



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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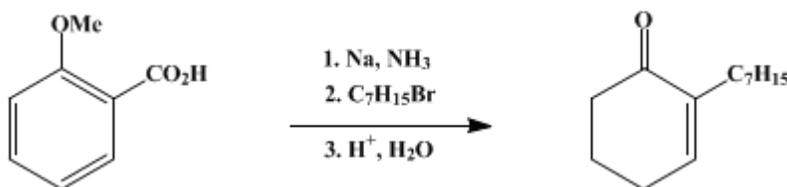
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 7, p.249 (1990); Vol. 61, p.59 (1983).

ALKYLATION OF THE ANION FROM BIRCH REDUCTION OF *o*-ANISIC ACID: 2-HEPTYL-2-CYCLOHEXENONE



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1. Procedure

Caution! Liquid ammonia should be used only in a well-ventilated hood.

2-Heptyl-2-cyclohexenone. A 1-L, three-necked, round-bottomed flask is charged with 15.2 g (0.1 mol) of *o*-anisic acid (Note 1) and 100 mL of tetrahydrofuran (Note 2). An acetone–dry ice condenser and mechanical stirrer are put in place, the flask is immersed in an acetone–dry ice bath, and 400 mL of ammonia is distilled in (Note 3), (Note 4). The resulting thick white suspension (the ammonium salt of the acid) is stirred mechanically. Sodium, washed sequentially with xylenes and ether, is added in small pieces. The suspension dissolves to give a pale yellow solution which, upon introduction of more sodium, changes to the characteristic blue color of excess sodium. When the deep blue color persists, a mixture of 1-bromoheptane (21.49 g, 0.12 mol) and 1.0 mL (2.4 mmol) of 1,2-dibromoethane is added in one portion. The blue color is discharged immediately, leaving a yellow solution. The acetone–dry ice bath and the condenser are removed, and the ammonia is allowed to evaporate under a gentle stream of nitrogen.

The residue is diluted with 700 mL of water, and the resulting aqueous solution is washed with three 40-mL portions of dichloromethane, acidified with cold concentrated HCl, and extracted with five 40-mL portions of 1,2-dichloroethane. The combined 1,2-dichloroethane extracts are placed in a 500-mL, one-necked, round-bottomed flask bearing a reflux condenser; water (50 mL), concentrated HCl (50 mL), and hydroquinone (300 mg) are added; and the mixture is heated at reflux under a positive pressure of nitrogen for 30 min. The mixture is cooled to 25°C, the layers are separated, and the organic layer is washed with 60 mL of 0.5 M aqueous sodium bicarbonate solution. The organic phase is dried over anhydrous potassium carbonate, concentrated by rotary evaporation at aspirator vacuum, and distilled through a 10-cm Vigreux column to yield a center cut, bp 100–104°C (0.02 mm), 9.0–11.5 g (46–59%) (Note 5), (Note 6), (Note 7).

2. Notes

- o*-Anisic acid was obtained from Aldrich Chemical Company, Inc.
- Tetrahydrofuran was dried and made oxygen-free by boiling over sodium/benzophenone ketyl under argon, and distilling just before use.
- Reduction in refluxing liquid ammonia (–33°C) led to substantial cleavage of the methoxyl group with resultant formation of alkylated dihydrobenzoic acid.
- Arrangements for cooling or condensing the liquid ammonia over sodium in a preliminary drying operation could be made, but were not necessary. The results reported here were achieved by simply passing ammonia gas from a cylinder into the cold reaction system through heavy Tygon tubing.
- The spectral properties of 2-heptyl-2-cyclohexenone are as follows: IR (CCl₄) cm⁻¹: 2920, 2860, 1670, 1455, 1435, 1370, 1170, 1120, 1095, 905; ¹H NMR(CDCl₃) δ: 0.85 (br t, 3 H, *J* = 7), 1.28 (br s, 10 H), 1.8–2.6 (m, 8 H), 6.70 (br s, 1 H); *n*_D²⁶ 1.4738.
- Before distillation, the crude enone contained substantial amounts of the β,γ-isomer. As an alternative to equilibrium on distillation, this mixture could be converted to the α,β-isomer by stirring with 0.1 M

sodium methoxide in methyl alcohol under nitrogen at 0°C for 2 hr.

7. Professor L. N. Mander has advised us that addition of 1.0 equivalent of potassium *t*-butoxide prior to addition of sodium metal significantly improved the yield of this procedure: Hoole, J. M.; Mander, L. N.; Woolias, M. *Tetrahedron Lett.* **1982**, 23, 1095.

3. Discussion

Cyclohexenones with 2-alkyl substituents are usually prepared by alkylation of dihydroresorcinol followed by enol ether formation, reduction, and hydrolysis.² A variety of other approaches have been employed.^{3 2 4 5 6 7 8} The procedure outlined here is simple, occurring in essentially one pot, using commercially available starting materials. The alkylating agent can equally well be an alkyl iodide or *p*-toluenesulfonate ester. A variety of other alkylating agents have been employed using an earlier, unoptimized version of this procedure.⁹

References and Notes

1. Department of Pharmacology, School of Medicine, Vanderbilt University, Nashville, TN 37232.
2. Alkylation of cyclohexane-1,3-dione followed by enol ether formation, reduction, and hydrolysis: Angell, M. F.; Kafka, T. M. *Tetrahedron* **1969**, 25, 6025.
3. Alkylation of cyclohexenone: Conia, J.-M.; Le Craz, A. *Bull. Soc. Chim. Fr.* **1960**, 1934.
4. Bromination-dehydrobromination of a 2-alkylcyclohexanone: Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth. Coll. Vol. IV* **1963**, 162.
5. Sulfenylation of a 2-alkylcyclohexanone followed by oxidation and elimination: Trost, B. M.; Salzman, T. N. *J. Am. Chem. Soc.* **1973**, 95, 6840.
6. Selenation of a 2-alkylcyclohexanone followed by oxidation and elimination: Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, 97, 5434.
7. Reduction of a 2-alkylpyridine followed by hydrolysis and aldol condensation: Danishefsky, S.; Cain, P. *J. Org. Chem.* **1975**, 40, 3607.
8. Oxidation of a 1-alkylcyclohexene: Belyaev, V. F. *Zhidkofaznoe Okislenie Nepredel'nykh Organ. Soedin., Sb.* **1961**, No. 1, 97–104; *Chem. Abstr.* **1963**, 58, 4435d.
9. Taber, D. F. *J. Org. Chem.* **1976**, 41, 2649.

Appendix

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

potassium carbonate (584-08-7)

HCl (7647-01-0)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

1,2-dichloroethane (107-06-2)

nitrogen (7727-37-9)

sodium methoxide (124-41-4)

sodium (13966-32-0)

1,2-dibromoethane (106-93-4)

dichloromethane (75-09-2)

1-bromoheptane (629-04-9)

Tetrahydrofuran (109-99-9)

Dihydroresorcinol

argon (7440-37-1)

2-Heptyl-2-cyclohexenone (87588-68-9)

dihydrobenzoic acid

potassium t-butoxide (865-47-4)

o-ANISIC ACID (579-75-9)