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-cyanopropionaldehyde(8) : The grignard
reaction of -cyanopropionaldehyde

その他（別言語等） のタイトル	-シアノプロピオンアルデヒドよりの合成研究(第 8報) : -シアノプロピオンアルデヒドのグリニヤ ール反応
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Synthetic Studies Starting from β -Cyanopropionaldehyde VIII.
The Grignard Reaction of β -Cyanopropionaldehyde

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β -シアノプロピオンアルデヒドよりの
合成研究 第VIII報

β -シアノプロピオンアルデヒドの
グリニヤール反応

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概 要

β -シアノプロピオンアルデヒドの利用研究シリーズの1つとして、今回はグリニヤール化合物との反応による各種の4-ヒドロキシニトリル類および4-ケトアルデヒド類の合成について報告する。ここに得られた生成物のほとんどは、現在まで、文献に記載されていない新しい化合物であり、いずれも反応性に富む二つの官能基を有することから、今後の有機合成原料として、広い利用面をもつと期待される。

β -シアノプロピオンアルデヒド(1)はアルデヒド基、シアノ基をもち、両基ともグリニヤール試薬と反応するが、その反応性に大きな差がある。低温ではアルデヒド基のみ変化したヒドロキシニトリル(3)が、アルデヒド基を保護した後、高温で反応させればニトリル基の変化でケトアルデヒド(5)が生成すると考えられる。本研究では、アルキルハライドとしてヨウ化メチル(2a)、臭化エチル(2b)、臭化n-プロピル(2c)、塩化n-ブチル(2d)および塩化n-ヘキシル(2e)をもちい、それぞれ金属マグネシウムとの反応で相当するグリニヤール試薬とした後、化合物1と反応させた。

アルデヒド基のみと反応させるため、温度範囲として $-30\sim 20^{\circ}\text{C}$ 、 $-5\sim 0^{\circ}\text{C}$ 、 $0\sim$

5°Cをもちい実験をおこなった。化合物2の量が低いうちは-5~0°Cの温度範囲で充分な収率を示すが、量高くなると0~5°Cの温度範囲が必要であった。さらに温度を上げると、ニトリル基まで変化するおそれがあるため、5°C以上では実験をおこなわなかった。温度をもっと下げた場合(-30~-20°C)は-5~0°Cでの約半分の収率を示し、原料が相当量回収された。反応時間も種々変えておこなってみた。最高収率時間は2aの場合4, 2a~2dの場合6, 2eの場合10であった。すなわち、量高くなるにしたがい中間体が立体的制約をうけ、活性化エネルギーが大きく、反応速度が小さくなるためである。

化合物3は、グリコールに対するハロゲン化水素続いての青酸カリの作用により得られているが、選択的ハロゲン化を伴うため収率はあまり高くない。著者等の方法は反応段階が1つでありしかも高収率であることから、3の一般的合成法になり得ると考えられる。

化合物1のアルデヒド基をジメチルアセタールとして保護しておき、エーテルの沸点でグリニヤール試薬を作用させると、化合物5が約50%の収率で得られた。この場合時間、温度等条件を一定して反応をおこない、グリニヤール試薬の反応性の比較検討をおこなった。文献記載の4-ケトアルデヒドはレブリンアルデヒドのみであり、その合成方法は二重結合化合物のオゾン分解という技術的にやや難のあるものである。著者等の方法では、任意の置換基を導入でき、しかも反応が容易におこなえることから、5のよりよい一般的合成法として今後広く活用されるものと考えられる。

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The Grignard Reaction of β -Cyanopropionaldehyde

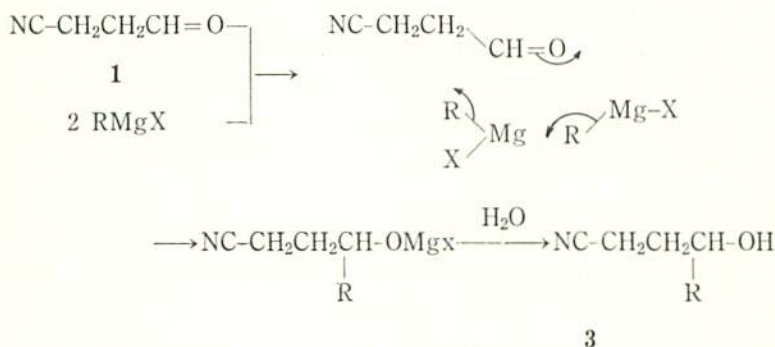
In a previous paper,¹⁾ we have reported the condensation reactions of β -cyanopropionaldehyde (**1**) with several compounds having an active methylene group to prepare the new unsaturated cyano esters. We will describe the reactions of **1** with Grignard reagents to yield cyano-alcohols or keto-aldehydes, in this paper. Almost all of the reaction products prepared in this investigation have not been reported in literature, and are hard to derive from other materials. Thus, the above products are regarded as the organic synthetic materials of wide utilities, since they have reactive two functional groups.

Grignard found that alkyl halide reacts with metallic magnesium suspended in ether to give the ether-soluble substance, Grignard reagent.²⁾ This reagent is highly reactive and versatile substance capable of entering into many useful reactions.³⁾ The most important application is a addition of the reagent to the carbonyl group or to the cyano group and hydrolysis of the addition product provides an efficient method for the synthesis of alcohol or ketone. The key reaction can be regarded as a nucleophilic addition initiating in attack of the positively polarized carbon of the carbonyl function or of the cyano function by a potential carbanion.

In the present study, methyl iodide (**2a**), ethyl bromide (**2b**), n-propyl bromide (**2c**), n-butyl chloride (**2d**) and n-hexyl chloride (**2e**) were used as alkyl halide, and were allowed to react with β -cyanopropionaldehyde (**1**). The reaction of **1** with **2a** in the presence of metallic magnesium were carried out in ether at low temperature in order to react only with aldehyde group, not with cyano group. The addition of Grignard reagent to the cyano group is normally slower than to the carbonyl group, and cyano-containing aldehyde add the Grignard reagent without disturbing the cyano group. The magnesium is employed in the form of thin turnings or granules of the metal. The

ether is not merely a convenient solvent but forms a complex essential to the reaction, and must be pure and free from traces of moisture. A trace of water in the ether or a film of moisture in the flask not only destroys an equivalent amount of Grignard reagent but also may prevent the reaction from starting.

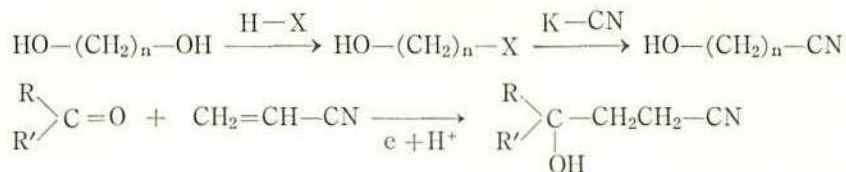
The structure of the reaction product of **1** with **2a** was established by combination of analytical values, mass spectrum and ir spectrum presented in Table 2 to be the expected product, 4-hydroxypentanenitrile (**3a**). The ir spectrum of **3a** displays characteristic absorption bands at 2220 and 3405 cm^{-1} assignable to cyano and hydroxy group, respectively, and no absorption exhibited in the carbonyl group region. As seen in Table 1, the yield was the highest when the reaction was carried out at -5 to 0°C for 4 hr. The yield reduced to about a half at lower temperature, -30 to -20°C .



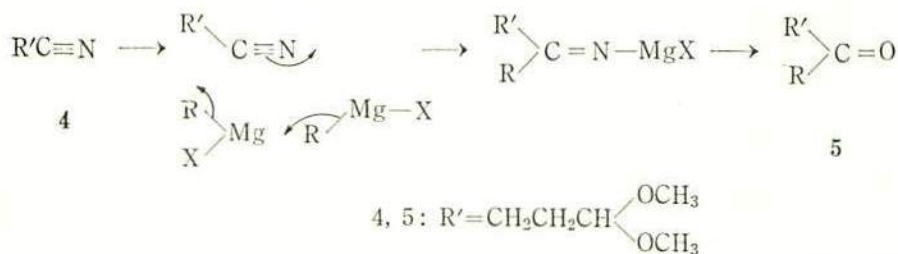
The reaction of **1** with **2b**, **2c**, **2d** or **2e** was also carried out and the expected 4-hydroxyalkanenitrile (**3**) was obtained. In order to increase of the yield, the reaction temperature was elevated or the reaction time was prolonged, according to increase of the bulk of alkyl group in the reagent. The results obtained are presented in Table 1 and 2.

4-Hydroxyalkanenitriles can be prepared generally from potassium cyanide and the corresponding halogenoalcohols which were obtained by the action of hydrohalogenic acid on glycols.⁴⁾ On account of selective halogenation, however, the reaction to give halogenoalcohols take place in comparatively low yield. In recent year, 4-hydroxynitriles were prepared by cathodic crossed hydrocoupling of ketones with acrylonitrile,⁵⁾ and this reaction is generalized as one of the method of the synthesis of **3**. We also simplified the synthesis of **3** in better yield to one reaction stage, thus the present reaction is also

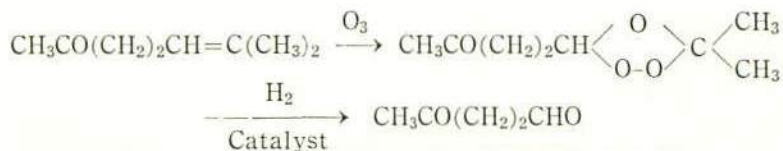
regarded to be a convenient method of the preparation of **3**.



The Grignard reaction was also extended to cyano group in **1** to prepare keto-aldehyde. The aldehyde group of **1** was previously protected as dimethyl acetal (**4**), and allowed to react with **2** in refluxing ether for 5 hr. The results of the products thus obtained are presented in Table 3. The values of elemental analyses and mass spectra were well in accord with those of the expected structures. The ir spectra of **5** exhibited strong carbonyl absorptions at $1720\text{--}1725\text{ cm}^{-1}$, C-O-C-O-C at $1090\text{--}1105$ and $1130\text{--}1145\text{ cm}^{-1}$, and no absorption in the nitrile region at about 2220 cm^{-1} . All of the reactions of **4** with **2** were carried out in the same condition, and the reactivities of the reagents used were compared. The yield of the reaction of **4** with **2a** was 58%, with **2b**, **2c**, **2d** or **2e** was 53, 48, 40 or 38%, respectively. That is, the group order of decreasing reactivity is as follows; Me, Et, *n*-Pr, *n*-Bu, *n*-Hex.



Aliphatic 4-ketoaldehydes are the compounds of hard to obtain, and have rarely been appeared in the literature except for laevulic aldehyde formed by the ozonolysis of 6-methyl-5-hepten-2-one.⁶⁾ The ketoaldehydes, however, were readily



prepared by the reaction of 4 with alkyl magnesium halide in fairly good yield as for the addition of aliphatic Grignard reactions to nitrile group. Moreover, the advantage of this method lies in the preparation of the optional 4-alkyl-4-ketoaldehydes, the ease of reaction method and the ease of isolation of the product. Thus, this reaction of 1 could be generalized as a preparative method for 4-ketoaldehydes and is regarded as a reaction of wide employment.

Experimental

4-Hydroxyalkanenitrile (3). In a three necked flask, fitted with a stirrer, separatory funnel, and a reflux condenser to the upper end of which a calcium chloride tube was attached, was placed 4.8 g (0.2 g atom) of magnesium turning. A mixture of 0.2 mol of alkyl halide and 100 ml of anhydrous ether was added and the flask was warmed gently until the magnesium became null. To the solution of the Grignard reagent, cooled (-5 to 0°C or 0 to 5°C) in an ice salt bath, a mixture of 0.2 mol of β -cyanopropionaldehyde (1) and 100 ml of dried ether was slowly added with stirring. The addition product thus obtained was then decomposed by adding, with stirring, 200 ml of water and cracked ice, and then 50 ml of cold dilute hydrochloric acid. When the

Table 1.

$$\text{NC-CH}_2\text{CH}_2\text{CHO} + \text{RX} \xrightarrow[2) \text{H}_2\text{O}]{1) \text{Mg}} \text{NC-CH}_2\text{CH}_2\underset{\text{OH}}{\text{CH}}-\text{R}$$

1		2	3	
R	X	Reac Temp. (°C)	Reac Time (hr)	Yield (%)
CH ₃	I	-5 - 0	2	53
"	"	"	4	76
"	"	-30 - -20	4	40
"	"	-5 - 0	8	75
C ₂ H ₅	Br	"	4	70
"	"	"	6	79
n-C ₃ H ₇	"	"	4	58
"	"	"	6	65
n-C ₄ H ₉	Cl	"	6	38
"	"	0 - 5	6	59
n-C ₆ H ₁₃	"	"	6	44
"	"	"	10	58

Table 2.
 $\text{NC}-\text{CH}_2\text{CH}_2\underset{\text{OH}}{\text{CH}}-\text{R}$ (3)

Product		R	Bp °C/mmHg	Yield %	Formula
3a:	4-hydroxypentanenitrile	CH ₃	91-94/5	76	C ₅ H ₉ ON
3b:	4-hydroxyhexanenitrile	C ₂ H ₅	105-107/5	79	C ₆ H ₁₁ ON
3c:	4-hydroxyheptanenitrile	n-C ₃ H ₇	109-111/3	65	C ₇ H ₁₃ ON
3d:	4-hydroxyoctanenitrile	n-C ₄ H ₉	107-109/1	59	C ₈ H ₁₅ ON
3e:	4-hydroxydecanenitrile	n-C ₆ H ₁₃	129-131/3	58	C ₁₀ H ₁₉ ON

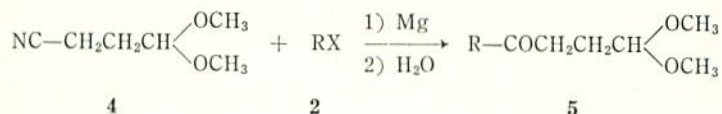
	Ir, cm ⁻¹	Analyses		Mol Weight		Mass M ⁺
		Calcd	Found	Calcd	Found	
3a	3405 (OH)	C: 60.61	60.38	99	103	99
	2220 (CN)	H: 9.09	9.34			
		N: 14.14	14.40			
3b	3410 (OH)	C: 63.72	63.51	113	109	113
	2220 (CN)	H: 9.73	9.90			
		N: 12.39	12.21			
3c	3415 (OH)	C: 66.14	65.85	127	130	127
	2215 (CN)	H: 10.24	10.50			
		N: 11.02	11.27			
3d	3420 (OH)	C: 68.09	67.81	141	138	141
	2215 (CN)	H: 10.64	10.77			
		N: 9.93	10.03			
3e	3425 (OH)	C: 71.01	70.90	169	174	169
	2220 (CN)	H: 11.24	11.38			
		N: 8.28	8.52			

decomposition was complete, the ether layer separated and the aqueous layer was extracted with a little ether. This ether extract was combined with the ether layer, and the whole was washed with 5% aqueous sodium carbonate solution and then with water. The solution was dried with anhydrous sodium sulfate. Distillation of the extract gave the results shown in Table 1 and 2.

β -Cyanopropionaldehyde Dimethyl Acetal (4). A mixture of 1 mol of **1**, 10 mol of methanol and 15 g of concentrated hydrochloric acid was refluxed for 5 hr. The solution was then concentrated to about 150 ml and the residue was poured into water. The oil was extracted with ether and dried with anhydrous sodium sulfate. The fractional distillation of the extract gave 94.4 g of **4**; bp 71-73°C/3 mmHg, yield 73%.

Anal. Calcd for C₆H₁₁O₂N: C, 55.81; H, 8.53; N, 10.85. Found: C, 55.57; H, 8.71; N, 11.02.

Table 3.



Product (-dimethyl acetal)	R	Bp °C/mmHg	Yield %	Formula
5a: 4-Ketopentanal-	CH ₃	84-86/16	58	C ₇ H ₁₄ O ₃
5b: 4-Ketohexanal-	C ₂ H ₅	63-65/2	53	C ₈ H ₁₆ O ₃
5c: 4-Ketoheptanal-	n-C ₃ H ₇	74-77/2	48	C ₉ H ₁₈ O ₃
5d: 4-Ketooctanal-	n-C ₄ H ₉	84-87/2	40	C ₁₀ H ₂₀ O ₃
5e: 4-Ketodecanal-	n-C ₆ H ₁₃	109-110/2	38	C ₁₂ H ₂₄ O ₃

	Ir, cm ⁻¹		Analyses		Mol Weight		Mass M ⁺
	C=O	COCOC	Calcd	Found	Calcd	Found	
5a	1725	1145 1105	C: 57.75 H: 9.59	57.49 9.81	146	151	146
5b	1725	1145 1105	C: 60.00 H: 10.00	59.82 10.08	160	155	160
5c	1720	1145 1100	C: 62.07 H: 10.34	61.84 10.63	174	178	174
5d	1720	1140 1100	C: 63.83 H: 10.64	63.59 10.79	188	193	188
5e	1720	1130 1090	C: 66.67 H: 11.11	66.41 11.34	216	212	216

4-Ketoalkanal Dimethyl Acetal (5). A solution of alkyl magnesium halide was prepared from 4.8 g of magnesium, 0.2 mol of alkyl halide and 100 ml of dried ether by the same manner as 3.

To the above solution, a mixture of 0.2 mol of 4 and 100 ml of dried ether was added at room temperature, and the solution stirred and heated under reflux for 5 hr. The reaction mixture was cooled, and the addition compound was decomposed by adding 200 ml of water and ice, and then 50 ml of cold dilute sulfuric acid. The ether layer was washed with 5% aqueous sodium carbonate, and then distilled. The results obtained are summarized in Table 3.

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