BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 41 1372—1375 (1968)

Syntheses of Some Heterocyclic Compounds from α-Benzoyliminobenzyl Cyanide and Related Compounds[*1,*2]

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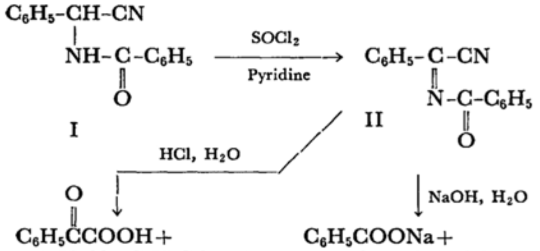
(Received October 25, 1967)

The reaction of α-benzamidobenzyl cyanide (I) with thionyl chloride and pyridine in benzene gave α-benzoyliminobenzyl cyanide (II) in a 52% yield. II is a novel compound which can react readily with nucleophilic reagents, such as alcohols, mercaptans and amines. The reaction of II with ethyl-mercaptan and with alcohols gave α-ethylthio-α-benzamidobenzyl cyanide and α-alkoxy-α-benzamidobenzyl cyanide respectively. Furthermore, II reacts with bifunctional nucleophilic reagents to form heterocyclic compounds. The reaction of II with hydrazine and with hydroxylamine afforded 3,5-diphenyl-1,2,4-triazole and 3,5-diphenyl-1,2,4-oxadiazole respectively.

During the course of investigations concerning the reactions of α-aminonitriles, we happened to find a novel method for the preparation of α-benzoyliminobenzyl cyanide (II) from α-benzamidobenzyl cyanide (I) and thionyl chloride in pyridine. The structure of II was confirmed by the following experimental evidence: (i) The infrared spectrum shows the presence of C=N and C≡N bonds at 1620 and 2250 cm^{-1}, but shows no N–H bond near 3200 cm^{-1}. (ii) An acid hydrolysis of II with hydrochloric acid gave benzoylformic acid (62.5 mol%), benzamide (9.7 mol%), and a small amount of ammonium chloride. (iii) An alkaline hydrolysis of II gave benzoic acid (105.3 mol%) and benzamide (42.6 mol%), along with a small amount of sodium cyanide, as is shown below:



The formation of II is obviously due to the oxidation of I with thionyl chloride, even though the products derived from thionyl chloride could not be identified. Only a few reactions in which thionyl chloride acts as an oxidizing agent have been reported.[1-4] Hence, sulfuryl chloride, the oxidizing ability of which is usually stronger than that of thionyl chloride, was used for the above reaction instead of thionyl chloride. However, the yield of II was only 5%, and 70—75% of the starting material was recovered, as Table 1 shows. *N*-Bromosuccinimide (NBS) or *t*-butyl hypochlorite was also used as the oxidizing agent for the above reaction. As is shown in Table 1, *t*-butyl hypochlorite produced II in a yield of 51%, but NBS did not.

TABLE 1. OXIDATION OF α-BENZAMIDOBENZYL CYANIDE (I)

Oxidizing agent	Reaction temp (°C)	Yield of II (%)	I. Recovered (%)
Thionyl chloride	0—5	52	0
Thionyl chloride	Room temp.	2	0
Sulfuryl chloride	0—5	5	70
Sulfuryl chloride	Room temp.	5	70
Sulfuryl chloride	50—60	11	62
t-Butyl hypochlorite	Room temp.	51	0
NBS	Room temp.	0	55
NBS	50—60	0	52

It seems to be very strange that no α-acyliminobenzyl cyanide, represented by II, has ever been prepared in spite of the simplicity of its structure. Compound II has three carbon atoms, indicated by Gothic letters in Formula II, which a nucleophilic reagent may attack. We studied the reactions of II with several nucleophiles. The results

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[*1] Part VI of "Studies of the Syntheses of Heterocyclic Compounds."

[*2] Part V: E. Haruki, Y. Hirai and E. Imoto, This Bulletin, **41**, 267 (1968).

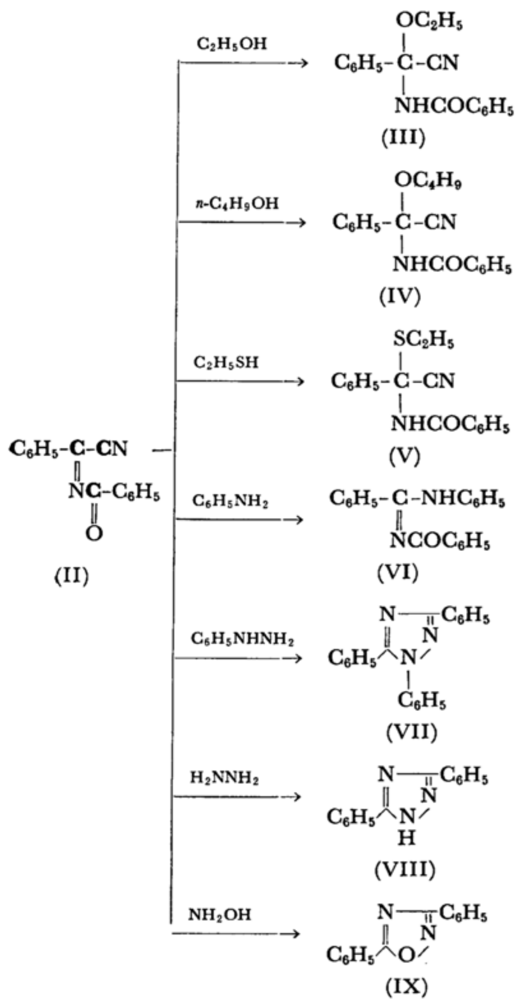
1) H. Takimoto and L. Krbechek, *J. Org. Chem.*, **27**, 4688 (1962).

2) K. A. Pollart and H. J. Harwood, *ibid.*, **27**, 4444 (1962).

3) S. Patai and F. Bergmann, *J. Am. Chem. Soc.*, **72**, 1035 (1950).

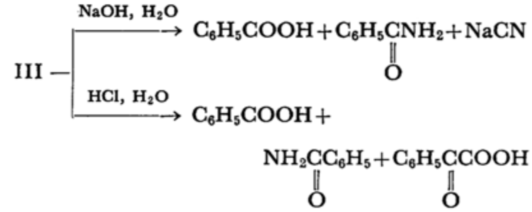
4) W. B. Brownell and L. C. King, *ibid.*, **71**, 2926 (1949).

are shown in the following scheme:



Alcohols and thioalcohols attacked the α-carbon atom of II and added to the C=N bond. Similarly, an amine attacked the cyano group, as aniline produced VI in a 65% yield as a result of the reaction with II. The bifunctional nucleophilic reagents, such as hydrazines and hydroxylamines, form 1,2,4-triazoles (VII) and (VIII) or oxadiazoles (IX) respectively. This reaction may be caused by a substitution of the cyano group with the amino group, followed by a cyclization between the carbonyl carbon and the amino or the hydroxyl group. All these cyclization reactions are, of course, novel reactions.

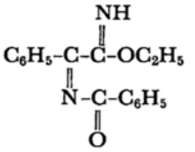
The structures of Compounds, VI, VII, VIII, and IX were confirmed by a comparison of their properties with those of authentic samples. The structures of Compounds, III, IV, and V were unknown. Hence, their structures were confirmed by elemental analyses, by a study of their infrared spectra, and by the results of the acid and alkaline hydrolysis described below:



$$\mathrm{III}\xrightarrow{\mathrm{NaOH,\ H_2O}} C_6H_5COOH + C_6H_5CONH_2 + NaCN$$

$$\mathrm{III}\xrightarrow{\mathrm{HCl,\ H_2O}} C_6H_5COOH + NH_2COC_6H_5 + C_6H_5COCOOH$$

If the reaction between ethanol and II does not form Compound III, but forms another compound such as Compound X, which is formed by the addition of ethanol to the cyano group, Compound X, an imino ether, must be very unstable toward water and must be hydrolyzed quickly.


(X)

The actuality was opposite, in fact. The compound obtained from ethanol and II was not hydrolyzed at all but was recovered in a quantitative yield after having been treated with a water-ethanol mixture for 6 hr at 40—50°C. Therefore, Compound III does not have the structure of X. The structure of IV was also confirmed by methods similar to those used in the determination of III. The structure V was assumed on the basis of the data of elemental analyses, the presence of the N-H and C≡N groups in the infrared spectrum, and the similarity of the chemical behavior of thioalcohol to that of alcohol on a nucleophilic reaction.

The starting material for the above reaction, α-benzamidobenzyl cyanide, was prepared by the benzoylation[5] of α-aminobenzyl cyanide, which can be prepared easily from benzaldehyde, hydrogen cyanide, and ammonia. Another kind of α-(benzoylamino)-nitrile could be obtained by the *N*-benzoylation of the α-aminonitriles, when aldehydes other than benzaldehyde were used for the preparation of an α-aminonitrile. We tried to prepare α-benzamidopropionitrile from acetaldehyde, but this attempt failed.

Next, we prepared α-acetamidobenzyl cyanide and carried out its reaction with thionyl chloride in pyridine, but no crystalline product was obtained from the reaction mixture. Furthermore, we tried to react thionyl chloride with ethyl α-benzamidophenylacetate,[6] (XI), in which the cyano group is replaced by the ethoxycarbonyl group; we thus obtained ethyl α-benzoyliminophenyl acetate, (XII), in a yield of 18%, together with ethyl benzoylformate and benzamide. Ethyl benzoylformate and benzamide must be formed by the

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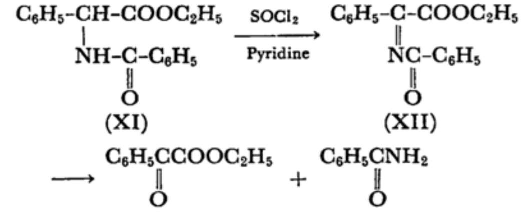
[5] R. Ruggeri and G. Rigoli, *Gazz. Chim. Ital.*, **54**, 555 (1924); *Chem. Abstr.*, **19**, 262 (1925).

[6] A. Kossel, *Ber.*, **24**, 4151 (1901).

oxidation of XI with thionyl chloride, followed by the hydrolysis of the C=N bond:



$$\underset{\text{(XI)}}{C_6H_5\text{-}CH(NHCOC_6H_5)\text{-}COOC_2H_5} \xrightarrow[\text{Pyridine}]{SOCl_2} \underset{\text{(XII)}}{C_6H_5\text{-}C(=NCOC_6H_5)\text{-}COOC_2H_5} \longrightarrow C_6H_5COCOOC_2H_5 + C_6H_5CONH_2$$

From the above observations, it may be concluded that the oxidation with thionyl chloride would be facilitated by the benzoyl group attached to the amino group, and also be favored by the aryl group attached to the α-carbon atom in II. Furthermore, among the compounds of the II type, II was the only one which was accessible. It is, therefore, unlikely, in view of these limitations, that the reaction is of general utility for the synthesis of α-acyliminonitriles from α-acylamidonitriles.

However, the reactions are still of considerable interest in that thionyl chloride acts as an oxidizing reagent for the conversion of the acylamino group into the acylimino group in α-acylaminonitriles. The mechanism of this oxidation reaction is not at all clear. One can postulate that the active hydrogen atom attached to the α-carbon of Compound II is responsible in some manner for this oxidation. This postulation prompted us to examine the reaction of the three compounds, ethyl benzamidoacetate, diethyl acetamidomalonate, and, *N*-benzoylbenzylamine, all of which have an active hydrogen atom, with thionyl chloride. However, in no case was the expected reaction product obtained.

Experimental

The melting points and boiling points were not corrected. The molecular weights were measured with Hitachi Perkin-Elmer 115 Molecular Weight Apparatus, using benzene as the solvent.

α-Benzoyliminobenzyl Cyanide (II). To a solution of α-benzamidobenzyl cyanide (I) (5.0 g, 0.021 mol) in dry benzene (40 m*l*), there was added dry pyridine (3 m*l*) and then thionyl chloride (3.0 g, 0.026 mol), drop by drop, at 0—5°C. The mixture was stirred at this temperature for 3 hr and then left to stand overnight at room temperature. The precipitate pyridinium hydrochloride, was collected by filtration and washed with a small amount of dry benzene. After the combined filtrate had been concentrated under reduced pressure at 30—40°C, the solid residue obtained was recrystallized from ligroin to give α-benzoyliminobenzyl cyanide (II) (2.6 g, 52%), mp 80—82°C (decomp.).

Found: C, 76.93; H, 4.27; N, 11.80%; mol wt, 248. Calcd for $C_{15}H_{10}ON_2$: C, 76.91; H, 4.30; N. 11.96%; mol wt, 234.

Acid Hydrolysis of α-Benzoyliminobenzyl Cyanide (II). α-Benzoyliminobenzyl cyanide (1 g, 0.0043 mol) was dissolved in a mixture of 15 m*l* of 6 N hydrochloric acid and 15 m*l* of dioxane, and the solution was stirred at 45—50°C for 6 hr. After the reaction mixture had been concentrated *in vacuo* at 30—40°C, the viscous residue was mixed with 30 m*l* of water and extracted with ether. The ethereal extract was evaporated and treated with a solution of 2,4-dinitrophenylhydrazine in a dilute hydrochloric acid; benzoylformic acid 2,4-dinitrophenylhydrazone (0.85 g, 0.0027 mol) was thus obtained. The 2,4-dinitrophenylhydrazone obtained was recrystallized from ethanol, mp 180—185°C (decomp.). Its mixed melting point with an authentic sample showed no depression and its infrared spectrum coincided with that of the authentic sample. The aqueous layer was evaporated *in vacuo*, and the residue obtained was washed with a small amount of benzene to obtain ammonium chloride (0.12 g, 0.0024 mol). The evaporation of the benzene gave benzamide (0.05 g, 0.0004 mol).

Alkaline Hydrolysis of α-Benzoyliminobenzyl Cyanide (II). α-Benzoyliminobenzyl cyanide (1 g, 0.0043 mol) and sodium hydroxide (1 g, 0.025 mol) were dissolved together in a mixture of 15 m*l* of water and 15 m*l* of dioxane, and the solution was stirred at 45—60°C for 6 hr. After the evaporation of the solvent from the reaction mixture *in vacuo*, the solid residue was washed with 20 m*l* of water and separated by filtration, thus giving benzamide (0.22 g, 0.0018 mol). The acidification of the filtrate with 10 m*l* of 6 N hydrochloric acid gave benzoic acid (0.55 g, 0.0045 mol).

Hydrolysis of α-Benzoyliminobenzyl Cyanide (II) in a Neutral Medium. α-Benzoyliminobenzyl cyanide (0.5 g, 0.0021 mol) was dissolved in a mixture of 5.0 m*l* of water and 15 m*l* of dioxane, and the solution was stirred at 45—50°C for 6 hr. The reaction mixture was evaporated *in vacuo*, and the residue obtained was washed with 10 m*l* of a 10% aqueous solution of sodium carbonate. The insoluble crystals, benzamide (0.22 g, 0.0018 mol), were collected by filtration. The acidification of the filtrate with 6 N hydrochloric acid gave benzoic acid (0.25 g, 0.0020 mol).

α-Ethoxy-α-benzamidobenzyl Cyanide (III). α-Benzoyliminobenzyl cyanide (1.0 g, 0.0043 mol) was dissolved in absolute ethanol (20 m*l*), and the solution was refluxed for 3 hr. After the reaction mixture had been cooled in an ice bath, the precipitates were collected by filtration and recrystallized from 99% ethanol. Needle crystals of α-ethoxy-α-benzamidobenzyl cyanide melting at 153—154°C (decomp.) were thus obtained. Yield, 92%.

Found: C, 72.76; H, 5.67; N, 9.73%; mol wt, 291. Calcd for $C_{17}H_{16}O_2N_2$: C, 72.84; H, 5.75; N, 9.99%; mol wt, 280.

Acid Hydrolysis of α-Ethoxy-α-benzamidobenzyl Cyanide. α-Ethoxy-α-benzamidobenzyl cyanide (1 g, 0.0036 mol) was dissolved in a mixture of 15 m*l* of 6 N hydrochloric acid and 15 m*l* of dioxane, and the solution was stirred at 45—50°C for 6 hr. Benzoylformic acid 2,4-dinitrophenylhydrazone was obtained by treating a small portion of the reaction mixture with an acidic solution of 2,4-dinitrophenylhydrazine. Another portion of the reaction mixture was evaporated, and the residue obtained was washed with 20 m*l* of benzene to give ammonium chloride (0.15 g, 0.0028 mol). The benzene extract was washed with 10 m*l* of a 10% aqueous solution of sodium carbonate. The concentration of the benzene extract gave benzoic acid (0.4 g, 0.0033 mol).

Alkaline Hydrolysis of α-Ethoxy-α-benzamidobenzyl Cyanide. α-Ethoxy-α-benzamidobenzyl cyanide (1 g, 0.0036 mol) and sodium hydroxide (1 g, 0.025 mol) were disolved in a mixture of 15 m*l* of water and 15 m*l* of dioxane, and the solution was stirred at 45—50°C for 6 hr. After the reaction mixture had been evaporated *in vacuo*, the residue obtained was washed with 20 m*l* of water to give benzamide (0.22 g, 0.0018 mol). The acidification of the aqueous filtrate with 10 m*l* of 6 N hydrochloric acid evolved hydrocyanic acid, which was recognized by its characteristic odor and which gave benzoic acid (0.55 g, 0.0045 mol).

α-*n*-Butoxy-α-benzamidobenzyl Cyanide (IV). α-Benzoyliminobenzyl cyanide (0.5 g, 0.0021 mol) was dissolved in a 20 m*l* of *n*-butyl alcohol, and the mixture was stirred at 80—90°C for 3 hr. After standing in an ice-bath for 6 hr, the reaction mixture gave a precipitate of α-*n*-butoxy-α-benzamidobenzyl cyanide (0.12 g). The concentration of the filtrate *in vacuo* gave an addition 0.47 g of the same product. The total yield was 0.59 g (0.0019 mol, 90%). Recrystallization from carbon tetrachloride gave colorless needle crystals with a mp of 125—127°C.

Found: C, 73.68; H, 6.61; N, 9.07%. Calcd for $C_{19}H_{20}O_2N_2$: C, 74.00; H, 6.54; N, 9.09%.

α-Ethylthio-α-benzamidobenzyl Cyanide (V). A solution of α-benzoyliminobenzyl cyanide (1 g, 0.0043 mol) and ethyl mercaptan (1 g, 0.016 mol) in dioxane (15 m*l*) was stirred at 50—60°C for one hour. The subsequent concentration of the reaction mixture gave colorless needle crystals of α-ethylthio-α-benzamidobenzyl cyanide. Mp 159—161°C after recrystallization from benzene.

Found: C, 68.91; H, 5.48; N, 9.71%. Calcd for $C_{17}H_{16}ON_2S$: C, 68.90; H, 5.44; N, 9.45%.

***N*-Benzoyl-*N'*-phenylbenzamidine (VI).** After a solution of α-benzoyliminobenzyl cyanide (0.5 g, 0.0021 mol) and aniline (1 g, 0.011 mol) in 15 m*l* of dioxane had been stirred at 80—90°C for 3 hr, the reaction mixture was concentrated *in vacuo*. The recrystallization of the residue from ethanol gave *N*-benzoyl-*N'*-phenylbenzamidine (0.42 g, 0.0014 mol, 65%), mp 140—141°C (lit.,[7] 141°C). Admixture with an authentic sample[7] showed no depression of the melting point, and the infrared spectrum coincided with that of the authentic sample.

Found: C, 79.78; H, 5.47; N, 9.28%. Calcd for $C_{20}H_{16}ON_2$: C, 79.98; H, 5.37; N, 9.33%.

1,3,5-Triphenyl-1,2,4-triazole (VII). After a solution of α-benzoyliminobenzyl cyanide (2 g, 0.008 mol) and phenylhydrazine (2.0 g, 0.019 mol) in dioxane (40 m*l*) had been stirred at 70—80°C for 2.5 hr, the reaction mixture was concentrated *in vacuo*; the viscous residue thus obtained was recrystallized from ethanol to give 1,3,5-triphenyl-1,2,4-triazole (2.1 g, 0.0072 mol, 83.9%). Mp 103—104°C (lit.,[8] 104°C). No depression of melting point was observed on admixture with an authentic specimen, and the infrared spectrum of the compound obtained was identical with that of the authentic specimen.

Found: C, 80.54; H, 5.06; N, 13.67%. Calcd for $C_{20}H_{15}N_3$: C, 80.78; H, 5.09; N, 14.13%.

3,5-Diphenyl-1,2,4-triazole (VII). After a solution of α-benzoyliminobenzyl cyanide (2.0 g, 0.0086 mol) and hydrazine (1.0 g, 0.031 mol) in 40 m*l* of 99% ethanol had been stirred at 70—80°C for 2.5 hr, the reaction mixture was concentrated *in vacuo* to give a viscous residue. The residue was recrystallized from chloroform to produce 3,5-diphenyl-1,2,4-triazole (1.78 g, 0.0084 mol, 97.2%), mp 189—190°C (lit.,[9] 192°C). Admixture with an authentic sample showed no depression of the melting point, and the infrared spectrum was identical with that of the authentic sample.

Found: C, 75.85; H, 5.01; N, 18.69%. Calcd for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01; N, 18.99%.

3,5-Diphenyl-1,2,4-oxadiazole (IX). A solution of hydroxylamine hydrochloride (1 g, 0.014 mol) in methanol (15 m*l*) was neutralized by a solution of sodium methoxide in methanol which had been prepared from sodium (0.33 g, 0.0014 gram atoms) and methanol (10 m*l*). The sodium chloride which precipitated was removed by filtration, and the filtrate was mixed with α-benzoyliminobenzyl cyanide (1 g, 0.0043 mol). The mixture was stirred at 50—60°C for 2 hr and then cooled to give precipitates. The precipitates were collected by filtration and recrystallized from ethanol. Mp 106—107°C (Needle crystals). A mixed-melting-point determination with an authentic sample[10] showed no depression and the infrared spectra was identical with that of the authentic sample.

Found: C, 75.70; H, 4.41; N, 12.41%. Calcd for $C_{14}H_{10}ON_2$: C, 75.65; H, 4.54; N, 12.61%.

Ethyl α-Benzoyliminophenylacetate (XII). To a solution of ethyl α-benzamidophenylacetate (XI) (25 g, 0.088 mol) in dry benzene (200 m*l*), there was added pyridine (40 m*l*) and then thionyl chloride (30 g, 0.25 mol), drop by drop, at room temperature. The mixture was stirred at 70—80°C for 6 hr. After the removal of the pyridinium hydrochloride by filtration, the filtrate was evaporated to afford a viscous residue. The distillation of the residue under a reduced pressure gave two fractions. The first fraction (bp 90—100°C/1.0 mmHg) consisted of ethyl benzoylformate, which showed the same infrared spectrum as that of an authentic sample. The second fraction (bp 165—180°C/1.0 mmHg) was a yellow oil, which solidified partly upon standing overnight. The filtration of the oily solid gave benzamide (2.0 g, 0.0165 mol). The distillation of the filtrate gave 4.5 g of pure ethyl α-benzoylimidophenyl acetate (X), which was hydrolyzed very quickly by moisture in air to ethyl benzoylformate and benzamide. The elemental analyses were carried out immediately after the distillation.

Found: C, 72.80; H, 5.45; N, 4.80%. Calcd for $C_{17}H_{15}O_3N$: C, 72.58; H, 5.37; N, 4.98%.

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7) H. L. Wheeler, T. B. Johnson and D. F. McFarland, *J. Am. Chem. Soc.*, **25**, 788 (1903).

8) O. Silberrad, *J. Chem. Soc.*, **77**, 1189 (1900).

9) R. Engelhart, *J. Prakt. Chem.*, [2] **54**, 153 (1896).

10) E. Tiemann and P. Kruger, *Ber.*, **17**, 1694 (1884).