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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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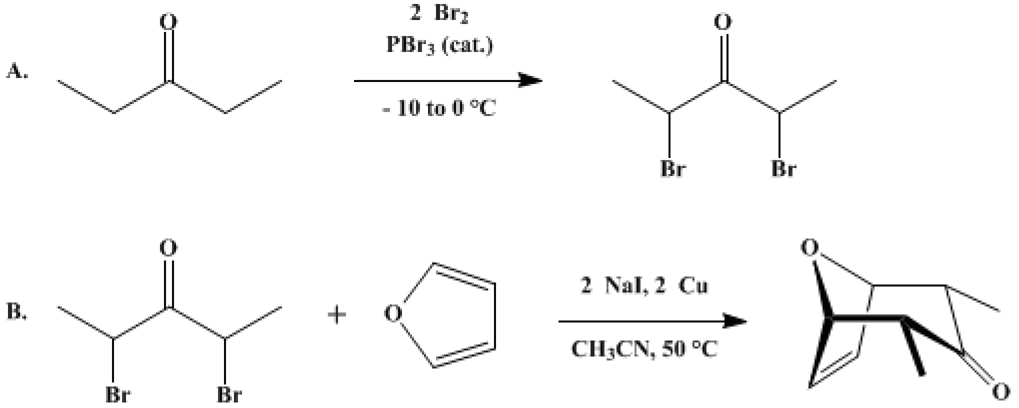
BICYCLIC KETONES FOR THE SYNTHESIS OF TROPINOIDS: 2α,4α-DIMETHYL-8-OXABICYCLO[3.2.1]OCT-6-EN-3-ONE

[8-Oxabicyclo[3.2.1]oct-6-en-3-one, 2α,4α-dimethyl-]



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Checked by D. M. Lokensgard and O. L. Chapman.

1. Procedure

> *Caution! This reaction should be carried out in an efficient hood. 2,4-Dibromo-3-pentanone is a potent lachrymator and a readily absorbed skin irritant. Contact with the skin produces a sensation of sunburn and should be treated immediately by washing with a soap solution, followed by washing with sodium hydrogen carbonate solution.*

A. 2,4-*Dibromo*-3-*pentanone* (**1**). A three-necked, 250-ml. flask is fitted with a stirrer, a dropping funnel, and a condenser protected by a calcium chloride drying tube. Bromine (160 g., 1.00 mole) is added rapidly to a stirred solution of 45 g. (0.52 mole) of 3-pentanone (Note 1) and 1 ml. of phosphorus tribromide maintained between −10° and 0° with an acetone–dry ice bath in an efficient hood. Toward the end of the reaction very large amounts of hydrogen bromide are evolved, and the rate of addition must be controlled to allow the hood to exhaust the gas. Alternatively, a gas trap may be used. Depending on the efficiency of the hood, the addition should take 20–40 minutes. The flask is then evacuated with a water pump, removing dissolved hydrogen bromide, and the reaction mixture is immediately fractionally distilled through a 40-cm. column packed with glass helices (or, more quickly, with a Dufton column)[2] under reduced pressure. The dibromoketone **1**, a mixture of *dl*- and *meso*-isomers,[3] distills at 67–82° (10 mm.), and 91 g. (72%) of product is collected as a colorless liquid (Note 2).

B. 2α,4α-*Dimethyl*-8-*oxabicyclo*[3.2.1]*oct*-6-*en*-3-*one* (**2**). A 1-l., three-necked, round-bottomed flask is fitted with a 100-ml. dropping funnel having a nitrogen inlet tube, a magnetic stirrer, a thermometer, and an efficient double-surface condenser carrying a nitrogen outlet tube connected to a bubbler, and placed on a combined hotplate–magnetic stirring unit in a heat-resistant glass dish, acting as a water bath. Dry acetonitrile (200 ml.) (Note 3) is introduced into the flask, followed by 90 g. (0.60 mole) of dried powdered sodium iodide (Note 4), with vigorous stirring under a slow stream of nitrogen. When the stirring bar rotates steadily, 20 g. (0.31 g.-atom) of powdered copper bronze (Note 5) is added, followed by 28 g. (30 ml., 0.41 mole) of freshly-distilled furan (Note 6). The dropping funnel is then charged with a solution of 24.4 g. (0.100 mole) of dibromoketone **1** in 50 ml. of dry acetonitrile, which is rapidly added to the stirred reaction mixture (Note 7). On addition of dibromoketone **1**, the temperature rises to 45–50°, and a characteristic oatmeal-colored precipitate forms. After about 2 hours the temperature begins to drop, and the reaction is maintained at 50–60° with the water bath for a total reaction time of 4 hours (Note 8).

The flask is cooled to 0° with crushed ice (Note 9), and 150 ml. of dichloromethane is added with stirring. The reaction mixture is poured into a 2-l. beaker containing 500 ml. of water and 500 ml. of crushed ice; material remaining in the flask is rinsed into the beaker with 10 ml. of dichloromethane. The mixture is stirred thoroughly, further salts being precipitated, until the ice just melts, and filtered into a cooled filter flask under reduced pressure through a sintered or Büchner funnel and a kieselguhr filter-aid cake (Note 10). The beaker and filter cake are washed with 50 ml. of dichloromethane, and the clear combined filtrate is transferred to a 2-l. separatory funnel while still cold (Note 11).

The mixture is shaken vigorously, the lower layer is separated and stored in ice, and the aqueous layer is extracted with two, 50-ml. portions of dichloromethane. The combined, organic extracts are shaken with 100 ml. of ice-cold, concentrated aqueous ammonia (35% w/w) filtered through a filter-aid cake, and separated (Note 12). The extraction and filtration are repeated with fresh ammonia solution using the same filter (Note 13). The filter is washed with 50 ml. of dichloromethane, and the organic layer is separated and dried over anhydrous magnesium sulfate. The dried solution is filtered, the filter is washed with 50 ml. of dichloromethane, and the solvent is removed on a rotary evaporator at 30°. The flask containing the residual oil is cooled to 0° before exposure to air (Note 14).

The light-yellow oil is dissolved in 60 ml. of 30% anhydrous diethyl ether in pentane and treated with 2 g. of anhydrous sodium sulfate and 0.5 g. of decolorizing carbon. The mixture is swirled for a few minutes, allowed to settle, and filtered by gravity through three sheets of fine filter paper into a 100-ml., round-bottomed flask with a 14/20 joint. The filter is washed with 10 ml. of pentane, and the flask is sealed by wiring on a 14-mm. serum cap. The flask is placed on a cork ring, lowered into an insulated container (large Dewar bottle, styrofoam box, etc.) half filled with dry ice, and cooled slowly to −78°. When recrystallization is complete, a nitrogen supply is connected to the flask *via* a syringe needle; the supernatant liquid is then withdrawn by syringe and replaced with 50 ml. of pentane, previously cooled to −78°.

The flask is swirled, washing the crystals (Note 15), and the pentane is withdrawn. The flask is connected to a vacuum (water pump) *via* the nitrogen inlet and warmed to room temperature. The crude cycloadduct **2** (6.1–7.3 g., 40–48%) is isolated as colorless needles, m.p. 43.5–45°, from the first recrystallization (Note 16). Pure 2α,4α-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**2**) can be obtained by recrystallization from pentane at −78° with minimal loss, m.p. 45–46° (Note 17).

2. Notes

1. 3-Pentanone is available from Aldrich Chemical Company, Inc.
2. A slight coloration has no effect on the yield of the subsequent reactions. The dibromoketone **1** should be stored cold in a well-stoppered bottle (dark) under nitrogen and is best handled cold to minimize spread of lachrymator vapors.
3. Commercial acetonitrile from Hopkins and Williams (GPR grade, given analysis 0.1% water, 0.02% acid) was used. Further purification of the solvent had no effect on the yield. The checkers used MCB reagent grade acetonitrile, refluxed over and distilled from calcium hydride.
4. The sodium iodide was dried at 150° for at least 3 hours, cooled in a desiccator, and finely powdered in a mortar. Although the use of less sodium iodide (*e.g.*, 33 g., 0.22 mole) gives similar yields, the separation of the aqueous phase on extraction with dichloromethane and the following work-up are easier under the given conditions.
5. The copper bronze was supplied by BDH Chemicals Ltd. (Poole, England) as an extremely fine powder. The use of more granular electrolytic copper had no effect on the yield, but made magnetic stirring more difficult.
6. Commercial furan was refluxed over and distilled from calcium hydride and anhydrous potassium carbonate prior to use. Furan, b.p. 31°, is more volatile than diethyl ether, and precautions must be taken to minimize losses through evaporation.
7. Addition of dibromoketone **1** has been carried out all at once, slowly over a period of half an hour, and over 1 hour with no apparent change in yield.
8. Although a filtered sample of the reaction mixture analyzed by ^{1}H NMR ($CDCl_3$) shows no more dihaloketone after a reaction time of 2 hours (excess of furan was discernible), the reaction mixture

must be heated for an additional 2 hours to destroy traces of dihaloketone which make the subsequent work-up and analytical TLC of the product mixture difficult. When the reaction was carried out with less sodium iodide (33 g., 0.22 mole), the presence of diiodoketone in the final product was noted by formation of an iodine color and rapid decomposition of the cycloadduct to a black solid; also, the pentane washings developed an iodine color on exposure to light.

9. Since the dihaloketones may induce the decomposition of the product, it is essential that the solution be cooled in ice before allowing entry of air. Otherwise, the oily cycloadduct becomes brown, and polymeric material has to be removed, before crystallization, by passage down a 2 × 5 cm. column of silica gel (impregnated with 12% silver nitrate solution and redried).

10. Filtration through Hopkins and Williams kieselguhr filter-aid cake speedily removes even colloidal copper halides and breaks up any emulsion.

11. If the temperature is allowed to rise above 0°, the cycloadduct decomposes and the yellow copper compound present liberates blue-green copper(**II**) salts which make the work-up difficult.

12. The checkers, using 15 ml. of acetonitrile instead of 10 ml. of dichloromethane for rinsing the reaction vessel, found that no solid formed and filtration was not necessary. In this case three extractions with ammonia solution are required before addition of more ammonia fails to produce a blue color.

13. Using the same filter ensures that the ammonia solution is saturated with halide salts, which aid final separation.

14. The oil is essentially pure cycloadduct 2, but owing to traces of impurity, crystallization may be difficult at 0°. Analytical TLC on alumina, using low-polarity solvents such as pentane or carbon tetrachloride, was not successful in the presence of traces of dihaloketone, although it gave high resolution with related compounds. When dehalogenation is complete, however, the resolution is restored (see also (Note 9)).

15. If product **2** appears to be colored at this point, the pentane solution can simply be warmed to dissolve the crystals and cooled to recrystallize.

16. Approximately 0.4 g. of product **2** remaining in the supernatant solution can be recovered by repeated recrystallizations from the ether–pentane solution; however, the presence of 10 impurities (TLC) makes this rather impractical.

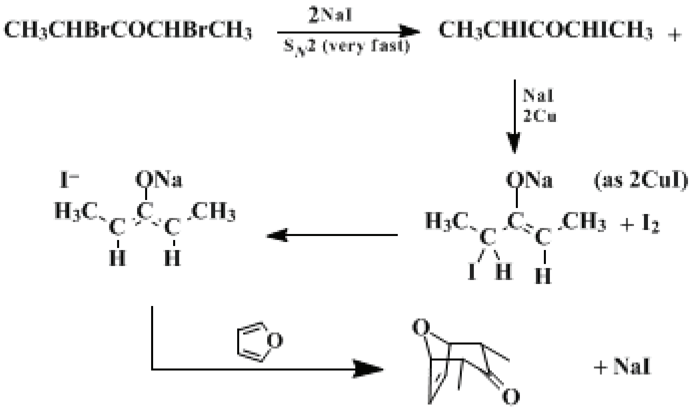
17. IR (CCl_4) cm.$^{-1}$: 1721 (very strong); ^1H NMR ($CDCl_3$), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 0.98 (d, $J = 7$, 6H, 2CH_3), 2.8 (d of q, $J = 5$ and 7, 2H, CHCOCH), 4.86 (d, $J = 5$, 2H, CHOCH), 6.35 (broad s, 2H, 2 olefinic H).[4]

3. Discussion

The reaction of 1,3-dibromo-1,3-diphenyl-2-propanone with sodium iodide in the presence of furan and cyclopentadiene, giving bridged seven-membered rings has been reported by Cookson,[5] who followed up earlier work by Fort.[6] Chidgey[7] [8] demonstrated that the reaction can be extended to simple dibromoketones such as **1** and improved by using metallic copper to remove molecular iodine liberated during the reaction. Mechanistically, the reaction seems to involve two very fast S_N2 displacements of bromide by iodide, as seen by the precipitation of sodium bromide. A subsequent slower nucleophilic attack of excess iodide ion on the positively polarized iodine of the diiodoketone is envisioned, yielding an allylic iodide which forms an allyl cation in a fairly facile S_N1 reaction. The allyl cation is trapped by furan, giving the oxygen-bridged seven-membered ring.[8] The secondary–tertiary dibromoketone, $CH_3CHBrCOCBr(CH_3)_2$, can also be used as an allyl cation precursor in this reaction, but the yields with the primary–tertiary dibromoketone, $CH_2BrCOCBr(CH_3)_2$, are less satisfactory. Zinc-induced cycloaddition works well,[9] in this instance, and also in the case of the ditertiary dibromoketone, $(CH_3)_2CBrCOCBr(CH_3)_2$, which fails to undergo the initial S_N2 displacement with sodium iodide. Hence, although the sodium iodide–copper procedure is probably less general than the zinc[4] and silver ion–promoted[10] cycloaddition, it is experimentally convenient and yields preferentially the thermodynamically more stable adduct *via* an allyl cation in a W-configuration and compact transition state.[8] The reaction involves inexpensive starting materials, proceeds under homogeneous conditions, and can be scaled-up readily.

The procedure described here has been used for the preparation of sensitive 6,7-dehydrotropinones in modest to good yields.[9] If in the present experiment furan is replaced by cyclopentadiene, an epimeric mixture of *cis*-diequatorial and *cis*-diaxial 2,4-dimethylbicyclo[3.2.1]oct-6-en-3-one is formed in almost

90% yield.[11] Instead of zinc or sodium iodide/copper, diiron nonacarbonyl may also be used as a reducing agent for dibromoketones.[12] Recently, 2α,4α-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**2**) has been used as a precursor for the synthesis of (±)-nonactic acid, the building block of the macrotetrolide antibiotic nonactin.[13]



This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 584

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

copper bronze

Diiron nonacarbonyl

cis-diequatorial and cis-diaxial 2,4-dimethylbicyclo[3.2.1]oct-6-en-3-one

(±)-nonactic acid

potassium carbonate (584-08-7)

ammonia (7664-41-7)

ether,
diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydrogen carbonate (144-55-8)

silver nitrate (7761-88-8)

hydrogen bromide (10035-10-6)

bromine (7726-95-6)

sodium bromide (7647-15-6)

sodium sulfate (7757-82-6)

phosphorus tribromide (7789-60-8)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

copper (7440-50-8)

iodine (7553-56-2)

decolorizing carbon (7782-42-5)

zinc (7440-66-6)

sodium iodide (7681-82-5)

Furan (110-00-9)

Pentane (109-66-0)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

3-pentanone (96-22-0)

CYCLOPENTADIENE (542-92-7)

calcium hydride (7789-78-8)

2α,4α-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one,
8-Oxabicyclo[3.2.1]oct-6-en-3-one, 2α,4α-dimethyl-

1,3-dibromo-1,3-diphenyl-2-propanone (958-79-2)

2,4-Dibromo-3-pentanone (815-60-1)