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MAKING N-SULFONYLUREAS

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As a general rule urea derivatives of aromatic sulfonic acids which are substituted at the nitrogen cannot be prepared in the simple manner of a reaction of ureas upon sulfonylchlorides, as it is the case in obtaining the corresponding urea derivatives of the organic carboxylic acids. It is true that hydrogen chloride is split off during the reaction, if we attempt such a reaction between urea and sulfonylchloride; still we do not obtain the sulfonylurea, but merely sulfonic acids alongside of products derived from urea by splitting off water, or products of polymerisation thereof, such as dicyandiamide.

The desired N-sulfonylurea may be expressed by the formula:

$$Aryl—SO_2—NR_1—CO—NH—R_2$$

wherein aryl is an unsubstituted or substituted aromatic nucleus or condensed aromatic system, and R_1 and R_2 are hydrogen, alkyl, aralkyl or aryl radicals.

This invention is based upon the surprising discovery, that a product of said formula may be readily and easily obtained by starting from N-sulfonylamides of the formula:

$$Aryl—SO_2—NH—R_1$$

and by subjecting them to a treatment by the same methods which are commonly used for converting amides into ureas. The agents used in these methods are cyanic acid, isocyanic acid in the form of its esters, or compounds which change during the reaction into cyanic or isocyanic acid or from which these compounds are split off, e.g. nitrourea, urea, urethane and the like. Since the reaction is comparable to that of amines, it is more particularly rendered surprising by the acid character of the sulfamides on account of which salts of the cyanic acid or of the nitrourea may also be used, or basic compounds or acid binding salts like carbonate of soda may be present. In that case and provided also that a hydrogen atom is linked to the nitrogen atom neighbouring the sulfonyl group, the salts of the N-sulfonylureas, which react substantially neutral in watery solution, may be immediately obtained.

In the end there reactions take place according to the following formulae:

$$Aryl—SO_2—NH—R_1+(CON)—R_2= Aryl—SO_2—NR_1—CO—NH—R_2$$

In case R_1 is hydrogen, and potassium cyanate is the cyanic acid derivative used, the following course of reaction may be suggested:

(1) $$Aryl—SO_2—NH_2+KOCN= Aryl—SO_2—NK—CO—NH_2$$

For nitrourea-sodium:

(2) $$Aryl—SO_2—NH_2+H_2N—CO—NNa—NO_2= Aryl—SO_2—NNa—CO—NH_2+N_2O+H_2O$$

For urethane:

(3) $$Aryl—SO_2—NH_2+H_2N—CO—O—Alkyl= Aryl—SO_2—NH—CO—NH_2+Alkyl—OH$$

wherein alkyl stands for an alkyl-radical.

For urea:

(4) $$Aryl—SO_2—NH_2+H_2N—CO—NH_2= Aryl—SO_2—N(NH_4)—CO—NH_2.$$

For isocyanic acid ester:

(5) $$Aryl—SO_2—NH_2+O=C=N—R_2= Aryl—SO_2—NH—CO—NH—R_2.$$

Generally speaking the reaction is preferably carried out under heat, e.g. at temperatures between 60°–100° C.

If the resulting N-sulfonylureas still carry hydrogen at the nitrogen atom which adjoins the sulfonyl group, they are strongly acid compounds which yield neutral alkali salts and are therefore most readily soluble in soda. If that is not the case, they are neutral compounds.

Compounds of this invention may be used for technical as well as medicinal purposes. Of particular value are compounds, which have an amino group in p-position to the SO_2-group on the aromatic sulfonyl nucleus and also carry a hydrogen atom on the nitrogen atom which is linked to the sulfonyl radical. These compounds serve as remedies for infectious diseases. The amino group may either be present as such, as illustrated by example 7, or it may be introduced as an acylated group together with the sulfonic acid component (examples 3 to 6) to be subsequently made free by saponification, or as a nitro-group, which is reduced to an amino group after the urea compound has been prepared.

Example 1

50 gr of benzenesulfamide and 28 gr of potassium cyanate are boiled in alcohol (80–90%), until a test shows complete solubility in water. That means that the potassium salt of the benzenesulfonylurea has been formed, which may be recrystallized as such from water, possibly under addition of potassium carbonate in order to reduce the solubility. When dissolved in water

and acidulated by glacial acetic acid, the free benzenesulfonylurea is presipitated with a yield of about 90% and shows, when dry, a melting point of 170–171° C.

Example 2

50 gr of p-toluenesulfamide and 25 gr of nitrourea-sodium are gently heated in alcohol (80–90%) until the evolution of nitrous oxide is completed. The alcohol is distilled off and the residue is placed into a liberal amount of water, neutralized by carbonate of soda and filtered unter suction off the starting material which has remained undissolved. A yield of approximately 80% of p-toluene-sulfonyl-N-urea crystallizes out of the filtrate after acidulation. The rest may be recovered as starting material from the portion which is not soluble in alkaline solution. By increasing the quantity of nitrourea the yield may be substantially improved. Purification of the toluenesulfonyl-urea is preferably brought about by crystallization of the potassium salt from a small quantity of water to which potassium carbonate is added. The beautiful crystals may be dissolved in water and the free urea may be precipitated from the solution by acetic acid. It decomposes when melted at 184°–188° C.

Example 3

50 gr of acetylsulfanilamide and 30 gr of Potassiumcyanate are heated several hours in 200 cc of alcohol and 20 cc of water. Upon cooling the reaction product is sucked off and weighs 70–71 gr, after drying. This represents a substantially 100% yield of the potassium salt of the p-acetylsulfanilylurea. The salt crystallizes out of water under addition of potassium carbonate in the form of beautiful, long needles. By precipitation with acetic acid the free acetylsulfanilylurea may be obtained, which decomposes at a melting point of 185°–188° C.

Example 4

A similarly satisfactory yield of acetylsulfanilyl-urea may be obtained, if 50 gr of acetylsulfanilamide, 50 gr of nitrourea and 30 gr of carbonate of soda are heated to the boiling point in 80% alcohol for 5–6 hours. After the alcohol has been boiled off, the mass is almost completely soluble in water and represents the sodium salt of the desired urea.

Example 5

	Parts
Acetysulfanilamide	5
Urea	3
Carbonate of soda	2
Alcohol	15
Water	5

are heated on a steam bath. Soon the sublimation of ammonium carbonate or—carbamate sets in, and after about 10–12 hours the reaction is approximately half complete, as recognized from the portion which has been rendered water-soluble. Further heating fully completes the reaction. A solvent of a higher boiling point, like butylalcohol, may also be used, as well as other basic compounds, such as potassium hydroxide, potassium carbonate, sodium alcoholate, or a tertiary amine, the reaction thus being in some instances materially accellerated.

Similar results are obtained with urethanes, e. g. ethylurethane, the reaction being however slower than in the case of urea.

In all these cases, the acetylsulfanilylurea is obtained which decomposes after melting at 185°–188°C. When saponified with caustic soda solution or concentrated hydrochloric acid it yields the p-aminobenzene-sulfonyl-N-urea which decomposes at its melting point of 149°–154°C.

Example 6

20 gr of acetylsulfanilamide and 12 gr of phenylisocyanate are heated for an extended period of time to 100°C. The product of reaction is washed up in water, neutralized, while hot, by a sodium carbonate solution and, after cooling, sucked off from the insoluble sediment. Acetic acid precipitates from the filtrate a thick white deposit of the free urea derivative, which is preferably crystallized by way of the potassum salt from water with addition of sodium carbonate. The potassium salt forms beautiful needles, and from these we may obtain by means of acetic acid a good yield of the N-(acetylsulfanilyl)-N'-phenylurea.

Example 7

p-Aminobenzenesulfonylcarbamide is produced as follows:

350 gr of sulfanilamide, 178 gr of potassiumcyanate (technical) and 1050 cc of denatured alcohol are boiled for 6 hours under reflux. As soon as the original mass has passed into solution, the potassium salt of the new compound starts crystallizing out until it finally forms a thick mass of crystals. The mass is sucked off while hot and again washed with the first named amount of hot 90% alcohol. Upon drying 470 gr of crystal powder are obtained. These are stirred up with 550 cc of cold water, and washed with 50 cc of a saturated potassium carbonate solution. About 450 gr of the potassium salt of the p-aminobenzenesulfonylcarbamide are obtained, i.e. 87% of the theoretical yield. The missing part is contained in the mother liquor in form of sulfanilamide and further heating with potassium cyanate will convert that part also to potassiumaminosulfonylcarbamide. The potassium salt crystallizes from water in colorless flakes, which exhibit but moderate solubility in cold water, particularly so, when potassium salts or alcohol are added. Upon dissolution in four times the amount of hot water and addition of acetic acid, the free sulfonylcarbamide is precipitated in large needles, which contain 1 mol of crystal water.

The sodium salt is readily soluble in water and completely neutral in reaction. When boiled for some time in neutral, acid or alkaline solution, the compound is hydrolized into sulfanilamide. The free acid, which contains crystal water, decomposes under effervescence at about 125°–127° C.

Other isocyanic acid esters add in like manner, or even still more readily, to sulfamides to form N'-substituted N-sulfonylureas.

Having thus given a careful outline of my invention in detail, yet I do not wish it to be limited thereby, except as the state of the art and the appended claims may require, for it is obvious that various modifications and changes may be made in the form of embodiment of my invention, without departing from the spirit and scope thereof.

Some of the subject matter herein described is dealt with or claimed in my companion patent application, Serial No. 369,117, filed December 7th 1940, for N-sulfonylureas and method of making same.

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