[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

The Reaction of Amides with Isocyanates

BY PAUL F. WILEY

The reaction of amides with isocyanates was discovered in 1884 by Kühn,[1,2] who found that amides reacted as shown

$$RCONH_2 + R'NCO \longrightarrow RCONHCONHR'$$

Although experiments were limited it appeared that R and R′ could be either aliphatic or aromatic. It was observed that some N-substituted amides, such as acetanilide, gave a reaction of the above type, but others reacted in a much more complex manner. The reaction has never been investigated extensively and has been reported infrequently until its recent use in the preparation and curing of polymers.[3,4] Some employment of the reaction has been made occasionally in the preparation of aroylarylureas,[5,6,7,8,9,10] and a very similar reaction, the reaction of urea derivatives with isocyanates, has been studied.[11,12,13]

The purpose of the present study was to investigate optimum conditions for the reaction of amides with isocyanates and to extend the reaction to other amides and isocyanates. The isocyanates used were ethyl, phenyl and α-naphthyl, and of these only phenyl isocyanate was studied extensively. The amides used and optimum conditions are shown in Table I and the Experimental. The most generally useful solvent was found to be toluene, and it was used in all experiments listed in Table I except where indicated that no solvent was used.

It was found that inclusion of aluminum chloride and stannic chloride in the reaction mixtures caused a marked decrease in yields. Triethylamine had no discernible effect on yields when included.

A totally unexpected result appeared when phenyl isothiocyanate was allowed to react with acetamide or benzamide. The reactions in both cases required prolonged heating without solvents, and the resultant products were acetanilide and benzanilide. Low yields of about 10% were obtained in both cases. This result can be readily explained only by the operation of a different mechanism than prevails in the case of isocyanates. Apparently the nitrogen atom of the isothiocyanate molecule reacts with the carbonyl carbon atom of the amide followed by the expulsion of the elements of thiocyanic acid.

This reaction of amides with isocyanates would be a very convenient one to use in the preparation of derivatives of unsubstituted amides for identification purposes.

TABLE I

Amide	Isocyanate	Time in hours	Yield, %
Benzamide	Phenyl	18	86
Acetamide	Phenyl	18	89
Nicotinamide	Phenyl	12	94
p-Nitrobenzamide	Phenyl	24	95
β,β-Diphenylbutyramide	Phenyl	18	..
Butyramide	Phenyl	18	60
Diethylaminoacetamide	Phenyl	24	35
Nicotinamide	α-Naphthyl	24	96
p-Nitrobenzamide[a]	α-Naphthyl	*ca.* 1	87
Benzamide	Ethyl	18	38
Nicotinamide	Ethyl	24	34
Butyramide	Ethyl	24	24
Diethylaminoacetamide	Ethyl	24	27

[a] This experiment was run using no solvent.

TABLE II

Compound	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	M. p., °C.[a]
1-Nicotinoyl-3-(α-naphthyl)-urea	$C_{17}H_{13}N_3O_2$	14.42	14.14	222–223
1-(*p*-Nitrobenzoyl)-3-(α-naphthyl)-urea	$C_{18}H_{13}N_3O_4$	12.52	12.53	244–247
1-(*p*-Nitrobenzoyl)-3-phenylurea	$C_{14}H_{11}N_3O_4$	14.74	14.90	241–243
1-(β,β-Diphenylbutyryl)-3-phenylurea	$C_{23}H_{22}N_2O_2$	7.81	7.83	184.5–186
1-Diethylaminoacetyl-3-phenylurea	$C_{13}H_{19}N_3O_2$	16.85	17.11	155 at 0.2 mm.
1-Nicotinoyl-3-ethylurea	$C_9H_{11}N_3O_2$	21.74	21.77	120.5–122.5
1-Diethylaminoacetyl-3-ethylurea	$C_9H_{19}N_3O_2$	20.87	20.65	108–110 at 0.8 mm.

[a] Where pressure is indicated the figure represents boiling point.

Experimental[14]

The experiments recorded here are representative of those used throughout this study. At least one of the methods recorded is illustrative of and applicable to all the pairs of reactants studied. New compounds not discussed in connection with their preparation are listed in Table II with analytical data. The isocyanates and amides used with the exception of diethylaminoacetamide and β,β-diphenylbutyramide were commercial products. Diethylaminoacetamide was prepared by the method of Einhorn and Hamburger.[15]

β,β-Diphenylbutyramide.—A solution of 17.9 g. (0.075 mole) of β,β-diphenylbutyric acid in 44.6 g. (0.375 mole) of thionyl chloride was refluxed for one hour. The excess thionyl chloride was removed by evaporation under re-

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(1) Kühn, *Ber.*, **17**, 2880 (1884).

(2) Kühn, *ibid.*, **18**, 1476 (1885).

(3) Berchet, U. S. Patent 2,333,914 (November 9, 1943), *C. A.*, **38**, 2421 (1944).

(4) Belgian Patent 448,187 (December 31, 1942), *C. A.*, **39**, 1572 (1945).

(5) Swartz, *Am. Chem. J.*, **19**, 295 (1897).

(6) Folin, *ibid.*, 19, 339 (1897).

(7) Stieglitz and Earle, *ibid.*, **30**, 412 (1903).

(8) French and Wirtel, THIS JOURNAL, **48**, 1736 (1926).

(9) Hahn, Stiehl and Schulz, *Ber.*, **72**, 1291 (1939).

(10) Huber, Boehme and Laskowski, THIS JOURNAL, **68**, 188 (1946).

(11) Kühn and Henschel, *Ber.*, **21**, 504 (1888).

(12) Biltz and Beck, *ibid.*, **58**, 2187 (1925).

(13) Lakra and Dains, THIS JOURNAL, **51**, 2220 (1929).

(14) Melting points are uncorrected.

(15) Einhorn and Hamburger, *Ann.*, **361**, 127 (1908).

duced pressure. A cold solution of the residue in 200 cc. of dry benzene was stirred while ammonia was bubbled in until reaction appeared to be complete. The reaction mixture was filtered, and the filter cake was triturated with water and again isolated by filtration. The dried solid obtained was dissolved in 500 cc. of benzene, and the benzene solution was filtered. The filtrate was concentrated until crystals appeared. Cooling gave 11.7 g. (65%) of amide, m. p. 103–105°. Three recrystallizations from benzene gave a sample with no higher melting point.

Anal. Calcd. for $C_{16}H_{17}NO$: N, 5.85. Found: N, 5.25.

1-Benzoyl-3-phenylurea.—(a) With Solvent: A solution of 12.1 g. (0.1 mole) of benzamide and 11.9 g. (0.1 mole) of phenyl isocyanate in 200 cc. of dry toluene was refluxed for twenty-four hours. The cooled reaction mixture deposited a crystalline product which was removed by filtration and dried. The crude product weighed 24.0 g. and melted at 193–198°. Recrystallization from 135 cc. of dioxane gave 21.5 g. (89%) of 1-benzoyl-3-phenylurea, m. p. 203–204° (lit. 204°). (b) Without Solvent:—A mixture of 12.1 g. (0.1 mole) of benzamide and 11.9 g. (0.1 mole) of phenyl isocyanate was heated slowly to about 115°. At this temperature a vigorous reaction began, and the temperature mounted rapidly to 185°. External heating was stopped when the reaction began to occur vigorously. The mixture became almost completely liquid while the temperature was climbing rapidly, but at about 185° solidification began. The cooled reaction mixture was crystallized from dioxane to give 19.8 g. (82%) of 1-benzoyl-3-phenylurea, m. p. 203–204°.

1-Benzoyl-3-ethylurea.—A solution of 7.1 g. (0.1 mole) of ethyl isocyanate and 12.1 g. (0.1 mole) of benzamide in 150 cc. of dry toluene was refluxed for eighteen hours. When the reaction mixture was refrigerated, a crystalline precipitate formed. This precipitate proved to be 4.5 g. of benzamide, m. p. 120–124° and no depression in melting point upon admixture with benzamide. Evaporation of the toluene solution under reduced pressure left a white residue. This residue was recrystallized three times from alcohol. The final product was 7.3 g. of white needle-like crystals, m. p. 112–114° (lit. 114–115°); yield 38%.

1-Butyryl-3-ethylurea.—A mixture of 8.7 g. (0.1 mole) of butyramide and 7.1 g. (0.1 mole) of ethyl isocyanate was dissolved in 100 cc. of dry toluene. The solution was refluxed for twenty-four hours, cooled and filtered. The solvent was removed from the filtrate by evaporation under reduced pressure. Two recrystallizations of the residue from alcohol gave 4.0 g. (25%) of 1-butyryl-3-ethylurea, m. p. 98.5–100°, crystallizing in irregular oblong plates.

Anal. Calcd. for $C_7H_{14}N_2O_2$: N, 17.72. Found: N, 17.79.

Phenyl Isothiocyanate and Benzamide.—A mixture of 12.1 g. (0.1 mole) of benzamide and 13.5 g. (0.1 mole) of phenyl isothiocyanate was heated at a temperature of 180–190° for four hours. The reaction mixture was recrystallized four times from alcohol. The only product isolated was 2.9 g. of a light tan solid melting at 149–153°. Several more recrystallizations from alcohol gave a cream colored product melting at 157–159°. The melting point of a mixture with benzanilide (m. p. 160°) was 158–160°.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.84; H, 5.95; N, 7.56. Found: C, 78.18; H, 5.74; N, 7.34.

Phenyl Isothiocyanate and Acetamide.—A mixture of 13.5 g. (0.1 mole) of phenyl isothiocyanate and 5.9 g. (0.1 mole) of acetamide was heated at 180–190° for four hours. Cooling gave a dark brown liquid which had no isothiocyanate odor or lachrymatory properties but did smell strongly of hydrogen sulfide. The residue was dissolved in an equal volume of absolute alcohol and cooled. The precipitate which formed was removed and recrystallized from alcohol. There was obtained 2.3 g. of acetanilide melting at 110–112°. The mixed melting point with authentic acetanilide (m. p. 113–115°) was 112–114°.

Summary

1. The reaction of isocyanates with unsubstituted amides to give acylaryl- or alkylureas has been found to be quite general. The effects on the reaction of temperature, solvent, time, catalysts, and different types of amides and isocyanates have been studied.

2. Phenyl isothiocyanate has been found to react with amides only under severe conditions giving anilides.

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Hydrogen Bonding in Some 4-Substituted Cyclohexanols

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The spectroscopic evidence for hydrogen bonding in liquid alcohols has been studied extensively. In pure liquid alcohols there is a broad intense absorption band peaked between 2.95 and 3.00μ attributed to associated molecules, which decreases in intensity with dilution in an inert solvent, and a sharper band appears at 2.75μ, arising from single molecules.

Fox and Martin[1] resolved the association band of certain alcohols into two components. They suggested that the shorter wave length component is due to dimers and the longer wave length component is due to higher polymers. In the dimer form no single molecule serves as both donor and acceptor of hydrogen and the OH stretching force constant thus differs from that of the higher polymer.

In a study of several of the isomeric hexanols[2] it was found that the formation of polymers higher than dimers was inhibited in all of those isomers which contained the structures —C(R)—C—OH or —C(R)—OH.

With the *cis* and *trans* 4-phenyl and cyclohexylcyclohexanols at hand,[3] the question arose as to whether differences in steric inhibition of hydrogen bonding could be detected spectroscopically in such compounds. On the basis of viscosity and molecular weight determinations, the *cis* alcohols are thought to be less associated than the *trans* alcohols, but the 4-substituents are less effective than the 2-substituents in preventing association.[4]

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(1) Fox and Martin, *Proc. Roy. Soc. (London)*, **A162**, 419 (1937).

(2) Stanford and Gordy, THIS JOURNAL, **62**, 1247 (1940).

(3) Ungnade, *J. Org. Chem.*, **13**, 361 (1948).

(4) Hückel, Kumetat and Preuss, *Ann.*, **517**, 229 (1935); Gough, Hunter and Kenyon, *J. Chem. Soc.*, 2052 (1926).