Facile Synthesis of Methylene cyclobutyl-Related Compounds via Rearrangement of Methylene cyclopropylcarbinols in the Presence of Multifluorosulfonyl Fluorides and Base

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Abstract: Methylene cyclopropylcarbinols treated with multifluorosulfonyl fluorides and triethylamine form the 3-methylene cyclobutyl fluorides and 3-methylene cyclobutyl (2-methylene cyclopropyl)methyl ethers in good to high total yields. A proposed mechanism is based on the obtained results.

Key words: methylene cyclopropylcarbinols, multifluorosulfonyl fluorides, base, rearrangement, etherification

There has been a mounting interest in the application of methylene cyclopropane (MCP) derivatives in synthetic transformations.1 Particular attention has been paid to the transition-metal-catalyzed reactions of MCPs with various reactants in organic synthesis over the past decades and some excellent reviews are available.2 Recent research has resulted in the renaissance of Lewis acid catalyzed chemistry of MCPs, and some novel reaction patterns have been found by us and other groups.3–6 Previous reports revealed that when 2-(hydroxymethyl)-substituted MCPs (methylene cyclopropylcarbinols) 1 are treated with sulfonation reagents and triethylamine, they give the normal sulfonates 2, which can be transformed into their isomers, the 3-methylene cyclobutyl analogues 3, when a silica gel column is used as a workup step (Scheme 1).8

In the mechanism, it can be seen that if –OSO2R3 is a weak nucleophile and/or a good leaving group, the carbon skeletons in the transition state A and/or in the intermediate B would be attacked by the relatively stronger nucleophiles present in the reaction system. This hypothesis encouraged us to further utilize other sulfonation reagents to examine the reaction pattern of methylene cyclopropylcarbinols 1. For this purpose, multifluorosulfonyl fluorides 4 were selected as the sulfonation reagent since R2SO2O– (R F = multifluoro group) is a good leaving group and also a very weak nucleophilic agent.

As a consequence, we found that fluorides 5 and ethers 6, both of which bearing a 3-methylene cyclobutyl group, were obtained as the products if methylene cyclopropylcarbinols 1 were treated with multifluorosulfonyl fluorides 4 and a base (Scheme 3). Initial examinations of the reactions of methylene cyclopropylcarbinol 1a (R1 = Ph, R2 = H) with perfluorobu-
tane-1-sulfonyl fluoride (4a) were carefully carried out at room temperature. We found that the reactions took place smoothly to give the 3-methylenecyclobutyl fluoride 5a and the corresponding ether 6a in moderate to high total yields with various bases and solvents, as shown in Table 1. The combination of triethylamine as the base and 1,2-dichloroethane (DCE) as the solvent is the best choice for this transformation, leading to the formation of products 5a in 57% yield and 6a in 35% yield, respectively.

Table 1 Optimization for the Reaction of Methylene cyclopropylcarbinol 1a with Fluoride 4a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>5a</th>
<th>6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et3N</td>
<td>DCE</td>
<td>57</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>DBU</td>
<td>DCE</td>
<td>22</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DABCO</td>
<td>DCE</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DMAP</td>
<td>DCE</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>DIPEA</td>
<td>DCE</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Et3NH</td>
<td>DCE</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>pyridine</td>
<td>DCE</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>i-Pr2NH</td>
<td>DCE</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Et3N</td>
<td>Et2O</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Et3N</td>
<td>benzene</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Et3N</td>
<td>toluene</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Et3N</td>
<td>MeCN</td>
<td>24</td>
<td>35</td>
<td></td>
</tr>
</tbody>
</table>

a All reactions were carried out using 1a (0.3 mmol) and 4a (0.6 mmol) in the presence of the listed base (0.4 mmol) and solvent (1.0 mL) at r.t. for 24 h.
b Isolated yields.
c Ratio of syn:anti = 1:1, as determined by 1H NMR spectroscopy.

To further examine the generality of this transformation, a variety of methylenecyclopropylcarbinols 1 was examined with perfluorobutane-1-sulfonyl fluoride (4a) under the optimized conditions. For each of the substrates 1 examined, either as the E- or Z-isomers, the reactions proceeded smoothly to give the corresponding products 5 and/or 6 in moderate to high total yields (Table 2). For substrates 1j (R1 = 4-FC6H4, R2 = H) and 1k (R1 = R2 = H), only the corresponding products 5j and 5k, respectively, were obtained in very low yields (Table 2, entries 9 and 10). To further determine the structure of products 5, fluoride 5c was unambiguously confirmed by an X-ray diffraction analysis (Figure 1). For all products 6, mixtures of syn- and anti-isomers were obtained in a ratio of 1:1 (Table 2).

To further examine the generality, we also carried out the transformation of substrates 1 with another multifluorosulfonyl fluoride 4b under the optimized conditions. Again, all reactions proceeded smoothly to give the corresponding products 5 and 6 in good to high total yields (Table 3).

The reaction of methylenecyclopropylcarbinol 1a with trifluoromethanesulfonic anhydride was also carried out under the standard conditions. Unfortunately, we found that the reaction system became disordered and no major product could be obtained (Scheme 4).
Based on the results obtained above, a plausible mechanism for this transformation of methylenecyclopropylcarbinols 1 is outlined in Scheme 5. Firstly, methylenecyclopropylcarbinols 1 react with R\(^3\)SO\(_2\)F in the presence of triethylamine to give the normal sulfonates 7 and triethylamine hydrofluoride (HEt\(_3\)N\(^+\)F\(^-\)). The enhanced leaving-group ability of R\(^3\)SO\(_2\)O\(^-\) is well known\(^{10}\) and the C–O bond will become more polarized according to this property, which will result in a separate ion pair as shown as intermediate 8 (maybe it is more reasonable to show 8 as an intermediate with more polarization in the C–O bond rather than a separated ion pair). Subsequently, the carbon skeleton part in 8, that is, the methylenecyclopropylmethyl cation, will quickly rearrange to the methylenecyclobutyl cation, as shown as intermediate 9, which will also be a separated ion pair for the same reason.\(^{10}\) Nucleophilic attack of 9 by F\(^-\) from HEt\(_3\)N\(^+\)F\(^-\) will give product 5, while nucleophilic attack by substrate 1 will furnish product 6. At the same time, intermediate 9 can also be shown as the sulfonate 10, which will also result in products 5 and 6, if it is attacked by the appropriate nucleophiles (Scheme 5).

In summary, we have found that methylenecyclopropylcarbinols 1 treated with multifluorosulfonyl fluorides 4 can give 3-methylenecyclobutyl fluorides 5 and the corresponding 3-methylenecyclobutyl-related ethers 4 in good to high total yields. A plausible mechanism has been proposed on the basis of the obtained results, which puts its emphasis on the rearrangement of methylenecyclopropylmethyl multifluorosulfonates to methylenecyclobutyl analogues due to the easy leaving-group ability of R\(^3\)SO\(_2\)O\(^-\). Furthermore, the reaction also introduces a new and sim-

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**Table 3** Reaction of Methylenecyclopropylcarbinols 1 with Fluoride 4b in the Presence of Triethylamine\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Carbinol 1R(^1)</th>
<th>R(^2)</th>
<th>Yield(^b) (%)</th>
<th>5</th>
<th>6(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Ph</td>
<td>5a, 64</td>
<td>6a, 27</td>
<td></td>
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<tr>
<td>2</td>
<td>1c</td>
<td>4-BrC(_6)H(_4)</td>
<td>5c, 44</td>
<td>6c, 26</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>4-MeC(_6)H(_4)</td>
<td>5d, 23</td>
<td>6d, 42</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>4-CIC(_6)H(_4)</td>
<td>5e, 41</td>
<td>6e, 36</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) All reactions were carried out using 1 (0.3 mmol) and 4b (0.6 mmol) in the presence of Et\(_3\)N (0.4 mmol) and DCE (1.0 mL) at r.t. for 24 h.  
\(^b\) Isolated yields.  
\(^c\) Ratio of syn/anti = 1:1, as determined by \(^1\)H NMR spectroscopy.
ple one-step synthetic method for 3-methylene cyclobutyl fluorides 5 from methylene cyclopropylicarbonilo 1 with easy manipulation and a simple experimental procedure. Efforts are underway in our laboratory to elucidate the mechanistic details and to determine the scope and limitations of the reaction.

1H and 13C NMR spectra were recorded on a Varian Mercury VX-300 spectrometer for solutions in CDCl3 with tetramethylsilane as an internal standard. IR spectra were measured on a Perkin–Elmer 983 spectrometer. Mass spectra and HRMS were recorded with a HP-5989 instrument, a Finnigan MA+ mass spectrometer and a Micromass GCT mass spectrometer. Satisfactory CHN microanalyses were obtained with a Carlo–Erba 1106 analyzer. Organic solvents were dried by standard methods when necessary. Melting points are uncorrected. All reactions were monitored by TLC using Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure.

3-(Arylmethylene)cyclobutyl Fluorides 5 and 3-(Arylmethylenecyclobutyl) [2-(Arylmethylene)cyclopropyl]methyl Ethers
6; General Procedure

Under an argon atmosphere, a methylenecyclopropylcarbinol 1 (0.3 mmol), a multifluorosulfonylefluorene 4 (0.6 mmol), Et3N (0.4 mmol) and DCE (1.0 mL) were added successively into a flash-dried Schlenk tube. The reaction mixture was stirred at r.t. and was monitored by TLC. The reaction usually was completed within 24 h. Then, the reaction was quenched with H2O (10 mL) and the mixture was extracted with CH2Cl2 (3 × 20 mL). The combined organic soln (10 mL), and dried (anhyd MgSO4), then the solution was concentrated under reduced pressure. Pure products were obtained by flash column chromatography (PE–EtOAc, 50:1). 5a

5a Colorless liquid.

IR (CH3Cl): 2924, 2853, 1789, 1705, 1599, 1463, 1540, 1435, 1269, 1162, 1023, 742 cm−1.

1H NMR (300 MHz, CDCl3): δ = 3.11–3.35 (m, 4 H), 5.17 (d quin, J = 56.1, 6.0 Hz, 1 H), 6.29 (t, J = 2.4 Hz, 1 H), 7.17–7.23 (m, 3 H, Ar), 7.31–7.34 (m, 2 H, Ar).

13C NMR (75 MHz, CDCl3): δ = 21.8 Hz), 41.9 (d, JCF = 22.4 Hz), 84.2 (d, JCF = 7.9 Hz), 123.6, 125.3, 133.4, 133.5, 134.3, 136.5, 137.3, 153.1, 153.2.

HRMS: m/z (%) = 252 (80) [M]+, 237 (20), 221 (100), 191 (46).

HRMS: m/z calcd for C14H17FO3: 252.1162; found: 252.1161.

6b Colorless liquid.

IR (CH3Cl): 2939, 2839, 1737, 1687, 1506, 1463, 1417, 1350, 1235, 1238, 1184, 1127, 1071, 1008, 931, 879, 826, 700 cm−1.

1H NMR (300 MHz, CDCl3): δ = 3.13–3.37 (m, 4 H), 3.85 (s, 3 H, MeO), 3.86 (s, 6 H, 2 × MeO), 5.19 (d quin, J = 56.1, 6.0 Hz, 1 H), 6.23 (t, J = 2.1 Hz, 1 H), 6.42 (s, 2 H, Ar).

13C NMR (75 MHz, CDCl3): δ = 141.7, 135.0, 132.5, 131.5, 123.7, 123.6, 120.7, 117.3, 111.0, 106.5, 101.9, 97.8, 93.4, 879, 822, 782 cm−1.

HRMS: m/z (%) = 482 (40) [M]+, 233 (66), 232 (42), 202 (100), 189 (32).

HRMS: m/z calcd for C22H22O: 302.1674; found: 302.1672.
6e
White solid; mp 33–35 °C.

IR (CHCl₃): 3029, 2970, 2913, 1502, 1492, 1405, 1349, 1226, 1207, 1179, 1091, 1073, 912, 936, 875, 824 cm⁻¹.

HRMS: m/z (%) = 196 (36) [M⁺], 161 (91), 150 (33), 141 (52), 115 (100).

HRMS: m/z calc for C₃H₆O: 196.0455; found: 196.0455.

6f
Yellow solid; mp 84–86 °C.

IR (CHCl₃): 3032, 2961, 2925, 2854, 1735, 1491, 1403, 1261, 1188, 1090, 1012, 969, 871, 822 cm⁻¹.

HRMS: m/z (%) = 370 (1) [M⁺], 177 (23), 142 (100), 141 (56).

HRMS: m/z calc for C₃H₆Cl₂O: 370.0891; found: 370.0889.

5f
Colorless liquid.

IR (CHCl₃): 3020, 2971, 2920, 2853, 1680, 1580, 1557, 1450, 1410, 1351, 1275, 1261, 1224, 1183, 1158, 1096, 1074, 1045, 1020, 970, 940, 888, 863, 798, 781, 765, 750 cm⁻¹.

HRMS: m/z (%) = 230 (33) [M⁺], 197 (25), 195 (72), 184 (26), 175 (40), 160 (24), 151 (28), 149 (100).

HRMS: m/z calc for C₃H₆Cl₂F: 230.0065; found: 230.0065.
6g
Yellow liquid.
IR (CDCl3): 3082, 3059, 3025, 2964, 2905, 1738, 1597, 1494, 1449, 1340, 1188, 1116, 1076, 1008, 912, 865, 768, 744 cm⁻¹.

1H NMR (300 MHz, CDCl3) (syn- or anti-isomer): δ = 1.08–1.12 (m, 1 H), 1.46 (t, J = 9.0 Hz, 1 H), 2.08–2.17 (m, 1 H), 2.87–3.25 (m, 5 H), 3.80 (dd, J = 6.3, 9.9 Hz, 1 H), 4.16 (quin, J = 6.3 Hz, 1 H), 5.23 (s, 1 H). 6.76 (s, 1 H), 7.13–7.35 (m, 8 H, Ar), 7.51 (d, J = 7.5 Hz, 2 H, Ar).

1H NMR (300 MHz, CDCl3) (anti- or syn-isomer): δ = 1.08–1.12 (m, 1 H), 1.46 (t, J = 9.0 Hz, 1 H), 2.08–2.17 (m, 1 H), 2.87–3.25 (m, 5 H), 3.80 (dd, J = 6.3, 9.9 Hz, 1 H), 4.16 (quin, J = 6.3 Hz, 1 H), 5.23 (s, 1 H). 6.76 (s, 1 H), 7.13–7.35 (m, 8 H, Ar), 7.51 (d, J = 7.5 Hz, 2 H, Ar).

13C NMR (75 MHz, CDCl3) (syn- or anti-isomer): δ = 21.46, 21.48, 40.6, 41.0, 70.4, 70.6, 120.2, 122.7, 123.8, 124.1, 125.5, 126.9, 127.5, 127.8, 127.9, 128.2, 128.4, 134.7, 137.3, 137.7, 137.9, 138.0.

HRMS: m/z calcd for C₁₂H₁₃FO: 176 (75) [M⁺], 161 (100), 156 (25), 141 (39), 130 (32), 129 (49), 128 (39), 115 (71).

HRMS: m/z calcd for C₂₄H₂₆O₃: 362 (12) [M⁺], 173 (68), 158 (100).

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References
(3) For a recent review on the Lewis acid catalyzed ring-opening reactions of MCPs, see: Shao, L.-X.; Shi, M. *Curr. Org. Chem.* 2007, 11, 1135; and references cited therein.


(9) The crystal data for 5c has been deposited as CCDC 623472. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Empirical formula: C_{11}H_{10}BrF; formula weight: 241.10; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 4.539 (3) Å, b = 9.933 (6) Å, c = 11.135 (7) Å, α = 90°, β = 93.865 (10)°, γ = 90°; V = 500.9 (5) Å³; space group: P2₁; Z = 2; D_{calc} = 1.599 g/cm³; F_{000} = 240; diffractometer: Rigaku AFC7R; residuals: R, Rw: 0.0577, 0.1406.