Studies of Isocyanides. I. The Formation of Urethanes and Ureas from Isocyanides

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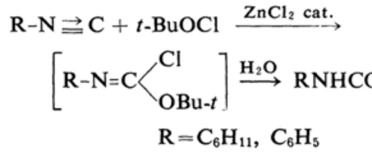
In recent years new addition reactions of isocyanides have been widely developed by Ugi and his co-workers. Their studies mainly covered the reactions with several carbonyl and similar compounds, such as ketenes, carboxylic acids, acyl chlorides and Schiff bases.[1] It seems that these new reactions, as well as the well-known Passerini reaction,[2] essentially involve an electrophilic attack by the positive carbon of these reagents on the negatively-charged carbon of isocyanides. Since the electrophilic nature of *t*-butyl hypochlorite[3] and *N*-bromosuccinimide (NBS)[4] in aromatic halogenations and that of hydroxylamine[5] (with a Lewis acid catalyst) in aromatic amination have previously been established, we have now examined the reactions of these electrophiles with isocyanides, which may be expected to yield urethanes and ureas, after successive hydrolysis if necessary.

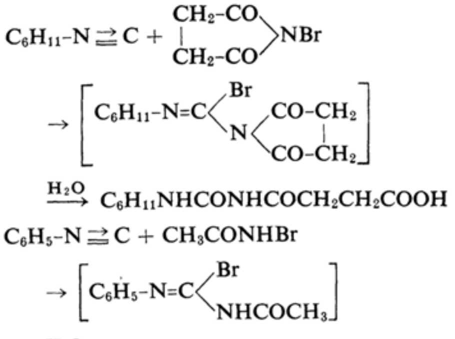
When cyclohexyl isocyanide was treated with *t*-butyl hypochlorite in the presence of zinc chloride catalyst, an instantaneous reaction took place, and a 20% yield of *t*-butyl *N*-cyclohexylcarbamate, in addition to cyclohexyl isocyanate (16%), was obtained by successive treatment with water. In the absence of the catalyst, however, the isocyanate (40%) was the sole product. Similarly, the addition of phenyl isocyanide to *t*-butyl hypochlorite, followed by hydrolysis, afforded *t*-butyl *N*-phenylcarbamate in a 69% yield. The use of other Lewis acid catalysts (e.g., aluminum trichloride, boron trifluoride and ferric chloride) is not suitable, since isocyanide itself rapidly converts to a tarry matter when the catalysts are added. A reasonable path for this reaction would involve the formation of an imidoyl-chloride intermediate,[6] as in the case of the reaction between isocyanide and acyl chloride:[7]



$$\text{R-N}\stackrel{\rightarrow}{=}\text{C} + t\text{-BuOCl} \xrightarrow{\text{ZnCl}_2\text{ cat.}} \left[\text{R-N=C}\begin{matrix}\text{Cl}\\ \text{OBu-}t\end{matrix}\right] \xrightarrow{\text{H}_2\text{O}} \text{RNHCOOBu-}t$$

$$\text{R}=\text{C}_6\text{H}_{11},\ \text{C}_6\text{H}_5$$

The reaction of cyclohexyl isocyanide with wet NBS (containing ca. 5～10% of water) proceeded smoothly at room temperature and gave a 21% yield of *N*-(cyclohexylcarbamoyl) succinamic acid after hydrolysis. When the reaction was conducted under completely anhydrous conditions, the formation of a tarry matter was observed after a short induction period and the above acid could not be isolated by successive treatment with water. A preliminary test indicated that the addition of zinc bromide caused the decomposition of NBS; therefore, no effort was made to examine the zinc salt-catalyzed reaction. An analogous reaction of phenyl isocyanide with *N*-bromoacetamide (NBA) yielded the expected adduct, *N*-acetyl-*N'*-phenylurea, in a 38% yield. Since this type of reaction proceeds smoothly even in the dark, an ionic process appears to be favorable; on this point, however, more conclusive evidence would be desirable.



$$\text{C}_6\text{H}_{11}\text{-N}\stackrel{\rightarrow}{=}\text{C} + \begin{matrix}\text{CH}_2\text{-CO}\\ |\\ \text{CH}_2\text{-CO}\end{matrix}\!\!>\!\text{NBr} \rightarrow \left[\text{C}_6\text{H}_{11}\text{-N=C}\begin{matrix}\text{Br}\\ \text{N}\begin{matrix}\text{CO-CH}_2\\ |\\ \text{CO-CH}_2\end{matrix}\end{matrix}\right]$$

$$\xrightarrow{\text{H}_2\text{O}} \text{C}_6\text{H}_{11}\text{NHCONHCOCH}_2\text{CH}_2\text{COOH}$$

$$\text{C}_6\text{H}_5\text{-N}\stackrel{\rightarrow}{=}\text{C} + \text{CH}_3\text{CONHBr} \rightarrow \left[\text{C}_6\text{H}_5\text{-N=C}\begin{matrix}\text{Br}\\ \text{NHCOCH}_3\end{matrix}\right]$$

$$\xrightarrow{\text{H}_2\text{O}} \text{C}_6\text{H}_4\text{NHCONHCOCH}_3$$

Lastly, the treatment of a mixture of cyclohexyl isocyanide and hydroxylamine hydrochloride with zinc chloride afforded a 42% yield of *N*-cyclohexylurea, as shown in the following equation:

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[1] I. Ugi et al., *Chem. Ber.*, **94**, 734, 1116, 2233, 2797, 2802 (1961); *Angew, Chem.*, **74**, 10 (1962).

[2] M. Passerini, *Gazz. chim. ital.*, **51**, 181 (1921) [*Chem. Abst.*, **16**, 556 (1922)].

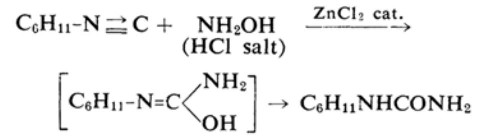
[3] D. Ginsberg, *J. Am. Chem. Soc.*, **73**, 2723 (1951).

[4] S. D. Ross, M. Finkelstein and R. C. Petersen, ibid., **80**, 4327 (1958). NBS is generally considered to be a homolytic brominating agent, especially for an allylic system; however, Ross et al. recently cited the possibility of the heterolytic bromination of reactive aromatics with NBS.

[5] C. Graebe, *Ber.*, **34**, 1778 (1901); G. F. Jaubert, *Compt. rend.*, **132**, 841 (1901).

[6] Unfortunately, an attempt to isolate the intermediate oil was not successful because of its thermal instability.

[7] I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 1116 (1961).



$$C_6H_{11}\text{-}N\overset{\rightarrow}{=}C + \underset{\text{(HCl salt)}}{NH_2OH} \xrightarrow{ZnCl_2\ \text{cat.}} \left[C_6H_{11}\text{-}N{=}C\begin{smallmatrix}NH_2\\ OH\end{smallmatrix}\right] \rightarrow C_6H_{11}NHCONH_2$$

Unfortunately, in a similar reaction with phenyl isocyanide, no adduct could be isolated from the tarry reaction product. Phenylhydroxylamine also did not give the expected *N*-cyclohexyl-*N'*-phenylurea under similar conditions; rather, somewhat unexpectedly, *N, N'*-dicyclohexylurea (53%) was obtained. Controlled experiments in which the isocyanide was treated with phenylhydroxylamine alone or with zinc chloride alone did not afford any product. Thus, it is highly probable that phenylhydroxylamine acts as an oxygen donor, though the reaction mechanism is not quite clear.

Experimental[8]

The Reaction of Cyclohexyl Isocyanide with *t*-Butyl Hypochlorite.—Into a mixture of 5.4 g. (0.05 mol.) of *t*-butyl hypochlorite (prepared by the procedure of Teeter and Bell[9]) and 1.3 g. (0.01 mol.) of zinc chloride in 20 ml. of dry ethylene dichloride, 5.5 g. (0.05 mol.) of cyclohexyl isocyanide was added dropwise with stirring, at such a rate that the reaction temperature was kept below 10°C. The stirring was continued at that temperature for an additional hour, and then the reaction mixture was allowed to stand overnight at room temperature. After removal of the unchanged hypochlorite and the solvent, the residue was poured into water. After this mixture had stood for 2 hr., the organic layer that separated was extracted with ether. The ethereal solution was washed twice with water, dried, and evaporated. The resulting oil was distilled in vacuo to yield 1.0 g. (16%) of cyclohexyl isocyanate (b. p. 60~65°C/18 mmHg), identified as dicyclohexylurea (m. p. 228°C), and a dark residue. Recrystallization of the residue from methanol afforded 2.0 g. (20%) of *t*-butyl *N*-cyclohexylcarbamate (m. p. 68~69°C). The melting point was undepressed on admixture with a sample prepared from cyclohexyl isocyanate and *t*-butyl alcohol.

Found: C, 66.13; H, 10.64; N, 7.42. Calcd. for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03%.

When this reaction was carried out in the absence of the catalyst, only cyclohexyl isocyanate (40%) was isolated.

The Reaction of Phenyl Isocyanide with *t*-Butyl Hypochlorite.—The procedure employed was similar to that used for the above reaction except that dry dioxane was used as the solvent. The working up of the reaction mixture, as described above, gave *t*-butyl *N*-phenylcarbamate (69%), which after recrystallization from ethanol melted at m. p. 134~135°C. No mixed melting point depression was observed with an authentic material prepared by the usual method. In the non-catalyzed reaction, phenyl isocyanate (13%) was the sole isolable product.

The Reaction of Cyclohexyl Isocyanide with NBS.—After 8.9 g. (0.05 mol.) of NBS had been moistened with 0.9 g. of water, the mixture was gradually stirred into a solution of 5.5 g. (0.05 mol.) of cyclohexyl isocyanide and 50 ml. of dry carbon tetrachloride. The reaction temperature was maintained at ca. 10~15°C by means of a water bath. At the end of the addition, a color change from dark red to yellow was observed. Then the reaction mixture was allowed to stand overnight at room temperature. The solid that separated was collected and treated with water. There were obtained 1.3 g. (11%) of *N*-(cyclohexylcarbamoyl), succinamic acid, which after recrystallization from acetone had an m. p. of 162~164°C. Some additional product was also obtained from the solvent layer; it weighed 1.2 g. (10%). The acid showed no depression in melting point when mixed with an authentic material which had been prepared from *N*-cyclohexylurea and succinic anhydride in acetic acid.

Found: C, 54.68; H, 7.52; N, 11.44. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.53; H, 7.48; N, 11.56%.

The Reaction of Phenyl Isocyanide with NBA. In a smimilar way, 7.2 g. (0.07 mol.) of phenyl isocyanide was added dropwise to a mixture of 9.5 g. (0.07 mol.) of wet NBA (prepared by the procedure of Oliveto and Gerold[10]) and 50 ml. of dry chloroform. The reaction mixture was worked up as in the preceeding experiment to give 4.7 g. (38%) of *N*-acetyl-*N'*-phenylurea. Recrystallization from ethanol gave the pure product (m. p. 183°C). No depression in melting point was observed upon admixture with an authentic material which had been prepared by the addition reaction of acetamide to phenyl isocyanate.[11]

The Reaction of Cyclohexyl Isocyanide with Hydroxylamine Hydrochloride.—A mixture of 3.5 g. (0.05 mol.) of hydroxylamine hydrochloride, 5.5 g. (0.05 mol.) of cyclohexyl isocyanide, 1.3 g. (0.01 mol.) of zinc chloride and 30 ml. of dioxane was heated at 50°C for 3 hr. with stirring. The reaction mixture was evaporated in vacuo to remove dioxane, and the residue was poured into 30 ml. of water; then the solution was made slightly basic with aqueous sodium hydroxide. The crude product which separated from the solution was redissolved in ethanol to remove zinc hydroxide, and the alcohol was evaporated to dryness. Recrystallization of the resulting solid from water afforded 3.0 g. (42%) of *N*-cyclohexylurea (m. p. 189°C). A mixed melting point with an authentic sample, prepared from cyclohexyl isocyanate and aqueous ammonium hydroxide, showed no depression.

The Reaction of Cyclohexyl Isocyanide with Phenylhydroxylamine.—A mixture of 6.5 g. (0.06 mol.) of phenylhydroxylamine, 5.5 g. (0.05 mol.) of cyclohexyl isocyanide, 1.3 g. (0.01 mol.) of zinc chloride and 30 ml. of dioxane was stirred at 50°C for 25 hr. After removal of the solvent in vacuo,

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[8] All boiling and melting points are uncorrected.

[9] H. M. Teeter and E. W. Bell, "Organic Syntheses," 32, 20 (1952).

[10] E. P. Oliveto and C. Gerold, ibid., 31, 171 (1951).

[11] P. F. Wiley, *J. Am. Chem. Soc.*, **71**, 1310 (1949).

the reaction mixture was poured into water, and the organic layer was extracted with ether. The evaporation of the ether and the unreacted isocyanide in vacuo afforded 3.0 g. (53%) of *N,N'*-dicyclohexylurea. Two recrystallizations from acetone or ethanol gave a pure sample (m. p. 228°C), which was identified with an authentic sample by a mixed melting point determination.

Summary

The reactions of isocyanides with alkyl hypochlorite, *N*-bromoamides, and hydroxylamine have been investigated. Cyclohexyl and phenyl isocyanides give *t*-butyl carbamates (urethanes) by the zinc chloride-catalyzed reaction with *t*-butyl hypochlorite, followed by treatment with water. An analogous reaction with *N*-bromosuccinimide or *N*-bromoacetamide in the presence of a small amount of water gives the corresponding acylureas. On treatment with hydroxylamine hydrochloride and zinc chloride, cyclohexyl isocyanide affords *N*-cyclohexylurea.

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