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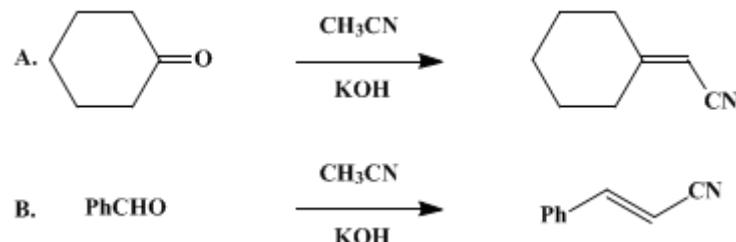
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SYNTHESIS OF α,β -UNSATURATED NITRILES FROM ACETONITRILE: CYCLOHEXYLIDENEACETONITRILE AND CINNAMONITRILE

[Acetonitrile, cyclohexylidene- and 2-propenenitrile, 3-phenyl, (E)- and (Z)-]



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1. Procedure

A. *Cyclohexylideneacetonitrile*. A 1-L three-necked, round-bottomed flask equipped with a reflux condenser, mechanical stirrer, and addition funnel is charged with potassium hydroxide (85% pellets, 33.0 g, 0.5 mol, (Note 1)) and acetonitrile (250 mL, (Note 2) and (Note 3)). The mixture is brought to reflux and a solution of cyclohexanone (49 g, 0.5 mol, (Note 4)) in acetonitrile (100 mL) is added over a period of 0.5–1.0 hr. Heating at reflux is continued for 2 hr (Note 5) after the addition is complete and the hot solution is then poured onto cracked ice (600 g). The resulting binary mixture is separated and the aqueous phase is extracted with ether (3×200 mL). The combined organic extracts are evaporated under reduced pressure, or may be placed in a 2-L Erlenmeyer flask containing several boiling chips and the volume reduced on a steam bath (internal temperature ca. 50°C). The resulting sweet-smelling, yellow to yellow-orange oil is transferred to a 1- or 2-L, three-necked, round-bottomed flask (depending on whether internal or external steam generation is used) and steam distilled (bp 81–99°C, (Note 6)). The distillate is extracted with three to five 200-mL portions of ether until the aqueous phase is clear (Note 7). The ether phase is washed with brine (2×100 mL), dried over sodium sulfate, and evaporated under reduced pressure to give a pale yellow oil (29–36 g, (48–60%)) that consists of a mixture of isomers (α,β 80–83%, (β,γ 17–20%, (Note 8)).

Isolation of the pure α,β -isomer. A 250-mL Erlenmeyer flask equipped with a magnetic stirring bar is charged with the isomeric nitriles (20 g, 0.165 mol), prepared in Section A above, and carbon tetrachloride (20 mL). A solution of bromine in carbon tetrachloride (1/9, v/v, ca. 25–30 mL) is added dropwise until the color of excess bromine persists. The reaction vessel is cooled in an ice bath for 30 min and filtered by gravity and the solvent evaporated under reduced pressure. The crude oil is distilled at reduced pressure (bp 40–42°C/0.15 mm) to give a colorless liquid (11–15 g, 55–75%) that is the pure α,β -isomer (Note 9) and (Note 10).

B. *Preparation of E- and Z-Cinnamonnitrile*. A 1-L, three-necked, round-bottomed flask equipped with a mechanical stirrer, reflux condenser, and addition funnel is charged with potassium hydroxide pellets (33 g, 0.5 mol, (Note 1)) and acetonitrile (400 mL, (Note 2)). The mixture is brought to reflux under nitrogen and a solution of benzaldehyde (53 g, 0.5 mol, (Note 4)) in acetonitrile (100 mL) is added in a stream (1–2 min). After addition, stirring is continued for 10 min (Note 5) and the hot solution is then poured onto 500 g of cracked ice in a 1-L beaker. After being cooled for a few minutes, the two-phase mixture is transferred to a 2-L, three-necked flask and steam-distilled (Note 11). The distillate is transferred to a separatory funnel, and the upper aqueous phase is separated and then extracted with two 500-mL portions of ether (Note 7). The combined organic material is dried briefly over Na_2SO_4 and the ether evaporated to yield pure cinnamonnitrile (20–29 g, 31–45%) as a pale-yellow oil (E/Z ratio ca. 5.5; (Note 12)).

2. Notes

1. Potassium hydroxide (85% pellets, AR grade) should be as fresh as possible (see (Note 5)).
2. Acetonitrile (99%) was obtained from Aldrich Chemical Company, Inc. and may be used without purification.
3. The yield of product is dependent on concentration. An increase in the amount of acetonitrile in Step A to ca. 1000 mL increases the yield of the isomer mixture to 65–75% without affecting isomer distribution. Further dilution to ca. 5000 mL increases the yield to 80–85%.
4. Cyclohexanone and benzaldehyde were purchased from either Aldrich Chemical Company, Inc. or Eastman Organic Chemicals and used without additional purification.
5. The reaction time depends on the quality of the potassium hydroxide employed. An induction period is often observed when older potassium hydroxide samples are used, possibly because surface formation of carbonates reduces the solubility of the salt in acetonitrile. An attempt was made to monitor the cinnamononitrile reaction by GLC, following loss of starting material. Although formation of the product was observed and reached a maximum, the starting material peak never completely disappeared. Prolonged reaction times (>2 hr) resulted in failure to isolate any of the desired product. Reaction times of less than 30 min gave the expected yields. Undissolved potassium hydroxide was observed in the reaction vessel when these reactions were terminated. At a column temperature of 150°C and a gas flow rate of ca. 60 mL/min (5-ft × 0.25-in. column, 10% SE-30 on firebrick), the retention times are as follows: cyclohexylideneacetonitrile and isomer, 2.8 min; Z-cinnamononitrile, 3.0 min; E-cinnamononitrile, 3.7 min). The reaction may also be monitored by a 2,4-dinitrophenylhydrazone spot test.
6. Distillation may be conducted using an apparatus designed for either internal or external steam generation. The first 1000-mL portion of distillate contains ca. 35 g of product. An additional 500 mL of distillate yields less than 1 g. Vacuum distillation gave product in 22% yield.
7. To facilitate phase separation, solid sodium chloride was added to the aqueous layer.
8. The product thus obtained is of high purity. The trace of color may be removed by distillation at reduced pressure (bp 50°C/0.5 mm).
9. Bromination can be monitored by ^1H NMR in CCl_4 . The vinyl protons are observed at 5.08 (α,β -isomer) and 5.65 ppm.
10. The ^1H NMR spectra (in CCl_4) for the two isomers are as follows. Cyclohexylideneacetonitrile: δ 1.25–2.0 (m, 6 H), 2.0–2.8 (m, 4 H, methylene protons), 5.08 (m, 1 H, olefin); 2-(1-cyclohexenyl) acetonitrile: 1.25–2.0 (m, 4 H), 2.0–2.8 [m, 4 H, -(CH_2)₄], 3.05 (pseudo-s, 2 H, - CH_2CN), 5.65 (m, 1 H, olefin).
11. Steam distillation may be conducted using apparatus designed either for internal or external steam generation. Using internally generated steam, 2.5 L of distillate was collected. The last 500 mL contained less than 1 g of product.
12. Isomer distribution and purity were assessed by GLC (see (Note 5)). The ^1H NMR spectra (in CCl_4) for the pure isomers are as follows: E-isomer: δ 5.71 [d, 1 H, J = 17, ArCH=CH-CN; 7.44 (d, 1 H, J = 17, ArCH=CHCN), 7.3 (pseudo-s, 5 H, aromatic protons). Z-Isomer: δ 5.31 (d, 1 H, J = 12, ArCH=CHCN), 6.98 (d, 1 H, J = 12, ArCH=CHCN), 7.3 (pseudo-s, 5 H, aromatic protons).

3. Discussion

Introduction of the two-carbon fragment is a cornerstone of synthetic methodology and many of the condensation reactions frequently used have been known for decades, if not for a century. Examples include the malonic ester² and acetoacetic ester³ reactions, the Perkin⁴ condensation, and the Doeblner-Knoevenagel⁵ reaction. Addition of the cyanomethyl group has been accomplished by a variety of methods,⁶ mostly circuitous, and is certainly not in the group of classical reactions named above. The direct approach is found in a recent application of lithio trimethylsilylacetonitrile,⁷ but the difference in expense and convenience between using this method and a mixture of potassium hydroxide and acetonitrile is manifest.

The direct synthesis of α,β -unsaturated nitriles can be accomplished by treating the appropriate carbonyl compound with potassium hydroxide in acetonitrile.⁸ In order for direct condensation to succeed, acetonitrile must be deprotonated by the relatively weak base potassium hydroxide and the carbanion thus formed must add to the carbonyl. The cyanohydrin is presumably dehydrated to leave the

α,β -unsaturated compound, which may or may not isomerize in the medium. We have run this reaction with a large number of carbonyl compounds⁸ and have found that it is most successful for aromatic aldehydes (36–86%) and other nonenolizable carbonyl compounds such as **benzophenone** (84%). Yields are also acceptable for most cyclic ketones with six or more carbons in the ring (e.g., **2-methylcyclohexanone**, 78%; **cis-octalane**, 80%; **cycloheptanone**, 78%; **cyclooctanone**, 66%, **cyclododecanone**, 45%), and for aliphatic ketones having three or more carbons bonded on each side (e.g., **diethyl ketone**, 35%; **di-n-propyl ketone**, 65%, **di-n-butyl ketone** 65%). Ketones that are sterically hindered (**camphor**) or highly enolized (**cyclopentanone**) are not useful substrates in this reaction.

We present here examples of this condensation with an aromatic aldehyde and a cyclic ketone. Both of these examples are useful because, although other methods are available for their preparation, problems often attend these syntheses. In the synthesis of **cyclohexylideneacetonitrile**, for example, the standard method⁹ results exclusively in the β,γ -isomer and none of the α,β -isomer. In Part A of this procedure, **cyclohexanone** is condensed with **acetonitrile** to give predominantly the conjugated isomer (80–83%), which is then separated from the nonconjugated isomer by selective bromination.

The procedures presented here are simple, inexpensive, and may be used on a large scale. The use of **potassium hydroxide** in this reaction may, however, prove incompatible with certain base-sensitive functional groups.

References and Notes

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

brine

E- and Z-Cinnamonnitrile
2,4-dinitrophenylhydrazone
cis-octalone
2-propenenitrile, 3-phenyl, (E)- and (Z)-
ether (60-29-7)
acetonitrile (75-05-8)
Cyclohexanone (108-94-1)
sodium chloride (7647-14-5)
bromine (7726-95-6)
sodium sulfate,
 Na_2SO_4 (7757-82-6)
carbon tetrachloride (56-23-5)
nitrogen (7727-37-9)
benzaldehyde (100-52-7)
potassium hydroxide,
potassium hydroxide pellets (1310-58-3)
Benzophenone (119-61-9)
Cyclopentanone (120-92-3)
camphor (21368-68-3)
diethyl ketone (96-22-0)
2-methylcyclohexanone (583-60-8)
Cycloheptanone (502-42-1)
di-n-propyl ketone (123-19-3)
Cyclooctanone (502-49-8)
cyclododecanone (830-13-7)
Cinnamonnitrile (4360-47-8)
di-n-butyl ketone (502-56-7)

Cyclohexylideneacetonitrile,
Acetonitrile, cyclohexylidene- (4435-18-1)

Z-Cinnamonitrile

lithio trimethylsilylacetonitrile

E-cinnamonitrile (4360-47-8)

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