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A new and efficient strategy for the rapid formation of novel fluorinated tetrahydropyridazines and dihydrooxazines has been developed by fluoro cyclisation of β,γ-unsaturated hydrazones and oximes with the hypervalent fluoriodane reagent. Mecha nochemical synthesis delivered fluorinated tetrahydropyridazines in similar excellent yields to conventional solution synthesis, whereas fluorinated dihydrooxazines were prepared in much better yields by ball-milling.

Over 85% of small molecule pharmaceuticals approved by the FDA in 2019 contained a nitrogen-based heterocycle and over a quarter of all FDA approved drug molecules on the market contain at least one fluorine atom. The prominence of heterocycles comes from their activity in vivo, where, specifically their structure provides rigidity to molecular shape and enables effective binding. The pharmaceutical industry is particularly interested in heterocycles with a high sp³ content and the C-F bond has a great influence on the pharmacokinetic properties of biologically active molecules.

Fluorinated N-heterocycles can be accessed in a single step by intramolecular fluoro cyclisations of unsaturated substrates containing an internal nucleophile. The fluoro cyclisations of β,γ-unsaturated hydrazones with Selectfluor produced the 5-membered, fluorinated dihydropyrazoles (Scheme 1A). In one report, fluorinated tetrahydropyridazines were formed along with the dihydropyrazoles when R was an aryl group. Similarly, the fluoro cyclisations of β,γ-unsaturated oximes formed the 5-membered, fluorinated dihydroisoxazoles using either Selectfluor or hypervalent iodine reagent, PhI(OPiv)₂, with HF-pyridine. The synthesis of the 6-membered, fluor-inated dihydrooxazines has not been reported (Scheme 1B).

Since its inception, the hypervalent iodine(III) reagent, fluoroiodane 1 (Scheme 1C), has emerged as an excellent fluorinating reagent with a wide range of applications. In many cases, fluoroiodane 1 exhibits differing reactivity to that observed with fluoraza reagents such as Selectfluor. We recently employed fluoroiodane 1 in the synthesis of fluorinated lactones using either AgBF₄ or hexafluoroisopropanol (HFIP) to activate the fluoroiodane reagent. Looking to further explore the utility of this reagent in fluoro cyclisation reactions, we investigated the synthesis of fluorinated tetrahydropyridazines and dihydrooxazines. We also applied ball-milling to the fluoro-cyclisations since mecha nochemical synthesis can minimise solvent requirement and in many cases, can provide enhanced and altered reactivity. Ball-milling has shown promise in bromocyclisations and in fluoration reactions, where Selectfluor can selectively mono- or di-fluorinate 1,3-dicarbonyl compounds, fluorinate pyrazolone rings and be used in asymmetric organocatalysis. Herein, we report the regioselective synthesis of novel fluorinated 6-membered...
heterocycles, tetrahydropyridazines and dihydrooxazines, alongside the use of mechanochemistry to minimise halogenated solvents and to improve the yields in the preparation of fluorinated dihydrooxazines.

We began our studies by investigating the fluorocyclisation of hydrazone 2a. To our delight, 2a was fluorocyclised at room temperature in 4 hours using fluoroiodane 1 (1.5 equiv.) with AgBF₄ (1 equiv.) in CH₂Cl₂ to produce the desired fluorinated tetrahydropyridazine 3a in 91% yield (Table 1, entry 1). The reaction time could be reduced to just 15 minutes with minimal decrease in yield (entry 3). Alternatively, the amount of AgBF₄ could be decreased to 0.2 equivalents in a 1 hour reaction to form the product in 86% yield (entry 4). On further investigation of solvent and temperature (entries 5-10), a set of metal-free conditions were identified using HFIP as the solvent and activator of fluoroiodane 1 giving 3a in 93% yield after only 15 minutes (entry 10). Notably, whilst use of acetoniitrite as solvent did furnish the desired fluorinated heterocyclic product, Ritter product 4 was also formed in 23% yield suggesting that a tertiary carbocation is a key intermediate in the fluorocyclisation. In entries 7 and 8 where product yield was lower at 40 °C, elimination byproduct 5 was also observed in 10-15% yield.

Using mechanochemistry the unsaturated hydrazones could efficiently undergo fluorocyclisations with fluoroiodane 1 (1.5 equiv.) and just 2 equivalents of HFIP (an 8 fold reduction in the amount of HFIP required, SI Table S3) to provide an alternative, solvent minimised method. For this protocol, a 10 mL stainless steel milling jar was used with a 2.5 g stainless steel milling ball, and the reaction mixture was milled at 30 Hz for 15 minutes.

With optimal conditions for both a solution and ball-milling method in hand, application to a range of unsaturated hydrazones was explored (Scheme 2). The reaction was tolerant for a series of aryl substituted hydrazones (Scheme 2, 3a-h) with examples of both electron-donating (3e) and electron-withdrawing aryl groups (3b). Although synthesis of the thiophene substituted hydrazone proceeded efficiently (3h), the aromatic byproduct, 5-methyl-3-thiophen-2-yl pyridazine, was also formed in 16% yield. The fluorocyclisation proved successful on
alkyl substituted hydrazones (3i–k) including benzyl and the more hindered isopropyl hydrazones. Bis-tetrahydropyridazine (3l) was prepared by a double fluorocyclisation. In all cases, metal-free protocols could be employed and delivered similar yields in comparison to reactions containing AgBF₄. The mechanochemical approach was applied to a small range of substrates (3b–e, 3k and 3l) and provided comparable excellent yields to those observed in solution demonstrating an efficient, solvent minimised method. Further studies into the activation of fluoroiodane 1 revealed that sub-stoichiometric HFIP could be used in CH₂Cl₂ with minimal impact on yield (Scheme 3).

Initial results with β,γ-unsaturated oximes demonstrated that they could undergo fluorocyclisation to form dihydrooxazines. This class of fluorinated heterocycle has not been reported previously. After optimisation of traditional solution conditions (SI Table S4), dihydrooxazine 7a could be formed in 46% yield after 15 minutes with 1 equivalent of AgBF₄ (Scheme 4A). Notably, dihydroisoxazole 8, intercepted by the benzylalkyl backbone of the fluoroiodane reagent, was also isolated as a side product in 15% yield. In an attempt to improve yield and selectivity towards the desired product, attention was turned to mechanochemical techniques commencing with the conditions used for hydrazone fluorocyclisations (Scheme 2). Fluorocyclisation of unsaturated oxime 6b using fluoroiodane 1 proceeded to give 36% of the desired product with 2 equivalents of HFIP (Table 2, entry 1). Increased loading of HFIP improved the yield of dihydrooxazine 7b, but also increased the amount of unwanted dihydroisoxazole 9 (Table 2, entry 2). A small amount of oxazine 10, resulting from elimination, was also observed. Switching to AgBF₄ showed decreased activity initially (entry 3). However, using AgBF₄ with 5 equivalents of CH₂Cl₂ provided a dramatic improvement in the yield of dihydrooxazine 7b (80% isolated yield), and reduced the formation of side products 9 and 10 to 1% (entry 5). Further studies on the two additives and reaction time revealed that 2 equivalents of AgBF₄ and 5 equivalents of CH₂Cl₂ in a 1 hour reaction was optimal (entries 6–10). In the absence of HFIP or AgBF₄ the reaction showed no activity and returned quantitative amounts of oxime 6b (entry 11).

A range of β,γ-unsaturated oximes was examined and under traditional solution conditions, aryl unsaturated oximes could undergo fluorocyclisation in moderate yield (Scheme 4A, 7a–7d, 42–53%). However, applying mechanochemical conditions to these substrates greatly improved the yields delivering products 7a–7d in 71–80% yield. Alkyl oximes could also be tolerated (Scheme 4A, 7e–7f), but oxime 6e gave a lower yield as it contained a 1:1 mixture of (Z)– and (E)–isomers and only the (Z)–isomer fluorocyclised. Unsatuated oxime 6g with a mono-substituted alkene selectively formed dihydroisoxazole 11, as reported by Wang using Phl(OPiv)₂ and HF.pyridine. This result supports our proposed mechanism (Scheme 4B) where there is initial formation of a 5-membered heterocycle (Scheme 4A). Notably, dihydroisoxazole 46% yield after 15 minutes with 1 equivalent of AgBF₄ (Scheme 4A). Notably, dihydroisoxazole 8, intercepted by the benzylalkyl backbone of the fluoroiodane reagent, was also isolated as a side product in 15% yield. In an attempt to improve yield and selectivity towards the desired product, attention was turned to mechanochemical techniques commencing with the conditions used for hydrazone fluorocyclisations (Scheme 2). Fluorocyclisation of unsaturated oxime 6b using fluoroiodane 1 proceeded to give 36% of the desired product with 2 equivalents of HFIP (Table 2, entry 1). Increased loading of HFIP improved the yield of dihydrooxazine 7b, but also increased the amount of unwanted dihydroisoxazole 9 (Table 2, entry 2). A small amount of oxazine 10, resulting from elimination, was also observed. Switching to AgBF₄ showed decreased activity initially (entry 3). However, using AgBF₄ with 5 equivalents of CH₂Cl₂ provided a dramatic improvement in the yield of dihydrooxazine 7b (80% isolated yield), and reduced the formation of side products 9 and 10 to 1% (entry 5). Further studies on the two additives and reaction time revealed that 2 equivalents of AgBF₄ and 5 equivalents of CH₂Cl₂ in a 1 hour reaction was optimal (entries 6–10). In the absence of HFIP or AgBF₄ the reaction showed no activity and returned quantitative amounts of oxime 6b (entry 11).

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methylenic site forms the 5-membered product. Good evidence that tertiary carbocation B is a key intermediate was provided by the formation of Ritter product 4 in the fluorocyclisation of 2a in acetonitrile (Table 1, entry 6). Hara has also reported a similar ring expansion in the fluorocyclisation of 1-decen-5-ol by the formation of Ritter product 6a,b. These products can only be obtained from a reaction mechanism involving a fluorocyclisation and an aryl migration (Scheme 5B). It is remarkable that the aryl migration occurred in the ball-mill with a 6 fold reduction in the volume of HFIP. To demonstrate this further, treatment of unsaturated carboxylic acid 12f with Selectfluor under ball-milling conditions for 1 hour at 30 Hz furnished fluorocyclisation product 14 without an aryl migration, and so, the product could be switched by merely changing Selectfluor for fluoriodane.

In summary, we have developed efficient protocols for accessing two new classes of fluorinated heterocycles using fluoroiodane reagent 1. Alternative selectivity to that displayed by electrophilic fluorinating reagents (e.g. Selectfluor) is clearly demonstrated and thus, this study shows that fluoroiodane 1 is a complementary reagent for diversifying fluorination methodology. Mechanochemistry has provided a dramatic improvement in the yield and selectivity to fluorinated dihydrooxazines, and in so doing has highlighted that mechanistically complex reactions can be readily achieved in a ball-mill.

Notes and references
