Effect of the *N*-Substituent on the Course of the Reaction of α-Aminonitriles with Organometallic Reagents[1]

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It is generally known that Grignard reagents or lithium alkyls react with nitriles to afford ketimines or ketones. On the other hand, one of the present authors has previously reported that the cyano group of *N*-phenyl-3, 4 ; 5, 6-di-*O*-isopropylidene-D-glucosaminonitrile was predominantly substituted with alkyls of various Grignard reagents or lithium alkyls to afford levo- and dextro-rotating diasteromers respectively.[2] Such substituted products have often been obtained along with the normal addition products[3] by Grignard reactions using a nitrile with an amino or a hydroxyl group on its α-carbon.

In the present work, the reactions of Grignard or lithium alkyl reagents with various *N*-substituted α-aminonitriles will be examined in order to clarify the factors governing the reaction courses, namely, the substitution and addition reactions.

Materials

N-Phenyl-3,4-*O*-isopropylidene-D-threosamino- and -erythrosaminonitrile (Ib and Ic), the corresponding *N*-benzyl derivatives (Id and Ie),[4] diastereomeric mixtures of the *N*-ethyl and *N*-dimethyl derivatives (Ia and Ig), and racemic α-phenyl α-dimethylaminoacetonitrile (III)[5] were prepared by the reaction of the corresponding amines, hydrogen cyanide, and either acetone-D-glyceraldehyde or benzaldehyde.

3, 4-*O*-Isopropylidine-*N*-acetyl-*N*-benzyl-D-threosaminonitrile (If) and α-acetamido butyronitrile (II) were prepared by the acetylation of the corresponding α-aminonitriles produced by the above-mentioned procedure.

Table I. Cyanide ion (%) liberated in the reaction of α-aminonitriles with organometallic reagents, and products

Run	α-Amino-nitrile	Reagent	CN^- liberated %	2,4-Dinitro-phenylhydrazine test	Product
1	Ia	PhMgBr	43		VIa
2	Ib	PhMgBr	60		VIb+VIc
3	Ic	PhMgBr	55		VIb+VIc
4	Id	PhMgBr	56		VId+VIe
5	Ie	PhMgBr	73		VId+VIe
6	If	PhMgBr	0	+	IVf+Vf
7	Ig	PhMgBr	51		VIg
8	II	PhMgBr	0	+	VIII
9	Ia	PhLi	87		VIa
10	Ib	PhLi	91		VIb+VIc
11	Ic	PhLi	99		VIb+VIc
12	Id	PhLi	91		VId+VIe
13	Ie	PhLi	99		VId+VIe
14	If	PhLi	0	+	—
15	Ig	PhLi	0	+	—
16	II	PhLi	7	+	VII+VIII
17	III	EtLi	0	+	IX

1) A part of this work was presented at the 15th Annual Meeting of the Chemical Society of Japan, April, 1962.
2) J. Yoshimura, This Bulletin, 35, 536 (1962).
3) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York (1954).
4) J. Yoshimura, Y. Ohgo and T. Sato, This Bulletin, 34, 1197 (1961).
5) T. S. Stevens, J. M. Cowan and J. Mackinnon, *J. Chem. Soc.*, **1931**, 2568.

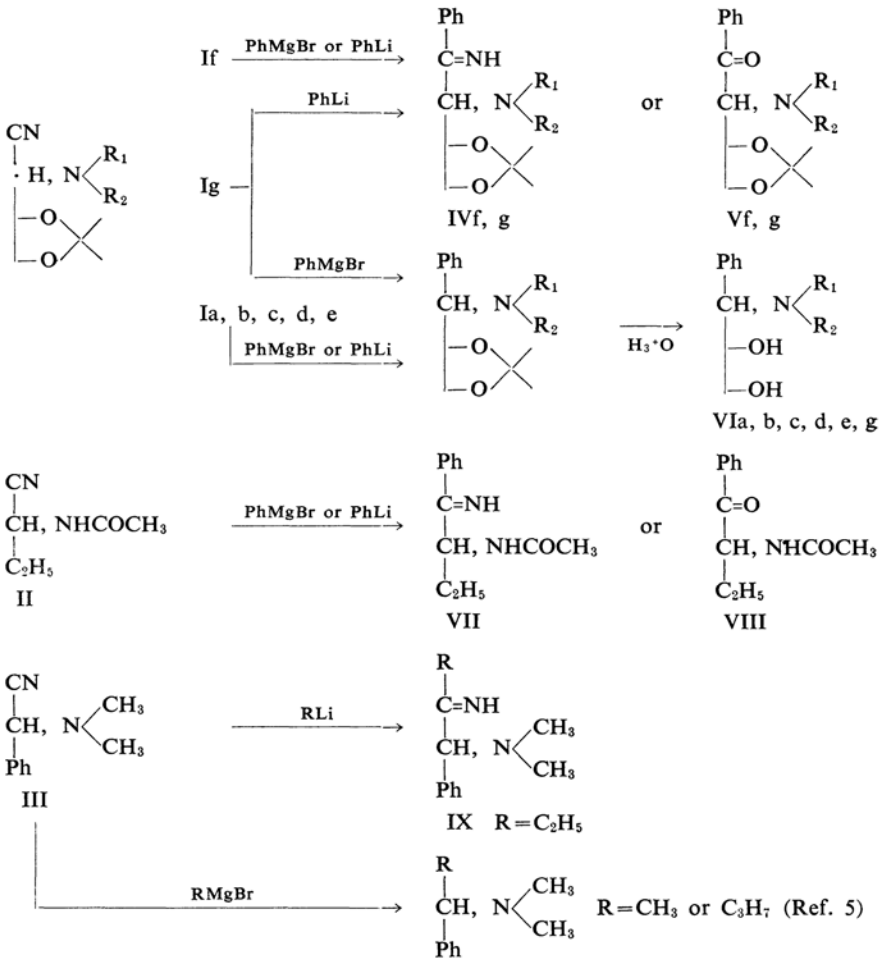
Results and Discussion

N-Substituted 3, 4-*O*-isopropylidene-D-tetrosaminonitriles (Ia—Ig), α-acetamido butyronitrile (II) and α-phenyl α-dimethylaminoacetonitrile (III) were treated with phenylmagnesium bromide, phenyllithium or ethyllithium in ether, and each reaction mixture was decomposed with ice-water.

The amount of cyanide ions liberated in the water layer was determined by titration with a 0.5 N silver nitrate solution; the results are summarized in Table I.

The 2, 4-dinitrophenylhydrazine test was applied to the syrup obtained from the reaction mixtures in which no detectable amount or only a very small amount of cyanide ions was produced. As shown in Table I, the test was positive in all the cases tried. Moreover, elemental analyses of each fraction isolated by high-vacuum distillation from runs 6, 8, 16 and 17 agreed with the structures of the addition products, IV (V),* VIII, VII (VIII)* and IX respectively, as shown in Scheme 1. (Yield: 20—30%; see Experimental section.)

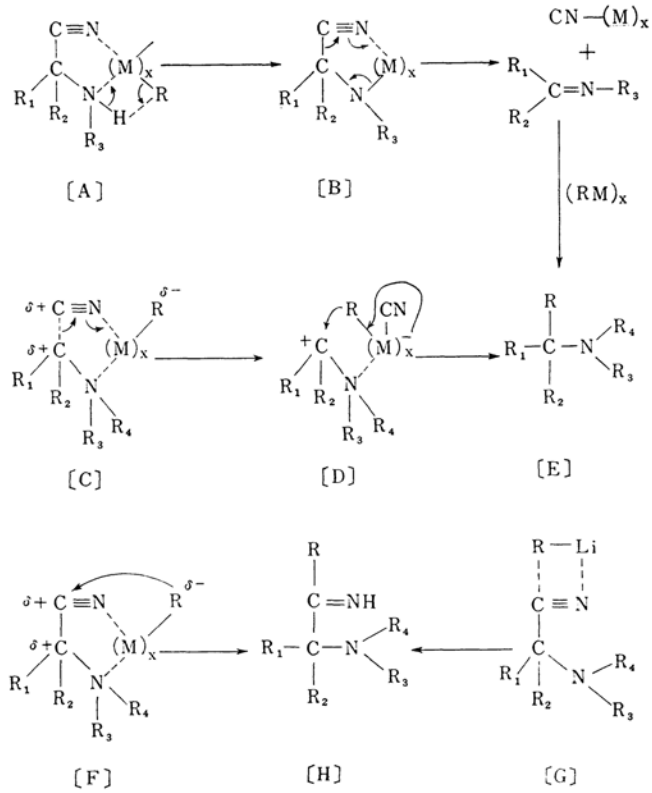
When a considerable amount of cyanide ions was detected in the reaction mixture, the substituted products were derived to VI by treatment with hot 6 N hydrochloric acid and isolated in yields of 20—50%, as shown in Scheme 1.



	R_1	R_2	Configuration		R_1	R_2	Configuration
a	H	Ethyl	A diastereomeric mixture	b	H	Phenyl	Threo
c	H	Phenyl	Erythro	d	H	Benzyl	Threo
e	H	Benzyl	Erythro	f	Benzyl	Acetyl	Threo
g	Methyl	Methyl	A diastereomeric mixture				

Scheme 1

* The substance in parenthesis is a minor product.



$(M)_x$ means that x molecules of organometallic reagents are involved in the transition state.

Scheme 2

The structure of VId was confirmed[6] by leading it to the known *N*-acetyl-D(−)-phenylglycine, while those of VIa, VIb, VIc, VIe and VIg were presumed from the analogy of these infrared absorption spectra with that of VId and from their analytical data. VIb and VIc or VId and VIe are diastereomeric to each other.

The analytical data, physical properties, and configurational assignments of the substituted products have been shown in a previous paper.[6]

The results are summarized in Scheme 1.

As runs 1—5 and 9—13 show, both the Grignard reagent and lithium alkyl attack not nitrile carbon but α-carbon to give a substituted product when the α-aminonitrile has an active hydrogen on its aminonitrogen.

Active hydrogen is known to be highly sensitive to organometallic reagents.[3] Consequently, in the case of the α-aminonitrile with an active hydrogen on the aminonitrogen, this reagent may expel the hydrogen in the first step via coordination, thus making an *N*-metal covalent bond. The metal in this state will be coordinated with the neighboring cyano group to form a five-membered ring.

This cyclic chelation may be favored for electron migration, as shown in diagram [B], and the cyano group could smoothly migrate to the metal. The imines thus formed are attacked by another molecule of organometallic reagents to give substituted products [E].

On the other hand, a marked difference appeared in the products between Grignard and lithium alkyl reactions with α-dialkylaminonitriles; Grignard reagents attack α-carbon to give substituted products, but lithium alkyls attack nitrile carbon (runs 5, 15 and 17).

Since there is no place to make a *N*-metal covalent bond in dialkylaminonitriles, this marked differnce between Grignard and lithium alkyl reactions may be attributed to the difference in the coordination ability of the reagents. The elimination of the cyano group of α-dialkylaminonitriles in the Grignard reaction may be interpreted by assuming the initial formation of a coordinative complex [C]. The formation of the complex decreases electron density not only at the nitrile carbon but also at the α-carbon, and it may facilitate the dissociation of the C_α–CN bond to form

6) J. Yoshimura, Y. Ohgo and T. Sato, *J. Am. Chem. Soc.*, **86**, 3858 (1964).

the cyanide ion and a carbocation [D].* Lithium alkyls would not have as strong a power of attracting electron from these ligands as magnesium, and they would be considered to form the four-center transition state [G],[7] which in turn leads to ketimines. This seems to be related to the fact that the addition reaction of conjugeted carbonyl compounds with lithium alkyls gives the 1, 2 addition product predominantly, while that with Grignard reagents the 1, 4 addition product[8].

Runs 6, 8, 14 and 16 shows that the aminonitriles bearing acetyl group on its amino-nitrogen are not attacked at α-carbon but at nitrile carbon with both the reagents, thus giving the addition products.

It may be considered that the dissociation of the C_α–CN bond of these aminonitriles does not occur, for aminonitrogen whose basicity is weakened by the acetyl group can not coordinate to the metal.

From the above mechanism concerning the Grignard reaction, it may be expected that the existence of factors to prevent the coordination of the aminonitrogen suppress the substitution reaction. In fact, certain α-aminonitriles with oxygen in the dialkylamino portion are attacked at nitrile carbon to afford ketones predominantly.[9]

Recent investigations[10] on the composition of Grignard compounds in a solution have shown that a Grignard solution is an equilibrium mixture of several species, such as R_2Mg, MgX_2, $RMgX$, $(RMgX)_2$ and $R_2Mg \cdot MgX_2$, and that the natures of the alkyl group, the halogen atom and the solvent all have an effect on the equilibrium.

It would be of interest to investigate which species do play a principal role in the substitution or the addition reaction.

Experimental

The General Procedure for the Reaction of α-Aminonitriles with an Organometallic Reagent.—Into an ethereal solution of phenyllithium or phenylmagnesium bromide, prepared from 0.06 mol. of bromobenzene and 0.12 mol. of metal lithium or 0.06 mol. of magnesium, was added 0.02 mol. of aminonitrile with stirring at 0—5°C. The mixture was refluxed for about ten hours, and then it was cautiously poured into ice water covered with 100 ml. of ether. The water layer was separated from the ether layer and extracted twice 50 ml. of ether. The water layer was then titrated by a 0.5 N silver nitrate solution, using potassium iodide as an indicator, in order to determine the amount of cyanide ions liberated in the reaction mixture. In the case of the Grignard reaction, 25 ml. of a 4 N potassium hydroxide solution had previously been added to the water layer in order to prevent the cyanide ions from escaping as hydrogen cyanide; also, an amorphous precipitate was removed by filtration. The filtrate was used for the quantitative determination of the cyanide ions. The ether layer was washed with water, dried, and concentrated in vacuo to a syrup. When a considerable amount of cyanide ion were detected in the water layer, the above syrup was subjected to hydrolysis with a 6 N hydrochloric acid solution (20 ml.) at 100°C for two hours. After tar-like substances insoluble in hydrochloric acid had been removed by filtration through activated carbon, followed by steam distillation, the filtrate was decolorized with activated carbon. After the filtrate had been adjusted to pH 10 with a sodium hydroxide solution it was extracted four times with 50 ml. of ethyl acetate.

The combined ethyl acetate solution was washed twice with 50 ml. of water and dried with anhydrous sodium sulfate. After the ethyl acetate fraction had been concentrated under reduced pressure to dryness, a crude diastereomeric mixture of 1-*C*-phenyl-1-alkylamino-1-deoxy-D-glyceritol became crystals, except for the product from run 9, whose yields were from 20 to 50%.

When no remarkable amount of cyanide ion was detected in the water layer, a small portion of the syrup from the ether layer was tested for the precipitation reaction by 2,4-dinitrophenylhydrazine after the removal of isopropylidene group; in some cases the isolation of addition products from the residual syrup was attempted by high-vacuum distillation.

***N*-Ethyl-3, 4-*O*-isopropylidene-D-tetrosaminonitrile (A Diastereomeric Mixture) (Ia).**—A benzene solution (1.2 l.) of acetone-D-glyceraldehyde[11] prepared from 40 g. of diacetone-D-mannitol by oxidative scission using lead tetraacetate (70 g.) was neutralized with a 50 per cent aqueous potassium carbonate solution (50 ml.). The benzene layer was separated, dried with anhydrous sodium sulfate, and then shaken with 70 per cent ethylamine (50 ml.) for thirty minutes. The resulting reaction mixture was concentrated under reduced pressure to about 200 ml., and to it was added ethanol (100 ml.) and hydrogen cyanide (40 ml.) with cooling. The mixture was then left to stand overnight in a refrigerator and then concentrated in vacuo to a syrup; the syrup was then purified by distillation under reduced pressure.

Yield, 18.9 g. B. p. 88°C (0.35 mmHg).

Found: C, 58.18; H, 9.09; N, 14.59. Calcd. for $C_9H_{16}O_2N_2$: C, 58.67; H, 8.75; N, 15.21%.

***N*-Dimethyl-3, 4-*O*-isopropyridene-D-tetrosaminonitrile (A Diastereomeric Mixture) (Ig).**—A benzene

* In the Grignard reaction a minor path from [F] to [H] may be included.

7) E. A. Braude, "Progress in Organic Chemistry," 3, Butterworths Scientific Publications, London (1955), p. 185.

8) A. Lüttringhaus, *Chem. Ber.*, 67, 1602 (1934); H. Gilman and R. H. Kirby, *J. Am. Chem. Soc.*, 63, 2046 (1941); S. H. Tucker and M. Whalley, *J. Chem. Soc.*, 1949, 50; E. A. Braude and J. A. Coles, ibid., 1950, 2012; 1952, 1425.

9) L. H. Goodson and H. Christopher, *J. Am. Chem. Soc.*, 72, 358 (1950).

10) R. M. Salinger and H. S. Mosher, ibid., 86, 1782 (1964); E. C. Ashby and M. B. Smith, ibid, 86, 4363 (1964); 85, 118 (1963).

11) E. Baer and H. O. L. Fisher, *J. Biol. Chem.*, 128, 463 (1939).

solution of 50 g. of acetone-D-glyceraldehyde was shaken with 60 ml. of a 30 per cent dimethylamine solution. The mixture was concentrated to about 200 ml. under reduced pressure, mixed with 100 ml. of ethanol and 30 ml. of hydrogen cyanide with chilling, and then left to stand in a refrigerator overnight. The reaction mixture was then concentrated to a syrup, which was distilled to give 21.2 g. of the product. B. p. 81°C (0.2 mmHg).

Found: C, 58.16; H, 8.40; N, 14.21. Calcd. for $C_9H_{16}O_2N_2$: C, 58.67; H, 8.75; N, 15.21%.

N-Benzyl-N-acetyl-3, 4-O-isopropylidene-D-threosaminonitrile (If).—To a solution of 4 g. of *N*-benzyl-3,4-*O*-isopropylidene-D-threosaminonitrile (m. p. 86—87°C) in 40 ml. of pyridine 15 ml. of acetic anhydride was added with cooling. After the reaction mixture had been left standing at room temperature for two days, it was poured into ice water. The suspension was extracted with chloroform, and the chloroform layer was repeatedly washed with water, dried, and concentrated to a syrup. The syrup was dissolved in a suitable amount of ethanol and then left to stand overnight in a refrigerator. The crystals which appeared were recrystallized from ethanol-petroleum ether to give colorless plates (2.8 g.). M. p. 81—82°C, $[\alpha]_D$ −34° (*c* 1.03, ethanol).

Found: C, 66.03; H, 7.23; N, 9.73. Calcd. for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72%.

N-Acetylbutyronitrile (II). — To a 100 ml. of ethanol containing 7.4 g. of ammonia was added 25 g. of propionaldehyde and then 40 ml. of hydrogen cyanide with chilling. After the reaction mixture had been left standing in a refrigerator for two hours, it was concentrated carefully under reduced pressure. The syrup obtained was dissolved in 50 ml. of pyridine and then 50 ml. of acetic anhydride was added to the solution with chilling. After it had stood two days at room temperature, the reaction mixture was poured into ice water and extracted with 200 ml. of ethyl acetate. The ethyl acetate layer was separated, washed with water, and dried over anhydrous sodium sulfate. After the ethyl acetate had been removed under reduced pressure, a syrup was obtained by distillation; 101°C (0.03 mmHg).

Found: C, 56.77; H, 7.93; N, 22.48. Calcd. for $C_6H_{10}N_2O$: C, 57.11; H, 7.99; N, 22.21%.

Addition Products.—When no cyanide ion could be detected in the reaction mixture, the isolation of the addition product from the ether fraction was attempted by high vacuum distillation in some cases. The addition products were obtained as follows.

Addition Products from Run 6. — Three fractions were obtained by the distillation of the syrup from run 6.

I. B. p. 125—126°C (0.01 mmHg); 0.25 g.

Found: N, 4.82%.

The analytical value in nitrogen was agreed with that of the carbonyl structure (V).

II. B. p. 143—144°C (0.002—0.003 mmHg)/bath temp. 197°C; 0.25 g.

Found: N, 7.13%.

III. B. p. 200—205°C (0.005 mmHg); m. p. 159—161°C; 1.4 g.

Found: C, 72.58; H, 6.35; N, 7.78. Calcd. for $C_{22}H_{26}O_3N_2$: C, 72.10; H, 7.15; N, 7.65%.

The analytical values of this fraction agreed with those of the imino compound (IV).

The Addition Product from Run 8 (VIII). — The evolution of ammonia gas was perceived from the reaction mixture of run 8 after it has stood for a week. An oily substance was obtained, besides a small amount of biphenyl, on the distillation of the syrup. Yield, 1.1 g.; b. p. 125°C (0.08 mmHg); R_f 0.89 (BuOH saturated with water).

Found: C, 70.79; H, 7.17; N, 6.78. Calcd. for $C_{12}H_{17}O_2N$: C, 70.22; H, 7.37; N, 6.82%.

The Addition Products from the Reaction Mixture of Run 16.—The evolution of ammonia gas was perceived from the reaction mixture of run 16. The distillation of the syrup gave the following fractions.

I. B. p. 135—140°C (0.1—0.2 mmHg); 0.5 g.

The infrared spectrum of this syrup was consistent with VIII.

II. B. p. Over 150°C (0.1 mmHg); 0.3 g. The fraction became crystals. Its analytical value in nitrogen was agreed with that of VII.

Found: N, 13.12. Calcd. for $C_{12}H_{16}N_2O$: N, 13.72%.

III. A small amount of a crystalline product condensed at the top of the thermometer. This substance was identical in analytical value with the substance of fraction II.

Found: N, 13.82. Calcd. for $C_{12}H_{16}N_2O$: N, 13.72%.

The Addition Product from Run 17 (IX). — B. p. 111—112°C (20 mmHg).

Found: N, 14.48. Calcd. for $C_{12}H_{18}N_2$: N, 14.75%.

Summary

The reactions between various *N*-substituted-α-aminonitriles and organometallic reagents have been investigated in order to clarify the effect of the *N*-substituent on the reaction course.

The results indicate that:

(1) Both Grignard reagent and lithium alkyl attack not nitrile carbon but α-carbon to give substituted product when the α-aminonitrile has an active hydrogen on its aminonitrogen.

(2) In the case of α-dialkylaminonitriles, Grignard reagents attack the α-carbon to give substituted products, but lithium alkyls attack the nitrile carbon.

(3) The aminonitriles bearing acetyl group on its aminonitrogen are not attacked at α-carbon but at nitrile carbon by both the reagents, thus giving addition products.

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