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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

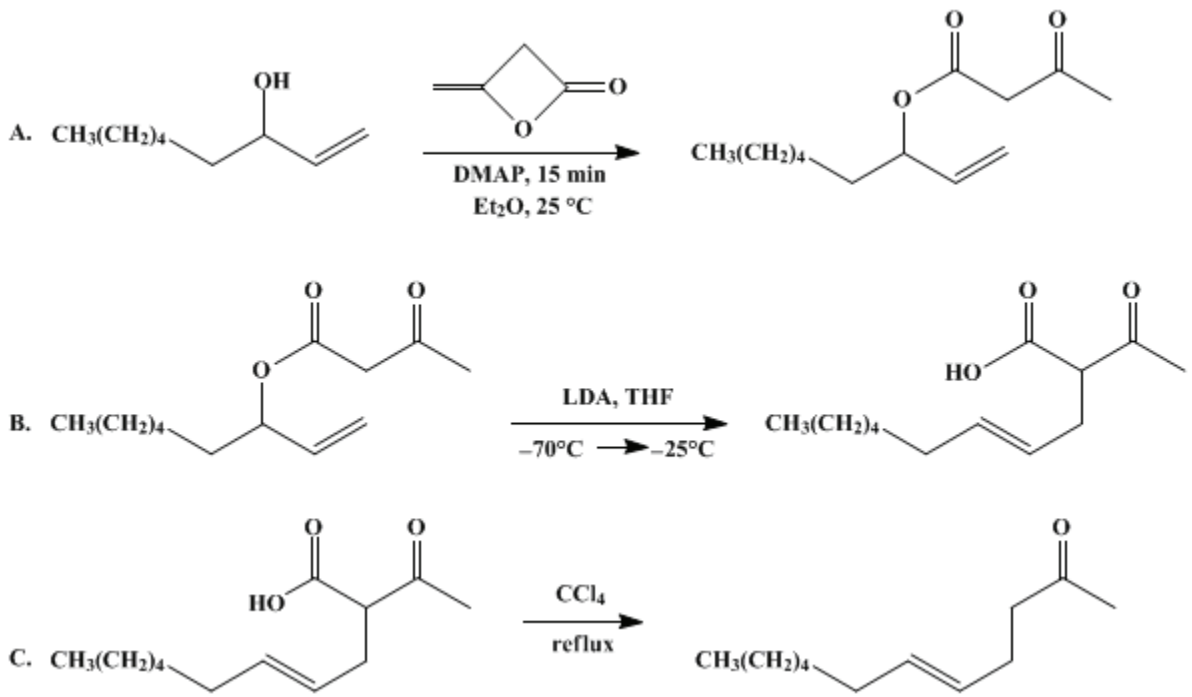
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.068.0210

Organic Syntheses, Coll. Vol. 8, p.235 (1993); Vol. 68, p.210 (1990).

THE CARROLL REARRANGEMENT: 5-DODECEN-2-ONE

[5-Dodecen-2-one, (*E*)-]



Submitted by Stephen R. Wilson and Corinne E. Augelli[1].
Checked by T. R. Vedananda and James D. White.

1. Procedure

A. *(1-Ethenyl)heptanyl 3-ketobutanoate.* 3-Hydroxy-1-nonene ((Note 1), 7.5 g, 0.053 mol) is stirred in 250 mL of anhydrous ether (Note 2) in a 500-mL, three-necked, round-bottomed flask, fitted with a thermometer, a nitrogen/mineral oil bubbler, a Teflon-covered magnetic stirring bar, and a rubber septum. A constant flow of nitrogen is maintained throughout the reaction. To this clear homogeneous solution, diketene ((Note 3), 5.04 g, 0.060 mol) is added in one portion by syringe, followed by 4-dimethylaminopyridine (DMAP) (0.591 g, 0.0049 mol, (Note 4)). A slightly exothermic reaction (to 32° C) is observed. After 15 min, the reaction is complete (Note 5). The reaction mixture is quenched with 100 mL of 0.1% sodium hydroxide solution and 100 mL of anhydrous ether. The layers are separated and the organic phase is washed once with 50 mL of 0.1% sodium hydroxide solution and once with brine. Drying over magnesium sulfate and concentration under reduced pressure affords 11.3 g (0.05 mol, 94%) of a pale-yellow oil. The β-keto ester is of high purity, as shown by TLC, GLC, and spectral analyses (Note 6); however, distillation (bp 113–114°C/1.4 mm) leads to a colorless oil.

B. *2-Carboxy-5-dodecen-2-one.* A solution of lithium diisopropylamide (LDA, (Note 7)) in 150 mL of tetrahydrofuran (Note 8) is prepared from 0.199 mol (20.12 g) of diisopropylamine (Note 9) and 0.181 mol of butyllithium (Note 10) and (Note 11). The solution is cooled to −78°C (acetone–dry ice) and a solution of 10.0 g (0.044 mol) of (1-ethenyl)heptanyl 3-ketobutanoate in 50 mL of tetrahydrofuran (Note 8) is added via a 12-mL, pressure-equalizing dropping funnel at −78°C over a 15-min period. After the addition is complete, the reaction mixture is stirred at −78°C for 45 min and is then allowed to warm gradually to room temperature. When the reaction mixture finally reaches 25°C (about 2 hr), it has a deep-red color. After the mixture is stirred for 18 hr at room temperature, the reaction is complete (Note 12). To this mixture, 100 mL of water and 100 mL of pentane are added in portions with stirring, maintaining the temperature below 25°C with an ice bath. As the deep-red reaction mixture is quenched,

an orange heterogeneous mixture results. The layers are separated and the pentane layer is extracted 2 times with 50 mL of 0.1% sodium hydroxide solution (Note 13). All aqueous layers are combined in a 800-mL beaker equipped with a Teflon-covered magnetic stirring bar. A 100-mL aliquot of pentane is added to this aqueous mixture, which is stirred vigorously, and then 100 mL of 10% hydrochloric acid solution is added in 10-mL portions until pH 2 is reached (Note 14). The heterogeneous solution is poured into a 1-L separatory funnel and the layers are quickly separated. The aqueous layer is extracted 3 times more, each time with 50 mL of pentane. The combined organic layers (ca. 250–300 mL) are dried ($MgSO_4$), and evaporated at reduced pressure without heating, to give 9.6 g (0.04 mol, 97%) of a red-orange oil. This carboxylic acid is of high purity as shown by TLC and spectral analyses (Note 15).

C. *5-Dodecen-2-one.* The 3-carboxy-5-dodecen-2-one (9.0 g, 0.040 mol) is stirred in 150 mL of carbon tetrachloride (Note 16) in a 500-mL, three-necked, round-bottomed flask that is fitted with a reflux condenser, a thermometer, a Teflon-covered magnetic stirrer, and a ground-glass stopper. After the orange-yellow solution is heated at reflux for 1 hr, TLC analysis shows the reaction to be complete (Note 17). The reaction mixture is concentrated under reduced pressure with warming to afford 7.1 g (0.039 mol, 98%) of a red-orange oil. The product is sufficiently pure for most purposes. It may be purified by vacuum distillation at 105–107°C/2.7 mm (5.2 g, 0.03 mol, 71%), which yields a pale-yellow oil (Note 18).

2. Notes

1. 3-Hydroxy-1-nonene was prepared by the following procedure. First, 0.219 mol (25.0 g) of heptaldehyde (Eastman Kodak Co.), distilled prior to use, was stirred in 450 mL of anhydrous ether (Note 2) under a nitrogen atmosphere. The solution was cooled to 0°C with an ice bath and 0.260 mol (260.4 mL) of vinylmagnesium bromide (1.0 *M* solution in tetrahydrofuran, Aldrich Chemical Company, Inc., 1.2 equiv) was then added dropwise over a 0.5-hr period. The reaction mixture was allowed to warm gradually to room temperature and was stirred for 0.5 hr. The reaction mixture was added, in portions with stirring, to 400 mL of a saturated ammonium chloride solution, maintaining the temperature below 25°C with an ice bath. This quenched reaction mixture was stirred for 15 min. The layers were separated and the aqueous layer was extracted 2 times, each time with 200 mL of ether. The combined organic layers were extracted with 200 mL of brine, dried ($MgSO_4$), and concentrated under reduced pressure with warming to afford a yellow oil in quantitative yield. The allylic alcohol was distilled (bp 185°C/760 mm, 25 g, 0.158 mol, 73%) before use. Silica gel TLC showed one spot: R_f = 0.34 (20% ethyl acetate/ligroin). GLC: retention time, 4.56 min. Program: 40°C/1 min; 20°C/1 min to 320°C; 2% OV-101, 0.2% Carbowax on Chromosorb. This program and column were used throughout the entire sequence of reactions. IR (neat) cm^{-1}: 3610 (OH); 3000 (C-H, alkenes); 1650 (C=C); 1000 (C-O). Mass spectrum: *m/e* 57 [100% M^+-$CH_2(CH_2)_4CH_3$], 85 (7.7% M^+-$CHOHCH{=}CH_2$), 113 (2.5% M^+-CH_2CH_3). ^1H NMR ($CDCl_3$) δ: 0.91 (t, 1 H, J = 6.9), 1.54–1.31 (m, 11 H), 4.12 (q, 1 H, J = 6.3), 5.27–5.11 (m, 1 H), 5.95–5.84 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 22.6, 25.4, 29.3, 31.9, 37.1, 72.9, 114.0, 141.5.
2. Anhydrous ether (Fisher Scientific Company) was used without further drying.
3. Diketene (Aldrich Chemical Company, Inc.) was distilled immediately prior to use.
4. 4-Dimethylaminopyridine (DMAP) was purchased from Aldrich Chemical Company, Inc. A catalytic amount of 4-dimethylaminopyridine is necessary for this reaction to proceed.
5. Reaction progress can be monitored by GLC analysis of the disappearance of diketene.
6. Silica gel TLC shows one spot at R_f = 0.45 (20% ethyl acetate/ligroin); GLC shows >95% purity of the β-keto ester. The β-keto ester undergoes partial cleavage to the corresponding allylic alcohol under the following GLC conditions. Retention time, 7.8 [(1-ethenyl)heptanyl 3-ketobutanoate]; retention time, 4.88 (3-hydroxy-1-nonene). Mass spectrum for the β-keto ester: *m/e* 43 (100% M^+-$COCH_3$), 85 [46.5% $(CH_2)_5CH_3$], 141 (13.3% M^+-$COCH_2COCH_3$). Mass spectrum for allylic alcohol: *m/e* 57 [100% M^+-$CH_2(CH_2)_4CH_3$], 85 (8.7% M^+-$CHOHCH{=}CH_2$), 113 (2.8% M^+-CH_2CH_3). IR (neat) cm^{-1}: 3000 (C-H, alkenes); 1725 (C=O); 1650 (C=C); ^1H NMR ($CDCl_3$) δ: 0.89 (t, 3 H), 1.30–1.64 (m, 10 H), 2.3 (s, 3 H), 3.47 (s, 2 H), 5.19–5.31 (m, 3 H), 5.72–5.84 (m, 1 H). Anal. calcd. for $C_{13}H_{22}O_3$: C, 68.99; H, 9.8. Found: C, 69.25; H, 10.06.
7. Lithium diisopropylamide (LDA) was prepared by the method described in *Org. Synth., Coll. Vol. VII* **1990**, 208.
8. Tetrahydrofuran was distilled from lithium aluminum hydride immediately prior to use.

9. Diisopropylamine, purchased from Aldrich Chemical Company, Inc., was distilled immediately prior to use.
10. Butyllithium, 2.5 *M* solution, in hexanes was purchased from Aldrich Chemical Company, Inc. Butyllithium was titrated with diphenylacetic acid[2] before each use.
11. An amount of 4.1 equiv of lithium diisopropylamide (LDA) is absolutely necessary for this reaction to go to completion. An equilibrium exists between the formation of the second anion of the β-keto ester and the formation of lithium diisopropylamide from diisopropylamine.
12. Reaction progress can be followed most accurately by silica gel TLC and GLC analysis. In TLC analysis, one sees the disappearance of (1-ethenyl)heptanyl 3-ketobutanoate, R_f = 0.45 (20% ethyl acetate/ligroin) and the appearance of baseline material that is indicative of the corresponding carboxylic acid salt. In GLC analysis, an aliquot (3 drops of reaction mixture, 3 drops of ether, 3 drops of 10% hydrochloric acid) will show complete disappearance of peaks at R_t = 7.44 and 4.56 [which correspond to (1-ethenyl)heptanyl 3-ketobutanoate and cleavage of this β-keto ester under GLC conditions to the 3-hydroxy-1-nonene, respectively] and appearance of a peak at R_t = 7.04 that corresponds to 5-dodecen-2-one. The 3-carboxy-5-dodecen-2-one decarboxylates upon injection yielding the GLC spectrum of the ultimate product.
13. Sodium hydroxide (0.1%) is used to extract all of the carboxylate from the ether layer in the form of the sodium salt.
14. A slight exotherm was noted from 25 to 32°C. Acidification is necessary to extract all of the desired carboxylate from the aqueous layer into the organic layer.
15. Silica gel TLC shows one major spot at the baseline (20% ethyl acetate/ligroin) with a very slight impurity (<5%) at R_f = 0.47. Mass spectrum of 5-dodecen-2-one: *m/e* 43 (100% $COCH_3$), 97 [6.1% M^+-$CH_2(CH_2)_4CH_3$], 125 (1.7% M^+-CH_2COCH_3). IR (neat) cm^1: 3000 (COOH); 1725 (COOH, RCOR); ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, *J* = 6.3); 1.28 (m, 8 H); 2.00 (m, 2 H); 2.31 (s, 3 H); 2.60 (t, 2 H, *J* = 6.9); 3.48–3.59 (m, 1 H); 5.27–5.44 (m, 1 H, *trans J* = 15.3); 5.49–5.61 (m, 1 H, *trans J* = 15.3).
16. Carbon tetrachloride was used as purchased from Fisher Scientific Company.
17. Reaction progress was followed most accurately by TLC analysis. The disappearance of the baseline material (i.e., 3-carboxy-5-dodecen-2-one) and appearance of the desired ketone at R_f = 0.33 (10% ethyl acetate/ligroin) indicates the completeness of the reaction.
18. Silica gel TLC shows one spot at R_f = 0.33 (10% ethyl acetate/ligroin). GLC shows >95% purity; one peak at R_t = 7.04. Mass spectrum: *m/e* 43 (100% $COCH_3$), 97 [6.3% M^+-$CH_2(CH_2)_4CH_3$], 125 (2.0% M^+-CH_2COCH_3). IR (neat) cm^{-1}: 1700 (R'COR); ^1H NMR ($CDCl_3$) δ: 0.90 (t, 3 H, *J* = 6.5), 1.28 (m, 8 H), 1.98 (q, 2 H, *J* = 6.3), 2.16 (s, 3 H), 2.28 (q, 2 H, *J* = 6.6), 2.51 (t, 2 H, *J* = 7.4), 5.34–5.51 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ: 14.0, 22.6, 26.9, 28.8, 29.5, 29.8, 31.7, 32.5, 43.6, 128.2, 131.5, 207.9. Anal. calcd. for $C_{12}H_{22}O$: C, 79.06; H, 12.17. Found: C, 78.79; H, 12.10.

3. Discussion

The Carroll rearrangement,[3,4] an old and well-established thermal rearrangement, involves the rearrangement of allylic esters to β-keto acids followed by decarboxylation to provide γ,δ-unsaturated methyl ketones. Even though the Carroll rearrangement is a versatile complement to the Claisen rearrangement,[5] it is not of widespread use. This may be due to (a) the lack of a convenient, high-yield method for the formation of β-keto esters and (b) the harsh conditions required to effect rearrangement.[6] Often, procedures involve direct conversion of allylic alcohols to the rearranged and decarboxylated products in one step and low yield.

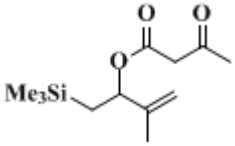
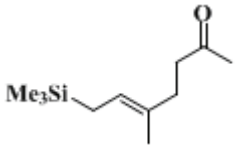
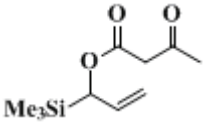
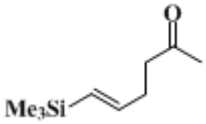
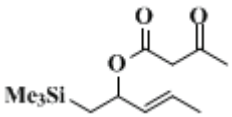
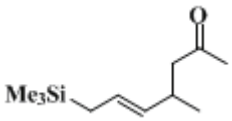
The method of preparation of 5-dodecen-2-one presented here is a version of the literature procedure published earlier.[10] It offers several advantages over existing methodology:

1. The ester enolate modification of the Carroll rearrangement provides the allylic acetoacetates via a mild, fast, and high-yield synthesis. This procedure represents a significant improvement over other routes.[7 8 9]
2. Dianions of the allylic acetoacetates rearrange at room temperature and the resulting β-keto acids can be readily isolated. Isolation of the acetoacetic acids adds to the versatility of the synthesis of γ,δ-unsaturated methyl ketones and makes purification much more simple than pyrolysis method.
3. Finally, the general pyrolysis procedure, although one step, leads to side products and low

yields (typically 10–40%). For example, pyrolysis of (1-ethenyl)heptanyl 3-ketobutanoate[4] gives two major products, 5-dodecen-2-one and 3-hydroxy-1-nonene, whereas the method of preparation described here yields only the desired γ,δ-unsaturated methyl ketone.

Table I contains representative examples of the method of preparation described here.

TABLE I
PREPARATION OF γ,δ-UNSATURATED METHYL KETONES

SUBSTRATE	PRODUCT	YIELD(%)	REF.
		40	10
		80	10
		84	10

References and Notes

1. Department of Chemistry, New York University, Washington Square, New York, NY 10003.
2. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.
3. Carroll, M. F. *J. Chem. Soc.* **1940**, 1266.
4. Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992.
5. Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227.
6. Rearrangement is normally carried out at temperatures of 130–220°C by heating the β-keto ester neat or in a high-boiling solvent (xylene, diphenyl ether), usually *in situ* after preparation of the β-keto ester.
7. Acetoacetate formation has previously been carried out by using the following. (a) Et_3N: Kato, T.; Chiba, T. *Chem. Pharm. Bull.* **1975**, *23*, 2263;
8. NaOR: see [4];
9. *p*-TsOH: Boese, A. B., Jr. *Ind. Eng. Chem.* **1940**, *32*, 16.
10. Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.

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

ligroin

brine

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

diketene (674-82-8)

Diphenylacetic acid (117-34-0)

vinylmagnesium bromide (1826-67-1)

Pentane (109-66-0)

magnesium sulfate,
$MgSO_4$ (7487-88-9)

butyllithium (109-72-8)

Tetrahydrofuran (109-99-9)

lithium aluminum hydride (16853-85-3)

heptaldehyde (111-71-7)

lithium diisopropylamide (4111-54-0)

diisopropylamine (108-18-9)

4-dimethylaminopyridine (1122-58-3)

5-Dodecen-2-one

(1-Ethenyl)heptanyl 3-ketobutanoate (133538-60-0)

3-Carboxy-5-dodecen-2-one (133538-61-1)

3-Hydroxy-1-nonene (21964-44-3)

5-Dodecen-2-one, (E)- (81953-05-1)

2-Carboxy-5-dodecen-2-one