforded the sulfonyl derivative **25**. In the course of ^{1}H-NMR analysis of sulfone **25** in MeOD as the solvent it was clear that there was a gradual exchange of two C-H protons on the ring. The proton *alpha* to the amide group (δH 4.2 ppm) exchanged more rapidly (hours) than that *alpha* (C-3) of the sulfonyl (days) (Figure S1). The introduction of deuterium was also evident in the ^{19}F{^{1}H}-NMR spectrum where fluorine signals experience isotope induced α- and β-shifts of between 0.12-0.22 ppm (Figure S2). This isotope exchange could be completely reversed in MeOH.

This study has established a general route to the α,β,β-trifluorocyclopropane motif. Aryl oxidation of the trifluorocyclopropane derivative generated carboxylic acid **18** which could be converted to amides. The amides had a clear conformational preference and underwent an elimination addition reaction with phenols and thiophenols, which suggests a potential role in mechanism based inhibition of enzymes.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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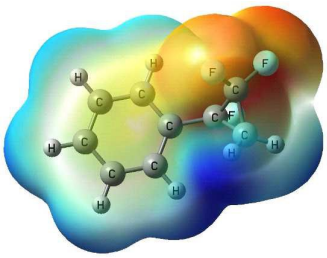

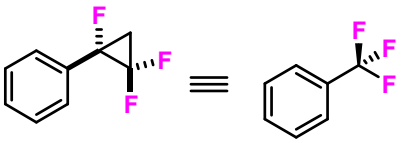

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