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Working with Hazardous Chemicals

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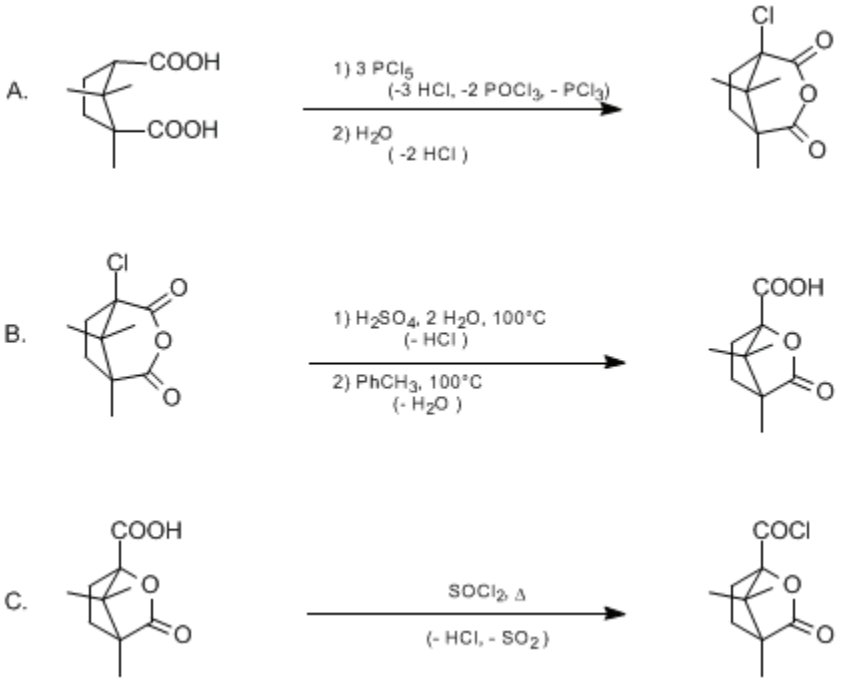
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.071.0048

Organic Syntheses, Coll. Vol. 9, p.151 (1998); Vol. 71, p.48 (1993).

(−)-(1S,4R)-CAMPHANOYL CHLORIDE

[2-Oxabicyclo[2.2.1]heptane-1-carbonyl chloride, 4,7,7-trimethyl-3-oxo-, (1S)-)]



Submitted by Hans Gerlach[1], Dag Kappes, Robert K. Boeckman, Jr.[2], and Graham N. Maw.
Checked by D. Zhao, D. Hughes, and I. Shinkai.

1. Procedure

A. *(−)-(1R,3R)-3-Chlorocamphoric anhydride.* (+)-(1R,3S)-Camphoric acid (Note 1), (125 g, 0.625 mol) is added in small portions to a 1000-mL, three-necked flask charged with 455 g of phosphorus pentachloride (2.19 mol) and equipped with a ground glass adaptor connected to a T-tube with one outlet open to the atmosphere and the remaining outlet connected to a gas trap (Note 2). The mildly exothermic reaction is controlled by gently swirling the flask in an ice bath as required (Note 3). After the addition is complete, the flask is equipped with a reflux condenser topped by a calcium chloride ($CaCl_2$) drying tube, and the reaction mixture is heated under reflux (using an oil bath at 125°C) for 12 hr. The reaction mixture is cooled to room temperature and the volatile material is removed by distillation using a bath temperature of 50°C under aspirator vacuum with the distillate boiling at 30–35°C (Note 4). The residual liquid is then added to a mechanically-stirred mixture of ice (2 kg) and dimethylformamide (DMF, 125 ml), and stirring is continued until all the ice has melted. The resulting waxy white precipitate is collected by vacuum filtration while cold (2°C), washed with three, 500-mL portions of cold water, and dried under vacuum (Note 5). The crude white solid, (−)-(1R,3R)-3-chlorocamphoric anhydride (122 g, 90%), is of sufficient purity to be used in the next step (Note 6) and (Note 7).

B. *(−)-(1S,4R)-Camphanic acid.* A 2000-mL, three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser is charged with 1000-mL of 0.1 N sulfuric acid and heated by means of an oil bath to 80°C. Finely powdered (−)-(1R,3R)-3-chlorocamphoric anhydride (115 g, 0.53 mol) is added in portions over about 10 min to the stirred acid solution, the necks are sealed with glass stoppers and the resulting suspension is brought to a gentle reflux (Note 2). After all the solids have dissolved (4–6 hr), the resulting solution is refluxed for an additional 2 hr (Note 8). The solution is allowed to cool to room temperature with stirring overnight (~12 hr), and the resulting off-while solid is collected by vacuum filtration and washed with water (3 × 250 mL). The remaining camphanic acid is

obtained by extraction of the aqueous filtrate with three 250-mL portions of chloroform (Note 9). After evaporation of the combined organic phases, the combined vacuum-dried solids are added to a 1000-mL, round-bottomed flask containing 500 mL of toluene, a condenser is added and the mixture is brought to gentle reflux until dissolution is complete (Note 2). The water/toluene azeotrope (85°C) is removed by distillation until no further water is obtained (Note 10). Distillation of the toluene (110°C) is then continued until the residual volume has been reduced to ~350 mL (Note 10) and (Note 11). The resulting solution is allowed to cool to room temperature during which time the acid crystallizes. After 4 hr at room temperature, the solids are collected by vacuum filtration and air-dried, affording (−)-(1S,4R)-camphanic acid (76 g, 72%) as colorless needles, mp 197–201°C, of sufficient purity for use in the next step (Note 12) and (Note 13).

C. *(−)-(1S,4R)-Camphanoyl chloride*. A 500-mL, three-necked, round-bottomed flask, equipped for magnetic stirring and protected from moisture by a reflux condenser topped by a $CaCl_2$ drying tube, is charged with 200 mL of thionyl chloride using a graduated cylinder. (−)-(1S,4R)-Camphanic acid (63.8 g, 0.322 mol) is added in portions using a powder funnel over 30 min, and the reaction mixture is heated under reflux for 3 hr, then allowed to cool to room temperature (Note 2). Excess thionyl chloride is removed by rotary evaporation (Note 14) to afford a solid that is freed of any residual thionyl chloride by the addition of toluene (500 mL) and subsequent evaporation under reduced pressure (repeated three times). The resulting solids are dried under high vacuum (Note 5) to afford 69 g of (−)-(1S,4R)-camphanoyl chloride (99%) as an off-white solid, mp 69–71°C (Note 15) and (Note 16).

2. Notes

1. (+)-(1R,3S)-Camphoric acid (99% purity) was obtained from Aldrich Chemical Company, Inc.
2. The acidic gases may be absorbed in 10% NaOH solution using the absorption trap as described in *Org. Synth., Coll. Vol. I* **1941**, 97.
3. The reactants initially form a paste that may form sizable lumps upon agitation, but the mixture liquifies upon further reaction as the result of the production of phosphorus oxychloride ($POCl_3$) and phosphorus trichloride (PCl_3).
4. The resulting liquid sometimes contains small amounts of white solid, but this solid does not require removal by filtration.
5. A freeze dryer (lyophilizer) was employed for vacuum drying (23°C at ~0.05 mm).
6. If desired, a pure sample of the anhydride (mp 225–229°C) can be obtained by recrystallization of the crude anhydride from carbon tetrachloride (CCl_4) (1 g/5 mL).
7. Spectroscopic data for the purified anhydride are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 3 H), 1.14 (s, 3 H), 1.36 (s, 3 H), 2.11 (m, 2 H), 2.50 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.0, 17.9, 18.7, 31.5, 35.2, 48.7, 54.1, 166.0, 170.3; IR (cm^{-1}): 3019, 1821, 1773, 1215; $[\alpha]_D^{25}$ −17.6° (chloroform, *c* 2.04).
8. A total period of heating of 6–8 hr at 80–100°C was required.
9. Alternatively, a second crop of material can be obtained from the aqueous filtrate after several hours. However, a considerable amount of camphanic acid still remains in the aqueous layer; thus chloroform extraction of the aqueous phase as described is recommended. *To avoid undue exposure to the chloroform vapor, these extractions should be performed in a fume hood*.
10. The volume of toluene required will depend on the amount of water in the crude material. Additional toluene should be added as required, so that the final, residual volume of dry toluene solution is ~350 mL as described.
11. Colored impurities, if produced, can be removed by treatment of the solution, prior to cooling, with charcoal (Norit) followed by filtration.
12. If desired, pure acid (mp 201–204°C) can be obtained by recrystallization of the crude acid from hot toluene.
13. Spectroscopic data for the purified acid are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.03 (s, 3 H), 1.11 (s, 3 H), 1.15 (s, 3 H), 1.74 (ddd, 1 H, J = 4.3, 9.3, and 13.2), 1.98 (ddd, 1 H, J = 4.5, 10.6, and 13.2), 2.11 (ddd, 1 H, J = 4.5, 9.3, and 13.5), 2.48 (ddd, 1 H, J = 4.2, 10.6, and 13.5), 8.80 (br, 1 H, (s)); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.60, 16.70, 16.73, 29.02, 30.73, 54.60, 55.11, 90.89, 172.41, 177.90; (IR cm^{-1}):3418, 3019, 1785, 1716, 1215; $[\alpha]_D^{25}$ −20.4° (dioxane, *c* 1.71).
14. Corrosive thionyl chloride may destroy the rubber vacuum seals of a rotary evaporator. Thionyl chloride can also be removed by vacuum distillation.

15. (−)-(1S,4R)-Camphanoyl chloride produced in this manner is of sufficient purity to be used directly in most acylation reactions. However, pure acid chloride (mp 69–71°C) can be conveniently obtained by recrystallization of the crude acid chloride from cold CCl_4 (1 g/1 mL, ~75% recovery).

16. Spectroscopic data for the purified acid chloride are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.06 (s, 3 H), 1.12 (s, 3 H), 1.15 (s, 3 H), 1.76 (ddd, 1 H, J = 4.2, 9.3, and 13.3), 1.99 (ddd, 1 H, J = 4.6, 10.6, and 13.3), 2.18 (ddd, 1 H, J = 4.6, 9.3, and 13.6), 2.52 (ddd, 1 H, J = 4.2, 10.6, and 13.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.55, 16.55, 16.64, 28.76, 31.46, 55.40, 55.52, 94.86, 170.87, 176.52; IR (cm^{-1}): 2975, 1794, 1231; $[\alpha]_D^{25}$ −24.7° (chloroform, *c* 3.57).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995. (See (Note 2).)

3. Discussion

The resolution of alcohols by fractional crystallization or chromatography of diastereoisomeric esters with (−)-camphanic acid was introduced some time ago.[3] The method has proven to be both convenient and efficient. A substructure search in the Chemical Abstracts Service (CAS) registry file has shown that more than 500 camphanic acid derivatives have been described in the last two decades. Besides resolution, camphanic acid esters of primary alcohols have been used to distinguish the signals of diastereotopic α-hydrogen atoms in ^{1}H NMR spectra and to determine the optical purity of α-deutero primary alcohols.[4] Camphanoates are well suited for characterizing alcohols. They are easily prepared with camphanoyl chloride in pyridine and generally have high melting points.

Because both enantiomers, (+)- and (−)-camphoric acid, are available by oxidation either from natural (+)-D-camphor or from natural (−)-L-borneol, both enantiomers of camphanoyl chloride can be prepared conveniently.[3,5] The corresponding enantiomers of camphanic acid were described for the first time by Wreden[6] and Aschan.[7] The three-step procedure, described above is an adaptation of procedures described by Aschan,[8] Zelinsky et al.,[9] Meyer et al.,[10] and Gerlach.[3]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 275

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(-)-(1S,4R)-CAMPHANOYL CHLORIDE

2-Oxabicyclo[2.2.1]heptane-1-carbonyl chloride, 4,7,7-trimethyl-3-oxo-, (1S)-)

(-)-(1R,3R)-3-Chlorocamphoric anhydride

(-)-(1S,4R)-Camphanic acid

(-)-camphanic acid (+)- and (-)-camphoric acid

(-)-L-borneol

sulfuric acid (7664-93-9)

phosphorus pentachloride (10026-13-8)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

carbon tetrachloride (56-23-5)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

toluene (108-88-3)

phosphorus trichloride (7719-12-2)

dioxane (123-91-1)

(+)-D-camphor (21368-68-3)

dimethylformamide (68-12-2)

(+)-(1R,3S)-Camphoric acid camphanic acid camphanoyl chloride