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A New Method for Preparation of Alkylnitriles from Alkyl Halide and Alkylammonium Cyanide.

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The reaction between alkyl halides and metal cyanides has long been known as the method of preparation of various alkylnitriles,[1] aqueous alcohol or acetone being used as a solvent to ensure a homogeneous mixture. Among other solvents lately recommended are ethylene glycol,[2] ethylene glycol monomethylether,[3] polyethylene glycol,[4] methyl cellosolve,[5] and dimethylformamide.[5]

Quite recently, almost at the same time, Smiley, *et al.*[6] and Friedman, *et al.*[7] introduced dimethyl sulfoxide as an excellent solvent for this reaction. According to them all features of the above-mentioned solvents are present in this solvent and the reaction is usually completed in shorter time and with a good yield of the product. A special mention was made of *sec*-alkyl halides, which also could be converted to the corresponding nitriles with a better yield.

The role of these solvents in this reaction exists how to keep the water soluble metal cyanide in intimate contact with the water insoluble alkyl halides throughout the reaction. It was found that alkyl nitrile can be conveniently prepared from alkyl halide and benzyltrimethylammonium cyanide in aqueous solution in the absence of any organic solvent. Sometimes other ammonium cyanide may be used (cited in Table), but benzyltrimethylammonium cyanide was exclusively used in the experiment, which served not only as a nitrile introducing agent but also acted as a surface active agent to promote the reaction to go smoothly according to the following equation :

$$\mathrm{R{\cdot}X} + \mathrm{Ph{\cdot}CH_2\text{-}\overset{+}{N}(CH_3)_3\text{-}\overset{-}{CN}} \longrightarrow \mathrm{R{\cdot}CN} + \mathrm{Ph{\cdot}CH_2\text{-}\overset{+}{N}(CH_3)_3\overset{-}{X}}$$

$$\mathrm{R{=}alkyl} \qquad \mathrm{X{=}halogen}$$

With some alkyl halides the reaction was so vigorous that external cooling or portionwise addition of alkyl halides was necessary.

In practice alkyl halide is added to a mixture of alkylammonium halide and water solution of sodium cyanide, when the latter two react with first to form alkylammonium cyanide, which in turn enters into reaction with alkyl halide to form alkyl nitrile recovering ammonium halide as shown in the above equation. The latter then enters again into the reaction cycle, thus plays a role as a transporter of cyanide anion. Thus a limited ammount of the original ammonium halide appears to be enough to carry the reaction to the end, although its optimal amount may be closely connected with the reaction time and temperature, which depends upon the reactivity of alkyl halide.

As can be seen from the Table this new method was successfully applied to those

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alkyl halides, which have been known to yield the corresponding nitriles by the established method, giving a better yield with some halides, while yields were inferior with others.

Benzyltrimethylammonium rhodanate was used instead of benzyltrimethylammonium cyanide in the above reaction which provides alkyl rhodanate usually in a good yield.

TABLE I.

No.		Alkyl halide	Reaction		Nitrile or rhodanate	Yield (%)	b.p. (°C/mm.Hg)
			(°C)	hr.			
1	A	Benzyl chloride	35 95	1.5 0.2	Phenylacetonitrile	92	110∼115/8
	B	〃	35 95	1.5 1.0	〃	89.5	110∼115/18
2	A	Phenethyl bromide	95	3.0	3-Phenylpropionitrile[a]	91.6	114∼118/18
	B	〃	95	6.0	〃	93.1	114∼118/8
3	A	n-Butyl bromide	85	3.0	Valeronitrile[b]	69	138∼140/760
	B	〃	90	6.0	〃	71.4	138∼140/760
4	A	1.5-Dibromopentane	95	3.0	Pimelonitrile[c]	70.6	150∼152/6
5	A	2-Bromopropionitrile	70	1.5	Succinonitrile	50	115/4
6	A	1-Chloro-3-bromopropane	90	1.5	3-Chlorobutyronitrile Glutaronitrile[d]	48.3 23.4	90∼95/25 155∼158/25
	B	〃	90	6.0	〃	52.1 25.1	90∼95/25 155∼158/25
7	A	1,2-Dichloroethane	80	4.0	Succinonitrile[e]	40	110/4
8	A	Ethyl 2-bromopropionate	85	2.0	Ethyl 2-cyanopropionate[f]	40.9	90∼94/20
9	A	Ethyl 4-chlorobutylate	85	2.0	Ethyl 4-cyanobutylate[g]	22.7	123∼126/20
10	A	2-Chloroacetoanilide	95	3.0	2-Cyanoacetoanilide[h]	50	198∼200 (m.p.)
11		(2-Hydroxy-3-chloropropyl)-trimethylammonium chloride	60	3.0	(2-Hydroxy-3-cyanopropyl)-trimethylammonium chloride[i]	88	218∼220 (m.p.)
12	A	Benzyl chloride	85	4.0	Benzyl rhodanate	94.6	157∼160/30
	B	〃	90	5.0	〃	94.6	157∼160/30
13	A	n-Butyl bromide	90	4.0	n-Butyl rhodanate[j]	88.5	76∼79/20
14	A	Benzyl chloride[k]	70∼75	3.0	Phenylacetonitrile	53.0	112∼116/20

Reaction of Alkyl halide (0.1*M*), Benzyltrimethylammonium chloride (0.12*M*···(A) or 0.012*M*···(B)) and Sodium cyanide (0.12*M*) or Potassium rhodanate (0.12*M*) in water (40∼50 ml.).

a) H. Rupe, K. Glenz: Helv. Chim. Acta., **5**, 941 (1922).

b) R. Adams, C.S. Marvel: J. Am. Chem. Soc., **42**, 310 (1920).

c) Used the ammonium chloride (0.24*M*) and sodium cyanide (0.24*M*). (J.V. Braun: Ber., **37**, 3588 (1904).)

d) Obtained glutaronitrile as by-product. (C.F.H. Allen: Org. Syn., **8**, 52 (1928).

e) Used the ammonium chloride (0.24*M*) and sodium cyanide (0.24*M*). (R.A. Smiley, C. Arnold: J. Org. Chem., **25**, 257 (1960)).

f) N. Zelinsky: Ber., **21**, 3162 (1888).

g) A. Karronen: C.A., **18**, 1982 (1924). About 51% of the original substance was recovered.

h) K.G. Naik, Y.N.B. Hat: J. Indian. Chem. Soc., **4**, 548 (1927).

i) Not used the ammonium chloride. M. Tellinek: Feda. Proc., **19**, (1) 255 (1960).

j) R.J. Kaufmann, R. Adams: J. Am. Chem. Soc., **45**, 1947 (1923).

k) Used resin, Amberlite IRA-400 instead of the ammonium salt.

The corresponded nitriles were not obtained from cyclohexyl bromide, *t*-butyl chloride, 1-chloro-4-nitrobenzen and 6-chloro-2,4-dimethoxypyrimidine.

Experimental

General procedure

Sodim cyanide (0.12 mole) and benzyltrimethylammonium chloride (0.12 mole or 0.012 mole) were dissolved in 40∼50 ml. of water in a flask fitted with a stirrer, reflux condenser, dropping funnel and thermometer.

Alkyl halide (0.1 mole of mono halide or 0.05 mole of dihalide) was added under cooling (below

35°) to the well-stirred mixture, and the resulting emulsion was heated on a steam bath at 80~95° for 1~6 hr. The reaction mixture gradually turned to a yellow or red solution.

The reaction mixture was then extracted several times with $CHCl_3$ or ethyl ether. The combined extracts were washed with saturated sodium chloride solution and dried over calcium chloride. After removing the solvent, the residue was distilled to give a pure material.

Summary

Reaction of alkyl halides with benzyltrimethylammonium cyanide in water proceeds rapidly and efficiently to result in an improved general method for preparing nitriles. Benzyltrimethylammonium chloride and alkali cyanide can be used instead of benzyltrimethylammonium cyanide. A general procedure is described and many examples are listed. In this reaction, alkali rhodanate can be used in place of alkali cyanide to obtain alkyl rhodanate in a good yield.

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Hiromu Mori : Studies on Steroidal Compounds. VIII. A New Synthesis of 4-Chloro-4-en-3-oxo-steroids.[1]

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4-Chloro-4-en-3-oxo-steroids were first synthesized by Kirk,[2] Camerino,[3] and Ringold[4] in 1956. 4-Chlorotestosterone and its acylates, particularly among these compounds, have high ratio of anabolic-androgenic activity[5] and are excellent anabolic steroids. It has been shown that the treatment of 4-en-3-oxo-steroid (I) with alkaline hydrogen peroxide leads to 4,5-epoxide (Ⅱ), which on treatment with hydrogen chloride including fission of epoxide and dehydration gives 4-chloro-4-en-3-oxo-steroids (Ⅲ).[3,4] On the other hand, Kirk has shown that 4-en-3-oxo-steroid (I) is converted into 4-chloro-4-en-3-oxo-steroid (Ⅲ) by addition of chlorine and dehydrochlorination with pyridine (I→Ⅳ→Ⅲ).[2] In the present paper, another synthetic method for 4-chloro-4-en-3-oxo-steroids (Ⅲ) will be described.

A better result may be otained, if a mild chlorination reagent such as sulfuryl chloride is used instead of chlorine in the method of Kirk. However, it has recently been reported that the treatment of 4-en-3-oxo-steroid with sulfuryl chloride in benzene leads to 2-chloro-4-en-3-oxo-steroid.[6] On the other hand, it has been shown that 4-en-3-oxo-steroid (I) is converted directly into 4-chloro-4-en-3-oxo-steroid (Ⅲ) on treatment with chlorine in the presence of pyridine.[2] Chlorination of 4-en-3-oxo-steroid with sulfuryl chloride in pyridine solution was therefore attempted and 4-chloro-4-en-3-oxo-steroid (Ⅲ) was found to be prepared directly in a high yield. On the first attempt, one equivalent

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