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ACCELERATION OF SOLID-LIQUID TWO-PHASE REACTION BY MEANS OF ALUMINA-WATER-ULTRASOUND. A SUBSTITUTE FOR A PHASE TRANSFER CATALYST

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Combined use of alumina, a trace of water, and ultrasound greatly accelerated a solid-liquid two-phase nucleophilic substitution by cyanide ion in nonpolar organic solvents. The efficiency under the optimum conditions were compared with that of phase transfer catalysts such as 18-crown-6.

The use of inorganic solid support for organic synthesis has been a growing concept in recent years.$^{1)}$ It is of interest whether an inorganic support can facilitate a solid-liquid two-phase reaction as a substitute for a phase transfer catalyst. However, the degree of acceleration by the former is highly susceptible to the reaction conditions and considerably less than that by the latter. On the other hand, ultrasound has been successfully applied to a number of heterogeneous reactions. Most of these applications have been related to the reactions with metals,$^{2)}$ whereas the reactions with other inorganic reagents in organic solvents have been rare.$^{3)}$ In order to establish a new synthetic method utilizing a solid-liquid interface, we studied the effect of ultrasound on the alumina-assisted substitution with cyanide anion (Eq. 1).$^{4)}$

$$\mathrm{RBr} \quad + \quad \mathrm{KCN\,/\,alumina} \ \xrightarrow[\text{in toluene}]{\text{ultrasound}} \ \mathrm{RCN} \quad + \quad \mathrm{KBr} \qquad (1)$$

A heterogeneous mixture of benzyl bromide, potassium cyanide, and alumina in toluene was irradiated by ultrasound at 50 °C. The substitution proceeded smoothly to give benzyl cyanide in a 67% yield after 16 h. In contrast, under mechanical agitation only a side reaction proceeded to give a mixture of *o*- and *p*-benzyltoluene in a 87% yield after 3 h;$^{5)}$ when hexane was used as a solvent, the substitution scarcely proceeded without sonication after 16 h. In the absence of alumina ultrasonic acceleration was recognized to a certain extent; the cyanide was formed in a 27% yield after 16 h. Thus, ultrasound was found to be a good accelerator for the heterogeneous cyanide substitution.

In the previous paper we reported the importance of a trace of water as one of the activating factors in the alumina-assisted substitution with alkali acetates.$^{6)}$ The maximum reactivity was obtained with a trace of water whose

Table 1. Alumina-Assisted Reaction of Alkyl Bromide with Potassium Cyanide[a]

Series	Substrate	Ultrasound[b]	H_2O/n[c]	Time/h	yield/%[d]		
					RCN	ROH	ROR
I	$1\text{-}C_8H_{17}Br$	none[e,f]	0	46	0	0	0
			0.2	46	11	11	0
			0.6	46	56	11	0.4
			0.93	46	67	3.9	0.2
			1.44	46	7.4	1.0	0
II	$PhCH_2Br$	none[e]	0[g]	3	0	0	0
			0[h]	16	1.0	8.5	5.4
			0.2	6	5.5	2.2	8.6
			0.4	6	23	2.9	6.9
			0.61	6	32	3.0	6.0
				24	55	5.0	5.8
			0.83	6	27	2.1	7.0
			1.2	6	2.2	2.1	7.0
III	$PhCH_2Br$	irradiation	0	6	34	0	9.4
				16	67	0	9.3
			0.2	6	26	6.7	12
			0.4	6	61	6.7	3.9
			0.6	6	68	4.1	3.9
			0.81	6	47	3.3	4.4

a) Reaction of alkyl bromide (3.2 mmol), KCN (1.0 g, 16 mmol), and alumina (1.6 g, Merck, Type 90 for column chromatography, neutral, activity I) in toluene was carried out at 50 °C. b) A thermostated ultrasonic cleaner (Branson, 100 W, 45 kHz) was used. c) Molar ratio of H_2O to KCN. d) Determined by GLPC using tetradecane as an internal standard. Alkyl alcohol and ether were obtained as by-products. e) With mechanical agitation using a vibrating apparatus (Tokyo Rikakikai Mini Vapour S-10). f) At 90 °C. g) An 87% yield of *o*- and *p*-benzyltoluene mixture was obtained.[5] h) Hexane was used as a solvent.

amount depended on the alkali metal cation of the acetate salt. Thus, the effect of added water in alumina-assisted cyanide displacement was also studied: with addition of various amounts of water the heterogeneous reaction of octyl (or benzyl) bromide was carried out under mechanical agitation at 90 °C (or 50 °C). The results are shown as Series I and II in Table 1. In both Series the cyanide substitutions did not occur in the absence of water, but the yields showed maxima for certain amounts of water. The optimum amount n, molar ratio of H_2O to KCN, was 0.8 for octyl bromide at 90 °C (Series I), and 0.7 for benzyl bromide at 50 °C (Series II). It is now evident that a limited amount of water is important for promoting alumina-assisted nucleophilic substitution in general.

The difference in the n number is rather small for these two cyanide substitutions as compared with the large difference in reactivity.[7] On the contrary, the n number for cyanide ion in the octyl system differs greatly from that for acetate ion ($n = 0.4$ at 90 °C).[6)] Thus, the optimum amount is dependent not only on the cation[6)] but also on the anion of the inorganic salt, while it is rather insensitive to the substrate reactivity. This observation further supports the idea that the role of water is to attack the crystal lattice of an inorganic reagent and to produce an active ion or ion aggregate on alumina surface for promoting a solid-liquid interfacial reaction.

In order to attain higher reactivity for the alumina-assisted substitution, we applied ultrasound together with various amounts of water for the reaction of benzyl bromide with cyanide anion. The results are shown as Series III in Table 1 and plotted in Fig. 1 together with those obtained by mechanical agitation (Series II). Figure 1 clearly shows that ultrasound facilitates the alumina-assisted substitution to a great extent either with or without added water. The maximum reactivity in the ultrasonic system (Series III) was obtained for a similar amount of water ($n = 0.6$) to that in the agitation system (Series II, $n = 0.7$). This amount of added water little varied when the reaction solvent was changed from toluene to cyclohexane. Thus, sonication together with addition of a limited amount of water was found to be an excellent method to promote the alumina-assisted nucleophilic substitution. Furthermore, ultrasonic pretreatment of a mixture of alumina, potassium cyanide, and water in a solvent before the addition of a substrate suppressed the formation of the hydrolysis by-products, the corresponding alcohol and ether, and increased the yield of the cyanide. By the application of these optimum conditions, cyanide substitution of several primary alkyl halides proceeded smoothly in nonpolar organic solvents (Table 2); the acceleration was even greater than that by solid-liquid phase transfer catalysts such as 18-crown-6 or tetrabutylammonium chloride. In conclusion, the combined use of alumina-water-ultrasound could be a substitute for a phase transfer catalyst in some heterogeneous reactions.

At present we can not specify the role of ultrasound in the alumina-assisted reaction, but following possibilities may be presented: 1) to strip off interfering

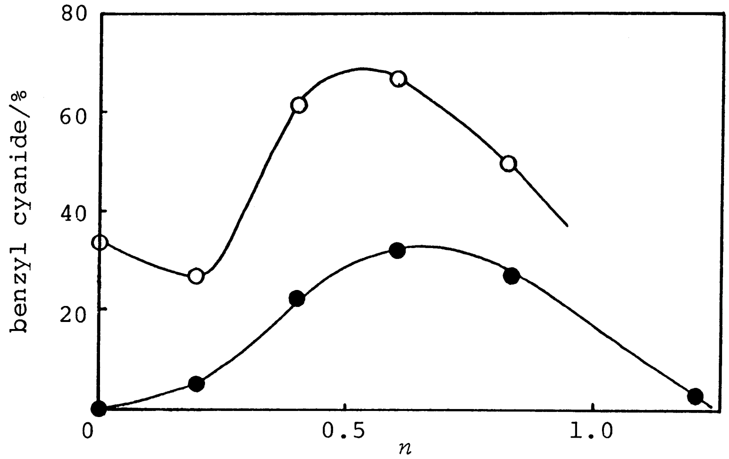

Fig. 1. Plots of benzyl cyanide yields *vs.* the molar ratio (n) of the added H_2O to KCN.
○ : under ultrasonic irradiation for 6 h (Series III)
● : with mechanical agitation for 6 h (Series II)

species (adsorptive, resulting salt, etc.) from the surface of an inorganic solid to keep the surface clean and reactive; 2) to bring an inorganic solid reagent into contact with alumina to produce an active ion or ion aggregate on alumina surface; 3) to accelerate the nucleophilic attack of the cyanide species to the substrate.

Table 2. Alumina-Assisted Cyanide Substitution under Ultrasonic Irradiation[a]

Alkyl halide	Solvent	Time/h	Alkyl cyanide	Yield/%[b]	Yield by PTC method[c]
$PhCH_2Br$	toluene	6	$PhCH_2CN$	71	34 (18-crown-6)
		10		92 (78)	9 (Bu_4NCl) for 6 h
$PhCH_2Cl$[d]	toluene	65	$PhCH_2CN$	76 (74)	
	cyclohexane	72		80	
	hexane	72		79	
$1-C_4H_9Br$	chlorobenzene	96	$1-C_4H_9CN$	63	
$1-C_8H_{17}Br$	toluene	48	$1-C_8H_{17}CN$	44	23 (18-crown-6)[e] at 90 °C for 47 h
		72		64	
$PhCH_2CH_2Br$	toluene	72	$PhCH_2CH_2CN$	61	
		85		(71)	
$CH_2{=}CHCH_2Br$	chlorobenzene	8	$CH_2{=}CHCH_2CN$	55	
$BrCH_2CH_2CH_2Br$	toluene	85	$NCCH_2CH_2CH_2CN$	(77)	

a) A heterogeneous mixture of KCN (16 mmol), alumina (1.6 g) and water (9.6 mmol, $n = 0.6$) in a solvent (5 cm^3) was previously irradiated by ultrasound at 50 °C for 1-3 h. After alkyl halide (3.2 mmol) was added to the above mixture, the reaction was carried out at 50 °C under continued ultrasonic irradiation. b) Isolated yields after purification are shown in parentheses, and the others are those determined by GLPC using internal standards. c) Reaction of alkyl halide (3.2 mmol) was carried out with KCN (16 mmol) and a phase transfer catalyst (0.16 mmol) in toluene (5 cm^3) under mechanical agitation at 50 °C. d) Benzyl chloride was reported to react much more rapidly than benzyl bromide in the presence of 18-crown-6 in acetonitrile. See F. L. Cook, C. W. Bowers, and C. L. Liotta, J. Org. Chem., 39, 3416 (1974). e) The data from reference 4a.

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