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Working with Hazardous Chemicals

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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.

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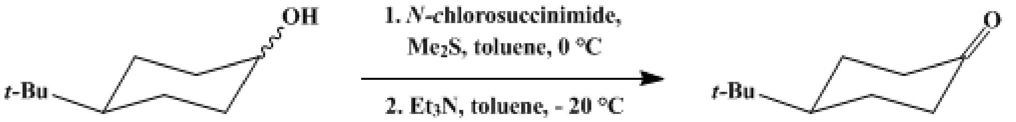
OXIDATION OF ALCOHOLS BY METHYL SULFIDE – *N*-CHLOROSUCCINIMIDE – TRIETHYLAMINE: 4-*tert*-BUTYLCYCLOHEXANONE

[Cyclohexanone, 4-(1,1-dimethylethyl)-]



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Checked by S. Yamamoto and W. Nagata.

1. Procedure

> *Caution! Benzene has been identified as a carcinogen; OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.*

A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer (Note 1), a thermometer, a dropping funnel, and an argon-inlet tube is charged with 8.0 g. (0.060 mole) of *N*-chlorosuccinimide (Note 2) and (Note 3) and 200 ml. of toluene (Note 4). While a continuous positive argon pressure is maintained, the solution is stirred and cooled to 0°, and 6.0 ml. (0.10 mole) of methyl sulfide (Note 2) is added. A white precipitate appears immediately after addition of the sulfide. The mixture is cooled to −25° using a carbon tetrachloride-dry ice bath (Note 5), and a solution of 6.24 g. (0.0400 mole) of 4-*tert*-butylcyclohexanol (mixture of *cis*- and *trans*-) (Note 2) in 40 ml. of toluene is added dropwise over 5 minutes (Note 6). The stirring is continued for 2 hours at −25° ((Note 5)) before a solution of 6.0 g. (0.59 mole) of triethylamine (Note 2) in 10 ml. of toluene is added dropwise over 3 minutes (Note 7). The cooling bath is removed; after 5 minutes 400 ml. of diethyl ether is added (Note 8). The organic layer is washed with 100 ml. of 1% hydrochloric acid, then with two 100-ml. portions of water (Note 9), dried over anhydrous magnesium sulfate, and evaporated under reduced pressure. The residue is transferred to a 50-ml., round-bottomed flask and distilled bulb to bulb at 120° (25 mm.), yielding 5.54–5.72 g. (90–93%) of 4-*tert*-butylcyclohexanone, m.p. 41–45° (Note 10).

2. Notes

1. Efficient magnetic stirring could be used as well.
2. The submitters used *N*-chlorosuccinimide, 4-*tert*-butylcyclohexanol, methyl sulfide, and triethylamine, available from Aldrich Chemical Company, Inc., without further purification.
The checkers used *cis*- and *trans*-4-*tert*-butylcyclohexanol (36:64) obtained from E. Merck A G, Darmstadt, methyl sulfide obtained from Tokyo Kasei Kogyo Co., Ltd., and triethylamine obtained from Wako Pure Chemical Industries, Ltd., without further purification.
3. The checkers observed that, when *N*-chlorosuccinimide of 93–95% purity, m.p. 128–132° (checked by iodometry), obtained from E. Merck A G, Darmstadt, was used without purification, the oxidation was incomplete, resulting in 93–94% yields of a product containing a 12–15% amount of the starting alcohol (a mixture of the *cis*- and *trans*-). The use of 98% pure *N*-chlorosuccinimide, m.p. 150–151° (recrystallized from benzene), resulted again in recovery of the alcohol in a considerable amount, mainly because of low solubility of the pure reagent in toluene. Therefore, the checkers modified slightly the earlier part of the procedure as follows: the 98% pure *N*-chlorosuccinimide (8.0 g., 0.06 mole) m.p. 150–151°, is dissolved in 400 ml. of toluene (twice as much as the volume used by the submitters) at 40°, and the solution is cooled to room temperature, stirred under nitrogen atmosphere, and cooled to 0–5°. Methyl sulfide (6 ml., 0.10 mole) is added at this temperature and, after addition,

the reaction mixture is stirred for an additional 20 minutes at 0–3°, during which time white precipitate appeared.

4. Reagent grade toluene employed by the submitters was obtained from Mallinckrodt Chemical Works. The checkers used reagent grade toluene purchased from Wako Pure Chemical Industries, Ltd., and dried over molecular sieves (4 Å) before use. Regarding the volume of the toluene used by the checkers, see (Note 3).

5. The checkers observed that the internal temperature was −20° with this cooling mixture.

6. The checkers observed that the reaction was slightly exothermic as judged from an internal temperature rise of *ca.* 5°.

7. The checkers needed a little longer time (3–5 minutes) for this operation to maintain the internal temperature at −15 to −20°.

8. The checkers successively added 100 ml. 1% hydrochloric acid to the reaction mixture.

9. Vigorous shaking is necessary for complete removal of succinimide. The triethylamine hydrochloride is also removed in this step. The methyl sulfide codistils with the ether.

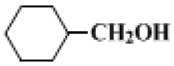
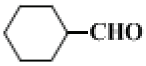
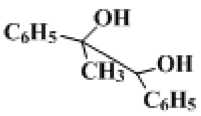
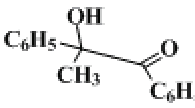
10. An authentic sample from Aldrich Chemical Company, Inc., had m.p. 45–50°. The product was analyzed by GC at 80° on F & M Research chromatograph model 1810 with 3% OV-17 column, which indicated the contamination of the product by 4-*tert*-butylcyclohexanol (<2%) and 4-*tert*-butylcyclohexylmethyl methylthiomethyl ether (<2%).[3] The submitters reported a yield of 6.0 g. (96%) of purity greater than 96%.

The checkers recrystallized the product from petroleum ether (dissolved at room temperature and cooled to −20°) and obtained a pure product, m.p. 45–46° (88.5% recovery); IR ($CHCl_3$) cm^{-1}: 1712 (C=O); ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 0.93 [s, 9H, $C(CH_3)_3$], 1.3–2.2 (m, 5H, CH_2CHCH_2), and 2.2–2.5 (m, 4H, CH_2COCH_2).

3. Discussion

The procedure described here is general for the oxidation of primary and secondary alcohols to carbonyl compounds,[3] but not for allylic and dibenzylic alcohols, which give halides in high yields.[4] The yields of carbonyl compounds are usually high, and the formation of methyl thiomethyl ether can be minimized in nonpolar media. Some examples are listed in Table I. The quantitative conversion of catechols to *o*-quinones using this oxidation procedure has been reported.[5] For oxidation of allylic and dibenzylic alcohols to the corresponding carbonyl compounds, a dimethyl sulfoxide–chlorine reagent[6] is suitable.

TABLE I
OXIDATION OF PRIMARY AND SECONDARY ALCOHOLS[3]

Alcohol	Product	Yield (%)
$C_6H_5CH_2OH$	C_6H_5CHO	90
		96
		94
		91
		86[7]

References and Notes

1. Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138.
2. Medicinal Chemical Research Department, Bristol Laboratories, Syracuse, New York 13201.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether,
diethyl ether (60-29-7)

nitrogen (7727-37-9)

chlorine (7782-50-5)

toluene (108-88-3)

N-chlorosuccinimide (128-09-6)

Triethylamine hydrochloride (554-68-7)

magnesium sulfate (7487-88-9)

methyl sulfide (75-18-3)

dimethyl sulfoxide (67-68-5)

triethylamine (121-44-8)

argon (7440-37-1)

Cyclohexanone, 4-(1,1-dimethylethyl)-,
4-tert-Butylcyclohexanone (98-53-3)

trans-4-tert-Butylcyclohexanol (21862-63-5)

4-tert-Butylcyclohexanol (98-52-2)

cis-4-tert-Butylcyclohexanol (937-05-3)

4-tert-butylcyclohexylmethyl methylthiomethyl ether