

HYDROLYSIS OF ARYLACETONITRILES

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Arylacetic acids are generally prepared by hydrolysis of the corresponding nitriles (7). Almost every text-book of organic chemistry describes this important reaction for the special case of phenylacetic acid (1, 3).

Difficulties encountered when the known methods for saponification were applied to large scale manufacture prompted the following investigation, which resulted in a simple method for the hydrolysis of arylacetonitriles.

It was found that *rapid stirring with aqueous conc'd hydrochloric acid* at moderate temperatures readily leads to hydrolysis of the arylacetonitriles without the use of an organic solvent as solubilizer. Depending upon the conditions, free arylacetic acids or their amides may thus be prepared in high yields.

Rapid stirring of benzyl cyanide with conc'd hydrochloric acid leads to the formation of a clear solution of phenylacetamide. The reaction takes place even at temperatures as low as 10°. However, the hydrochloric acid has to be at least of about 30% strength to effect conversion of the nitrile into the amide. Hydrobromic acid will not lead to saponification under similar conditions. Up to temperatures of 50° the resulting phenylacetamide is not easily saponified further. To prepare phenylacetamide, therefore, the homogeneous solution obtained by stirring benzyl cyanide with conc'd hydrochloric acid is simply diluted with water, whereupon the amide crystallizes.

Further hydrolysis to free phenylacetic acid proceeds rather slowly when the initial homogeneous solution is heated higher. However, the formation of phenylacetic acid is speeded up considerably when the amide is heated with more dilute acid. In order to prepare free phenylacetic acid, the original solution of the amide is, therefore, diluted with water and is then refluxed. In a few hours hydrolysis is complete.

Homologs of benzyl cyanide likewise form the corresponding amides when they are stirred with conc'd hydrochloric acid at temperatures below 100°. Up to about 60° the amide is formed, which in these cases remains undissolved. At higher temperatures the corresponding acids result. Several polynuclear arylacetonitriles were saponified in the same way without difficulty.

Alkoxy substituted nitriles yield the corresponding amides under the conditions specified if the reaction temperature does not exceed 50–60°. At higher temperatures the conc'd hydrochloric acid will lead to cleavage of the alkoxy groups. Saponification of the amides to the free acids is accomplished by diluting the mixture after formation of the amides and subsequent boiling of the mixture.

The method is a striking illustration of the usefulness and importance of stirring in chemical reactions. It provides a simple procedure for the technical preparation of several commercially important arylacetic derivatives, and it has been found to be superior to the known saponification methods in the course of our research work in numerous instances.

EXPERIMENTAL

The melting points are uncorrected. The periods of time given to effect solution apply to stirrer speeds of about 700-1000 r.p.m.

1. *Phenylacetamide*: Benzyl cyanide (100 g.) and 200 cc. of conc'd hydrochloric acid were stirred (starting at 30°) for 2 hours. The temperature rose to 40° during the first hour and remained there. Homogeneity resulted about 10 minutes later. Ice-cooling and slow addition of 400 cc. of water gave 100 g. of crude phenylacetamide. The mother liquor contained small amounts of phenylacetic acid.

When carried out at +4-6° the reaction requires about 10 hours; at 60-65° it is complete in about 25-30 minutes.

2. *Phenylacetic acid*: Stirring 200 g. of benzyl cyanide with 800 cc. of conc'd hydrochloric acid at 40-50° yields a homogeneous solution about 1-2 hours later. When this solution is heated to 80-90° for 10 more hours, phenylacetic acid is formed and separates as an oil which solidifies on cooling. About 200 g. of crude acid, m.p. 72-75°, is obtained.

When the homogeneous solution of phenylacetamide, formed from 200 g. of benzyl cyanide and 800 cc. conc'd hydrochloric acid by stirring at 50°, is diluted with 800 cc. of water (precipitating most of the phenylacetamide) and refluxed for about 4 hours, a yield of about 200 g. of phenylacetic acid is obtained.

3. *4-Methylphenylacetic acid*: 4-Methyl- α -tolunitrile (50 g.) and 200 cc. of conc'd hydrochloric acid is stirred at 50° for 8 hours. The mixture is cooled, and 200 cc. of water is added. A solid forms which is filtered and washed with water and ether. It is practically pure 4-methylphenylacetamide. Recrystallization from benzene gives the pure amide of m.p. 180-182°

4. *4-Isopropylphenylacetic acid*: 4-Isopropyl- α -tolunitrile (20 g.) (2) and 200 cc. of conc'd hydrochloric acid are stirred for 10 hours at 90-100°. The mixture, which does not become homogeneous, is then diluted with 200 cc. of water, cooled to room temperature, and extracted with ether. 4-Isopropyl- α -toluic acid is extracted with sodium carbonate solution from the ether solution. The acid is liberated by the addition of hydrochloric acid, extracted with ether, and the ether solution distilled to dryness; yield 20 grams. Vacuum distillation gives the pure acid of b.p.¹⁴ 170-174°, m.p. 38-40°.

5. *4-Isopropylphenylacetamide*: 4-Isopropyl- α -tolunitrile (20 g.) and 100 cc. of conc'd hydrochloric acid are stirred for 8 hours at 50-55°. Water (100 cc.) is added, and the mixture is cooled; twenty grams of crude 4-isopropylphenylacetamide is obtained. Recrystallization from toluene yields the pure compound of m.p. 156-157°.

6. *1-Naphthaleneacetic acid*: 1-Naphthaleneacetonitrile (20 g.) is stirred with 100 cc. of conc'd hydrochloric acid for 5 hours at 60-70°. Water (50 cc.) is then added, and the mixture is refluxed with stirring for 10 hours. After cooling, ether is added. The ether layer is separated and extracted with sodium carbonate solution. The extract is acidified and extracted with benzene. The benzene layer is concentrated to a small volume, and ligroin is added. Yield, 14 g. of 1-naphthaleneacetic acid, m.p. 111-113°.

7. *1-Naphthaleneacetamide*: 1-Naphthaleneacetonitrile (20 g.) and 100 cc. of conc'd hydrochloric acid are stirred for 10 hours at about 40°. Shortly after the start of the reaction crystals of the amide appear. At the end of 10 hours about 200 cc. of water is added, and the amide is filtered, weight 12 g. Recrystallization from benzene or alcohol yields the pure compound of m.p. 175°.

The mother liquor contains some free acid which is isolated as described in Experiment 6.

8. *5,6,7,8-Tetrahydro-2-naphthaleneacetic acid*: 5,6,7,8-Tetrahydro-2-naphthaleneacetonitrile (6 g.) is stirred with 60 cc. of conc'd hydrochloric acid at 70-80° for 8 hours. Water is added after cooling, and the mixture is extracted with ether. The ether solution is extracted repeatedly with sodium carbonate solution. The combined sodium carbonate extracts are acidified and extracted with ether. The ether solution is evaporated, leaving 6 g. of crude 5,6,7,8-tetrahydro-2-naphthaleneacetic acid. It is obtained pure by crystallization from benzene-petroleum ether and melts at 95-97° (6).

9. *5,6,7,8-Tetrahydro-2-naphthaleneacetamide*: 5,6,7,8-Tetrahydro-2-naphthaleneacetamide (15 g.) is stirred with 75 cc. of conc'd hydrochloric acid at 25°. The temperature is raised after 1 hour to 50° for 4 more hours. An oil separates which solidifies upon the addition of 150 cc. of water. The crude amide (15 g.) is recrystallized from benzene, yielding pure 5,6,7,8-Tetrahydro-2-naphthaleneacetamide of m.p. 142°.

10. *4-Methoxyphenylacetic acid*: 4-Methoxy- α -tolunitrile (50 g.) and 250 cc. of conc'd hydrochloric acid are stirred at room temperature for 15 hours. Water (250 cc.) is added, and the mixture is heated with stirring to 70° for 15 hours. After cooling, the solution is extracted with ether. The ether solution is evaporated, and the residue is distilled *in vacuo* to give 43 g. of 4-methoxy- α -toluic acid, b.p. 184–186°. The acid solidifies on cooling and on recrystallization from benzene-petroleum ether melts at 84–86°.

11. *4-Methoxyphenylacetamide*: 4-Methoxy- α -tolunitrile (20 g.) and 100 cc. of conc'd hydrochloric acid are stirred and heated to 50° for 3 hours. Water (200 cc.) is added; the amide crystallizes and is filtered. It is extracted with dilute sodium carbonate solution to remove a small amount of free acid (about 2 g.). Yield, 17 g. of amide, m.p. 188°.

12. *3,4-Dimethoxyphenylacetic acid (homoveratric acid)*: 3,4-Dimethoxy- α -tolunitrile (100 g.) is stirred with 200 cc. of conc'd hydrochloric acid, the temperature being kept below 40°. After about 3 hours, when the nitrile is dissolved, the temperature is raised to 50° for 2 more hours. Water (700 cc.) is added, and the mixture is refluxed with stirring. A short time later the solution becomes turbid, and an oil separates. After 7 hours the mixture is cooled to 0°. The oil solidifies and is filtered. Crude homoveratric acid, containing one molecule of water of crystallization, is obtained in about 95% yield. Recrystallization from benzene yields the pure acid, m.p. 99°.

13. *3,4-Dimethoxyphenylacetamide*: 3,4-Dimethoxy- α -tolunitrile (500 g.) is stirred with 1000 cc. of conc'd hydrochloric acid at room temperature. The nitrile dissolves slowly, the temperature rising about 5°. About 2–3 hours later the amide starts to crystallize. In the course of about 3 more hours a thick slurry is formed. About 2000 cc. of water is added, and the mixture is filtered, yielding 470–500 g. of homoveratramide. It contains small amounts of homoveratric acid which can be removed with sodium carbonate. The amide is crystallized from water and melts then at 142°.

14. *2,3-Dimethoxyphenylacetic acid (o-homoveratric acid)*: 2,3-Dimethoxy- α -tolunitrile (20 g.) and 100 cc. of conc'd hydrochloric acid are stirred at room temperature. After 3 hours 300 cc. of water is added, and the mixture is heated with stirring to 80° for 10 hours. An oil separates which is extracted with ether after cooling. The ether layer is extracted with sodium carbonate solution. The aqueous extract is acidified, and the free acid is dissolved in ether. Evaporation of the ether layer leaves 21 g. of crude 2,3-dimethoxyphenylacetic acid which crystallizes on standing. Vacuum distillation yields the pure acid, b.p. 235–240°/20 mm. and m.p. 82–83°.

15. *2,3-Dimethoxyphenylacetamide*: 2,3-Dimethoxybenzyl cyanide (20 g.) is stirred with 100 cc. of conc'd hydrochloric acid for 4 hours at 20–30°. The solution is diluted with 300 cc. of water. The amide remains in solution and is extracted with chloroform. The chloroform extract is distilled to dryness, yielding 20 g. of crude 2,3-dimethoxyphenylacetamide. Recrystallization from benzene gives the pure amide, m.p. 109–111°.

Anal. Calc'd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71.

Found: C, 61.79; H, 6.63.

16. *4-Phenoxyphenylacetic acid*: 4-Phenoxybenzyl chloride (4) is refluxed with sodium cyanide in aqueous alcohol, yielding 4-phenoxy- α -tolunitrile of b.p._{0.15} 155–160°.

Twenty grams of the nitrile is stirred with 200 cc. of conc'd hydrochloric acid at 80–90° for 16 hours. After cooling, 300 cc. of water is added, and the mixture is extracted with ether. The acid is extracted from the ether with dilute sodium carbonate solution, precipitated with dilute hydrochloric acid, and is taken up in ether. Evaporation of the ether gives 20 g. of 4-phenoxyphenylacetic acid. Recrystallization from dilute acetic acid gives the pure acid, m.p. 55–56°.

Anal. Calc'd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30.

Found: C, 73.94; H, 5.22.

17. *2-Dibenzofuranacetic acid*: Ten grams of 2-cyanomethyldibenzofuran (5), m.p. 89–90°, is stirred with 150 cc. of conc'd hydrochloric acid for 15 hours at 80–90°. Water (200 cc.) is added, the crystals are filtered, and then stirred with sodium carbonate solution. Most of the material dissolves. The solution is filtered and acidified with hydrochloric acid. The precipitated acid is filtered and washed with water. Recrystallization from 70% acetic acid yields pure 2-dibenzofuranacetic acid, m.p. 162–163°; yield, 8 g.

Anal. Calc'd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46.

Found: C, 74.23; H, 4.84.

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SUMMARY

Vigorous stirring with aqueous conc'd hydrochloric acid at low temperatures converts arylacetonitriles into the corresponding amides. These amides are easily saponified further to the free acids by heating with dilute hydrochloric acid.

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REFERENCES

- (1) ADAMS-THAL, *Org. Syntheses*, Coll. Vol. I, 2nd ed., p. 436 (1941).
- (2) BAIN, *J. Am. Chem. Soc.*, **68**, 638 (1946).
- (3) GATTERMANN-WIELAND, *Die Praxis des Organischen Chemikers*, 27th Edition, 1940, Walter de Gruyter, Berlin, page 146.
- (4) I. G. FARBENINDUSTRIE, German Patent 569,570; *Frdd.*, **18**, 552 (1931).
- (5) KIRKPATRICK, *Iowa State Coll. J. Sci.*, **11**, 75 (1936).
- (6) NEWMAN AND ZAHN, *J. Am. Chem. Soc.*, **65**, 1097 (1943).
- (7) STAEDEL, *Ber.*, **19**, 1949 (1886).