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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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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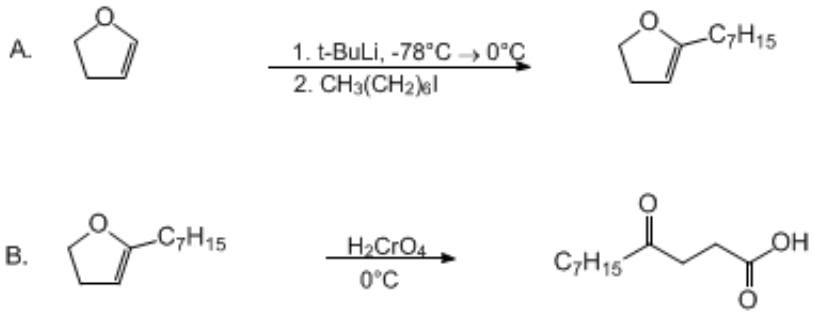
4-KETOUNDECANOIC ACID

[Undecanoic acid, 4-oxo-]



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Checked by T. M. Kamenecka and L. E. Overman.

1. Procedure

Caution! tert-Butylithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 20-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see Aldrich Technical Bulletin AL-134. [Note added August 2009].

A. *2-Heptyl-4,5-dihydrofuran*. An oven-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar, and fitted with a rubber septum, is flushed with argon and charged with 8.00 mL of 2,3-dihydrofuran (105.8 mmol) (Note 1) and 600 mL of dry tetrahydrofuran (THF) (Note 2). The solution is stirred and cooled to −78°C using an external acetone–dry ice bath. After stirring at −78°C for 30 min, 50.0 mL of a solution of tert-butyllithium in pentane (2.60 M in pentane, 130 mmol) (Note 3) is added dropwise via syringe over 60 min. The acetone–dry ice bath is replaced by an ice–water bath for 30 min, at which time the reaction mixture is recooled to −78°C. A solution of 17.35 mL of 1-iodoheptane (105.8 mmol) (Note 4) in 30 mL of dry tetrahydrofuran is added dropwise via syringe, and the resulting solution is allowed to warm to room temperature and stir for 60 min. The solution is recooled to 0°C and quenched by the careful addition of 100 mL of 50% aqueous ammonium chloride. The contents are transferred to a 1-L separatory funnel, and the organic phase separated. The aqueous phase is extracted three times with 100-mL portions of pentane–ether (1:1 v/v), and the combined organic phases are dried over Na_2SO_4, filtered, and concentrated under reduced pressure without heating to afford crude 2-heptyl-4,5-dihydrofuran (17.77 g, 100%) as a yellow oil (Note 5). This crude material is used directly in the next step.

B. *4-Ketoundecanoic acid*. A 2-L, round-bottomed flask, equipped with a magnetic stirring bar and a 250-mL addition funnel, is charged with 17.77 g of the crude 2-heptyl-4,5-dihydrofuran (105.8 mmol) and 400 mL of tetrahydrofuran (Note 6). The resulting solution is cooled to 0°C using an external ice bath, and 117.5 mL of a 2.7 M solution of aqueous chromic acid (317.4 mmol) (Note 7) is added dropwise via the addition funnel over 90 min, and the solution is allowed to stir overnight (Note 8). The reaction mixture is diluted with 300 mL of diethyl ether and 300 mL of water, and the resulting mixture is allowed to stir vigorously for 30 min. The reaction mixture is transferred to a separatory funnel, and the organic phase is separated (Note 9). The aqueous phase is extracted four times with 200-mL portions of diethyl ether. The combined organic phases are washed with three times with 100-mL portions of water (Note 10), followed by extraction three times with 150-mL portions of 10% aqueous sodium hydroxide solution. The combined basic extracts are acidified with 6 N hydrochloric acid to pH ~1

(*CAUTION:* Exothermic reaction!). The cloudy mixture is extracted 4 times with 150 mL of dichloromethane, and the combined organic extracts are dried over $MgSO_4$, followed by concentration under reduced pressure to afford crude 4-ketoundecanoic acid (12.4–14.7 g, 59–69%) as a white solid: mp 74–77°C (Note 11).

2. Notes

1. 2,3-Dihydrofuran was purchased from Fluka Chemical Corporation and used without further purification.
2. Tetrahydrofuran was freshly distilled over sodium/benzophenone prior to use.
3. tert-Butyllithium was purchased from Lithco Chemical Corporation (the checkers used tert-butyllithium purchased from Aldrich Chemical Company, Inc.) and titrated prior to use.
4. 1-Iodoheptane was purchased from Fluka Chemical Corporation and passed through activated basic aluminum oxide prior to use.
5. Because of the product's volatility, a hot water bath should not be used during solvent evaporation. GC and GC/MS analysis of an aliquot indicate that the product ranges in purity from 75–95% with unreacted 1-iodoheptane also present. The addition of 0.5 equiv of hexamethylphosphoramide (HMPA) prior to addition of the iodoheptane was found to improve the yield of this alkylation. The addition of 0.5 to 2.0 equiv of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) did not improve the yield. The checkers found the following GC conditions useful for monitoring the alkylation reaction: initial column temperature, 40°C; heating increment, 10°C/min; iodoheptane R_f = 3.3 min, product R_f = 5.7 min. Column specifications were as follows: SPB-1 (stationary phase), fused silica gel capillary column, 30 m × 0.32 mm ID, 0.25-mm film thickness.
6. Acetone is commonly used as a solvent in Jones oxidations; however, the desired keto acid tends to be retained by the chromium salts during work-up. A benzene/THF solution has also been employed for the oxidation, but this modification did not seem to have much effect on the overall yield.
7. Aqueous chromic acid solution (the Jones reagent) was prepared according to "Reagents in Organic Syntheses", Fieser & Fieser; J. Wiley, 1967; Vol. 1, p. 142.
8. Chromium salts may precipitate upon addition of the Jones reagent. A minimal amount of water may be added to dissolve them.
9. Additional water may be added to facilitate separation of layers.
10. At this point, it is important to remove as much of the blue chromium impurities from the organic phase as possible.
11. The product may be recrystallized from hexanes to mp 79–80°C. The spectral data of the recrystallized material are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.86 (t, 3 H, J = 7.0), 1.30 (s, 8 H), 1.57 (quintet, 2 H, J = 7.3), 2.43 (t, 2 H, J = 7.5), 2.61 (dd, 2 H, J = 6.23, 5.87), 2.71 (dd, 2 H, J = 6.60, 6.23); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.0, 22.6, 23.8, 27.7, 29.0, 29.1, 31.6, 36.7, 42.7, 178.5, 208.9; IR (thin film) cm^{-1}: 3056, 2987, 2957, 2933, 2873, 2858, 1710, 1421, 1265, 748. Other electrophiles were used to give the corresponding keto acids as shown below:

Electrophile	Keto Acid Yield
C_4H_9I	64%
$C_{11}H_{23}I$	82%
$C_6H_5CH_2Br$	62%

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Because of a long standing research program centering on chiral bicyclic lactams, the submitter's laboratories have required a variety of 4-keto acids as precursors to these versatile intermediates.[2] [3] Generally these acids are useful for the preparation of many important compounds.[4] [5] [6] [7] [8] [9] [10] [11] [12] A general route to 4-keto acids is the Larson procedure involving the C-silylation of butyrolactone followed by Grignard addition, elimination and in situ oxidation.[13] [14] [15] [16] [17] However, the major disadvantage to this process is the need for stoichiometric amounts of the expensive chlorodiphenylmethylsilane.

The procedure described here involves the metallation of dihydrofuran and subsequent alkylation with an alkyl iodide (bromides are much less reactive).[18] [19] [20] The resulting substituted dihydrofuran, the intermediate postulated in the Larson procedure, is then treated with chromic acid to hydrolyze the enol ether and oxidize the resulting primary alcohol to the corresponding carboxylic acid as in the Larson procedure. The isolated oxidation product is of suitable purity for subsequent reactions, but if necessary, recrystallization from hexanes is readily accomplished .

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 457

References and Notes

1. Department of Chemistry, Colorado State University, Fort Collins, CO 80523.
2. Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503;
3. Meyers, A. I.; Berney, D. *Org. Synth., Coll. Vol. VIII* **1993**, 241.
4. Ellison, R. A. *Synthesis* **1973**, 397;
5. Ho, T.-L. *Synth. Commun.* **1974**, *4*, 265;
6. Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 81;
7. Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368;
8. Shimada, J.-i.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759;
9. Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z.-i. *Tetrahedron Lett.* **1985**, *26*, 5559;
10. Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83;
11. Sato, T.; Okazaki, H.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1988**, *110*, 5209 and references therein;
12. Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 6541.
13. Larson, G. L.; Fuentes, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 2418;
14. Fuentes, L. M.; Larson, G. L. *Tetrahedron Lett.* **1982**, *23*, 271;
15. Betancourt de Perez, R. M.; Fuentes, L. M.; Larson, G. L.; Barnes, C. L.; Heeg, M. J. *J. Org. Chem.* **1986**, *51*, 2039.
16. For a related procedure, see (d) Larson, G. L.; Montes de Lopez-Cepero, I.; Mieles, L. R. *Org. Synth., Coll. Vol. VIII* **1993**, 474;
17. Viso, M.; Reid, J. R.; U.S. Patent 5 103 047, 1992; *Chem. Abstr.* **1992**, *116*, 235086k.
18. Schlosser, M.; Schaub, B.; Spahic, B.; Sleiter, G. *Helv. Chim. Acta* **1973**, *56*, 2166;
19. Boeckman, Jr., R. K.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997;
20. Kocienski, P.; Wadman, S.; Cooper, K. *J. Org. Chem.* **1989**, *54*, 1215.

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

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

acetone (67-64-1)

Benzophenone (119-61-9)

sodium (13966-32-0)

chromic acid (7738-94-5)

Butyrolactone (96-48-0)

Pentane (109-66-0)

dichloromethane (75-09-2)

chromium (7440-47-3)

keto

aluminum oxide (1344-28-1)

Tetrahydrofuran (109-99-9)

argon (7440-37-1)

hexamethylphosphoramide (680-31-9)

1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (7226-23-5)

tert-Butyllithium (594-19-4)

4-Ketoundecanoic acid,
Undecanoic acid, 4-oxo- (22847-06-9)

2-Heptyl-4,5-dihydrofuran

2,3-dihydrofuran,
dihydrofuran (1191-99-7)

1-iodoheptane,
iodoheptane (4282-40-0)

chlorodiphenylmethylsilane (144-79-6)