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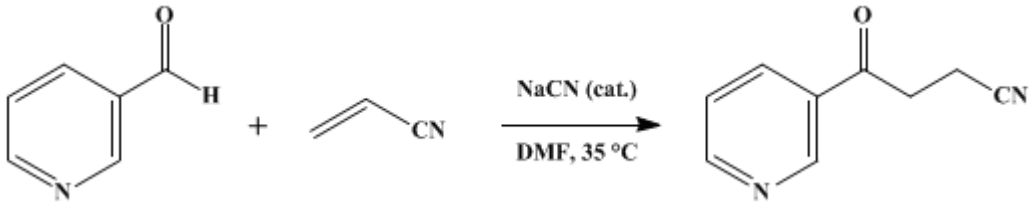
CYANIDE-CATALYZED CONJUGATE ADDITION OF ARYL ALDEHYDES: 4-OXO-4-(3-PYRIDYL)BUTYRONITRILE

[3-Pyridinebutanenitrile, γ-oxo]



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Checked by Benjamin G. Padilla and George Büchi.

1. Procedure

Caution! Sodium cyanide is highly toxic. Care should be taken to avoid direct contact of the chemical or its solutions with the skin, and impervious gloves should be worn to handle the reagent.

A 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, a reflux condenser fitted with a potassium hydroxide drying tube, and a pressure-equalizing dropping funnel mounted with a nitrogen-inlet tube is charged with 4.9 g. (0.18 mole) of finely ground sodium cyanide (Note 1) and 500 ml. of dry *N,N*-dimethylformamide (Note 2). The flask is immersed in a water bath kept at 35°, stirring is begun, and the apparatus is purged thoroughly with dry nitrogen (Note 3). After 15 minutes 107.1 g. (1.001 mole) of 3-pyridinecarboxaldehyde (Note 4) is added dropwise over a period of 30 minutes. The dark brown solution is stirred for another 30 minutes (Note 5), after which 39.8 g. (0.751 mole) of freshly distilled acrylonitrile is added over 1 hour. The solution, now red-orange in color and quite viscous (Note 6), is stirred for 3 hours, 6.6 g. (0.11 mole) of acetic acid is added, and stirring is continued for 5 additional minutes. The solvent is removed with a rotary evaporator, the residue is dissolved in 500 ml. of water, and the solution is extracted continuously (Note 7) with 500 ml. of chloroform for 12 hours (Note 8). The solvent is evaporated under reduced pressure, and the residual liquid is distilled under reduced pressure through a short-path distillation apparatus. An initial fraction, consisting mainly of 3-pyridinecarboxaldehyde, collects in the cold trap. The product, b.p. 150–152° (0.1 mm.), solidifies in the condenser and is freed by heating the water in the cooling jacket to nearly 100°, yielding 94–101 g. (78–84%) of the light yellow, solid distillate. Recrystallization from 400 ml. of 2-propanol gives 77–82 g. (64–68% based on acrylonitrile) of 4-oxo-4-(3-pyridyl)butyronitrile as yellow-tinged, white crystals, m.p. 70–72° (Note 9).

2. Notes

1. Analytical grade (*pro analysi*) sodium cyanide, purchased by the submitters from Merck, Darmstadt, Germany, was dried for 24 hours in a vacuum desiccator containing potassium hydroxide pellets. The checkers obtained sodium cyanide from Fisher Scientific Company and dried the reagent in the same manner.
2. The submitters purified technical grade *N,N*-dimethylformamide by distillation from powdered calcium hydride. The checkers used *N,N*-dimethylformamide that had been dried over Linde type 4A molecular sieves. A small amount of dimethylamine in the solvent does not interfere with the reaction.
3. The drying tube was connected to a Nujol bubbler. A nitrogen atmosphere was maintained during the reaction by passing nitrogen through the apparatus at a rate of *ca.* one bubble per second.
4. 3-Pyridinecarboxyaldehyde (nicotinaldehyde) was supplied by Aldrich-Europe, Beerse, Belgium. The checkers purified this reagent by fractional distillation, b.p. 95–97° (15 mm.). The submitters stress that 3-pyridinecarboxaldehyde should be completely free from contamination by the acid. They stirred 150

g. of the aldehyde with 100 g. of potassium carbonate and 300 ml. of ethanol for 12 hours, filtered the suspended solid, and fractionally distilled the filtrate through a 30-cm. Vigreux column, using a water aspirator. However, the checkers found that the recovery of aldehyde from this procedure was very low, and recommend vacuum distillation instead. 3-Pyridinecarboxaldehyde is a powerful skin irritant and should be handled with protective gloves.

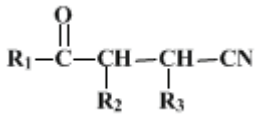
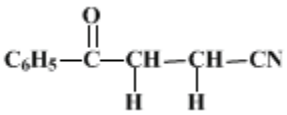
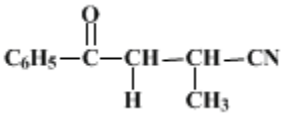
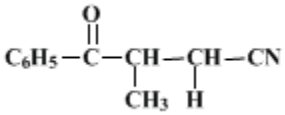
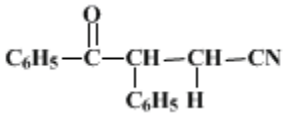
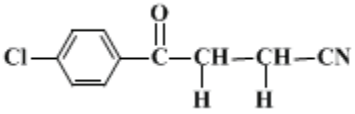
5. The solution, in which some sodium cyanide remains suspended, becomes quite thick at this stage owing to formation of the benzoin-type dimer of 3-pyridinecarboxaldehyde. An adequate amount of *N,N*-dimethylformamide should be used as solvent to ensure that the dimer does not crystallize.

6. Although the solution becomes very viscous at this point, stirring is still possible and should be continued.

7. Continuous extraction is only necessary if the product is appreciably soluble in water. Products such as those shown in Table I may be isolated by extraction in a separatory funnel.

TABLE I

γ-KETONITRILES PREPARED BY CYANIDE-CATALYZED CONJUGATE ADDITION OF ARYL ALDEHYDES TO α,β-UNSATURATED NITRILES

	Distilled Yield (%)[a]	Recrystallized Yield (%)[b]	B.p.(°) (pressure, mm.)	M.p. (°)
$R_1 = C_6H_5$, $R_2 = R_3 = H$				
	71	50[c]	131–134 (0.2)	72–73
$R_1 = C_6H_5$, $R_2 = H$, $R_3 = CH_3$				
	73–76	34–37[d]	113–115 (0.1)	42–43
$R_1 = C_6H_5$, $R_2 = CH_3$, $R_3 = H$				
	62–64	45–47[d]	111–113 (0.15)	58–59
$R_1 = R_2 = C_6H_5$, $R_3 = H$				
	83	56[e]	157–159 (0.05)	83–84
$R_1 = 4\text{-}ClC_6H_4$, $R_2 = R_3 = H$				
	88–89	71–72[c]	152–154 (0.1)	70–71

[a]The distilled products were almost pure.

[b]The recrystallized products were pure, but considerable losses were entailed.

[c]Recrystallized from aqueous ethanol (decolorized with activated carbon).

[d]Recrystallized from ethyl acetate–petroleum ether at −30°.

[e]Recrystallized from 2-propanol.

8. The submitters state that the solution need not be dried, since water is removed by azeotropic distillation as the chloroform is evaporated. However, the checkers dried the chloroform solution with anhydrous magnesium sulfate prior to evaporation.
9. The checkers dried the product in a vacuum desiccator for 24 hours to remove all the 2-propanol and obtained 77–79 g. (64–66%), m.p. 70–72°. The yield reported by the submitters was 82–89 g. (68–74%), m.p. 73–74° (lit.,[2] m.p. 66–67°). The product's ^{1}H NMR spectrum (90MHz., $CDCl_3$), δ (multiplicity, coupling constant J in Hz., number of protons, assignment): 2.84 (t, J = 6.6, 2H, CH_2CH_2CN), 3.40 (t, J = 6.6, 2H, CH_2CH_2CN), 7.49 (d of d, J = 4.4 and 7.3, 1H, H_5), 8.24 (d of t, J = 2.0 and 7.3, 1H, H_4), 8.82 (d of d, J = 2.0 and 4.5, 1H, H_6), 9.16 (d, J = 2.0, 1H,H_2); mass spectrum *m/e* (relative intensity): 160 (M^+, 8), 106 (74), 78 (100), 51 (100).

3. Discussion

4-Oxo-4-(3-pyridyl)butyronitrile has been prepared in three steps by Leete, Chedekel, and Bodem,[2] and in one step by Stetter and Schreckenberg[3] using a method closely related to the present procedure. This compound serves as precursor in syntheses of myosmine[2] and various nicotine analogs. Other general methods for the preparation of γ-ketonitriles include the addition of hydrogen cyanide to α,β-unsaturated ketones,[4] the reaction of potassium cyanide with the hydrochlorides of Mannich bases from ketones,[5] and a variety of new methods for nucleophilic acylation.[6]

The addition of 3-pyridinecarboxyaldehyde to acrylonitrile is only one example of a wide range of reactions involving the conjugate addition of aldehydes to electron-deficient olefins. The reaction is not limited to α,β-unsaturated nitriles;[3,7] For example, γ-diketones[7,8] and γ-keto esters[7,9] may be similarly prepared by addition of aldehydes to α,β-unsaturated ketones and esters. Important advantages of this method are the simplicity of the procedure, the catalytic nature of the reaction, and low-cost reagents.

The γ-ketonitriles shown in Table I were prepared by the cyanide-catalyzed procedure described here. While this procedure is generally applicable to the synthesis of γ-diketones, γ-keto esters, and other γ-ketonitriles, the addition of 2-furancarboxaldehyde is more difficult, and a somewhat modified procedure should be employed.[10] Although the cyanide-catalyzed reaction is generally limited to aromatic and heterocyclic aldehydes, the addition of aliphatic aldehydes to various Michael acceptors may be accomplished in the presence of thioazolium ions,[7,11] which are also effective catalysts for the additions.[7,12]

The mechanism of the cyanide- and thioazolium ion-catalyzed conjugate addition reactions[7] is considered to be analogous to the Lapworth mechanism for the cyanide-catalyzed benzoin condensation. Thus, the cyano-stabilized carbanion, resulting from deprotonation of the cyanohydrin of the aldehyde, is presumed to be the actual Michael donor. After conjugate addition to the activated olefin, cyanide is eliminated, forming the product and regenerating the catalyst.

References and Notes

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539 (1974)]; H. Stetter and H. Kuhlmann, Ger. Pat. 2,437,219 (1974) [*Chem. Abstr.*, **84**, 164172t (1976)].

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

petroleum ether

ethanol (64-17-5)

potassium carbonate (584-08-7)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

chloroform (67-66-3)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

nitrogen (7727-37-9)

potassium cyanide (151-50-8)

potassium hydroxide (1310-58-3)

2-propanol (67-63-0)

2-furancarboxaldehyde (98-01-1)

dimethylamine (124-40-3)

magnesium sulfate (7487-88-9)

acrylonitrile (107-13-1)

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

calcium hydride (7789-78-8)

4-Oxo-4-(3-pyridyl)butyronitrile,
3-Pyridinebutanenitrile, γ-oxo (36740-10-0)

3-pyridinecarboxaldehyde,
3-Pyridinecarboxyaldehyde,
nicotinaldehyde (500-22-1)