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# Selective α-Monoalkylation of Phenylacetonitrile Using Alkali Metal Hydroxide Impregnated on Alumina

Kazuaki Sukata
*Nihon Tokushu Kagaku Kogyo Co., Ltd., 3-36, Tohda-cho, Moriguchi, Osaka 570*

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In the alkylation of phenylacetonitrile with alkyl halides, alkali metal hydroxides impregnated on alumina act as efficient bases for selective α-monoalkylation in benzene. It is proposed that the reaction may take place exclusively in the pore. The selectivity for α-monoalkylation is explained in terms of steric hindrance.

In recent years, processes using inorganic solids have been rapidly developed for organic syntheses.[1] The unique effectiveness of inorganic solids may be due to their large effective surface area, the presence of pores, and the adsorption of reactants.

This paper describes results of the following selective α-monoalkylation of phenylacetonitrile (PAN) with alkyl halides on a chromatographic-grade alumina impregnated with sodium or potassium hydroxide ($NaOH/Al_2O_3$ or $KOH/Al_2O_3$):

$$PhCH_2CN + RX \xrightarrow{\text{base}} PhCHRCN + PhCR_2CN. \qquad (1)$$

## Results and Discussion

In order to elucidate the effect of supports, the alkylation of PAN with ethyl bromide in the presence of different supports impregnated with KOH was carried out in benzene. Table 1 shows the results. The reactivity of $KOH/Al_2O_3$ was extremely high in comparison with the other solid suppotrs examined and its selectivity for α-monoalkylation was also high. The pore size of $Al_2O_3$[2] is much larger than those of Meculear Sieves.[3] The surface area of Celite is very small in comparison with those of the other supports. These facts and the present findings suggest that the reaction of $[Ph\bar{C}HCN]^-$ or $[Ph\bar{C}RCN]^-$ with alkyl halide may take place predominantly in the pore, so that the reactivity of the impregnated KOH may be ascribed to the pore size of the support. The present findings can be interpreted as follows: The pore size of $Al_2O_3$ is suitable for the reaction,[4] whereas those of Molecular Sieves are too small. In the case of Celite, the reaction is very slow probably because of its small surface area.[5]

Table 1. Alkylation of PAN with ethyl bromide using KOH impregnated on several supports[a]

| Support | | Yield[b]/% Mono | Di |
|---|---|---|---|
| Molecular Sieve 5A | (60—80 mesh) | <1 | — |
| | (powder) | <1 | — |
| 13X | (60—80 mesh) | <1 | — |
| | (powder) | <1 | — |
| Celite[c] | (powder) | 3.5 | — |
| $Al_2O_3$ | (70—230 mesh) | 91 | 4 |

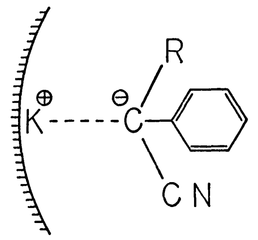
a) Unless otherwise noted, reactions were carried out with KOH (75 mmol)/support (20 g), PAN (10 mmol), ethyl bromide (12 mmol), and benzene (30 mmol) as a solvent at 40 °C for 4 h. b) Determined by GLC with dodecane as an internal standard. c) Fifteen grams of Celite and 40 ml of benzene were used.

Table 2. Alkylation of PAN with ethyl bromide using $KOH/Al_2O_3$ in several solvents[a]

| Solvent | Reaction time/h | Yield[b]/% Mono | Di |
|---|---|---|---|
| Acetonitrile | 0.5 | 69 | 23 |
| THF | 2.0 | 81 | 12 |
| Dioxane | 2.0 | 83 | 4 |
| | 4.0 | 84 | 6 |
| Benzene | 4.0 | 91 | 4 |

a) All reactions were carried out with KOH (75 mmol)/$Al_2O_3$ (15 g), PAN (10 mmol), ethyl bromide (12 mmol), and a solvent (15 ml) at 40 °C. b) Determined by GLC with dodecane as an internal standard.

In order to reveal the effect of solvents, the alkylation of PAN with ethyl bromide was carried out using $KOH/Al_2O_3$ in several solvents. Table 2 shows the results. The order of rates of the reaction was acetonitrile > tetrahydrofuran > dioxane ≈ benzene. On the contrary, the order of the selectivities for α-monoalkylation was benzene > dioxane > tetrahydrofuran > acetonitrile. In a nonpolar solvent such as benzene, $[Ph\bar{C}RCN]^-$ formed would be strongly adsorbed onto the wall of the pore as the carbanion is directed toward $K^+$:



Consequently, the reaction of $[Ph\bar{C}RCN]^-$ with the second alkyl halide will be strongly sterically hindered On the other hand, polar solvents would weaken the degree of the interaction, decreasing the degree of the steric hindrance. Also, the reaction in the bulk organic phase should not be ignored when polar solvents are employed.

The influence of the molecular size of alkylating agent was examined by use of the alkylation of PAN with various alkyl halides using $KOH/Al_2O_3$ or $NaOH/Al_2O_3$ in benzene. Table 3 summarizes the results. In a phase-transfer alkylation[6] using aqueous alkali

Table 3. Alkylation of PAN using $KOH/Al_2O_3$ or $NaOH/Al_2O_3$ [a)]

| | Alkyl halide | Reaction Time h | Reaction Temp °C | Yield[b)]/% Mono | Yield[b)]/% Di |
|---|---|---|---|---|---|
| $KOH/Al_2O_3$ | $C_2H_5Br$ | 4 | 40 | 91 | 4 |
| | $C_2H_5I$ | 2 | 40 | 89 | 6 |
| | $C_2H_5I$ | 2 | 30 | 92 | 3 |
| | $n$-$C_3H_7Br$ | 6 | 40 | 91 | 2 |
| | $n$-$C_3H_7I$ | 2 | 40 | 92.5 | 1.5 |
| | $n$-$C_4H_9Br$ | 6 | 40 | 94 | 1.5 |
| | $n$-$C_4H_9I$ | 2 | 40 | 94 | 1 |
| | $i$-$C_3H_7Br$ | 7 | 40 | 70 | ≈0 |
| | $i$-$C_4H_9Br$ | 7 | 40 | 68 | ≈0 |
| | $s$-$C_4H_9Br$ | 7 | 40 | 69 | ≈0 |
| $NaOH/Al_2O_3$ | $C_2H_5Br$ | 4 | 40 | 90 | 1 |
| | $C_2H_5Br$[c)] | 4 | 40 | 55 | ≈0 |
| | $C_2H_5I$ | 4 | 40 | 64 | ≈0 |
| | $n$-$C_3H_7Br$ | 6 | 40 | 82 | ≈0 |
| | $n$-$C_3H_7Br$[c)] | 6 | 40 | 47 | ≈0 |
| | $n$-$C_3H_7I$ | 6 | 40 | 68 | ≈0 |
| | $n$-$C_4H_9Br$ | 6 | 40 | 79 | ≈0 |
| | $n$-$C_4H_9Br$[c)] | 6 | 40 | 48 | ≈0 |
| | $n$-$C_4H_9I$ | 6 | 40 | 55 | ≈0 |

a) All reactions were carried out with KOH or NaOH (75 mmol) / $Al_2O_3$ (15 g), PAN (10 mmol), alkyl halide (12 mmol), and benzene (15 ml) as a solvent. b) Determined by GLC with dodecane as an internal standard. c) Water was added to NaOH in 15% by weight.

metal hydroxide as a base, formation of *ca.* 10% of α,α-dialkylated products has been unavoidable under a similar molar ratio of alkyl halide to PAN. The alkylation using $KOH/Al_2O_3$ or $NaOH/Al_2O_3$ gave rapidly and exclusively α-monoalkylated products. In the case of $NaOH/Al_2O_3$, the addition of *ca.* 15% by weight of water to NaOH resulted only in slowing down the reaction. In regard to the selectivity for α-monoalkylation, however, $NaOH/Al_2O_3$ was better than $KOH/Al_2O_3$. When $KOH/Al_2O_3$ was employed, the reaction with alkyl iodides was faster than that with alkyl bromides. In contrast to $KOH/Al_2O_3$, the reaction with alkyl iodides was slower than that with alkyl bromides when $NaOH/Al_2O_3$ was employed. Since the ionic radius of $Na^+$ is smaller than that of $K^+$, $Na^+$ may attract the carbanion formed more closely to the wall of the pore than $K^+$, increasing to a greater extent the degree of the steric hindrance against the reaction of the carbanion with alkyl halide. It can also be explained in terms of the steric hindrance that the increase in the bulkiness of alkyl groups raises the selectivity for α-monoalkylation. In general, alkyl iodide is slightly better than alkyl bromide with respect to the selectivity for α-monoalkylation. Since alkyl iodide is bulkier than the corresponding alkyl bromide, alkyl iodide would be more sterically hindered than alkyl bromide for the reaction with $[\mathrm{Ph\bar{C}RCN}]^-$, giving a small amount of α,α-dialkylated product.

## Experimental

*Materials.* Unless otherwise stated, all reagents were obtained commercially and dried with Molecular Sieve 4A. Alumina (Merck Ltd. Type 90 for column chromatography, activity I, 70—230 mesh), Molecular Sieves (for gas chromatography), Celite (for column chromatography), 85% KOH, and NaOH were also obtained commercially and used as obtained.

*Impregnation of Alkali Metal Hydroxide on Inorganic Supports.* An inorganic support was added to an aqueous alkali metal hydroxide, and the water was removed under reduced pressure at 50 °C. The impregnated reagent was further dried under vacuum (0.1 mmHg)(1 mmHg=133.322 Pa) at 90 °C for 1 h. By this procedure, the NaOH impregnated became nearly anhydrous. However, the KOH impregnated contained *ca.* 15% by weight of water. After the drying of the impregnated reagent for further 7 h, almost no decrease in its weight could be observed.

*Typical Procedure for Alkylation of PAN.* All the products were known compounds and identified by comparing GLC retention times with those of authentic samples prepared by the literature procedures.[6)] A typical procedure is as follows: A mixture of $KOH/Al_2O_3$ (20.0 g) obtained from 85% KOH (5.0 g, 75 mmol) and $Al_2O_3$ (15.0 g), PAN (10 mmol), ethyl bromide (12 mmol), and benzene (15 ml) as a solvent was heated at 40 °C for 4 h with vigorous stirring. The yields of α-mono- and α,α-dialkylated products were determined by GLC with dodecane as an internal standard.

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2) According to Regen *et al.*, the average pore diameter of neutral alumina is 40 Å (80% being<120 Å): S. L. Regen, S. Quici, and M. D. Ryan, *J. Am. Chem. Soc.*, **101**, 7629 (1979).

3) The pore diameters of Molecular Sieves 5A and 13X are 5 and 10 Å, respectively.

4) The impregnated reagent was washed with water until almost all the alkali was recovered and then the amount of the eluted aluminium ion was determined to be *ca.* 4 mol% to the alkali used by the chelatometry using EDTA. This result indicates that the destruction of the pore structure of $Al_2O_3$ by concentrated aqueous alkali and the action of alkali metal aluminate as the base can be practically ignored under the present experimental conditions.

5) An alternative explanation is as follows. The KOH impregnated on Celite which is an acidic solid support might be neutralized and consequently the reactivity of KOH/Celite might be weakened.

6) E. Chiellini, R. Solaro, and S. D'Anton, *Makromol. Chem.*, **178**, 3165 (1977); E. Chiellini and R. Solar, *J. Org. Chem.*, **43**, 2550 (1978); K. Sukata, *Yuki Gosei Kagaku Kyokai Shi*, **39**, 1132 (1981).