Cyanoacetamide Synthesis in Liquid Ammonia

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Synopsis

Just analogical to liquid ammonia-malondiamide synthesis, liquid ammonia-cyanoacetamide synthesis has been established, obtaining the following results:

1. Conducting the benzylation of ethyl cyanoacetate, cyanoacetamide and malononitrile in liquid ammonia, C-dibenzyl cyanoacetamide and C-dibenzyl malononitrile have been obtained in high yields. As metalation reagents, metallic sodium, sodium alcoholate, sodium amide and potassium amide were smoothly used. Alkali metals gave, however, slightly lower yields. When an excess of cyanoacetamide was used, monobenzylation predominated, producing monobenzyl cyanoacetamide alone. When benzylation was conducted in benzene solution, dibenzylcyanoacetamide was obtained in very low yield although they were heated for a long time.

2. By alkylating cyanoacetamide with ethyl, propyl and butyl halides, corresponding C-alkyl cyanoacetamides and C-dialkyl cyanoacetamides were obtained respectively. Almost same yields were obtained when alkyl bromides and iodides were used as alkylating reagents.

3. Dialkylating reactions were promoted according to the kind of active methylene group as follows: malondiamide<cyanoacetamide<malononitrile. The effect of alkyl groups on these methylene group was distinct and the alkylating result of cyanoacetamide showed that the tendency of dialkylation was increased according to the following order: $C_6H_5CH_2 \gg n\text{-}C_4H_9 > iso\text{-}C_4H_9 = n\text{-}C_3H_7 > C_2H_5 > iso\text{-}C_3H_7 \gg tert\text{-}C_4H_9$. The system was in coincidence with the order of the +I effect.

I. Introduction

In the former report,[1] the authors have reported on liquid ammonia-malondiamide synthesis, in which the alkylation of malondiamide was conducted in liquid ammonia. In the present report, the anthors will report liquid ammonia-cyanoacetamide synthesis in detail, in which cyanoacetamide and malononitrile having strongly active methylene group were alkylated. Namely, ethyl cyanoacetate (CAE), cyanoacetamide (CAA) and malononitrile (MN) were used as materials. They were treated with alkali metals or alkali amides for metalation and then alkylated with alkyl halides in liquid ammonia, obtaining alkyl cyanoacetamide and alkyl malononitrile. In these case, differing in case of malondiamied, a large amount of dialkyl compounds was produced in addition to monoalkyl compounds, the mechanism of which was discussed.

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* The 'Fifth Report of Organi Synthetic Chemistry in Non-Aqueous Solution; published in Japanese in J. Chem. Soc. Japan (Pure Chem. Section) **78** (1957), 803.

(1) Shimo and Asami, J. Soc. Chem. Japan (Pure Chem. Section) **78** (1957), 798; Rep. RITU **A9**, (1957), 319.

II. Experimental method

1. The reaction vessel used was same with that used in the former report.

2. Materials

CAE was obtained by redistilling a commercial product, b p., 112~115°C/31 mmHg CAA was synthesized by treating the ester with concd aqueous ammonia or liquid ammonia, m. p., 118~120°C. MN was prepared by dehydrating CAA with phosphorus pentachloride according to the ordiuary method, m. p., 30°C, b. p. 98~100°C/5 mmHg. Other materials were same with those used in the former report.

3. Metalation of CAA and MN, and the reaction with alkyl nalides

CAE, CAA, MN and their alkali substituted compounds were all soluble in liquid ammonia. Their metalation and alkylating processes were same with those in the liquid ammonia-malondiamide synthesis. In this case, phenolphthalein was also used as an indicator for observing the progress of alkylation.

III. Experimental results

1. Ammonolysis CAE with liquid ammonia

For examining the amidation velocity of CAE with liquid ammonia, the following experiments were performed.

A mixture of 20 g of CAE and 40 cc of liquid ammonia was stood for 24 hours. After evaporating off liquid ammonia, the residue was recrystallized from alcohol, isolating CAA, m. p., 114~118°C, yield 13.5 g (91.0%). The result was shown in Table 1.

Table 1

CAE (g)	Liq. NH_3 (cc)	NH_3/CAE (mol/mol)	Temperature (°C)	Time (hr)	Yield (%)
20	20	4.0	15	24	67
20	40	8.0	15	24	91
2.8	25	35.6	0	24	97*

* Result obtained by Audrieth and Kleinberg(2).

2. Benzylation of CAE, CAA and MN

Alkylating condition of the active methylene compounds with benzyl chloride has been established. When CAE was used as a material, the process was follows: Seven grams (0.06 mol) of CAE were dissolved in 20 cc of liquid ammonia and KNH_2 prepared from 2.4 g (0.06 mol) of metallic potassium in 60 cc of liquid ammonia. By mixing the two solutions together, potassiocyanoacetate was produced and remained in solution. Phenolphthalein in the solution gave red color. After 1 hour, 8.5 g (0.07 mol) of benzyl chloride were added to the solution and shaken. Potassium chloride separated out quickly and the indicator became

(2) L. F. Audrieth and J. kleinberg, J. Org. Chem., **3** (1938), 312.

colorless, showing the completion of benzylation. After standing one night at room temperature, liquid ammonia was evaporated off, obtaining a residue containing a small amount of oily substance. The residue was extracted with ether, which was washed with water containing hydrochloric acid, dehydrated and an oily substance (B) containing white crystals (A) was obtained. On the other hand, ether insoluble substance gave cold water insoluble white crystals (A′). (A) and (A′) were treated with hot water. The insoluble substance gave sandy crystals (A″) from alcohol, m. p., 160~163°C, yield, 4.0 g (49%); N, 10.26% (10.60). From hot aqueous solution, needles (C) were obtained, m. p. 128~130°C, yield, 0.4 g, N, 16.49% (16.06). By vaccum distillation, (B) gave a viscous liquid (B′), b. p., 158~159°C/1 mmHg; yield, 2.2 g (24%); N, 5.2% (4.77). Melting points and nitrogen contents of (A″) and (C) were in coincidence with those of dibenzylcyanoacetamide (II) and monobenzylcyanoacetamide (I) given in the literature and idenified by mixed melting point test. Boiling point and nitrogen content of (B) were concidental with those of ethyl dibenzylcyanoacetate (III). From the aqueous solution, CAA, m. p., 115~120°C, was obtained in the yield of 1.7 g, which was produced by ammonolysis of CAE not reacted with benzyl chloride.

The above obtained compounds were C-benzyl ones, but not N-benzyl compounds. It was, therefore, confirmed that the alkylation occurred at the hot methylene group.

When CAA was used as a material, 5 g (0.06 mol) of CAA, 2.3 g (0.06 mol) of potassium and 8.5 g (0.07 mol) of benzyl chloride were used for the reaction. The residue, after evaporating off liquid ammonia, gave a mixture of (I), (II) and an inorganic salt. After removing the salt, the residue was treated with hot water and alcohols, obtaining 5.5 g (70%) of (II) and 0.6 g of (1).

When benzene was used as the solvent, the process was as follows: Sodiocyanoacetamide was prepared in liquid ammonia using 5 g (0.06 mol) of CAA and 1.4 g (0.06 mol) of sodium. A calciumchloride tube was fixed to the reaction vessel and liquid ammonia in the vessel was completely evaporated off, preventing moisture. Fifty cc of dehydrated benzene and 9.0 g (0.07 mol) of benzyl chloride was added into the vessel and heated for 8 hours at the boiling point of benzene. After the reaction was completed, inorganic salt was filtered off while the solution being hot and crystals of (II) were isolated after cooling, m. p., 153~160°C, yield, 1.5 g (19%).

In case of MN, the benzylation was performed using 3.3 g (0.05 mol) of MN, 2.8 g (0.05 mol) of KNH_2 and 7.0 g (0.06 mol) of benzyl chloride, as in case of CAA. After evaporating off liquid ammonia, the residue was washed with water and the insoluble substance was recrystallized from alcohol, obtaining needles(D), m. p., 130~131°C; yield, 5.2 g (84%); N, 11.12% (11.37). Melting point and percentage of nitrogen were in coincidence with those of dibenzylmalononitrile(IV). The nitrile is soluble in liquid ammonia at room temperature but is slight soluble under 5°C, and separated out as needles. The above results ore shown in Tables 2, 3 and 4.

Table 2. Benzylation of CAE with benzyl chloride. (Reaction temperature: room temperature)

CAE (g)	M	NH_3 (cc)	Time (hr)	I (g)	II (g)	II (%)*	III (g)	III (%)*
11.3	Na	70	20	0.5	5.0	38	3.2	22
11.3	$NaNH_2$	70	20	0.9	5.3	40	5.0	34
7.0	KNH_2	80	20	0.4	4.0	49	2.2	24
7.0	KNH_2	80	1.5	0.6	4.7	58	1.5	17

* The yield was calculated assuming the dibenzylation as the main reaction.

Table 3. Benzylation of CAA with benzyl chloride (Reaction temperature: room temperature)

(i) CAA : M : RX = 1 : 1 : 1.1

CAA (g)	M	NH_3 (cc)	Time (hr)	I (g)	II (g)	II (%)
5.0	Na	60	20	0	3.8	48
10.0	Na	80	1	0.2	8.5	54
10.0	Li	80	1	0	6.2	39
5.0	$NaOC_2H_5$	70	1	0.5	5.1	65
5.0	KNH_2	70	1	0.6	5.5	70
5.0	KNH_2	60	1	1.1	5.2	66
5.0	Na	Benzene 50	8 (80°C)	0	1.5	19
7.0	Na	Benzene 50	30 (80°C)	0	2.5	21

(ii) CAA : M : RX = 3 : 1 : 1.1

CAA (g)	M	NH_3 (cc)	Time (hr)	I (g)	I (%)*	II (g)
15.0	Na	80	20	3.9	38	0
15.0	KNH_2	85	20	4.4	43	0.3

* The yield was calculated assuming that only 1 mol of CAA reacted.

Table 4. Benzylation of MN (Reaction temperature: room temperature and Reaction time: 20 hours)

MN (g)	M	RX	NH_3 (cc)	IV (g)	IV (%)
3.3	Na	$C_6H_5CH_2Cl$	60	4.7	76
3.3	KNH_2	$C_6H_5CH_2Cl$	60	5.2	84
3.3	KNH_2	$C_6H_5CH_2I$	60	5.9	95

3. Alkyaltion of CAA

Using alkyl halides, CAA was alkylated obtaining alkyl cyanoacetamides. The procedure and reacting conditions of the alkylation were practically same with those of benzylation. Differing from the case of benzylation, a mixture of monoalkyl cyanoacetamide (R-CAA) and dialkyl cyanoacetamide (RR-CAA) was produced in many cases, the separation of the two was performed especially with care. The experimental results with individual alkyl halides are as follows:

When ethyl bromide was used as an alkylating agent, only C_2H_5-CAA was obtained, plates, m. p., 105~108°C, N, 24.99% (24.99).

When *n*-propyl bromide was used as an alkylating agent, the reaction product was treated with hot water for removing monopropyl derivative. Diprooyl derivative was obtained by recrystallizing the insoluble sabstance from alcohol. Monopropyl compound was obtained by cooling hot water solution and recrystallized from alcohol.

n-C_3H_7-CAA, needles, m. p. 116~118°C, N, 23.13% (22.21).

(*n*-C_3H_7)$_2$-CAA, sandy crystals, m. p. 149~151°C, N, 16.93% (16.65).

iso-Propyl bromide and CAA gave *iso*-C_3H_7-CAA alone, needles, N, 22.5% (22.21)

The reaction product from *n*-butyl bromide was washed with cold water for removing inorganic compound. The mixed crystals of mono- and di-butyl derivatives were treated with hot ligroin, in which dibutyl compound was soluble, while monobutyl compound insoluble. After separation, they were recrystallized from alcohol.

n-C_4H_9-CAA, needles, m. p. 124~125°C, N, 20.36% (19.99).

(*n*-C_4H_9)$_2$CAA, needles, m. p. 116~119°C, N, 14.45% (14.27).

When *iso*-butyl bromide was used, monobutyl compound was recrystallized from hot water and insoluble dibutyl compound from alcohol. Di-isobutyl cyanoacetamide, (*iso*-C_4H_9)$_2$C$<^{CN}_{CONH_2}$, was not found in literature, which was confirmed by analysis of nitrogen.

iso-C_4H_9-CAA, needles, m. p. 90-92°C, N, 20.57% (19.99).

(*iso*-C_4H_9)$_2$C$<^{CN}_{CONH_2}$, needles, m. p., 129~130°C, N, 14.16% (14.27).

The above results are summarized in Table 5.

Table 5

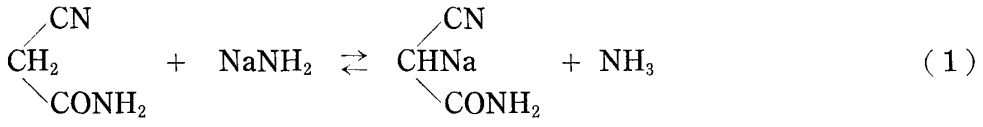
(CAA, 4.5 g (0.054 mol); Liquid ammonia, 60~70 cc,; Reaction temp., room temp,; Alkylation time, 20 hr.)

M	RX	R-CAA		RR-CAA	
		(g)	(%)	(g)	(%)
KNH_2	C_2H_5Br	2.5	42	0	0
KNH_2	*n*-C_3H_7Br	3.7	55	1.0	11
KNH_2	*n*-C_3H_7I	3.6	54	1.2	13
KNH_2	*iso*-C_3H_7Br	5.3	79	0	0
KNH_2	*n*-C_4H_9Br	3.4	44	1.4	13
KNH_2	*n*-C_4H_9I	4.0	53	1.7	16
KNH_2	*iso*-C_4H_9I	1.7	23	1.5	14

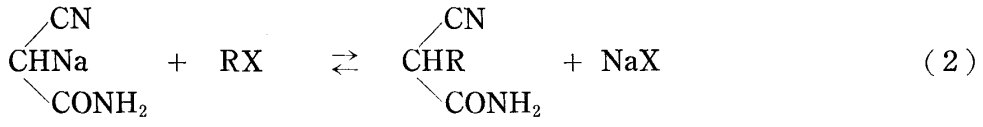
IV. Discussion

The alkylation products of CAE, CAA, and MN in liquid ammonia were C-alkyl compounds just same with those of malondiamide, but not N-alkyl compound, i. e., active methylene group was alkylated and the yield was high. Differing from the case of malondiamide, a large amount of dialkyl compounds were produced in addition to monoderivatives. Especially, as shown in Table 2~4, a very large amount of dibenzyl derivatives were produced in case of benzylation. Such a fact was perceived in the cyanoacetic ester synthesis or in the alkylation of aceto-

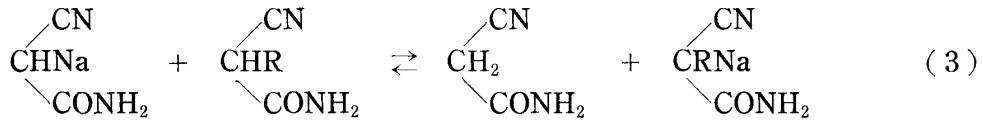
nitrile in liquid ammonia. Dialkylation was caused, as shown in the following formula, when the activity of methine group is stronger than that of methylene group. The activity of methine group not perceived in MDA is caused by replacing one or two of acid amide group ($-CONH_2$) with more elecronegative group such as nitrile group (-CN). The activity of methine group is deservedly affected by alkyl group (-R), which will be stated lately.



(1)



(2)



(3)

Table 2 shows benzylation of CAE. Alike in the case of MDE, ester amides of alkylated compounds were produced in different ratio according to the reaction conditions. As explained in the case of malondiamide, the fact shows that amidation of CAE to CAA is accelerated when the metalation with alkaliamide is conducted, but not ethyl dibenzylcyanoacetate is changed into dibenzylcyanoacetamide by ammonolysis.

Generatizing the results shown in Table 2 and 3, the conditions of benzylating reaction are as follows: The amount of used liquid ammonia and alkylating time do not affect the yield of the alkylated product. And the reaction is completed within a very short time at room temperature. On the effect of the kind of metalation reagents, alkaliamide gives generally higher yield than alkali metal, the yield being about 70~80 per cent. When alkali metals are used, hydrogen is generated in the metalation, reducing one part of the material, which is assumed to be the cause of low yield, reduction product was however not isolated. Lithium metal gave especially low yield, but sodium alcoholate high yield. After metalation, ammonia was completely removed and benzylation was conducted using benzyl chloride suspended in benzene. It was heated for a long time, but benzylated product was poor. As such an alkylating reaction is ionic one, it is perceived that a solvent having large polarity such as liquid ammonia is more beneficial for the reaction than a solvent of small polarity such as benzene. For promoting monobenzylation, a large excess of CAA was used resulting the production of monobenzyl compound alone. The fact is coincidental with that walker[5] used thrice mol of CAE for the preparation of monobenzylcyanoacetate Namely, it is due to the fact that the reaction shown in the formula (3) will

(5) T.K. Walker, J. Chem. Soc., **125** (1924), 1622.

proceed from right to left as $CH_2(CN)(CONH_2)$ is excess.

Benzylation of MN was shown in Table 4, in which only dibenzyl compound was obtained in high yield (80~95%), but no monobenzyl compound. Namely, it was perceived that methine group in benzylmalononitrile was very strongly activated in this case.

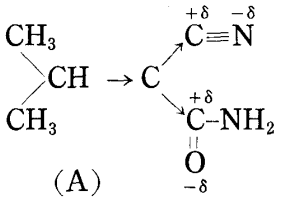
Table 5 showed the alkylating results of CAA with various alkyl halides. Propyl, butyl and *iso*-butyl halides, except ethyl and *iso*-propyl halides, gave mono- and di-alkyl compounds. On the kind of halogen of alkyl halides, the yield of the product due to iodides and bromides was almost same. *iso*-Propyl halide gave no di-*iso*-propyl compound, that was in coincidence with the results of Hessler[6] and Fischer,[7] Hauser[8] stated the difficulty of synthesizing di-*iso*-propyl malonate, which was due to +1 effect of $>CH(CH_3)_2$ group. Such a phenomenon occurred in case of liquid ammonia.

Summerizing the above results, it may be concluded that dialkylating reaction of active methylene compounds is on the following order: Malondiamide<cyano-acetamide<malonoitrile. That is due to the increase of activity of each methine group by replacing acid amide group ($-CONH_2$) with more electronegative nitrile group ($-CN$).

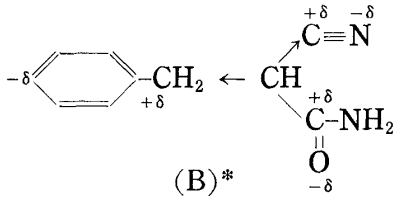
$$RCH(CONH_2)_2 < RCH(CN)(CONH_2) < RCH(CN)_2$$

Moreover, the effect of alkyl group (-R) to the activity of methine group is very large beyond expectation. In the alkylation experiments of CAA, the tendency of dialkylating reaction is as follows: $C_6H_5\text{-}CH_2 \gg n\text{-}C_4H_9 > iso\text{-}C_4H_9 \fallingdotseq n\text{-}C_3H_7 > C_2H_5 > iso\text{-}C_3H_7 \gg tert.\text{-}C_4H_9$. This series is coincidental with the order of +1 effect, if benzyl radical is excepted. This is, by introducing electron repulsing groups the methine group decreases its activity.

That benzyl radical strongly activate methine group is not explained by the above reason. The authors gave a new explanation on the fact that, noticing benzyl radical has dipole,[9] it acts as a negative radical in the formula of (B):



(A)



(B)*

(6) J. C. Hessler, J. Am. Chem. Soc., **35** (1913) 990.
(7) E. Fischer and E. Flatn, Ber., **42** (1909) 2983.
(8) J. C. Shivers, B. E. Hudson, and C. R. Hauser, J. Am. Chem. Soc., **66** (1944), 309.
(9) Ingold, Structure and Mechanism in Organic Chemistry, P. 103 (1953). London.
* The symbols followed to E. R. Alexander '*Principle of Ionic Organic Reaction*'