An environment friendly preparation of 3-bromocamphor and camphorquinone

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The bromination of camphor has been carried out on a multi-gram scale by a mixture of KBr and $KBrO_3$ in the presence of acid or with HBr/NaBr - H^+ and H_2O_2/oxone® as the oxidant. The 3-bromocamphor is then efficiently converted to camphorquinone by an improved oxidation protocol using DMSO and sodium carbonate of tetrabutyl ammonium iodide.

Keywords: green bromination, bromocamphor, camphorquinone

Halogen containing organic compounds play an important role in synthetic organic chemistry. When bromination is carried out with elemental bromine hydrobromic acid is produced as a byproduct, making the method only 50% atom efficient and leading to hazardous and waste. Efforts are now directed towards the development of safer and greener methods for such reactions.[1–5] Considerable attention is directed towards developing efficient methods of bromination using bromide ion instead of elemental bromine. The bromide ion is converted to a bromonium ion species through a two electron oxidation sequence and then it is trapped *in situ* by an appropriate organic substrate. Reagents reported for this oxidation include hydrogen peroxide,[6–8] oxone®,[9,10] ceric ammonium nitrate,[11] sodium periiodate,[12] lead tetraacetate[13] and Selectrafluor®.[14] Many of these bromination reactions mimic the naturally occurring enzyme vanadium bromoperoxidase[15] and some of its synthetic equivalents.[16]

Converting ketones and esters possessing an α-hydrogen to α-bromo derivative is comparatively less explored from the view point of green chemistry.[17–19] Furthermore bromination of rigid bicyclic ketones is less favourable since their enolisation is difficult compared to open-chain ketones. We now describe a simple procedure for the preparation of 3-bromocamphor from camphor and its oxidation to camphorquinone. Both these derivatives of the bicyclo[2.2.1]heptane framework have applications arising from their stereochemistry and photochemistry.[20–24]

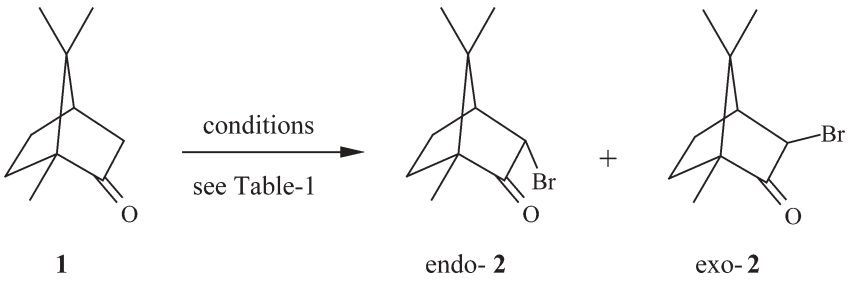
Results and discussion

Bromination of camphor is usually achieved by its reaction with liquid bromine.[25] However, the byproduct, hydrobromic acid needs to be either neutralised or recovered. In our present work several alternative conditions were examined to carry out bromination of camphor without using elemental bromine and with a high atom efficiency of bromine. Recently a brominating reagent based on a mixture of bromate-bromide has been developed[26,27] and applied to a variety of substrates including aromatic compounds, alkenes, alkynes and simple ketones. In the first of the bromine-free methods, the bromination of camphor is achieved by a combination of potassium bromide-potassium bromate in presence of sulfuric acid in acetic acid at the elevated temperature (Scheme 1). The reaction was found to be sluggish at room temperature. The GC analysis of the product confirmed a good conversion to 3-bromocamphor predominantly as the *endo* isomer (see Table 1 for the details). Initially, camphor (2.0 mol) was treated with KBr (2.0 mol), $KBrO_3$ (1.0 mol) in the presence of acid (3.0 mol). This mixture will furnish HOBr (3.0 mol) (entry 1, Table 1). Acetic acid was a suitable solvent for all the reagents, but the conversion was found to be poor. The ratio of the reagents was changed to camphor (1.0 mol), KBr (2.5 mol), $KBrO_3$ (0.5 mol) and acid (3.0 mol) to furnish Br_2 (1.5 mol) *in situ* (entry 2, Table 1). Under these conditions where excess reagents are used, better conversion was observed. Other solvents such as dioxane, methanol, water and dichloroethane were less effective and the product was formed in poor yield.

Having established good conditions for the bromination the same experiment was conducted on a larger scale (0.1 mol) to test the efficacy of the procedure. It is noteworthy to see similar results with an even higher *endo* selectivity (Scheme 2).

The α-keto derivative of camphor, camphorquinone **3** is an important starting material for several applications. Direct oxidation of camphor **2** with selenium dioxide gives camphorquinone efficiently.[28] However, this method is not very practical due to the toxic nature of the reagent. Kornblum type oxidation of 3-bromocamphor has been reported[29] which involves the *in situ* conversion to its iodo derivative. In the present work, we have modified this procedure and achieved the oxidation of **2** by using much milder conditions with a catalytic amount of tetrabutylammonium iodide (Scheme 3).

We have developed an environmentally friendly synthesis of bromocamphor and its oxidation to camphorquinone. Both these products are important synthetic materials.



1 endo- **2** exo- **2**

Scheme 1 Green bromination of camphor.

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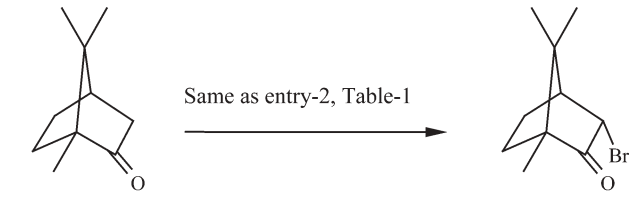
Table 1 Environment friendly bromination of camphor with various reagents/conditions

Entry	Conditions for Scheme-1.	Conversion[a] (*endo:exo*)
1	**1** (2.00 equiv.), KBr (2.0 equiv.), $KBrO_3$ (1.0 equiv.), conc. H_2SO_4 (3.0 equiv.) in acetic acid.[b] 80–85 °C. 24 h.	35.5 (67:33)
2	**1** (1.00 equiv.), KBr (2.5 equiv.), $KBrO_3$ (0.5 equiv.), conc. H_2SO_4 (3.0 equiv.) in acetic acid.[b] 80–85 °C. 24 h.	99.1 (89:11) [86%][c]
3	**1** (1.00 equiv.), KBr (2.5 equiv.), $KBrO_3$ (0.5 equiv.), conc. H_2SO_4 (3.0 equiv.) in methanol.[b] 80–85 °C. 24 h.	39.2 (47:53)
4	**1** (1.00 equiv.), KBr (2.5 equiv.), $KBrO_3$ (0.5 equiv.), conc. H_2SO_4 (3.0 equiv.) in 1,4-dioxane.[b] 80–85 °C. 24 h.	21.1 (87:13)
5	**1** (1.00 equiv.), KBr (2.5 equiv.), $KBrO_3$ (0.5 equiv.), conc. H_2SO_4 (3.0 equiv.) in dichoroethane.[b] 80–85 °C. 24 h.	35.3 (66:34)
6	**1** (1.00 equiv.), NaBr (2.5 equiv.), $NaBrO_3$ (0.5 equiv.), conc. H_2SO_4 (3.0 equiv.) in acetic acid.[b] 80–85 °C. 30 h.	73.0 (86:14)
7	**1** (1.00 equiv.), HBr in acetic acid (30%) (1.5 equiv.), Oxone® (1.5 equiv.), in acetic acid.[b] 80–85 °C. 24 h.	61.05 (81:19) [56%][c]
8	**1** (1.00 equiv.), HBr (1.5 equiv.), H_2O_2 (1.5 equiv.), in AcOH.[d] 80–85 °C, 24 h.	41.92 (53:47)
9	**1** (1.00 equiv.), NaBr (2.5 equiv.), H_2SO_4 (3.0.), H_2O_2 (0.5 equiv.), in AcOH. [d] 80–85 °C, 24 h	26.46 (85:15)

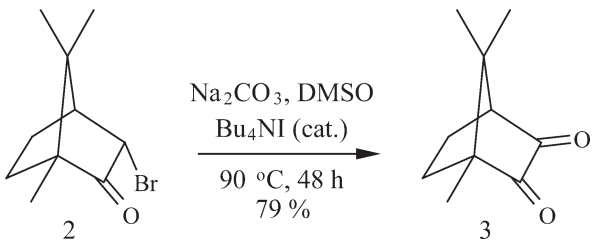
[a]Conversion and ratio of *endo-exo* of **2** determined by GC analysis of the crude sample; [b]mixture of solid KBr–$KBrO_3$ (or Oxone®) added portion wise at 80–85 °C; [c]isolated yield; [d]HBr and H_2O_2 (or NaBr, H_2SO_4 and H_2O_2) were mixed in AcOH at 5–10 °C for 10 min and then added to the solution of **1** in same solvent and gradually heated to 80–85 °C.



1
15.3 g (0.1 mol)

2
81 % isolated yield
endo:exo :: 98:2

Scheme 2 Multi-gram bromination of camphor.



2 3

Scheme 3 Oxidation of 3-bromocamphor.

Experimental

Reagents were purchased from Sigma-Aldrich Chemicals Limited, SD Fine, Sisco Research Laboratory (SRL), Qualigens Limited. TLC was performed on Merck 60 F_{254} aluminium coated plates and the spots were visualised with iodine vapour and under UV light. All the compounds were purified by column chromatography using silica gel (60–120 mesh). ^{1}H NMR spectra were recorded on Bruker Avance 400 spectrometer in $CDCl_3$. Mass spectra were recorded on Thermo-Fischer DSQ II GCMS instrument. IR spectra were recorded on a Shimadzu Prestige 21 spectrometer as KBr pellets. Melting points were recorded in a Thiele's tube using paraffin oil and are uncorrected. The GC was run on Shimadzu GC2010 machine on DB64 column (30 m × 0.32 mm; 80 μm film thickness), with nitrogen, hydrogen and oxygen as flow gases (mL min^{-1}) with injector temperature of 180 °C and the detector kept at 250 °C.

Preparation of 3-bromo-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (2) using potassium bromate/potassium bromide

Camphor (2.0 g, 13.0 mmol) was dissolved in glacial acetic acid (40 mL) and concentrated sulfuric acid (3.82 g, 39.0 mmol) was added to the solution which was stirred for 10 min at room temperature. The temperature of the mixture was slowly raised to 80–85 °C and, at this temperature, a finely powdered mixture of $KBrO_3$/KBr (1.09 g, 6.5 mmol/3.87g, 32.5 mmol respectively) was added over 60 to 90 minutes. On completion of the addition, the mixture was stirred at the same temperature for 24 h. The completion of the reaction was monitored by GC analysis and the mixture was then cooled to room temperature. The mixture was filtered to remove the unwanted solids. The filtrate was concentrated to a thick suspension which was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution to neutral pH. The organic layer was separated, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the crude product. The product was purified by column chromatography by eluting with hexane–ethyl acetate to give 3-bromo camphor 2.6 g (86% yield); m.p. 68–72 °C (lit.[25] 75–77 °C). The product was identified by comparison with the NMR and IR spectra of authentic sample. IR (KBr) υ 3100, 1730, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (s, 3H),0.93 (s, 3H),1.10 (s, 3H),1.65–1.81 (m, CH, 4 H), 2.55 (m, CH, 1 H), 4.98 (s, 1H). EI-MS (*m/z*, %): 232 (M+ 100%), 151 (M-Br).

Bromination of camphor using Oxone®/hydrogen bromide solution

Camphor (1.0 g, 6.57 mmol) was dissolved in glacial acetic acid (20 mL) and treated with HBr in acetic acid solution (30% solution, 2.0 mL, 0.78 g, 9.8 mmol) and stirred for 10 min at room temperature. The temperature of the reaction was slowly increased to 85 °C and at this temperature powdered Oxone® (1.50 g, 9.8 mmol) was added over 90 min. After completion of the addition, the reaction mixture was maintained at the above temp for 24 h. The completion of the reaction was monitored by GC analysis and the mixture was then cooled to room temperature. The reaction was filtered to remove the unwanted solids. The filtrate was concentrated to a thick mass and was dissolved in dichloromethane (10 mL), it was then washed with saturated sodium bicarbonate solution to neutral pH. The dichloromethane layer was dried over anhydrous sodium sulfate, filtered and distilled to give the crude product. This was purified by column chromatography by eluting with hexane-ethyl acetate to give the pure product (0.85 g, 56%); m.p. = 69–72 °C (lit.[25] 75–77 °C). The product was identified by comparison with the NMR and IR spectra of the authentic sample.

1,7,7-Trimethylbicyclo[2.2.1]heptane-2,3-dione **(3)**: Pure 3-bromocamphor **2** (2.5 g, 10.8 mmol) was dissolved in dimethylsulfoxide (20 mL) and treated with anhydrous sodium bicarbonate (2.72 g, 32.5 mmol) and stirred for 5 to 10 min at room temperature. Tetrabutylammonium iodide (0.80 g, 2.16 mmol) was added stirring was continued for 30 min at room temperature. The temperature of the reaction was slowly increased to 85 to 90 °C and the reaction was continued for 48 h at this temperature to complete the reaction (TLC). The reaction was cooled to room temperature and then filtered to remove the inorganic byproducts and washed with dimethylsulfoxide. The clear filtrate was added to a mixture of water (100 mL) and ethyl acetate (60 mL), stirred at room temperature (15 min) and the layers were separated. The organic layer was washed with water (3 × 25 mL) and dried with anhydrous sodium sulfate. The ethyl acetate was distilled off to give crude camphorquinone, which was purified by column chromatography and eluted with hexane-ethyl acetate to give a yellow crystalline product (1.43 g, 79%); m.p. 194–197 °C. (lit.[28] 200–203 °C) The product was identified by comparison with the NMR, IR &Mass spectra of the authentic sample. IR (KBr) υ 1751, 1740, 994 cm.$^{-1}$ NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 3H) 1.07 (s, 3H), 1.12 (s, 3 H), 1.64 (m, 2H), 1.95 (m, 1H), 2.15 (m, 1H), 2.50 (d, 1H). EI-MS (*m/z*, %) 167 (M+1 100).

We wish to thank the management of Apicore Pharmaceuticals and Prof. B.V. Kamath, Head, Department of Chemistry for their support and encouragement.

Received 22 January 2012; accepted 27 January 2012
Paper 1201123 doi: 10.3184/174751912X13295761942437
Published online: 22 March 2012

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