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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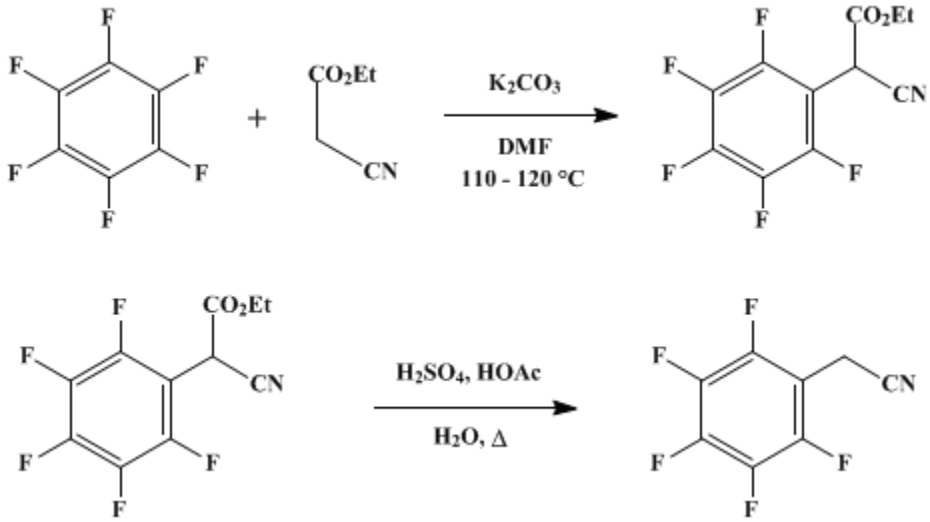
(PENTAFLUOROPHENYL)ACETONITRILE

[Benzeneacetonitrile, 2,3,4,5,6-pentafluoro-]



Submitted by Robert Filler[1] and Sarah M. Woods[2].
Checked by Andrew E. Feiring and William A. Sheppard.

1. Procedure

A. *Ethyl cyano(pentafluorophenyl)acetate*. A 2-l., four-necked flask equipped with mechanical stirrer, addition funnel, thermometer, and condenser is charged with 650 ml. of *N,N*-dimethylformamide (Note 1) and 140 g. (1.01 mole) of anhydrous potassium carbonate. The rapidly stirred mixture is heated to 152–154° and 113 g. (1.00 mole) of ethyl cyanoacetate is added dropwise over 10–15 minutes without further heating. The temperature of the mixture is allowed to drop to 110–120° and maintained within this range while 186 g. (1.00 mole) of hexafluorobenzene (Note 2) is added dropwise over 1 hour. The dark mixture is stirred for 3 hours after the addition is complete, poured into 3 l. of ice water contained in a 5-l. Erlenmeyer flask, and acidified *(Caution! Foaming)* with 20% sulfuric acid. After being cooled overnight in the refrigerator, the top, aqueous layer is decanted from a lower viscous organic layer. The organic layer is dissolved in 600 ml. of diethyl ether, washed with water, and aqueous 10% sodium hydrogen carbonate, and dried over anhydrous magnesium sulfate. The ether is removed on a rotary evaporator, affording 217 g. (78%) of dark oil which crystallizes on standing (Note 3). An analytical sample is prepared by dissolving 2 g. of the crude material in 5 ml. of boiling 95% ethanol. Hexane is added until mixture becomes turbid. Crystallization occurs when the mixture is cooled with vigorous stirring in an acetone–dry ice bath. The solid is quickly collected on a Büchner funnel and transferred to a sublimator. Sublimation at 30° (0.5–1.0 mm.) affords white crystals, m.p. 38–38.5°, of analytically pure ethyl cyano(pentafluorophenyl)acetate (Note 4).

B. *(Pentafluorophenyl)acetonitrile*. A 1-l., one-necked flask equipped with magnetic stirrer and a reflux condenser is charged with 139.5 g. (0.500 mole) of crude ethyl cyano(pentafluorophenyl)acetate, 350 ml. of aqueous 50% acetic acid, and 12.5 ml. of concentrated sulfuric acid. The mixture is heated at reflux for 15 hours. After cooling to room temperature, the mixture is diluted with an equal volume of water and cooled in an ice bath for 1 hour. The top layer is decanted from a dark organic layer which settles to the bottom of the flask. The organic phase is dissolved in 200 ml. of ether and washed with water and aqueous 10% sodium hydrogen carbonate. After being dried over anhydrous magnesium sulfate, the ether is removed on a rotary evaporator. The residue is distilled through a 25-cm. jacketed Vigreux column, affording 74–78 g. (71–75%) of (pentafluorophenyl)acetonitrile as a colorless liquid, b.p. 105° (8 mm.), n_D^{25} 1.4370 (Note 5).

2. Notes

1. Technical grade *N,N*-dimethylformamide was stirred over anhydrous cupric sulfate, filtered, and distilled under reduced pressure. The submitters used reagent grade *N,N*-dimethylformamide without purification.
2. Hexafluorobenzene was purchased from PCR, Inc., Gainesville, Florida, and distilled (b.p. 80–81°) before use.
3. In one run the checkers obtained only 135 g. of crude product by this procedure. The aqueous solution which was decanted from the crude product was divided into three portions and each portion was extracted with one 250-ml. portion of ether. The combined ether extracts were washed with water and aqueous 10% sodium hydrogen carbonate, dried over anhydrous magnesium sulfate, and concentrated on the rotary evaporator, affording an additional 83 g. of crude product, for a total of 218 g.
4. ^{1}H NMR (CCl_4), δ (multiplicity, number of protons): 1.38 (t, 3H) 4.35 (q, 2H), 5.05 (s, 1H); IR ($CHCl_3$) cm.$^{-1}$: 3003, 2933, 2257, 1760, 1661, 1527, 1513; ^{19}F NMR (CCl_4, $CFCl_3$ internal standard): δ 141.2 (sym. m, 2 *ortho* F), 151.8 (t of t, $J_{1,2}$ = 20.3 Hz., $J_{1,3}$ = 2.5 Hz., *para* F), 161.1 (m, 2 *meta* F). The pKa in dimethyl sulfoxide is 5.06 ± 0.02.[3]
5. ^{1}H NMR (CCl_4), δ: 3.75 (s, with fine structure); IR (neat) cm.$^{-1}$: 2985, 2273, 1667, 1527, 1515; ^{19}F NMR (CCl_4, $CFCl_3$ internal standard), δ 142.4 (sym. m, 2 *ortho* F), 153.8 (t, with fine structure, J = 20 Hz., *para* F), 161.7 (m, 2 *meta* F). The pKa in dimethyl sulfoxide is 15.8 ± 0.3.[3]

3. Discussion

The formation of ethyl cyano(pentafluorophenyl)acetate illustrates the *intermolecular* nucleophilic displacement of fluoride ion from an aromatic ring by a stabilized carbanion. The reaction proceeds readily as a result of the activation imparted by the electron-withdrawing fluorine atoms.[4] The selective hydrolysis of a cyano ester to a nitrile has been described.[5] (Pentafluorophenyl)acetonitrile[6] has also been prepared by cyanide displacement on (pentafluorophenyl)methyl halides. However, this direct displacement is always accompanied by an undesirable side reaction, yielding 15–20% of 2,3-bis(pentafluorophenyl)propionitrile. The reaction of one equivalent of hexafluorobenzene with one equivalent of lithioacetonitrile (prepared from acetonitrile and *n*-butyllithium) provides a low yield (7–10%) of (pentafluorophenyl)acetonitrile and about a 22% yield of bis(pentafluorophenyl)acetonitrile (m.p. 65°; the pKa in dimethyl sulfoxide is 7.95 ± 0.04[3]). The yield of the latter compound can be increased by use of excess lithioacetonitrile.[7]

(Pentafluorophenyl)acetonitrile is a useful intermediate to 4,5,6,7-tetrafluoroindole.[8] The nitrile is readily converted to 2-(pentafluorophenyl)ethylamine hydrochloride in 80% yield by catalytic hydrogenation in dilute hydrochloric acid. Although the salt is stable, the amine undergoes a facile intermolecular nucleophilic aromatic substitution reaction, even at room temperature. However, freshly distilled 2-(pentafluorophenyl)ethylamine is converted by heating in the presence of anhydrous potassium fluoride in *N,N*-dimethylformamide to 4,5,6,7-tetrafluoroindoline (62% yield) by intramolecular nucleophilic displacement of fluoride ion.[9] The indoline is aromatized by treatment with activated manganese dioxide,[10] giving 4,5,6,7-tetrafluoroindole (82% yield). The anion of (pentafluorophenyl)acetonitrile is converted to bis(pentafluorophenyl)acetonitrile on treatment with hexafluorobenzene (*vide supra*).[11]

References and Notes

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

ethanol (64-17-5)

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ether,
diethyl ether (60-29-7)

acetonitrile (75-05-8)

sodium hydrogen carbonate (144-55-8)

cupric sulfate (7758-98-7)

manganese dioxide (1313-13-9)

Ethyl cyanoacetate (105-56-6)

magnesium sulfate (7487-88-9)

n-butyllithium (109-72-8)

potassium fluoride (7789-23-3)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

dimethyl sulfoxide (67-68-5)

Fluorine (7782-41-4)

(Pentafluorophenyl)acetonitrile,

Benzeneacetonitrile, 2,3,4,5,6-pentafluoro- (653-30-5)

hexafluorobenzene (392-56-3)

Ethyl cyano(pentafluorophenyl)acetate (2340-87-6)

octafluorotoluene (434-64-0)

2,3-bis(pentafluorophenyl)propionitrile

lithioacetonitrile

bis(pentafluorophenyl)acetonitrile

4,5,6,7-tetrafluoroindole (16264-67-8)

2-(pentafluorophenyl)ethylamine hydrochloride

2-(pentafluorophenyl)ethylamine

4,5,6,7-tetrafluoroindoline