[CONTRIBUTION FROM THE CHEMICAL LABORATORY, MONTANA STATE UNIVERSITY]

Addition Reactions of Atroponitrile (α-Cyanostyrene)[1,2]

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The addition reactions of atroponitrile with some labile hydrogen-containing types of compounds to give 2-phenyl-3-substituted propanenitriles have been studied. Primary and secondary amines, with the exception of aromatic amines, and mercaptans added readily in the presence of Triton B catalyst. Phenol gave a low yield of adduct in the presence of sodium as catalyst. Alcohols, ammonia, and aromatic amines failed to add in the presence of either acidic or basic type catalysts.

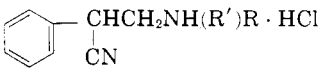
The addition reaction of atroponitrile with a number of primary and secondary amines, with several mercaptans, and with phenol has been successfully accomplished. This was a part of a general comparative study of such reactions for all of the isomeric cyanostyrenes.

Atroponitrile has been prepared previously by pyrolysis of acetophenone cyanohydrin acetate[4] and by the reaction of formaldehyde with phenylacetonitrile followed by pyrolysis of the methylol compound.[5] The second of these methods has been used in this work. The addition reactions of atroponitrile, with the exception of its dimerization and polymerization,[5,6,7] have not been studied previously. The use of basic catalysts was found to promote the addition reactions and a 40% solution of Triton B (benzyltrimethylammonium hydroxide) was used as catalyst in all examples reported except in the case of the sodium-catalyzed reactions with phenol. Alcohols failed to react in the presence of either acid or basic type catalysts and at a variety of temperatures.

Both primary and secondary amines, with the exception of aromatic amines, reacted readily with atroponitrile to give fair yields of 2-phenyl-3-substituted-amino propanenitriles. These products underwent extensive decomposition when attempts were made to purify them by distillation. They were, therefore, isolated and purified as their hydrochloride salts. Table I lists the amines used, percentage yields of the hydrochlorides based upon the unredistilled atroponitrile used, and the melting points and analyses for the hydrochlorides. The basicity of the amine and steric hindrance apparently both play a role in determining the yields obtained. Ammonia, aniline, and methylaniline failed to react under a variety of conditions. Diethylamine gave a product whose hydrochloride could not be crystallized. In no case were any secondary products, derived from the addition of two molecules of atroponitrile to one of a primary amine, obtained.

TABLE I

HYDROCHLORIDE SALTS OF 2-PHENYL-3-SUBSTITUTED-AMINO PROPANENITRILES



Amine Used	Yield of Crude Hydrochloride, %	Pure Hydrochloride, M.p., °C.	Chlorine Calc'd	Chlorine Found
Ethyl	42.6	159–160	16.82	16.82
Isopropyl	38.8	151–152	15.78	15.76
n-Butyl	40.5	128–129	14.85	14.57
Cyclohexyl	37.8	146–147	13.39	13.42
Benzyl	55.0	164–165	13.00	13.03
Dimethyl	45.2	133–134	16.83	16.81
Piperidine	56.0	140–141	14.14	14.04
Morpholine	51.4	135–137	14.03	14.15
Diethyl	35.7	Oil		

The amine adducts could readily be hydrolyzed in concentrated hydrochloric acid to the corresponding 2-phenyl-3-substituted-amino propanoic acids—isolated as the hydrochloride salts. However, only three of these were actually purified and analyzed. The data for these is given in the experimental section.

In the reactions of atroponitrile with mercaptans and thiophenols, six different compounds were tried. The adducts obtained from *n*-butyl and *tert*-butyl mercaptans were oils which could be distilled without decomposition. Three of the other four compounds obviously reacted to form adducts, but these products could not be purified. The adducts from thiophenol and from benzyl mercaptan were oils which could not be distilled without decomposition, and the principal impurities in these cases were polymers of atroponitrile. The adduct from thioglycolic acid was a resinous substance which could not be crystallized nor distilled, but which was freed from starting materials, polymeric substances,

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(2) Taken in part from the thesis submitted by Mr. Hung Chang in partial fulfillment of the requirements for the Master of Science degree.

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(4) Clifford and Long, U. S. Patent 2,362,049 [*Chem. Abstr.*, **39**, 2296 (1945)].

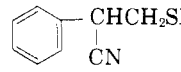
(5) Walker, U. S. Patent 2,478,990 [*Chem. Abstr.*, **44**, 2009 (1950)].

(6) Clifford, U. S. Patent 2,444,870 [*Chem. Abstr.*, **42**, 8527 (1948)].

(7) Newery and Erickson, *J. Am. Chem. Soc.*, **72**, 5645 (1950).

TABLE II

2-PHENYL-3-THIOALKYL PROPANENITRILES



Mercaptan Used	Yield, %	B.p., °C.	Mm.	Ref. Index	t, °C.	Analyses C Calc'd	C Found	H Calc'd	H Found
n-Butyl	51.4	144–146	2	1.5340	22	71.18	71.38	7.81	7.68
tert-Butyl	23.0	132–134	1	1.5340	20	71.18	71.34	7.81	7.85
Thioglycolic acid	39.8 (crude)								

and other likely impurities. Thio-β-naphthol apparently did not react under the conditions used. Table II lists the yields, physical properties and analyses for the purified mercaptan adducts.

No reaction took place between phenol and atroponitrile in the presence of Triton B as catalyst. Use of sodium as catalyst under varying temperature conditions gave low yields of an oily product which could be distilled without decomposition to give pure 2-phenyl-3-phenoxypropanenitrile.

EXPERIMENTAL[8,9]

Preparation of atroponitrile. Atroponitrile was prepared essentially as described in Example VII of the Walker patent.[5] The following example gives the details of this preparation: A solution of 0.7 g. (0.030 mole) of sodium dissolved in 50 ml. of methanol was prepared in a 250-ml. three-necked flask equipped with a stirrer, a thermometer, and a condenser fitted with a dropping-funnel at the top, and surrounded with a water-bath. To this solution was added with stirring 22 g. (0.733 mole) of paraformaldehyde at a temperature of 50–55°. After a solution was formed, 78 g. (0.666 mole) of phenylacetonitrile was added dropwise from the dropping funnel during 20 minutes, keeping the temperature at 50–55°. After the exothermic reaction was over, stirring was continued for 90 minutes at 55–60°. The mixture then was neutralized by adding the required amount of a dry hydrogen chloride-methanol solution. The bulk of the methanol was stripped off under a partial vacuum at room temperature, and the remaining viscous material was flash-distilled by adding it dropwise through a long-stemmed dropping-funnel into a Claisen flask maintained at a temperature of 220–245° and a pressure of 4–6 mm. The distilling flask and the receiver contained small amounts of some polymerization inhibitor such as hydroquinone, picric acid, phenyl β-naphthylamine, or cupric acetate. The flash distillate was dried over magnesium sulfate.

Yields of crude atroponitrile from the flash distillation ranged from 70–80%, n_D^{25} 1.5490–1.5505. (Literature value[4,5] of n_D^{25} 1.5490 for pure atroponitrile was also obtained by the authors on redistilled samples.) This flash-distillation product was used immediately in the addition reactions, since either redistillation or standing for several hours resulted in dimerization or polymerization of much of the atroponitrile—even in the presence of the various polymerization inhibitors.

Amine addition reactions. To 0.2 mole of the amine and 1 drop of 40% Triton B solution in a pressure bottle was added dropwise with shaking 12.9 g. (0.1 mole) of atroponitrile. The temperature at which the initial reaction was carried out varied according to the boiling points of the amines used—5 to 10° for ethylamine and dimethylamine, room temperature for isopropylamine and diethylamine, and 50 to 60° for the others. After the addition had been completed, the bottle was sealed and the mixture was heated in a water-bath at about 50° for a half-hour and then was allowed to stand overnight at room temperature. In most cases, the low-boiling amine then was stripped off under a partial vacuum at room temperature. In the case of cyclohexylamine, the excess was distilled off under a vacuum, and in the cases of benzylamine, piperidine and morpholine, water washing removed the excess amine. The remaining mixture was taken up in 50 ml. of benzene or ether and was extracted several times with small portions of 3 *N* hydrochloric acid until the remaining solution was acidic. The combined acid extracts were washed once with 30 ml. of benzene or ether and then were made basic by addition of 3 *N* sodium hydroxide with cooling. The basic solution was extracted three times with 30-ml. portions of ether or benzene and the extracts were dried over potassium carbonate. The crude product then was obtained by stripping off the solvent, or the solution was bubbled with dry hydrogen chloride, and the precipitated hydrochloride was filtered off, washed with ether, and dried under a vacuum. After this product was weighed to obtain the percentage yield, it was recrystallized several times from absolute ethanol-ether mixtures. Table I lists the yields and data on these hydrochlorides. In addition to the information given in the table, the following experimental results were also obtained:

2-Phenyl-3-piperidinopropanenitrile was a solid, which on recrystallization from petroleum ether melted at 46–47°.

2-Phenyl-3-morpholinopropanenitrile was a solid, which on recrystallization from ether melted at 80–81°.

Anal. Calc'd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46. Found: C, 72.02; H, 7.44.

2-Phenyl-3-diethylaminopropanenitrile did not form a crystalline hydrochloride and was converted to a crystalline *picrate* for analysis, m.p. 128.5–130°.

Anal. Calc'd for $C_{19}H_{21}N_5O_7$: C, 52.89; H, 4.90. Found: C, 52.68; H, 4.72.

2-Phenyl-3-benzylaminopropanenitrile was converted to a *benzenesulfonamide* derivative, m.p. 127–128°.

Acid hydrolysis of the 2-phenyl-3-substituted-amino propropanenitriles was accomplished by heating them for several hours in conc'd hydrochloric acid. The resulting acid solutions were evaporated to dryness on a steam-bath, after which the dry salts were extracted with cold absolute ethanol and the alcohol solutions were filtered. Addition of ether then precipitated the hydrochlorides of the 2-phenyl-3-substituted-aminopropanoic acids. Several recrystallizations from absolute ethanol-ether were usually necessary to re-

(8) Melting points are uncorrected.

(9) Microanalyses for carbon and hydrogen were performed by the Clark Microanalytical Laboratory, Urbana, Ill.

move the last traces of ammonium chloride. Following are data on three of these purified compounds:

2-Phenyl-3-n-butylaminopropanoic acid hydrochloride, m.p. 137–139°.

Anal. Calc'd for $C_{13}H_{20}ClNO_2$: Cl, 13.76. Found: Cl, 13.60.

2-Phenyl-3-piperidinopropanoic acid hydrochloride, m.p. 176–177°.

Anal. Calc'd for $C_{14}H_{20}ClNO_2$: Cl, 13.18. Found: Cl, 13.20.

2-Phenyl-3-benzylaminopropanoic acid hydrochloride, m.p. 171–173°.

Anal. Calc'd for $C_{16}H_{18}ClNO_2$: Cl, 12.15. Found: Cl, 11.98.

Mercaptan addition reactions with atroponitrile were carried out in a manner similar to that employed with the amines. Atroponitrile was added dropwise to an excess of the mercaptan containing Triton B catalyst, either at room temperature or at 60°. After the addition was completed, the mixtures were heated at about 60° for a half hour and then were sealed and allowed to stand at room temperature for at least 24 hours. The reaction mixture then was taken up in ether, washed repeatedly with 5% aqueous potassium hydroxide, and dried over calcium chloride. Ether was removed under a vacuum and an attempt was made to distill the crude product. In the cases of thiophenol and benzyl mercaptan, the crude products could not be purified by distillation nor by crystallization and could not be obtained free of polymeric materials.

In the reaction of thioglycolic acid and atroponitrile, 0.1 mole of atroponitrile was added to a mixture of 0.15 mole of thioglycolic acid and 64 g. of 40% Triton B solution heated to 60°. After the heating and standing periods, the reaction mixture was taken up in 50 ml. of benzene and was washed with four 25-ml. portions of 5% sodium carbonate solution. The combined alkaline extracts then were acidified with 3 *N* hydrochloric acid, saturated with sodium chloride, and extracted several times with ether. The ether extracts were dried over magnesium sulfate, and the ether was stripped off under a vacuum. The residue was submitted to a vacuum-distillation under an argon atmosphere to remove unreacted thioglycolic acid, leaving 8.8 g. (39.6%) of resinous material in the flask. This material was fairly water soluble and it was considered likely that this might be the crude product free of starting materials and polymers of atroponitrile. It could not, however, be further purified by distillation nor recrystallization.

Phenol addition reaction. To 13.8 g. (0.15 mole) of phenol, 0.1 g. of sodium, and a little cupric acetate, mixed with 50 ml. of benzene and heated to 60°, was added dropwise 12.9 g. (0.1 mole) of atroponitrile. The mixture was further heated for a half hour and allowed to stand at room temperature for 48 hours. It then was washed with three 25-ml. portions of 10% sodium hydroxide solution and two 25-ml. portions of water. The benzene solution was dried over calcium chloride and the benzene was stripped off under a vacuum. Vacuum distillation yielded 2 g. (9%) of product, b.p. 95–98° (2–3 mm.); n_D^{29} 1.5360. On redistillation the pure 2-phenyl-3-phenoxypropanenitrile was obtained as a colorless oil, b.p. 84–85° (1 mm.); n_D^{27} 1.5340. *Anal.* Calc'd for $C_{15}H_{13}NO$: C, 80.72; H, 5.85. Found: C, 80.56; H, 6.03.

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