Tetrahedron Letters No. 6, pp 389 - 392, 1975. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF SMALL RINGS *via* THE PROTECTED CYANOHYDRIN METHOD.

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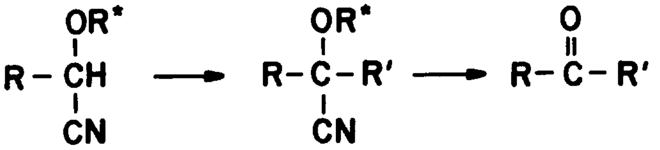
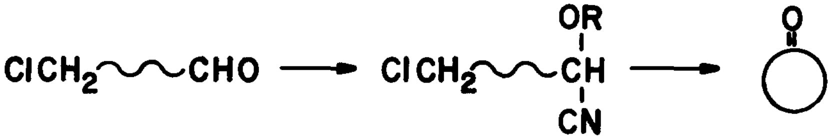
(Received in USA 30 October 1974; received in UK for publication 23 December 1974)

We have reported that the anion derived from the readily available protected cyanohydrins of aldehydes are generally useful as acyl carbanion equivalents and can be used in the synthesis of ketones *via*, *inter alia*, alkylation and Michael addition.[1]



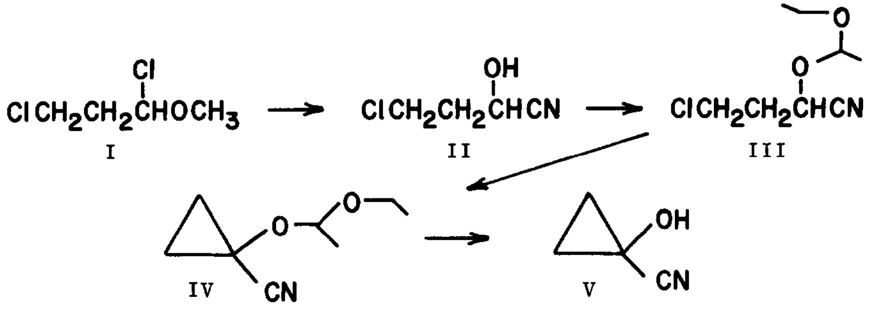
$$R-\overset{OR^*}{\underset{CN}{CH}} \longrightarrow R-\overset{OR^*}{\underset{CN}{C}}-R' \longrightarrow R-\overset{O}{\overset{\|}{C}}-R'$$

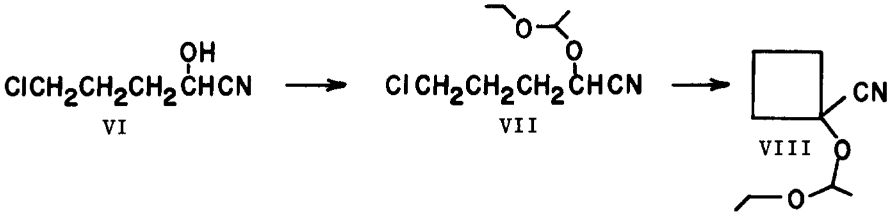
The possible use of these reactions in the synthesis of *cyclic* ketones from the protected cyanohydrins of haloaldehydes would be especially interesting for systems not otherwise readily available. We report here on the application of



the method to particularly facile syntheses of cyclopropanone and cyclobutanone cyanohydrins.

2-Cloropropionaldehyde cyanohydrin (II) was conveniently made by hydrolysis of the chloroether I, readily prepared[2] from acrolein, in the presence of sodium cyanide. Protection by reaction with ethyl vinyl ether gave the protected cyanohydrin III which was cyclized in good yield to IV with the sodium salt of hexamethyldisilazane in refluxing benzene. Removal of the protecting group with aqueous acid then gave cyclopropanone cyanohydrin (V). Its properties and nmr spectrum agreed with those described for the substance made from cyclopropanone and hydrocyanic acid.[3] In a similar manner, we found no difficulty in applying this procedure to 4-chlorobutyraldehyde cyanohydrin (VI) which, as its ethoxyethyl derivative VII, was cyclized to the protected cyclobutanone cyanohydrin VII.

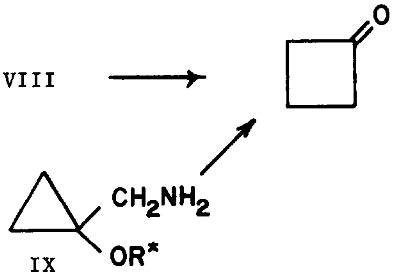




Cyclobutanone itself can be obtained easily from the protected ether VIII by successive treatment with aqueous acid and aqueous base.

It is interesting that cyclobutanone can also be made from the cyclopropane derivative IV. Reduction with lithium aluminum hydride gave the amino ether IX which underwent ring enlargement[4]-hydrolysis to cyclobutanone, with aqueous nitrous acid.

There appears to be no reason why the method should not be applicable to the synthesis of ring-substituted analogs of IV and VIII.



The details of these experiments are given below.

Cyclopropanone cyanohydrin (V). Slow simultaneous addition of 83 g of the chloroether I and 35 g of solid sodium cyanide to a mixture of 80 ml of 4N hydrochloric acid in 70 ml of tetrahydrofuran at 0°. The crude cyanohydrin II thus obtained in 75% yield after ether extraction (caution!), was converted to its α-ethoxyethyl ether III by addition of one equivalent of ethyl vinyl ether, maintaining the temperature of the reaction at 60-70°. Extraction, washing (sodium bicarbonate) and distillation gave the pure protected cyanohydrin III, bp 80-81° (2mm), in 50% yield. Cyclization to IV was carried out by heating (3 hr, 95°) with one equivalent of the sodium salt of hexamethyldisilazane. The pure product (62% yield; bp 48-50° (0.2mm); ir: ν(film) 2240 cm^{-1}, nmr: δ($CDCl_3$) 1.25 ppm (ring methylenes)) was converted by hydrolysis with 0.2 N sulfuric acid in methanol (room temperature, 5 min) to cyclopropanone cyanohydrin (V),[3] bp 48° (0.35mm); ir: ν(film) 2250 cm^{-1}; nmr: δ($CDCl_3$) 1.23 ppm (m, 4H, ring methylenes).

Cyclobutanone cyanohydrin. The protected cyanohydrin IV (bp 93° (0.6mm), nmr δ(CCl_4) 4.9 (m, $-OC\underline{H}O-$), 4.45 (m, $-OC\underline{H}CN$)ppm) from 4-chlorobutyraldehyde[5] was prepared in 85% yield by reaction of the cyanohydrin (dropwise addition of 25.4 g of the aldehyde to a solution of 30 g of sodium bisulfite in 200 ml of water at -5°, followed after 30 min by washing with ether and addition of 14.5 g of sodium cyanide in 50 ml of water) with ethyl vinyl ether (35g, few drops of HCl) Cyclization, as described above for the synthesis of IV, gave VII, the protected cyanohydrin of cyclobutanone, in 61% yield after distillation (bp 48° (0.3mm), nmr: δ(CCl_4) 4.9 (q, $OC\underline{H}-O$), 1.85 (m, cyclobutane β - CH_2), 2.32 (m, cyclobutane α - CH_2's)ppm).

Cyclobutanone. A. From the protected cyanohydrin of cyclobutanone. Removal of the protecting group of VII by hydrolysis for 15 min at room temperature was carried out as described for IV and the resulting crude cyanohydrin[6], dissolved in pentane, was stirred for 5 min at 0° with 1 N sodium hydroxide solution saturated with sodium chloride. The yield of cyclobutanone from VII was 85%.[7]

B. From the protected cyanohydrin of cyclopropanone. Reduction of the protected cyanohydrin IV with lithium aluminum hydride (1 hr reflux in ether) gave a quantitative yield of the crude amino ether IX. Addition of sodium nitrite (1.4 g in 3 ml of water) at 0° to a solution of 1.11 g of IX in 7.5 ml of 33% acetic acid, followed after 30 min by neutralization (3.5 g sodium bicarbonate and 3 ml of water at 0°) and extraction with pentane gave cyclobutanone in 75% yield from IV.[8]

References

1. G. Stork and L. Maldonado, J. Amer. Chem. Soc., 93, 5286 (1971) and 96, 5272, (1974).

2. G. Poullain, Bull Soc. Chim. France, 488 (1964).

3. W.J.M. Tilborg, S.E. Schaafsma, H. Steinberg and T.J. deBoer, Rec. Trav. Chim., 86, 419 (1967). The stability of the cyclopropanol ring to acid is undoubtedly enhanced by the electron withdrawing cyano group.

4. Cf. B. Tchoubar, Bull. Soc. Chim. France, 164 (1949).

5. R.B. Loftfield, J. Amer. Chem. Soc., 73, 1365 (1951).

6. The interesting ring enlargement reactions obtained by reaction of cyclobutanone cyanohydrin with organometallic reagents are described in a separate paper (J. d'Angelo, Bull. Soc. Chim. France, in press).

7. Use of stronger base causes considerable adolization of cyclobutanone. The solution of cyclobutanone in pentane can be used for reactions with the ketone which is freed from solvent only with difficulty. The yields reported here were determined by careful quantitative gas chromatography (5% carbowax at 50°) using pure cyclobutanone as standard. The cyclobutanone had all physical constants (bp, ir, nmr, mp of 2,4-dinitrophenylhydrazone) in agreement with literature values: J.M. Conia, Bull Soc. Chim. France, 1803 (1961); K.B. Wiberg and B.J. Mist, J. Amer.Chem. Soc., 83, 1226 (1962).

8. We thank the National Science Foundation for partial support of this work.