Unexpected reactivity of trifluoromethylated olefins with indole: a mechanistic investigation

Mónica S. Estevão, Filipe J. S. Duarte, Eduarda Fernandes, A. Gil Santos, M. Manuel B. Marques

ABSTRACT

Several trifluoromethylated compounds were reacted with indole sodium salt, leading to monofluorinated compounds. The unexpected products formation was rationalized by DFT calculations.

Organic fluorinated compounds have received great attention in all fields of science. Currently approximately 30% of all agrochemicals and 20% of pharmaceuticals contain fluorine. Incorporation of fluorine has also been applied in material sciences such as the useful polymer polytetrafluoroethylene (Teflon) that is perfluorinated fluorine has also been applied in material sciences such as the useful polymer polytetrafluoroethylene (Teflon) that is perfluorinated...
The change in solvent influenced the products formation (entries 1 and 6), and best results were obtained when DMF was used as solvent. Inverting the order of the reagents addition, addition of a suspension of sodium salt 2 to a solution of 1b, enhanced the yield of the isomerized 5a and almost suppressed the formation of 3 (entry 8), supporting that two competitive mechanisms take place. When 1c was used the corresponding products 4 were isolated (entry 10). In any case was observed the SN2 product. The importance of the electron-withdrawing effect of the CF3 group on the reaction outcome was confirmed, as when the CF3 group was replaced by a methyl group, compound 1d,11 the SN2 product was obtained with both NaH and BuLi (entry 11). The same group observed the formation of a difluorinated diene as a product in SN2 reactions of Grignard reagents toward CF3-containing allylic acetates, in the presence of CuCN and TMSCl.13

Additionally, the reaction of α-substituted trifluoromethylated alkenes to give functionalized 1,1-difluoroalkenes, in the presence of a nucleophile in aprotic solvents has already been reported (Scheme 1, route a).2,6

In contrast with the literature known substrates, compound 1 has a good leaving group at β-position (mesyl or tosyl group), and as it is accepted that the C–F bond is strong and chemically stable, the formation of 3 from 1b under our experimental conditions was an unexpected reaction outcome.

Thus, aiming at a proposal of a possible mechanism, we envisaged a full density functional theory (DFT) study,14 by calculating all the intermediates (some of them observed by MS) and transition states (TSs) along the possible reaction pathways. In Scheme 3 is depicted a proposed mechanism on the basis of our calculated data, which indicates that the reaction occurs in three steps.

Scheme 3. Possible reactions of the trifluoromethylated alkenes.
mely high or the TS structures cannot even be obtained, which is in agreement with the experimental data.

For the reaction of 1b with 2, we studied six different pathways (see SI). However, Scheme 4 shows only the two pathways (TS-1 and TS-2) that lead to experimentally observed products (5a (Z) and 3). All the other calculated TSs are more energetic than TS-1 and TS-2 in, at least, 20 kJ mol⁻¹, which means that they are irrelevant for the discussion.

The energy difference between the double-bond migration (TS-1) and the indole addition with concerted elimination of fluorine anion (TS-2) is minimal. Thus, these two pathways can co-exist and one or the other can be dominant depending on the reaction conditions (solvent, temperature, concentration), as was experimentally observed. The Z isomer of 5a is preferentially formed due to strong restrictions on the TS conformation, as the sodium ion has to coordinate between the mesylic and the indolic groups. GC-MS experiments were carried (see SI, Table 4) and an intermediate with m/z (300) consistent with intermediate 7 was observed.

While compound 5a (Z) is a dead-end, intermediate 7 can undergo fluorine substitution by indole anion to afford intermediate 8. According to our calculations, only the E isomer of 8 can be formed, due to the lack of important electrostatic interactions in the TS with Z configuration. An alternative mechanism for the formation of 8 was tested, via an addition–elimination process, in which the indole anion adds to the intermediate 7 to form an anionic intermediate that undergoes fluorine elimination to originate 8.

However, this possibility is not discussed in Scheme 4, as it originates considerably higher energetic TSs (see SI). Indole can be eliminated from intermediate 8 via two diastereomeric concerted TSs (TS-4), but high selectivity is expected, as TS-4 (Z/E) is ca. 11.5 kJ mol⁻¹ less energetic than TS-4 (E/E). Thus, product 3a (Z/E) is predicted to be preferentially formed, which does not fully agree with the experiment. Indeed, while the double-bond at the mesy group side was experimentally obtained in Z configuration, the second double-bond was obtained as a Z/E mixture, with preference for the Z configuration. However, this result can be ex-

### Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 R¹; R²</th>
<th>Solvent</th>
<th>Base (equiv)</th>
<th>Products</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b CF₃; Ms</td>
<td>DMF</td>
<td>NaH (1)</td>
<td>3 (Z)/(Z)/E (1:0.6)</td>
<td>38</td>
</tr>
<tr>
<td>2ᵇ</td>
<td>1b CF₃; Ms</td>
<td>DMF</td>
<td>NaH (1)</td>
<td>3 (Z)/(Z)/E (1:0.6)</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>1b CF₃; Ms</td>
<td>DMF</td>
<td>NaH (0.5)</td>
<td>3 (Z)/(Z)/E (1:0.6)</td>
<td>22</td>
</tr>
<tr>
<td>4ᶜ</td>
<td>1b CF₃; Ms</td>
<td>DMF</td>
<td>NaH (2)</td>
<td>3 (Z)/(Z)/E (1:0.5)</td>
<td>83</td>
</tr>
<tr>
<td>5ᵈ</td>
<td>1b CF₃; Ms</td>
<td>MeCN</td>
<td>NaH (1)</td>
<td>3 (Z)/(Z)/E (1:0.5)</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>1b CF₃; Ms</td>
<td>THF</td>
<td>NaH (1)</td>
<td>3 (Z)/(Z)/E (1:0.9)</td>
<td>3</td>
</tr>
<tr>
<td>7ᵈ</td>
<td>1b CF₃; Ms</td>
<td>THF</td>
<td>t-BuOK (1)</td>
<td>3 (Z)/(Z)/E (1:0.6)</td>
<td>29</td>
</tr>
<tr>
<td>8ᵉ</td>
<td>1b CF₃; Ms</td>
<td>THF</td>
<td>NaH (1)</td>
<td>3 (Z)/(Z)/E (1:0.5)</td>
<td>10</td>
</tr>
<tr>
<td>9ᶠ</td>
<td>1b CF₃; Ms</td>
<td>THF</td>
<td>n-BuLi (1)</td>
<td>4 (Z)/(Z)/E (1:0.3)</td>
<td>17</td>
</tr>
<tr>
<td>10</td>
<td>1c CF₃; Ts</td>
<td>DMF</td>
<td>NaH (1)</td>
<td>5b</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>1d CH₃; Ms</td>
<td>DMF</td>
<td>NaH (1)</td>
<td>5b</td>
<td>34</td>
</tr>
<tr>
<td>12ᶠ</td>
<td>1b CF₃; Ms</td>
<td>THF</td>
<td>–</td>
<td>5b</td>
<td>72</td>
</tr>
</tbody>
</table>

ᵃ The yields were calculated based on ¹H NMR of the isolated mixture of 3 and 5, except entries 10, 11 and 12. 1 equiv of indole 6 has been used except in entry 5.
b The reaction was diluted 5 times.
c 2 equiv of 2 were used.
d Addition of crown-ether (1 mol %).
e Inverted order of reagents addition.
ᶠ No reaction.
ˢ Cyclohexylamine was used as the nucleophile.

![Scheme 3. Proposed mechanism for the formation of 3.](image-url)
plained, as the indole can catalyze the conversion of $3a$ ($Z/E$) into $3a$ ($Z/Z$), via TS-5, thus allowing for a mixture of configurations, as experimentally observed. The conclusion is that while structure $3a$ ($Z/E$) is formed under kinetic control, isomer $3a$ ($Z/Z$) is formed under thermodynamic control, which explains the relative variable amounts of both isomers, depending on the reaction conditions.

In summary, an unexpected reactivity was observed when compounds $1b$ and $1c$ were treated with indole sodium salt. A

Scheme 4. Proposed mechanism for the formation of 3. B3LYP/6-311++G(2df,2p)//B3LYP/6-31G(d,p), DMF, $T = 25$ °C (similar conclusions at 0 °C), radii = uaks.
mechanism was proposed, based on DFT studies, which fully rationalizes the experimental data. Six possible reaction pathways were considered, but only two lead to experimentally observable products (3 and 5a). The proposed mechanism identifies the importance of the metal ion and the reaction conditions on the final reaction outcome.

Acknowledgments

The authors acknowledge the Fundação para a Ciência e Tecnologia for financial support (PTDC/QUI/65187/2006) and for the PhD fellowship to M. E. (SFRH/BD/46234/2008).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.055.

References and notes