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Fluorine containing cyclopropanes: Synthesis of aryl substituted all-cis 1,2,3-trifluorocylopropanes, a facially polar motif

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The synthesis of substituted all-cis-1,2,3-trifluorocylopropanes are described for the first time. The three fluorines located on each of the cyclopropyl carbons with a stereochemistry where they are all on the same face of the cyclopropane, imparts a significant polarity to the molecule, and the inherent conformational rigidity and lowering of Log P makes this motif attractive for exploration as a substituent for pharmaceuticals and agrochemicals research.

Fluorine is widely used in bioactive pharmaceutical and agrochemical products to refine pharmacokinetic profiles as a lead compound is progressed through development. 1 Although the incorporation of fluorine is synonymous with increasing lipophilicity, this is almost entirely confined to the replacement of an aryl or heterocyclic hydrogen by -F or -CF3 and higher levels of fluorination. 2 Selective fluorination generally increases polarity, particularly where there are adjacent geminal and vicinal hydrogens, which become polarised due to the electronegative fluorine and therefore aliphatic fluorination actually lowers Log P values. 2d This adds another attractive feature associated with the introduction of fluorine in the arena of bioactives discovery, where Log P values require to be contained as a lead compound is developed. An extreme example of this polarity phenomenon is found in 1,2,3,4,5,6-all-cis hexafluorocyclohexane 1, a molecule with a fluorine on each of the six carbons, and with a stereochemistry where all the fluorines are on one face of the ring. 3a Cyclohexane 1 is among the most polar aliphatic motifs known. It has attracted significant attention in its ability to coordinate both anionic and cationic species to the hydrogen and fluorine faces respectively, and it has clear prospects in supramolecular chemistry. 4 The potential for derivatives of cyclohexane 1 in drug discovery is in its infancy, but looks attractive as the ring should coordinate electropositive and electronegative substituents on proteins. These prospects have improved recently as substituted ring systems are now available due to direct hydrogenation of pentafluoroaryl substrates 3b to the corresponding all-cis 1,2,3,4,5-pentafluorocyclohexyl derivatives.

With this background we became interested in preparing derivatives of all-cis-1,2,3-trifluorocylopropane 2. Progressing from a cyclohexane to a cyclopropane reduces the carbon count and with that the lipophilicity and unlike cyclohexane, cyclopropane has a rigid conformation which favours entropic factors in binding to proteins (Fig 1a). Similar to the properties of cyclohexane 1, cyclopropanes such as 2 are predicted to have the unusual property of facial polarity 4 with different coordinating preferences for the fluorine and hydrogen faces.

Figure 1. (a) Facially polarised fluorocycloalkanes. (b) Fluorocyclopropanes in medicinal chemistry.

More generally the cyclopropyl ring has been used widely in drug development programmes. 5 As a subset, some fluorinated cyclopropanes have featured in medicinal chemistry however examples are confined almost exclusively to mono-fluorinated cyclopropanes (Fig 1b). 6 Fluorocyclopropyl-amines are the most common variant of this class such as the cyclopropane found in the 6-fluoroquinolone antibiotic sitafloxin 5, and LY-341,495 6 a selective orthosteric antagonist. 7 There has been extensive exploration by Haufe and coworkers into the
At the outset we explored reactions of difluorostyrenes or generate cis-1,2,3-trifluorocyclopropanes dominates entries in the chemical and patent literature. Vicinal monofluorocyclopropanes are rarely quoted, where the fluorines are located on two adjacent carbons, rather than as a \( \text{CF}_2 \) group. Again there are some patent claims to vicinal difluoro cyclopropanes, but examples in the primary literature are confined to theory studies where properties are computationally predicted. The focus of this study was to explore synthesis routes to substituted all-cis-1,2,3-trifluorocyclopropanes 3a and 4a. We are not aware of any derivatives of all-cis 1,2,3-trifluorocyclopropanes 2 having been reported, however both isomers of the unsubstituted parent 1,2,3, and trifluorocyclopropane, 2a and 2b have been prepared at analytical levels. The isomers emerge as minor products of the ozonolysis of cis-1,2-difluoroethylene. Analytical samples of each isomer were secured by preparative gas chromatography and their integrity and stereochemistry was assigned by vibrational and microwave spectroscopy.

In this paper we report the first preparations of derivatives of all-cis-1,2,3-trifluorocyclopropanes. In this context the phenyl 3a and para-biphenyl 4a derivatives, as well as their trans isomers 3b and 4b are reported. We also compare the relative polarity (Log Ps) of the phenyl derivative 3a and 3b to other selectively fluorinated phenycyclopropanes and demonstrate that 3a is the most polar of the series.

Our synthesis approach to the all-cis-1,2,3-cyclopropane motif envisaged either direct monofluorocarbene (:CHF) or fluoroalcoholic carbene (CFX) addition to (Z)- \( \alpha, \beta \)-difluoroethene 16 or the corresponding \( \beta \)-phenyl-\( \alpha, \beta \)-difluoroethene 17. The \( \beta \)-phenyl series was developed to render products less volatile and crystalline. The required styrenes were prepared from fluoroacetones 12 and 13 following the protocol of Leroy. The fluoroacetones were prepared efficiently from vinyl azides 10 and 11 using recent methodology developed by Wu, and they were then treated with DAST to generate the aryltrifluoroethyl products 14 and 15. A stereoselective base (tBuOK) induced hydrogen fluoride elimination from 14 and 15, gave the required (Z)-\( \alpha, \beta \)-difluoroylesterynes 16 and 17, with the fluorines in the required syn arrangement. The route is summarised in Scheme 1.

At the outset we explored reactions of 16 and 17 with monofluorocarbon (CHF) generated from CHF\(_2\), to try to generate 3a/b and 4a/b directly, but these reactions were unsuccessful presumably because these olefins are poor nucleophiles and the CHF carbene is not so electrophilic. Consistent with this, the more electrophilic fluorohalocarbenes (\( \text{CFX} \), where \( X = \text{Cl}, \text{Br} \) and I) all successfully reacted with (Z)-\( \alpha, \beta \)-difluoroylesterynes 16 and 17 at room temperature, and also with the less electrophilic carbene (CFCl\(_3\) generated from the Ruppert-Prakash (TMS-CF\(_3\)) reagent but at high temperature. This gave the various trifluorocyclopropanes 18 - 24. In the case of the chlorocyclopropanes 20 and 21 the required \( \text{CCIF} \) carbene was generated from CFCI\(_3\) using the method of Dolbier, and the iodo- 22 and bromo- cyclopropanes 23 and 24 were generated from CHFCl and CHFBr\(_2\) derived fluorohalo carbены respectively, following the methods developed by Weyerstahl et al. For these reactions it proved necessary to prepare the required haloform precursors CHFCl and CHFBr\(_2\) as they are not commercially available. These reactions are summarised in Scheme 2.

Given that the monofluorocarbene reactions with 16 and 17 were unsuccessful and the fluorohalocarbon additions were more fruitful, our approach towards the target 1,2,3-trifluorocyclopropanes 3 and 4 envisaged reductive removal of the non-fluorine halogen from the product cyclopropanes 20 - 24. In the first instance reductive removal of the chlorine from cyclopropanes 20 and 21 was investigated. The individual \( \alpha \) (fluorines all cis) and \( \beta \) (fluorine trans) isomers of 20 and 21 were not easily separated and the mixture was explored in each case for dehalogenation (Bu\(_3\)SnH/AIBN), in the event this high temperatures and led to product mixtures, although containing the desired cyclopropanes (as determined by \( ^{19}\text{F-NMR} \) but with significant levels of unidentified products. Due to this poor selectivity, attention turned to the iodo cyclopropanes 22a/b. Isomers 22a and 22b, were separated and treated individually. Each could be reduced at a...
Stereochemistry, however the 1,2,3-trifluorocyclopropane chlorocyclopropanes. The lower temperature than the corresponding chlorocyclopropanes. The trans isomer 22b resulted in trans-1,2,3-trifluorocyclopropane 4b with retention of stereochemistry, however the cis-isomer 22a lead to the formation of the α,β-unsaturated ketone 25 as the only isolatable product, the nature of which was confirmed by X-ray structure analysis (Scheme 3).

Due to the inability to access cis-1,2,3-trifluorocyclopropane 4a from the iodine series, attention turned to the bromocyclopropanes 23 and 24. The isomer mixture of 23a and 23b was also subjected to reductive dehalogenation to generate the anticipated 1,2,3-trifluorocyclopropanes 3a and 3b (scheme 4). These product isomers could be readily separated by chromatography. The all-cis isomer 3a has characteristic second order 1H- and 19F-NMR spectra associated with the symmetry of the nuclei on the cyclopropane ring (see SI). A similar reduction was carried out on isomers 24a and 24b, which gave rise to the all-cis isomer 4a and the trans isomer 4b respectively. In the case of 4a a suitable crystal was selected for X-ray structure analysis as illustrated in Scheme 4. This confirmed the all-cis configuration of the three C-F bonds.

It was anticipated that the all-cis phenyl-1,2,3-trifluorocyclopropane 3a would display a significant polarity relative to phenylcyclopropane 29, following from our previous observations with all-cis multifluorocyclohexanes.21 A calculated electrostatic surface potential map of 3a is shown in Figure 2 and this clearly illustrates the different electrostatic profile on each face of the cyclopropane ring. To explore polarity in the context of bioactives discovery Log P values for the selectively fluorinated cyclopropanes 3a, 3b, 26-28 as well as phenylcyclopropane 29 as a reference, were evaluated experimentally by reverse phase HPLC on a C18 coated silica column, a method which has been widely validated.25 The selected phenyl cyclopropanes are directly compared as they differ only by the degree of fluorination on the cyclopropane ring. From this analysis it emerged that all of the partially fluorinated cyclopropanes 3a, 3b, 26-28 are more polar than phenylcyclopropane 29 itself consistent with the fluorine polarising geminal, and to a lesser extend vicinal, hydrogens around the ring. The all cis-1,2,3-trifluorocyclopropane 3a (Log P 2.56) is the most polar of the series, and more polar than the trans isomer 3b (Log P 2.74) where in the latter case the anti fluorine is compromising the overall polarity. Notably cyclopropanes 18 and 28 which contain CF₂ groups are significantly more lipophilic than those with their fluorines in fluoromethylene (CHF) groups, indicating that geminal CHF hydrogens are particularly polarised and contribute significantly to lowering Log P.

In conclusion, all-cis-1,2,3-trifluorocyclopropanes 3a and 4a have been prepared by halofluorocarbene addition to α,β-difluorostyrenes, and then by removal of the non-fluoro halogen by reductive dehalogenation. The study was stimulated by a recognition that the facially polarised characteristics of such a cyclopropyl ring system could offer unique polar properties for an alicyclic ring. This tendency was demonstrated by evaluation of Log P’s across a series of selectively fluorinated phenylcyclopropanes where the all cis isomer 3a was the least hydrophobic of the series. The study reports the first synthetic access to cyclopropanes of this class and demonstrates attractive characteristics for optimizing pharmacokinetic profiles in bioactive discovery programmes.

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Conflicts of interest
There are no conflicts to declare.

Notes and references


18. The haloforms are not commercially available in the UK and were prepared according to an early procedure; J. Hine, R. Butterworth, P. B. Langford, J. Am. Chem. Soc., 1958, 80, 819-822.


22. The synthesis of compounds 26 and 27 are described in the Supplementary Information. The stereochemistry of these vicinal difluoro cyclopropanes was established after a synthesis and X-ray structural analysis of biphenyl-3,3-difluorocyclopropane 31.