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CYANOHYDRINS - A GENERAL SYNTHESIS

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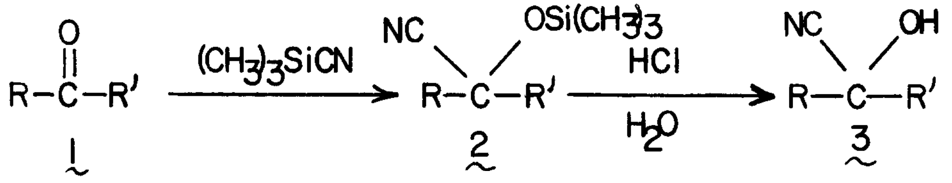
The formation of cyanohydrins is generally considered to be a reaction which is achieved under equilibrating conditions.[1] Thus, it is not surprising that statements appear which claim that highly substituted cyanohydrins, such as that of benzophenone, cannot be made under such conditions.[1-3] This appeared to constitute a major problem for us, since we were in need of large amounts of pure cyanohydrins in connection with another study. We now wish to report a general synthesis of cyanohydrins which does not involve equilibrating conditions and which works with even very hindered ketones, such as benzophenone and *t*-butyl phenyl ketone.

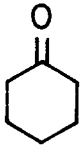
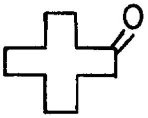
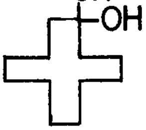
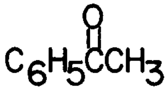
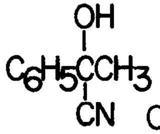
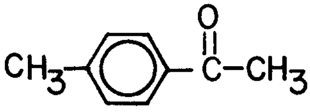
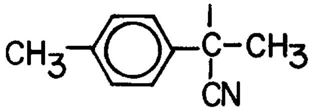
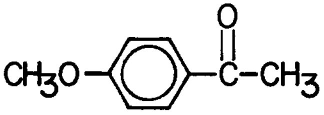
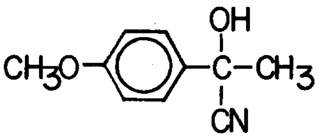
While cyanohydrins represent a class of compounds which are often very difficult to prepare, the trimethylsilyl ethers of these compounds are readily accessible.[4,5] It would seem reasonable that these trimethylsilyl ethers should be able to be converted into cyanohydrins. However, it has been stated that (a) "the silyloxynitrile protective group is inherently unstable to both nucleophiles and aqueous media"[4d] and that (b) "the carbonyl derivative may be readily regenerated in dilute aqueous acid or base."[4a] Conceptually, one can write a reasonable mechanism for the conversion of the silyloxynitrile protected ketone into a ketone under basic conditions. In contrast, we found it difficult to conceive of a rational mechanism for an analogous acid-catalyzed process. Thus, we have studied the acid-catalyzed hydrolysis of trimethylsilyl ethers of cyanohydrins and we have found that the process yields the desired cyanohydrins in almost quantitative yield instead of ketones as reported previously.

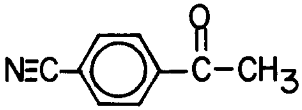
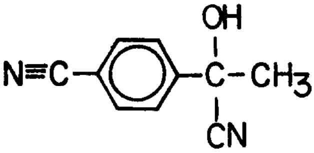
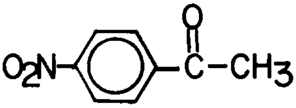
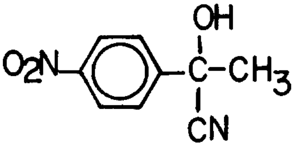
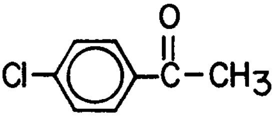
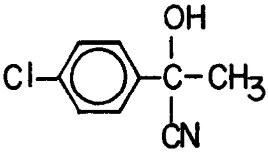
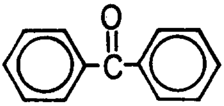
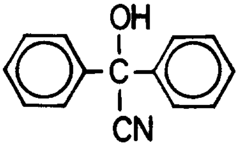
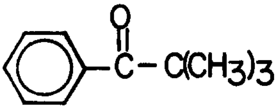
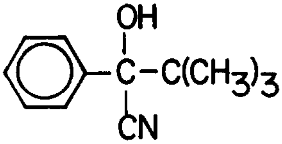
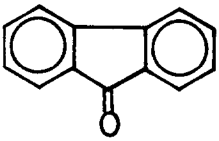
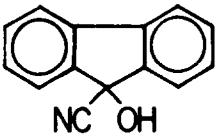
In a typical procedure, 1.0 equivalent of ketone, **1**, in methylene chloride was allowed to react with 1.1-1.2 equivalents of trimethylsilyl cyanide[6] in the presence of a catalytic amount of zinc iodide at room temperature to 65°C for 2-48 h. The solvent was removed under reduced pressure to yield **2**, which was used in the next step without purification. The crude trimethylsilyl cyanohydrin (1-2 g) was added to 15 mL of 3N hydrochloric acid at 25-45°C for 0.5-3.0 h. The product was extracted with ether. The solution was dried over anhydrous magnesium sulfate, filtered, and the solvent removed under reduced pressure. The crude cyanohydrin was then purified by either recrystallization or distillation. Table 1 lists the yield of purified cyanohydrins obtained by this process.



As can be seen from a perusal of Table 1, the yields obtained for the two step process are generally in the ninety percentile range. The process works with dialkyl, diaryl, and alkyl-aryl substituted ketones. A wide variety of other functionality can be tolerated as demonstrated by the cross-section of acetophenones which has been subjected to this con-

Table 1. Yields of purified Cyanohydrins Obtained from Selected Ketones[a]

Ketone	Cyanohydrin	% Yield	Melting Point (°C)
		90	27-28°[b]
		93	115-116°[c]
 $C_6H_5\overset{\overset{O}{\|}}{C}CH_3$	 $C_6H_5\underset{CN}{\overset{OH}{C}}CH_3$	91	d
		97	79.5-80.0°
		96	78-80°

Ketone	Cyanohydrin	% Yield	Melting Point (°C)
		95	77.5-78.5°
		89	112-113°
		94	91.5-92.5°
		98	131.0-132.5°[e]
		99	82-83°
		98	118.5-120.0°

(a) Satisfactory elemental analyses and/or exact mass molecular weights have been obtained on all new compounds. (b) Lit[7] mp 27-28°C; bp 63°C (10^{-6} mm). (c) Lit[8] mp 115-116°C. (d) Product[9] obtained by Kugelrohr distillation, oven temperature 170°C (0.05 mm). (e) Lit[3] mp 127-130°C.

version of ketones to cyanohydrins. The aspect of this reaction which merits most emphasis is the ease with which highly hindered ketones, such as benzophenone and *t*-butyl phenyl ketone, are converted to their respective cyanohydrins.

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