Organic Syntheses

A Publication of Reliable Methods for the Preparation of Organic Compounds

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.

DIAZO KETONE CYCLIZATION ONTO A BENZENE RING: 3,4-DIHYDRO-1(2H)-AZULENONE

[1(2H)-Azulenone, 3,4-dihydro-]
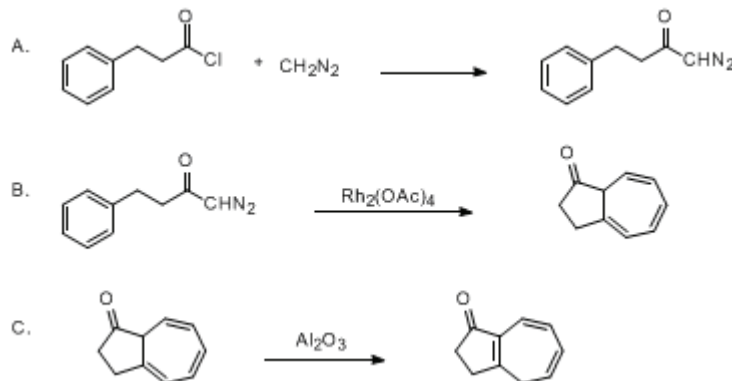
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Checked by John M. Fevig and Larry E. Overman.

1. Procedure

Caution! Diazomethane is toxic and explosive; all operations should be carried out in a well-ventilated hood with adequate shielding. (See (Note 1).)

A. *1-Diazo-4-phenyl-2-butanone.* A 1-L Erlenmeyer flask equipped with a two-in. magnetic stirring bar and a two-hole rubber stopper fitted with a 125-mL Teflon stopcock separatory funnel (Note 2) and a drying tube filled with potassium hydroxide (Note 3) is charged with a solution of 200 mmol (3.4 equiv) of diazomethane (Note 4) in 600 mL of dry ether. The solution is cooled to 0°C and stirred at high speed (Note 5). To this cooled solution, 10.0 g (59 mmol) of hydrocinnamoyl chloride (3-phenylpropionyl chloride) (Note 6) diluted to 125 mL with anhydrous ether is added dropwise over a 1-hr period. The resulting reaction mixture is stirred cold for an additional 0.5 hr and then at room temperature for 1 hr. After this period of time the reaction is complete, and excess diazomethane is removed by evacuating the Erlenmeyer flask with a water aspirator pump in the hood (Note 7). The Erlenmeyer flask is evacuated by connecting the aspirator to a one-hole stopper that has been fitted with a plastic or fire-polished glass tube. After the diazomethane has been removed, the remaining ethereal solution is concentrated by rotary evaporation to give 10.5–10.6 g (> 100% crude yield) of 1-diazo-4-phenyl-2-butanone as a yellow oil (Note 8). This oil is used without purification for the next reaction.

B. *3,4-Dihydro-1(2H)-azulenone.* A 250-mL, one-necked, round-bottomed flask is equipped with an egg-shaped magnetic stirring bar and a high dilution trident (Fig. 1)[2] (Note 9). The high-dilution trident is further equipped with a 100-mL pressure-equalizing addition funnel attached to a nitrogen inlet and an efficient reflux condenser attached to a nitrogen outlet. The round-bottomed flask is charged with 100 mL of dry freshly distilled methylene chloride and 12 mg of rhodium diacetate dimer (Note 10). This heterogeneous mixture is stirred at high speed (Note 11) and heated to a rapid reflux without bumping. The addition funnel is charged with a solution of 8.7 g (50 mmol) of 1-diazo-4-phenyl-2-butanone (Note 12) diluted to 50 mL with methylene chloride. As soon as the high-dilution trident reservoir (20 mL) fills up and begins to overflow back into the round-bottomed flask, dropwise addition of the diazo ketone solution is initiated (1:20, one drop of diazo ketone solution to every 20 drops of solvent entering the trident reservoir from the condenser). After the addition is complete (2.5–3 hr), the reaction mixture is allowed to reflux for an additional 1 hr. The reaction mixture is then cooled, and the yellow-green solution of the initially formed unstable trienone (Note 13) is suction-filtered through 110 g of neutral alumina (Note 14) in a 250-mL fritted-glass funnel to isomerize the β,γ double bond into conjugation with the carbonyl group and to remove the rhodium diacetate dimer. The alumina is then

washed with 100 mL of ethyl acetate, and the combined organic filtrates are concentrated by rotary evaporation to give a yellow oil. Vacuum distillation of this oil through a short-path distillation head gives 5.5–5.7 g (75–78% yield) of a colorless to slightly green oil that solidifies at 0°C, bp 73–75°C/0.2 mm (Note 15). This material is sufficiently pure for most purposes (Note 16). Recrystallization from hexane (80 mL per gram of trienone) yields colorless needles, mp 28.5–29.0°C (Note 17).

Figure 1
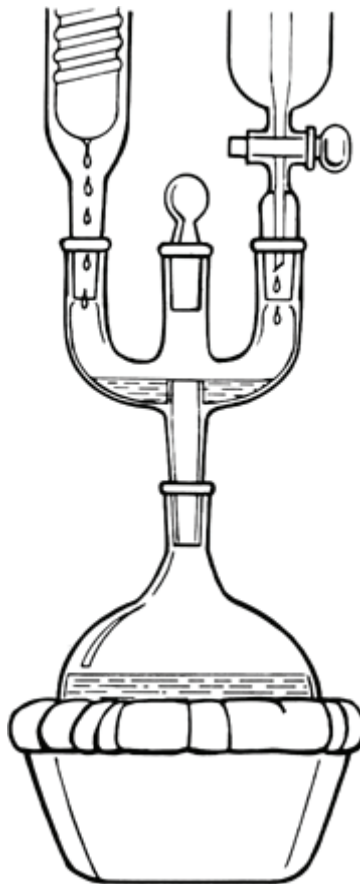
2. Notes

1. See full warning in *Org. Synth., Coll. Vol. II* **1943**, 165, and *Aldrichimica Acta* **1983**, *16(1)*, 3–10.

2. Ground glass can cause explosions; therefore, a Teflon stopcock must be used.

3. Potassium hydroxide must be used as the drying agent since calcium sulfate and other drying agents can react with diazomethane and cause an explosion.

4. Diazomethane is prepared as described in *Org. Synth., Coll. Vol. IV* **1963**, 250, with 50 g of Diazald (from Aldrich Chemical Company, Inc.) in 300 mL of ether added to 15 g of KOH in 25 mL of water, 30 mL of ether, and 50 mL of 2-(2-ethoxyethoxy)ethanol. One equivalent of diazomethane becomes incorporated in the reaction product, and the remainder serves as a scavenger for the HCl produced as a reaction by-product. The excess of diazomethane called for in this procedure is necessary to inhibit the undesired formation of 1-chloro-4-phenyl-2-butanone. The submitters report that this reaction can be performed on twice this scale with comparable results.

5. The high rate of stirring reduces the production of 1-chloro-4-phenyl-2-butanone, a by-product of this reaction.

6. This compound can be purchased from Aldrich Chemical Company, Inc. or prepared according to standard methods.[3]

7. Two hundred milliliters of ether and diazomethane are removed before transfer for rotary evaporation. Diazomethane in a rotary evaporator can cause explosions.

8. A pure sample of diazo ketone can be obtained by chromatography on silica gel using 15% ethyl

acetate/hexane as an eluent, $R_f = 0.37$. The checkers estimate the purity of the crude diazo ketone to be 90–91% based on careful column chromatography of 1.0-g aliquots. They further estimate that approximately 5–6% of 1-chloro-4-phenyl-2-butanone is also produced in the reaction. The spectral properties of 1-diazo-4-phenyl-2-butanone are as follows: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.59–2.64 (m, 2 H), 2.95 (t, 2 H, $J = 7$), 5.20 (broad s, 1 H), 7.17–7.31 (m, 5 H).

9. The high-dilution trident in this example dilutes the diazo ketone solution to 10^{-3}–10^{-4} M before it reaches the reaction mixture.

10. The rhodium diacetate dimer is used in catalytic amounts; 0.132% (weight of dimer/weight of diazo ketone) has worked out to be the best ratio for this reaction.

11. The high-speed stirring minimizes undesired bimolecular reactions.

12. The submitters report that this step can be performed on a 0.5-mol scale (87 g of diazo ketone) in 86.5–94.9% yield. This amount of diazo ketone was prepared in multiple batches as described in Step A. The submitters were reluctant to prepare and handle diazomethane on scale large enough to make 0.5 mol of diazo ketone in one batch.

13. The initially formed trienone isomerizes quantitatively to β-tetralone on treatment with catalytic amounts of trifluoroacetic acid. This acid sensitivity precludes chromatography of the crude product on normal silica gel.

14. F20 Alumina (60–200 mesh) from Schoofs, Inc. was used. The checkers used chromatography grade neutral alumina (100–125 mesh) supplied by Fluka.

15. The oil bath temperature maximum must be maintained below 120°C or the yield of product drops.

16. The checkers found that on this scale a bulb-to-bulb (Kugelrohr) distillation could also be employed. The distilled product is contaminated with approximately 4–5% of 1-chloro-4-phenyl-2-butanone, which was produced in Step A. This impurity is easily removed by recrystallization from hexane. Alternatively, this impurity can be removed at the diazo ketone stage by column chromatography. The use of purified diazo ketone in Step B affords purer distilled product, but this modification has no significant effect on the overall yield.

17. The spectral properties of 3,4-dihydro-1(2H)-azulenone are as follows: ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.50 (narrow m, 2 H), 2.70 (narrow m, 2 H), 2.78 (apparent d, 2 H, $J = 6$), 5.38 (dt, 1 H, $J = 9.6, 6.3$), 6.09 (dd, 1 H, $J = 9.2, 6.2$), 6.47 (dd, 1 H, $J = 11, 5.7$), 6.68 (d, 1 H, $J = 11$); IR (film) cm^{-1}: 1697.

3. Discussion

The cyclopropanation of alkenes, alkynes, and aromatic compounds by carbenoids generated in the metal-catalyzed decomposition of diazo ketones has found widespread use as a method for carbon−carbon bond construction for many years, and intramolecular applications of these reactions have provided a useful cyclization strategy. Historically, copper metal, cuprous chloride, cupric sulfate, and other copper salts were used most commonly as catalysts for such reactions; however, the superior catalytic activity of rhodium(II) acetate dimer has recently become well established.[4] This commercially available rhodium salt exhibits high catalytic activity for the decomposition of diazo ketones even at very low catalyst : substrate ratios (< 1%) and is less capricious than the old copper catalysts. We recommend the use of rhodium(II) acetate dimer in preference to copper catalysts in all diazo ketone decomposition reactions. The present synthesis describes a typical cyclization procedure.

A special feature of the synthesis described here is the glass apparatus used to achieve high-dilution reaction conditions (Fig. 1).[2] This "trident" is simple but effective and can be fabricated quite easily from standard parts. The one shown here is designed to accept an overhead mechanical stirrer.

The product of this synthesis is an especially useful, highly functionalized hydroazulene that is not available commercially. We have used it as a synthetic precursor to homoazulene,[5] [6] and to a variety of homoazulene derivatives,[7] [8] bridged homotropylium cations,[9] [10] and azulene quinones.[11] [12] It could undoubtedly serve as a precursor to numerous natural products. The cyclization reaction tolerates electron-donating substituents[4,13,14] but not halogens[15] on the aromatic ring.

References and Notes

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

rhodium diacetate dimer

HCl (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

cupric sulfate (7758-98-7)

copper (7440-50-8)

calcium sulfate (7778-18-9)

potassium hydroxide,
KOH (1310-58-3)

cuprous chloride (7758-89-6)

methylene chloride (75-09-2)

Diazomethane (334-88-3)

hydrocinnamoyl chloride,
3-phenylpropionyl chloride (645-45-4)

hexane (110-54-3)

trifluoroacetic acid (76-05-1)

β-Tetralone (530-93-8)

2-(2-ethoxyethoxy)ethanol (111-90-0)

1-Diazo-4-phenyl-2-butanone (10290-42-3)

(5503-41-3)

1-chloro-4-phenyl-2-butanone

3,4-Dihydro-1(2H)-azulenone,
1(2H)-Azulenone, 3,4-dihydro- (52487-41-9)