Tetrahedron Letters No.18, pp. 1913-1918, 1966. Pergamon Press Ltd.
Printed in Great Britain.

ALKYLALUMINUM CYANIDES AS POTENT REAGENTS FOR HYDROCYANATION (1)

Wataru Nagata and Mitsuru Yoshioka
Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan

(Received 26 February 1966)

IN 1962, we reported a new mode of hydrocyanation using hydrogen cyanide and an alkylaluminum in an aprotic solvent (2a) and have demonstrated that the new method has greatly enhanced the usefulness of the hydrocyanation reaction in synthetic organic chemistry (2b). In the same paper (2a) we suggested that in tetrahydrofuran the reacting species in the new reagent system are both a complex acid I and an alkylaluminum cyanide II formed by following equation (i), and showed that diethylaluminum cyanide (II: $R=C_2H_5$) itself reacts with cholestenone in a more enhanced rate than the combination reagent of hydrogen cyanide and triethylaluminum. This experiment was however only preliminary and a detailed examination of this point was needed. The present communication deals with the preparation and reactivities of a series of alkylaluminum cyanides as highly potent hydrocyanating agents.

$$R_3Al + HCN \rightleftharpoons \underset{(I)}{H[R_3AlCN]} \longrightarrow \underset{(II)}{R_2AlCN} + RH \qquad (i)$$

Alkylaluminum cyanides were prepared conveniently by adding a solution of an equi-molar amount of hydrogen cyanide to a solution of alkylaluminum under cooling according to equation (i). The reaction was completed after evolution of one molar equivalent of gas (RH) except for the case of diisobutyl aluminum cyanide and the product was purified by vacuum distillation or recrystallization. As a solvent benzene or a lower alkyl ether was proved to be most suitable, in which the reaction proceeded rapidly and the product was not decomposed. In contrast to alkylaluminums, alkylaluminum cyanides thus obtained are not bound with solvents, when ether or tetrahydrofuran was employed.

Preparation of diethylaluminum cyanide

To a magnetically stirred solution of 15.7 g (0.137 mole) of triethylaluminum in 40 ml of benzene was added dropwise under ice-cooling a solution of 3.70 g (0.137 mole) of hydrogen cyanide in 35 ml of benzene. Vigorous gas-evolution occurred during the addition and ceased when the addition was completed, yielding 3.22 l. of ethane (calcd: 3.40 l.). Benzene was evaporated and the residue was distilled to give 14.1 g (93%) of diethylaluminum cyanide boiling at ca. 150°/0.07 mmHg (bath temperature 200-220°) as a highly viscous oil.

Table I shows the yields, physical properties and the analysis values of the various alkylaluminum cyanides thus prepared, of which dimethylaluminum cyanide has already been described in the literature (3). These compounds are believed to exist in a polymeric form as evident from their high boiling points, the infrared data of the nitrile group (ν_{CN} falls in the range of 2164-2239 cm^{-1} corresponding to bridging nitrile) (3, 4,5) and from molecular weight determination.

Although from structural point of view, alkylaluminum cyanide might be expected to react as both an alkylation and a hydrocyanation agent, this is not the case. A number of examples using diethylaluminum cyanide show that hydrocyanation prevails markedly over alkylation. Reluctance of the reagent to the latter reaction is easily presumed from the results obtained by Ziegler et al. (6) on the addition reaction of trialkylaluminum to carbonyl compounds. Among the four alkylaluminum cyanides described, reactivity of diethylaluminum cyanide was most intensively examined in relation to the earlier reagent of triethylaluminum and hydrogen cyanide (for distinguishing from the alkylaluminum cyanides, we designate this reagent as "combination reagent"). Although in less basic solvents such as methylene chloride, benzene or

TABLE 1

	Formula[a]	m.p. or b.p.	Yield (%)	IR ν_{CN} (cm^{-1})	NMR [e] in toluene
III	$(CH_3)_2AlCN$ [b]	m.p. 85-86°	74	2213 (CCl_4)[b] 2224 (mull)	—
IV	$(C_2H_5)_2AlCN$	$b.p._{0.07}$ ca 150°	93	2211 (film)	CH_3; 48.8, 57.0, 64.2 CH_2; 111.2, 119.2, 127.2, 135.5
V	$C_2H_5AlClCN$	m.p. 130-132°	65	2231 (nujol)	—
VI	$(i\text{-}C_4H_9)_2AlCN$	$b.p._{0.04}$ ca 250° [c]	58[d]	2210 (film)	CH_3; 59.7, 65.7 CH_2; 110.7, 117.5

	Molecular weight (solvent)	Analysis (%)[f]				
		Al[g]	C_2H_5[h]	CH_3[h]	CN[i]	Cl[i]
III	330[b] (benzene)	31.0 (32.47)	—	34.7 (36.20)	31.3 (31.34)	—
IV	ca 510 (benzene) ca 550 ($i\text{-}Pr_2O$)	23.03 (24.29)	52.9 (52.31)	—	22.0 (23.4)	—
V	—	22.1 (22.95)	24.7 (24.73)	—	22.1 (22.14)	29.5 (30.17)
VI	ca 800 (benzene)	15.95 (16.13)	—	—	15.00 (15.56)	—

a) The formulas are shown in monomeric forms, inspite of the fact that these compounds actually form polymers. b) The values are taken from the literature (ref. 3). c) Bath temperature. d) Extremely high viscosity of this compound reduced the yield markedly. e) C.p.s. upfield from the methyl signal of toluene at 60MC. f) The calculated values are indicated in parenthesis. g) Determined by titration using E.D.T.A. h) Determined by the gasmetric method. i) Determined by titration using silver nitrate.

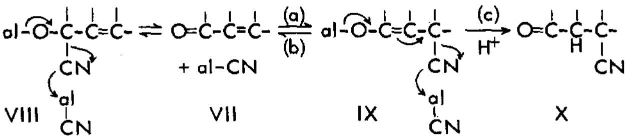
cyclohexane, these two reagents are considered to be essentially identical as evident from the method of preparation of diethylaluminum cyanide, in more basic and polar solvents such as tetrahydrofuran these two are considerably different in that in the combination reagent system fairly high concentration of proton exists (vide infra). As expected from the preliminary result (vide supra) (2) conjugate addition of cyanide anion to αβ-conjugated ketone using diethylaluminum cyanide was proved to be extremely rapid as compared with the combination reagent. Kinetic study shows that the reaction rate is markedly changed depending on solvent basicity, as predicted from the Lewis acid character of the reagent. These results are exemplified in hydrocyanation of cholestenone in diluted solution and illustrated in Table 2. As is clear from the table, when toluene is employed as a solvent, hydrocyanation of cholestenone using diethylaluminum cyanide at -5° proceeds about six hundred times as fast as when tetrahydrofuran is employed and approximately ten thousand times as fast as in the case using the combination reagent. Furthermore it is easily predicted that $\tau_{1/2}$ value of cholestenone falls in within one second, when the reaction is performed in practical concentration (0.1 and 0.3 M. solution of cholestenone and the reagent respectively at room temperature (25°). LiCN (7) and Na[Et_3AlCN] (8) were also examined as possible hydrocyanation reagents soluble in aprotic solvent, but proved to be extremely less efficient, probably because of poor ability to activate the enone systems.

TABLE 2. Half life time ($\tau_{1/2}$) of cholestenone in hydrocyanation giving 5-cyano-cholestan-3-one in 0.005 M. solution using 0.07 M. solution of the reagent

Temp. °C	$\tau_{1/2}$ (minutes)			
	$AlEt_3$-HCN	Et_2AlCN		
	THF	THF	i-Pr_2O	toluene
- 5	2860	189	25	0.3
5	758	45	0.67	-
15	328 [a]	11.5 [b]	-	-
25	169 [a]	3.5 [b]	-	-

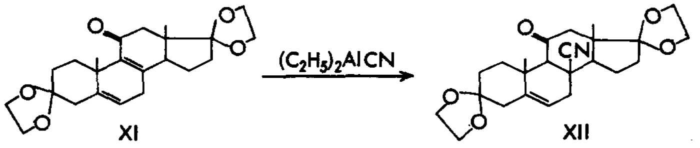
a) Obtained extrapolatively from the value using 0.02 molar solution of the reagent. b) A value obtained extrapolatively.

As just mentioned, alkylaluminum cyanides were proved to be really very efficient hydrocyanating agents, but in contrast to the combination reagent these reagents were found to accelerate both a forward (a) and a reverse (b) reaction, resulting in rapid equilibration (VII $\rightleftharpoons$ IX) as illustrated in equation (ii). This can be rationalized from



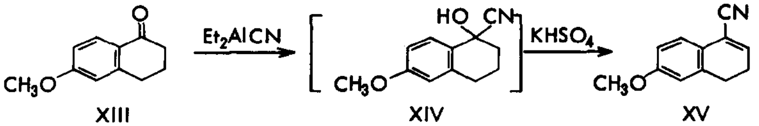
(ii)

the view that whereas the intermediate IX can be converted irreversibly to the product X by action of the proton in the combination reagent system (course c), in the absence of proton sources IX returns to the starting enone VII with dialkylaluminum cyanides R_2AlCN. Thus hydrocyanation of steroidal Δ^8-ene-11-one XI with diethylaluminum cyanide in benzene - toluene at 0° showed that within five minutes the reaction



reached to an equilibrium composing of about 80% of the product XII and 20% of the starting enone XI. A repeated hydrocyanation with the recovered enone XI gave cyano ketone XII in 91.6% total yield.

The high efficiency of diethylaluminum cyanide was also demonstrated by others than conjugate addition reaction. Thus 6-methoxy-1-tetralone (XIII), hydrocyanation of which had never been successful (9), was converted smoothly by treating with 2.3



molar equivalents of diethylaluminum cyanide in benzene and toluene at -25° into the cyanohydrin XIV, which without purification was dehydrated with potassium bisulfate to give 1-cyano-6-methoxy-3,4-dihydronaphthalene (XV), m.p. 52.0-52.3°, in 85% yield and the unchanged material in 12% yield. Another example of the hydrocyanation reaction which is successful only when diethylaluminum cyanide was used is the cleavage of highly hindered steroidal epoxides such as 9,11α-epoxide giving diaxial 1,2-cyanohydrins and was already reported in the preceding paper of this series (1).

Hydrocyanation of 3,3-, 17,17-bisethylenedioxyandrosta-5,8-dien-11-one (XI→XII)

To a solution of 2.000 g (5.175 mmole) of XI in a mixture of 32 ml of anhydrous benzene and 19 ml of anhydrous toluene was added under ice-cooling a solution of 3.45 g (31.1 mmole) of diethylaluminum cyanide in 22 ml of benzene. The reaction mixture was kept at 0° for 10 min., poured into a stirred mixture of 20 g of sodium hydroxide and 500 ml of ice-water, and extracted with chloroform. The organic layer was worked up in the usual way and crystallization of the product from methanol gave 1.567 g (73.3%) of XII melting at 198-200°. The residue from the mother liquor was hydrocyanated again with 4 molar equivalents of diethylaluminum cyanide in a similar way. Crystallization and chromatography of the product afforded an additional crop of XII, 391 mg. The total yield is 91.6%. Analytical sample melted at 199.5-200.5°, $[\alpha]_D^{24}$ +61.3° (c=0.983, Chf.). Anal. Calcd. for $C_{24}H_{31}O_5N$: C, 69.71; H, 7.56; N, 3.39. Found: C, 69.89; H, 7.60; N, 3.24.

REFERENCES

1. Hydrocyanation Part III. Part II, W. Nagata, M. Yoshioka and T. Okumura, Tetrahedron Letters, No.8, 847 (1966). A part of this work was presented at the annual lecture meeting organized by Yuki-Gosei Kyokai held at Osaka, September 1964.
2. a) W. Nagata, M. Yoshioka and S. Hirai, Tetrahedron Letters, No.11, 461 (1962). b) W. Nagata, M. Narisada and T. Sugasawa, Tetrahedron Letters, No.23, 1041 (1962); W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi and Y. Hayase, J. Am. Chem. Soc., 85, 2342 (1963); W. Nagata, T. Terasawa and T. Aoki, Chem. Pharm. Bull. (Tokyo), 11, 819 (1963); Tetrahedron Letters, No. 14, 865 (1963); ibid., No.14, 869 (1963); W. Nagata, T. Sugasawa, Y. Hayase and K. Sasakura, Proc. Chem. Soc., 1964, 241; H. Minato and T. Nagasaki, Chem. Commun., 1965, 377.
3. G.E.Coates and R.N.Mukherjee, J. Chem. Soc., 1963, 229.
4. D.D.Dows, A.Haim and W.K.Wilmarth, J. Inorg. Nucl. Chem., 21, 33 (1961).
5. G.Heise, H.Wittle and P.Mischke, Angew. Chem., 77, 380 (1965).
6. K.Ziegler, K.Schneider and J.Schneider, Liebigs Ann., 623, 9 (1959).
7. LiCN was prepared from LiH and HCN, cf. I.B.Johns and H.R.DiPietro, J. Org. Chem., 29, 1970 (1964).
8. K.Ziegler, R.Köster, H.Lehmkuhl and K.Reinert, Liebigs Ann., 629, 33 (1960).
9. A.J.Birch and R.Robinson, J. Chem. Soc., 1944, 503.