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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.

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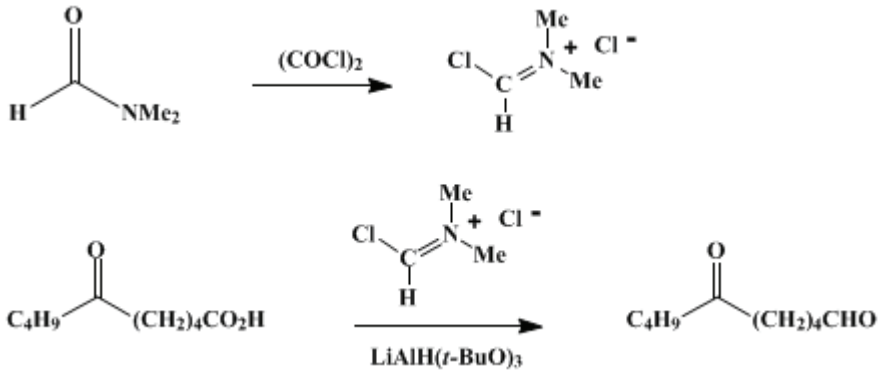
REDUCTION OF CARBOXYLIC ACIDS TO ALDEHYDES: 6-OXODECANAL

[Decanal, 6-oxo-]



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Checked by Cynthia Smith and Andrew S. Kende.

1. Procedure

Caution! Oxalyl chloride is toxic. This preparation should be carried out in a well-ventilated hood.

A. *N,N-Dimethylchloromethylenammonium chloride.* A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a thermometer (Note 1), and a three-way stopcock fitted with a drying tube containing anhydrous calcium chloride and a rubber septum. The flask is charged with 50 mL of dichloromethane (Note 2) and 3.07 (0.042 mol) of *N,N*-dimethylformamide (Note 3) added through the septum from a syringe, and cooled in an ice bath. To the cooled mixture is slowly added 5.23 mL (0.06 mol) of oxalyl chloride (Note 4) by means of a syringe. The addition is accompanied by gas evolution and formation of a white precipitate. The reaction mixture is stirred for an additional hour at 0°C. Excess oxalyl chloride and solvent are removed under reduced pressure by first using a water aspirator and then a rotary pump at room temperature through the drying tube. The white solid remaining in the flask is *N,N*-dimethylchloromethylenammonium chloride, which is used directly in Part B.

B. *6-Oxodecanal.* The drying tube is removed and the flask is flushed with nitrogen. A nitrogen atmosphere is maintained throughout the subsequent reaction. A dropping funnel is attached and charged with 7.45 g (0.04 mol) of 6-oxodecanoic acid (Note 5), 3.32 g of pyridine (Note 6), and 80 mL of tetrahydrofuran (Note 7), which are mixed well by shaking. The flask is charged with 45 mL of acetonitrile (Note 8) and 80 mL of tetrahydrofuran and cooled (methanol–liquid nitrogen) to −30°C. The contents of the funnel are added to the flask at −30°C over 30 min. The reaction mixture is stirred at −30°C for an additional hour and at −20°C for 30 min. After the mixture is cooled to −90°C (Note 9), 34 mL (0.046 mol) of a 1.35 *M* solution of lithium tri(*tert*-butoxy)aluminum hydride in tetrahydrofuran (Note 10) is injected through the septum by means of a syringe over 30 min, while the internal temperature is kept below −85°C. Stirring is continued for an additional 30 min at −90°C. To the flask is added 50 mL of 2 *M* hydrochloric acid solution, and the cooling bath is immediately removed. The organic layer is separated and the aqueous layer is extracted with three 50-mL portions of ether. The combined organic extracts are washed with two 50-mL portions of saturated sodium hydrogen carbonate solution and 50 mL of brine, dried over anhydrous sodium sulfate, and filtered. The solvent is removed with a rotary evaporator and the residual liquid is distilled under reduced pressure to yield 5.78–6.35 g (85–93%) of 6-oxodecanal as a fragrant liquid, bp 85–90°C (1.4 mm) (Note 11).

2. Notes

1. The thermometer must be able to measure temperatures as low as −90°C.
2. Dichloromethane was distilled from calcium hydride and stored over Linde 4A molecular sieves.
3. *N,N*-Dimethylformamide was distilled under reduced pressure, bp 45–47°C (20 mm), and stored over Linde 4A molecular sieves.
4. Oxalyl chloride purchased from Wako Chemicals was used without purification. The checkers found that oxalyl chloride, purchased from Aldrich Chemical Company, Inc., gives better yields if freshly distilled.
5. 6-Oxodecanoic acid was obtained by hydrolysis of methyl 6-oxodecanoate prepared by the *Organic Syntheses*[2] method as follows: 20 g (0.100 mol) of methyl 6-oxodecanoate was treated with 200 mL of 1 *M* potassium hydroxide solution at room temperature overnight. The alkaline solution was washed with two 50-mL portions of ether, and acidified with 50 mL of 6 *M* hydrochloric acid solution at 0°C. The acidic layer was extracted with three 100-mL portions of ether. The ethereal extracts were dried over sodium sulfate and filtered. Removal of the solvent under reduced pressure and recrystallization of the residual white solid from hexane gave 17.85 g (96%) of 6-oxodecanoic acid, mp 45.0–45.5°C (lit.[3] mp 45–46°C).
6. Pyridine was distilled from calcium hydride, and stored over Linde 4A molecular sieves.
7. Tetrahydrofuran was freshly distilled from the sodium ketyl of benzophenone.
8. Acetonitrile was distilled from calcium hydride, and stored over Linde 4A molecular sieves.
9. The checkers used a 1 : 1 methanol : ethanol/liquid nitrogen bath.
10. Lithium tri(tert-butoxy)aluminum hydride was purchased from Kanto Chemicals or Aldrich Chemical Company, Inc.
11. GLC analysis of the product using a 3-mm × 1-m stainless-steel column, 15% SE-30 on Chromosorb W (AW), 60–80 mesh, 150°C, 50 mL of nitrogen per minute showed a purity of 99.2% (the retention times is 4.0 min). The spectral properties of the product are as follows: IR (liquid film) cm^{-1}: 2950, 2930, 2870, 2720, 1710, 1455, 1410, 1370; ^1H NMR (60 MHz, CCl_4) δ: 0.87 (t, 3 H, J = 7, CH_3), 1.1–1.9 (m. 8 H, CH_2), 2.1–2.6 (m, 6 H, $CH_2C{=}O$), 9.73 (t, 1 H, J. = 1.4, H-C=O).

3. Discussion

Various reagents have been suggested for the conversion of carboxylic acids into aldehydes, such as modified aluminum hydride reagents,[4] Grignard reagents catalyzed by dichlorobis(π-cyclopentadienyl) titanium,[5] lithium in methylamine,[6] and boron hydride reagents.[7] However, these reagents have some drawbacks in availability, lack of chemoselectivity due to the high reactivity of the reagents, and isolation of products.

The present procedure, a modified one reported earlier by the submitters, illustrates a general method of aldehyde synthesis from carboxylic acids in a one-pot operation using the readily available, *N,N*-dimethylchloromethylenammonium chloride.[8] Strong activation of carboxylic acids by the iminium salt via the carboxymethylenammonium salt[9] and a weak reducing reagent, lithium tri(*tert*-butoxy) aluminum hydride, achieve the chemoselective reduction of carboxylic acids to aldehydes. The present procedure has several advantages: (a) easy availability of the reagents; (b) use of a slight excess of the hydride reagent; (c) high yields of both aliphatic and aromatic aldehydes; (d) high chemoselectivity, which tolerates nitrile, ester, halide, olefin, and even ketone; and (e) easy isolation of the product.

References and Notes

1. Chemistry Department of Resources, Mie University, Tsu, Mie 514, Japan.
2. Fujisawa, T.; Sato, T. *Org. Synth., Coll. Vol. VIII* **1993**, 441.
3. Holmquist, H. E.; Rothrock, H. S.; Theobald, C. W.; Englund, B. E. *J. Am. Chem. Soc.* **1956**, *78*, 5339.
4. Muraki, M.; Mukaiyama, T. *Chem. Lett.* **1974**, 1447; Zakharkin, L. I.; Khorlina, I. M. *Zh. Obshch. Khim.* **1964**, *34*, 1029; *Chem. Abstr.* **1964**, *60*, 15724*f*; Hubert, T. D.; Eyman, D. P.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 2279.

5. Sato, F.; Jinbo, T.; Sato, M. *Synthesis* **1981**, 871.
6. Bedenbaugh, A. O.; Bedenbaugh, J. H.; Bergin, W. A.; Adkins, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 5774.
7. Brown, H. C.; Cha, J. S.; Nazer, B.; Yoon, N. M. *J. Am. Chem. Soc.* **1984**, *106*, 8001.
8. Fujisawa, T.; Mori, T.; Tsuge, S.; Sato, T. *Tetrahedron Lett.* **1983**, *24*, 1543.
9. Bohme, H.; Viehe, H. G. "Iminium Salts in Organic Chemistry," Taylor, E. C., Ed.; in *Advances in Organic Chemistry*; Wiley: New York, 1976, Vol. 9, Part 1; 1979, Vol. 9, Part 2.

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

brine

sodium ketyl of benzophenone

dichlorobis(π-cyclopentadienyl)titanium

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

acetonitrile (75-05-8)

sodium hydrogen carbonate (144-55-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

methylamine (74-89-5)

dichloromethane (75-09-2)

lithium (7439-93-2)

boron hydride (7440-42-8)

Tetrahydrofuran (109-99-9)

oxalyl chloride (79-37-8)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

calcium hydride (7789-78-8)

Methyl 6-oxodecanoate (61820-00-6)

6-Oxodecanal,
Decanal, 6-oxo- (63049-53-6)

6-Oxodecanoic acid (4144-60-9)

Lithium tri(tert-butoxy)aluminum hydride

N,N-Dimethylchloromethylenammonium chloride