Tetrahedron Letters,Vol.23,No.27,pp 2729-2732,1982 0040-4039/82/272729-04$03.00/0
Printed in Great Britain

ULTRASOUND IN ORGANIC SYNTHESIS: CYCLOPROPANATION OF OLEFINS WITH ZINC-DIIODOMETHANE

Oljan Repič* and Susi Vogt
Chemical Research and Development, Pharmaceutical Division
Sandoz, Inc., E. Hanover, N.J. 07936, U.S.A.

Summary: Activation of zinc with ultrasonic irradiation facilitates the Simmons-Smith reaction.

The Simmons-Smith cyclopropanation does not proceed readily unless the zinc is first activated. Historically[1] this was accomplished by forming zinc-copper or zinc-silver couples and/or by employing iodine or lithium[2] as the activating agent. Even so, the reaction of zinc with diiodomethane tends to show a delayed sudden exotherm which is especially violent with large-scale preparations (our observations). For example, on a 5-liter scale, utilizing diethyl ether, the solvent boiled off in spite of a good condenser; utilizing higher-boiling ethers, eg., 1,2-dimethoxyethane, the reaction mixture crept up and out of the condenser! We now wish to report that ultrasonic irradiation[3] activates zinc to such an extent that its reaction with diiodomethane proceeds rapidly but smoothly to give, in the presence of olefins, high yields of cyclopropanated products. Turning the ultrasound off in the middle of the experiment clearly (see Diagram) slows down the reaction; on switching the ultrasound on, the reaction picks up again. We have noted the following advantages to this method: no chemical activation of zinc is needed, no delayed exotherm is observed, the reaction proceeds smoothly, rapidly, with unusually high yields, the reaction time and yield are reproducible, and cruder zinc (eg., mossy, rods, or foil) can be employed successfully. The reaction is very exothermic, nevertheless. We are presently studying the application of this technique to the Reformatsky reaction.

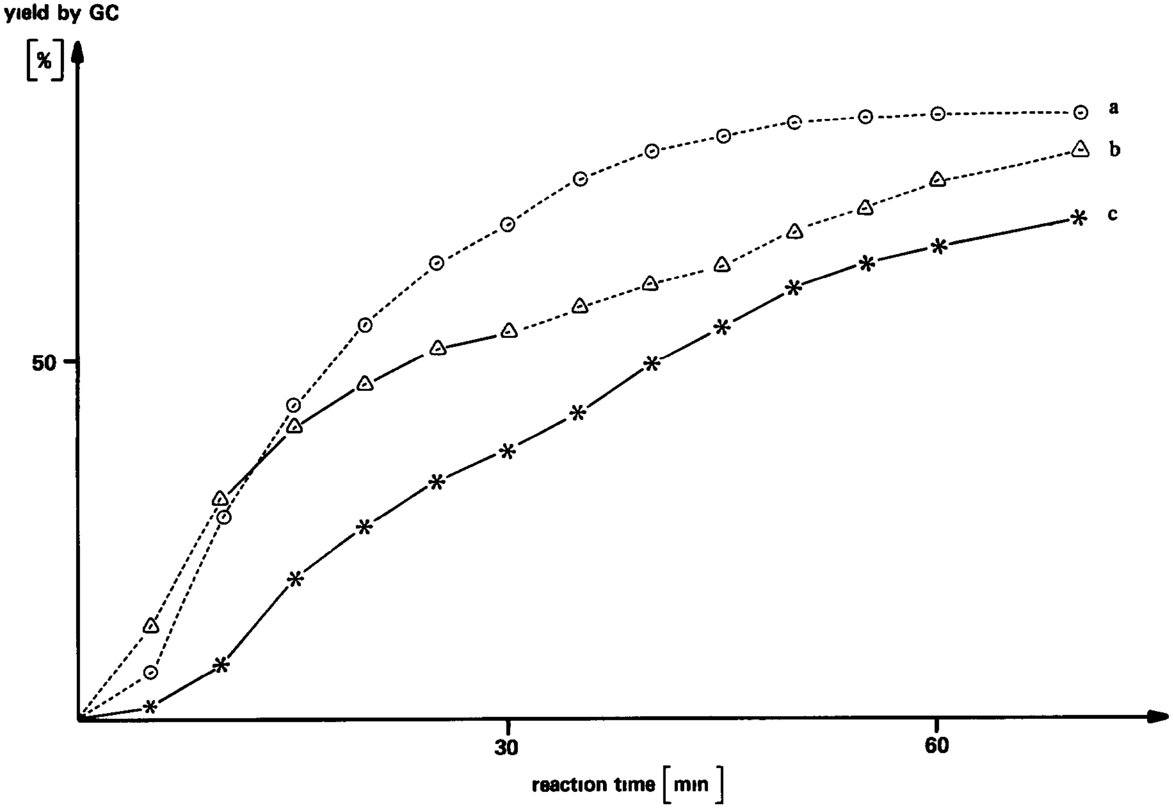

DIAGRAM. Cyclopropanation of methyl oleate with 4 equivalents of zinc dust and diiodomethane. a = continuous ultrasound; b = interrupted ultrasound; c = no ultrasound; ······· = ultrasound; ——— = no ultrasound.

TABLE. Cyclopropanation of olefins with excess mossy zinc and diiodomethane in refluxing 1,2-dimethoxyethane with concomitant ultrasonic irradiation.

olefin	rxn. time	product yield			product data	
		gc	isolated	lit.	found^a	literature
methyl oleate	2 hrs	99%	91%^{b}	51%[5]	bp$_{0.6}$ 159°	bp$_{0.5}$ <200° [6]
methyl linoleate	2 hrs	99%	97%^{c}	75%[1]	bp$_{0.25}$ 133° (dec.)	ms [7]
(-)-α-pinene	4 hrs	90%	67%^{b}	12%[8]	bp$_{36}$ 78-80°	bp$_{36}$ 78° [8]
(+)-5α-androst-2-en-17β-yl acetate	6 hrs	95%	75%^{c}	50%[9]	mp 101-102°^{d}	mp 98-104° [9]
(-)-camphene	4 hrs	90%	74%^{b}	--	mp 115-117°^{e} (sealed tube)	mp 55-56° [10]

a) Structure confirmed by nmr and ms;
b) distilled; c) chromatographed; d) crystallized; e) sublimed

Experimental. A laboratory ultrasonic cleaner (150 W, 50-55 kHz) manufactured by Branson Co. was employed. Before use, in order to minimize the content of iodine, diiodomethane was fractionally distilled at 5 mm, fractionally crystallized by partial freezing[4] and stored over mercury. 1,2-Dimethoxyethane was purchased from Aldrich and used without purification or drying. Methyl oleate and linoleate were purchased from U.S. Biochemical Co., pinene and camphene were purchased from Aldrich, and the steroid was prepared in-house.

Illustrative Procedure. (-)-2,7,7-Trimethyltricyclo[4.1.1.0^{2,4}]octane. A 1-liter, 4-neck round-bottomed flask, equipped with a thermometer, two condensers, mechanical stirrer and nitrogen-inlet tube, was charged with 1,2-dimethoxyethane (200 mL) and mossy zinc (35.6 g, 0.544 mol), and it was irradiated with ultrasound for 2 hrs. (-)-α-Pinene (21.0 g, 0.154 mol) was added rapidly, and the mixture was heated to reflux. Diiodomethane (44.8 mL, 0.556 mol) was added with stirring. The mixture was heated to reflux (the reaction temperature rises from 85° to 96°, therefore an efficient condenser is required) and continuously irradiated with ultrasound, until gc indicated that the reaction had stopped at 90% completion (4 hrs); [gc conditions: 2 m x 2 mm 3% OV®-1 on 80/100 Supelcoport, isothermal 100°, helium 30 mL/min; retention time: starting material 1.7 min, product 3.2 min]. The reaction mixture was cooled to 25°, pentane (200 mL), saturated aqueous ammonium chloride (200 mL), and solid ammonium chloride were added slowly until all solids dissolved. The aqueous phase was extracted with two 150-mL portions of pentane, and the combined organic layers were washed with two 150-mL portions of saturated aqueous sodium chloride. The solution was dried over magnesium sulfate, filtered, and evaporated at atmospheric pressure. The residual yellow oil (30 mL) was fractionally distilled at 78-80° at 36 mm (lit.[8] 78° at 36 mm) to obtain 15.5 g of an oil (67% yield, 97% pure by gc); $[\alpha]^{25}_{589}$ -70.0 (c = 1.67, ethanol); m/e 150 [M$^+$]; ^{1}H-nmr (deuteriochloroform): δ = 2.02 (2,m), 1.84 (1,dd), 1.65 (2,m), 1.26 (3,s), 1.08 (3,s), 1.04 (3,s), 0.93 (1,d), 0.72 (2,m), 0.20 (1,m); ^{13}C-nmr (deuteriochloroform): δ = 16.0 d, 19.1 t, 20.3 s, 21.1 q, 25.5 q, 27.0 q, 27.1 t, 27.5 t, 41.0 s, 41.6 d, 45.5 d.

Acknowledgement. We would like to thank Dr. M.J. Shapiro for obtaining nmr spectra, Dr. E. Fu for providing mass spectra, and Mr. W. Bonkoski for measuring optical rotations.

REFERENCES

1. H.E. Simmons, T.L. Cairns, S.A. Vladuchick and C.M. Hoiness, Org. Reactions, 20, 1 (1973).

2. R.D. Rieke, P.T.-J. Li, T.P. Burns, S.T. Uhm, J. Org. Chem., 46, 4323 (1981).

3. For recent uses of ultrasound in organic synthesis see B.H. Han and P. Boudjouk, Tet. Letters, 1981, 2757, and references therein.

4. D.D. Perrin, W.L.F. Annarego and D.R. Perrin: "Purification of Laboratory Chemicals"; Pergamon Press, New York, 1980, p. 216.

5. H.E. Simmons and R.D. Smith, J. Amer. Chem. Soc., 81, 4256 (1959).

6. D.G. Brooke and J.C. Smith, J. Chem. Soc., 1957, 2732.

7. W.W. Christie and R.T. Holman, Lipids, 1, 176 (1966).

8. C. Filliatre and C. Gueraud, C.R. Acad. Sc. Paris Ser. C, 273, 1186 (1971).

9. M.E. Wolff, W. Ho and R. Kwok, J. Med. Chem., 7, 577 (1964).

10. G. Mehta and S.K. Kapoor, J. Organomet. Chem., 80, 213 (1974).

(Received in USA 12 April 1982)