A Convenient Synthesis of Aliphatic α,β-Unsaturated Nitriles from Acetonitrile

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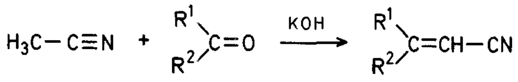
The most obvious route to α,β-unsaturated nitriles from aliphatic ketones or aldehydes is a base-catalyzed condensation of acetonitrile with the carbonyl compound. Elimination of water from the presumed β-cyanohydrin intermediate would yield the unsaturated nitrile directly. Unfortunately, this approach has met with little success in the past because of several problems. First, under polar, protic conditions, the aldol condensation of the ketone or aldehyde tends to be a major side reaction when the condensation of acetonitrile with a carbonyl compound is attempted. In addition, acetonitrile itself undergoes facile self-condensation reactions leading to oligomers[1]. Second, under conditions where strong, kinetic bases have been used to generate the cyanomethyl anion, proton transfer from the carbon acid can be a problem, but more important is the fact that the non-polar solvents required for anion generation are usually unfavorable for direct elimination of water from the intermediate β-cyanohydrin[2]. Third, the classical Doebner-Knoevenagel reaction of carbonyl compounds with cyanoacetic acid to give α-cyanoacrylates usually yields isomerized nitriles after decarboxylation[3]. We wish to report that we have overcome most of these difficulties and have developed a method for the direct condensation of acetonitrile (**1**) with a variety of aliphatic ketones (**2**) to give the nitriles (**3**).



$$H_3C-C\equiv N + \begin{matrix}R^1\\R^2\end{matrix}{>}C=O \xrightarrow{KOH} \begin{matrix}R^1\\R^2\end{matrix}{>}C=CH-CN$$

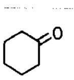
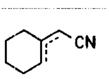
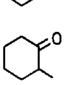
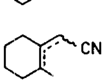
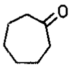
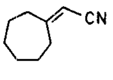
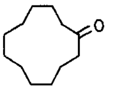
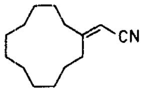
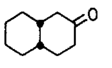
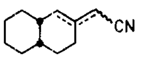
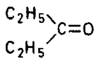
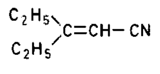
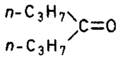
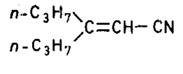
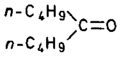
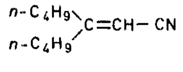
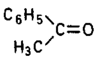
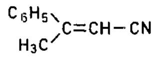
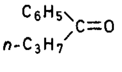
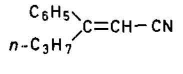
1 **2** **3**

Using potassium hydroxide pellets as the base in acetonitrile solution, we have obtained good yields of a variety of β,β-dialkylacrylonitrile derivatives (**3**). A representative sample of these products is shown in the Table and a detailed procedure is given below for the preparations of β,β-pentamethyleneacrylonitrile (from cyclohexanone) and 2-(β-cyanovinylidene)-decalin (from 2-decalone). We have found that the reaction is successful for many ketones, but fails or gives only poor yields for highly enolized ketones (cyclopentanone), aldehydes (heptanal), or methyl ketones (acetophenone, see Table). But even for alkyl ketones bearing a propanoyl group, the yields are in the 60–70% range and the products are readily obtained in high purity.

We presume that potassium hydroxide is, although soluble, poorly solvated by acetonitrile and the basicity of hydroxide is consequently enhanced. Hydroxide apparently deprotonates acetonitrile yielding the cyanomethyl carbanion which then attacks the carbonyl group of the ketone. The intermediate β-cyanohydrin then loses water to the medium resulting in formation of the α,β-unsaturated nitrile. There are certain peculiarities inherent to this reaction which may contradict this presumed mechanism but we reserve a discussion of these anomalies for the full report of this work.

We wish to call particular attention to the condensation of acetonitrile with cyclohexanone. Cope and coworkers[3c] condensed cyanoacetic acid with cyclohexanone and then decarboxylated the resulting cyanoacrylic acid. They obtained only 1-cyclohexenylacetonitrile and none of the conjugated nitrile. By our method, the product is predominantly conjugated and the non-conjugated isomer can

Table. Preparation of Unsaturated Nitriles (**3**) from Ketones (**2**) and Acetonitrile (**1**)[a]

Ketone **2**	Nitrile **3**	Yield [%][b]	Reaction time[8]	Isomer ratio	m.p. or b.p./torr	Molecular formula[c] or Lit. m.p. or b.p.
		70	1.5 h	α,β/β,γ=4.5	50°/0.5	107–108°/22 torr[3a,10]
		78	4 h	α,β/β,γ=0.98	44°/0.15	101°/14 torr[3a]
		78	6 h	α,β-isomer only	123–124°/20	105–112°/15 torr[11]
		45	72 h	α,β-isomer only	50–52°	$C_{14}H_{23}N$ (205.3)
		80	5 h	α,β/β,γ=3.4	77–82°/0.1	$C_{12}H_{17}N$ (175.3)
 $\begin{matrix}C_2H_5\\C_2H_5\end{matrix}{>}C=O$	 $\begin{matrix}C_2H_5\\C_2H_5\end{matrix}{>}C=CH-CN$	35	24 h	α,β-isomer only	69–70°/20	178–179°/756 torr[12]
 $\begin{matrix}n\text{-}C_3H_7\\n\text{-}C_3H_7\end{matrix}{>}C=O$	 $\begin{matrix}n\text{-}C_3H_7\\n\text{-}C_3H_7\end{matrix}{>}C=CH-CN$	65	48 h	α,β-isomer only	45°/0.35	$C_9H_{15}N$ (137.2)
 $\begin{matrix}n\text{-}C_4H_9\\n\text{-}C_4H_9\end{matrix}{>}C=O$	 $\begin{matrix}n\text{-}C_4H_9\\n\text{-}C_4H_9\end{matrix}{>}C=CH-CN$	65	72 h	α,β-isomer only	48–50°/0.1	$C_{11}H_{19}N$ (165.3)
 $\begin{matrix}C_6H_5\\H_3C\end{matrix}{>}C=O$	 $\begin{matrix}C_6H_5\\H_3C\end{matrix}{>}C=CH-CN$	15	6 h	α,β-isomer, E/Z=4.1	78°/0.2	91–93°/3 torr[2f]
 $\begin{matrix}C_6H_5\\n\text{-}C_3H_7\end{matrix}{>}C=O$	 $\begin{matrix}C_6H_5\\n\text{-}C_3H_7\end{matrix}{>}C=CH-CN$	30	36 h	α,β-isomer, E/Z=3.6	73–83°/0.4	$C_{12}H_{13}N$ (171.2)

[a] Acetonitrile is used both as reagent and solvent.

[b] Yield of isolated, purified material having the expected spectral properties.

[c] All new compounds gave satisfactory microanalyses (C ±0.12%, H ±0.10%, N ±0.30%) and/or high resolution mass spectra (±10 ppm).

be easily removed by addition of a small amount of bromine which reacts much faster with the β,γ- than with the α,β-isomer. In the acyclic systems, the α,β-isomer is the exclusive product. These observations appear to verify earlier findings of Linstead and coworkers[3a, 4] on the preference of the double bond for conjugation in such systems. An exception is in the case of 2-methylcyclohexanone which gave a slight excess of the non-conjugated (β,γ) isomer. We feel this may be due to the additional stability afforded by a tetrasubstituted olefin and the difference in solvent (acetonitrile vs. ethanol).

A patent, which was issued after we had begun the work reported herein, described the essential features of our reaction, but our results differ substantially from those reported in the patent[5]. We have no explanation for the difference; we have been unable to obtain the stated yields and products at the temperatures and concentrations described in the patent.

In general, the presence of 18-crown-6[6] has little influence on the rate or course of the reactions when they are conducted in acetonitrile. When the reaction is conducted in the presence of a cosolvent (for example, an equal volume of benzene) the presence of crown ether is salutary. In the case of certain ketones, addition of crown ether often affords a rate enhancement.

Preparation of β,β-Pentamethyleneacrylonitrile:

A 50 ml, three-necked, round-bottomed flask, equipped with a pressure equalizing addition funnel, reflux condenser, nitrogen purge and magnetic stirring bar is charged with powdered potassium hydroxide (pellets 85%, 0.66 g, 0.01 mol) and dry acetonitrile (15 ml). The mixture is brought to reflux and a solution of cyclohexanone (0.98 g, 0.01 mol) in acetonitrile (5 ml) is added dropwise over a period of 0.5–1.0 h[7]; after which, the reaction mixture is stirred at reflux for 1.5 h[8] and then the hot solution is poured on to cracked ice (~50 g). This mixture is extracted with three portions of dichloromethane (3 × 25 ml), dried over sodium sulfate, and evaporated in vacuo (bath temp. ~25°). The crude product thus obtained is purified by chromatography (alumina, 80–325 mesh) with ether/hexane (1/9, v/v) to give a colorless oil: yield 0.85 g (70%)[9]; consisting of a mixture of isomers (α,β ~83%, β,γ ~17%, by N.M.R.).

α,β-Isomer: b.p. 50°/0.5 torr.

^{1}H-N.M.R. (CCl_4/TMS): $\delta = 1.25$–2.0 (m, 6H); 2.0–2.8 (m, 4H); 5.08 ppm (m, 1H, $>C{=}C\underline{H}{-}CN$).

I.R. (neat): $\nu = 2220$ (CN); 1635 cm^{-1} ($>C{=}C<$).

M.S.: $m/e = 120$ ($M^{\oplus} - 1$).

β,γ-Isomer:

^{1}H-N.M.R. (CCl_4/TMS): $\delta = 3.05$ (s, 2H); 5.75 ppm (m, 1H, vinyl proton).

I.R. (neat): $\nu = 2242$ cm^{-1} (CN).

Large Scale Preparation of β,β-Pentamethyleneacrylonitrile:

A 1 l three-necked, round-bottomed flask equipped with a reflux condenser, mechanical stirrer, and addition funnel, is charged with potassium hydroxide pellets (85%, 33.0 g, 0.5 mol) and acetonitrile (250 ml). The mixture is brought to reflux and a solution of cyclohexanone (49 g, 0.5 mol) in acetonitrile (100 ml) is added dropwise over a period of 0.5–1 h[7]. Heating is continued for 2 h[8] after addition and then the hot solution is poured on to cracked ice (600 g). The resulting binary mixture is separated and the aqueous phase extracted with ether (3 × 200 ml). The combined organic phase is reduced on a steam bath (int. temp. ~50°) and there is obtained, after steam distillation (b.p. 81–99°), a pale yellow oil consisting of a mixture of isomers (α,β ~83%, β,γ ~17%): yield: 35 g (58%).

Isolation of the Pure α,β-Isomer:

A 250-ml Erlenmeyer flask equipped with a magnetic stirring bar is charged with the isomeric nitriles (see above: 20 g, 0.165 mol) and carbon tetrachloride (20 ml) and a solution of bromine in carbon tetrachloride (1/9, v/v) is added dropwise until the bromine color persisted (~25–30 ml). The reaction mixture is cooled in an ice bath (30 min), filtered, and the solvent evaporated in vacuo. There is obtained after distillation the pure (by ^{1}H-N.M.R. α,β-isomer; yield: 15 g, 0.124 mol (75%); b.p. 45–55°/0.4–0.5 torr.

Preparation of β,β-cis-Decahydronaphthalacrylonitrile:

cis-2-Octalone (1.52 g, 0.01 mol) is condensed with acetonitrile and purified as above to give a colorless oil consisting of a mixture of isomers (α,β ~78%, β,γ ~22% by ^{1}H-N.M.R.); yield: 1.4 g (80%).

α,β-Isomer: b.p. 77–82°/0.1 torr.

^{1}H-N.M.R. (CCl_4/TMS): $\delta = 1.0$–2.1 (m, 12H); 2.1–2.8 (m, 4H); 5.0 ppm (4d, 1H, vinyl proton).

I.R. (neat): $\nu = 2222$ (CN); 1621 cm^{-1} ($>C{=}C<$).

High resolution M.S.: $m/e = 175.1361$ (calc. for $C_{12}H_{17}N$: 175.1360).

β,γ-Isomer:

^{1}H-N.M.R. (CCl_4/TMS): $\delta = 2.95$ (m, 2H); 5.62 ppm (m, 1H, vinyl proton).

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(b) T. L. Cairns, A. W. Larchar, B. C. McKusick, *J. Am. Chem. Soc.* **74**, 5633 (1952).
(c) Y. Ogata, Y. Izawa, Y. Osumi, *Bull. Soc. Chim. Jpn.* **37**, 74 (1964).

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(b) E. M. Kaiser, C. R. Hauser, *J. Org. Chem.* **33**, 3402 (1968).
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(d) I. Pattison, K. Wade, B. K. Wyatt, *J. Chem. Soc.* **1968**, 837.
(e) T. Kametani, Y. Yamaki, K. Ogasaware, *Yakugaku Zasshi* **89**, 154 (1969); *C.A.* **70**, 106342 (1969).
(f) A. Uchida, S. Saito, S. Matsuda, *Bull. Chem. Soc. Jpn.* **42**, 2989 (1969).
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(h) A. Uchida, A. Doyama, S. Matsuda, *Bull. Chem. Soc. Jpn.* **43**, 963 (1970).
(i) R. Das, C. A. Wilkie, *J. Am. Chem. Soc.* **94**, 4555 (1972).
(j) K. Takahashi, K. Sasaki, H. Tanabe, Y. Yamada, H. Iida, *J. Chem. Soc. Jpn, Jpn. Chem. Ind. Chem.* **1973**, 2347.
(k) W. Stilz, H. Pommer, *Ger. Offen.* 1, 108, 208; *C.A.* **56**, 11422 (1962).
(l) G. P. Schiemenz, H. Engelhard, *Chem. Ber.* **95**, 195 (1962).
(m) J. Ghosez, *Bull. Soc. Chim. Belg.* **41**, 477 (1932).
See also: J. G. Krause, S. Shaikh, *Synthesis* **1975**, 502.
J. J. Lauvar, A. K. Sparks, *Ger. Offen.* 2,041,563; *C.A.* **75**, 199897 (1971).
(n) H. J. Arpe, I. Leupold, *Angew. Chem.* **84**, 767 (1972); *Angew. Chem. Int. Ed. Engl.* **11**, 722 (1972).

[3] (a) R. P. Linstead, A. Kandiah, *J. Chem. Soc.* **1929**, 2139.
(b) E. J. Corey, G. Fraenkel, *J. Am. Chem. Soc.* **75**, 1168 (1953).
(c) A. C. Cope, A. A. D'Addieco, D. E. Wayte, S. A. Glickman, *Org. Synth.* **31**, 25 (1951).

[4] (a) R. P. Linstead, G. A. R. Kon, *J. Chem. Soc.* **1929**, 1269.
(b) R. P. Linstead, C. J. May, *J. Chem. Soc.* **1927**, 2565.
(c) R. P. Linstead, *J. Chem. Soc.* **1927**, 2579.

[5] *U. S. Patent* 3,960,923 (1976); *C.A.* **85**, 123387 (1976).

[6] G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, F. L. Cook, *J. Org. Chem.* **39**, 2445 (1974).

[7] Rapid addition of the carbonyl substrate resulted in a reduction in yield (~20%) see G. W. Gokel, S. A. DiBiase, B. Lipisko, *Tetrahedron Lett.* **1976**, 3495.

[8] Reaction times are very sensitive to the quality of KOH employed. The times quoted are for finely divided reagent grade potassium hydroxide. However, if pellets are employed the reaction can be conveniently monitored via G.L.C. and/or DNP formation.

[9] The yield obtained is somewhat concentration dependent in this case, when the concentration of cyclohexanone is lowered to 0.1 molar in acetonitrile, the yield rises to 86% with the same isomer distribution.

[10] G. Descotes, P. Laconche, *Bull. Soc. Chim. Fr.* **1968**, 2149.

[11] F. Šorm, J. Beránek, *Chem. Listy.* **47**, 708 (1953).

[12] P. Colmant, *Bull. Soc. Chim. Belg.* **39**, 568 (1930).

Errata:

S. A. DiBiase, G. W. Gokel, *Synthesis* **1977**, 629; the following acknowledgement was omitted:

We thank the Donors of the Petroleum Research Fund, Administered by the American Chemical Society, for support of this work.

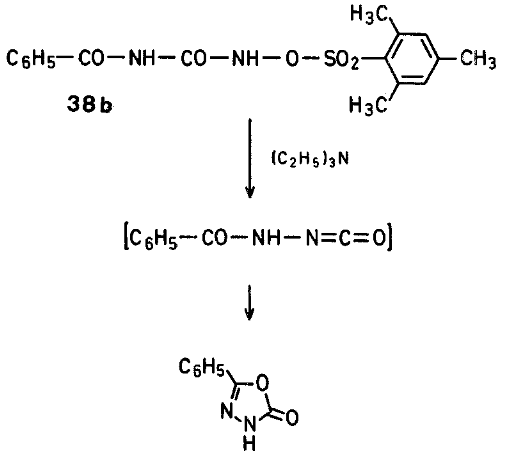
R. J. K. Taylor, *Synthesis* **1977**, 564; Table 2 should be as follows:

Table 2. Reactions of α,β-Unsaturated Ketones **4** and **5** with Diethyl α-Ethoxycarbonyl-α-sodiomethanephosphonate

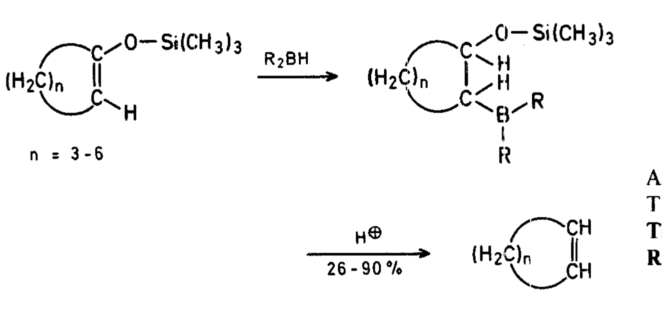
Substrate	Reaction Conditions solvent/temp./time	Product	Yield [%]	m.p.[a]	Molecular formular[b]	^{1}H-N.M.R. ($CDCl_3$, 60 MHz) δ [ppm] (vinylic protons)
4	C_6H_6/r.t./1 h	**2c**	6	see Table 1		
		3c	46			
5	C_6H_6/r.t./0.5 h	**2d**	11	oil	$C_{14}H_{20}O_4$ (252.3)	5.67 (m, 2H)[c]
		3d	41	33–35°	$C_{14}H_{20}O_4$ (252.3)	5.87 (s, 2H)

Errata 1977

Y. Tamura, J. Minamikawa, M. Ikeda, *Synthesis* **1977**, 1–17.
Formula scheme on page 16, right-hand column should be:



J. K. Rasmussen, *Synthesis* **1977**, 91–111.
The 1st formula scheme on page 106, left-hand column should be:



G. Cahiez, D. Bernard, J. F. Normant, *Synthesis* **1977**, 130–133.
The boiling point for the 18th compound in Table 1 ($R^1 = n\text{-}C_4H_9$, $R^2 = C_6H_5$) should be 136°/13 torr.

Abstract no. 4860, *Synthesis* **1977**, 141.
The title should be:
Dehydrogenation of Open-Chain and Cyclic Diketones by Palladium-(II) Compounds

S. M. Ali, T. V. Lee, S. M. Roberts, *Synthesis* **1977**, 155–166.
The correct name for compound **85** (page 164, left-hand column) is: *cis*-4-carboxymethyl-2,2-dimethylcyclobutanecarboxylic acid.

B. Unterhalt, H. Koehler, *Synthesis* **1977**, 265–266.
The name for compounds **4** should be:
3-(dialkylaminomethoximino)-1-phenylbutene or 1-phenylbutenon-*O*-(dialkylaminomethyl)-oxime.

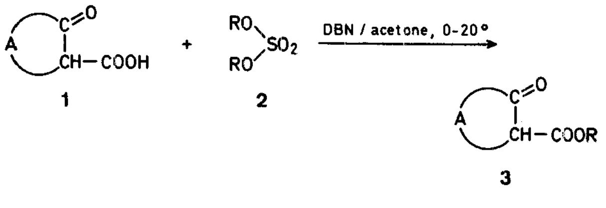
R. C. Brown, H. Cairns, J. L. Suschitzky, *Synthesis* **1977**, 276–277.
The name for compounds **9** and **4a** (page 277, right-hand column) should be: 6-carboxy-9-hydroxy-8-oxo-10-propyl-1,2,3,8-tetrahydroindazolo [4,3a,3,2-*hij*]quinoline and 2-carboxy-1-ethyl-5-hydroxy-4-oxo-6-propyl-1,4,7,8,9,10-hexahydrobenzo[*h*]quinoline, respectively.

Abstract No. 4924, *Synthesis* **1977**, 350.
The title should be:
Selective Cleavage of Aryl Esters by Potassium or Cesium Carbonate

Abstract No. 4937, *Synthesis* **1977**, 354.
The title should be:
3-Alkanolides by Cycloaddition of Lithium Alkynoxides with Carbonyl Compounds

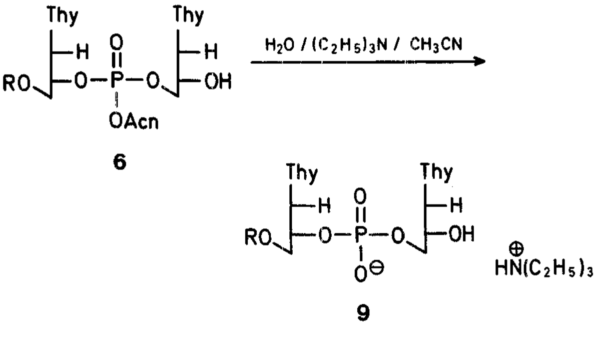
W. Flitsch, W. Schulten, *Synthesis* **1977**, 414–415.
The name for compound **5** should be:
4,9-Dichloro-3,8-dihydro-10b,10c-diazadicyclopenta[*ef,kl*]-heptalen.

Abstract No. 4951, *Synthesis* **1977**, 434.
The formula scheme should be:



Abstract No. 4958, *Synthesis* **1977**, 436.
The title (and name of reagent **2**) should be:
Trimethylsilyl Trimethylsilylamidosulfate; A new Silylating Reagent

F. Ramirez, E. Evangelidou-Tsolis, A. Jankowski, J. F. Marecek, *Synthesis* **1977**, 451–453.
The formula Scheme **B** should be:



Abstract No. 4976, *Synthesis* **1977**, 508.
The title (and name of reagent **1**) should be:
2-Alkenenitriles from Ethyl 2-Cyanoalkanoates.

S. A. DiBiase, G. W. Gokel, *Synthesis* **1977**, 629–632.
The heading for the last experimental procedure (page 631, right-hand column) should be:
Preparation of Decahydronaphthalen-2-ylidenacetonitrile.
Acknowledgement should be added:
We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.