Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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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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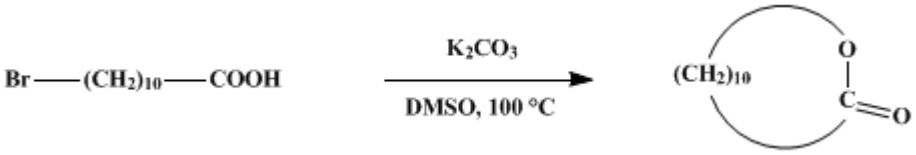
MACROLIDES FROM CYCLIZATION OF ω-BROMOCARBOXYLIC ACIDS: 11-HYDROXYUNDECANOIC LACTONE

[Oxacyclododecan-2-one]



Submitted by C. Galli and L. Mandolini[1].
Checked by Kaoru Mori and Carl R. Johnson.

1. Procedure

A 1-l., three-necked, round-bottomed flask equipped with an internal thermometer, mechanical stirrer, dropping funnel, and calcium chloride drying tube is charged with 500 ml. of dimethyl sulfoxide and 15 g. (0.11 mole) of potassium carbonate (Note 1). The mixture is heated to 100°, and a solution of 10.0 g. (0.0377 mole) of 11-bromoundecanoic acid (Note 2) in 200 ml. of dimethyl sulfoxide is added dropwise with vigorous stirring over 1 hour. After cooling at room temperature, the mixture is decanted and filtered free of any suspended solid material (Note 3) through a Büchner funnel with occasional suction. The solid residue is rinsed with 50 ml. of dimethyl sulfoxide, and the washings are added to the original filtrate. The resulting clear solution is diluted with 250 ml. of water and extracted with three 250-ml. portions of petroleum ether. The combined organic layers are washed with 200 ml. of water, dried over anhydrous sodium sulfate, and concentrated, leaving *ca.* 7 g. of crude material. Simple distillation at reduced pressure from a small Claisen flask yields 5.5–5.8 g. (79–83%) of pure 11-hydroxyundecanoic lactone as a colorless, musk-smelling liquid, b.p. 124–126° (13 mm.), n_D^{19} 1.4721 (Note 4) and (Note 5). The residue is ground with 5 ml. of hexane and filtered, affording 0.4–0.7 g. (6–10%) of the 24-membered dilactone 1,13-dioxacyclotetracosane-2,14-dione as white crystals, m.p. 71.5–72° (from hexane) (Note 6).

2. Notes

1. Reagent grade dimethyl sulfoxide and anhydrous potassium carbonate were used.
2. 11-Bromoundecanoic acid, available from Aldrich Chemical Company, Inc., was used without further purification.
3. Filtration is optional; however, it does reduce the extent of emulsion formation during the subsequent extractions.
4. The submitters report that the pure lactone and dilactone can also be obtained by chromatography of the crude product on silica gel with chloroform as the eluant.
5. The product is pure by GC and TLC; IR (CCl_4) cm^{-1}: 1740; ^1H NMR (CCl_4), δ (multiplicity, number of protons, assignment): 1.2–1.8 (m, 16H), 2.30 (broad t, 2H, CH_2CO), 4.14 (broad t, 2H, CH_2O).
6. Stoll and Rouvè[2] report m.p. 71.5–72°.

3. Discussion

Available methods for the synthesis of macrolides include the cyclization of long-chain bifunctional precursors,[3] depolymerization processes,[4] ring-enlargement reactions,[5] and special methods such as the thermal decomposition of tricycloalkylidene peroxides.[6] The method reported here is essentially that of the submitters.[7] Its improvements result from a quantitative approach to the cyclization of a series of ω-bromo fatty acids under conditions well defined from the kinetic point of view. A unique feature of this procedure in comparison with other methods involving cyclization of α,ω-bifunctional precursors,

which are generally run under Ziegler's high-dilution conditions, is that high rates of feed can be used, so that the special devices usually employed for the slow addition of the reagent into the reaction medium are not required. The synthesis is characterized by relatively mild reaction conditions and simple work-up. Moreover, it is suited for relatively large-scale preparations. Up to 50 g. of 11-bromoundecanoic acid can be cyclized in more than 70% yield in a single run, employing no more than 1 l. of solvent and an addition time of 3–4 hours.

The reaction illustrates a typical preparation of a macrolide. Lactones with more than 12 members can be obtained in even better yields. For example, 15-hydroxypentadecanoic lactone (m.p. 35–37°) and 17-hydroxyheptadecanoic lactone (m.p. 40–41°) were prepared by the submitters in about 95% yield, practically pure, with no trace of the corresponding dilactones.

Recent progress in chemistry and biochemistry of macrolides was recently reviewed.[8]

References and Notes

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

petroleum ether

potassium carbonate (584-08-7)

chloroform (67-66-3)

sodium sulfate (7757-82-6)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

11-Hydroxyundecanoic lactone,
Oxacyclododecan-2-one (39282-36-5)

1,13-dioxacyclotetracosane-2,14-dione

11-Bromoundecanoic acid (2834-05-1)

17-hydroxyheptadecanoic lactone

15-hydroxypentadecanoic lactone (106-02-5)