

Synthetic studies starting from
-cyanopropionaldehyde(7) : Condensation
reaction with the compound having an active
methylene group

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Synthetic Studies starting from β -Cyanopropionaldehyde. VII.
Condensation Reaction with the Compound
having an Active Methylene Group

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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VII報

活性メチレン基を含む化合物との縮合反応

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β -シアノプロピオンアルデヒドは、分子量が100にもみたない化合物でありながら、アルデヒド基、シアノ基および2ケの活性メチレン基を含み、それ故に合成化学的見地からみて、非常に興味ある化合物と考えられる。著者らは1964年よりこの化合物に対して種々の化学的反応を適用し、新化合物、既知重要化合物を多く合成してきた。今回はこのシアノアルデヒドのシリーズ研究の1つとして、活性メチレン基を含む多くの化合物との、縮合反応の研究を報告する。

カルボニル化合物と活性メチレン基を含む化合物との縮合は、クネーフェナーゲル以来主として有機塩基の触媒下におこなわれてきたが、 β -シアノプロピオンアルデヒドの低い安定性から考え、著者らは数種の有機塩類を触媒としてもちいてみた。その結果、有機塩類は有機塩基より不安定カルボニル化合物に対しては触媒能に富んでいること、有機塩の種類によりこの能力に大きな差があること、この種の反応には酢酸ピペリジンがより有効な触媒であることが明らかとなった。また同一触媒下での実験方法の改良をおこなひ、85%もの高収率で生成物を得ることに成功した。 β -シアノプロピオンアルデヒドはそれ自身活性メチレン基をもつため、アセトンのような単純カルボニル化合物との縮合はおこなわないが、ジケテンとの反応により、アセトンとの縮合体に相当する化合物をえることができた。この反応においては、さらに溶媒効果をも調べた。

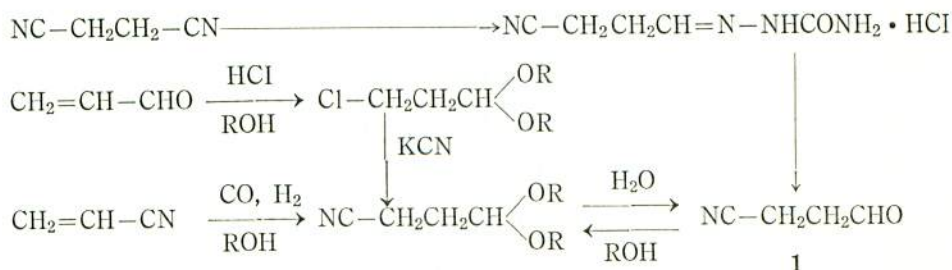
上記のようにして、 β -シアノプロピオンアルデヒドとマロン酸ジエチル、アセト酢酸エチル、アセチルアセトン、マロン酸およびジケテンとの反応で、それぞれ相当する化合物を好収率で得ることができたが、これら生成物はすべて文献に記載のない新しい化合物で

あり、それ故に元素分析、分子量測定、IR 分析、NMR 分析等の手段をもちい、それらの構造の确实なる同定をおこなった。

Synthetic Studies starting from β -Cyanopropionaldehyde. VII.

Condensation Reaction with the Compound
having an Active Methylene Group

β -Cyanopropionaldehyde (1) is an interesting compound which has reactive functional groups; aldehyde, cyano and two active methylene groups. Accordingly, it is expected that many useful organic compounds will be synthesized from this cyano-aldehyde (1). The synthesis of 1 had been investigated by several workers. One consisted of the addition of hydrogen chloride to acrolein followed by substitution of the chloro-aldehyde with potassium cyanide^{1,2}, and the other was the conversion of succinonitrile into 1 through the partial reduction of the nitrile group³. All of them, however, rather cumbersome as the method of preparation, so this cyano-aldehyde (1) had rarely appeared in literature. In 1960, an improved technique for the oxo reaction of acrylonitrile in the presence of cobalt carbonyl to form 1 has been developed by the member of Ajinomoto Co. Ltd. in high yield^{4,5}, and 1 is now being used as an useful reactive material in organic syntheses.



The purpose of our work is to extend synthetic studies starting from 1 as

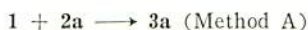
reported already⁶. As one of this series, studies on some condensation reactions of **1** with the compounds having an active methylene group (**2**) will be presented in this paper. The reaction products prepared are all new compounds and are hard to derive from other materials.

The earlier attempts to bring about condensation of aldehyde with diester, ketonic ester and 1, 3-diketone were carried out by Claisen, who used hydrogen chloride as a reaction catalyst. Knoevenagel investigated this reaction, and found that much more effective catalyst for this purpose were such base as primary or secondary amine.

At first, we tried the reaction of **1** with **2** in the presence of hydrogen chloride, diethyl amine or piperidine, and obtained a large amount of tarry material and unreacted **2**. That is, acid or base was not suitable catalyst for the condensation of **1** with **2** because of the unstableness of the former. On the other hand, no condensation occurred in the absence of catalyst, almost all of materials were recovered. It is general known that ammonium acetate (AA) is also excellent catalyst in the condensation of ketone with cyanoacetic ester⁷. So, we examined the catalytic effect of acetic salt (sodium acetate, acetamide, triethylamine acetate, pyridine acetate, ammonium acetate or piperidine acetate) and found that piperidine acetate (PA) was better catalyst in the condensation reaction than others, as shown in Table 1. The acidic salts of organic bases caused the formation of a relatively large proportion of high boiling polymeric material.

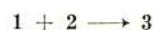
The condensation of **1** with diethyl malonate (**2a**), ethyl acetoacetate (**2b**) or acetylacetone (**2c**) was examined by three methods. A benzene solution of an equimolecular mixture of **1** and **2** was refluxed in the presence of PA, the water formed in the reaction being removed continuously by azeotropic distillation with benzene (Method A). Diethyl 3-cyanopropylidenemalonate (**3a**), ethyl 3-cyanopropylideneacetoacetate (**3b**) and 3-cyanopropylideneacetyl-

Table 1.



Catalyst name	Catalyst mol	Yield 3a, %
sodium acetate	0.01	7
acetamide	0.01	16
triethylamine acetate	0.01	15
pyridine acetate	0.01	18
ammonium acetate	0.005	25
	0.01	30
	0.02	21
piperidine acetate	0.005	38
	0.01	41
	0.02	32

Table 2.



Product	Method	Catalyst	Yield, %
3a	A	AA	30
3a	A	PA	41
3a	B	AA	40
3a	B	PA	65
3b	A	PA	46
3b	B	PA	73
3c	A	PA	52
3c	C	PA	85

acetone (**3c**) were thus obtained in yield of 30-50%. When this experiment was carried out in the absent of water separator, the reaction proceeded too slowly.

Since some resinification of **1** was observed in Method A, the following modifications were adopted. In Method B, **1** was added slowly into the refluxing benzene solution of an excess molecular of **2a** or **2b**. In Method C, **1** was added to the benzene solution of **2c** at room temperature with stirring, and then refluxed. This Method C was used to prevent the self condensation of **2c** under the reaction condition of Method B. The yield of conversion of **1** into condensation product **3** was then raised up to a yield of 65-85% (Table 2). The structure of the product was confirmed by elemental analyses, molecular weight measurement by the cryoscopic method with benzene, infrared spectra and nucleo megnetic resonance spectra, as seen in Table 3.

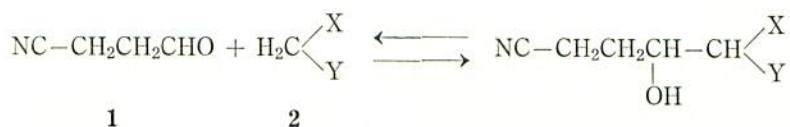
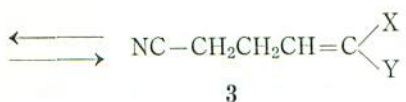


Table 3. $\text{NC}-\text{CH}_2\text{CH}_2\text{CH}=\text{C}\begin{matrix} \text{X} \\ \text{Y} \end{matrix}$ (3)

Product	X	Y	Method	Yield %	Bp °C/mmHg	Molecular formula
3a	COOC_2H_5	COOC_2H_5	B	65	165-7/3	$\text{C}_{11}\text{H}_{15}\text{O}_4\text{N}$
3b	COCH_3	COOC_2H_5	B	73	161-2/2	$\text{C}_{10}\text{H}_{13}\text{O}_3\text{N}$
3c	COCH_3	COCH_3	C	85	144-5/3	$\text{C}_9\text{H}_{11}\text{O}_2\text{N}$

	NMR spectral data* δ , ppm	IR, cm^{-1}		Analyses		Mol Weight	
				Calcd	Found	Calcd	Found
3a	6.63 (t, 1H)	2250	C :	58.65	58.39	225	229
	4.23 (q, 4H)	1730	H :	6.71	6.99		
	2.42-1.98 (m, 4H)	1720	N :	6.22	6.51		
	1.27 (t, 6H)	1645					
3b	6.78 (t, 1H)	2250	C :	61.52	61.27	195	200
	4.28 (q, 2H)	1720	H :	6.71	7.09		
	2.65 (s, 3H)	1680	N :	7.18	7.22		
	2.41-2.12 (m, 4H)	1640					
	1.32 (t, 3H)						
3c	6.89 (t, 1H)	2250	C :	65.44	65.15	165	164
	2.88 (s, 3H)	1680	H :	6.71	6.88		
	2.78 (s, 3H)	1640	N :	8.48	8.71		
	2.48-2.25 (m, 4H)						

* NMR Spectra were observed in CCl_4 by means of Varian A-60 NMR spectrometer, using tetramethylsilane as an internal standard. The chemical shifts were followed by the splitting pattern: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

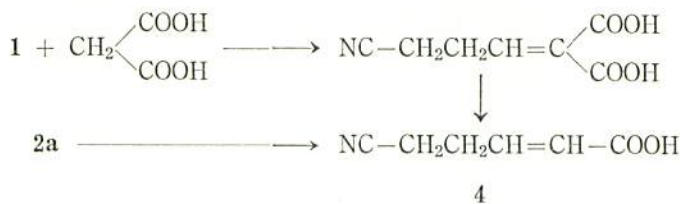


a: $\text{X}=\text{Y}=\text{COOC}_2\text{H}_5$

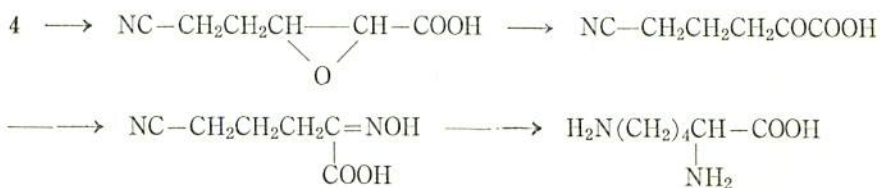
b: $\text{X}=\text{COCH}_3$, $\text{Y}=\text{COOC}_2\text{H}_5$

c: $\text{X}=\text{Y}=\text{COCH}_3$

The reaction of **1** with malonic acid gave 3-cyanopropylideneacetic acid (**4**) by the usual Doebner's method⁸. The compound **4** was also obtained by heating **2a** with 10% sulfuric acid.



This product **4** will be used as an important intermediate in the preparation of lysine as follows:

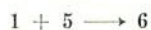


Almost all of the aromatic compound was recovered in the reaction of **1** with less reactive aromatic compound having an active methylene group such as benzyl cyanide (**2d**), ethyl phenylacetate (**2e**), diphenylmethane (**2f**) or desoxybenzoine (**2g**). It is considered that the methylene group of **1** is more reactive than that of the aromatic compound and self condensation of **1** proceeds preferentially. Actually, besides recovered aromatic compound, considerable amount of high boiling product was obtained. Several attempts to carry out the condensation of **1** with other carbonyl compound were resulted in failure.



On the other hand, the reaction of aromatic carbonyl compound with diketene (**5**) to give α , β -unsaturated ketone has appeared in the literature⁹. Condensation of carbonyl group with active methylene group and subsequent decarboxylation of β -ketoacid is effected in one step by heating the two reactants. This procedure, however, is not applied to unstable or inert

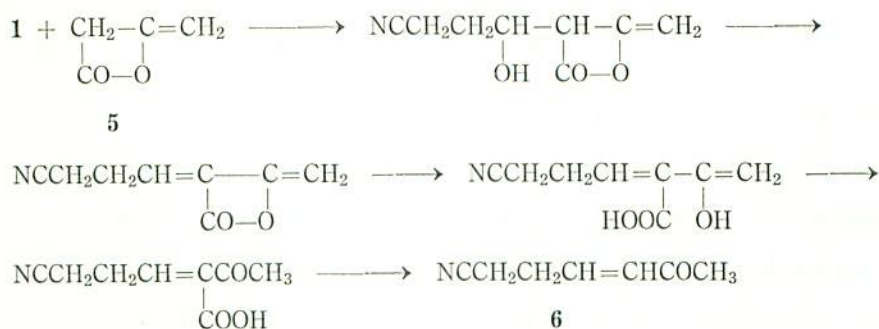
Table 4.



Solvent	Catalyst	Time, hr	Yield, %
-	-	45	-
benzene	-	45	26
benzene	PA	25	63
toluene	-	45	54
toluene	PA	25	85

compound on account of no solvent or no catalyst. For example, only a viscous tar was resulted when this method applied for **1**.

In benzene or toluene solution, the expected 3-cyanopropylideneacetone (**6**), the structure of which correspond to that of the condensation product of **1** with acetone, was obtained with a relatively high yield. The yield appeared to be higher in toluene than in benzene. The effect of catalyst was also examined, and it has been found that PA catalyse the reaction and the reaction time was shortened to about the half with improvement of the yield (Table 4). Acidic catalyst such as p-toluenesulfonic acid only gave rise to the formation of dehydroacetic acid. In this reaction an intermediate hydroxy diketene is believed to be formed, which subsequently loses water. The water eliminated reacts with the condensation product and results in the formation of a β -ketocarboxylic acid, which, in turn, loses carbon dioxide; the end product is the unsaturated ketone.



Experimental

Method A. β -Cyanopropionaldehyde (**1**) (0.2 mol), compound having an active methylene group (**2**) (0.2 mol), piperidine acetate (1.5 g) and 200 ml of benzene were placed in a flask attached to a water separator, which in turn was attached to a reflux condenser. The mixture was refluxed for 8 hours, the water formed being removed continuously by azeotropic distillation, washed with water and distilled. The results obtained are summarized in Table 2 and 3.

Method B. In a three necked flask, fitted with a stirrer, dropping funnel and reflux condenser attached to a water separator were placed 0.4 mol of **2**, 1.5 g of piperidine acetate and 200 ml of benzene. The mixture was gently refluxed, and 0.2 mol of **1** was added slowly over a two-hour period, the water formed being removed. After another 4 hours' refluxing, the reaction mixture was cooled and washed with water. Distillation of the benzene solution gave the results shown in Table 2 and 3.

Method C. Into a solution of 0.4 mol of **2c**, 1.5 g of piperidine acetate and 200 ml of benzene, 0.2 mol of **1** was added over a two-hour period with good agitation at room temperature. The mixture was then refluxed for two hours, the water formed being removed, washed with water. Fractional distillation of this benzene solution gave the results shown in Table 2 and Table 3.

3-Cyanopropylideneacetic Acid (**4**). Into a solution of 0.3 mol of malonic acid in 30 ml of pyridine, 0.3 mol of **1** was added slowly at room temperature with good agitation. The reaction mixture was then heated on a steam bath for two hours. After the evolution of carbon dioxide was ceased, the mixture was cooled, neutralized with 50% sulfuric acid and extracted with

ether. After removal of ether, the residual white solid was recrystallized from benzene: yield 54%, mp 74°C, IR 2550, 2260, 1700, 1650 cm⁻¹.

Anal. Calcd for C₆H₇O₂N: C, 57.59; H, 5.65; N, 11.20. Found: C, 57.25; H, 5.81; N, 11.26. Neutralization equivalent. Calcd: 125. Found: 124.

3-Cyanopropylideneacetone (6). A solution of 0.3 mol of **1**, 0.3 mol of diketene (**5**), 1.5 g of piperidine acetate in 50 ml of toluene was refluxed for 25 hours. The reaction mixture was then cooled, washed with water and distilled to give product **6**: yield 85%, bp 125-6°/6mmHg.

Anal. Calcd for C₇H₉ON: C, 68.32; H, 7.37; N, 11.38; MW, 123. Found: C, 68.02; H, 7.35; N, 11.61; MW, 125.

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