Organic Syntheses

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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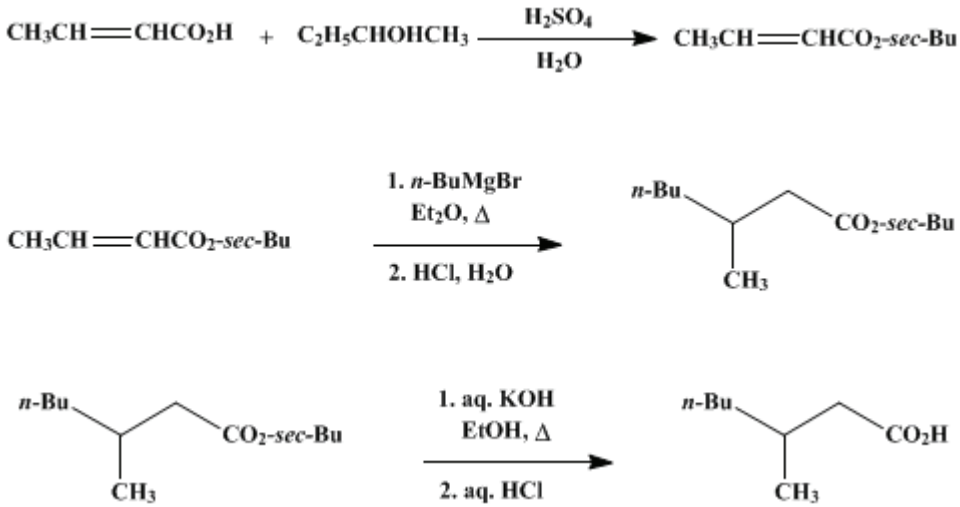
3-METHYLHEPTANOIC ACID

[Heptanoic acid, 3-methyl-]



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1. Procedure

A. *sec-Butyl crotonate*. In a 2-l. round-bottomed flask are placed 258 g. (3 moles) of crotonic acid (Note 1), 370 g. (5 moles) of *sec*-butyl alcohol in which has been dissolved 6–7 ml. of concentrated sulfuric acid, and 300 ml. of benzene. A few boiling chips are added, and the flask is fitted with a suitable water separator (Note 2) in the top of which is placed a reflux condenser. The mixture is heated under reflux for about 12 hours or until no further separation of aqueous phase occurs. About 65 ml. of water is collected. The cooled reaction mixture is diluted with 200 ml. of ether, washed with 10% sodium carbonate solution until neutral to litmus, washed with saturated sodium chloride solution, and finally dried over magnesium sulfate. The solvent is distilled, and the ester is fractionated under reduced pressure through a small column. The yield of *sec*-butyl crotonate, b.p. 74–75°/30 mm. or 83–84°/45 mm., n_D^{25} 1.4261, is 360–390 g. (85–90%) (Note 3).

B. *3-Methylheptanoic acid*. In a 2-l. three-necked flask fitted with a mercury-sealed stirrer, a reflux condenser carrying a calcium chloride tube, and a dropping funnel are placed 25.0 g. (1.04 g. atoms) of magnesium turnings. The flask is heated to about 100° for a few minutes and then cooled to room temperature. A solution of 178 g. (1.30 moles) of *n*-butyl bromide in 300 ml. of dry ether is prepared; and of this solution about 10 ml., together with 30 ml. of dry ether, is run into the flask. The reaction is started by heating to reflux for a few seconds, the stirrer is started, and the remainder of the bromide solution is added at such a rate as to maintain constant reflux (about 1 hour).

After the addition has been completed, the solution is heated under reflux for 10–15 minutes. The flask is now surrounded by an ice and water bath, and stirring is continued for 15 minutes (Note 4). From a graduated dropping funnel, a solution of 56.8 g. (0.4 mole) of *sec*-butyl crotonate (Note 5) in 400 ml. of dry ether is then added dropwise during a period of about 3 hours (Note 6) while the reaction mixture is effectively stirred and cooled in the ice bath. After the addition of the ester solution is complete, the reaction mixture is stirred in the ice bath for an additional 15 minutes. The ice bath is then removed, and stirring of the grayish brown solution is continued at room temperature for 1 hour.

In a 3-l. Erlenmeyer flask are placed about 500 g. of crushed ice, 110 ml. (1.3 equivalents) of concentrated hydrochloric acid, and 100 ml. of ether. This mixture is vigorously swirled and shaken while the Grignard reaction mixture is cautiously added in small portions. More ice is added to the

Erlenmeyer flask as required to keep the temperature near 0°. The resulting mixture is poured into a separatory funnel and shaken thoroughly. The water layer is separated and extracted three times with 100 ml. of ether. The combined ether solutions are washed with 100 ml. of saturated sodium bicarbonate solution, and then with 100 ml. of water. The solution is dried over anhydrous magnesium sulfate, and the ether distilled on a water bath. The residue is fractionated at reduced pressure through a modified Claisen flask to yield 54–62 g. (68–78%) (Note 4) of *sec*-butyl 3-methylheptanoate, b.p. 92–93°/9 mm., n_D^{25} 1.4190.

A solution of 40 g. (0.2 mole) of *sec*-butyl 3-methylheptanoate in 100 ml. of ethanol containing 18.5 g. (0.3 mole) of potassium hydroxide and 20 ml. of water is heated under reflux for 30 minutes (Note 7) and (Note 8). The cooled solution is diluted with 200 ml. of water and acidified by the addition of 60 ml. of concentrated hydrochloric acid. The organic acid is extracted with three 100-ml. portions of 1:1 benzene-ether, and the combined benzene-ether extracts are washed with 50 ml. of saturated sodium chloride solution. The resulting solution is filtered by gravity through a bed of anhydrous magnesium sulfate. After removal of solvents by distillation, 26–27 g. (90–94%) of 3-methylheptanoic acid, b.p. 116–117°/10 mm., n_D^{25} 1.4242, is obtained by distillation in a modified Claisen flask (Note 9).

2. Notes

1. Eastman Organic Chemicals practical grade of crotonic acid (containing 10% water) was used by the checkers without further purification.
2. The water separator preferred by the submitter is that described by Wideqvist,[2] but any continuous water separator which will return the benzene to the reaction mixture may be used, e.g., the modified Dean-Stark water separator.[3]
3. By essentially the same procedure the submitter has prepared the following *sec*-butyl esters: *sec*-butyl acrylate, b.p. 127–129°, n_D^{20} 1.4158; *sec*-butyl methacrylate, b.p. 59–62°/34 mm., n_D^{25} 1.4161; *sec*-butyl tiglate, b.p. 84.5°/27 mm., n_D^{25} 1.4332; *sec*-butyl β,β-dimethylacrylate, b.p. 68–70°/13 mm., n_D^{25} 1.4379; *sec*-butyl cinnamate, b.p. 122°/2 mm., n_D^{25} 1.5382. With *sec*-butyl acrylate and methacrylate, 2–3% of hydroquinone should be added to the reaction mixtures and 0.1% of hydroquinone to the esters if stored at room temperature.
4. Recent investigations[4] by the submitter have shown that the yield of *sec*-butyl 3-methylheptanoate is improved to 80–85% if 1.4 g. (1.4 mole% with respect to the Grignard reagent) of cuprous chloride (commercial grade, analytically pure) is added in seven portions during the course of the addition of the ester.
5. Ethyl crotonate may be used with the same yield (70%) of addition product if cuprous chloride is present during the addition[5] (Note 4). Methyl crotonate under these conditions yields methyl α,γ-di-(2-hexyl)-acetoacetate [methyl 2-(2'-hexyl)-3-keto-5-methylonanoate], b.p. 135°/2.5 mm., n_D^{25} 1.4419, in 67% yield.[6]
6. The large excess of Grignard reagent, the dilution of the ester, and the slow addition are essential features of the procedure. If these conditions are not fulfilled the yields drop considerably, and a greater amount of high-boiling residue, di-*sec*-butyl α-(2-hexyl)-β-methylglutarate, b.p. 145°/1.5 mm., n_D^{25} 1.4400, is formed.[6] When the reaction is run on a 0.2-mole scale the addition time of the ester may be reduced to 1.5 hours.
7. In the case of the analogous products obtained by the addition reactions with *sec*-butyl tiglate (Note 9) considerably more drastic conditions are necessary in order to secure complete saponification. The submitter generally employs reflux for 6–8 hours with 35 g. (0.6 mole) of potassium hydroxide dissolved in 250 ml. of 95% ethanol.
8. An alternative procedure is used by the submitter from this point to the final distillation of solvent and ester: The condenser is then set for downward distillation, and about 40 ml. of alcohol is distilled. Then 100 ml. of water is added, and an additional 100 ml. of alcohol and water is distilled. The cooled residue is diluted with 200 ml. of water and the solution freed of insoluble organic material by washing three times with 50 ml. of ether. After acidification with 40 ml. of concentrated hydrochloric acid, the organic layer is extracted with three 50-ml. portions of ether. The combined ether extracts are washed with water and dried over anhydrous magnesium sulfate.
9. The submitter has, by either cuprous chloride-catalyzed or uncatalyzed reactions, prepared a variety of 3-methyl-substituted fatty acids from the adducts of *sec*-butyl crotonate and other Grignard reagents.[4,5,6,7,8,9] The uncatalyzed reaction has also been used with *sec*-butyl tiglate to obtain 2,3-

dimethyl-substituted fatty acids.[7]

3. Discussion

3-Methylheptanoic acid has been prepared by mixed electrolysis of β-methylglutaric acid monomethyl ester and butyric acid, followed by saponification of the methyl ester,[10] and by the malonic ester synthesis from 2-bromohexane.[11] The present method[7] has the advantage of avoiding the use of secondary bromides, which are often difficult to secure entirely pure.[12]

4. Merits of Procedure

The reactions here described are of considerable general utility for the preparation of a variety of fatty acids from the addition products of Grignard reagents and α,β-unsaturated esters.[4,5,6,7,8,9,13]

References and Notes

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

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

hydroquinone (123-31-9)

sodium bicarbonate (144-55-8)

magnesium turnings (7439-95-4)

sodium chloride (7647-14-5)

sodium carbonate (497-19-8)

n-butyl bromide (109-65-9)

potassium hydroxide (1310-58-3)

butyric acid (107-92-6)

cuprous chloride (7758-89-6)

methyl (2229-07-4)

magnesium sulfate (7487-88-9)

crotonic acid (3724-65-0)

ethyl crotonate (623-70-1)

methyl crotonate (623-43-8)

β-methylglutaric acid monomethyl ester

sec-butyl alcohol (78-92-2)

3-Methylheptanoic acid,
Heptanoic acid, 3-methyl- (59614-85-6)

methacrylate

methyl α,γ-di-(2-hexyl)-acetoacetate

2-bromohexane (3377-86-4)

sec-Butyl crotonate (10371-45-6)

sec-butyl 3-methylheptanoate (16253-72-8)

sec-butyl acrylate (2998-08-5)

sec-butyl methacrylate (2998-18-7)

sec-butyl tiglate

sec-butyl β,β-dimethylacrylate

sec-butyl cinnamate

di-sec-butyl α-(2-hexyl)-β-methylglutarate