Synthesis of Bridgehead Derivatives; 2. Preparation of 1-Substituted Bicyclo[2.2.1]heptanes

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The reaction of bridgehead trifluoromethanesulfonates 1- and 4-trifluoromethylsulfonyloxycamphene (1A, B) with magnesium iodide or magnesium bromide in carbon disulfide yields the corresponding halides 2 and 3. The reaction time was reduced by sonication. The 1-(2-cyanoethyl) and 2-methoxycarbonylmethylcamphenes 6A and 7A, and the corresponding 4-substituted analogues 6B and 7B are prepared by radical addition of 2A and 2B to methyl acrylate (4) or acrylonitrile (5), respectively.

The chemistry of bridgehead derivatives with the bicyclo[2.2.1]skeleton is of interest, not only because of the structure reactivity relationship of the corresponding strained reactants and intermediates, but also due to their often interesting physiological activities. However, there exists no general method for the preparation of such bridgehead derivatives. A useful access to these bridgehead compounds is provided by the reaction of bicyclo[2.2.1]heptan-2-ones with trifluoromethanesulfonic anhydride, which leads to the rearranged bridgehead trifluoromethanesulfonates (triflates), 1- (1A) and 4-trifluoromethylsulfonyloxycamphene (1B). Subsequently the triflate group can be easily substituted by other nucleophiles such as hydroxy and amine functions, although strained nonplanar carbonium ions are considered as intermediates in these processes.

We report here on the reaction of 1A and 1B with magnesium iodide or magnesium bromide in carbon disulfide (or in diethyl ether) to give the structurally analogous 1- and 4-iodocamphenes (2A and 2B, respectively) or 1- and 4-bromocamphene (3A and 3B, respectively) (Scheme 1) (Table 1).

<table>
<thead>
<tr>
<th>ROAST</th>
<th>MgX2/Solvent/ Reaction Conditions</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>MgI2/CS2, Δ</td>
<td>48</td>
<td>36</td>
<td>2A  75</td>
</tr>
<tr>
<td></td>
<td>MgI2/CS2(κ=1)</td>
<td>48</td>
<td>5</td>
<td>2A  75</td>
</tr>
<tr>
<td>1B</td>
<td>MgCl2/CS2/Δ</td>
<td>48</td>
<td>36</td>
<td>2B  80</td>
</tr>
<tr>
<td></td>
<td>MgCl2/CS2(κ=1)</td>
<td>48</td>
<td>12</td>
<td>2B  80</td>
</tr>
<tr>
<td></td>
<td>MgBr2/Et2O/Δ</td>
<td>140</td>
<td>168</td>
<td>3B  2</td>
</tr>
<tr>
<td></td>
<td>MgBr2/CS2/Δ</td>
<td>140</td>
<td>168</td>
<td>3B  48</td>
</tr>
</tbody>
</table>

* Pseudo first order reaction rate. Ratio of MgX2/triflate = 2 : 1.
Δ = Thermal reaction. (κ=1) = sonication.
* Yield of isolated product.

The bridgehead halides 2 and 3 prepared as above were also investigated with respect to possible radical halogenation reactions. The reaction of alkyl halides with electron poor olefins, which proceeds via radical intermediates is an important method for the formation of carbon–carbon bonds. This reaction succeeds also with bulky pyramidal radicals. Thus, the reaction of 4-camphenylmercuric chloride with methyl acrylate (4) and sodium borohydride leads to methyl 3-(3-camphenyl)propanoate (6B) in 61% yield.

To achieve a radical alkylation of the iodide 2, it was reacted with methyl acrylate (4) and acrylonitrile (5), respectively. Tributyltin hydride was used as the hydride donor and azobisisobutyronitrile (AIBN) as the initiator. The reactions (Scheme 2) proceed under comparable conditions as that for the acyclic and less strained cyclic radicals (in toluene at 110°C, 24 h), with the formation of ester 6 or nitriles 7 in good yields (Table 2).

The reaction takes place probably via an SN1 (κ1) process, whereby the heterolytic of the triflate group is facilitated by coordination with the magnesium halide. As seen from Table 1, magnesium iodide is a stronger Lewis acid than magnesium bromide (the reaction time and temperature is lower for magnesium iodide than for magnesium bromide). The reaction rate in diethyl ether is diminished, although diethyl ether has a higher ionizing power than carbon disulfide. This is due to the preferential coordination of diethyl ether with the active sites of magnesium, which leads to a slow SN1 reaction of magnesium halides with the triflates 1 in diethyl ether. The reaction time can be reduced considerably by sonication with ultrasound (Table 1). The reaction mixture is homogeneous at first, however, a precipitate of magnesium triflate forms slowly.

\[ \text{CO}_2\text{Me} (4) \text{ or } \text{CN} (5b) + \text{Bu}_3\text{SnH}{/}\text{AIBN/toluene, reflux, 24h} \]

\[ \text{CO}_2\text{Me} (6) \text{ or } \text{CN} (7) \]

| Scheme 2 |
Table 2. Compounds 2, 3, 6 and 7 Prepared

<table>
<thead>
<tr>
<th>Prod-</th>
<th>Yield (%)</th>
<th>mp (°C) or bp (°C)/Tor</th>
<th>Molecular Formula* or Lit. bp (°C)/Tor</th>
<th>IR (CCl₄) v cm⁻¹</th>
<th>¹H-NMR (CCl₄/TMS) δ ppm</th>
<th>MS (100 eV) m/z (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>75</td>
<td>57–59</td>
<td>C₁₄H₁₇I (262.1)</td>
<td>1650 (C=I), 1390, 1360 (C=Me₂), 900 (=CH₂)</td>
<td>1.03, 1.10 (2s, 3H each, CH₂), 1.5–2.4 (7H, ring CH₂ + CH), 4.45, 4.65 (2s, 1H each, =CH₂)</td>
<td>262 (M⁺, 16), 135 (M⁺–I, 100), 107 (C₇H₅, 57), 93 (C₇H₆, 71), 91 (C₅H₃, 43)</td>
</tr>
<tr>
<td>2b</td>
<td>80</td>
<td>68/2</td>
<td>C₁₆H₁₆Br (215.1)</td>
<td>3060 (CH₃), 1660 (C=O), 1390, 1365 (C=Me₂), 900 (=CH₂)</td>
<td>1.05 (s, 6H, CH₃), 1.80 (m, 7H, ring CH₂ + CH), 4.65, 5.05 (2s, 1H each, =CH₂)</td>
<td>214 (M⁺, 29), 185 (M⁺–C₆H₅, 19), 171 (M⁺–C₆H₄, 100), 135 (M⁺–Br, 95), 91 (C₅H₃, 71), 69 (C₄H₃, 72)</td>
</tr>
<tr>
<td>3b</td>
<td>48</td>
<td>26–27/0.01</td>
<td>C₁₆H₁₅Br (222.3)</td>
<td>3090 (CH₃), 1750 (C=O), 1400, 1380 (C=Me₂), 900 (=CH₂)</td>
<td>0.97, 1.01 (2s, 3H each, CH₂), 1.1–2.6 (m, 11H, ring CH₂ + CH and CH₃CH₂CO₂Me), 3.66 (s, 3H, OCH₃), 4.50, 4.70 (2s, 1H each, =CH₂)</td>
<td>222 (M⁺, 100), 207 (M⁺–OCH₃, 14), 148 (C₅H₃, 31), 135 (C₅H₃, 32), 105 (C₄H₄, 30)</td>
</tr>
<tr>
<td>6a</td>
<td>45</td>
<td>46–47/0.01</td>
<td>C₁₆H₁₅O₂</td>
<td>3090 (CH₃), 1750 (C=O), 1400, 1380 (C=Me₂), 900 (=CH₂)</td>
<td>0.98, 1.02 (2s, 3H each, CH₂), 1.1–2.6 (m, 11H, ring CH₂ + CH and CH₃CH₂CO₂Me), 4.50, 4.70 (2s, 1H each, =CH₂)</td>
<td>189 (M⁺, 50), 174 (M⁺–CH₂, 43), 160 (M⁺–C₆H₅, 42), 146 (M⁺–C₆H₄, 100), 135 (C₆H₅, 32), 105 (C₄H₄, 37)</td>
</tr>
<tr>
<td>6b</td>
<td>60</td>
<td>150/12</td>
<td>C₁₆H₁₅N (189.3)</td>
<td>3090 (CH₃), 2260 (C=N), 1670 (C=O), 1395, 1370 (C=Me₂), 900 (=CH₂)</td>
<td>0.98, 1.05 (2s, 3H each, CH₂), 1.1–2.4 (m, 11H, ring CH₂ + CH and CH₃CH₂CN), 4.50, 4.70 (2s, 1H each, =CH₂)</td>
<td>189 (M⁺, 49), 174 (M⁺–CH₂, 43), 160 (M⁺–C₆H₅, 42), 146 (M⁺–C₆H₄, 100), 133 (C₆H₅, 27), 105 (C₄H₄, 36)</td>
</tr>
<tr>
<td>7a</td>
<td>56</td>
<td>60–62</td>
<td>C₁₆H₁₅N (189.3)</td>
<td>3090 (CH₃), 2260 (C=N), 1665 (C=O), 1400, 1370 (C=Me₂), 900 (=CH₂)</td>
<td>0.98, 1.05 (2s, 3H each, CH₂), 1.1–2.4 (m, 11H, ring CH₂ + CH and CH₃CH₂CN), 4.50, 4.70 (2s, 1H each, =CH₂)</td>
<td>189 (M⁺, 49), 174 (M⁺–CH₂, 43), 160 (M⁺–C₆H₅, 42), 146 (M⁺–C₆H₄, 100), 133 (C₆H₅, 27), 105 (C₄H₄, 36)</td>
</tr>
</tbody>
</table>

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* Satisfactory HRMS values obtained: ± 0.0019 amu.

The present method to prepare 6 and 7 is the best available route to the bridgehead alkyl derivatives. All products were characterized by IR, ¹H-NMR and mass spectra (Table 2).

IR spectra were obtained on a Perkin-Elmer 257 spectrophotometer. ¹H-NMR spectra were measured on a Varian T 80-A (80 MHz) spectrometer. Mass spectra were run on a Varian MAT 711 spectrometer.

The bridgehead triflates 1a and 1b were prepared from camphor and trifluoromethanesulfinic anhydride according to the literature procedure.²

**Reaction of Bridgehead Triflates 1 with Magnesium Halides; General Procedure:**

In a 100 mL round-bottom flask equipped with a reflux condenser and a CaCl₂ drying tube is placed a solution of 1a or 1b (3.12 g, 11 mmol) and anhydrous magnesium halide³ (22 mmol) in CS₂ (50 mL). The mixture is sonicated under reflux in a preheated diethylene glycol bath (constant temperature 48 °C) using a ultrasonic cleaner (14 × 14 × 8 cm, 50–55 kHz, 125 W). For reactions conducted without sonication, the reaction mixture is refluxed at 48 °C or heated to 140 °C in a glass ampule. The solvent is removed on a rotary evaporator and the residue is dissolved in Et₂O (100 mL). The organic phase is washed with sat. NaHSO₃ solution (3 × 50 mL), water (3 × 50 mL), and dried (MgSO₄). After removal of the solvent, the crude product is taken up in hexane (25 mL) and evaporated again. The residue is purified by distillation and the products are analyzed by GC (OV-101, capillary column, 25 m, 60–100 °C) and identified spectroscopically, where by only the bridgehead derivatives 2 or 3 is detected. The products are purified by distillation or recrystallization (Table 2).

**Radical Alkylation of Bridgehead Derivatives, General Procedure:**

A solution of 2 (0.6 g, 2.3 mmol), AIBN (10 mg, 0.06 mmol), Bu₃SnH (0.81 g, 2.8 mmol) and methyl acrylate (4; 0.43 g, 5 mmol) or acrylonitrile (5; 0.53 g, 5 mmol) in toluene (10 mL) is refluxed for 24 h. Toluene is removed on a rotary evaporator and the residue is purified by column chromatography on silica gel (pentane/Et₂O, 9:1). The products 6 or 7 obtained, respectively, are spectroscopically pure (Table 2).

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(4) Unpublished work.
(11) In this work 4-camphyl radical is designated as 1-cam-phenyl.