CHEMISTRY LETTERS, pp. 687-690, 1987.

Useful Synthesis of α-Aminonitriles by Means of Alumina and Ultrasound†

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Combined use of alumina and ultrasound facilitates the synthesis of α-aminonitriles under solid-liquid two phase conditions from carbonyl compounds, salts of amines and potassium cyanide in organic solvents.

In the preparation of α-amino acids α-aminonitriles are important intermediates.$^{1)}$ They have been prepared conventionally by the Strecker synthesis starting from ketones or aldehydes, alkaline cyanides, and salts of amines. The reaction is generally carried out in aqueous solution, and the work-up procedures are tedious. A modified Strecker synthesis with trimethylsilyl cyanide$^{2)}$ or diethyl phosphorocyanidate$^{3)}$ has been recently reported to be an excellent alternative to the above preparation. On the other hand, the synthetic application of ultrasound has recently attracted increasing interest, particularly in heterogeneous reactions of metals.$^{4)}$ There has also been a concurrent growth in the use of inorganic supports for organic synthesis.$^{5)}$ We have revealed that ultrasound together with alumina support accelerates a solid-liquid two phase nucleophilic substitution of alkyl halide by potassium cyanide in organic solvents.$^{6)}$ We now report the convenient method for the preparation of α-aminonitriles by the combined use of alumina and ultrasound in organic solvents.$^{7)}$

A typical procedure was as follows. The mixture of potassium cyanide (10 mmol), ammonium chloride (11 mmol), and alumina (1.5 g) in acetonitrile was preliminarily subjected to ultrasonic irradiation$^{8)}$ at 50 °C for 10 min.

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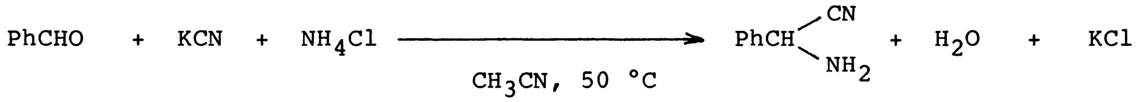
† This paper is dedicated to the late Professor Ryozo Goto, Kyoto University.

To the above mixture was added benzaldehyde (5 mmol) and sonication was continued at 50 °C for 24 h. After filtration of solid substances α-amino-phenylacetonitrile was isolated in 90% yield.



$$\mathrm{PhCHO} + \mathrm{KCN} + \mathrm{NH_4Cl} \xrightarrow[\mathrm{CH_3CN,\ 50\ ^\circ C}]{} \mathrm{PhCH}\begin{matrix}\mathrm{CN}\\ \mathrm{NH_2}\end{matrix} + \mathrm{H_2O} + \mathrm{KCl} \quad (1)$$

Table 1 shows the results obtained under several reaction conditions for the reaction 1. When the same heterogeneous mixture was agitated mechanically without alumina, the reaction gave a slight amount of the desired product. In this case, the cyanohydrin and benzoin were produced in substantial amounts (Run 1). Either the addition of alumina or sonication promoted the formation of the aminonitrile, compared with Run 1 (Runs 2 and 3). To attain the desired reaction, the combined use of alumina and ultrasound (Run 4) was found to be superior to the separate use of the two.

Interestingly, alumina not only promotes the Strecker reaction but also appears to suppress benzoin condensation by cyanide ion, while ultrasound has no effect on the latter. Other inorganic supports such as silica gel, Celite, or bentonite also were found to accelerate the reaction, but among them alumina was the most effective as an inorganic support for the synthesis of α-aminonitriles.

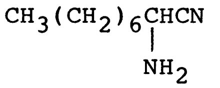
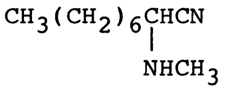
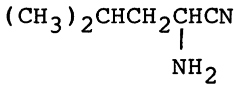
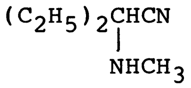
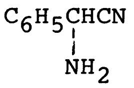
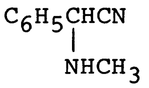
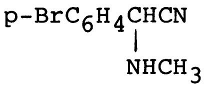
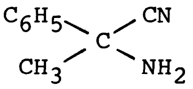
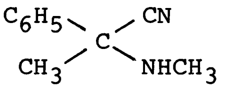
Table 1. The Heterogeneous Reaction of Benzaldehyde with Potassium Cyanide and Ammonium Chloride[a)]

Run	Support	Conditions	Relative Ratio[b)]			
			PhCHO	PhCH(CN)OH	$PhCH(CN)NH_2$	PhCH(OH)COPh
1	None	Mechanical Agitation	35	38	6	21
2	Al_2O_3	Mechanical Agitation	8	19	64	9
3	None	Ultrasonic Irradiation	11	45	23	22
4	Al_2O_3	Ultrasonic Irradiation	0	3	90	7

a) In acetonitrile at 50 °C for 24 h. b) Determined by ^{1}H-NMR of their benzylic protons, of which δ values (in CH_3CN) are 9.95, 5.65, 4.95, and 6.05 ppm, respectively.

Although the reaction conditions were not fully optimized, several α-aminonitriles were obtained in excellent yields from aliphatic or aromatic aldehydes and ketones by using both alumina and ultrasound. Typical examples were summarizd in Table 2. By taking advantage of the solid-liquid two phase reaction, a product was easily isolated with simple and non-aqueous work-up, i. e., filtration of inorganics, evaporation of the solvent, and, when necessary, purification by short column chromatography.

Table 2. The Synthesis of α-Aminonitriles Using Alumina and Ultasound[a)]

Carbonyl Compound	$RNH_2 \cdot HCl$	Time/h	Product	Yield/%[b)]	IR/cm^{-1}	
					ν_{NH}	ν_{CN}
$CH_3(CH_2)_6CHO$	R= H	7	 $CH_3(CH_2)_6\underset{NH_2}{\underset{\vert}{C}}HCN$	82	3370, 3300	2225
$CH_3(CH_2)_6CHO$	CH_3	22	 $CH_3(CH_2)_6\underset{NHCH_3}{\underset{\vert}{C}}HCN$	100		
$(CH_3)_2CHCH_2CHO$	H	6	 $(CH_3)_2CHCH_2\underset{NH_2}{\underset{\vert}{C}}HCN$	94	3380, 3320	2230
$(C_2H_5)_2CHCHO$	CH_3	5	 $(C_2H_5)_2\underset{NHCH_3}{\underset{\vert}{C}}HCN$	94	3340	2230
C_6H_5CHO	H	24	 $C_6H_5\underset{NH_2}{\underset{\vert}{C}}HCN$	90	3380, 3320	2225
C_6H_5CHO	CH_3	5	 $C_6H_5\underset{NHCH_3}{\underset{\vert}{C}}HCN$	94	3325	2225
p-BrC_6H_4CHO	CH_3	8	 p-$BrC_6H_4\underset{NHCH_3}{\underset{\vert}{C}}HCN$	94	3325	2220
$C_6H_5COCH_3$	H	48		93	3380, 3320	2230
$C_6H_5COCH_3$	CH_3	24		100	3340	2230

a) A heterogeneous mixture of carbonyl compound (5 mmol) in acetonitrile with potassium cyanide (10 mmmol), hydrochloride of amine (11 mmol), and alumina (1.5 g, Merck, Type 90 for column chromatography, neutral, activity I) is ultrasonically irradiated at 50 °C. b) Isolated yields.

The present method was provided to be one example of recent efficient synthetic methods utilizing solid-liquid interface, although the mechanism of acceleration by alumina and ultrasound has not been clearly elucidated.

The present work was partially supported by a Grant-in-Aid for Scientific Research No. 60470022 from the Ministry of Education, Science and Culture.

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8) A thermostatted ultrasonic cleaner (Branson, 100 W, 45 kHz) was used.

(Received January 30, 1987)