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PROCESS FOR THE REDUCTION OF ARYLNITROALKENES

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Our invention relates to a process for the reduction of arylnitroalkenes, and more specifically, to a method for the production of arylalkanones, arylalkanone oximes, and arylalkylamines.

The arylnitroalkenes may be produced by the condensation of aromatic aldehydes and nitroparaffins (Knoevenagel and Walter, Ber. vol. 37, p. 4502 (1904); Worrall, Jour. Am. Chem. Soc. vol. 56, p. 1556 (1934); Alles, Jour. Am. Chem. Soc. vol. 54, p. 271 (1932)). Compounds of this type are desirably reduced to form amino compounds, and more or less successful reductions have been obtained in the case of compounds such as omega-nitrostyrene, obtained by the condensation of nitromethane with an aromatic aldehyde. However, in the case of nitroalkenes of the type

$$AR-CH=\underset{NO_2}{\underset{|}{C}}-R$$

it has been found to be extremely difficult to effect satisfactory reduction. For example, "Benzedrine" (1-phenyl-2-aminopropane) may theoretically be obtained by the reduction of 1-phenyl-2-nitropropene, but in practice it has been found to be almost impossible to effect the desired reaction. Relatively low yields of "Benzedrine" have been secured by electrolytic reduction of the nitropropene but catalytic hydrogenation appears to yield only high molecular weight polymerization products.

We have now discovered that arylnitroalkenes of the type

$$AR-CH=\underset{NO_2}{\underset{|}{C}}-R$$

may be successfully reduced to arylalkanones or arylalkanone oximes by a single stage reduction by means of iron, and can be reduced to amino compounds of the "Benzedrine" type in a two-stage reduction in which the initially obtained oxime is further reduced. One advantage of our process is the fact that the initial reduction may be controlled to yield either predominantly the ketone compound or predominantly the oxime, depending upon the reduction conditions. Other advantages of our process will be evident from the following description.

The initial reduction of our process is effected in aqueous solution in the presence of sufficient finely divided iron to effect the reduction of all of the nitroalkene. An acid need not be employed in conjunction with the iron, but if employed, the concentration of the acid will affect the nature of the reduction process. With no acid or only low concentrations of acid, the reaction product is predominantly the oxime, whereas in the presence of relatively high concentrations of acid the reaction product is predominantly the ketone. The mechanism of the reactions is not definitely known, but the following type reactions are probably involved:

$$2AR-CH=\underset{NO_2}{\underset{|}{C}}-R+3Fe+2H_2O \longrightarrow 2AR-CH_2-\underset{NOH}{\underset{\|}{C}}-R+Fe_3O_4$$

$$2AR-CH=\underset{NO_2}{\underset{|}{C}}-R+3Fe+4H_2O \longrightarrow 2AR-CH_2-\underset{O}{\underset{\|}{C}}-R+2NH_2OH+Fe_3O_4$$

$$AR-CH=\underset{NO_2}{\underset{|}{C}}-R+3Fe+7HCl \longrightarrow AR-CH_2-\underset{O}{\underset{\|}{C}}-R+NH_4Cl+3FeCl_2+H_2O$$

As may be seen from the above reactions, an amount of iron equal to at least 1.5 mol per mol of nitroalkene is required, and the amount required by one of the equations is 3 mols per mol of nitroalkene. At least the lower limit of 1.5 mol of iron should be employed to effect satisfactory reduction, and we prefer, in general, to use more than 3 mols of iron per mol of nitroalkene. An excess of iron is not harmful and it serves to insure as complete reduction as possible.

It may also be seen from the above equations that at least 1 mol of water is required per mol of nitroalkene in order to secure reduction to the oxime. We prefer, however, to utilize a considerable excess of water in order to obtain a mixture which can be satisfactorily handled, and agitated during the reaction. Other solvents can be employed in conjunction with water if desired, but these should preferably be miscible with water in order to maintain a single liquid phase and thus facilitate the reduction. The use of an organic solvent in conjunction with water may be an advantage in controlling the type of reduction product secured. Thus, if it is desired to obtain the oxime rather than the ketone, the use of an aliphatic alcohol in conjunction with water will tend to increase the ratio of oxime to ketone in the products.

Although the reduction to the oxime may be effected in the absence of any acid, we prefer to employ an acid in conjunction with the iron for reduction either to the oxime or to the ketone. Any acid may be utilized for this purpose, and the term acid in this connection is to be construed as a material yielding hydrogen ions. In general, however, we prefer to employ a mineral acid such as hydrochloric acid or a relatively strong organic acid such as acetic acid. The concentration of acid employed will depend upon the nature of the product desired. If it is desired to produce predominantly the oxime, an acid concentration not substantially higher than 0.06 mol of hydrochloric acid per mol of nitro-olefin should be employed, or the equivalent amount of another acid, as for example, 0.03 mol of sulfuric acid. Increasing concentration of acid will produce an increase in the ratio of ketone to oxime in the reduction product. Approximately 2 mols of hydrochloric acid per mol of nitro-olefin will produce almost entirely the ketone with only a trace of the oxime or none at all. Intermediate concentrations of acid can of course be employed if it is desired to produce intermediate ratios of the two products.

When employing no acid in conjunction with the iron it is desirable to employ a small amount of an iron salt as a catalyst, for example, ferric chloride. When acid is used in conjunction with the iron, on the other hand, no such catalyst is required since the initial reaction of acid with the iron in the process will produce some of the necessary catalytic material. The use of a catalyst in conjunction with acid will, however, eliminate the short induction period required for the formation of a salt by the action of acid on the iron, and for this reason it may be advantageous to employ a catalyst in addition to acid, especially for large scale operations. The amount of catalyst to be employed is not critical, amounts ranging from 0.01 mol to 0.10 mol per mol of nitroalkene being generally satisfactory.

The reduction of nitroalkenes to ketones and oximes may be further illustrated by the following specific example:

Example I

1-phenyl-2-nitropropene was dissolved in water, organic solvent or aqueous organic solvent. Forty mesh iron filings were added and in some cases acid and/or ferric chloride was incorporated into the mixture. The molar quantities of solvent, iron, acid, and catalyst, per mol of 1-phenyl-2-nitropropene, for the various reductions are shown in the table below. In each case the mixture was agitated for a period of approximately 5½ hours in a vessel equipped with a reflux condenser. At the conclusion of this period, the mixture was made alkaline with sodium hydroxide solution and steam distilled. The products were recovered from the steam distillate, dried, and carefully fractionated in a rectifying column to determine the yield of phenylpropanone and of the oxime of phenylpropanone. The conversions to these products, based on original 1-phenyl-2-nitropropene, are shown in the table below:

Table

Mols H_2O	Mols organic solvent	Mols $FeCl_3$	Mols Fe	Mols acid	Percent conversion based on phenylnitropropene: Oxime of phenylpropanone	Percent conversion based on phenylnitropropene: Phenylpropanone
28	0	0	2	0	0.0	0.0
28	0	0.06	2	0	20.1	0.0
28	0	0	2	[1] 0.06	49.0	5.2
28	0	0.06	2	[1] 0.06	45.0	3.7
28	0	0	2	[1] 0.23	27.4	24.6
28	0	0	2	[1] 0.46	23.1	36.5
28	0	0.06	2	[1] 1.39	20.2	41.1
28	0	0.06	2	[1] 1.74	13.4	56.0
28	0	0.06	7.15	[1] 1.74	0.0	75.0
28	0	0.06	7.15	[1] 1.97	0.0	77.0
28	0	0	2	[2] 0.10	32.5	11.3
28	0	0	2	[3] 0.52	37.5	10.5
0	[4] 12.4	0.06	2	[1] 0.06	0.0	0.0
14	[4] 12.4	0.06	2	[1] 0.06	62.6	10.5
14	[5] 4.4	0.06	2	[1] 0.06	64.2	9.9
14	[5] 8.9	0.06	2	[1] 0.06	63.0	9.7

[1] Hydrochloric acid.
[2] Sulfuric acid.
[3] Acetic acid.
[4] Methyl alcohol.
[5] Ethyl alcohol.

In the second stage of our reduction process the oxime obtained in the first stage is further reduced to the amine. Any suitable means for reducing the oxime without undue hydrolysis may be employed for this purpose. Among these methods may be mentioned reduction with sodium amalgam and acetic acid, reduction with metallic sodium in alcoholic solution, and hydrogenation with a platinum, palladium or nickel catalyst. We prefer to employ hydrogenation with a nickel catalyst, and this process is illustrated in the example below:

Example II

Approximately 9 parts by weight of the oxime of phenylpropanone was dissolved in approximately 60 parts by weight of 95% ethanol, containing 5 parts by weight of a nickel catalyst, prepared by dissolving aluminum from a nickel-aluminum alloy by means of caustic alkali. The resulting mixture was sealed in a bomb under a hydrogen pressure of 1880 lbs. per sq. in. and reduction was effected for a period of 3⅓ hrs. at a temperature of 25° C., at the conclusion of which period the pressure was found to have dropped to approximately 1680 lbs. per sq. in. The pressure was then released and the catalyst removed by filtration. The filtrate was acidified with concentrated hydrochloric acid and the product was recovered by crystallization as the hydrochloride of 1-phenyl-2-amino-propane (melting point 144–146° C.). A conversion of 78%, based on the original oxime was obtained.

It is to be understood, of course, that the above examples are merely illustrative and do not limit the scope of our invention. Although our invention is particularly adapted to the production of 1-phenyl-2-aminopropane ("Benzedrine"), any of the arylnitroalkenes of the type

$$\mathrm{AR{-}CH{=}\underset{\displaystyle NO_2}{\underset{|}{C}}{-}R}$$

may be reduced in accordance with our process. In this formula AR may represent any aryl group, but preferably phenyl or substituted phenyl, and R may represent any alkyl group. It will be apparent to those skilled in the art that the procedures employed in the above examples could be modified in numerous respects, and the use of any such modifications or any equivalents which would naturally occur to those skilled in the art is to be considered within the scope of our invention.

Our invention now having been described, what we claim is:

1. In a process for the reduction of an arylnitroalkene of the type

$$AR-CH=\underset{\underset{NO_2}{|}}{C}-R$$

in which AR represents an aryl group and R represents an alkyl group, the step which comprises subjecting said nitroalkene, in the presence of water, to the reducing action of iron.

2. In a process for the reduction of an arylnitroalkene of the type

$$AR-CH=\underset{\underset{NO_2}{|}}{C}-R$$

in which AR represents an aryl group and R represents an alkyl group, the step which comprises subjecting said nitroalkene, in the presence of water and an iron salt, to the reducing action of iron.

3. In a process for the reduction of an arylnitroalkene of the type

$$AR-CH=\underset{\underset{NO_2}{|}}{C}-R$$

in which AR represents an aryl group and R represents an alkyl group, the step which comprises subjecting said nitroalkene, in the presence of water and a water-miscible organic solvent, to the reducing action of iron.

4. In a process for the reduction of an arylnitroalkene of the type

$$AR-CH=\underset{\underset{NO_2}{|}}{C}-R$$

in which AR represents an aryl group and R represents an alkyl group, the step which comprises subjecting said nitroalkene, in the presence of water, to the reducing action of iron and an acid.

5. In a process for the reduction of an arylnitroalkene of the type

$$AR-CH=\underset{\underset{NO_2}{|}}{C}-R,$$

in which AR represents an aryl group and R represents an alkyl group, the step which comprises subjecting said nitroalkene, in the presence of water, to the reducing action of iron and a mineral acid.

6. In a process for the reduction of an arylnitroalkene of the type

$$AR-CH=\underset{\underset{NO_2}{|}}{C}-R$$

in which AR represents an aryl group and R represents an alkyl group, to form primarily the oxime of the corresponding ketone, the step which comprises subjecting the said nitroalkene to the reducing action of iron in an aqueous medium having an acid content not substantially greater than 0.06 equivalent of acid per mole of nitroalkene.

7. In a process for the reduction of 1-phenyl-2-nitropropene, the step which comprises subjecting said 1-phenyl-2-nitropropene, in the presence of water, to the reducing action of iron and an acid.

8. In a process for the reduction of 1-phenyl-2-nitropropene to form primarily the oxime of phenylpropanone, the step which comprises subjecting said 1-phenyl-2-nitropropene to the reducing action of iron in an aqueous organic solvent medium having an acid content not substantially greater than 0.06 equivalent of acid per mole of 1-phenyl-2-nitropropene.

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