An Efficient Preparation of *l*-Ketopinic Acid Chloride by Ozonolysis of 10-Chlorocamphor-10-sulfine

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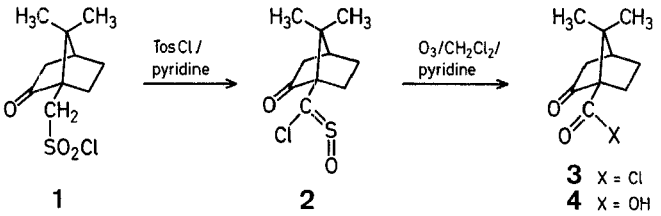
Ketopinic acid derivatives have been used to resolve alcohols[1] and hemiacetals[2], most notably in Woodward's prostaglandin synthesis[3]. However, the use of these versatile, chiral derivatives is currently limited by the availability of ketopinic acid or its chloride. Ketopinic acid may be obtained from 10-camphorsulfonyl chloride by treatment with hot, basic permanganate[4]. We and others[5] have repeatedly found that the procedure of Ref.[4] gives a low (~20–25%) yield of the desired acid. Obviously, an efficient synthesis of the required ketopinate antipode would be desirable for the use of this agent in large scale resolutions or chiral syntheses. Herein we report a high-yield method for the large-scale synthesis of optically pure ketopinic acid or its acid chloride from camphor-10-sulfonyl chloride.

In 1923, a novel product from treatment of camphor-10-sulfonyl chloride **(1)** with pyridine or triethylamine was reported[6]. The structure which was originally proposed and supported by subsequent investigation[7] is 10-chlorocamphor-10-sulfine **(2)**. In a study of the mechanism of this rearrangement it was demonstrated[8] that the yield of chlorosulfine **2** could be significantly increased by adding camphor-10-sulfonyl chloride to tosyl chloride and pyridine. By modification of this improved procedure we obtain crystalline *l*-chlorosulfine **2** in 76% yield. Interestingly, only one isomer about the C=S double bond is generated by this method. None of the other isomer was detected in the product or in the reaction mixture[9].

Chlorosulfine **2** has been converted to ketopinic acid **(4)** in moderate yield by oxidative cleavage with permanganate[6]. Since ozone is regarded as a clean, mild, and selective reagent for oxidative cleavage, it was considered as an alternative. In this case it was particularly attractive since it could potentially lead to either ketopinic acid or its acid chloride. Ozonolysis of *l*-chlorosulfine **2** at −78 °C in the presence of an equivalent of pyridine gives *l*-ketopinic acid acid chloride **(3)** contaminated with ~10% ketopinic acid **(4)** (based on ^{13}C-N.M.R. analysis). The acid chloride **3** may be purified by recrystallization or preferably by treatment with oxalyl chloride to yield the optically pure ketopinic acid chloride. The ketopinic acid generated in the ozonolysis does not appear to arise from adventitious water since the same proportion of acid is found regardless of rigorous drying of solvents or reagents or manipulation under a dry atmosphere. The pyridine is essential to trap the sulfur trioxide generated during the ozonolysis. Omission of pyridine results in substantially lower yields. Ketopinic acid **(4)** may be obtained in high yield by direct hydrolysis of the ozonolysis mixture.



Whereas the ozonolysis of diaryl sulfines to give ketones has already been reported[10] the reaction **2**→**3** described here appears to be the first use of ozone for the direct conversion of an alkyl chlorosulfine to a carboxylic acid chloride[11]. *l*-Camphor-10-sulfonyl chloride (**1**; or its enantiomer) can be prepared in quantitative yield from the corresponding enantiomer of camphor-10-sulfonic acid, both of which are commercially available. The rearrangement and ozonolysis may be readily done on a 0.2–0.5 mol scale. Thus, this route constitutes an efficient preparation of versatile reagents, *d*- or *l*-ketopinic acid or its acid chloride.

Melting points were taken in an open glass capillary and are uncorrected. ^{13}C-N.M.R. spectra were taken on a JEOL FX60Q at 15 MHz. Rotations were measured on a Perkin-Elmer 141 polarimeter.

l-10-Chlorocamphor-10-sulfine (2):
A well stirred mixture of recrystallized tosyl chloride (83.9 g, 0.44 mol) and pyridine (96.4 ml, 1.2 mol) is heated at 100 °C (bath temperature) and a solution of *l*-camphor-10-sulfonyl chloride[12] (**1**; 100 g, 0.4 mol) in 1,2-dichloroethane (100 ml) is added over 45 min. Upon completion of addition, the mixture is heated for 30 min with stirring, then allowed to cool, and poured into ether (3 l). The resultant precipitate is isolated (the ether solution is saved) and digested with ether (3 l). The combined ether solutions are concentrated and the residual crude product is digested with hot hexane (3 × 2 l). Product **2** crystallizes from the hexane solution upon cooling; yield: 70.5 g (75%); m.p. 84–85 °C (Ref.[9], m.p. 85 °C); $[\alpha]_D$: −135.3° (*c* 1.9, chloroform) (Ref.[6], $[\alpha]_D$: −136.2°).

^{13}C-N.M.R. (acetonitrile-d_3/TMS): δ = 210.3, 182.5, 69.4, 52.7, 45.1, 44.0, 28.2, 27.2, 22.1, 20.1 ppm.

l-Ketopinic Acid Chloride (3, 7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-carbonyl Chloride):
A solution of *l*-10-chlorocamphor-10-sulfine (**2**; 47.8 g, 0.21 mol) and dry pyridine (17 g, 0.22 mol) in dichloromethane (600 ml) is treated with ozone at −78 °C (at a rate of 1.2–3.6 mmol/min) until ozone is detected in the effluent stream or the reaction mixture turns light blue. The mixture is purged with nitrogen and poured into pentane (3.5 l).

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The pyridine-SO_3 complex is filtered off and the filtrate evaporated in vacuo to yield the crude product which is treated with oxalyl chloride (6.35 g, 0.05 mol) in benzene (100 ml). Solvent and excess oxalyl chloride are evaporated, the crude product taken up in pentane, the solution filtered, and product **3** crystallizes upon concentration in vacuo; yield: 37.2 g (88%); m.p. 112 °C; $[\alpha]_D$: −41° (*c* 1.9, chloroform) (Ref.[1], $[\alpha]_D$: 40.3).

^{13}C-N.M.R. ($CDCl_3$/TMS): δ = 207.1, 171.6, 75.8, 50.2, 44.1, 43.6, 28.3, 26.1, 20.8, 19.4 ppm.

l-Ketopinic Acid (4, 7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-10-carboxylic Acid):

A solution of *l*-10-chlorocamphor-10-sulfine (**2**; 4.65 g, 20 mmol) and pyridine (1.6 g, 20.3 mmol) in dichloromethane (60 ml) is treated with ozone at −78 °C (at a rate of 1.2–3.6 mmol/min) until ozone is detected in the effluent stream or the mixture turns light blue. The mixture is then purged with nitrogen and poured into a mixture of aqueous 1 normal potassium hydroxide (80 ml) and tetrahydrofuran (100 ml). The resultant mixture is stirred for 45 min and the organic solvent then removed in vacuo. The aqueous solution is washed with ether (2 × 100 ml) and acidified with 6 normal sulfuric acid. The acidic aqueous phase is extracted with ether (3 × 100 ml), the organic extract washed with saturated sodium chloride solution (30 ml), dried with sodium sulfate, and evaporated. The residual crude product **4** is recrystallized from water; yield: 3 g (82%); m.p. 227–229 °C (Ref.[5], m.p. 226–228 °C); $[\alpha]_D$: −28° (*c* 1.5, methanol) (Ref.[5], $[\alpha]_D$: −25.8°).

^{13}C-N.M.R. ($CDCl_3$/TMS): δ = 208.0; 164.9; 68.4; 49.6; 44.3; 43.6; 26.3; 26.1; 20.8; 19.4 ppm.

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