



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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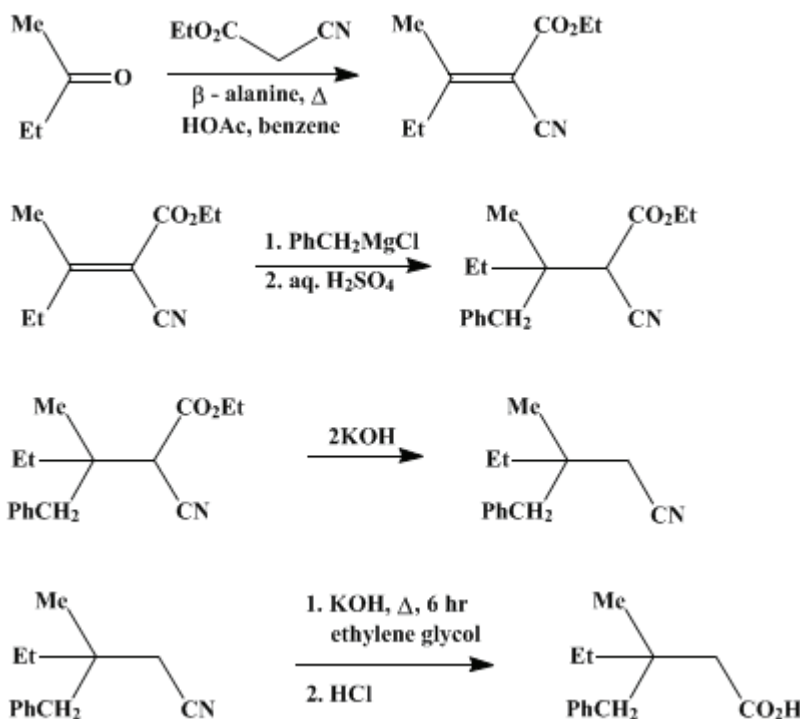
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 4, p.93 (1963); Vol. 35, p.6 (1955).*

### 3-BENZYL-3-METHYLPENTANOIC ACID

#### [Valeric acid, 3-benzyl-3-methyl-]



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#### 1. Procedure

A. *Ethyl sec-butyldenecyanoacetate*. In a 1-l. round-bottomed flask fitted with a 24/40 joint are placed 0.45 g. of  $\beta$ -alanine, 113 g. (106 ml., 1.0 mole) of ethyl cyanoacetate (Note 1), 87 g. (108 ml., 1.2 moles) of butanone, 20 ml. of glacial acetic acid, and 100 ml. of benzene. A Barrett-type water separator (Note 2) and a condenser are attached to the flask, and the mixture is heated briskly under reflux until water ceases to be collected in the trap (7–12 hours).

The reaction mixture is decanted into a 500-ml. round-bottomed flask which is attached to a fractionating column (Note 3). The solvent is removed at atmospheric pressure while the oil bath is heated finally at 160°. The residue is distilled at reduced pressure to furnish four fractions: (a) acetic acid and other materials boiling below 95°/16 mm.; (b) ethyl cyanoacetate, b.p. 95–110°/16 mm.; (c) intermediate, b.p. 110–124°/16 mm.; and (d) ethyl sec-butyldenecyanoacetate, b.p. 124–126°/16 mm.,  $n_D^{25}$  1.4640–1.4648. Fraction d amounts to 117–122 g., and refractionation of fraction c yields an additional 18–24 g.; total yield, 135–146 g. (81–87.5%) (Note 4).

B. *Ethyl 3-benzyl-2-cyano-3-methylpentanoate*. A 2-l. three-necked round-bottomed flask, fitted with a tantalum wire Hershberg stirrer, a condenser, and a separatory funnel, is arranged for use of a nitrogen atmosphere.<sup>2</sup> Magnesium (19.2 g., 0.79 g. atom) and 100 ml. of dry ether<sup>3</sup> are placed in the flask, and a solution of 100 g. (91 ml., 0.79 mole) of benzyl chloride in 500 ml. of dry ether is added in a period of 1.5–2.0 hours, with stirring, while the mixture boils spontaneously. The mixture is boiled for 15 minutes after completion of the addition, then a solution of 110 g. (0.66 mole) of ethyl sec-butyldenecyanoacetate in 130 ml. of benzene is added over a 30-minute period with spontaneous reflux. The reaction mixture is stirred and heated under reflux for an additional hour. A precipitate separates after about 30 minutes.

The reaction mixture is poured onto about 400 g. of cracked ice and is made acidic with 20% [sulfuric acid](#). After two clear phases have formed the mixture is poured into a separatory funnel, and the lower layer is removed. This aqueous layer is extracted with two 100-ml. portions of [benzene](#) and discarded. The three organic extracts are washed separately and successively with 125 ml. of water and 125 ml. of saturated [sodium chloride](#) solution, then filtered successively through a layer of anhydrous [sodium sulfate](#).

The combined extract (about 1 l.) is flash-distilled at atmospheric pressure from a 250-ml. Claisen flask. After the solvent and a small amount of fore-run (ca. 15 g., b.p. 45°/3 mm.) have been removed, the product is distilled to yield 157–162 g. (92–95%), b.p. 150–162°/3 mm. (bath temperature, 180–190°),  $n_D^{25}$  1.5053–1.5063 ([Note 5](#)), ([Note 6](#)), and ([Note 7](#)).

C. *3-Benzyl-3-methylpentanenitrile*. Sixty-seven grams (1 mole) of [potassium hydroxide](#) (85%) is dissolved by heating in 360 ml. of [ethylene glycol](#) and is added to a 1-l. round-bottomed flask containing 155 g. (0.6 mole) of [ethyl 3-benzyl-2-cyano-3-methylpentanoate](#) (above). A condenser is attached with a rubber stopper, and the mixture is heated under gentle reflux for 3 hours ([Note 8](#)). The resulting two-phase mixture is cooled, diluted with 350 ml. of water, and extracted with three portions of ether (250 ml., 100 ml., 100 ml.). The three extracts are washed successively with 100 ml. of water and 100 ml. of saturated [sodium chloride](#) solution, then filtered through a layer of anhydrous [sodium sulfate](#) ([Note 9](#)). The combined extracts are flash-distilled at atmospheric pressure from a 250-ml. Claisen flask to remove the [ether](#). The residue is distilled at reduced pressure to furnish 102–105 g. (91–93%) of nitrile, b.p. 150–160°/11 mm. (bath temperature, 190–200°),  $n_D^{25}$  1.5111–1.5128 ([Note 10](#)) and ([Note 11](#)).

D. *3-Benzyl-3-methylpentanoic acid*. A solution of 112 g. (1.6 moles) of [potassium hydroxide](#) (85%) in 400 ml. of [ethylene glycol](#) is added to 93.6 g. (0.5 mole) of *3-benzyl-3-methylpentanenitrile* in a 1-l. round-bottomed copper or stainless-steel flask. A condenser with a rubber stopper is attached, and the solution is heated under brisk reflux for 6 hours ([Note 12](#)). The reaction mixture is cooled, diluted with 400 ml. of water, and extracted with three portions of ether (250 ml., 100 ml., 100 ml.). The [ether](#) extracts are washed successively with two 75-ml. portions of water and then discarded ([Note 13](#)).

The combined aqueous phases are acidified to Congo red with 200 ml. of concentrated [hydrochloric acid](#) and extracted with three portions of [benzene](#) (200 ml., 75 ml., 75 ml.). The [benzene](#) extracts are washed successively with 100 ml. of water and 100 ml. of saturated [sodium chloride](#) solution, then filtered through anhydrous [sodium sulfate](#). The combined extract is flash-distilled from a 250-ml. Claisen flask at atmospheric pressure (bath temperature, up to 160°). The residue is distilled at reduced pressure to give 94–96 g. (91–93%) of acid; b.p. 173–177°/7 mm. (bath temperature, 207–220°),  $n_D^{25}$  1.5160–1.5163 ([Note 14](#)) and ([Note 15](#)).

## 2. Notes

1. [Ethyl cyanoacetate](#) was obtained from Kay-Fries Chemicals, 180 Madison Avenue, New York, New York.
2. The submitters used a Barrett Distilling Receiver, Corning No. 3622, Corning Glass Works, Corning, New York.
3. The submitters used a 60-cm. heated Vigreux column to effect this fractionation. The checkers used a similar column with partial take-off head.
4. Fractions *b–d* consist entirely of [ethyl cyanoacetate](#) and the product. Pure [ethyl cyanoacetate](#) and [ethyl sec-butylidene cyanoacetate](#) have  $n_D^{25}$  1.4151 and 1.4650, respectively. The purity of fractions *b–d* can be estimated by their indexes of refraction, which are proportional to the weight per cent.
5. The pure product obtained by fractional distillation has  $n_D^{25}$  1.5052. The product obtained by distillation from a Claisen flask is contaminated mainly with [bibenzyl](#), b.p. 122–125°/3 mm., f.p. 44°. The purity of the product can be estimated by determination of the saponification equivalent in [ethanol](#).
6. The use of [dibenzylcadmium](#) gave no improvement in yield.
7. [Phenylmagnesium bromide](#) gives a 79% yield of product, b.p. 178–180°/11 mm.,  $n_D^{25}$  1.5063; and [n-propylmagnesium bromide](#) gives 33–42% yields, b.p. 150–153°/22 mm.,  $n_D^{25}$  1.4429, of alkylation product when essentially the same procedure is used. The yield obtained with [n-propylmagnesium bromide](#) depends upon the efficiency of separation from the reduction product, [ethyl sec-](#)

butylcyanoacetate, b.p. 126°/22 mm.,  $n_D$  1.4277.<sup>4</sup>

8. After 30 minutes of reflux the second phase begins to separate. The formation of this nitrile layer is probably complete after 2.5–3.0 hours. A small amount of solid, presumably ammonium carbonate, collects in the condenser during the heating.

9. When the combined aqueous washes from three runs were acidified, extracted, and distilled, there was obtained 1.8 g. of 3-benzyl-3-methylpentanoic acid,  $n_D^{25}$  1.5158.

10. This nitrile is contaminated with some lower-boiling bibenzyl and some higher-boiling amide. The pure nitrile, obtained by fractional distillation, has  $n_D^{25}$  1.5110.

11. Hydrolyses of ethyl 2-cyano-3-methyl-3-phenylpentanoate and ethyl 2-cyano-3-ethyl-3-methylhexanoate (Note 7) by essentially this procedure gave 71% (b.p. 149–151°/16 mm.,  $n_D^{25}$  1.5149) and 68% (b.p. 103–104°/31 mm.,  $n_D^{25}$  1.4291) yields of nitriles, respectively. In the second case, about 12% additional yield of nitrile could be obtained from the acidic fraction, which contains some undecarboxylated product, 2-cyano-3-ethyl-3-methylhexanoic acid.

12. The two-phase solution becomes homogeneous after 1.5–2.0 hours of boiling. This alkaline solution is very corrosive, and a glass flask can be used only a few times in this reaction. A stainless-steel or copper flask is preferable.

13. If emulsions are encountered, the addition of a few milliliters of saturated aqueous sodium chloride clears them readily. The combined ether extracts contain 4–5 g. of solid, neutral material. This product is mainly bibenzyl, b.p. 138–143°/7 mm., f.p. 40°.

14. The best sample of this acid obtained by fractional distillation had  $n_D^{25}$  1.5160; neut. equiv., 207.3 (calcd., 206.3).

15. Hydrolyses of 3-methyl-3-phenylpentanenitrile and 3-ethyl-3-methylhexanenitrile (Note 11) by the described procedure gave 88% and 95% yields of 3-methyl-3-phenylpentanoic acid (b.p. 190–194°/26 mm.,  $n_D^{25}$  1.5182) and 3-ethyl-3-methylhexanoic acid (b.p. 136–137°/15 mm.,  $n_D^{25}$  1.4377), respectively.

### 3. Discussion

Ethyl *sec*-butylidenecyanoacetate has been prepared by this condensation using various amino acids,<sup>5</sup> ammonium acetate,<sup>6</sup> sodium sulfate-piperidine,<sup>7</sup> and zinc chloride-aniline.<sup>8</sup>

The ethyl 3-benzyl-2-cyano-3-methylpentanoate, 3-benzyl-3-methylpentanenitrile, and 3-benzyl-3-methylpentanoic acid preparations follow the procedure given by Prout, Huang, Hartman, and Korpics.<sup>9</sup>

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### References and Notes

1. De Paul University, Chicago 14, Illinois.
2. Cason and Rapoport, *Laboratory Text in Organic Chemistry*, 2nd ed., p. 452, Prentice-Hall, Englewood Cliffs, New Jersey, 1962; *Org. Syntheses Coll. Vol. 3*, 601 (1955).
3. Cason and Rapoport, *Laboratory Text in Organic Chemistry*, 2nd ed., p. 460, Prentice-Hall, Englewood Cliffs, New Jersey, 1962.
4. Prout, *J. Am. Chem. Soc.*, **74**, 5915 (1952).
5. Prout, *J. Org. Chem.*, **18**, 928 (1953).
6. Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).
7. Cowan and Vogel, *J. Chem. Soc.*, **1940**, 1528.
8. Scheiber and Meisel, *Ber.*, **48**, 259 (1915).
9. Prout, Huang, Hartman, and Korpics, *J. Am. Chem. Soc.*, **76**, 1911 (1954).

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### Appendix

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

sodium sulfate-piperidine

zinc chloride-aniline

ethanol (64-17-5)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonium carbonate (506-87-6)

Benzene (71-43-2)

ether (60-29-7)

ammonium acetate (631-61-8)

magnesium (7439-95-4)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

benzyl chloride (100-44-7)

ethylene glycol (107-21-1)

Ethyl cyanoacetate (105-56-6)

Phenylmagnesium bromide (100-58-3)

$\beta$ -Alanine (107-95-9)

butanone (78-93-3)

bibenzyl (103-29-7)

3-Benzyl-3-methylpentanoic acid,  
Valeric acid, 3-benzyl-3-methyl- (53663-16-4)

Ethyl 3-benzyl-2-cyano-3-methylpentanoate (70289-04-2)

3-Benzyl-3-methylpentanenitrile

dibenzylcadmium

ethyl 2-cyano-3-methyl-3-phenylpentanoate

ethyl 2-cyano-3-ethyl-3-methylhexanoate (70289-02-0)

2-cyano-3-ethyl-3-methylhexanoic acid

3-methyl-3-phenylpentanenitrile (50843-73-7)

3-ethyl-3-methylhexanenitrile (138808-09-0)

3-methyl-3-phenylpentanoic acid

3-ethyl-3-methylhexanoic acid

ethyl 3-benzyl-2-cyano-3-methylpentanoate, 3-benzyl-3-methylpentanenitrile

n-propylmagnesium bromide

Ethyl sec-butylidenecyanoacetate (868-47-3)

ethyl sec-butylcyanoacetate