

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Pyrolysis of Esters. XVIII. Synthesis of Nitriles by Pyrolysis of Cyanoacetic Esters¹BY WILLIAM J. BAILEY AND JOHN J. DALY, JR.²

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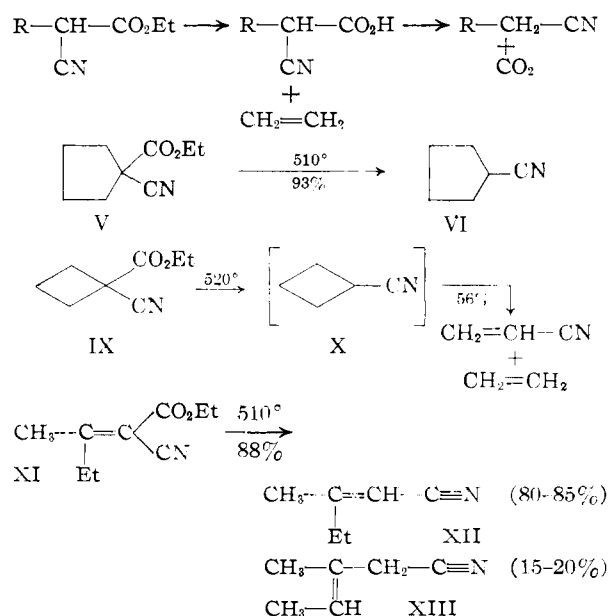
The pyrolysis of cyanoacetic esters has been shown to be a convenient and often the best method for their transformation into the corresponding nitriles. For example, the pyrolysis of ethyl (1-methylpropyl)-cyanoacetate (I) gave an 86% yield of 2-methylvaleronitrile (II). Similarly, the pyrolysis of 1-cyano-1-carbocyclopentane (V) gave a 93% yield of cyclopentanecarbonitrile (VI). The pyrolysis of an α,β -unsaturated cyanoacetic ester produced a mixture of unsaturated nitriles very similar to that obtained by conventional hydrolysis followed by decarboxylation.

Since the pyrolysis of esters has been shown to be an excellent method for the synthesis of strained or reactive olefins, including isomers of aromatic compounds,³⁻⁵ a program to find possible uses of this pyrolytic method for the synthesis of acids and their derivatives was initiated. It was shown that pyrolysis has many advantages over hydrolysis in the conversion of an ethyl ester to the corresponding acid, particularly if the acid was water soluble or sterically hindered. For example, ethyl glutarate was pyrolyzed to give a 94% yield of glutaric acid, while ethyl 1,3,5-trimethylbenzoate was pyrolyzed to give a 91% yield of the corresponding hindered acid.⁶ It was found further that the ketone cleavage of acetoacetic esters by pyrolysis was superior in many respects to conventional basic hydrolysis, particularly if the acetoacetic ester contained a branched group or the resulting ketone was moderately soluble in water. For example, in the pyrolysis of ethyl α -isopropylacetoacetate at 525°, the ester portion decomposes to give ethylene, and the resulting acetoacetic acid almost simultaneously loses carbon dioxide to give an 82% yield of methyl isobutyl ketone, more than double the yield reported for conventional hydrolysis.⁷ The fact that ketone cleavage by pyrolysis saves time and reagents and can be adapted for large scale preparations recommends this method for the synthesis of many ketones.

Although Cope and Alexander⁸ developed an excellent method for the preparation of monosubstituted cyanoacetic esters through a reductive Knoevenagel reaction, these readily available intermediates have not found wide use in the preparation of nitriles, apparently because of the difficulty in the selective hydrolysis of the ester group. It seemed possible that pyrolysis, which would not affect the nitrile group, would be an excellent method for the removal of the carboxy group. For this reason, methyl ethyl ketone was reductively condensed with ethyl cyanoacetate to give an 88% yield of ethyl (1-methylpropyl)-cyanoacetate (I). Pyrolysis of the ester I at 520° over Pyrex helices resulted in the elimination of ethylene to form the intermediate cyanoacetic

acid, which almost immediately lost carbon dioxide to give a 73% conversion to 2-methylvaleronitrile (II). Since 15% of the starting ester I also was obtained, the yield of II, based on unrecovered material, was 86%. This pyrolytic procedure compares very favorably with an alternative synthesis of II by Chiang⁹ in which methyl ethyl ketone was condensed with cyanoacetic acid, followed by decarboxylation and reduction of the resulting intermediate in an over-all yield of 49%.

By the method of Cope,¹⁰ cyclohexanone was condensed with cyanoacetic ester and the resulting unsaturated intermediate was hydrogenated to give a 76% yield of ethyl α -cyclohexylcyanoacetate (III). Pyrolysis of III at 520° resulted in the simultaneous loss of ethylene and carbon dioxide to give a 77% conversion to cyclohexylacetonitrile (IV). Since an 11% recovery of starting ester III was obtained, the yield of IV, based on unrecovered material, was 87%. Chiang⁹ reported an over-all yield of 58% for the preparation of IV by the condensation of cyclohexanone with cyanoacetic acid, followed by decarboxylation and reduction of the resulting intermediate.

(1) Previous paper in this series, *THIS JOURNAL*, **81**, 2126 (1959).

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(3) W. J. Bailey and R. Barclay, *ibid.*, **80**, 5393 (1959).(4) W. J. Bailey, R. L. Hudson and C.-W. Liao, *ibid.*, **80**, 4358 (1958).(5) W. J. Bailey and J. Economy, *ibid.*, **77**, 1133 (1955).(6) W. J. Bailey and W. N. Turek, *J. Am. Oil Chemists' Soc.*, **33**, 317 (1956).(7) W. J. Bailey and J. J. Daly, *J. Org. Chem.*, **22**, 1189 (1957).(8) A. C. Cope and E. R. Alexander, *THIS JOURNAL*, **66**, 886 (1944).

Disubstituted cyanoacetic esters can be prepared conveniently by the alkylation of ethyl cyanoacetate, but the hydrolysis to the corresponding

(9) M.-C. Chiang, *J. Chinese Chem. Soc.*, **18**, 65 (1951) [*C. A.*, **46**, 4171 (1952)].(10) A. C. Cope, C. M. Hoffmann, C. Wyckoff and E. Hardenbergh, *THIS JOURNAL*, **63**, 3452 (1941).

nitrile is still difficult. Osman and Cope¹¹ developed a treatment with sodium ethoxide that would convert a disubstituted cyanoacetic ester directly to the corresponding nitrile by a reverse Claisen condensation in yields varying from 22 to 91%. The yields were high only when the substituents were bulky. Brown and Van Gulick,¹² in a modification of this procedure, converted ethyl diisopropylcyanoacetate to diisopropylacetonitrile in an 83% yield by a series of distillations from potassium hydroxide.

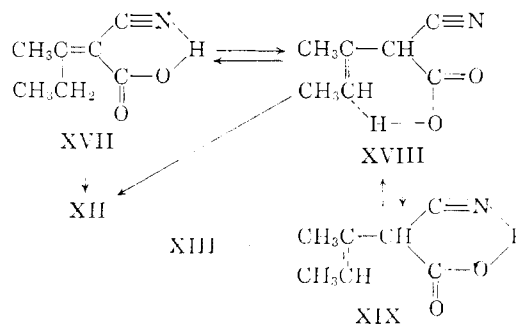
As a test for the synthesis of disubstituted acetonitriles by pyrolysis, 1-cyano-1-carbethoxycyclopentane (V) was prepared by the alkylation of cyanoacetic ester with 1,4-dichlorobutane in a 60% yield. Pyrolysis of V at 520° gave an 83% conversion to 1-cyanocyclopentane (VI). Since 11% of the starting ester was recovered, the yield of VI, based on unrecovered material, was 93%. This preparation of VI compares favorably with previously reported procedures. Paul and Tchelitcheff¹³ alkylated acetonitrile with 1,4-dihalobutanes and sodamide in yields varying from 25 to 50%. Wislicenus and Gartner¹⁴ prepared VI in an unreported yield from cyclopentyl iodide and sodium cyanide, while Rogers and Roberts¹⁵ later carried out a similar preparation with cyclopentyl bromide to give a 27% yield of the cyclic nitrile. McElvain and Starn¹⁶ recently developed a four-step synthesis of VI in an over-all yield of 64%, starting from cyclopentanone and involving as one of the steps the pyrolysis of an acetate.

In a similar fashion, cyanoacetic ester was dialkylated with ethyl bromide to produce ethyl α,α -diethylcyanoacetate (VII) in a 75% yield. Pyrolysis of VII at 510° gave a 64% conversion to α -ethylbutyronitrile (VIII) plus a 17% recovery of starting ester. The yield of VIII, based on unrecovered material, was 77%. This yield compares favorably with the 60% that Bowden¹⁷ reported for the hydrolysis and decarboxylation of VII. For the alkylation of acetonitrile with sodamide and ethyl bromide Schuerch and Huntress¹⁸ reported a 14% yield, while with ethyl chloride Bergstrom and Agestinko¹⁹ reported a 20% yield. The highest yield reported for preparation of VIII was the 88% reported by Brown and Van Gulick²⁰ for a three-step conversion starting from α -ethylbutyric acid through the amide, an improvement on the 76% reported by Stevens and Coffield²¹ for a similar conversion. Thus it appears that, if the corresponding acid is not available, the pyrolysis of a cyanoacetic ester is an attractive route to a disubstituted acetonitrile.

A limitation of this method was found, however, in an attempted synthesis of 1-cyanocyclobutane. Although alkylation of cyanoacetic ester with tri-

methylene bromide proceeded normally to produce a 72% yield of 1-cyano-1-carbethoxycyclobutane (IX), pyrolysis of IX at 520° did not produce 1-cyanocyclobutane (X). Instead, the pyrolysis gave a 56% yield of acrylonitrile. The formation of the acrylonitrile can be rationalized by the assumption that the four-membered ring in either the expected X (or the starting ester IX) was cleaved by heat into two olefins. Such a thermal cleavage of the cyclobutane ring has been demonstrated previously.²²

It was hoped that the pyrolysis of an α,β -unsaturated cyanoacetic ester would give a single product. Although the pyrolysis gave a high yield of unsaturated nitriles, the product proved to be a mixture. Thus the pyrolysis of ethyl (1-methylpropylidene)-cyanoacetate (XI) at 510° gave a 66% conversion to a mixture containing 80 to 85% of 3-methyl-2-hexenitrile (XII) and 15-20% of 3-methyl-3-hexenitrile (XIII). Since 25% of the starting ester XI was recovered, the total yield of XII and XIII was 88%. In a similar fashion the pyrolysis of ethyl cyclohexylidene-cyanoacetate (XIV) at 510° gave a 67% conversion to a mixture of unsaturated nitriles. This mixture contained 85 to 90% of 1-cyclohexenylacetonitrile (XVI) and 10 to 15% of cyclohexylideneacetonitrile (XV). Since 20% of the starting ester XIV was recovered unchanged, the yield of XV and XVI was 84%. Apparently the intermediate cyanoacetic acid XVII can decompose by at least two different mechanisms to give two isomeric nitriles. A possible explanation is that XVII can form two different quasi-six-membered ring intermediates XVIII and XIX. This mechanism would be similar



to that suggested by Corey²³ for the decarboxylation of half-esters of α,β -unsaturated malonic acids.

One must conclude that the pyrolysis of cyanoacetic esters has, in many cases, advantages over the conventional hydrolysis. This advantage often can make a route through the cyanoacetic esters the preferred preparative method for some substituted acetonitriles.

Experimental²⁴

2-Methylvaleronitrile (II).—By the method of Cope and Alexander⁸ a mixture of 169.5 g. of ethyl cyanoacetate, 118.8 g. of methyl ethyl ketone, 11.7 g. of ammonium acetate, 18 g. of acetic acid, 300 ml. of 95% ethanol and 3 g. of palladium-on-carbon catalyst was hydrogenated at room tem-

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 (18) C. Schuerch and E. H. Huntress, *ibid.*, **70**, 2824 (1948).
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 (20) R. F. Brown and N. M. Van Gulick, *ibid.*, **77**, 1070 (1955).
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perature for 36 hours to yield 223.5 g. (88%) of ethyl (1-methylpropyl)-cyanoacetate (I), b.p. 103–104.5° (9 mm.), n_D^{25} 1.4268 [reported⁸ b.p. 99–100° (7 mm.), n_D^{25} 1.4267]. Over a period of 3.75 hours, 153 g. (0.905 mole) of I was added dropwise to the top of a Vycor tube packed with Pyrex helices and externally heated at 520° with a Hoskins FD 303A electric furnace, as previously described.²⁵ In order to minimize charring, the tube was continuously swept with a slow stream of oxygen-free nitrogen. The pyrolysate, which had been collected in a flask cooled in a Dry Ice-acetone-bath, was distilled directly through an 8-inch, helix-packed column to yield 63.7 g. (73%) of 2-methylvaleronitrile (II), b.p. 88° (92 mm.), n_D^{25} 1.4051 [reported⁹ b.p. 152–153°, n_D^{25} 1.4089], and 23 g. (15% recovery) of the starting ester I. The yield of II, based on unrecovered material, was, therefore, 86%.

Cyclohexylacetoneitrile (IV).—Ethyl cyclohexylidenecyanoacetate (XIV), b.p. 148–149° (9 mm.), n_D^{25} 1.4938 [reported¹⁰ b.p. 150–151° (9 mm.), n_D^{25} 1.4950], was prepared in an 83% yield by the condensation of cyclohexanone with ethyl cyanoacetate. Catalytic hydrogenation of 93 g. of XIV, followed by distillation of the reaction mixture through an 8-inch, helix-packed column, gave 86 g. (91%) of ethyl cyclohexylcyanoacetate (III), b.p. 146–148° (12 mm.), n_D^{25} 1.4580 [reported⁸ b.p. 138–139° (8 mm.), n_D^{25} 1.4574]. By use of the apparatus and procedure described above, 80 g. (0.41 mole) of III was pyrolyzed over a period of 2 hours at a temperature of 520°. Direct distillation of the pyrolysate through an 8-inch, helix-packed column gave 38.8 g. (77%) of cyclohexylacetoneitrile (IV), b.p. 86° (12 mm.), n_D^{25} 1.4548 [reported²⁶ b.p. 57° (1 mm.), n_D^{25} 1.4575], and 9 g. (11% recovery) of starting material. The yield of IV, based on unrecovered starting ester, was 87%.

1-Cyano-1-carbomethoxycyclopentane (V).—To a solution of 46 g. (2 moles) of sodium in 500 ml. of absolute ethanol was added 226 g. (2 moles) of ethyl cyanoacetate. After the solution was stirred for 15 minutes, 254 g. (2.02 moles) of 1,4-dichlorobutane was added rapidly and the reaction mixture was heated under reflux for 48 hours. A solution of 46 g. (2 moles) of sodium in 500 ml. of absolute ethanol was added, and the mixture was heated under reflux for an additional 72 hours. After most of the alcohol had been removed by distillation, the residue was dissolved in water and the solution was extracted with three portions of ether. After the extracts had been dried over Drierite, the ether was removed by distillation. Fractionation of the residue through a 6-inch, helix-packed column gave 200 g. (60%) of 1-cyano-1-carbomethoxycyclopentane (V), b.p. 118° (18 mm.), n_D^{25} 1.4452.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.70; H, 7.79. Found: C, 64.77; H, 7.85.

Cyclopentanecarbonitrile (VI).—Over a period of 2.8 hours, 101 g. (0.605 mole) of 1-cyano-1-carbomethoxycyclopentane (V) was pyrolyzed at 510° as described above. Fractionation of the pyrolysate through an 8-inch, helix-packed column gave 47.3 g. (83%) of cyclopentanecarbonitrile (VI), b.p. 67–68° (20 mm.), n_D^{25} 1.4403 [reported¹⁵ b.p. 75° (30 mm.), n_D^{25} 1.4404], and 11.1 g. (11% recovery) of starting ester. The yield of VI, based on unrecovered material, was 93%.

α -Ethylbutyronitrile (VIII).—Ethyl α,α -diethylcyanoacetate (VII), b.p. 92° (10 mm.), n_D^{25} 1.4200 [reported²⁷ b.p. 109–110° (27 mm.)], was prepared in a 75% yield by the alkylation of ethyl cyanoacetate with ethyl bromide, according to the method of Lin and Li.²⁷ Pyrolysis of 57 g. (0.337 mole) of VII at 510° over a period of 1.7 hours, followed by fractionation of the pyrolysate through an 8-inch, helix-packed column, gave 20.5 g. (64%) of α -ethylbutyronitrile (VIII), b.p. 60–62° (38 mm.), n_D^{25} 1.3995 [reported b.p.

142–146,²¹⁷ n_D^{20} 1.4021¹⁸], and 9.5 g. (17% recovery) of starting ester VII. The yield of VIII, based on unrecovered VII, was, therefore, 77%.

1-Cyano-1-carbomethoxycyclobutane (IX).—A modification of the general method of Cason and Allen²⁸ was used to prepare the ester IX. A cold solution of 18 g. (0.8 mole) of sodium in 400 ml. of absolute ethanol was added concurrently with 202 g. (1 mole) of trimethylene bromide to a stirred and heated solution of 27.6 g. (1.2 moles) of sodium in 600 ml. of absolute alcohol and 135.6 g. (1.2 moles) of ethyl cyanoacetate over a 1-hour period. After the solution was heated for an additional 1.5 hours, most of the alcohol was removed by distillation, and the residue was extracted with water. The aqueous extracts were re-extracted with benzene, and the combined benzene extracts and original organic layer were dried over magnesium sulfate. Distillation through a 6-inch, helix-packed column produced 110 g. (72%) of 1-cyano-1-carbomethoxycyclobutane (IX), b.p. 94.5–97.5° (10 mm.), n_D^{25} 1.4395.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.70; H, 7.20. Found: C, 62.45; H, 7.22.

Pyrolysis of 1-Cyano-1-carbomethoxycyclobutane (IX).—The pyrolysis of 39.5 g. (0.258 mole) of IX at 520° over a period of 1 hour, followed by fractionation of the pyrolysate through a 6-inch, helix-packed column, gave 7.5 g. (56%) of crude acrylonitrile, b.p. 76–77°, but no isolable cyclobutanecarbonitrile (X). The acrylonitrile was characterized by conversion to α,β -dibromopropionamide, m.p. 131–132° [reported²⁹ m.p. 130–133°], by bromination, followed by partial hydrolysis of the resulting nitrile with sulfuric acid.

Pyrolysis of Ethyl (1-Methylpropylidene)-cyanoacetate (XI).—Condensation of methyl ethyl ketone and ethyl cyanoacetate according to the procedure of Cope¹⁰ gave a 75% yield of ethyl (1-methylpropylidene)-cyanoacetate (XI), b.p. 111–112° (9 mm.), n_D^{25} 1.4648 [reported¹⁰ b.p. 116–118° (11 mm.), n_D^{25} 1.4650]. Pyrolysis of 167 g. (1 mole) of XI at 510° over a period of 3.75 hours, followed by fractionation of the pyrolysate through an 8-inch, helix-packed column, gave 62.3 g. (66%) of a mixture of 3-methyl-2-hexenonitrile (XII) and 3-methyl-3-hexenonitrile (XIII), b.p. 90–91° (80–84 mm.), n_D^{25} 1.4386 [reported³⁰ for XII, b.p. 162–164°, n_D^{25} 1.4445; for XIII, n_D^{25} 1.4236], and 42 g. (25% recovery) of starting ester.

The yield of XII plus XIII, based on unrecovered material, was 88%. On the basis of the refractive indices, the mixture was assumed to contain 80 to 85% of XII and 15 to 20% of XIII.

Anal. Calcd. for C_8H_9N : C, 75.80; H, 9.47. Found: C, 76.06; H, 9.46.

Pyrolysis of Ethyl Cyclohexylidenecyanoacetate (XIV).—Pyrolysis of 158 g. (0.82 mole) of XIV at 510° over a period of 3.2 hours, followed by fractionation of the pyrolysate through an 8-inch, helix-packed column, gave 65.7 g. (67%) of a mixture of 1-cyclohexenylacetoneitrile (XVI) and cyclohexylideneacetoneitrile (XV), b.p. 89.5–90° (10 mm.), n_D^{25} 1.4832 [reported³¹ for XVI, b.p. 105° (22 mm.), n_D^{15} 1.4843; for XV, b.p. 107–108° (22 mm.), n_D^{15} 1.4928], and 32.2 g. (20% recovery) of the starting ester. The yield of XV and XVI, based on unrecovered XIV, was, therefore, 84%. On the basis of refractive indices, the mixture of nitriles was assumed to contain 85 to 90% of XVI and 5 to 10% of XV.

Anal. Calcd. for $C_8H_{11}N$: C, 79.40; H, 9.10. Found: C, 79.33; H, 8.92.

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