configuration results in a sufficiently large change in the symmetry of the electric-field gradient of the nitrogen that the spin-lattice relaxation time of N^{14} becomes comparable with the reciprocal of the spin–spin coupling constant and decoupling occurs.

Experimental

All spectra were measured in D_2O using a Varian A-60 n.m.r. spectrometer. All values were measured from five to nine times, each measurement being made on a different day.

All compounds were rigorously purified. The preparation of the new compounds listed in this study will be published separately.

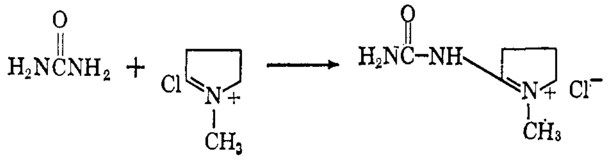
A Preparation of Aroyl and Acyl Formamidinium Salts

Herman Finkbeiner

General Electric Company Research Laboratory,
Schenectady, New York

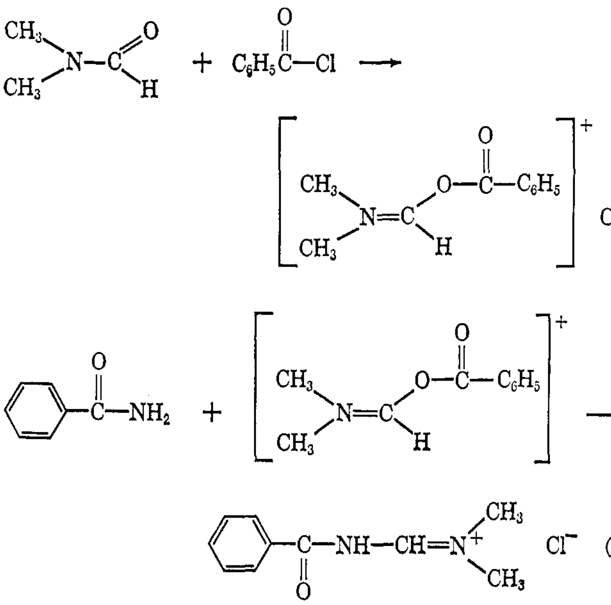
Received March 19, 1965

In a recent review on amido chlorides, Eilingsfeld, Seefelder, and Weidinger[1] comment that urea and its derivatives react with amido chlorides to produce amidinium salts (eq. 1). The preparation and physical properties of a number of these urea derivatives from thionyl chloride and dimethylformamide has been disclosed in the German patent literature.[2] However, Eilingsfeld states[1] that carboxamides do not undergo the corresponding reaction but rather undergo dehydration to nitriles when treated with acid chlorides or carbamido chlorides.[1,3]


(1)

While this appears to be true for such acid chlorides as phosgene, phosphorus oxychloride, and thionyl chloride, it has now been found that the use of benzoyl chloride or acetyl chloride leads to good yields of formamidinium salts.

A solution of carboxamide, *e.g.*, benzamide, in dimethylformamide was cooled to 5° and 1.1 equiv. of benzoyl chloride was slowly added. After spontaneously warming to room temperature and stirring overnight, the reaction mixture was poured into a mixture of benzene and ether and refrigerated. A 68% yield of N-benzoyl-N′,N′-dimethylformamidinium chloride was obtained. This reaction can probably be interpreted in the same fashion as the amido chloride reactions except that benzoate anion is the leaving group rather than chloride ion, as illustrated in eq. 2. Acetyl chloride was equally effective in this reaction; however, when ethyl chloroformate was used, no identifiable product was obtained.


(2)

Vapor phase chromatographic examination of the filtrate from the reaction showed that in no case was dehydration to nitrile entirely absent. Benzonitrile was produced in amounts varying from 20 to 80% as the solvent was changed from neat dimethylformamide to 50% dioxane.

Elemental analysis, n.m.r. spectroscopy and hydrolysis to the known N-formylamides served to identify the products. Table I lists several examples of the reaction.

The reaction between urea and dimethylformamide may also be carried out using benzoyl chloride or acetyl chloride rather than phosgene or thionyl chloride. With urea and benzoyl chloride, a 92% yield of N,N-dimethyl-N′-carbamidoformamidinium chloride, m.p. 191–192° dec. (lit.[2] 190–192° dec.), was obtained, and aniline, benzoyl chloride, and dimethylformamide gave an 81% yield of N,N-dimethyl-N′-phenylformamidinium chloride, m.p. 243–244° dec. (lit.[4] 239–241°).

Although Bredereck[4] prepared N,N-dimethyl-N′-phenylcaprinamidine from aniline, phosphorus oxychloride, and N,N-dimethylcaprinamide, the substitution of N,N-dimethylacetamide for N,N-dimethylformamide in the present study was unsuccessful. The reaction between benzamide, benzoyl chloride, and N,N-dimethylacetamide gave tribenzamide as the only identified product. N-Benzoylurea was obtained when urea was used in a reaction with N,N-dimethylacetamide.

Experimental

Preparation of Formamidinium Chlorides.—A solution of 0.1 mole of amide in 50 ml. of freshly distilled dimethylformamide was prepared. After solution was complete, the solution mixture was cooled to 0–5° and 16 g. of benzoyl chloride was slowly added without allowing the temperature to rise above 5°. After the benzoyl chloride was added, the temperature was maintained below 10° for an additional 2 hr. The reaction mixture was allowed to spontaneously warm to room temperature and was stirred for an additional 16 hr.

---

[1] H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

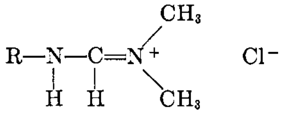
[2] K. H. Beyer, H. Eilingsfeld, and H. Weidinger, German Patent 1,110,625 (1961).

[3] R. Greenhalgh, British Patent 488,036 (1938).

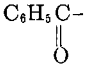
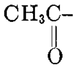
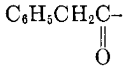
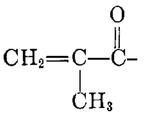
[4] H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Ber.*, **92**, 837 (1959).

TABLE I

FORMAMIDINIUM CHLORIDES FROM AMIDES[a]



$R-\underset{H}{N}-\underset{H}{C}=N^{+}(CH_3)_2 \quad Cl^-$

R	M.p., °C.	Yield, %	Calcd., % C	Calcd., % H	Calcd., % Cl	Calcd., % N	Found, % C	Found, % H	Found, % Cl	Found, % N
 $C_6H_5\underset{\underset{O}{\|}}{C}-$	173–175 dec.	68	56.47	6.16	16.67	13.17	56.3	6.3	17.0	12.9
 $CH_3\underset{\underset{O}{\|}}{C}-$	188–190 dec.	71	39.87	7.36	23.54	18.60	40.0	7.5	. . .	18.6
 $C_6H_5CH_2\underset{\underset{O}{\|}}{C}-$	128–132	59	58.28	6.67	15.64	12.36	58.0	7.0	15.2	12.0
 $CH_2=\underset{\underset{CH_3}{\vert}}{C}-\overset{\overset{O}{\|}}{C}-$	121–125	62	47.60	7.42	20.07	15.86	47.2	7.8	20.8	15.2

[a] These salts are extremely hygroscopic, and good melting points and analyses were difficult to obtain even when precautions were taken to prevent contact with air.

The reaction mixture was poured, with vigorous stirring, into a mixture of 250 ml. each of dry benzene and ether. After cooling the mixture at 5° in a refrigerator for several hours, the product crystallized. The formamidinium chlorides were recrystallized from hot benzene–dimethylformamide.

Hydrolysis of N,N-Dimethyl-N′-benzoylformamidinium Chloride.—To 15 ml. of water was added 4.0 g. of the formamidinium chloride. After a few minutes, a white crystalline precipitate formed. After 1 hr. the solid was filtered off and dried. The yield of N-formylbenzamide was 2.8 g. (99%), m.p. 107–108°. Authentic N-formylbenzamide was prepared by the method of Thompson,[5] m.p. 106–108°. The infrared spectrum was identical with the product obtained from the hydrolysis of N,N-dimethyl-N′-benzoylformamidinium chloride and a mixture melting point was undepressed.

Hydrolysis of N,N-Dimethyl-N′-phenylacetylformamidinium Chloride.—The hydrolysis was carried out exactly as above. The yield was 93%, m.p. 129–131°.

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.7; H, 5.5; N, 8.3.

Tribenzamide.—A reaction was carried out as given for the preparation of formamidinium salts except that N,N-dimethylacetamide replaced the dimethylformamide. After the reaction was complete, the mixture was poured into 150 ml. of water and was allowed to stand for 1 hr. The precipitated solid was filtered off, washed with ether, and dried. A 41% yield of tribenzamide, m.p. 209–210° (lit.[6] 208–210°), was obtained which proved to be identical with an authentic sample.

---

(5) Q. E. Thompson, *J. Am. Chem. Soc.*, **73**, 5914 (1951).

(6) C. Blacher, *Ber.*, **28**, 432 (1895).

The Synthesis of 3,5-Diaminoisoxazoles

WILLIAM J. FANSHAWE, VICTOR J. BAUER, AND S. R. SAFIR

Organic Chemical Research Section, Lederle Laboratories, a Division of American Cyanamid Company, Pearl River, New York

Received March 25, 1965

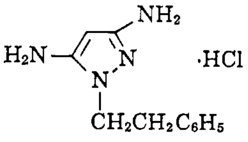
Phenethylbiguanide hydrochloride (**1**) is a clinically effective drug for the control of selected cases of diabetes.[1] We have sought to prepare novel related compounds for evaluation as hypoglycemic agents and have already reported the syntheses of phenethylmalonamidine dihydrochloride (**2**)[2] and 3,5-diamino-1-phenethylpyrazole hydrochloride (**3**).[3] We now wish to describe the synthesis of some representatives of 3,5-diaminoisoxazole, a new system related to **3**.

$C_6H_5CH_2CH_2NH\overset{\overset{NH}{\|}}{C}NH\overset{\overset{NH}{\|}}{C}NH_2\cdot HCl$

1

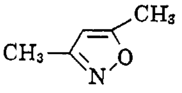
$C_6H_5CH_2CH_2NH\overset{\overset{NH}{\|}}{C}CH_2\overset{\overset{NH}{\|}}{C}NH_2\cdot 2HCl$

2

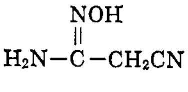


3

Added impetus was given to this investigation by the recent[4] report of hypoglycemic activity for 3,5-dimethylisoxazole (**4**).

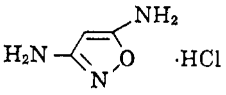


4



$H_2N-\overset{\overset{NOH}{\|}}{C}-CH_2CN$

5



6

An obvious precursor to 3,5-diaminoisoxazole is 2-cyanoacetamidoxime (**5**), whose synthesis had been described by Schmidtmann[5] in 1896. Since the compound is isomeric with 3,5-diaminoisoxazole and the only characterization published was an elemental analysis, verification of the structure appeared to be warranted. The infrared spectrum of 2-cyanoacetamidoxime exhibits a weak nitrile band at 4.40 μ, and the ultraviolet spectrum fails to show a maximum above 210 mμ. These data are consistent with the nonconjugated structure **5** which was confirmed by the n.m.r. spectrum, which displays singlets at τ 0.75

---

(1) G. Ungar, L. Freedman, and S. L. Shapiro, *Proc. Soc. Exptl. Biol. Med.*, **95**, 190 (1957).

(2) W. J. Fanshawe, V. J. Bauer, E. F. Ullman, and S. R. Safir, *J. Org. Chem.*, **29**, 308 (1964).

(3) W. J. Fanshawe, V. J. Bauer, and S. R. Safir, *ibid.*, **29**, 942 (1964).

(4) W. E. Dulin and G. C. Gerritsen, *Proc. Soc. Exptl. Biol. Med.*, **113**, 683 (1963).

(5) H. Schmidtmann, *Ber.*, **29**, 1168 (1896).