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Unexpected formation of 10-iodo- and 10-chlorocamphor under halosulfonylation conditions, and convenient routes to 10-chloro- and 10-bromocamphor

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Abstract—Generation of camphor-10-sulfonyl iodide in situ under halosulfonylation conditions or exposure of camphor-10-sulfonyl chloride to copper (II) chloride under Asscher-Vofs i conditions unexpectedly leads to the formation of 10-iodocamphor or 10-chlorocamphor respectively. Additionally, convenient syntheses of 10-bromocamphor and 10-chlorocamphor have been achieved by extension of previously reported methodology. © 2013 Elsevier Science. All rights reserved

1. Introduction

Unsaturated sulfoines have found widespread use as versatile intermediates in organic synthesis, especially as Michael acceptors and in cycloaddition reactions.\textsuperscript{1,2} However, there do not appear to have been any reports of either the synthesis or applications of vinylic sulfoines \textsuperscript{1} which possess homochiral alkyl groups R* that are directly attached to the sulfur atom. The conformationally rigid, monoterpenoid-based camphorsulfonyl framework \textsuperscript{2} (Figure 1), which is already widely exploited as a component of various practical chiral auxiliaries,\textsuperscript{3} and which is readily available in both enantiomeric forms, seemed to be a promising candidate for this purpose. In this paper, we describe the unexpected formation of 10-halocamphors \textsuperscript{3-5} (X = Cl/Br/I) during attempted halosulfonylation reactions of some alkenes, and show how these versatile chiral synthons can be readily accessed from (+)-camphor-10-sulfonic acid.

2. Results and Discussion

During the course of our ongoing work on the development of sulfonyl-based chiral auxiliaries, we sought to synthesize various chiral vinyl sulfoines via halosulfonylation reactions of alkenes. Initially, we opted to generate camphor-10-sulfonyl iodide \textsuperscript{7} in situ in the immediate presence of an alkene, by treating sodium (+)-camphor-10-sulfinate \textsuperscript{6} (available by reduction of (+)-camphor-10-sulfonic acid) with iodine, a strategy successfully utilised by others for reactions involving arenesulfonyl iodides.\textsuperscript{5}

\textbf{Figure 1.} Homochiral camphor-based vinyl sulfoines and the 10-halocamphors.

In the event, when an aqueous solution of sodium (+)-camphor-10-sulfinate \textsuperscript{6} was vigorously stirred at ambient temperature with a DCM solution of iodine and allyl benzyl ether, (−)-10-iodocamphor \textsuperscript{5} was unexpectedly formed and unchanged alkene was recovered, rather than the expected β-iodosulfone (Scheme 1). (−)-10-Iodocamphor \textsuperscript{5} was also obtained in the absence of the alkene, and when triethylamine (normally used to generate the vinyl sulfoine \textit{in situ} from the β-iodosulfone) was added before work-up. On the other hand, when either norbornene or 1,5-cyclooctadiene was the alkene, reaction with sodium (+)-camphorsulfinate \textsuperscript{6} and iodine in methanol as solvent, followed by \textit{in situ} treatment with potassium tert-butoxide did afford the expected vinylic sulfoines, albeit in only modest yields.\textsuperscript{6}

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We next showed that reaction of sodium (+)-camphor-10-sulfinate 6 with bromine in DCM solution formed the sulfonyl bromide 8, which could be converted into (+)-10-bromocamphor 4. This required the thermolysis of crude 8 in either refluxing xylene or toluene, demonstrating its greater stability over that of the sulfonyl iodide 7.

\[
\text{Scheme 1.}
\]

These results prompted us to investigate the addition of (+)-camphor-10-sulfonyl chloride 9 to alkenes under free-radical conditions. Asscher and Vofsi have described how the radical addition of arenesulfonyl chlorides to alkenes can be conveniently catalysed by the system CuCl₂ - Et₃N.HCl in refluxing toluene. However, when 1,5-cyclooctadiene was reacted with (+)-camphor-10-sulfonyl chloride 9 under these conditions none of the anticipated adduct was formed. Instead, the alkene was recovered and (+)-10-chlorocamphor 3 was obtained in excellent yield (Scheme 2). The same product 3 was efficiently formed in the absence of alkene, but it was not obtained in the absence of the Cu(II) catalyst. Other simple cycloalkenes such as cyclohexene also failed to yield radical addition products under Asscher-Vofsi conditions.

\[
\text{Scheme 2.}
\]

From the above results, we conclude that homolytic fission of the sulfonyl halides 7 or 9 leads to the rather hindered, neopentyl-like, sulfonyl radical 10 which loses sulfur dioxide to form the 10-camphoryl radical 11 more rapidly than it can react with an alkene. Recombination of 11 with either an iodine or chlorine atom then yields either (+)-10-iodocamphor 5 or (+)-10-chlorocamphor 3, respectively (Scheme 3). The failure of the sulfonyl halides 7 and 9 to form adducts with alkenes is perhaps not too surprising, given that analogous aliphatic alkanesulfonyl iodides are unstable and decompose with loss of sulfur dioxide.

The 10-halocamphors 3, 4 and 5 have been widely used both as sources of chirality in asymmetric synthesis, and as precursors to chiral synthons employed in total synthesis. Both (+)-10-bromocamphor 4 and (−)-10-iodocamphor 5 have been converted into various homochiral bidentate P-P, N-P and N-S donor ligands for asymmetric synthesis. Chiral imidazolium-based ionic liquids, telluronium salts and ligands for asymmetric Pauson-Khand reactions have been derived from (−)-10-iodocamphor 5, whilst chiral Brönsted acids have been synthesized from (±)-10-bromocamphor 4. Additionally, fragmentation of the C(1)(C(2)) bond in 4 and 5 affords chiral cyclopentenes which have been utilised as chiral synthons in the total synthesis of various natural products.

A convenient synthesis of (−)-10-iodocamphor 5 directly from commercially available (+)-camphor-10-sulfonic acid via reduction with I₂/PPh₃ has been previously reported, although to the best of our knowledge this methodology has not been previously applied to the synthesis of either 3 or 4. Given the widespread use of the 10-halocamphors 3, 4 and 5 as chiral synthons, we sought to extend this methodology to the synthesis of both (+)-10-bromocamphor 4 and (+)-10-chlorocamphor 3 by appropriate choice of electrophilic halogenating reagent. These results are summarised in Table 1. Reduction of (+)-camphor-10-sulfonic acid 12 with bromine (3 equivalents) and triphenylphosphine (5 equivalents) in refluxing toluene gave (+)-10-bromocamphor 4 in 78% yield after purification by chromatography. Encouraged by this result, we examined various halogen donors and found that both carbon tetrabromide and N-bromosuccinimide were also suitable reagents for the preparation of 4.
Table 1. Synthesis of 4 and 3 via reduction of (+)-camphor-10-sulfonic acid 12 with PPh₃ and various halogenating reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>PPh₃ (equiv)</th>
<th>Bu₄N (equiv)</th>
<th>Ratio of 3 or 4</th>
<th>Yield of 3 or 4 (%)</th>
<th>Yield of 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br₂ (3)</td>
<td>(5)</td>
<td>(0)</td>
<td>1:0⁺</td>
<td>78 (4)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>NBS (3)</td>
<td>(5)</td>
<td>(0)</td>
<td>1.5:1</td>
<td>44 (4)</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>CB₄ (3)</td>
<td>(5)</td>
<td>(0)</td>
<td>1.9:1</td>
<td>50 (4)</td>
<td>27</td>
</tr>
<tr>
<td>4</td>
<td>CB₄ (4)</td>
<td>(6)</td>
<td>(1)</td>
<td>1:0⁺</td>
<td>84 (4)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>C₂Cl₄ (3)</td>
<td>(5)</td>
<td>(0)</td>
<td>3.4:1</td>
<td>68 (3)</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>NCS (3)</td>
<td>(5)</td>
<td>(0)</td>
<td>3.7:1</td>
<td>70 (3)</td>
<td>17</td>
</tr>
<tr>
<td>7</td>
<td>CCl₃ (3)</td>
<td>(5)</td>
<td>(0)</td>
<td>3:1</td>
<td>66 (3)</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>CCl₃ (3)</td>
<td>(5)</td>
<td>(0)</td>
<td>4.1:1⁺</td>
<td>68 (3)</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>CCl₃ (4)</td>
<td>(6)</td>
<td>(0)</td>
<td>6.2:1</td>
<td>72 (3)</td>
<td>11</td>
</tr>
<tr>
<td>10</td>
<td>CCl₃ (5)</td>
<td>(7)</td>
<td>(0)</td>
<td>5.8:1</td>
<td>69 (3)</td>
<td>13</td>
</tr>
<tr>
<td>11</td>
<td>CCl₃ (4)</td>
<td>(6)</td>
<td>(1)</td>
<td>30:1</td>
<td>81 (3)</td>
<td>3</td>
</tr>
</tbody>
</table>

¹Determined by 'H NMR. ²Isolated yield.

Similarly, carbon tetrachloride, hexachloroethane and N-chlorosuccinimide could all be successfully employed for the synthesis of (+)-10-chlorocamphor 3. However, in a number of the reduction experiments bis(10-camphoryl) disulfide 13 was also obtained in variable quantities as by-product in addition to the desired 10-halocamphor 3 or 4 (Scheme 4).

Scheme 4.

By consideration of the mechanism of the analogous reduction of acid 12 with I₂/PPh₃,¹ we attribute the formation of disulfide 13 to the competitive trapping of mercaptotriphenylphosphonium ion 14 with 10-mercaptopcamphor 15,² rather than with bromide ion or (the somewhat less nucleophilic) chloride ion (Scheme 5). In order to minimize the formation of disulfide 13 and improve the yields of the desired 10-halocamphor 3 or 4, we briefly examined the influence of reaction stoichiometry, reaction time and the addition of base on the yields of 3 and 4.

It was found that prolonging the reaction time (entry 8), or the use of additional equivalents of both the halogenating reagent and triphenylphosphine (entries 9 and 10) led to only a modest improvement in the yield of 3. The best results were obtained when tributylamine (1 equivalent) was added to the reaction mixture prior to reflux. Under these conditions (+)-10-chlorocamphor 3 and (+)-10-bromocamphor 4 were obtained in improved yields of 81% (entry 11) and 84% (entry 4), respectively.

3. Conclusion

It has been found that camphor-10-sulfonyl iodide 7, formed in situ from sodium (+)-camphor-10-sulfinate 6, undergoes spontaneous and efficient conversion into (−)-10-iodocamphor 5. Similarly, exposure of (+)-camphor-10-sulfonyl chloride 9 to Asscher-Vošfi radical conditions generates (+)-10-chlorocamphor 3 in high yield. Failure to effect the halosulfonylation of alkenes under these conditions may be attributed to the competing rapid extrusion of sulfur dioxide from the sterically hindered camphorsulfonyl radical 10. In addition, a previously reported synthesis of (−)-10-iodocamphor 5 has been extended to deliver both (+)-10-chlorocamphor 3 and (+)-10-bromocamphor 4, leading to convenient syntheses of these important chiral synthons directly from commercially available (+)-camphor-10-sulfonic acid 12.

4. Experimental

4.1. General

NMR spectra were recorded using a Bruker AVANCE DPX 400 MHz spectrometer (400.1 MHz for ¹H and 100.6 MHz for ¹³C). Chemical shifts are reported in parts per million. Coupling constants (J) are quoted in Hertz. Optical rotations were measured using a Perkin-Elmer 141 polarimeter. IR spectra were recorded for Nujol mulls (N) on a Mattson Genesis II FTIR spectrometer. Mass spectra were obtained under electrospray conditions using a Micromass LCT instrument. All solvents and reagents were purified by standard techniques. Organic extracts of reaction products were dried over anhydrous magnesium sulfate.

4.2. (1S,4R)-(7,7-Dimethyl-2-oxobicyclo[2.2.1]hept-1-yl) methanesulfonyl chloride 9.

Thionyl chloride (37.7 mL, 516 mmol) was added to (+)-camphor-10-sulfonic acid 12 (40.0 g, 172 mmol) in a 1L flask. The mixture was stirred at room temperature for 1 hr, warmed at 40 °C for a further 6 hrs and then cooled back to room temperature and left stirring overnight. The mixture was diluted with ether (400 mL) and quenched over ice/H₂O. The aqueous layer was extracted with ether (400 mL). The combined organic extracts were washed with water (200 mL) and saturated sodium hydrogen carbonate...
solution (4 × 100 mL) until the evolution of CO₂ had ceased, and then dried and evaporated to afford (+)-camphor-10-sulfonyl chloride 9 as a white solid (38.0 g, 89 %); Mp 62-63 °C (ether); Lit.° 67-68 °C. [d]₀ = +30.9 (c 1.29, CHCl₃, 27 °C); Lit.° +28.8 (c 4.2, CHCl₃). IR: ¹ν max (N) 2921, 1743 (C=O), 1456, 1417, 1375, 1297, 1213, 1102, 1045 (SO), 4.4. (1.5 % (H NMR) of the corresponding sodium sulfonate.

6. The solution was then washed with water (50 mL) and then dried and evaporated to afford (+)-10-bromocamphor as a white solid (0.83 g, 84 %); Mp 75 °C. The solution was then allowed to cool to room temperature, water (50 mL) was added and the mixture was extracted with ether (3 × 50 mL). The combined organic extracts were dried and evaporated to yield an oil which was purified by column chromatography on silica gel, eluting with ether/hexane (1:1) to afford (+)-10-bromocamphor as a white solid (0.33 g, 72 %).


A solution of bromine (0.1 mL, 1.97 mmol) in DCM (100 mL) was vigorously mixed with a solution of sodium sulfinate 6 (0.54 g, 2.16 mmol) in water (50 mL) in a separating funnel. The organic phase was removed and evaporated and the resulting solid was dissolved in xylene (15 mL). The solution was then allowed to cool to room temperature, water (50 mL) was added and the mixture was extracted with ether (3 × 50 mL). The combined organic extracts were dried and evaporated to yield an oil which was purified by column chromatography on silica gel, eluting with ether/hexane (1:10) to afford (+)-10-bromocamphor as a white solid (0.33 g, 72 %).

4.5.2. Method B: From Sulfonic Acid 12.

(+)-Camphor-10-sulfonic acid 12 (1.00 g, 4.30 mmol) and triphenylphosphine (5.71 g, 17.21 mmol) was added, followed by tributylamine (1.02 mL, 4.30 mmol) and the solution was then allowed to cool to room temperature, water (50 mL) was added and was then stirred overnight. The mixture was evaporated to yield a white residue which was taken up in boiling methanol (ca. 100 mL) and filtered through celite. The filtrate was evaporated to afford sodium sulfinate 6 as a white solid (31.43 g, 94 %) together with ca. 5 % (1H NMR) of the corresponding sodium sulfonate. This was used without further purification: [d]₀ = +41.8 (c 0.76, H₂O, 22 °C); Lit.° -58.2 (c 0.885, H₂O, 19 °C). IR: ¹ν max (N) 3358, 2918, 1741 (C=O), 1460, 1375, 1278, 1197, 1020, 973, (S=O), 851, 816, 723 cm⁻¹. ¹H NMR (DCl): 0.80 (s, 3H, 7-CH₃), 0.93 (s, 3H, 7-CH₃), 1.33-1.40 (m, 1H), 1.43-1.51 (m, 1H), 1.88 (d, J = 19.0, 1H, 3-CH₂-endo), 1.92-2.00 (m, 1H), 2.00-2.06 (dd, J = 12.0, 2.5, 1H), 2.10 (t, J = 4.5, 1H, 4-CH₂), 2.13 (d, J = 13.5, 1H, CH₃SO₂Na), 2.35-2.42 (dd, J = 19.0, 4.5, 3.0, 1H, 3-CH₂-exo), 2.57 (d, J = 13.5, 1H, CH₃SO₂Na), 1.96 (1H, 5-CH₂-exo), 3.32 (d, J = 11.5, 1H, 6-CH₂-exo), 26.2 (C-5), 52.0 (C-6), 62.9 (C-7). ¹³C NMR (DCI): 18.3 (7-CH₃), 18.7 (7-CH₂), 25.6 (C-5), 25.9 (C-6), 42.0 (C-4), 42.3 (C-3), 47.6 (C-7), 58.5 (C-1), 59.5 (CH₃SO₂Na), 223.8 (C-2).

4.4. (1S,4R)-(1-Iodomethyl)-7,7-dimethylbicyclo[2.2.1]hept-2-en-5-one 5.

A solution of iodine (0.5 g, 1.97 mmol) in DCM (100 mL) was vigorously mixed with a solution of sodium sulfinate 6 (0.54 g, 2.16 mmol) in water (50 mL) in a separating funnel. The yellow organic phase was placed in a round bottomed flask and stirred at room temperature for 1.5 hrs. The solution was then washed with water (50 mL) and the aqeous layer was extracted with ether (50 mL). The combined organic extracts were washed with saturated aqeous sodium sulfite (50 mL), dried and evaporated to afford (−)-10-iodocamphor 5 as a white solid (0.36 g, 65 %); Mp 69 °C (DCM); Lit.° 71 °C. [d]₀ = +20.1 (c 1.28, CHCl₃, 23 °C); Lit.° -20.4 (c 1. CHCl₃, 23 °C). IR ¹ν max (N) 2921, 1743 (C=O), 1467, 1417, 1375, 1297, 1213, 1188, 1163, 1063, 1038, 955, 891, 766 cm⁻¹. ¹H NMR (CDCl₃): 0.91 (s, 3H, 7-CH₃), 1.08 (s, 3H, 7-CH₃), 1.40 (t, J = 9.5, 1H, 5-CH₂ endo), 1.62 (t, J = 9.5, 1H, 6-CH₂ endo), 1.92 (d, J = 18.5, 1H, 3-CH₂ endo), 1.96-2.05 (m, 2H, 5-CH₂ exo and 6-CH₂ exo), 2.17 (app dd, J = 5.5, 2.5, 1H, 4-CH₂), 2.41 (dd, J = 18.5, 5.0, 2.0, 1H, 3-CH₂ exo), 3.13 (d, J = 11.0, 1H, CH₃), 3.32 (d, J = 11.0, 1H, CH₃). ¹³C NMR (CDCl₃): 0.3 (CH₃), 19.6 (7-CH₃), 19.8 (7-CH₃), 26.2 (C-5), 30.0 (C-6), 42.5 (C-3), 43.5 (C-4), 47.8 (C-7), 58.6 (C-1), 214.7 (C-2). HRMS (EI, MeOH): m/z calc'd for C₁₀H₁₇OBr [M + Na]⁺: 253.0203; found: 253.0200.

Copper (II) chloride (0.02 g, 1.24 mol %) and triethylammonium chloride (0.03 g, 1.82 mol %) were added to a solution of (+)-camphor-10-sulfonyl chloride 9 (3.0 g, 11.96 mmol) in dry toluene (15 mL). The resulting mixture was heated under nitrogen at 110 °C during 4 hrs. The solvent was removed under reduced pressure and the residue was taken up in DCM (30 mL). The catalyst system was then precipitated using methanol (5 mL) and the organic layer was filtered and washed with 10 % sodium hydrogen carbonate solution (20 mL) and with water (20 mL). The extract was dried and evaporated under reduced pressure to afford (+)-10-chlorocamphor 3 as a white solid (2.19 g, 89 %) which was recrystallized from methanol.


(+)-Camphor-10-sulfonic acid 12 (1.00 g, 4.30 mmol) and triphenylphosphine (6.77 g, 25.82 mmol) were dissolved in dry toluene (30 mL) under an atmosphere of nitrogen. Carbon tetrachloride (1.66 mL, 17.21 mmol) was added dropwise via syringe, followed by tributylamine (1.02 mL, 4.30 mmol) and the solution was heated under reflux for 24 hrs. The solution was then allowed to cool to room temperature and water (50 mL) was added. The phases were mixed and separated and the aqueous phase was extracted with DCM (2 × 50 mL). The combined organic extracts were washed with water (50 mL), dried and evaporated to afford a brown solid (8.70 g) which was triturated with ether (ca. 20 mL) and filtered. The filtrate was evaporated to yield a brown solid which was purified by column chromatography on silica gel, eluting with ether/hexane (1:10) to afford two products. The first product to elute was (+)-10-chlorocamphor 3 as a white solid (0.65 g, 81 %);Mp 129-132 °C (ether/hexane); Lit.1 213-132 °C. [α]D20 = +39.7 (c 1.7, CHCl3). IR νmax (KBr) cm−1: 3056, 2931, 1596, 1463, 1367, 1272, 1144, 1105, 1054, 997, 935, 833, 762, 716, 639 cm−1. 1H NMR (CDCl3): 0.99 (s, 3H, 7-C3H3), 1.13 (s, 3H, 7-CH3), 1.39-1.46 (m, 1H, 5-CH2 endo), 1.48-1.54 (m, 1H, 6-CH2 endo), 1.92 (d, J = 18.5, 1H, 3-CH2 endo), 2.01-2.07 (m, 1H), 2.10 (t, J = 4.5, 1H, 4-CH3), 2.18 (td, J = 12.0, 4.0, 1H), 2.43 (dt, J = 18.5, 4.5, 1H, 3-CH2 exo), 3.62 (d, J = 12.0, 1H, CH3CH), 3.81 (d, J = 12.0, 1H, CH3CH). 13C NMR (CDCl3): 19.9 (7-CH3), 20.0 (7-CH3), 25.6 (C-5), 26.2 (C-6), 40.9 (CH2Cl), 42.6 (C-3), 43.3 (C-4), 47.3 (C-7), 60.6 (C-1), 215.5 (C-2). HRMS (EI, MeOH) m/z calculated for C20H32O3Cl [M + Na]+: 389.1584; found: 389.1531.

Acknowledgments

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References


25. 10-Mercapto camphor 15 can be detected by GLC analysis of the reaction mixture during the reduction of camphor-10-sulfonic acid 12 with iodine/triphenylphosphine; see reference 23 above.

26. See reference 4 (a) above.


28. See reference 10 (a) above.

29. See reference 22 (c) above.