Stereoselective access to trisubstituted fluorinated alkenyl thioethers

Indira Fabre, Thomas Poisson, Xavier Pannecoucke, Isabelle Gillaizeau, Ilaria Ciofini, Laurence Grimaud

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1. INTRODUCTION

Since the last decade, organofluorine chemistry has known a very fast expansion since fluorinated molecules became popular in the quest for drugs and agrochemicals. This is reflected in the continuing increase of the number of fluorinated drugs already approved or drug candidates entering clinical trials. Indeed, the presence of a fluorine atom or a fluorinated group strongly affects the physical and chemical properties of a molecule. These features result from the particular properties of the fluorine atom, like its electronegativity, its small size and the strength of the carbon fluoride bond, for instance. In that context, the development of new methodologies to access these strategic molecules is of high demand toward the discovery of new bioactive molecules. For this purpose, the direct C-H bond functionalization was recently recognized as an outstanding and efficient method for a straightforward access to the desired fluorine-containing molecules.

Besides, sulfur-containing molecules are prevalent in a broad range of pharmaceuticals and natural products, and often display interesting various biological activities. As part of these sulfur-containing molecules, alkenyl thioethers are a versatile chemical platform and represent an interesting motif to access complex sulfur-containing molecules. It is noteworthy, that Julia and coworkers developed the introduction of alkyl, allyl or silyl groups on 1-tert-butylthio-3-methoxy-1-alkenes using metallocating agents (Scheme 1a). However, most efforts to functionalize this motif focused on the development of palladium-catalyzed arylation of alkenyl thioethers (Scheme 1b). Concerning the synthesis of fluorinated alkenyl mercaptans, Marquet and coworkers described an approach based on the anodic functionalization of alkenyl thioethers allowing the introduction of a fluorine atom at the α or β position (Scheme 1c). More recently, β-trifluoromethyl-α-functionalized-vinyl sulfides were synthesized under anionic conditions by Hanamoto and coworkers. As a complementary approach, Zard and coworkers reported the synthesis of tri- and tetra-substituted functionalized alkenyl thioethers by radical allylation, including examples bearing a CF₃ motif. The fluorination of thiophenes and benzo thiophenes, which have an aromatic scaffold, have been reported with different metal catalysts (Ag, Pd, Fe and Ir) and under photochemical conditions (Scheme 1d). These reactions are selective for the C₂ position. To the best of our knowledge, no example of alkenyl thioether fluorination has been reported so far using functionalized fluorinated building blocks as the CF₃CO₂R group. Stimulated by our previous works dealing with the copper-catalyzed ethoxy carbonyl difluoromethylation of various scaffolds through a direct C-H functionalization, we report herein a successful application to the functionalization of alkenyl thioethers (Scheme 1e). In addition, significant insights regarding the mechanism of this reaction were also disclosed, demonstrating the existence of a radical pathway.
2. RESULTS AND DISCUSSION

2.1 Optimization of the Reaction

The reaction conditions were optimized using n-hexyl(3-ethyl)sulfane 1a as a model substrate. Standard screening of solvent, catalysts, bases, ligands, temperature and reagent stoichiometry confirmed that the best yield is obtained using the conditions previously settled for the ethoxy carbonyl difluoromethylation of enamides,\(^2\) with longer reaction time. A brief overview of the optimization of the reaction is displayed in Table 1 (for a more complete study, see Supporting Information). The desired product 2a was isolated in 82% yield (Table 1, entry 1) when using CuO (10 mol%), 1,10-phenanthroline (12 mol%) as a ligand and in the presence of K$_2$CO$_3$ (2 equiv) and BrCF$_3$CO$_2$Et (2 equiv), in acetonitrile at 80 °C for 24 h. Several copper sources were also found to be efficient (Table 1, entries 2-4); however, the use of different ligands (Table 1, entries 5-8) or bases (Table 1, entries 9-13) gave very low to no conversion. Unfortunately, the catalyst loading could not be reduced since the yield significantly dropped when using 2 mol% of copper salt (Table 1, entry 14). Similarly, we could perform the reaction with 2 equiv of BrCF$_3$CO$_2$Et but lowering its amount (1.3 equiv) greatly impacted the reaction yield (Table 1, entry 15). The reaction was carried out under air atmosphere, but with a lower yield (65%). Control experiments showed no reactivity in the absence of ligand, catalyst or base, and that no conversion occurred at room temperature. Under this optimized set of experimental conditions, the reaction turned out to be highly regio- and stereoselective. Indeed, the trisubstituted alkene 2a was isolated as the major compound with a 9:5 Z/E ratio\(^2\) starting from alkanyl thioether 1a as a Z/E (10:90). A NOE between the alkynyl proton and the alkyl chain on the sulfur atom allowed us to unambiguously confirm the regioselectivity of the reaction as shown in Table 2.

2.2 Scope of the Reaction

Having established the optimal reaction conditions, the scope of the reaction was further examined with a wide array of alkanyl thioether derivatives (see Table 2). Different thioether electrophiles were successfully functionalized under these conditions. The reaction turned out to be of similar efficiency when performed with S-secondary (2b) or S-tertiary (2c) alkyl substituents as well as with a benzyl group (2d). Aryl thioether electrophiles gave slightly lower yields of isolated adducts (2e to 2h) whatever the nature of the substituent on the aromatic ring. When replacing the thiol moiety with an alkyl-substituted olefin, the reaction behaved similarly affording excellent yields of the trisubstituted alkenes 2i-2k. However, the electron-deficient sulfanyl acrylate 1l was poorly reactive giving 2l in a modest yield (20%). When the gem-disubstituted alkyl thioether 1m was used, traces of the expected product were obtained (yield about 8%) along with the product 2m (55% yield) resulting from a subsequent isomerization.

The reaction turned out to be highly regio- and stereoselective. Indeed, when starting with a nearly equimolar Z/E mixture of alkanyl thioether (eg. 1b or 1c), the trisubstituted alkenes 2b and 2c were isolated in a diastereomeric ratio > 90:10 in favor of the E isomer. Except for 2i, no isomerization was observed when starting with pure E substrates as observed for 1j and 1k. NMR experiments were performed to determine the configuration of the trisubstituted thioethers. Heteronuclear NOESY experiments clearly demonstrated a correlation between fluorine and the olefinic proton on 2j and 2k, enabling us to establish the E selectivity of the reaction.\(^2\)

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**Table 1** Optimization of the reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from the standard conditions</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>82 %</td>
</tr>
<tr>
<td>2</td>
<td>Catalyst: Cu(OTf)$_2$</td>
<td>60 %</td>
</tr>
<tr>
<td>3</td>
<td>Catalyst: Cul</td>
<td>59 %</td>
</tr>
<tr>
<td>4</td>
<td>Catalyst: Cu(CH$_3$CN)$_2$PF$_3$</td>
<td>70 %</td>
</tr>
<tr>
<td>5</td>
<td>Ligand: Neocuproine</td>
<td>0 %</td>
</tr>
<tr>
<td>6</td>
<td>Ligand: TMEDA</td>
<td>0 %</td>
</tr>
<tr>
<td>7</td>
<td>Ligand: TMHD</td>
<td>0 %</td>
</tr>
<tr>
<td>8</td>
<td>Ligand: 2,2'-bipyridine</td>
<td>35 %</td>
</tr>
<tr>
<td>9</td>
<td>Base: Cs$_2$CO$_3$</td>
<td>28 %</td>
</tr>
<tr>
<td>10</td>
<td>Base: Na$_2$CO$_3$</td>
<td>12 %</td>
</tr>
<tr>
<td>11</td>
<td>Base: Et$_2$N</td>
<td>&lt; 5 %</td>
</tr>
<tr>
<td>12</td>
<td>Base: 2,6-lutidine</td>
<td>0 %</td>
</tr>
<tr>
<td>13</td>
<td>Base: nBu$_2$NOAc</td>
<td>0 %</td>
</tr>
<tr>
<td>14</td>
<td>Catalyst: CuO 2 mol%</td>
<td>24 %</td>
</tr>
<tr>
<td>15</td>
<td>BrCF$_3$CO$_2$Et: 1.3 equiv</td>
<td>30 %</td>
</tr>
</tbody>
</table>

Default catalyst, ligand and base are Cu$_2$O, 1,10-phenanthroline and K$_2$CO$_3$. \(^a\) Isolated yield. \(^b\) $^1$H NMR yield, $\alpha,\alpha,\alpha$-trifluorotoluene was used as an internal standard.
Table 2 Scope of the copper-catalyzed ethoxy carbonyl difluoromethylation of various alkenyl thioethers 1

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>NOE</th>
<th>HOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1b</td>
<td>1c</td>
<td>1d</td>
</tr>
</tbody>
</table>

The regioselectivity of the reaction was further confirmed using the β-disubstituted styryl thioether 1n. In this case, the compound 2’n was isolated in a modest 30% yield along with diphenyldisulfide. The latter could result from an α-addition-desulfination sequence due to the steric hindrance at the β-position (see Scheme 2). It is worth noting that this byproduct has been observed in 0 to 15 % yield also with 1a to 1l.

Scheme 2 Copper-catalyzed difluoroacetylation of 1n

Surprisingly, the replacement of BrCF₂CO₂Et with the bromodifluoracetamide or bromodifluorophosphonate failed to give the corresponding fluorinated alkenyl thiethers. However, the post-functionalization of product 2h turned out to be very efficient as shown in Scheme 3. The ester residue can be readily converted into the corresponding amide by treating compound 2e with an excess of benzyamine (Scheme 3). This transformation enlarges even more the molecular diversity accessible with this protocol.

Scheme 3 Transformation of fluorinated alkenyl thioether 2h

2.3 Mechanistic Studies

To get more insights into the mechanism, selected reactions were performed in the presence of radical scavengers.

When 1a was reacted under standard reaction conditions in the presence of Galvinoxyl (1 equiv), no product was formed, while in the presence of TEMPO (1 equiv, Table 3, entry 1), traces of product were obtained along with 53 % of the TEMPO-adduct 4, characterized both by 19F NMR and Mass Spectroscopy. These observations along with the formation of diphenyldisulfide previously reported suggest that a radical mechanism is involved in the process. These conclusions are consistent with the recent studies of fluorination of hydrazones with analogous copper systems and with similar radical reactions mediated by copper.

To identify the key players in the radical formation, the trapping by TEMPO was further examined under various conditions (Table 3). The yield of 4 is only slightly lower (44 %, Table 1, entry 2) when the reaction is performed in the absence of the alkenyl thioether 1a, suggesting that 1a is not essential for the formation of the difluoroacetate radical. Note that in the absence of copper, no radical was generated (Table 3, entry 6). As already observed during the optimization process, tetrakis(acetonitrile)copper(I) hexafluorophosphate behaved similarly (Table 3, entry 4). This copper source allowed us to test the effect of the ligand toward the formation of 4, indeed the use of Cu₂O without ligand was not conclusive due to solubility issues. In the absence of phenanthroline, no traces of 4 were detected (Table 3, entry 3), revealing its crucial role for the generation of the radical species, and explaining the failure of the reaction in the absence of ligand. Without a base the formation of 4 dropped significantly (Table 3, entry 5), unveiling its contribution in the generation of the reactive species. These experimental observations suggested that the combination of copper, 1,10-phenanthroline and K₂CO₃ might be responsible for the formation of a radical species in our reaction conditions.
Table 3 Mechanistic experiments performed in the presence of TEMPO

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Cu]</th>
<th>Base</th>
<th>Ligand</th>
<th>Yield of 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Cu₂O</td>
<td>K₂CO₃</td>
<td>1,10-Phen</td>
<td>53 %</td>
</tr>
<tr>
<td>2</td>
<td>Cu₂O</td>
<td>K₂CO₃</td>
<td>1,10-Phen</td>
<td>44 %</td>
</tr>
<tr>
<td>3b</td>
<td>Cu(CH₃CN)₄PF₆</td>
<td>K₂CO₃</td>
<td>-</td>
<td>0 %</td>
</tr>
<tr>
<td>4</td>
<td>Cu(CH₃CN)₄PF₆</td>
<td>K₂CO₃</td>
<td>1,10-Phen</td>
<td>61 %</td>
</tr>
<tr>
<td>5</td>
<td>Cu(CH₃CN)₄PF₆</td>
<td>K₂CO₃</td>
<td>-</td>
<td>15 %</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>K₂CO₃</td>
<td>1,10-Phen</td>
<td>0 %</td>
</tr>
</tbody>
</table>

Yields were evaluated by ¹⁹F NMR using α,α,α-trifluorotoluene as an internal standard. *In the presence of 1 equiv of 1a. 2 % of 2a was formed. † The copper source was changed for solubility issues in the absence of ligand.

For a better understanding of the elementary steps involved in this transformation, further investigations on the copper(I) complex involved in the reduction of BrCF₂CO₂Et were performed at the theoretical level using density functional theory (DFT). Bulk solvent effects were included by means of a polarizable continuum model (PCM) (see the Supporting Information for details). Two different mechanisms of activation of BrCF₂CO₂Et were compared: a single electron transfer (SET) and a halogen atom transfer (HAT). Though the approach used here cannot provide a good description of the entropic effects that can play a role in the present case, the energetic –i.e enthalpies- associated to these reaction can be trustfully estimated and it is here discussed. An estimate of the associated reaction free energies is reported in SI.

As starting complexes models, A to E were considered, where solvent molecules, alkynyl thioether 1b, 1,10-phenanthroline and hydroxide anion (the base formed in the reaction medium) were included as possible ligands (see Scheme 4 and Table 4, details in the Supporting Information).

Both SET and HAT were computed to be endothermic processes (ΔH > 0). In the absence of the ligand (A), the energy required for the SET is very high (ΔH = 55.2 kcalmol⁻¹). This energy is lowered by complexation with 1,10-phenanthroline (B: ΔH = 39.9 kcalmol⁻¹ and D: ΔH = 39.1 kcalmol⁻¹), and even more favorable when copper is bound to a hydroxide anion (C: ΔH = 11.7 kcalmol⁻¹ and E: ΔH = 16.7 kcalmol⁻¹). The presence of alkynyl thioether 1b has only a tiny effect, as one can see by comparing the energies computed for B to the ones for D and the energies computed for C to the ones for E. In all cases, the reaction energies for HAT reactions were lower than those calculated for SET. A similar behavior was observed whatever the presence of the alkynyl thioether; in the absence of phenanthroline, no radical was formed; and the absence of base significantly impacted the radical formation. These findings are consistent with experimental data from Table 3.

Overall, complexes C and E are the most likely to initiate the formation of the difluoroacetate radical by HAT (C: ΔH = 4.7 kcalmol⁻¹ and E: ΔH = 4.1 kcalmol⁻¹). In addition, the complexation of one molecule of 1a to the copper/phenanthroline complex in the absence of base (complex D) was evidenced by ¹H NMR, but not in its presence (complex E, see the Supporting Information). After HAT, both C and E formed a copper (II) complex, bearing a phenanthroline...
ligand, a hydroxide and a bromide. Surprisingly, the alkenyl thioether has low affinity for the copper complex and is expelled from the coordination sphere of copper at this step for E.

Scheme 5 Computed reaction pathways (in kcal mol⁻¹). Solid line: initiation with C. Dashed line: initiation with E. The last part of the reaction path after regeneration of E by SET is omitted for clarity. This part is the same as for C. Grey: path for the formation of the main byproduct. Blue: path for the formation of the minor stereoisomer.

The formed °CF₂CO₂Et radical can then add to the alkenyl thioether 1b. The addition at the α position with regards to the S atom (ΔH₂ = 7.6 kcal mol⁻¹, TS-1') had a higher activation barrier than at the β position (ΔH₂ = 5.1 kcal mol⁻¹, TS-1), but appeared achievable under the reaction conditions (Scheme 5). This small difference allowed us to explain the observed regioselectivity in some cases with the formation of the disulfide as byproduct. The addition of the °CF₂CO₂Et radical on the alkenyl thioether 1b on the copper (I) complex D has a higher energy barrier (ΔH₂ = 8.2 kcal mol⁻¹, see the Supporting Information), and is thus less favorable. The so formed radical I-1 can reduce the copper (II) complex to regenerate copper (I) (ΔH = 12.9 kcal mol⁻¹ to regenerate C, ΔH = 13.5 kcal mol⁻¹ to regenerate E). The resulting carbocation I-2 can then be deprotonated by the base to form the final product 2b. The different conformations of the carbocation I-2 are very close in energy (ΔH = 0.8 kcal mol⁻¹) and are in equilibrium. These conformers are similar whatever the configuration of the starting alkenyl thioether (Z or E). Both can undergo a deprotonation step: after interaction with the base (OH⁻) leading to two stable and closely lying intermediates (E)-I-3 and (Z)-I-3 (ΔG = 1.4 kcal mol⁻¹), the E and Z products can be formed. In agreement with the experiments, the transition state corresponding to the deprotonation step for the E form (that is (E)-TS-3) and leading to the most stable (E)-2b product is computed to be lower in energy than the one of the corresponding Z form. Similar conclusions can be drawn by considering the values for the Gibbs free energies. The interaction with the base leads to the two stable intermediates (E)-I-3 and (Z)-I-3 (ΔG = 2.7 kcal mol⁻¹). The transition state for the deprotonation leading to the major product E is the lowest in energy (ΔG = 1.7 kcal mol⁻¹) and this major product is the most stable one (ΔG = 0.9 kcal mol⁻¹). The complete Gibbs free energy profile can be found in Supporting Information.

Based on these findings, we suggested the mechanism depicted in Scheme 6. In the presence of 1,10-phenanthroline and a base, the copper(I) hydroxo complex reduced BrCF₂CO₂Et to form a copper (II) complex and a ethoxy carbonyl difluoromethyl radical. Then, the addition of this radical on the alkenyl thioether 1 proceeded according to an outersphere process and the observed stereoselectivity is related to the relative stability of the two possible isomers after the deprotonation step.
These findings can be generalized. Indeed, for the initiation step, we could rationalize the absence of reactivity of BrCF$_2$CONR$_2$, BrCF$_2$PO(OEt)$_2$ and BrCH$_2$CO$_2$Et with the higher barrier energies computed for the HAT as well as with their higher reduction potential measured by cyclic voltammetry (see the Supporting Information). Moreover, the fact that the radical initiation did not depend on the presence of the alkenyl thioether showed that this method is broadly applicable to the generation of CF$_2$CO$_2$Et radicals using copper catalyst. This hypothesis was confirmed by performing a radical trapping experiment with TEMPO in the presence of enamide (Table 5, entry 1) and benzofuranes (Table 5, entry 2 and 3) in previously reported conditions.\textsuperscript{25,26} For example, the adduct 4 was isolated in 30\% yields in the case of ene-carbamates without traces of the desired addition product, revealing a similar mechanism for these substrates. In a previous report,\textsuperscript{26} a non-radical mechanism was proposed based on stoichiometric reactions performed in the absence of the base. After ruling out the direct oxidative addition of the bromo compound with the cationic copper(I) complex (by both NMR and electrochemistry performed at RT)\textsuperscript{30}, a pre-complexation of the latter with enamide was established via cyclic voltammetry as evidenced here by $^1$H NMR in the case of the alkenyl thioether (in the absence of the base). This emphasized the important role of the base that transformed the cationic copper(I) complex to neutral copper(I) hydroxo complex. Finally, the radical mechanism established herein turned out to be quite general for these systems.

Table 5 Experiments in the presence of TEMPO for enamide and benzofuranes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent, time</th>
<th>Yield of 4 $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="" alt="Enamide" /></td>
<td>CH$_3$CN, 6 h</td>
<td>30 %</td>
</tr>
<tr>
<td>2</td>
<td><img src="" alt="Ene-carbamate" /></td>
<td>DMF, 20 h</td>
<td>10 %</td>
</tr>
<tr>
<td>3</td>
<td><img src="" alt="Benzofuran" /></td>
<td>DMF, 20 h</td>
<td>10 %</td>
</tr>
</tbody>
</table>

$^a$ $^1$F NMR yield, $\alpha,\alpha,\alpha$-trifluorotoluene was used as an internal standard.

3. CONCLUSIONS

We report herein a general regio- and stereoselective method for the ethoxy carbonyl difluoromethylation of alkenyl thioethers. The developed methodology was applied to a broad range of substrates with good yields and an excellent selectivity in favor of the E isomer. Mechanistic studies supported by experimental observations and theoretical calculations gave evidences for a radical mechanism. The generation of a difluoroacetate radical promoted by a well-defined copper complex was established by these studies. Compared to other strategies to introduce a fluorine atom or a fluorinated group,\textsuperscript{19-21,23,33-39} this method allowed the generation of a radical under mild conditions, without requirement of light irradiation, expensive metal or radical initiator, which constitutes a real asset. It allows an easy access to fluorinated chemical platform of interest, since post-functionalizations of these substrates are possible thanks to the versatility of the ester function.

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Notes and references