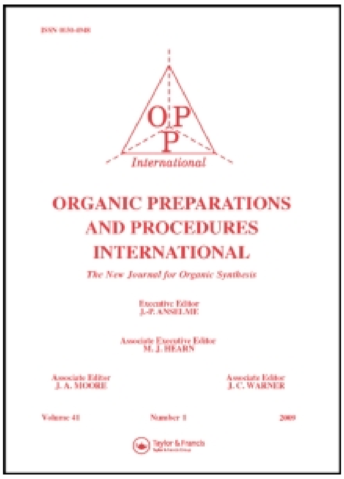

Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

LARGE-SCALE CYCLOPROPANATION

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To cite this Article Repič, Oljan , Lee, Paul G. and Giger, Urs(1984) 'LARGE-SCALE CYCLOPROPANATION', Organic Preparations and Procedures International, 16: 1, 25 — 30

To link to this Article: DOI: 10.1080/00304948409356163

URL: http://dx.doi.org/10.1080/00304948409356163

ORGANIC PREPARATIONS AND PROCEDURES INT. 16(1), 25-30 (1984)

LARGE-SCALE CYCLOPROPANATION

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Recently, we reported [Tetrahedron Lett., 1982, 2729] the use of ultrasonic irradiation in cyclopropanations with zinc-diiodomethane. In addition to the several advantages of this new method noted, we observed that finely divided zinc is no longer necessary for the reaction to occur. Employing one piece of zinc instead of zinc dust has the following additional advantages.

1. The foaming of the solution (due presumably to the formation of ethylene and cyclopropane) is reduced drastically;

2. the exotherm of the reaction is more evenly distributed over the reaction period as only a small area of fresh zinc surface is continuously being exposed to the reaction;

3. the zinc can be raised out of the reaction mixture at any time the exotherm and the reflux become too vigorous;

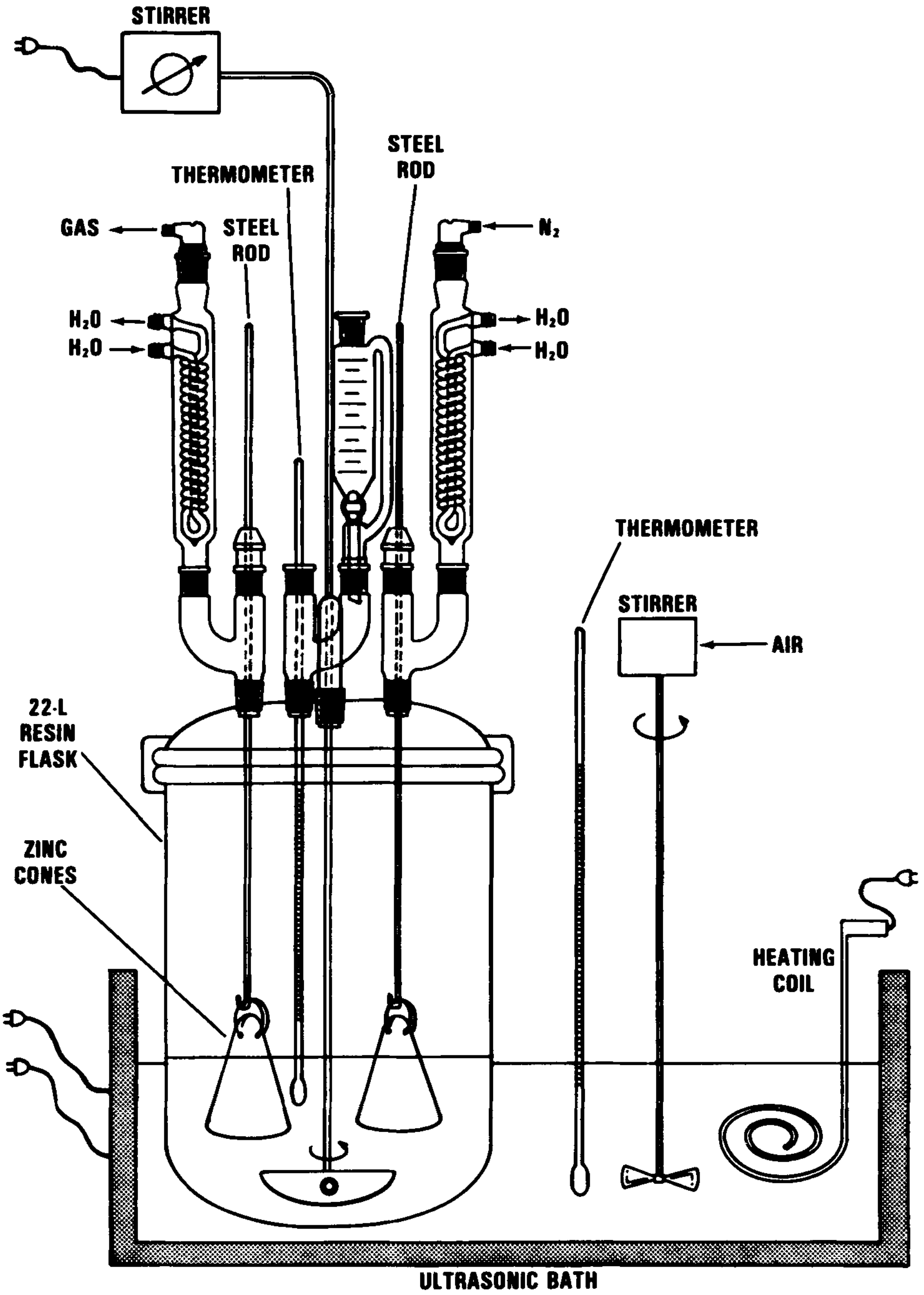
4. any excess zinc can easily be recovered.

These improvements allow, for the first time, a practical and safe scale-up of the Simmons-Smith reaction. We now wish to describe our unusual technique for cyclopropanations in a 22-L reaction flask. The zinc employed with great success in a 1-L reaction flask was in the form of rods or plates. For example, the plastic paddle of the mechanical stirrer was replaced with a sandwich of three zinc plates, each 1.6 mm thick, cut into the shape of the paddle and mounted onto the glass rod of the stirrer. By the end of the reaction, most of the zinc paddle had "dissolved" but enough remained to provide efficient stirring throughout the reaction. This technique, however, could not be utilized in a larger reaction vessel, as the paddle became prohibitively heavy. On a larger scale, a practical surface area to weight ratio was obtained by employing zinc cones, suspended into the reaction solution, as described below.

Even though ultrasonic irradiation alone, in the absence of chemical initiators, is sufficient to start and keep the reaction going, we added small amounts of iodine and Red-Al® as activators for the zinc to guarantee an undelayed start of the reaction.

EXPERIMENTAL SECTION

Apparatus.- The **reactor** (see Figure) consisted of a 22-L, 4-necked resin flask, equipped with three Claisen adapters to fit two spiral condensers, a mechanical stirrer, a thermometer, a nitrogen-gas inlet, a gas outlet, an addition funnel and two stainless steel rods (equipped with stainless steel bearings, e.g., SGA Scientific Inc. catalog #JS-1160) from each of which a cone of zinc was hung with copper wire.
A cork stopper was mounted on each steel rod just above the bearing; the cork hole was made tight enough to hold the rod and the zinc cones in any vertical position. A clamp holder was attached on top of the steel rod as a safety stop. Each **cone** was manufactured by melting ca. 900 g of zinc into a


STIRRER
THERMOMETER
STEEL ROD
GAS
STEEL ROD
N_2
H_2O
H_2O
H_2O
H_2O
THERMOMETER
STIRRER
AIR
22-L RESIN FLASK
ZINC CONES
HEATING COIL
ULTRASONIC BATH

FIGURE

125-mL suction flask, positioned over an acetylene gas burner. When the metal cooled, the flask was tapped onto the bench, the bottom of the flask fell off, and the zinc was recovered in one cone-shaped piece. Four holes were drilled through the neck of the cone, and copper wire was laced through the holes. The reactor was immersed (with great difficulty, due to buoyancy) into a 36 x 18 x 18-inch, 50-gallon **ultrasonic bath** (440 V, 3000 W, 80 kHz), model Z-5000 S, manufactured by Zenith Manufacturing and Chemical Company. The bath was filled with water-ethylene glycol (1:1), stirred with an air-driven propeller-stirrer and heated with two 1600-W electrical immersible heating coils, as well as by a 4000-W electrical heater built into the bath. The experiment was conducted inside a walk-in hood. The gaseous by-products of the reaction were vented from the top of the condenser into the hood exhaust.

Chemicals.- The zinc was purchased in the form of bars from Alfa (8 x 8 x 300 cm, 99.9%); 1,2-dimethoxyethane, 99%, and Red-Al® were purchased from Aldrich; diiodomethane, 98%, was purchased from Fluka, and methyl oleate, 99%, was distilled prior to use.

Procedure.- The reactor (see Figure) was charged under nitrogen with 1,2-dimethoxyethane (2700 mL), and two zinc cones (898 g + 902 g = 1800 g, 27.5 mol) were immersed into the solvent to about 3 cm below the vertex of the cone. The stirrers, the heaters, the ultrasonic irradiation, and a timer (time = zero) were turned on and left on throughout the experiment. After 30 min. (reaction temp. 30°), a stock solution of Red-Al® (72 mL, 0.017 mol; prepared by diluting 42 mL of commercial 3.4-molar solution in toluene with 1,2-dimethoxyethane to 600 mL) was added rapidly. At 60 min. from time zero (reaction temp. 55°), a solution of iodine (5 g, 0.019 mol) in 30 mL of 1,2-dimethoxyethane was added rapidly. At 130 min. (reaction temp. 85°), the zinc cones were raised above the solvent surface, and diiodomethane (1288 mL, 16 mol) was added rapidly, taking care to avoid splashing the zinc. At 150 min. (reaction temp. 86°), methyl oleate (593 g, 2 mol) was added rapidly. At 155 min. (reaction temp. 89°), the zinc cones were lowered into the solution. A vigorous reaction and reflux set in, with minimal foaming. [CAUTION: exothermic reaction and evolution of flammable gases!] The mixture was irradiated with ultrasound and heated at 100 ± 2° for 2.25 hours (until 290 min. from time zero), at which time GC indicated a complete reaction (less than 1% of methyl oleate). [GC conditions: 2 m x 2 mm 3% OV®-1 on 80/100 Supelcoport, helium 30 mL/min.; temperature program: 200°→ 300° at 10°/min.; retention times: methyl oleate, 5.6 min., methyl 9,10-methyleneoctadecanoate, trans: 6.0 min., cis: 6.5 min.]

The ultrasound and the heaters were turned off, and the zinc cones were raised above the solution surface. They were later weighed to determine that 806.5 g (12.3 mol) of zinc had reacted. Large amounts of ice were added to the bath to cool it to -15°. The reaction mixture was diluted with toluene (2 L), and the solid zinc iodide was dissolved by slowly adding cold 2 N hydrochloric acid (4 L) [CAUTION: exothermic!]. The clear solution was transferred to a 22-L separatory funnel. The aqueous layer was separated (8 L) and extracted with two 2-L portions of toluene. The organic layers were combined (8 L) and washed with two 2-L portions of water, one 0.5-L portion of saturated aqueous sodium thiosulfate, two 1-L portions of saturated aqueous sodium thiosulfate, two 1-L portions of water until pH=6, and one 0.5-L portion of saturated aqueous sodium chloride. The organic layer was evaporated at 50°/60 mm to obtain a yellow oil, containing some toluene, 2% of methyl trans-9,10-methyleneoctadecanoate and <1% of methyl oleate. This crude product was distilled at 150-155°/0.3 mm (85% yield) and filtered through silica gel (adsorbent-sample weight ratio 5:1) with dichloromethane as the solvent, to remove most of the colored impurities. Thus 510 g of methyl cis-9,10-methyleneoctadecanoate (97% pure, 82% yield) was obtained as a light-yellow oil; IR (neat): 1740 (ester), 3050, 1010 (cyclopropane) cm^{-1}; ^1H-NMR ($CDCl_3$): δ 3.65 (s, 3H, methoxy), 2.3 (t, 2H, α-methylene), 1.0-1.7 (m, 26H, methylenes), 0.9 (t, 3H, methyl), 0.6 (m, 3H, cis-cyclopropane), -0.3 (m, 1H, cyclopropane H cis to R), Me_4Si = 0.0; ^{13}C-NMR ($CDCl_3$): δ 174.20 s, 51.34 q, 34.07 t, 31.90 t, 30.17 t, 30.10 t, 29.66 t (2C), 29.42 t, 29.32 t, 29.27 t, 29.15 t, 28.69 t, 28.64 t, 24.94 t, 22.66 t, 15.75 q, 15.70 d, 14.07 d, 10.89 t, $CDCl_3$ = 77.00.

ACKNOWLEDGEMENT.-We thank Mr. Noel Porro for preparing the 99% methyl oleate from oleic acid.

(Received August 8, 1983; in revised form January 10, 1984)