Preparation of Amidine Salts by Reaction of Nitriles with Ammonium Salts in the Presence of Ammonia
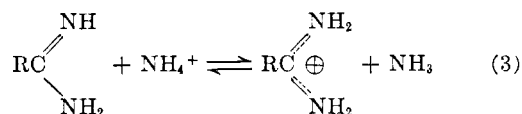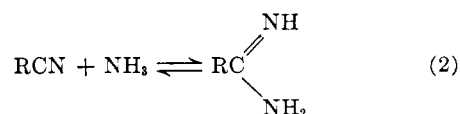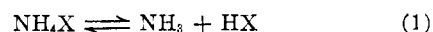
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A simple efficient amidine synthesis is provided by the reaction of nitriles with ammonium chloride or bromide in the presence of ammonia in pressure equipment at 125–150°.

Our interest in amidine chemistry has led us to review the available methods[1,2] for the preparation of these compounds to assess their suitability for large scale use. As reported recently we have found an excellent process for use with nitriles activated by electronegative substitution.[3] In the present paper we report a study of the conversion of nitriles to amidine salts by reaction with a mixture of ammonia and an ammonium salt at 120–150°. Yields in this simple and economical process are excellent, and it is well suited for the common relatively unreactive nitriles.

Cornell[4] reported in 1928 that "small quantities" of benzamidine and propionamidine hydrochlorides were formed when the corresponding nitriles were heated with equimolar amounts of ammonium chloride in ammonia at 200°, although there was no detectable reaction in the absence of the salt. Oxley and Short in introducing an extensive series of papers concerning the synthesis of amidines[2] did not include such a process in the group of reactions they considered useful.[5] Nevertheless, they reported promising results from reactions of nitriles with ammonium thiocyanate[2b] and ammonium benzenesulfonate[2a] and later showed some advantage in the presence of free ammonia in the reaction system.[2d] Despite the poor opinion of the ammonia–ammonium salt system which apparently still prevails, it seemed to us to be ideal for our purpose in view of the probable reaction mechanism.

A very simple description of the reaction of a nitrile with an ammonium salt is expressed by the following equilibria:

$$NH_4X \rightleftharpoons NH_3 + HX \tag{1}$$

$$RCN + NH_3 \rightleftharpoons RC\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\big<}} \tag{2}$$

$$RC\overset{\displaystyle NH}{\underset{\displaystyle NH_2}{\big<}} + NH_4{}^+ \rightleftharpoons RC\overset{\displaystyle NH_2}{\underset{\displaystyle NH_2}{\big<}}\oplus + NH_3 \tag{3}$$

Ammonia, produced by thermal dissociation of the salt (1) to a degree depending on the nature of the anion, X, reacts with the nitrile to form the amidine (2), which is stabilized by conversion to the amidinium ion (3). This last step may be brought about by free acid, HX, in the system or, in an ionizing medium, through proton transfer from an ammonium ion to the more basic amidine. The presence of excess ammonia will aid reaction (2) and impede (3).[6,7] It is well established that (2) is favored by the presence of electronegative sub-

(1) See R. L. Shriner and F. W. Newman, *Chem. Revs.*, **35**, 351 (1935).

(2) (a) P. Oxley and W. F. Short, *J. Chem. Soc.*, 147 (1946); (b) M. W. Partridge and W. F. Short, *ibid.*, 390 (1947); (c) P. Oxley, M. W. Partridge, and W. F. Short, *ibid.*, 1110 (1947); (d) P. Oxley, M. W. Partridge, and W. F. Short, *ibid.*, 303 (1948); (e) P. Oxley and W. F. Short, *ibid.*, 449 (1949); (f) J. Cymerman, J. W. Minnis, P. Oxley, and W. F. Short, *ibid.*, 2097 (1949).

(3) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961). In this paper is reported the preparation of amidine salts by base-catalyzed addition of methanol to activated nitriles and reaction of the imidates obtained with ammonium salts *in situ.*

(4) E. F. Cornell, *J. Am. Chem. Soc.*, **50**, 3311 (1928).

(5) These authors commented, "It is stated in almost all the standard textbooks of organic chemistry that amidines may be prepared by heating cyanides with ammonium chloride, but this statement appears to be an extrapolation of Bernthsen's discovery (1877) that *N*-aryl- and *N,N*-diaryl-amidines may be prepared by heating a cyanide with the hydrochloride of a primary aromatic amine or diphenylamine. Bernthsen expressly stated that amidines could not be obtained from cyanides and ammonium chloride. Very small yields of amidines have subsequently been obtained by heating acetamide with ammonium nitrate in liquid ammonia (Fichter, 1912) and from cyanides by heating under pressure with ammonium chloride and liquid ammonia (Cornell, 1928)."[2a]

(6) It is not intended that these views exclude the possibilities of (a) activation of the nitrile through formation of the more electrophilic conjugate acid by initial association with HX or (b) concerted addition of a proton and ammonia. There is no present advantage in defining these details.

(7) This interpretation has also been given by Oxley, Partridge, and Short[2d] as applying in those reactions where free ammonia was used. We see no validity in their distinction of such cases from those where only ammonium salts were employed. It is very probable that the observations upon which this distinction was based arise from kinetic effects. Catalysis undoubtedly plays an important role.[6]

TABLE I
PREPARATION OF AMIDINE SALTS
$$RCN + NH_4X \longrightarrow RC(NH)NH_2 \cdot HX$$

R	X	NH_4X[a]	NH_3[a]	Temp.[b]	Yield, %	M.P.	Recovered Nitrile, %
C_6H_5	Cl^-	1	18	200	8[c,d]		
		4	18	150	77	161–163[e]	5
		1	2.0[f]	125	81	166–168[e]	10
	Br^-	4	18	125	75	85–110[g]	5
		3	18	150[h]	78	109–111	
		1	1.2	155	70	121–123	
	NO_3^-	1	22	150[i]	48	116–120[j]	20
$4\text{-}ClC_6H_4$	Cl^-	4	20	125	72[k]	237–239[l]	
	SCN^-	4	20	125[m]	ca. 50	190–195	
$2\text{-}ClC_6H_4$	Br^-	3	40	125	30	236–237[n]	63
$4\text{-}CH_3OC_6H_4$	Br^-	2	40	140	48	o	13
$3\text{-}C_5H_4N$	Cl^-	1	50	125	86	166–175[p]	5
C_2H_5	Br^-	4	20	150	80	103–108[q]	
		0.8	1.2	150	80	100–108	
$n\text{-}C_3H_7$	Cl^-	4	20	150	55	ca. 90[r]	
	Br^-	4	20	150	83	106–110	
$i\text{-}C_3H_7$	Br^-	4	12	150	54	s	
$C_6H_5CH_2$	Cl^-	4	22	150	87	145–147[t]	
$t\text{-}C_4H_9OCH_2$	Br^-	2	45	125[u]	81	128–134[v]	
$(CH_3)_2CHCH_2OCHOCH$ (with CH_3, CH_3)	Br^-	2	50	135[u]	41	116–126[w]	35
4-Cyclohexenyl	Cl^-	4	22	150	53	162–163[x]	16

[a] Moles of reagent per equivalent of nitrile. [b] Reaction time 18 hr. except as noted. [c] Average of two runs approximating the procedure of Cornell[4]; 12% yield of 180°. [d] Yields based on chloride content of ethanol-soluble fraction. [e] Lit.[13] m.p. 169°. [f] Methanol present; 200 cc./mole RCN. [g] M.p. was 122–124° after recrystallization from acetonitrile. Anal. Calcd. for $C_7H_8N_2 \cdot HBr$: C, 41.81; H, 4.51; N, 13.94. Found: C, 41.53; H, 4.72; N, 14.16. [h] Reaction time 5 hr. [i] Reaction time 8 hr. [j] Purity 95% by nitrogen analysis. Lit.[14] m.p. 128°. [k] Recovered a 20% yield of 4-chlorobenzamide. [l] Lit.[15] m.p. 241–242°. [m] The autoclave was badly corroded and the reaction mixture was a black tarry mass. This was worked up in approximately the way described for the preparation of the amidine thiocyanate using the atmospheric-pressure fusion process. [n] Recrystallized from acetonitrile. Anal. Calcd. for $C_7H_8N_2BrCl$: C, 35.70; H, 3.42; N, 11.90. Found: C, 35.77; H, 3.75; N, 11.49. [o] The oily solid obtained gave a purple coloration with aqueous ferric chloride indicative of some demethylation to the phenol. A picrate crystallized from ethanol had m.p. 209–211°. Lit.[2b] m.p. 212–213°. [p] M.p. 189–190° after recrystallization from ethanol. Lit.[3] m.p. 192–194°. [q] M.p. 112–114° after recrystallization from acetonitrile. Anal. Calcd. for $C_3H_9N_2Br$: Br 52.22, Found: Br, 52.16. [r] Recrystallized m.p. 97–100°. Lit.[13] m.p. 94–96°. [s] Mushy crystals, 91% pure by bromide analysis. The yield is corrected for this. [t] Lit.[16] m.p. 151–153°. [u] Reaction time 4 hrs. [v] M.p. 134–145° after recrystallization from acetonitrile. [w] Infrared spectrum and water solubility confirm amidine structure. [x] Anal. Calcd. for $C_7H_{13}N_2Cl$: Cl, 22.07. Found: Cl, 22.0.

stituents in the nitrile.[8,9] Thermal dissociation of the amidine salt to the nitrile and ammonium salt, reversing the entire process, is generally substantial at temperatures near 200° but is strongly dependent on the anion used.[2b]

With this conception of the equilibrium system as a guide, we have made a systematic examination of the reaction variables. The significant results of this work are presented in Table I.

We have attempted to approximate Cornell's experiment by heating equimolar quantities of benzonitrile and ammonium chloride in a large amount of ammonia at 200° for eighteen hours. Only 8% conversion to the amidine salt resulted. In view of the probability that this temperature was too high,[2b] a second experiment was run at 150° and 22% conversion obtained. By a fourfold increase in the ammonium salt-nitrile ratio we were then able to increase the conversion at 150° and isolate a 77% yield of benzamidine hydrochloride.

The results in Table I cover a range of aromatic and simple aliphatic nitriles. Comparisons between examples serve to illustrate the effects of the reaction variables and the nitrile structure. Optimum conditions are discussed with the main features of the process under the headings below.

(8) Direct addition of ammonia to trichloroacetonitrile,[10] perfluoroalkanenitriles,[11] and ethyl cyanotartrate[12] gives the amidine in good yield.

(9) Electronegative substitution favors reaction with ammonium thiocyanate[2b] or ammonium benzenesulfonate.[2a]

(10) K. Dachlauer, Ger. Patent 671,875 (1939).

(11) W. L. Reilly and H. C. Brown, J. Org. Chem., 22, 698 (1957).

(12) R. S. Curtiss and L. F. Nickell, J. Am. Chem. Soc., 35, 885 (1913).

(13) A. Pinner, "Die Imidoäther und ihre Derivate," Robert Oppenheim (Gustav Schmidt), Berlin, Germany, 1892.

(14) R. Forsyth, V. K. Nimkar, and F. L. Pyman, J. Chem. Soc., 800 (1926).

(15) J. B. Ekeley, D. V. Tieszen, and A. Ronzio, J. Am. Chem. Soc., 57, 381 (1935).

(16) P. E. Fanta and E. A. Hedman, J. Am. Chem. Soc., 78, 1434 (1956).

Scope of the reaction; nitrile reactant: Since yields of the order of 80% are obtainable with both benzonitrile and propionitrile it may be expected that equally good results are obtainable with almost any nitrile which is not degraded by ammonia at 150°. The problem is largely one of reaction rate and not all reactions tabulated appear to have reached equilibrium.[17] The expected activating effect of electronegative substituents makes possible the effective use of short reaction times and low reactant ratios in some cases. *o*-Toluitrile was unreactive, but *o*-chlorobenzonitrile was converted to the amidine hydrobromide at a useful rate.[18]

Scope of the reaction[3]; ammonium salt reactant. The experiments with benzonitrile show that the equilibrium conversions obtained with ammonium chloride and ammonium bromide are essentially the same. However, reactions with the bromide are substantially faster. With the simple aliphatic nitriles the chloride was unattractively sluggish and the bromide has been preferred.

Other ammonium salts are not attractive reagents. The reaction is successful with ammonium thiocyanate, but even at 125° this reagent causes very serious corrosion in stainless steel equipment. Ammonium nitrate reacted very well with benzonitrile, but the inherent hazard discouraged further work with this salt. Ammonium sulfate and probably ammonium phosphate are not useful because of poor solubility. Ammonium acetate gives the amide instead of the amidine acetate.[19]

For best results a large excess of the ammonium salt was often used. This is not a disadvantage, as the excess is recovered quantitatively. The favorable effect is simply one of increased acid concentration in the reaction medium.

Ammonia concentration use of solvents. In much of this work relatively large amounts of ammonia were used to provide solvent for the reagents. This is disadvantageous, however, because of the equilibrium of reaction (3) above, and makes necessary the use of large amounts of ammonium salt for the more difficult reactions. Less extensive work shows that the ammonia-nitrile ratio can be reduced to 1.2 and probably lower without appreciably reducing the reaction rate. Excess ammonium salt is then not required.

A solvent may be useful in some reactions to promote mixing[20] and to aid in removing the autoclave contents. Methanol and ethanol are attractive for this purpose, having considerable solvent power for ammonia and the ammonium salts.[21] There is no significant effect on the yield or reaction rate, and the substantial reduction in the working pressure which results is an important practical advantage.

These studies provide the basis for a highly efficient practical process for the preparation of amidine salts. The relatively low pressures required, the ease of recovering all unchanged reactants, and the nearly complete absence of side reactions in those cases where it is applicable[22] make the method easily adaptable to large scale use.

In line with the objectives stated above, we have also evaluated and attempted to improve upon the process of Partridge and Short[2b] for the reaction of ammonium thiocyanate with nitriles at atmospheric pressure. The results obtained were in essentially complete agreement with those in the literature, however, and inadequate for our purpose. It had been hoped that the amidine thiocyanates could be isolated directly from the reaction mixture, but this could be achieved only with *p*-chlorobenzamidine thiocyanate which has relatively low solubility in water. In other cases tried, the solubilities of the product and unreacted ammonium thiocyanate were too similar. Our only contribution to this process is the demonstration that thiourea is equivalent to ammonium thiocyanate as a reagent.[23]

Reaction of nitriles with ammonium salts in liquid ammonia. The reactions were carried out in a stainless steel rocking autoclave which was charged with the nitrile, ammonium

(17) The 77% and 80% conversions given for benzonitrile (ammonium chloride) and propionitrile (ammonium bromide) are approximately equilibrium values at 150° as shown by other experiments in which longer and shorter times were used. At lower temperatures equilibrium conversions tend to be higher.

(18) Synthesis of this amidine by the Pinner method[13] fails because imidate hydrochloride formation is blocked by the *ortho*-substituent. G. D. Lander and F. T. Jervson, *J. Chem. Soc.*, **83**, 766 (1903); see also R. Roger and D. G. Neilson, *Chem. Revs.*, **61**, 179 (1961).

(19) The probable reaction is: $RCN + CH_3COOH \longrightarrow RCO-NH-COCH_3 \longrightarrow RCONH_2 + CH_3CONH_2$. The indicated first stage is well known; see C. E. Colby and F. Dodge, *Am. Chem. J.*, **13**, 1 (1891).

(20) When only a large excess of ammonia is used, the nature of the reaction mixture is a matter for speculation since the temperatures used were often above the critical temperature of pure ammonia.

(21) It is conceivable that the alcohols take part in the reaction itself and that the mechanism involves an imidate:

$$RCN + R'OH \rightleftharpoons RC(NH)OR' \xrightarrow{NH_4X} RC(NH)NH_2 \cdot HX + R'OH.$$ It is unnecessary to invoke such an explanation, however, as the reaction obviously does not require that an alcohol be present.

(22) Substituents which are reactive toward ammonia must be absent, of course. Loss of nitrile in some of the experiments described was due to traces of water which caused hydrolysis to be amide.

(23) Partridge and Short[2b] considered thiourea to be an inferior reagent, although Werner *et al.* [*J. Chem. Soc.*, **83**, 1 (1903); *ibid.*, **101**, 1167 (1912)] had shown that at 140–180° equilibrium between ammonium thiocyanate and thiourea is established quickly and that the former constitutes about 75% of the equilibrium mixture.

(24) Melting points were determined by the capillary method and are uncorrected. Microanalyses were carried out under the direction of Dr. J. A. Kuck.

salt, and solvent, if any. The desired quantity of ammonia was introduced by way of a transfer bomb. The reaction mixture was then heated as desired, subsequently cooled, and vented to atmospheric pressure. The contents of the autoclave were extracted with ether to recover unchanged nitrile and then with hot acetonitrile or ethanol to separate the amidine salt from unreacted ammonium salt. Most of the significant data is presented in Table I. Pressures in the absence of solvent ranged from about 1300 p.s.i.g. at 125° or 6500 p.s.i.g. at 180°. With solvent present, pressure at 150° was of the order of 350–400 p.s.i.g.

p-Chlorobenzamidine thiocyanate. A mixture of 5.50 g. (0.040 mole) of *p*-chlorobenzonitrile and 12.2 g. (0.16 mole)

of thiourea was heated at 190–200° for 5 hr. The mass was then cooled and extracted with ether from which 9% of the starting nitrile was recovered. The insoluble material was suspended in ice water, additional ammonium thiocyanate was added to near saturation, and the insoluble amidine thiocyanate was collected by filtration. The crude yield was 90% m.p. 160–195°. After recrystallization from water the melting point was 202–203°.

Anal. Calcd. for $C_8H_8N_3ClS$: C, 44.96; H, 3.77; N, 19.67. Found: C, 45.23; H, 3.74; N, 19.85.

STAMFORD, CONN.

Reactions of Triphenyltin Hydride with Thiophene Compounds and Certain Carboxylic Acids[1]

STUART WEBER AND ERNEST I. BECKER[2a,b]

Triphenyltin hydride reduces methyl and phenyl 2-thienyl ketones to the corresponding alcohols. Triphenyltin hydride reacts with acetic and propionic acids to give the corresponding triphenyltin esters, while with furoic and thenoic acids it gives both the triphenyltin ester and also the *sym*-tetraphenyldiaroyloxyditin, and with benzoic acid only the *sym*-tetraphenyldibenzoyloxyditin.

Kuivila and Beumel have found that triphenyltin hydride (I) reduces ketones to the corresponding alcohols,[3,4] but no heterocyclic ketones were examined. The purpose of the present work was to report on some similar reactions with heterocyclic compounds.

Thiophene derivatives were first to be examined. It was first ascertained that thiophene is not reduced at reflux nor at 130° in a sealed tube. Then a number of reactions were tried in which the ratio of I:ketone was varied. With a molar ratio of 1:1, methyl 2-thienyl ketone afforded 7% of methyl-2-thienylcarbinol, while a 2:1 ratio gave 15% of the carbinol. With phenyl 2-thienyl ketone ratios of 1:1, 2:1, and 5:1 were carried out, with the best yield (20%) of phenyl-2-thienyl-carbinol being formed with the highest ratio. Appreciable quantities of hexaphenylditin were also recovered, suggesting equation 1 for the stoichiometry.

$$RR'CO + 2(C_6H_5)_3SnH \longrightarrow$$
$$RR'CHOH + (C_6H_5)_3SnSn(C_6H_5)_3 \quad (1)$$
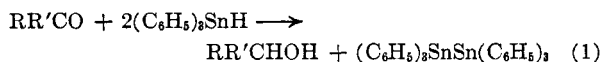
Related to the reduction of the ketones, it was

ascertained that the carbinols are not reduced to the methylene group under similar conditions.

The attempted reduction was next extended to 2-thenoic acid. The reaction of I and 2-thenoic acid gave triphenyltin 2-thenoate (II) in 32% yield at a molar ratio of 1:1 and *sym*-tetraphenyldithen-oyloxyditin (III) in 20% yield. With a 2:1 ratio of I:thenoic acid, 42% of III was obtained, while II could not be isolated from the reaction mixture.

II

III
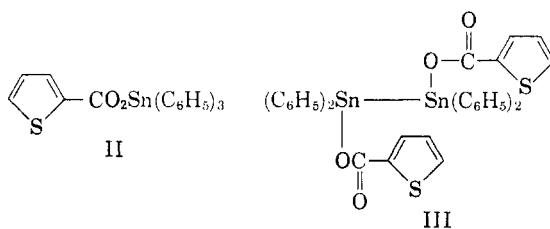
Obtaining III from the reaction with triphenyltin hydride was surprising. Structural assignment was based upon ultimate analysis, which was in agreement with the expected values, and the isolation of diphenyltin oxide and thenoic acid from the reaction of III with cold concentrated sodium hydroxide solution. No bistriphenyltin oxide was found. Owing to solubility difficulties, a molecular weight could not be obtained on III, but it was obtained, and the value agreed with that expected, for the corresponding product with benzoic acid.

Accompanying the reaction during which III appeared, were hydrogen and benzene. However, the precise origins of these by-products were not investigated, although several paths may be writ-

(1) From the thesis of S. W. submitted to the faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the Master of Science degree, 1962.

(2) (a) To whom inquiries should be directed. (b) Supported in part by the U. S. Army Research Office (Durham) under Grant DA-ORD-31 124-61-G39.

(3) H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.*, **80**, 3798 (1958).

(4) H. G. Kuivila and O. F. Beumel, Jr., *J. Am. Chem. Soc.*, **83**, 1246 (1961).