Hydrocyanation. IV.[1] New Hydrocyanation Methods Using Hydrogen Cyanide and an Alkylaluminum, and an Alkylaluminum Cyanide[2]

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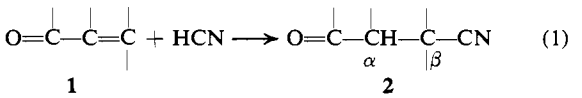
Abstract: Two new hydrocyanation methods using alkylaluminum compounds are described. The first method involves treatment of an α,β-unsaturated ketone with a combination of a trialkylaluminum or an alkylaluminum halide and hydrogen cyanide (R_3Al–HCN, method A) in tetrahydrofuran, and the second one involves treatment of an α-enone with dialkylaluminum cyanide (R_2AlCN, method B) in various aprotic solvents such as benzene, methylene chloride, ethers, and tetrahydrofuran; both methods are carried out at or below room temperature. Usually, Et_3Al or Et_2AlCl are used as the coreagents of HCN in the method-A hydrocyanation, although mechanistically $EtAlCl_2$–HCN represents the ideal reagent for this method. Diethylaluminum cyanide (Et_2AlCN) is the representative reagent for the method-B hydrocyanation. The high efficiency and the high uniformity of both methods compared with the hitherto known methods are demonstrated by the very rapid hydrocyanation of cholestenone (**3**) to give 3-oxo-5α- and-5β-cholestane-5-carbonitriles (**4** and **5**) in almost quantitative yield with no remarkable side reactions, and by the successful hydrocyanation of the Δ^8-11-oxosteroid **6** to yield the 8β-cyano steroid **7** in high yield, hydrocyanation of the compound **6** having been unsuccessful by any of conventional methods on steric grounds. Method-B hydrocyanation is solvent dependent, the rate being increased with decreasing basicity of the solvent. Method-A and method-B hydrocyanation have clearly distinct reaction modes. Whereas the method-A reaction is shown to be catalytic by nature (excess of the reagents is used in practice), method-B reaction proceeds with 1:1 substrate to reagent stoichiometry. Method-A hydrocyanation does not involve a 1,2-addition reaction, though this is the predominant reaction in the initial stage of method-B hydrocyanation. Method-A hydrocyanation is irreversible and gives kinetically controlled products. On the other hand, in the method-B hydrocyanation in benzene, the trans to cis product ratio (*e.g.*, the ratio of **4** to **5** in the hydrocyanation of cholestenone and of **9** to **10** in the hydrocyanation of the acetylhydrindene derivative **8**) is decreased dramatically by prolongation of the reaction time and ultimately reaches an equilibrium ratio, this time dependency showing clearly the reversibility of the reaction. In this connection, it is possible to prepare either a thermodynamically unstable stereoisomer or a stable isomer by application of either the method-A hydrocyanation or the method-B hydrocyanation.

We previously reported[3] a convenient procedure for 1,4 addition of hydrogen cyanide (conjugate hydrocyanation) to α,β-unsaturated ketones (α-enones) furnishing β-cyano ketones according to eq 1.[4,5] The



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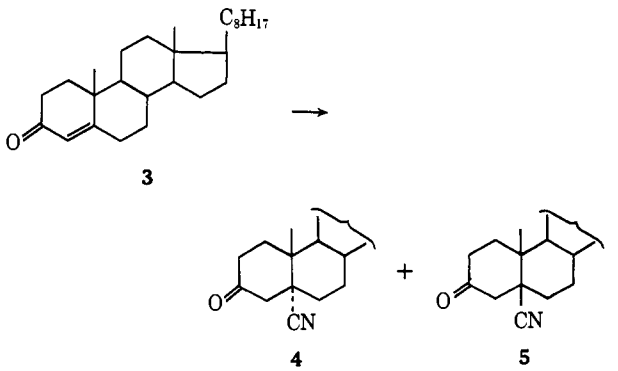
procedure, involving the use of potassium cyanide with an appropriate amount of ammonium chloride[3b] in dimethylformamide (DMF), has proved superior to the conventional procedure using alkali cyanide in an aqueous alcoholic solution, because the former procedure is devoid of undesirable side reactions such as hydrolysis, dimerization, and eventually competitive 1,4 addition of protic solvents, which usually accompany the latter procedure.[6] Thus, cholestenone (**3**) which is, from a structural point of view, seemingly a



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(1) Part III: W. Nagata and M. Yoshioka, *Tetrahedron Lett.*, 1913 (1966).

(2) For preliminary communications see W. Nagata, M. Yoshioka, and S. Hirai, *ibid.*, 461 (1962); and W. Nagata and M. Yoshioka, *ibid.*, 1913 (1966). This work was presented in part at the 2nd International Congress on Hormonal Steroids, Milan, Italy, May 1966. *Cf.* W. Nagata and M. Yoshioka, *Proc. Int. Congr. Horm. Steroids, 2nd, 1966*, 327 (1967).

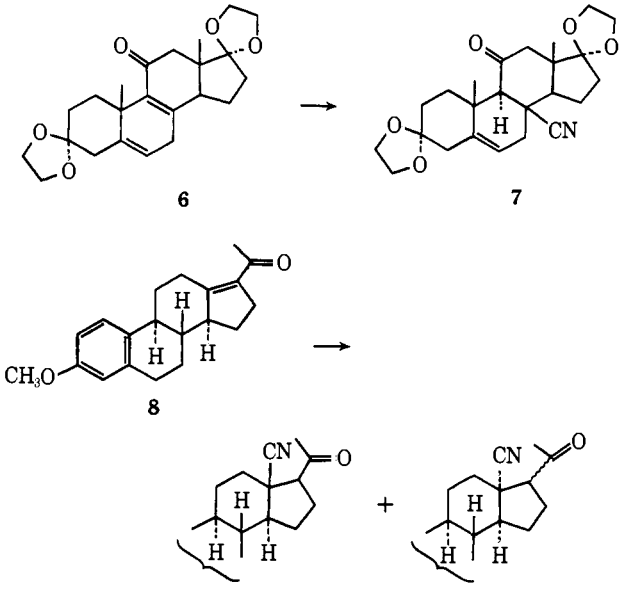
(3) (a) W. Nagata, S. Hirai, H. Itazaki, and K. Takeda, *J. Org. Chem.*, **26**, 2413 (1961); (b) the process, though similar to the Zelinsky–Stadnikoff procedure for synthesis of amino nitriles [N. Zelinsky and G. Stadnikoff, *Chem. Ber.*, **39**, 1722 (1906)], was first applied by our research group to the conjugate addition of HCN to α,β-unsaturated ketones.

(4) For reviews, on hydrocyanation see (a) P. Kurz in "Methoden der Organischen Chemie," Vol. VIII, Georg Thieme Verlag, Stuttgart, 1952, p 265; G. Dittus, *ibid.*, Vol. VI/3, 1963, p 371; (b) V. Migradichian, "The Chemistry of Organic Cyanogen Compounds," Reinhold, New York, N. Y., 1947, p 219; (c) D. T. Mowry, *Chem. Rev.*, 42, 189 (1948).

(5) For examples of 1,4-conjugate hydrocyanation of α,β-unsaturated ketones, see the following recent publications: (a) P. C. Mukharji, *Sci. Cult. (Calcutta)*, **13**, 39 (1947); *Chem. Abstr.*, 42, 2957*b* (1948); **43**, 2200 (1949); *J. Indian Chem. Soc.*, **25**, 365, 373 (1948); (b) W. F. Whitmore and C. W. Roberts, *J. Org. Chem.*, 13, 31 (1948); (c) H. H. Inhoffen, *et al.*, *Chem. Ber.*, 87, 684 (1954); *ibid.*, **91**, 2627 (1958); (d) D. K. Banerjee, J. Dutta, and G. Bagavant, *Proc. Indian Acad. Sci., Sect. A*, **46**, 80 (1957); *Chem. Abstr.*, **52**, 3701 (1958); (e) J. Romo, *Tetrahedron*, **3**, 37 (1958); (f) E. Alderová, L. Novák, and M. Protiva, *Collect. Czech. Chem. Commun.*, **23**, 681 (1958); (g) R. A. Barnes and R. Miller, *J. Amer. Chem. Soc.*, **82**, 4960 (1960); (h) N. G. Kunda and P. C. Dutta, *J. Chem. Soc.*, 533 (1962); (i) L. Novák, M. Borovička, and M. Protiva, *Collect. Czech. Chem. Commun.*, 27, 1261 (1962); (j) S. Julia, H. Linares, and P. Simon, *Bull. Soc. Chim. Fr.*, 2471 (1963); (k) E. W. Cantrall, R. Littel, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964); (l) R. D. Haworth, B. G. Hutley, R. G. Leach, and G. Rodgers, *J. Chem. Soc.*, 2720 (1962); (m) D. K. Banerjee and V. B. Angadi, *Tetrahedron*, 21, 281 (1965).

(6) (a) A. Bowers, *J. Org. Chem.*, **26**, 2043 (1961); (b) W. L. Meyer and N. G. Schnautz, *ibid.*, 27, 2011 (1962); (c) E. Wenkert, R. L. Johnson, and L. L. Smith, *ibid.*, **32**, 3224 (1967); (d) O. R. Rodig and N. J. Johnston, *ibid.*, 34, 1942 (1969).

poorly reactive α,β-unsaturated ketone was smoothly hydrocyanated by this method giving in excellent yield the *trans*- and the *cis*-cyano ketones **4** and **5** in a ratio of 3:5 without any appreciable amount of by-products.[3a] This improved procedure has proved to be suitable for introduction of a carbonitrile group into an angular position of various polycyclic systems (angular cyanation) and has been successfully applied by our[7] and other research groups[8] to syntheses of natural products, modified steroids, and other polycyclic carbonitriles. However, this procedure was still found to be unsatisfactory both in efficiency and stereoselectivity in certain cases. For example, androsta-5,8-diene-3,11,17-trione 3,17-bisethylene ketal (**6**) did not afford the 8β-cyano 11-ketone **7** at all[9] by this procedure, and hydrocyanation of the acetylhydrindene derivative **8**, which is an important intermediate in our steroid total syntheses,[7b] yielded only a low yield (22%) of the C/D-



trans-cyano ketone **9**, the undesired cis isomer **10a** being a major product (57%).

In this situation, a project to find new and more advantageous hydrocyanation reagents was initiated. At the outset, the following factors were considered for design of new reagents: (1) the reagent should be soluble in aprotic solvents to avoid formation of solvolysis products; (2) it should be only slightly basic or nonbasic to prevent isomerization or dimerization of both substrates and products; (3) it should be capable of activating the α-enone system sufficiently; and (4) it should have or produce a cyanide species. With these requirements in mind, we first examined, using cholestenone **3** as a substrate, reactivities of several cyanides of lithium, magnesium, and aluminum, and combinations of certain derivatives of these metals and hydrogen cyanide (HCN), mainly by analogy with other alkylating or reducing organometallic reagents. Among these, only lithium cyanide[10] and combinations[11] of certain aluminum alkoxides and HCN were found to show a moderate efficiency, and a combination of aluminum chloride and HCN[10] was not effective at all. These results indicated that, in agreement with an earlier observation,[4] a high concentration of cyanide anion or its equivalent species may be more important than strong activation of the α-enone function for effective hydrocyanation. This idea led us to investigate alkylaluminum cyanides and combinations of alkylaluminums and HCN, since the alkyl groups attached to the aluminum do not add to the carbonyl function readily[12] but do effect liberation of cyanide anion. As expected, various alkylaluminum cyanides or combinations of alkylaluminums and HCN were found to be excellent hydrocyanating reagents with high efficiency and high stereoselectivity.

The present paper describes the preparation and properties of these reagents, and general aspects of these new hydrocyanation reactions. Kinetics and mechanism[13] of the reactions, their broad application to conjugate hydrocyanation of α,β-unsaturated ketones, conjugated dienones, and conjugated enamines, preparation of α-cyanohydrins,[14] and the stereochemistry[15] will be reported in the accompanying papers. Hydrocyanation of α,β-unsaturated carboxylic acid derivatives,[16] synthesis of β-cyano aldehydes *via* conjugate hydrocyanation of allylideneenamines,[17] and cleavage of epoxides[18] with these reagents have already been reported.

Results and Discussion

Preparation and Properties of the Reagents. Commercially available alkylaluminum compounds including alkylaluminum halides (R_3Al; R = alkyl or halogen, at least one of R_3 represents an alkyl group) are used as coreagents of HCN in the combination procedure. They include trimethyl- (Me_3Al), triethyl- (Et_3Al), and triisobutylaluminium [$(i\text{-Bu})_3Al$], diethylaluminum chloride (Et_2AlCl), and ethylaluminum dichloride ($EtAlCl_2$). Alkylaluminum cyanides (R_2AlCN) can be conveniently prepared by reaction of alkylaluminums with a slight excess of HCN (1.05~1.1

(7) (a) W. Nagata, T. Terasawa, S. Hirai, and K. Takeda, *Tetrahedron Lett.*, No. 17, 27 (1960); W. Nagata, *Tetrahedron*, **13**, 278 (1961); (b) W. Nagata, I. Kikkawa, and K. Takeda, *Chem. Pharm. Bull.*, **9**, 79 (1961); (c) W. Nagata, M. Narisada, and T. Sugasawa, *Tetrahedron Lett.*, 1041 (1962); *J. Chem. Soc. C*, 648 (1967); (d) W. Nagata, I. Kikkawa, and M. Fujimoto, *Chem. Pharm. Bull.*, 11, 226 (1963).

(8) (a) J. A. Marshall and W. S. Johnson, *J. Amer. Chem. Soc.*, 84, 1485 (1962); W. S. Johnson and J. F. W. Keana, *Tetrahedron Lett.*, 193 (1963); W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. Franck, D. G. Martin, and V. J. Bauer, *Tetrahedron, Suppl.*, **8**, 541 (1966); (b) M. Torigoe and J. Fishman, *Tetrahedron Lett.*, 1291 (1962); *Tetrahedron*, **21**, 3669 (1965); (c) W. L. Meyer and J. F. Wolfe, *J. Org. Chem.*, **29**, 170 (1964); (d) A. T. Glen and J. McLean, *Tetrahedron Lett.*, 1387 (1964); (e) E. Wenkert and D. P. Strike, *J. Amer. Chem. Soc.*, **86**, 2044 (1964); (f) J. Fishman and M. Torigoe, *Steroids*, **5**, 599 (1965); (g) S. D. Levine, *ibid.*, 7, 477 (1966); (h) C. Djerassi, R. A. Schneider, H. Vorbrueggen, and N. L. Allinger, *J. Org. Chem.*, **28**, 1632 (1963); (i) K. Wiesner, A. Philipp, and Park-tsun Ho, *Tetrahedron Lett.*, 1209 (1968); (j) P. Crabbe, H. Caprio, A. Cervantes, J. Iriate, and L. Tökes, *Chem. Commun.*, 79 (1968); (k) D. H. R. Barton, E. F. Lier, and J. F. McGhie, *J. Chem. Soc. C*, 1031 (1968); (l) K. Wiesner, L. Poon, I. Jirkovsky, and M. Fishmann, *Can. J. Chem.*, 47, 433 (1969).

(9) W. Nagata, *Proc. Symp. Drug Res.*, 188 (1966). H. Itazaki, Ph.D. Dissertation, Tokyo University, 1969.

(10) Unpublished work of this laboratory.

(11) S. Hirai, *Chem. Pharm. Bull.*, **9**, 837 (1961).

(12) (a) K. Ziegler, K. Schneider, and T. Schneider, *Justus Liebigs Ann. Chem.*, **623**, 9 (1959); (b) K. Ziegler, *Experientia, Suppl.*, II, 278 (1955).

(13) W. Nagata, M. Yoshioka, and M. Murakami, *J. Amer. Chem. Soc.*, **94**, 4644 (1972).

(14) W. Nagata, M. Yoshioka, and M. Murakami, *ibid.*, **94**, 4654 (1972).

(15) W. Nagata, M. Yoshioka, and T. Terasawa, *ibid.*, **94**, 4672 (1972).

(16) W. Nagata, T. Okumura, and M. Yoshioka, *J. Chem. Soc. C*, 2347 (1970).

(17) W. Nagata, M. Yoshioka, T. Okumura, and M. Murakami, *ibid.*, 2355 (1970).

(18) W. Nagata, M. Yoshioka, and T. Okumura, *ibid.*, 2365 (1970).

Table I. Yields and Properties of Alkylaluminum Cyanides

Formula[a]	Yield, %	Appearance	Mp, °C, or bp, °C (mm)	ν_{max} (C≡N), cm^{-1}	Mol wt[b] (solvent)	Association degree
Et_2AlCN	80	Colorless syrup	162 (0.02)	2211 (film)	510 (benzene) 550 (*i*-Pr_2O) 207 (THF)	4–5 2
i-Bu_2AlCN	58[c]	Very viscous, colorless syrup	250[d] (0.04)	2210 (film)	792 (benzene)	5
Me_2AlCN	74	White crystals (distillable)	85–86[e] 155[d] (0.25)	*e*	*e*	*e*
EtAl(Cl)CN	65	White powder	130–132 dec	2231 (Nujol)		

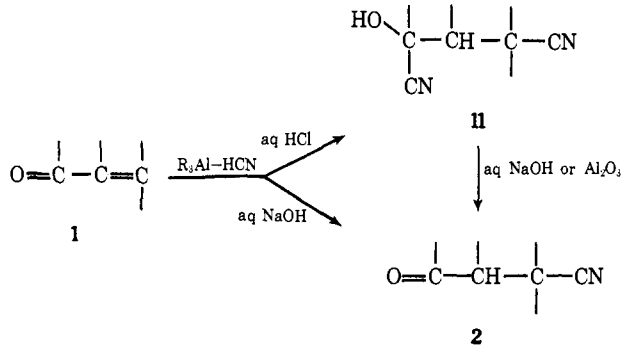
[a] Expressed in monomeric form. [b] Ebullioscopic. [c] The low yield is ascribable to the difficulty of collecting the very viscous distillate. [d] Bath temperature. [e] Lit.[23] mp 89° as colorless crystals; ν_{max} (C≡N) 2213 (in CCl_4), 2224 (in hexachlorobutadiene mull) cm^{-1}; mol wt 330 (tetramer).

molar equiv) below room temperature in less basic aprotic solvents, preferably in benzene, according to eq 2.[19,20] As solvents aromatic hydrocarbons and

$$R_3Al + HCN \longrightarrow R_2AlCN + RH \quad (2)$$

alkyl ethers such as diethyl ether or diisopropyl ether are suitable, but tetrahydrofuran (THF) is not, since the reaction is slow and the produced cyanides are more or less unstable in this solvent. In Table I are summarized the yields and the physical properties of various alkylaluminum cyanides thus prepared.[22] It may be noteworthy that, in contrast to alkylaluminums, diethylaluminum cyanide (Er_2AlCN) can be distilled free of alkyl ethers. It exists as a tetra- or pentamer in boiling benzene or diisopropyl ether and as a dimer in boiling THF; in contrast to very pyrophoric alkylaluminums it is not pyrophoric.

General Procedures.[25] **(A) By Use of Combination Reagents (Method A).** A reagent solution is prepared by addition of a THF solution of 2 mol of HCN to a THF solution of 3 mol of R_3Al with ice cooling. When this solution is added quickly to a THF solution of 1 mol of a substrate with ice cooling under nitrogen a yellow coloration occurs immediately in the reaction mixture. The color gradually fades on standing at room temperature, indicating disappearance of the substrate enone. A gradual evolution of an alkane according to eq 2 is also observed during the reaction. The reaction can be followed by working up a small aliquot and checking the product by usual techniques (tlc, ir, and uv). After completion of the reaction, the reaction mixture is treated with ice–water containing either hydrochloric acid (acid quenching) or sodium hydroxide (alkaline quenching) with efficient stirring.



Acid quenching followed by work-up gives usually the 1,3-dinitrile **11** which can be conveniently converted into the cyano ketone **2** by washing the extract solution with aqueous alkali or by passing through alumina. Alkaline quenching gives directly the β-cyano ketone **2**. Choice of quenching depends upon sensitivity of the product to alkali or acid. In this way, cholestenone (**3**) was hydrocyanated with Et_3Al–HCN giving a mixture of the *trans*- and *cis*-cyano ketones **4** and **5** in quantitative yield. Separation of the two stereoisomers was effected by a combination of fractional crystallization and chromatography, yielding 49% of **4** and 42% of **8**. No side reactions were observed. Similarly, hydrocyanation of the Δ^8-11-oxo steroid **6**, which, on steric grounds, could not be hydrocyanated by any of the known methods, was now successful with Et_3Al–HCN giving 74% of the 8β-cyano 11-ketone **7**, although in this case a larger excess of the reagent and a longer reaction time were necessary. The acetyl hydrindene **8** gave surprisingly the thermodynamically unstable C/D-*trans*-cyano ketone **9** in a high yield (over 70%) by the same procedure.

In general, conjugate hydrocyanation of most of α,β-unsaturated ketones of various types can be successfully carried out in this way, as demonstrated in the accompanying paper.[14] Usually, the reaction is carried out at or below room temperature depending upon reactivities of substrates.[14] THF is used as the solvent, but other alkyl ethers such as diethyl ether and diisopropyl ether may also be used at a lower temperature.[26]

(19) For preparation of diethylaluminum cyanide see W. Nagata and M. Yoshioka, *Org. Syn.*, in press.

(20) Recently, Ehrlich and Young[21] reported preparation of dimethyl- and diethylaluminum cyanides according to the following equations

$$Me_2AlH + HCN \xrightarrow[\text{at } 0°]{\text{in benzene}} Me_2AlCN + H_2$$

$$Et_2AlCl + NaCl \xrightarrow[\text{benzene, 21 days}]{\text{refluxed in}} Et_2AlCN + NaCl$$

The procedures are apparently disadvantageous, because of the low yield (10%) of Me_2AlCN or the prolonged reaction time.

(21) R. Ehrlich and A. R. Young, *J. Inorg. Nucl. Chem.*, **28**, (1966); *Chem. Abstr.*, **64**, 17265 (1966).

(22) After completion of the preparation of the alkylaluminum cyanides in our laboratories, we noticed that Coates and Mukherjee[23] have prepared dimethylaluminum cyanide in an analogous manner. Also, in the patent literature,[24] formation of diethylaluminum cyanide from triethylaluminum and HCN has been claimed. However, isolation and characterization of the product were not carried out.

(23) G. E. Coates and R. N. Mukherjee, *J. Chem. Soc.*, 229 (1963).

(24) R. S. Stearns, U. S. Patent, 3,078,263 (1963).

(25) See also Experimental Section.

(26) Aliphatic hydrocarbons are not suitable as solvents for method A, since HCN is not soluble in these solvents. When aromatic

As shown in the later section (Stoichiometry), method-A hydrocyanation, in principle, proceeds catalytically with respect to R_3Al. However, it was also found that the reaction was impractically slow with a catalytic amount of R_3Al (*cf.* Table II). Therefore, in practice, 1:2:3 ~ 1:3:5 molar ratios of a substrate to HCN to R_3Al are recommended as a standard procedure with substrate concentrations of 0.1~0.2 *M*. The reagent to substrate ratios should be changed depending upon reactivity of substrates, as illustrated in the accompanying paper.[14]

Et_3Al and Et_2AlCl are very often used as the coreagents for method-A hydrocyanation because of their comparably high efficiency,[13] ready availability, and moderate inflammability. Et_2AlCl, because of its stronger Lewis acidity, is more preferable than Et_3Al in cases where the α-enone function of the substrate is deactivated either electronically or sterically, as illustrated in the accompanying paper.[14] $EtAlCl_2$ is also suitable as a method-A coreagent, although the rate of hydrocyanation with this reagent is considerably low.[13] $(i\text{-Bu})_3Al$ is not preferable for method-A hydrocyanation, since this compound often reduces the carbonyl function of the product to some extent giving a γ-hydroxy carbonitrile as a by-product. Me_3Al proved as effective as Et_3Al, and other R_3Al such as $(n\text{-Pr})_3Al$, $(i\text{-Pr})_3Al$, Me_2AlCl, Et_2AlBr,[27] and Et_2AlI may also be used as coreagents. It is noteworthy and surprising that a trace of water was found to increase the rate of hydrocyanation with Et_3Al–HCN twofold[13] (see the later section), this indicating that in practice any rigorous exclusion of moisture from the reaction mixture is unnecessary so far as method-A hydrocyanation is concerned.[29,30]

Attention should be given to the point that in method-A hydrocyanation, R_3Al reacts, although slowly, with HCN in THF gradually producing R_2AlCN as described above. The *in situ* formed R_2AlCN themselves are also efficient hydrocyanating reagents of another type (method-B hydrocyanation; see below) and, at the same time, they act as coreagents with remaining HCN in the reaction medium. Thus, when Et_3Al is used, at least the following three different reactions take place in parallel: (1) the Et_3Al–HCN reaction, (2) the Et_2AlCN reaction, and (3) the Et_2AlCN–HCN reaction. With respect to this point, the reaction with a combination of $EtAlCl_2$ and HCN may represent an ideal method-A hydrocyanation process, since the reaction of $EtAlCl_2$ with HCN in THF is very slow.[13]

(B) By Use of Dialkylaluminum Cyanides (Method B). R_2AlCN can be stored as 1~2 *M* solutions in benzene, toluene, or diisopropyl ether.[26] The reaction is carried out simply by adding a stock solution of the reagent in 1~2 molar excess to a 0.1~0.3 *M* solution of the substrate α-enone in an aprotic solvent with ice cooling and then allowing reaction mixture to stand, usually at or below room temperature, for a short time. Quenching by either acid or alkali gives the same cyano ketone **2**, indicating that the initial product in method-B hydrocyanation is different from that in method-A hydrocyanation (see later discussion).

In general, method-B hydrocyanation is more rapid than method-A hydrocyanation, and among the R_2AlCN listed in Table I $(i\text{-Bu})_2AlCN$ was found to be the most reactive, followed by Et_2AlCN.[13] However, we usually use Et_2AlCN as the reagent for method B, because it can be purified easily.[31] As the solvent, various aprotic solvents such as benzene, toluene, methylene chloride, diethyl ether, isopropyl ether, dioxane, or tetrahydrofuran can be used. Analogous to other alkylations or reductions with organometallic compounds, efficiency of hydrocyanation by method B depends markedly upon the solvent species. The efficiency increases with decreasing basicity of solvent.[13] Thus, while hydrocyanation of cholestenone (**3**) with Et_2AlCN required a few hours in THF, the reaction was completed within a few minutes in benzene. In each case, the yield of a *ca.* 1:1 mixture of *trans*- and *cis*-cyano ketones **4** and **5** is quantitative. The Δ^8-11-oxo steroid **6** was treated with a large excess of Et_2AlCN in benzene at 0°. However, in this case the reaction rapidly (*ca.* 10 min) gave a 2:8 equilibrium mixture of the substrate and the product (see discussion in the later section). After isolation of the first crop (73%) of the cyano ketone **7**, the recovered substrate **6** was again treated with Et_2AlCN in benzene yielding an additional 18% yield of **7**.

General Aspects of the Reactions. (A) Stoichiometry. In order to determine the stoichiometry of method-A and -B hydrocyanation, hydrocyanation of cholestenone (**3**) was carried out with varied amounts of the reagents in THF at 25°. The reaction was followed by work-up and analysis (tlc and ir) of aliquots and an approximate half-lifetime ($\tau_{0.5}$) and conversion of **3** to **4** and **5** at the final stage were measured. For the method-A hydrocyanation, a large excess of HCN (10 molar equiv) was used, and the results are summarized in Table II. As is clear from Table II, R_3Al acts as a catalyst in method-A hydrocyanation. However, with

Table II. Data for Method-A Hydrocyanation of Cholestenone (0.1 *M*) with Varied Amounts of Alkylaluminums and Excess of HCN (1.0 *M*) in THF

$$\mathbf{3} \xrightarrow[2.5 \pm 0.03°]{R_3Al\text{–}HCN} \mathbf{4} + \mathbf{5}$$

(**3**:R_3Al:HCN = 1:*x*:10)

R_3Al	*x*, *M*	$\tau_{0.5}$, hr	Conversion, %
Et_3Al	0.50	4	100
Et_3Al	0.25	11	97
Et_2AlCl	0.50	10	98
Et_2AlCl	0.25	26	100
Et_2AlCl	0.10	72	80
$EtAlCl_2$	1.00	11	100
$EtAlCl_2$	0.50	32	100
$EtAlCl_2$	0.25	62	100

hydrocarbons are used as solvents, conversion of R_3Al into R_2AlCN is rapid, implying that the reaction should then be categorized as method B, described in the following section of the text.

(27) The usefulness of Et_2AlBr in method-A hydrocyanation has recently been shown by Strike, *et al.*[28]

(28) D. P. Strike, D. Herbst, and H. Smith, *J. Med. Chem.*, 10, 446 (1967).

(29) Needless to say, the presence of a larger amount of water retards the rate markedly because of decomposition of alkylaluminums.

(30) In method-B hydrocyanation, a trace of water was found to accelerate the reverse reaction considerably.

(31) Practically, a crude solution of Et_2AlCN may be used. However, in this case, an appreciable excess of HCN (1.1–1.2 molar equiv) should be employed for preparation of the solution, since a minor amount of Et_3Al remaining unchanged in the solution was found to retard the reaction markedly in hydrocyanation of the Δ^8-11-oxo steroid **6**. The retardation did not occur in THF. At present, we are unable to account for this retardation.

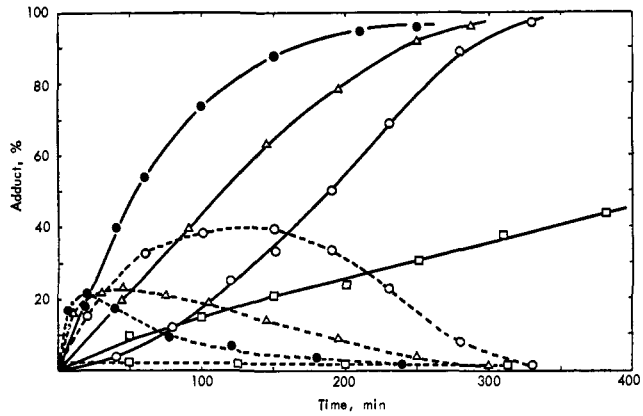


Figure 1. Formation (%) of the 1,2 (dotted line) (**12**) and the 1,4 (solid line) adducts (**4**, **5**, and **11**) *vs.* time for hydrocyanation of **3** (0.04 *M*) with HCN (0.28 *M*) and the following R_3Al (0.28 *M*) in THF at 25°: ○, Et_3Al; ●, Et_3Al + H_2O (0.026 *M*); △, Et_2AlCl; □, $EtAlCl_2$.

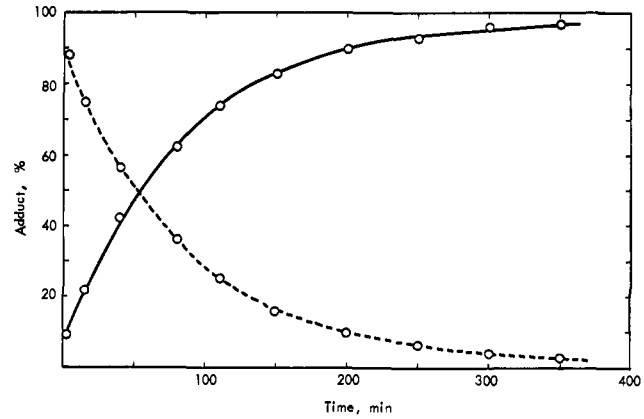
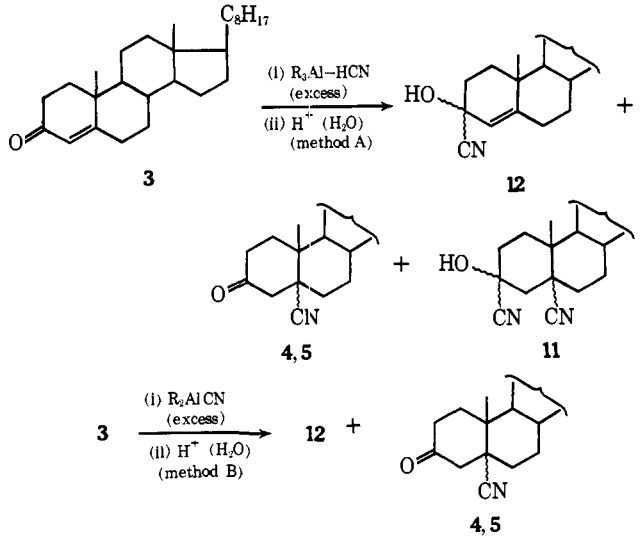


Figure 2. Formation (%) of the 1,2 (dotted line) (**12**) and the 1,4 (solid line) adducts (**4** and **5**) *vs.* time for hydrocyanation of **3** (0.01 *M*) with Et_2AlCN (0.07 *M*) in THF–*i*-Pr_2O (4:1) at 0°.

less than 0.25 molar equiv of R_3Al, the rate is extremely slow and the reaction often does not go to completion. Therefore, in practice, an excess of R_3Al is usually used as described for method A in the foregoing section. On the other hand, 92% completion of the reaction was observed within 7 hr in the method-B hydrocyanation of cholestenone with Et_2AlCN in equimolar amounts, implying that the method-B hydrocyanation proceeds with a 1:1 enone to R_2AlCN stoichiometry. However, in practice, a 1–2 molar excess of the reagent is used for the method-B hydrocyanation.

(B) Product Analysis and Competition of the 1,2 and 1,4 Additions. As pointed out in the foregoing section, method-A and -B hydrocyanations are different in several aspects, although both give after alkaline quenching and work-up the same β-cyano ketone, the 1,4-addition product **2**. In order to give further insight on this point, product analysis was carried out at the initial, intermediate, and final stages of the reactions using cholestenone (**3**) as a substrate (a more detailed description and discussion will be presented in the accompanying paper[13]). *A priori*, it was anticipated that 1,2 and 1,4 additions take place competitively in an intermediate stage of the reactions. In fact, acid quenching in method-A hydrocyanation of **3** with an excess of HCN–Et_3Al before completion of the reaction gave a product consisting of cholestenone (**3**) and epimeric mixtures of the 1,2-adducts **12**, the 1,4 adducts **4** and **5**, and the dinitriles **11**. Clearly, the dinitriles **11** are derived from the initially formed cyano ketones **4** and **5** with the excess of reagents, and, therefore, should be regarded as the 1,4 adducts. Amounts of these products were separately determined[32] and the product distribution *vs.* the reaction time is plotted in Figure 1. The plot shows clearly that in the initial stage the 1,2 addition exceeds the 1,4 addition and the situation becomes reverse in the intermediate to final stages. In this case, one must notice that the 1,2 adducts are indeed formed but do not exceed 40%. A similar plotting for the method-A hydrocyanation of **3** with HCN was also carried out using Et_3Al and a trace amount of water, Et_2AlCl, and Et_2AlCl_2 and the plots are shown also in Figure 1. There is observed a marked trend for the formation of the 1,2 adducts to decrease with increasing Lewis acidity of R_3Al, the formation being negligible with $EtAlCl_2$. The trend is in good accordance with that observed in ethane formation (eq 2), where a considerable amount of ethane is evolved with Et_3Al–HCN and a small amount with $EtAlCl_2$–HCN (see also the accompanying paper[13]). In this connection, it was anticipated that in contrast to method-A hydrocyanation an overwhelming amount of the 1,2 adducts would be formed in the initial stage of the method-B reaction. An analogous product analysis was thus carried out for the Et_2AlCN hydrocyanation of cholestenone in THF. Here, formation of 1,3-dinitriles **11** was not observed on acid quenching even by use of an excess of the reagent, and the cyano ketones **4** and **5** were formed as the 1,4 adducts. The data are shown in Figure 2. As expected, 1,2 addition occurs instantaneously in *ca.* 97% yield in the method-B hydrocyanation and the 1,2-adducts **12** thus formed decompose gradually giving cholestenone (**3**) and the 1,4 adduct with its enolate structure (see below). Since the concentration of cholestenone (**3**) is below 3% during the reaction period, the 1,4 adducts are formed with a curve almost symmetrical to that of the decomposition of the 1,2 adducts as shown in Figure 2. The kinetic pattern thus seems to be that the 1,4 addition occurs directly, starting with the 1,2



(32) For analysis of the remaining cholestenone and the 1,2 and 1,4 adducts see the accompanying paper (ref 13).

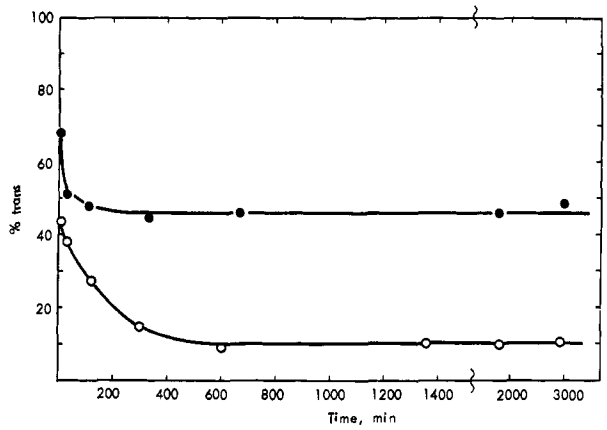
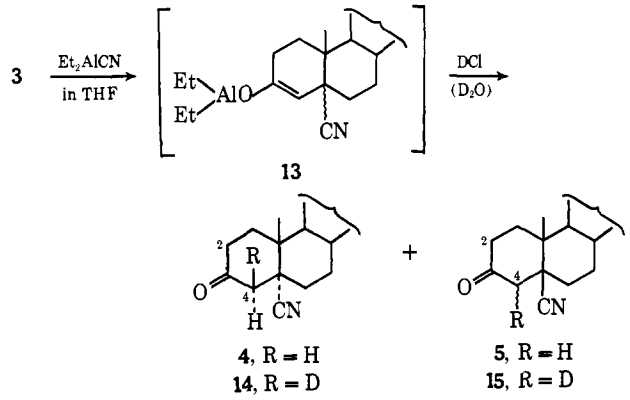


Figure 3. Plots of the amount (%) of the *trans*-cyano ketone **4** (○) and **9** (●) as a function of time in the method-B hydrocyanation of cholestenone (**3**) and the acetylhydrindene derivative **8** (each 0.1 *M*) with Et_2AlCN (0.3 *M*) in benzene.

adducts. In any case *the 1,2 addition occurs overwhelmingly in the initial stage of the method-B hydrocyanation, this fact being in marked contrast to the ideal method-A hydrocyanation, in which negligible amounts of 1,2 adducts are formed*, as shown in the case of the $EtAlCl_2$–HCN hydrocyanation. This great difference in product distribution in the initial stage may be considered a good way of differentiating method-A and -B hydrocyanations. On this basis, one may consider that in the Et_3Al–HCN, Et_3Al–H_2O(trace)–HCN, and Et_2AlCl–HCN procedures the method-A and -B type reactions occur intermingled to some extent.

As described above, acid quenching of a reaction mixture of the method-B hydrocyanation does not give the 1,3-dinitriles **11** even with the use of an excess of Et_2AlCN, and the cyano ketones **4** and **5** are obtained as the 1,4 adducts, this fact suggesting that in the method-B hydrocyanation the initial 1,4 adducts have an enol aluminate structure **13** just as those in conjugate addition of a Grignard reagent or in alkali metal



reduction of α,β-unsaturated ketones in liquid ammonia. For elucidation of the structure, a reaction mixture of cholestenone hydrocyanation with Et_2AlCN was worked up by quenching with an appropriate amount of DCl in D_2O. The resulting mixture of the *trans*- and *cis*-1,4-adducts **14** and **15** were analyzed by mass and nmr spectrometry. The mass analysis showed that the products are monodeuterated, and that incorporation of deuterium in the *trans*- **14** and *cis*-cyano ketone **15** amounts to 75 and 55%, respectively. The nmr data in $CDCl_3$ and benzene-d_6 are listed in Table III together with those for **4** and **5** as reference compounds. Assignment of C_4 protons in **4** and **5** is made from the AB type pattern. The axial or equatorial assignment of two C_4 protons is based on the following considerations: (1) in cis epimer **5**, the C_4 axial proton should appear in a lower field than the equatorial proton owing to van der Waals interaction between the C_4 axial proton and the C_7 and C_9 axial protons,[33a] (2) the C_4 equatorial protons in all the compounds should be broadened by W type coupling with the C_2 equatorial protons,[33b] and (3) shielding induced by benzene should be greater in the C_4 axial proton than in the C_4 equatorial proton.[33c] The data in Table III clearly show that only the C_4 axial position is deuterated in the *trans*-cyano ketone **14**, while both the C_4 axial and equatorial positions are deuterated in the *cis*-cyano ketone **15** with predominant deuteration at the axial position. Moreover, there is no evidence of C_2 deuteration. These results support strongly the structure of **13** for the initial product of the conjugate hydrocyanation with Et_2AlCN and more generally of conjugate hydrocyanation according to method B.

Table III. Nmr Data of the Cyano Ketones **4** and **5**, and of the Deuterated Cyano Ketones **14** and **15** (Me_4Si as an Internal Reference)

Compd	C_4 axial H, cps	C_4 equatorial H, cps[a]	*J*, cps	Solvent
4	149 (s)	149 (s)		$CDCl_3$
	117 (sharp d)	134 (br d)	16	Benzene-d_6
14		132 (br s)		Benzene-d_6
5	180 (sharp d)	141 (br d)	16	$CDCl_3$
	148 (sharp d)	133 (br d)	16	Benzene-d_6
15[b]	148 (br s)	129 (br s)		Benzene-d_6

[a] The signal pattern of C_4 equatorial H is broadened by W type coupling with C_2 equatorial H. [b] The signal strength of C_4 equatorial H is greater than that of C_4 axial H.

(C) Irreversibility and Reversibility. In the course of investigation on the new hydrocyanation methods, we observed two important facts. Firstly, whereas no starting α-enone was recovered in the method-A hydrocyanation of the Δ^8-11-oxo steroid **6**, considerable amounts (*ca.* 20%) of **6** were recovered besides the 1,4-adduct **7** (80%) in the more efficient method-B hydrocyanation using Et_2AlCN in benzene, even after prolonged reaction time, as described in the previous section. Secondly, while the trans (**4**) to cis (**5**) ratio of the conjugate cholestenone hydrocyanation was not altered by prolongation of the reaction time in method A, the ratio was remarkably lowered in method B using Et_2AlCN in benzene, indicating increase of the more stable cis isomer with increasing reaction time. These two facts strongly suggest that in method-A hydrocyanation, the 1,4 addition (no 1,2 addition occurs in an ideal method-A hydrocyanation) is irreversible because of the presence of proton, but, in the method-B hydrocyanation, not only the 1,2 addition but also the 1,4 addition is reversible. To clarify this point, we determined the alteration of the cis to trans ratios of the 1,4 adducts with time in the method-B hydrocyanation of cholestenone (**3**) and the acetylhydrindene derivative **8** using Et_2AlCN in benzene. The results are illustrated in Figure 3.[34] In cholestenone hydrocyana-

(33) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, (a) p 189, (b) p 115, (c) p 172.

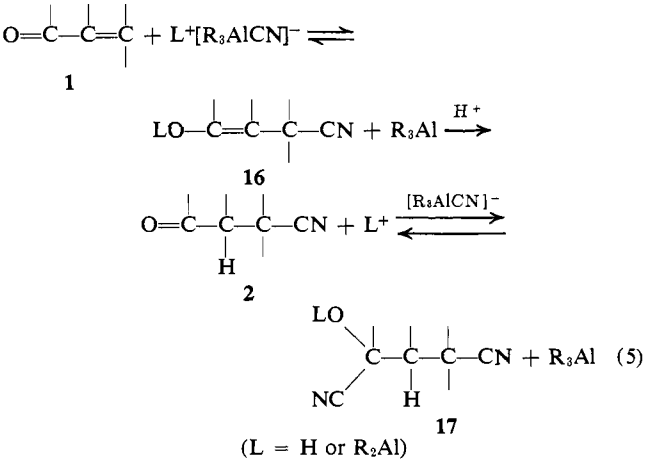
tion, the initial trans to cis ratio of 44:56 decreases rapidly with time and reaches an equilibrium mixture of *ca.* 90:10 in about 7 hr. The decrease of the initial kinetic ratio of 69:31 (trans:cis) is more rapid in the method-B hydrocyanation of **9** and the time required for equilbration producing a 45:55 mixture of **9** and **10** is only 3 hr. This time dependency of the product ratio is observed also in hydrocyanation with Et_2AlCN in THF, although the period for reaching an equilibrium is extremely long (see the accompanying paper[15]). On the contrary, no change in the product ratio was seen in the method-A hydrocyanation.[15] *The time dependency and nondependency of the product ratio in the method-B and -A hydrocyanation, respectively, show clearly the reversibility of the former reaction and the irreversibility of the latter reaction.* Apparently, the initial and the final ratios in the method-B hydrocyanation represent the ratios of kinetically and thermodynamically controlled processes, respectively. On the other hand, the method-A hydrocyanation is only kinetically controlled. Therefore, the thermodynamically unstable isomer can be obtained preferably by employing method A or by interrupting method-B hydrocyanation as early as possible.[15,35] On the other hand, the more stable isomer can be obtained by applying method-B hydrocyanation with sufficient reaction time using a less basic aprotic solvent such as benzene.

Reaction Pathways. From the discussions described above, distinct features of the method-A and method-B hydrocyanations became clear. The major differences may be summarized as follows. While the method-A hydrocyanation, although less efficient, proceeds catalytically by nature, the method-**B** hydrocyanation is very efficient and proceeds with the 1:1 substrate to reagent stoichiometry. In the method-A hydrocyanation, the 1,2 adduct is not formed, and, because of the presence of proton, the reaction proceeds irreversibly and the initial product is the β-cyano ketone **2** or the 1,3-dinitrile such as **11** in excess HCN. On the other hand, the 1,2 adduct is formed overwhelmingly at the initial stage of the reaction in the method-B hydrocyanation. In the absence of proton, this reaction proceeds reversibly giving ultimately the thermodynamic product, the structure of the initial 1,4 adduct being an enol aluminate such as **12**. With the accumulated evidence, one may outline the reaction pathways of the method-A and method-B hydrocyanations as follows (a more detailed discussion of the mechanisms will appear in the accompanying paper[13]). Trialkylaluminums and, particularly, alkylaluminum halides may dissociate to some extent in THF yielding the dialkylaluminum cation (R_2Al^+) and react with HCN producing a conjugate acid as shown by eq 3 and 4.

$$2R_3Al \rightleftharpoons R_2Al^+ + R_4Al^- \quad (3)$$

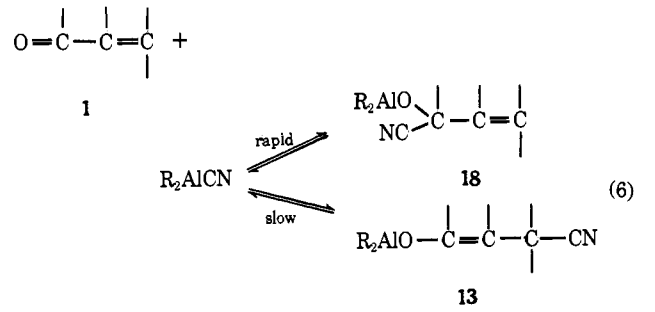
$$R_3Al + HCN \rightleftharpoons H^+ + [R_3AlCN]^- \quad (4)$$

In the method-A hydrocyanation, the α-enone function may be activated by the cationic species, proton or R_2Al^+ (yellow coloring), giving an activated carbonium ion, which is then attacked by the complex-anion $[R_3AlCN]^-$ at the β carbon yielding the enolate **16**. The enolate **16** is rapidly protonated to give the



(5)

1,4-adduct **2**, which is then further hydrocyanated by excess reagent and successively protonated to yield the 1,3-dinitrile **11** *via* the metalated intermediate **17** (eq 5). The mechanism of the method-A hydrocyanation is thus considered to be ionic and the protonation steps are apparently irreversible. On the other hand, a molecular mechanism seems to operate predominantly in the method-B hydrocyanation on several grounds,[13] and, thus, the monomerized neutral molecule R_2AlCN is assumed to act as both the enone-activating and the cyanating agent. An initial concerted activation and cyanation of the carbonyl function with R_2AlCN is very likely, since formation of the 1,2-addition product **18** is extremely rapid. The 1,4-product **13** is yielded slowly *via* the reconverted enone **1**, all the steps being reversible (eq 6). The postulated reaction pathways



(6)

for the method-A and -B hydrocyanations are well compatible with the observed experimental facts.

Conclusion

As demonstrated above, the new hydrocyanation methods are evidently superior to any of the hitherto known methods in every respect. The major advantages of the new reactions include (1) high efficiency (the reaction is usually very rapid under very mild conditions and hydrocyanation of certain less or nonreactive α-enones proved successful only with the new reagents), (2) high uniformity (the reaction is scarcely accompanied by undesirable side reactions), (3) high selectivity (other carbonyl functions such as acid, ester, lactone, carbonitrile, and amide are not usually affected

(34) An analogous determination was carried out with $\Delta^{4(10)}$-octalin-3-one and 9-methyl-$\Delta^{4(10)}$-octalin-3-one in the method-A and in the method-B hydrocyanation with different solvent systems. These results and a more detailed discussion will appear in the accompanying paper.[15]

(35) Since the efficiency of method-B hydrocyanation is very high, most of the reaction is completed very early, before equilibration occurs. This means that most of the method-B hydrocyanation is practically kinetically controlled with some exceptional cases such as the hydrocyanation of the Δ^8-11-oxo steroid **6**, in which the equilibration appears to be reached in about 10 min with Et_2AlCN in benzene (see also ref 15).

by the new reagents), and (4) high stereoselectivity in the 1,4 adducts (the thermodynamically more stable or less stable stereoisomer can be preferentially prepared at will by applying either the method-B or the method-A hydrocyanation, respectively).

Roughly speaking, the features of the method-A hydrocyanation are reminiscent of the known conjugate addition of various acids and those of the method-B hydrocyanation of the addition of bases. In the former reaction, activation of the enone system is evident and in the latter, addition of the nucleophiles plays an important role. Method-A reagents, R_3Al–HCN, are similar to metal aluminum hydrides in that the reacting nucleophiles are complex anions. Method-B reagents, R_2AlCN, are analogous to alkylaluminum hydrides and the Grignard reagents. Despite the structural similarity, the difference between the reaction mode of RMgX and R_2AlCN is obvious. Whereas the alkyl group of RMgX serves as a nucleophilic alkylating species, that of R_2AlCN serves essentially to liberate the cyanide anion. Moreover, unlike the Grignard reagents, dialkylaluminum cyanides do not abstract the acidic C–H proton leading to enolization of ketones. These differences may be accounted for by a greater covalent nature of the R–Al bond than that of the R–Mg bond. Another important difference between Grignard and the present reagents is seen in their steric requirements. The steric bulk of the new hydrocyanation reagents seems to be far smaller than that of the Grignard reagent and, therefore, the approach from the more hindered side is possible as shown in the hydrocyanation of the Δ^8-11-oxo steroid **6** (see also the accompanying paper[15]).

It should be pointed out that until recently utilization of hydrocyanation in organic syntheses, especially in syntheses of complex natural products, had been overlooked or limited owing to many disadvantages of the conventional methods, despite the great usefulness of the cyano group as a source of various carbon substituents. The substantial improvement made by the present new reactions will bring about a widespread application of the reaction to organic syntheses.

Experimental Section

For general directions, see an accompanying paper.[14] Molecular weights of dialkylaluminum cyanides were determined with a Shibayama-Kagaku ebulliometer in an atmosphere of high-purity argon.

Handling of Alkylaluminums. Alkylaluminums and their handling procedures are available from Ethyl Corp., La. Since alkylaluminums are pyrophoric, they must be handled with great care. We handled alkylaluminums and their solutions with hypodermic syringes in an inert atmosphere of nitrogen or argon. Reactions using alkylaluminums were carried out also in an inert atmosphere.

Solvents. All solvents used for reactions employing alkylaluminum compounds are anhydrous. They were distilled from sodium dispersion (50% in wax).

Diethylaluminum Cyanide (Et_2AlCN).[19] To a solution of 55 ml (45.7 g, 0.4 mol) of $AlEt_3$ in 150 ml of benzene kept in a round-bottomed flask fitted with a pressure-equalizing dropping funnel and a bubbler was added dropwise from the funnel a solution of 11.9 g (0.44 mol) of HCN in 100 ml of benzene with good magnetic stirring and ice cooling at a constant rate that the solution was added in about 2 hr. After the addition was complete,[36] the reaction mixture was allowed to stand overnight.[37] The benzene was evaporated by adding the reaction solution through a pressure-equalizing dropping funnel to a heated, 200-ml Claisen flask having a 16 × 30 mm Vigreux section and equipped with a cooling and receiving system. After the last trace of the benzene was removed under reduced pressure, the Claisen flask containing crude Et_2AlCN was attached directly (without condenser) to a vacuum adaptor with two clean flasks and heated at high vacuum. After about 1 ml of a fluid forerun was collected, very viscous Et_2AlCN distilled at 162° (0.02 mm) and was collected in a tared receiver by heating the side arm and the adaptor with a hot gun. The yield was 35.6 g (80%): ir (liquid film) 2211 (CN) cm^{-1}; nmr (toluene, the chemical shifts are expressed in ppm from the methyl signal of toluene, positive values denoting upfield shifts) 0.813, 0.950, 1.070 (3, CH_2CH_3); 1.853, 1.987, 2.120, 2.258 (2, CH_2CH_3).

Anal.[38] Calcd for Et_2AlCN: Et, 52.31; Al, 24.29; CN, 23.42. Found: Et, 52.90; Al, 23.03; CN, 22.0; mol wt, in benzene, 518 (*c* 1.02), 499 (*c* 1.54), and 520 (*c* 2.05); in *i*-Pr_2O, 576 (*c* 0.43) and 527 (*c* 0.86); in THF–*i*-Pr_2O (15:1), 207 (*c* 0.43) and 207 (*c* 0.85).

A 1.6 *M* solution of Et_2AlCN was prepared by adding 130 ml of benzene to the receiver, allowing the resulting mixture to stand with occasional swirling until the syrup went into solution, and then making the total volume of the solution 200 ml. The solution was stored in sealed ampoules.

Diisobutylaluminum Cyanide (*i*-Bu_2AlCN). Triisobutylaluminum was treated with HCN (the gas evolution was not detected) and the reaction mixture was worked up in the same way as described above. *i*-Bu_2AlCN was obtained in 58% yield as a highly viscous syrup, bp *ca.* 250° (bath temp) (0.04 mm); ir (liquid film) 2210 (CN) cm^{-1}; nmr (toluene, positive values expressed in ppm from the methyl signal of toluene denote upfield shifts) 0.995, 1.095 [6, $CH(CH_3)_2$]; 1.845, 1.985 (2, CH_2–*i*-Pr).

Anal.[38] Calcd for *i*-Bu_2AlCN: Al, 16.13; CN, 15.56. Found: Al, 15.95; CN, 15.00; mol wt, in benzene, 795 (*c* 2.1), 790 (*c* 1.5), and 838 (*c* 1.0).

Dimethylaluminum Cyanide (Me_2AlCN). In the same way as described above, 9.78 g (0.136 mol) of $AlMe_3$ in 40 ml of benzene was treated with 3.67 g (0.136 mol) of HCN in 40 ml of benzene. After being mixed with 150 ml of *n*-hexane to dissolve a crystalline material, the reaction mixture was worked up in the same way as described above to give 8.278 g (73.5%) of Me_2AlCN, bp 155° (bath temp) (0.25 mm), as a viscous syrup which crystallized on cooling, mp 85–86°.

Anal.[38] Calcd for Me_2AlCN: Me, 36.20; Al, 32.47; CN, 31.34. Found: Me, 34.7; Al, 31.0; CN, 31.3.

Ethyl(chloro)aluminum Cyanide (Et(Cl)AlCN). A solution of 1.73 g (0.064 mol) of hydrogen cyanide in 20 ml of benzene was added to a solution of 7.59 g (0.063 mol) of Et_2AlCl in 50 ml of *n*-hexane in the same way as described above, and the mixture was kept overnight. The white precipitate was filtered off, washed with *n*-hexane, and dried to give 3.83 g (52%) of Et(Cl)AlCN, mp 130–132° dec; ir (Nujol) 2231 (CN) cm^{-1}.

Anal.[38] Calcd for Et(Cl)AlCN: Et, 24.73; Cl, 30.17; Al, 22.95; CN, 22.14. Found: Et, 24.7; Cl, 29.5; Al, 22.1; CN, 22.1.

Evaporation of the mother liquor followed by addition of 15 ml of *n*-hexane gave an additional 0.95 g (13%) of Et(Cl)AlCN, mp 118–121° dec.

Hydrocyanation of Cholest-4-en-3-one (3). A. With Excesses of HCN–$AlEt_3$.[39] To a solution of **3** (0.385 g, 1 mmol) in 4.4 ml of THF was added a reagent solution prepared by adding 1.3 ml (2 mmol) of 1.5 *M* HCN solution in THF to 2 ml (3 mmol) of cold 1.5 *M* $AlEt_3$ solution in THF. The reaction mixture was kept at room temperature for 3.5 hr, poured into ice cold 2 *N* sodium hydroxide (NaOH), and extracted with dichloromethane. CD analysis[40] of a $^1/_{40}$ portion of the product indicated that the trans to cis ratio was 56:44. The residual portion (0.413 g) was subjected to repeated fractional recrystallization[41] from ethanol to afford 0.186 g

(36) Ethane evolution becomes slow suddenly after 1 molar equiv of HCN is added. When the change is recognized distinctly, the addition may be stopped.

(37) The reaction mixture containing about 13% (1.2 *M*) of Et_2AlCN and a small amount of ethylaluminum dicyanide may be used for most method-B reactions without further purification. Care must be taken to have no unchanged $AlEt_3$.[31]

(38) For procedures for analyzing alkylaluminum compounds, see technical bulletins of Ethyl Corp. on analytical methods.

(39) A typical method-A procedure will appear in *Org. Syn.* soon. See also ref 14.

(40) We are indebted to Dr. K. Kuriyama and his coworkers of this laboratory for performing the CD analysis. The CD data in methanol are **4**: $[\theta]_{285} +4000°$, $[\theta]^{max}_{290} +4310°$, $[\theta]_{295} +4120°$; **5**: $[\theta]_{285} -1056°$, $[\theta]^{max}_{289} -1090°$, $[\theta]_{290} -1089°$, $[\theta]_{295} -1012°$.

(41) The recrystallization was done by seeding crystals of a predominant epimer in the crystallization solution. Chromatography on neutral alumina (activity III) or silica gel can be used for the separation,

(46.3%) of 3-oxo-5α-cholestane-5-carbonitrile (**4**), mp 175–180° (a pure sample had mp 180–181°, *cf.* ref 3a), and 0.145 g (36.1%) of the cis epimer **5**, mp 115–121° (a pure sample had mp 122–123°, *cf.* ref 3a). Preparative tlc (silica gel) of the residue (61 mg) from the mother liquors gave 10 mg (2.5%) of **4** and 20 mg (5.0%) of **5**.

B. With an Excess of Et_2AlCN in THF. To a solution of 0.385 g (1 mmol) of **3** in 17 ml of THF kept at 15° was added 3 ml (3 mmol) of a 1 *M* solution of Et_2AlCN in *i*-Pr_2O. After being kept at 15° for 2 hr, the reaction mixture was worked up as described above. CD analysis[40] of a $^1/_{40}$ portion of the product showed a trans to cis ratio of 48:51. Separation of the residual portion (0.415 g) as described above gave 0.181 g (45.1%) of the *trans*-cyano ketone **4** and 0.167 g (41.6%) of the *cis*-cyano ketone **5**.

C. With an Excess of Et_2AlCN in Benzene. Cholestenone (**3**) (2.443 g, 6.36 mmol) in 55 ml of benzene was treated with 19 ml (12.7 mmol) of a 0.67 *M* solution of Et_2AlCN in benzene at room temperature for 10 min. The reaction mixture was worked up as described above. CD analysis[40] of a portion of the product (2.795 g) indicated a trans to cis ratio of 45:55. The residual portion (2.589 g) was subjected to fractional recrystallization and alumina chromatography to give 0.932 g (40.2%) of the *trans*-cyano ketone **3** and 0.982 g (42.3%) of the *cis*-cyano ketone **4**.

D. With HCN (Excess) and AlR_3 (Less Than 1 Molar Equiv) in THF. To a solution of 154 mg (0.40 mmol) of **3** in THF in an amount to make the total volume 4 ml were added at room temperature a 0.3–0.7 *M* solution of AlR_3 (purified by distillation) in THF and 0.57 ml (4.0 mmol) of 7.0 *M* HCN solution in THF. The concentration of the AlR_3 was adjusted as specified in Table II. The mixture was stirred and divided into four ampoules. The ampoules were sealed and kept at 25 ± 0.03°. The operation was done under argon. After appropriate times, the reaction mixtures were poured into 2 *N* NaOH–ice and extracted with ether–dichloromethane (4:1). The half-life and the conversion at infinity for conjugate hydrocyanation were estimated from ir spectra (for analyiss see ref 13) and tlc of the products. The results are shown in Table II.

E. With 1 Molar Equiv of Et_2AlCN in THF. In the same way as described in ref 13, enone **3** (0.1875 *M*) was allowed to react with Et_2AlCN (0.1875 *M*) in THF–*i*-Pr_2O (4:1) at 25 ± 0.03° and aliquots were analyzed at specified times. Conversions to the 1,4-adducts **4** and **5** after alkaline treatment were as follows: % conversion (time), 21% (3 min), 42% (20 min), 70% (90 min), 84% (200 min), 89% (300 min), 92% (422 min).

Hydrocyanation of 3,3:17,17-Bisethylenedioxyandrosta-5,8-dien-11-one (6). A. With HCN–$AlEt_3$.[39] A solution of 30.7 ml (21.8 g, 0.807 mol) of HCN in 307 ml of THF was added with ice cooling and magnetic stirring to a solution of 155 ml (129 g, 1.13 mol) of $AlEt_3$ in 1290 ml of THF. The resulting reagent solution was soon added to a solution of 62.39 g (0.1614 mol) of enone **6**[9] in 624 ml of THF. The resulting solution was kept at room temperature for 25 hr, poured into a vigorously stirred mixture of 240 g of sodium hydroxide and 15 l. of ice water, and extracted with chloroform. The crystalline product (70 g) was recrystallized from acetone–ether to give 49.5 g (74.2%) of 3,3:17,17-bisethylenedioxy-11-oxoandrost-5-ene-8-carbonitrile (**7**), mp 193–194.5° (lit.[9] mp 220–201°).

B. With Et_2AlCN. To a solution of 2.000 g (5.175 mmol) of the enone **6**[9] in 32 ml of benzene and 19 ml of toluene was added 26 ml (31 mmol) of a 1.2 *M* solution of Et_2AlCN in benzene with ice cooling. After being kept at 0° for 10 min, the reaction mixture was poured into a mixture of 20 g of NaOH and 500 ml of ice water and extracted with chloroform. Crystallization of the product from methanol gave 1.567 g (73.3%) of **7**, mp 198–200°. The residue from the mother liquor was hydrocyanated again with 4 molar equiv of Et_2AlCN in the same way as described above. Crystallization of the second product followed by alumina (neutral II) chromatography of the residue from the mother liquor afforded an additional 0.391 g (18.3%) of **7**.

A product from hydrocyanation of **3** with potassium cyanide and ammonium chloride in dimethylformamide[38a] was separated by fractional recrystallization to give **4** and **5** in 32.9 and 51.3% yields. CD analysis of the product showed a trans to cis ratio of 32:68.

Hydrocyanation of *dl*-3-Methoxy-18,19-dinorpregna-1,3,5(10),13-(17)-tetraen-20-one (8) with HCN–$AlEt_3$. A reagent solution consisting of 1.308 g (11.6 mmol) of $AlEt_3$, 0.206 g (7.65 mmol) of HCN, and 7.5 ml of THF was added to a solution of 1.13 g (3.82 mmol) of enone **8** in 5 ml of THF. The resulting solution was kept at room temperature overnight (the reaction was 80% complete after 2 hr), poured into cold 1% NaOH, and extracted with chloroform. The crystalline product (1.26 g) was subjected to recrystallization from acetone–ether and preparative tlc (silica gel) to give 818 mg (66.5%) of *trans*-nitrile **9**, mp 196–197° (lit.[7b] mp 196–199°), 112 mg (9.1%) of *cis*-nitrile **10a**, mp 164–166° (lit.[7b] mp 162–165°), and 8% of their mixture.

Kinetic Data. The kinetic data shown in Figures 1 and 2 are obtained from the data given in ref 13.

Treatment of the Reaction Mixture of Cholestenone (3) and Et_2AlCN with DCl–D_2O. To a solution of 177 mg (0.50 mmol) of cholestenone (**3**) in 0.9 ml of THF was added 0.86 ml (1.0 mmol) of a 1.17 *M* solution of Et_2AlCN in benzene. The reaction mixture was kept at room temperature for 2 hr, poured into an ice-cooled mixture of 0.29 ml (1.5 mmol) of 20% DCl and 15 ml of D_2O, and extracted with dichloromethane (no water washing). Preparative tlc (silica gel) of the product followed by recrystallization from ethanol gave 57 mg of deuterated *cis*-nitrile **15**, mp 121–122°, and 45 mg of trans epimer **14**, mp 180–182°. Their nmr and mass spectroscopic data are recorded in the text (Table III).

Cis–Trans Equilibration in Hydrocyanation of Cholestenone (3). To a solution of 576.9 mg (1.5 mmol) of **3** in 11 ml of benzene was added 3.85 ml of a 1.168 *M* solution of Et_2AlCN in benzene with magnetic stirring at 25 ± 0.03°. Benzene was added to make the total volume 15.0 ml, and the reaction solution was kept at 25 ± 0.03° under agron. At a given interval, a 1.0-ml aliquot was withdrawn, added to a mixture of 2 *N* NaOH (30 ml) and ice, and extracted with three 30-ml portions of ether–dichloromethane (3:1). The extracts were washed with cold 2 *N* NaOH and water, dried, and evaporated. The residue was analyzed by CD in methanol.[40] After 51 hr, the reaction solution containing 0.7 mmol of the cyano ketone was worked up as above. Fractional crystallization of the product (290 mg) from ethanol gave the cis isomer of mp 119.5–120.5° (98 mg) and mp 118–119.5° (26.4 mg) and a cis–trans isomeric mixture of mp 99–103° (90.4 mg, trans:cis = 25.4:74.6, estimated from CD) and mp 97° (15.4 mg, trans:cis = 27.6:72.4). The total trans:cis ratio of isolated materials is 12:88 in good agreement with the value (11:89) from CD analysis of the crude product at a reaction time of 47 hr.

Cis–Trans Equilibration in Hydrocyanation of *dl*-3-Methoxy-18,-19-dinorpregna-1,3,5(10),13(17)-tetraen-20-one (8). To a solution of 148.2 mg (0.5 mmol) of the conjugate ketone **8**[7a] (mp 109.0–110.5°) in 3.72 ml of benzene was added 1.28 ml of a 1.17 *M* solution of Et_2AlCN in benzene at 25 ± 0.03°. After being stirred for 1 min, the solution was divided into ten 0.5-ml portions which were transferred into 1-ml ampoules. The ampoules after being sealed were kept at 25 ± 0.03°. The content was poured into 2 *N* NaOH–ice at a given time and worked up as described for **3**. Glpc analysis of the product was carried out using a hydrogen flame ionization detector on a 1.88 m × 4 mm glass column packed with 1% QF-1 on Chromosorb W at 210° with a nitrogen flow rate of 66 cc/min. The chromatograph showed the presence of two known cyano ketones **9** and **10a**[7a] (retention time: 21.7 and 18.6 min, respectively) and an unknown compound (11.7 min) which was isolated and proved to be the 13α-cyano-17β-acetyl isomer **10b** as shown below.

The above crude products were collected and separated by preparative tlc to give 13.4 mg of crude **10b** as a semicrystalline solid. Recrystallization from acetone–ether gave crystals (6.6 mg), mp 151–154°. On repeated recrystallization, the melting point was raised to 156–158°; ir ($CHCl_3$) 2235 (CN), 1713 (C=O), and 1612 cm^{-1} (Ar).

Anal. Calcd for $C_{21}H_{25}O_2N$: N, 4.33. Found: N, 4.05.

This material was identical (mixture melting point and ir) with an authentic sample of *dl*-3-methoxy-20-oxo-13α-19-norpregna-1,3,5-(10)-triene-18-nitrile (**10b**) prepared by repeated isomerization of **10a** with *p*-toluenesulfonic acid in refluxing toluene.