The Addition Reaction of Iododifluoromethylated Compounds with Alkenes or Alkynes: A General Method of Synthesizing Functionalized gem-Difluoroalkanes

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Received 11 April 1996; revised 9 September 1996

1,1-Difluoro-1,3-diiodoheptane (1) and 4,4-difluoro-4-iodobutyronitrile (4) derived from difluorodiiodomethane reacted with alkenes or alkynes in the presence of sodium dithionite and sodium bicarbonate at room temperature to afford the various CF₂-containing compounds in good yields.

The difluoromethylene moiety has attracted much attention over the years because this group is usually regarded as an isolopar and isosteric replacement for oxygen. In addition, based on the closeness of the van der Waals radii of the elements hydrogen (1.20 Å) and fluorine (1.35 Å), the methylene group can be replaced by the difluoromethylene moiety, altering the biochemical activity with minimal disturbance of the overall stereochemistry. The compounds containing the difluoromethyl-ene group are often synthesized through the conversion of a carboxyl into a difluoromethylene group with (diethylamino)sulfur trifluoride (DAST), or other reagents. However, all these methods suffer from the disadvantages of toxic or expensive reagents and complex, time-consuming procedures. Therefore, this is of great value to develop an effective, convenient and general preparation method.

The free radical addition reaction of perfluoroalkyl iodides with various unsaturated substrates provides an efficient method for the preparation of perfluoroalkylated derivatives, and we are convinced that, similar to perfluoroalkyl iodides, the easily available iododifluoromethylated alkenes may proceed by free radical addition reaction under the appropriate conditions, thus presenting a new approach to difluoromethylene-containing compounds.

Generally, the addition of perfluoroalkyl iodides to unsaturated compounds can be effected by photolysis, electrolysis and free radical initiators. Metal catalysts are also very important initiators for the reaction. But the disadvantages of long reaction time, severe reaction conditions or unsatisfactory yields often found in these methods greatly limit their utility. Recently, it was reported that the sulfinitodehalogenation system works nicely to give high yields of the adducts within a short reaction time. We report here that iododifluoromethylated compounds, like perfluoroalkyl iodides, can be effectively initiated by the sulfinitodehalogenation system in the addition reaction with alkenes or alkynes.

Following our development of a simple, convenient method for preparing difluorodiiodomethane on a 100 g scale, we have shown that iododifluoromethylated compounds are readily obtained via the reaction of difluorodiiodomethane with alkenes in the presence of zinc or iron powder. Thus when electron-rich alkenes were used as the substrates, the iodine atom-transfer adducts were obtained; whereas, in the case of electron-deficient alkenes, the products with the transferred iodine atom being reduced were formed. Functional groups such as the cyano and the ester moiety can be tolerated in the reaction. For further study of addition reactions of iododifluoromethylated compounds thus obtained, two typical compounds, 1,1-difluoro-1,3-dioleohexane (1) and 4,4-difluoro-4-iodobutyronitrile (4) were chosen. They were readily prepared from the reaction of hexene or acrylonitrile with CF₂I₂.

The reactions of 1 or 4 with alkenes or alkynes were investigated in the presence of various initiators. Metals such as Zn, Fe, Cu and Mg failed to give the corresponding adducts, e.g. when copper powder was used, a mixture of 1 with diallyl ether in DMSO or DMF at 100°C for 11 hours gave very complex products. However, when sodium dithionite was employed as the initiator, the reactions of 1 or 4 with alkenes or alkynes with different functional groups proceeded smoothly affording the corresponding adducts in moderate to high yields.

As shown in Scheme 1, treatment of 1 with electron-rich alkenes, allyl alcohol 2a or allyl ethyl ether 2b, gave the corresponding 1:1 adducts, 3a, 3b. In the reaction of 1 with 2a, 20 hours were necessary to consume 1 completely in the presence of Na₂S₂O₄ and NaHCO₃ at 30°C. However, 0.5 hours was enough for the complete conversion of perfluoroalkyl iodide under similar conditions. It is evident that the perfluoroalkyl iodide was much more reactive than the iododifluoromethylated derivatives. 1,3-Dibromo-1,1-difluorohexane, the bromo analogue of 1, is inert to our system.

With acrylate 2c, no incorporation of the iodine atom at the α-position or the ester group was observed giving rise to 3c. This result is similar to that of the addition of perfluoroalkyl iodide to electron-deficient alkenes. Addition reaction of 1 with propargyl alcohol also proceeded to provide almost equal amounts of E/Z isomers, which were determined on the basis of ¹³C NMR. The reactions of 4,4-difluoro-4-iodobutyronitrile (4) with alkenes or alkynes were also carried out under similar
reaction conditions as for 1. Treatment of 4 with the radical detector, diallyl ether 2e, afforded only the tetrahydrofuran derivative 5e, indicating a probable radical mechanism. The bifunctionalized compound, 5-ethoxy-carbonyl-γ,γ-difluorotriethylamine (5f) was conveniently prepared from the reaction of 4 with ethyl acrylate. When alkenes were used, the corresponding γ,γ-difluoro-α,β-unsaturated nitriles were obtained. Regardless of 1 or 4, the reactions with electron-rich alkenes proceeded in a shorter time and with higher yields of adducts than those with electron-deficient ones or alkynes.

Effects of reaction temperature and solvent in the reaction of 1 with 2b are summarized in the Table. The reaction temperature significantly influenced the results. High temperature was beneficial for complete conversion of the iododifluoromethylated compounds. However, when the temperature was elevated to 40 °C, the adduct was obtained in lower yield (Entry 6). In the meantime, the conversion of 1 depended largely on the ratio of acetonitrile to water. It was shown that the existence of water significantly improved the reaction rate and conversion. In fact, no reaction was observed in the absence of water (Entry 1).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio (V/V, CH₂CN/H₂O)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Conversion (%)</th>
<th>Z/E (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>40</td>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1:5</td>
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<td>20</td>
<td>70</td>
<td>73</td>
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<td>2:5</td>
<td>30</td>
<td>20</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
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<td>2:5</td>
<td>10</td>
<td>24</td>
<td>40</td>
<td>78</td>
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<tr>
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<td>2:5</td>
<td>20</td>
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<td>70</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>2:5</td>
<td>40</td>
<td>18</td>
<td>100</td>
<td>51</td>
</tr>
</tbody>
</table>

- a 1:2b/Na₂SO₄/NaHCO₃ = 1:2:2:2.
- b Determined by ¹H NMR.

The advantages of being able to easily prepare difluorodiiodomethane and its adducts of 1, 4 in large quantities, conveniently and under mild conditions enable the addition reaction to be a very efficient route to bifunctionalized gem-difluoroalkanes.

IR spectra were obtained on a Schimadzu 440 model instrument (liquid films). ¹H NMR spectra were recorded on a FX 90Q model.
instrument were recorded using TMS or CHCl3 as an internal standard. 19F NMR spectra were recorded on an EM 360 model instrument at 56.4 MHz using CF3CO2H as an external standard and positive value of chemical shift (ppm) means upfield. Mass spectra were obtained on a Finnigan 4041 model instrument. Silica gel (40 μm) was used for column chromatography.

**Iododifluoromethylated Compounds: 1,1-Difluoro-1,3-diodoheptane (I): Typical Procedure:**

Under N2 atmosphere, Fe (2.8 g, 50 mmol), CF3I (15.2 g, 50 mmol) and hex-1-ene (16.8 g, 200 mmol) were mixed. After the solution was stirred at 50–60°C for 4 h, the mixture was poured into ice water (100 mL) and extracted with Et2O (3 × 150 mL). The combined organic layer was washed with brine (100 mL), dried (MgSO4) and evaporated in vacuo. The residue was subjected to column chromatography (silica gel, light petroleum) to give I, yield 14.2 g (73%); 18 yellow oil.

**HRMS (M+): C11H15F8I2**
Calc. 443.2957, Found 443.2933.

**6-Cyano-4,4-difluoro-2-iodohexan-1-ol (5a):** yield (72%).

**HRMS (M+): C10H14F2I2O**
Calc. 443.2957, Found 443.2933.

**5a:** m/z (%) = 272 (M+ - OH, 53.32), 81 (100.0).

**6-Cyano-4,4-difluoro-2-iodohex-2-en-1-ol (5a):** yield (51%).

**HRMS (M+): C10H14F2I2O**
Calc. 443.2957, Found 443.2933.

**5a:** m/z (%) = 272 (M+ - OH, 53.32), 81 (100.0).

**6-Cyano-4,4-difluoro-2-iodohex-2-en-1-ol (5a):** yield (78%).

**HRMS (M+): C10H14F2I2O**
Calc. 443.2957, Found 443.2933.

**5a:** m/z (%) = 272 (M+ - OH, 53.32), 81 (100.0).

We are grateful for support of this research from the National Natural Science Foundation of China.