A Novel and Efficient Synthesis of Camphorquinone from Camphoric Acid

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Abstract: Camphorquinone (1), an important fine chemical and medicinal product derived from camphor, was efficiently synthesized from easily available camphoric acid (2). The key steps include acyloin condensation using Me₃SiCl as a scavenger of alkoxides and oxidation of the bis(trimethylsilyl) derivative 4 by bromine in CCl₄. The new method offers an efficient alternative synthesis of camphorquinone (1).

Key words: camphor, camphorquinone, cyclization, condensation

Camphorquinone (1), an important product derived from camphor, is widely used as photosensitizer for visible light sensitive polymerization in dental area.¹⁻³ It is also an important intermediate for the synthesis of chiral catalysts⁴ and resolution reagent of 1,2-diols.⁵ Camphorquinone (1) has been prepared by a number of methods, including oxidation of camphor with SeO₂,⁶ benzeneselenenic anhydride,⁷ treatment of 3-bromocamphor with NaI in DMSO,⁸ reaction of camphor with LDA at –78 °C followed by treatment with Mo₂O₅·Py·HMPA.⁹ In the later 1980’s, Chaussin developed a mild method by ozonization of a thiocamphor derivative¹⁰ and Barton by treatment of thiocamphor with benzeneselenenic anhydride.¹¹ Camphorquinone (1) has also been prepared by photochemical method.¹² The triflate derivative of 3-hydroxycamphor can also be used to synthesize 1.¹³ The most common method of preparing camphorquinone (1) is by treatment of camphor with SeO₂,⁵¹⁴⁻¹⁶ however, the toxicity of SeO₂ diminishes the attractiveness of this method.¹⁷ All other methods have some disadvantages, either the procedures are tedious or the starting material is not easily available. We report here a convenient and efficient preparation of camphorquinone (1) from camphoric acid (2) (Scheme 1).

Camphoric acid (2) can be easily prepared from camphor using HNO₃ as an oxidation reagent.¹⁸ Esterification of camphoric acid (2) was carried out using concentrated sulfuric acid as a catalyst using a water separator to remove the water formed.¹⁹

We have also attempted to synthesize 1 by common acyloin condensation from 3 (Scheme 2), however, we failed to obtain 5 and 6 although these methods proved to be effective in other substrates.²⁰

Scheme 1

Reagents and conditions: (a) EtOH, benzene, H₂SO₄, reflux, 12 h, 85%; (b) Na, Me₃SiCl, toluene, reflux, 15 h, 75%; (c) Br₂ in CCl₄, r.t., 10 min, 81%

Scheme 2

It is known that most acyloin condensation can be successfully carried out in the presence of trimethylsilyl chloride (TMSCI)²¹,²² which serves as a scavenger of the base alkoxide that causes a lot of side products. The acyloin can be easily isolated in the form of its silyl enediol ester 4²³ which is relatively stable and can be conveniently transformed to a number of derivatives.²⁴,²⁵ In our experiment a mixture of ester 3 and TMSCI in toluene was added dropwise to sodium dispersed in toluene at a rate to maintain gentle reflux (Scheme 1). After reflux for several hours, the cooled solution was filtered and the toluene was evaporated. The residue was pure enough for the following reaction.

To a solution of 4 in CCl₄ was added dropwise a solution of bromine in CCl₄ until no further decolorization of bromine occurred, or until exactly one equivalent of bromine was added (Scheme 1). Crystals of 1 formed immediately after removal of the solvent and can be recrystallized in petroleum ether or hexane. Camphorquinone (1) was obtained as yellow needles and was identified by its analytical and spectral data (see experimental). Both d- and l-
Camphorquinones were prepared from \(d\)- and \(l\)-camphor via \(d\)- and \(l\)-camphoric acid by the same method.

In summary, by using the easily available camphoric acid (2) as starting material, we have accomplished an efficient and economic synthesis of optically pure camphorquinone (1) through three steps. The yield is high and the reaction can be carried out on a large scale. This offers a good method for the preparation of camphorquinone (1) instead of using SeO\(_2\) and other selenium-containing reagents.

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded in CDCl\(_3\) on Bruker DRX-500 (500 MHz) and AV-300 (300 MHz) spectrometers. Elemental analyses were performed by Elemental Vario ELIII equipment. Optical rotations were measured on Wzz-1 apparatus. TMSCl, camphoric acid (2) and other reagents were purchased from Aldrich and used as received. The boiling point range of petroleum ether used is 60–90°C.

**Diethyl Camphorate (3)**

Camphoric acid (2) (19.0 g, 0.095 mol), EtOH (60 mL) and benzene (30 mL) were introduced into a 1-L flask. Conc. H\(_2\)SO\(_4\) (10 mL) was added dropwise to the mixture. The flask was equipped with a water separator and a reflux condenser. The mixture was brought to reflux until no additional H\(_2\)O was collected. EtOH and benzene were removed and the residue was poured into ice (50 g). The mixture was neutralized with NaHCO\(_3\) and extracted with Et\(_2\)O (3 x 30 mL). The Et\(_2\)O extract was washed with brine and dried (Na\(_2\)SO\(_4\)). The solvent was then removed under reduced pressure to afford 3 as a colorless liquid; bp 135 °C/5 mmHg); yield: 20.6 g (85%); \([\alpha]_D^{20} = +33.6 (c = 1, EtOH).

**1H NMR (300 MHz, CDCl\(_3\))**: \(\delta = 0.66\) (s, 3 H), 1.09 (s, 3 H), 1.13–1.18 (m, 9 H), 1.30–1.42 (m, 1 H), 1.65–1.72 (m, 1 H), 2.04–2.09 (m, 1 H), 2.40–2.49 (m, 1 H), 2.67 (t, \(J = 9.3\) Hz, 1 H), 3.97–4.10 (m, 4 H).

**13C NMR (300 MHz, CDCl\(_3\))**: \(\delta = 13.8, 14.0, 20.8, 21.2, 22.2, 22.6, 32.2, 46.4, 52.4, 55.7, 59.6, 59.7, 173.2, 174.9.


**1,7,7-Trimethyl-2,3-bis(trimethysiloxy)bicyclo[2.2.1]hept-2-ene (4)**

A 500 mL three-necked flask fitted with a stirrer, a reflux condenser and an addition funnel was charged with toluene (100 mL) and hexane (11.2 g, 0.044 mol) in toluene (30 mL). TMSCl (22.5 mL, 0.18 mol) in toluene (80 mL) was added. The mixture was brought to gentle reflux. The stirrer was operated at a speed so that the Na could be fully dispersed. A mixture of camphoric acid (2) (19.0 g, 0.095 mol), EtOH (60 mL) and benzene (30 mL) was added dropwise to the mixture. The flask was equipped with a water separator and a reflux condenser. The mixture was brought to reflux until no additional H\(_2\)O was collected. EtOH and benzene were removed and the residue was poured into ice (50 g). The mixture was neutralized with NaHCO\(_3\) and extracted with Et\(_2\)O (3 x 30 mL). The Et\(_2\)O extract was washed with brine and dried (Na\(_2\)SO\(_4\)). The solvent was then removed under reduced pressure to afford 4 as a colorless liquid; bp 135 °C/5 mmHg); yield: 1.18 (m, 9 H), 1.30–1.42 (m, 1 H), 1.65–1.72 (m, 1 H), 2.04–2.09 (m, 1 H), 2.40–2.49 (m, 1 H), 2.67 (t, \(J = 9.3\) Hz, 1 H), 3.97–4.10 (m, 4 H).

**1H NMR (300 MHz, CDCl\(_3\))**: \(\delta = 0.16–0.21\) (m, 18 H), 0.69 (s, 3 H), 0.89 (s, 3 H), 0.97 (s, 3 H), 1.28 (m, 2 H), 1.52 (m, 1 H), 1.81 (m, 1 H), 2.10 (m, 1 H).

**13C NMR (500 MHz, CDCl\(_3\))**: \(\delta = 11.6, 10.73, 19.82, 19.96, 26.22, 33.20, 51.99, 52.80, 53.34, 133.77, 135.10.

Anal. Calcd for C\(_{16}\)H\(_{32}\)O\(_2\)Si\(_2\): C, 61.47; H, 10.32. Found: C, 61.30; H, 10.27.

**Camphorquinone (1)**

To a stirred solution of 4 (2.86 g, 0.01 mol) in CCl\(_4\) (15 mL) was added dropwise a solution of Br\(_2\) in CCl\(_4\) (10 mL) until no further decolorization of bromine occurred and the system became bright yellow. The solvent was then removed under reduced pressure and the residue crystallized immediately. The bright crystals were re-crystallized from petroleum ether; yellow needles; yield: 1.36 g (81%); mp 198 °C; \([\alpha]_D^{20} = 102.5 (c = 2, toluene).

**References**

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