## [Contribution from Goessmann Chemistry Laboratory, University of Massachusetts]

# A NEW NITRILE REACTION. N-CYCLOPENTYL- AND N-CYCLOHEXYL-AMIDES FROM NITRILES AND HALIDES<sup>1</sup>

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A new reaction, the formation of N-substituted amides in 5-55% yields by the reaction of nitriles with certain secondary halides under conditions of the Gattermann aldehyde reaction, is described in this paper. This report of the results obtained thus far is prompted by the recent description (1) of a closely related reaction in which N-(2-haloalkyl) amides are obtained from olefins, nitriles, and halogens.

Wieland, et al. (2) attempted to form tetrahydrobenzalimine or the isomeric hexahydrobenzonitrile from hydrogen cyanide and cyclohexene in the presence of aluminum chloride and hydrogen chloride; the chief product was N-cyclohexylformamide. The present investigation began as an effort to extend the reaction to olefins and nitriles in general.<sup>3</sup> Acetonitrile, phenylacetonitrile, and benzonitrile reacted with cyclohexene to give the corresponding N-cyclohexylamides in 13 %, 19.5 %, and 42 % yields, respectively. It seemed probable that the intermediate reacting with the nitriles was the carbonium ion (III) derived from cyclohexene (I) directly or via cyclohexyl chloride (II). As a partial test of this idea cyclohexyl chloride was substituted for cyclohexene; the same N-cyclohexyl amides were obtained in 4%, 29%, and 46.8% yields, respectively. The results with cyclohexene indicated that the Ritter method (3) is superior for the conversion of olefins and nitriles to the corresponding N-substituted amides with respect to both yields and reaction simplicity. However, the reaction in which an amide is obtained from a halide and a nitrile was of sufficient interest to merit further study.

The N-cyclohexyl amides also were prepared from cyclohexylamine and the acid chlorides and found, by the method of mixture melting points, to be identical with those obtained from cyclohexyl halides and nitriles. Thus, in the amides isolated rearrangement of the cyclohexyl group had not occurred. Wieland and Dorrer (2a) postulated that their reaction involved the isonitrile tautomer of hydrogen cyanide. That such a tautomerization is not prerequisite for the reaction is indicated by the discovery that nitriles as well as hydrogen cyanide

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<sup>3</sup> The reaction already may have been extended to acetonitrile. Bruson, Riener, and Riener, J. Am. Chem. Soc., **70**, 483 (1948) considered the product obtained by the action of aluminum chloride on 2-(cyclohexenyl)cyclohexanone and acetonitrile to be an imino ether. Recently, it has been suggested [Mowry and Ringwald, J. Am. Chem. Soc., **72**, 4439 (1950) and ref. 1] that the compound probably is the amide, 2-(1'-acetamido)cyclohexyl-cyclohexanone.

react with olefins to give the N-substituted amides. When benzonitrile was replaced by benzamide, no N-substituted amide was obtained, and it would seem improbable that the reaction proceeds through the amide or a derivative thereof. The following is suggested as a plausible mechanism for these nitrile reactions.



An attempt was made to determine the optimum conditions for the cyclohexyl chloride-benzonitrile reaction. The reaction was then tried on a variety of alkyl halides and nitriles using these conditions. In every case in which an amide was isolated<sup>4</sup> a secondary halide (cyclopentyl, cyclohexyl, or *sec*-butyl) had been employed. A possible explanation for this observation is that the order of the ease of formation of alkyl carbonium ions is tertiary > secondary > primary, whereas the order of their reactivity once they are formed is just the opposite (4). The reaction may be so sensitive to carbonium ion reactivity that only secondary halides furnish carbonium ions of sufficient reactivity and concentration that product can be isolated under the conditions employed.

Unreacted nitrile could be recovered from most of the reaction mixtures, but unreacted halide was recovered only in a few isolated cases. The formation of

<sup>4</sup> For a list of the halides from which amides were not obtained see Table II, footnote a.

liquid polymeric materials was frequently observed, especially with *tert*-butyl chloride, 1-chloro-1-methylcyclohexane, and 1-chloro-1-methylcyclopentane. This polymer formation suggests that the carbonium ions, especially those from tertiary halides, stabilize themselves by expulsion of a proton before they react with the nitrile. The resultant olefins can then polymerize.

The need for hydrogen chloride to form the cyclohexylcarbonium ion from cyclohexene is apparent. However, as is the case with many other aluminum chloride-catalyzed reactions (5), whenever hydrogen chloride was omitted<sup>5</sup> from the cyclohexyl chloride-benzonitrile reaction, the yield of pure amide dropped from 47 % to 7–9%. Hydrogen chloride reacts with nitriles to form imino chlorides (6, 7) and also nitrilium salts (8). The first step in the Hoesch Synthesis, which employs conditions similar to those of this new reaction, is believed (6, 7) to be the formation of the imino chloride; but mechanisms for the present reaction in which the imino chloride of the nitrile appears as an intermediate seem less attractive than that given here. Possible functions of the hydrogen chloride may be to faciliate the formation of carbonium ions by combining with the alkyl

NITRILE	PRODUCT	VIELD (purified), $\%$		
p-CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> CN	$p-CH_{3}OC_{6}H_{4}CONHC_{6}H_{11}$	12		
C <sub>6</sub> H <sub>5</sub> CN	C <sub>6</sub> H <sub>5</sub> CONHC <sub>6</sub> H <sub>11</sub>	47		
$C_6H_5CH_2CN$	$C_6H_5CH_2CONHC_6H_{11}$	29		
$CH_{3}CN$	$CH_{3}CONHC_{6}H_{11}$	4		
p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> CN	$p-NO_2C_6H_4CONHC_6H_{11}$	5		
Cl <sub>3</sub> CCN		0		

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halide (9) and/or the formation in some way of complexes which either are reactive intermediates or furnish a highly polar medium in which the ionic intermediates may form and react (10).

In the first reactions with cyclohexyl iodide, no reduction in yield was observed on omission of hydrogen chloride. Subsequent study disclosed that the halide contained free iodine and that when pure cyclohexyl iodide was used, the yields were much lower if hydrogen chloride was absent. Moreover, small amounts of either iodine or bromine could replace hydrogen chloride as an activating agent (Table II) in this and other reactions.

The less reactive Friedel-Crafts type catalysts, zinc chloride and ferric chloride, resulted in 10% and 0% yields, respectively, of amide from cyclohexyl chloride and benzonitrile.

If the reaction involves attack of a carbonium ion at the nitrile group, one would expect that an electron donor group in the nitrile (since it would aid the required polarization of the nitrile group) would facilitate the reaction and that electron-attracting groups would hinder the reaction. Rate studies have not

<sup>5</sup> It is almost certain that some hydrogen chloride was present even in these reactions; Thomas (5) has pointed out that completely anhydrous conditions are not obtained with aluminum chloride and the usual experimental techniques. been made. However, it is interesting to note (Table I) that the variations in the yield with changes in the structure of the nitrile are generally in the same direction as the expected variations in reaction rate.

At present it is difficult to satisfactorily explain (a) the formation of amides in greatest yield by the usually inert (11) cyclohexyl halides while primary and tertiary alkyl halides fail to give isolable amide, and (b) the manner in which hydrogen chloride, bromine, or iodine facilitate the reaction. It is hoped that

HALIDE <sup>a</sup>	R' <sup>b</sup>	<sup>™.₽.,</sup> °C.¢	ACTIVATING AGENT AND YIELD, $\%$							
			HCI		I2		Br <sub>2</sub>		None	
			Crude	Pure	Crude	Pure	Crude	Pure	Crude	Pure
Cyclohexyl chloride	$C_6H_5$	146-147ª	55e	47°	54	46	37	32	8.5	6.8
Cyclohexyl bromide	$C_6H_5$	146-1474	40	38	15	12				
Cyclohexyl iodide	$C_6H_5$	146-147 <sup>d</sup>	29	26						
Cyclopentyl chloride	C <sub>6</sub> H₅	154'	50	45	42	33				
Cyclopentyl bromide	$C_6H_5$	154'	25	22.6						
sec-Butyl chloride	$C_6H_5$	84-859	7	6						
Cyclohexyl chloride	$C_6H_5CH_2$	$134 - 135^{h}$	30	29	11	7	10	5		
Cyclohexyl chloride	$CH_3$	103-104;	5	4						
Cyclohexyl chloride	$p-\mathrm{CH}_3\mathrm{OC}_6\mathrm{H}_4$	$159 - 161^{i}$		12						
Cyclohexyl chloride	p-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	$197 - 198^{k}$	6	5	i				1	

TABLE II N-SUBSTITUTED AMIDES,  $RX + R'CN \rightarrow RNHCOR'$ 

<sup>a</sup> Attempts to react one or more nitriles with the following halides gave no isolable amide: 1-chloro-1-methylcyclopentane, 1-chloro-1-methylcyclohexane, allyl chloride, benzyl chloride, *n*-propyl chloride, isopropyl chloride, *n*-butyl bromide, *n*-butyl chloride sec-butyl bromide, *tert*-butyl bromide, and *tert*-butyl chloride. In most cases a small amount of liquid material, probably polymer, was obtained. This may have contained dissolved amide, but all attempts to crystallize or otherwise isolate the amides failed. <sup>b</sup> Trichloroacetonitrile did not give amide with any halides but was recovered (63-75%) as trichloroacetamide. <sup>c</sup> Uncorrected. <sup>d</sup> Baeyer, Ann., **278**, 104 (1893), m.p. 147°. • Yields with zinc chloride as catalyst, 13 and 10%; with ferric chloride, 0. <sup>f</sup> Anal. Calc'd for C<sub>12</sub>H<sub>15</sub>NO: C, 76.15; H, 7.99. Found: C, 76.46; H, 8.28. <sup>c</sup> Coleman and Howells, J. Am. Chem. Soc., **45**, 3084 (1923), m.p. 84-85°. <sup>h</sup> Anal. Calc'd forC <sub>14</sub>H<sub>19</sub>NO: C, 77.42; H, 8.71. Found: C, 77.50; |H, 8.78. <sup>i</sup> Baeyer, Ann., **278**, 104 (1893), m.p. 104°. <sup>j</sup> Anal. Calc'd for C<sub>14</sub>H<sub>19</sub>NO<sub>2</sub>: C, 72.02; H, 8.21. Found: C, 72.30; H, 8.58. <sup>k</sup> Anal. Calc'd for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: C, 62.87; H, 6.50. Found: C, 62.70; H, 6.53.

further work will give information concerning some of these factors and more clearly define the scope and limitations of the reaction.

### EXPERIMENTAL

All reactants were dried and refractionated. Frequently the best results were obtained only when the reactants were distilled just prior to use. After a large number of runs it was found that the following general procedure gave the maximum yield of N-cyclohexylbenzamide from cyclohexyl chloride and benzonitrile. Unless otherwise noted, the reactions with the other nitriles and halides were carried out under the same, and therefore not necessarily optimum, conditions. The results are collected in Table II.

In the reactions in which hydrogen chloride was replaced by a halogen as an activating agent, bromine (ca. 1 ml.) or iodine (ca. 1 g.) was added to the reaction flask.

The reactions with cyclohexene were carried out essentially according to the general procedure except that the halide was replaced by cyclohexene. Acetonitrile, phenylacetonitrile, and benzonitrile gave the corresponding N-cyclohexyl amides in 13, 19.5, and 42% yields after purification. *dl*-Camphene did not give an amide.

General procedure. A 500-ml. four-necked round-bottom flask was fitted with a condenser, a mechanical stirrer, a gas inlet tube, and a dropping-funnel and was placed in a cold water-bath. In the flask there was placed 66.7 g. (0.5 mole) of anhydrous aluminum chloride (resublimed), and 80 ml. of anhydrous ether was added with stirring. The cooling bath was then removed, 20.6 g. (0.2 mole) of benzonitrile was added, and hydrogen chloride gas was bubbled into the reaction mixture. The gas addition rate was rapid for the first hour of the reaction, but throughout the remainder of the reaction it was just fast enough to keep the reaction mixture saturated.

The flask was heated under reflux in an oil-bath, and 35.6 g. (0.3 mole) of cyclohexyl chloride in 30 ml. of anhydrous ether was then added dropwise over a period of 30 minutes. The reflux temperature of the reaction mixture gradually rose to 80-85° and was maintained at this temperature for the remainder of the reaction. Stirring and heating of the reaction mixture was continued for 12 hours after completion of the addition; the flask was then stoppered and allowed to stand at room temperature for 12 hours. The mixture was poured onto 150-200 g. of cracked ice and allowed to stand for 6 hours at room temperature under a gentle flow of air. After evaporation of the ether, the hydrolyzed mixture was cooled in a refrigerator for 12-15 hours, and the amide was separated by filtration.

Unreacted nitrile, in which the amide is soluble, was removed from the filtrate by steamdistillation. An additional yield of amide was obtained after the distillation residue had stood in the refrigerator for some time.

#### SUMMARY

The reaction of hydrogen cyanide with cyclohexene to give an N-cyclohexylamide has been extended to acetonitrile, phenylacetonitrile, and benzonitrile.

Cyclohexyl and cyclopentyl halides and sec-butyl chloride also react with these nitriles to form the N-substituted amides in 5-55% yields.

A mechanism is suggested and certain factors influencing the reaction are discussed.

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