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# Synthesis of Amino Compounds under Phase Transfer Conditions

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The phase transfer process was applied to the reaction of organic bromides with azide anion. The reduction of intermediary azide derivatives gave the corresponding amino compounds, benzylamine, glycine, alanine, butyrine, and serine in fairly good yields. Effective catalytic activity was demonstrated by the difference in chemical yields in the case of methyl bromoacetate and ethyl α-bromopropionate. In order to examine the role of phase transfer catalyst, two bromohydrins (methyl β-hydroxy-α-bromopropionate and styrene bromohydrin) were subjected to the present reaction. Methyl β-hydroxy-α-bromopropionate afforded serine exclusively in the presence of 18-crown-6 and tetrabutylammonium bromide, but in the absence of the catalyst a mixture of serine and isoserine was obtained. A different regioselectivity was observed in the case of styrene bromohydrin.

Use of quaternary ammonium and phosphonium salts and crown ethers as a phase transfer catalyst is epochal in synthetic organic chemistry. Many synthetic routes are now being developed, giving products in good yields under simple and mild conditions.[1]

The mechanism proposed by Starks[2] was verified[3] in accord with the reactivity of 2-bromooctane toward aqueous alkali solution. Herriott and Picker[3] concluded that the catalyst functions so as to solubilize the anionic reagents into the organic phase in their system, but not rigorously applicable to others.[1,4]

We describe herewith the substitution reaction of organic halides with sodium azide under phase transfer-catalyzed conditions, which permit easy access to amino compounds. The probable mechanism for the present systems in connection with the reactivity of bromohydrins is discussed.

## Experimental

IR spectra were recorded on a Hitachi 215 grating spectrophotometer and PMR spectra on a Varian model EM-360 spectrometer.

The general procedure for nucleophilic substitution of organic bromide with azide anion is exemplified by a typical run (run 1, Table 1). The reactions were repeated with the reaction parameters modified.

Benzyl bromide (10 mmol; 1.71 g) and sodium azide (15 mmol; 0.98 g) were stirred in a mixture of water (4 ml) and tetrabutylammonium bromide (0.5 mmol; 161 mg) at room temperature for 6 h, after which the solution was extracted 3 times with dichloromethane. The dried dichloromethane solution was evaporated and the residue was reduced with LAH. Benzylamine was obtained in the usual way. Yield, 936 mg (87.4%). IR and PMR spectra were identical with those of an authentic specimen. Identification of other products was also confirmed in satisfactory agreement with respective data in literature.

Determination of the ratio of isomeric serines, and amino alcohols (I and II) was made by a comparison of integral values of β-methylene and α-methin protons. The chemical shift of β-methylene proton of isomeric serines in $D_2O$–NaOH and TMDS as an internal standard: δ 3.80 for serine; 3.08 for isoserine. The chemical shift of α-methin proton in $CDCl_3$ and TMS of I and II: δ 4.58 for I; 3.97 for II.

## Results and Discussion

Organic bromides reacted with sodium azide in a two-phase (liquid–liquid or solid–liquid) system in the presence of a phase transfer catalyst such as tetrabutylammonium bromide and 18-crown-6,[5] to give the corresponding azides in good yields, which were easily converted into the amines. For example, benzyl bromide underwent nucleophilic substitution at room temperature. The end product, benzylamine, was obtained by the LAH reduction of intermediate azide (Table 1). Benzene was found to be superior to ether in the solid–liquid system.

TABLE 1. NUCLEOPHILIC DISPLACEMENT OF BENZYL BROMIDE BY SODIUM AZIDE

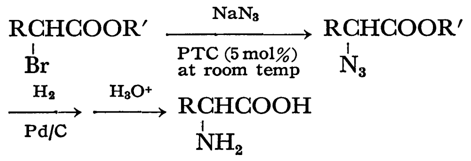
$$PhCH_2Br \xrightarrow[\text{PTC (5 mol\%) at room temp}]{NaN_3} PhCH_2N_3 \xrightarrow{LAH} PhCH_2NH_2$$

| Run | PTC[a] | Solvent | Reaction period (h) | % Yield |
|---|---|---|---|---|
| 1 | NX[b] | $H_2O$ | 6 | 87.4 |
| 2 | CE[c] | Benzene | 6 | 48.3 |
| 3 | CE | Ether | 6 | 27.1 |

a) PTC : phase transfer catalyst.
b) NX : tetrabutylammonium bromide.
c) CE : 18-crown-6.

Amination of α-halogenated esters is a conventional method for synthesis of α-amino acids, so that we duly applied the phase transfer technique to the reaction. Glycine, alanine, and butyrine were obtained in good

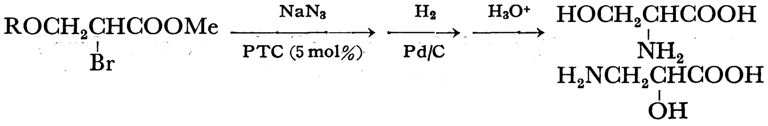
TABLE 2. NUCLEOPHILIC DISPLACEMENT OF α-BROMO ESTERS BY SODIUM AZIDE



$$\underset{\displaystyle Br}{RCHCOOR'} \xrightarrow[\text{PTC (5 mol\%) at room temp}]{NaN_3} \underset{\displaystyle N_3}{RCHCOOR'} \xrightarrow[Pd/C]{H_2} \xrightarrow{H_3O^+} \underset{\displaystyle NH_2}{RCHCOOH}$$

| Run | PTC | R | R′ | Solvent | Reaction period (h) | % Yield |
|---|---|---|---|---|---|---|
| 1 | NX | H | Me | $H_2O$ | 12 | 79.0 |
| 2 | CE | H | Me | Benzene | 6 | 97.1 |
| 3 | — | H | Me | Benzene | 6 | trace |
| 4 | NX | Me | Et | $H_2O$ | 1 | 82.3 |
| 5 | NX | Me | Et | $H_2O$ | 6 | 94.4 |
| 6 | — | Me | Et | $H_2O$ | 1 | 3.5 |
| 7 | NX | Et | Et | $H_2O$ | 6 | 90.3 |

TABLE 3. REACTION OF $\beta$-METHOXY- OR $\beta$-HYDROXY-$\alpha$-BROMOPROPIONATES WITH SODIUM AZIDE



$$\underset{\substack{|\\ Br}}{ROCH_2CHCOOMe} \xrightarrow[\text{PTC (5 mol\%)}]{NaN_3} \xrightarrow[Pd/C]{H_2} \xrightarrow{H_3O^+} \underset{\substack{|\\ NH_2}}{HOCH_2CHCOOH} \quad \underset{\substack{|\\ OH}}{H_2NCH_2CHCOOH}$$

| Run | PTC | R | Solvent | Reaction period (h) | Reaction temperature | % Yield | Serine : Isoserine | |
|---|---|---|---|---|---|---|---|---|
| 1 | NX | Me | $H_2O$ | 6 | room temp | 84.0 | only | |
| 2 | NX | H | $H_2O$ | 24 | 40 °C | 63.2 | only | |
| 3 | CE | H | $CH_3CN$ | 24 | 50 °C | 60.0 | only | |
| 4 | — | H | MeOH–$H_2O$ | 12 | reflux | 30.5 | 60 | 40 |

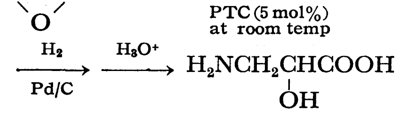
yields. Effectiveness of the phase transfer catalyst was reflected in the distinct difference in chemical yield (runs 2, 3 and 4, 5, 6 in Table 2).

The data obtained for the amination of methyl $\beta$-methoxy-[6] and $\beta$-hydroxy-$\alpha$-bromopropionate[7] to give serine in moderate yields by phase transfer catalysis are summarized in Table 3.

Levene and Schormüller[8] reported the formation of $\beta$-azido-$\alpha$-hydroxypropionate as the sole product of the reaction of methyl $\beta$-hydroxy-$\alpha$-bromopropionate with sodium azide in methanol–water medium. In contrast, we obtained a mixture of serine and isoserine (60: 40) as the end product of the same reaction under exactly the same conditions in the absence of catalyst (run 4, Table 3).[9] With ammonium halide and crown ether as a phase transfer catalyst, the reaction gave serine as the sole product in improved yields.

The present reaction would proceed through intermediate formation of methyl glycidate from bromohydrin followed by the nucleophilic attack of azide anion to give isomeric serines depending on whether it takes on $\alpha$- or $\beta$-carbon of the glycidate. In order to confirm the mechanism, we subjected ethyl glycidate[10] as the substrate to the same reaction under the same conditions. We see from Table 4 that isoserine was the sole product in all cases, regardless of the presence or absence of catalyst and difference in medium. The intervention of glycidate is thus excluded. Consequently, in the phase transfer-catalyzed reactions, the nucleophilic attack of azide anion took place directly on the $\alpha$-carbon of methyl $\beta$-hydroxy-$\alpha$-bromopropionate to displace bromine.

TABLE 4. REACTION OF ETHYL GLYCIDATE WITH SODIUM AZIDE

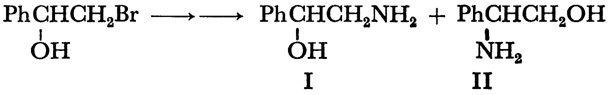


| PTC | Solvent | Reaction period (h) | % Yield of isoserine |
|---|---|---|---|
| NX | Buffer(pH 7) | 12 | 60.6 |
| — | Buffer(pH 7) | 12 | 59.1 |
| NX | $H_2O$ | 15 | 62.8 |
| — | $H_2O$ | 15 | 64.4 |
| CE | $CH_3CN$[a)] | 21 | 22.9 |

a) Heated under reflux.

The complete regiospecificity as well as improved chemical yields found for the present reaction systems can be utilized in synthetic organic chemistry.

In order to elucidate the function of phase transfer catalyst in the present systems, it seemed of interest to examine the reactivity of other substrates capable of easy rearrangement. For this purpose, styrene bromohydrin[11] seems to be suitable since it is prone to rearrangement. Upon nucleophilic substitution, styrene bromohydrin may give rise to the substitution product I and/or the rearrangement product II (Scheme 1).



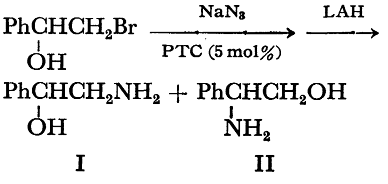
$$\underset{\substack{|\\ OH}}{PhCHCH_2Br} \longrightarrow\longrightarrow \underset{\substack{|\\ OH\\ I}}{PhCHCH_2NH_2} + \underset{\substack{|\\ NH_2\\ II}}{PhCHCH_2OH}$$

Scheme 1.

The experimental results are given in Table 5. In the system of styrene bromohydrin also, styrene oxide is considered to be the probable intermediate. However, the results with styrene oxide used as a substrate suggest that the contribution of oxiran intermediate is negligible (Table 6).

Styrene bromohydrin reacted with sodium azide in benzene in the presence of crown ether to give exclusively the substitution product I (run 1, Table 5). In polar protic environment (run 3, Table 5), only the rearrangement product II was obtained from the same substrate. The difference might be attributed to the ability of medium to solvate anion species; the reduced solvation of azide anion in crown ether–benzene system suppresses intramolecular hydroxyl rearrangement, whereas in polar protic medium, the neighboring

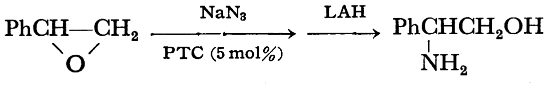
TABLE 5. REACTION OF STYRENE BROMOHYDRIN WITH SODIUM AZIDE



$$\underset{\substack{|\\ OH}}{PhCHCH_2Br} \xrightarrow[\text{PTC (5 mol\%)}]{NaN_3} \xrightarrow{LAH} \underset{\substack{|\\ OH\\ I}}{PhCHCH_2NH_2} + \underset{\substack{|\\ NH_2\\ II}}{PhCHCH_2OH}$$

| Run | PTC | Solvent | Reaction period (h) | Reaction temperature | % Yield | I | : II |
|---|---|---|---|---|---|---|---|
| 1 | CE | Benzene | 23 | 50 °C | 28.5 | 100 | |
| 2 | NX | $H_2O$ | 23 | 40 °C | 58.4 | 44 | 56 |
| 3 | — | MeOH–$H_2O$ | 14 | reflux | 63.0 | | 100 |

Table 6. Reaction of styrene oxide with sodium azide



$$\underset{\text{O}}{\text{PhCH—CH}_2} \xrightarrow[\text{PTC (5 mol\%)}]{\text{NaN}_3} \xrightarrow{\text{LAH}} \underset{\text{NH}_2}{\text{PhCHCH}_2\text{OH}}$$

II

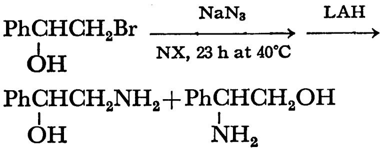
| PTC | Solvent | Reaction period (h) | Reaction temperature | % Yield of II |
|---|---|---|---|---|
| CE | $CH_3CN$ | 4 | reflux | trace |
| NX | $H_2O$ | 8 | room temp | 8 |
| NX | Buffer(pH 7) | 7 | room temp | 72 |
| CE | $H_2O$ | 8.5 | room temp | 53 |
| CE | Buffer(pH 7) | 6 | room temp | 50 |

hydroxyl participation has preference to the attack of solvated azide anion.

In the liquid–liquid system with tetrabutylammonium bromide used as phase transfer catalyst (run 2, Table 5), however, no clear-cut selectivity was observed.

For the purpose of clarifying the function of quaternary ammonium salt, we examined to what extent the product distribution is affected by the change in dosage of catalyst and by the addition of organic solvent such as chloroform and benzene to the organic phase. Since the solubility of azide anion in organic phase would be greatly increased under these circumstances, we could predict the preferential formation of the substitution product I due to the enhanced reactivity of azide anion. In accordance with expectation, the product ratio I : II increased with increase in the amount of catalyst and by addition of organic solvent (Table 7).

Table 7. Influence of the reaction parameters on the product distribution of isomeric amino alcohols



$$\underset{\text{OH}}{\text{PhCHCH}_2\text{Br}} \xrightarrow[\text{NX, 23 h at 40°C}]{\text{NaN}_3} \xrightarrow{\text{LAH}}$$

$$\underset{\text{OH}}{\text{PhCHCH}_2\text{NH}_2} + \underset{\text{NH}_2}{\text{PhCHCH}_2\text{OH}}$$

I  II

| Run | Mol % of NX | Solvent | % Yield | I | : | II |
|---|---|---|---|---|---|---|
| 1 | 5 | $H_2O$ | 58.4 | 44 | | 56 |
| 2 | 20 | $H_2O$ | 75.3 | 65 | | 35 |
| 3 | 60 | $H_2O$ | 77.9 | 77 | | 23 |
| 4 | 0 | $H_2O$ | 10.6 | | | 100 |
| 5 | 5 | $C_6H_6$-$H_2O$ | 36.2 | 77 | | 23 |
| 6 | 5 | $CHCl_3$-$H_2O$ | 48.6 | 85 | | 15 |

The experimental results in the present systems (Tables 5, 6, and 7) show that the reaction takes place in rather aprotic environment as indicated by the high product ratio (runs 3, 5, and 6, Table 7). The mechanism proposed by Starks and Herriott seems to be operative under these conditions. However, in the reaction system which involves the substrate alone as organic phase (run 1, Table 7), the predominant formation of rearrangement product II is observed in spite of the presence of quaternary ammonium salt. This might result from the sparing solubility of ammonium azide ion-pair in organic phase. Under such conditions as employed in run 1 (Table 7), therefore, the function of a co-sphere outside the interface between organic and aqueous phases to furnish a possible reaction site could not be entirely neglected. As another likelihood, the protic character of styrene bromohydrin constituting an organic phase may be responsible for the observed preferential formation of II, despite the fact that the reaction occurs in organic phase.

## References

1) G. W. Gokel and H. D. Durst, *Synthesis*, **1976**, 168; J. Dockx, *ibid.*, **1973**, 441; E. V. Dehmlow, *Angew. Chem. Int. Ed. Engl.*, **13**, 170 (1974); M. Makosza, *Pure Appl. Chem.*, **43**, 439 (1976).

2) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971); C. M. Starks and R. M. Owens, *ibid.*, **95**, 3613 (1973).

3) A. W. Herriott and D. Picker, *Tetrahedron Lett.*, **1972**, 4521; *J. Am. Chem. Soc.*, **97**, 2345 (1975).

4) J. H. Fendler and E. J. Fendler, "Catalysis in Micellar and Macromolecular Systems," Academic Press, New York (1975), pp. 387—389.

5) G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974).

6) J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **134**, 413 (1940).

7) K. C. Leibman and S. K. Fellner, *J. Org. Chem.*, **27**, 438 (1962).

8) P. A. Levene and A. Schormüller, *J. Biol. Chem.*, **105**, 547 (1934).

9) Levene and Schormüller reported the isolation of isoserine alone by the catalytic hydrogenolysis of distilled azide ester. This might be due to the probable fractionation during the procedure for obtaining the end product.

10) W. D. Emmons and A. S. Pagano, *J. Am. Chem. Soc.*, **77**, 89 (1955).

11) J. Read and W. G. Reid, *J. Chem. Soc.*, **1928**, 1487.