

The present invention relates to a novel process for the preparation of 2-alkoxybenzenesulfonamides.

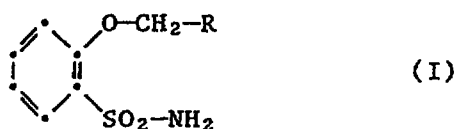
The 2-alkoxybenzenesulfonamides which can be prepared by the novel process are valuable intermediates for the synthesis of herbicidal 2-alkoxybenzenesulfonylureas. This class of highly effective herbicides has recently been described in a large number of patent applications and publications. The 2-alkoxybenzenesulfonamides which can be prepared by the process of this invention, the preparation thereof and the use thereof in the synthesis of the herbicidal final products from the class of sulfonylureas are described in European patent applications EP-A-23 422, EP-A-44 807 and EP-A-44 808.

The processes hitherto described for the preparation of alkoxybenzenesulfonamides are less suitable for large-scale industrial application since either unstable diazonium salts are obtained as intermediates and the exchange reaction of the Sandmeyer type with Cu(I) compounds has only an insufficient degree of selectivity or product mixtures are formed which require complicated separation methods.

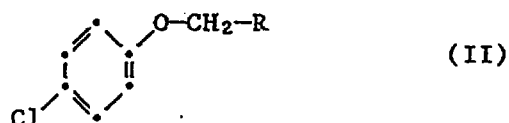
There is therefore a need for an inexpensive process for the preparation of 2-alkoxybenzenesulfonamides, which can be carried out on a large industrial scale.

Surprisingly, the novel process of this invention substantially meets that requirement.

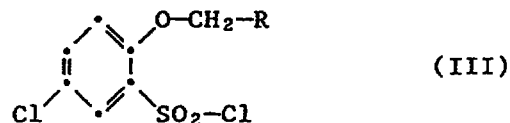
In accordance with the present invention, it is proposed to prepare the 2-alkoxybenzenesulfonamides of formula I



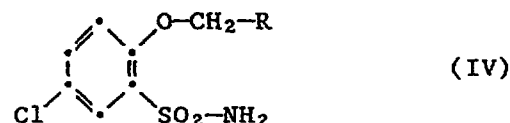
wherein R is chloromethyl, methoxymethyl, C₁-C₄alkyl or trifluoromethyl, by reacting a 4-alkoxychlorobenzene of formula II



wherein R is as defined for formula I, with chlorosulfonic acid ClSO₃H, converting the resultant sulfonyl chloride of formula III



wherein R is as defined for formula I, by reaction with ammonia into the sulfonamide of formula IV



wherein R is as defined for formula I, and hydrogenating said sulfonamide with hydrogen, in the presence of a noble metal catalyst.

In the above definitions, alkyl is methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl.

The reaction product of formula I can be converted directly into an agriculturally useful active ingredient of the class of sulfonylureas in a manner known per se by reaction with a suitable pyrimidinylcarbamate or triazinylcarbamate or with a corresponding isocyanate. As an alternative to this process, the 2-alkoxybenzenesulfonamides of formula I are first converted into the corresponding isocyanates or carbamates which are then reacted with suitable pyrimidinylamines or triazinylamines to give sulfonylureas effective in plants.

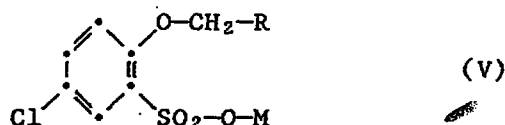
The starting materials of formula II are known and can be obtained by simple etherification reactions from 4-chlorophenol.

Commercially available chlorosulfonic acid is used for carrying out the first step (II→III) of the process of this invention. To effect reaction, at least 3 mol of chlorosulfonic acid are used per mole of the compound of formula II. It is advantageous to employ a larger excess of chlorosulfonic acid, e.g. at least 5 mol of chlorosulfonic acid per mole of the compound of formula II. In individual embodiments, the chlorosulfonic acid may be used as reactant and solvent simultaneously. In general, however, the reaction (II→III) is carried out in an inert solvent. Suitable solvents are carbon disulfide, toluene, xylene, saturated hydrocarbons such as hexane, decane or cyclohexane, and chlorinated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride, 1,2-dichloroethane, 1,2-dichloroethylene, tetrachloroethylene, chlorobenzene or dichlorobenzene. The preferred solvents are cyclohexane, n-decane, methylene chloride, 1,2-dichloroethane and chloroform. The reaction temperatures are usually in the range from -10°C to +100°C, preferably from -10°C to +80°C.

In a preferred embodiment of the first reaction step (II→III), the compounds of formula III are prepared by reacting the corresponding compound of formula II, in an inert solvent and at a temperature in the range from -10°C to +100°C, with at least 3 times the equimolar amount of chlorosulfonic acid. A particularly preferred embodiment

comprises carrying out the reaction (II→III) at a temperature in the range from -10°C to +80°C, in methylene chloride, 1,2-dichloroethane or chloroform, with at least 5 times the equimolar amount of chlorosulfonic acid.

The first reaction step (II→III) may also be carried out using an equimolar amount of chlorosulfonic acid, in which case an additional reaction step is necessary. The economic and ecological advantages reside in the fact that by using an equimolar amount of chlorosulfonic acid, there is no excess of chlorosulfonic acid to be worked up or neutralised. In accordance with this process variant, the compounds of formula II are reacted, at a temperature in the range from 0°C to +150°C, preferably from +20°C to +60°C, with an equimolar amount of chlorosulfonic acid or with a slight excess thereof. In this case, working up does not directly yield the sulfonyl chloride of formula III, but neutralisation of the reaction mixture with aqueous alkali metal hydroxide, at a temperature in the range from 0°C to +100°C, preferably from 50°C to 90°C, yields the corresponding sulfonic acid alkali metal salt of formula V



wherein R is as defined for formula I and M is a sodium or potassium atom. This reaction is advantageously carried out in an inert solvent such as an alkane or chloroalkane. In favourable cases, e.g. if all reaction components are liquid at the selected reaction temperature, a solvent can be dispensed with and the reaction can be carried out with the pure reactants. Solvents of the above-mentioned type are pentane, hexane, heptane, octane, decane, dodecane, and also cyclopentane or cyclohexane, as well as methylene chloride, chloroform, carbon tetrachloride, dichloroethane, trichloroethane or tetrachloroethane. Cyclohexane and n-decane are preferred.

The compound of formula V is converted into the sulfonyl chloride of formula III by reaction with customary chlorinating agents such as phosphorus oxychloride, thionyl chloride or, preferably, phosgene. It is advantageous to use a catalyst such as dimethylformamide or dimethylacetamide. The reaction conditions for the genesis of the sulfonyl chloride from the free acid or alkali metal salt ($V \rightarrow III$) correspond to the usual conditions for this type of reaction. The exclusion of moisture and neutrality of the solvent are essential features. Such conditions are indicated above in the description of the direct preparation of the sulfonyl chloride ($II \rightarrow III$). Preferred reaction temperatures are in the range from 60°C to 120°C .

The conversion of the sulfonyl chloride of formula III into the corresponding sulfonamide of formula IV is effected under the conditions usual for this per se known reaction step, for example by adding an aqueous solution of ammonia to the compound of formula III, under normal pressure and at a temperature in the range from 0°C to $+100^{\circ}\text{C}$, preferably from 0°C to $+30^{\circ}\text{C}$; or by treating a compound of formula III with ammonia, in an inert solvent, optionally in the presence of an acid acceptor. Examples of solvents and acid acceptors are: carbonates such as sodium carbonate and potassium carbonate, bicarbonates such as sodium bicarbonate and potassium bicarbonate, oxides such as calcium oxide and magnesium oxide, or hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide or magnesium hydroxide; ethers such as diethyl ether, tetrahydrofuran, dioxane, ethylene glycol dimethyl ether or diethylene glycol dimethyl ether; ketones such as acetone, 2-butanone, 3-pentanone or cyclohexanone; chlorinated hydrocarbons such as chlorobenzene, dichlorobenzene, methylene chloride, chloroform, carbon tetrachloride, trichloroethane or tetrachloroethane; secondary alcohols such as 2-butanol, isopropanol or cyclohexanol; or hydrocarbons such as cyclohexane, benzene, toluene or xylene. The reaction is preferably carried out with an aqueous solution of ammonia in the presence of toluene or xylene.

The dechlorination of the compound of formula IV to give the compound of formula I by catalytic hydrogenation with hydrogen is generally carried out under mild conditions, in the temperature range from 20°C to 70°C, in the pressure range from 1 to 5 bar, preferably from 1 to 1.5 bar, in an inert solvent and in the presence of an acid acceptor. In general, the catalysts employed are noble metal catalysts such as platinum in the form of platinum oxide or palladium, platinum black or platinum on barium sulfate, palladium black or palladium on carbon. The catalyst which can be most widely used is palladium on carbon in commercially available form as 5 % palladium on carbon. Acid acceptors normally employed are: hydroxides such as sodium hydroxide or potassium hydroxide, metal salts of carboxylic acids, e.g. sodium acetate, salts of phosphoric acid, e.g. disodium phosphate, bicarbonates, oxides such as magnesium oxide or calcium oxide, as well as, preferably, tertiary organic amines such as trimethylamine, triethylamine, diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, pyridine, quinoline or isoquinoline. These bases are either added to the reaction mixture continuously in order to maintain a constant pH-value, or preferably the required amount is placed in the reaction vessel

at the outset. Suitable solvents are: ethers such as diethyl ether, tetrahydrofuran or dioxane; ketones such as acetone, 2-butanone or cyclohexanone; esters such as ethyl acetate; alcohols such as methanol, ethanol, n-propanol, isopropanol or butanol; and hydrocarbons such as pentane, hexane, cyclohexane, benzene, toluene or xylene; or water. In the preferred embodiment, the compound of formula IV is hydrogenated with hydrogen, under normal pressure, in the temperature range from 50°C to 55°C and in the presence of a 5 % palladium on carbon catalyst in a mixture of 2-butanone, base and water.

A preferred embodiment of the process of this invention for the preparation of compounds of formula I comprises reacting a compound of formula II, at a temperature in the range from -20°C to +60°C and in n-decane, with an equimolar amount of chlorosulfonic acid;

neutralising the reaction mixture with alkali metal hydroxide, at a temperature in the range from 50°C to 90°C; adding phosgene to the resultant sulfonic acid alkali metal salt of formula V, in xylene and at a temperature in the range from 60°C to 120°C; treating the resultant sulfonyl chloride of formula III with an aqueous solution of ammonia, in the presence of toluene or xylene; and dechlorinating the resultant sulfonamide of formula IV by catalytic hydrogenation with hydrogen, in a 2-butanone/water/base mixture, under normal pressure, at a temperature in the range from 20°C to 70°C and in the presence of a 5 % palladium on carbon catalyst.

The intermediates of formulae III and IV wherein R is in each case chloromethyl, methoxymethyl or C₁-C₄alkyl, and the intermediates of formula V are novel. They have been specially developed for carrying out the process of this invention and therefore constitute an object of the present invention.

The present invention is illustrated in more detail by the following Examples. Example P2 shall be understood as being an alternative to the first and second reaction steps of Example P1. Example P3 may replace the last reaction step of Example P1.

Preparatory Examples:

Example P1: 2-(2-Chloroethoxy)benzenesulfonamide

a) 2-(2-Chloroethoxy)-5-chlorobenzenesulfonic acid sodium salt

With vigorous stirring, 122 g (1.05 mol) of chlorosulfonic acid are added over 2 hours, at a temperature in the range from 35°C to 40°C, to a solution of 191 g (1.00 mol) of 4-chloro-(2-chloroethoxy)benzene in 300 ml of n-decane. Hydrogen chloride gas evolves and a precipitate forms. The reaction solution is heated to +80°C, 50 ml of water are added and the mixture is neutralised to pH 7 by the addition of 160 g (1.20 mol) of a 30 % solution of sodium hydroxide. The hot aqueous phase is separated and 700 ml of xylene are added to it. The water is expelled from this mixture by distil-

lation with a water separator, whereupon the salt-like product precipitates from the xylene solution and a suspension forms. Filtration and drying affords 302 g (100 % of theory) of 2-(2-chloroethoxy)-5-chlorobenzenesulfonic acid sodium salt.

The corresponding potassium salt and the sodium or potassium salts of 2-(2-methoxyethoxy)-5-chlorobenzenesulfonic acid and 2-(2,2,2-trifluoroethoxy)-5-chlorobenzenesulfonic acid are obtained in analogous manner.

b) 2-(2-Chloroethoxy)-5-chlorobenzenesulfonyl chloride

1.5 g (0.02 mol) of dimethylformamide are added, at a temperature in the range from 85°C to 90°C, to the suspension [obtained in step (a)] of 302 g of 2-(2-chloroethoxy)-5-chlorobenzenesulfonic acid sodium salt in 700 ml of xylene. 150 g (1.51 mol) of gaseous phosgene are subsequently introduced into the mixture over 2 hours. Excess phosgene is expelled by introducing nitrogen gas for 30 minutes. 200 ml of water are added at 50°C to the mixture. The organic phase is separated and concentrated by evaporation, affording 287 g (99.2 % of theory) of 2-(2-chloroethoxy)-5-chlorobenzenesulfonyl chloride with a melting point of 94.5-95°C.

2-(2-Methoxyethoxy)-5-chlorobenzenesulfonyl chloride as an oil and 2-(2,2,2-trifluoroethoxy)-5-chlorobenzenesulfonyl chloride, m.p.: 76°C, are obtained in analogous manner.

c) 2-(2-Chloroethoxy)-5-chlorobenzenesulfonamide

142 g (2.5 mol) of a 30 % solution of ammonia are added over 2 hours, at a temperature in the range from 55°C to 60°C, to the solution [obtained in step (b)] of 287 g of 2-(2-chloroethoxy)-5-chlorobenzenesulfonyl chloride in 700 ml of xylene. A colourless crystalline precipitate forms. The temperature is held for a further 2 hours at 55°C and subsequently lowered to 0°C. The crystalline precipitate is separated and washed three times with isopropanol

(with one 150 ml portion and with two 500 ml portions). The product is dried, affording 250 g (92.6 % of theory) of 2-(2-chloroethoxy)-5-chlorobenzenesulfonamide with a melting point of 145°C.

2-(Methoxyethoxy)-5-chlorobenzenesulfonamide (m.p.: 121-123°C) and 2-(2,2,2-trifluoroethoxy)-5-chlorobenzenesulfonamide (m.p.: 142.5°C) are obtained in analogous manner.

d) In an agitator flask, a mixture consisting of 67.5 g (0.25 mol) of 2-(2-chloroethoxy)-5-chlorobenzenesulfonamide, 165 g of 2-butanone, 36 g of water, 3.4 g of 5 % palladium on carbon and 0.22 g of acetic acid is hydrogenated with hydrogen, at a temperature in the range from 50°C to 55°C under normal pressure. During the hydrogenation reaction, the pH is held constant at pH 10.5 to 11.0 by the dropwise addition of 33.5 g (0.25 mol) of a 30 % solution of sodium hydroxide. The reaction time required until the mixture is saturated with hydrogen is 45 minutes. The product is obtained by filtering the mixture and concentrating the filtrate. The yield is 58.2 g (99 % of theory) of 2-(2-chloroethoxy)benzenesulfonamide with a melting point of 119°C.

2-(2-Methoxyethoxy)benzenesulfonamide (m.p.: 111°C) and 2-(2,2,2-trifluoroethoxy)benzenesulfonamide (m.p.: 123°C) are obtained in analogous manner.

Example P2: 2-(2-Chloroethoxy)-5-chlorobenzenesulfonyl chloride

With stirring, 64.0 g (0.33 mol) of 4-chloro-(2-chloroethoxy)-benzene are added dropwise over 0.5 hours, at a temperature of +5°C, to a solution of 233 g (2 mol) of chlorosulfonic acid in 105 ml of 1,2-dichloroethane. The reaction mixture is stirred for a further 1½ hours at 20°C and then taken up in a mixture consisting of 230 g of ice, 170 ml of water and 60 ml of 1,2-dichloroethane. The organic phase is separated, washed with water and concentrated by evaporation, affording 77 g (80 % of theory) of 2-(2-chloroethoxy)-5-chlorobenzenesulfonyl chloride.

2-n-Propoxy-5-chlorobenzenesulfonyl chloride, 2-ethoxy-5-chlorobenzenesulfonyl chloride, 2-(2-methoxyethoxy)-5-chlorobenzenesulfonyl chloride and 2-(2,2,2-trifluoroethoxy)-5-chlorobenzenesulfonyl chloride are obtained in analogous manner.

Example P3: 2-(2-Chloroethoxy)benzenesulfonamide

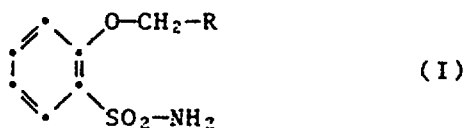
In an agitator flask 68.2 g of 2-(2-chloroethoxy)-5-chlorobenzenesulfonamide are dissolved in 184 g of 2-butanone. After the addition of 34.3 g of water, 34.3 g of a 20 % solution of sodium hydroxide and 3.4 g of 5 % palladium on carbon, the mixture is hydrogenated with hydrogen at 25°C to 30°C under normal pressure. The hydrogenation is continued for 30 minutes. The catalyst is removed by filtration. The filtrate is concentrated, yielding 58.7 g (98 % of theory) of 2-(2-chloroethoxy)benzenesulfonamide having a melting point of 119°C.

2-(2-Methoxyethoxy)benzenesulfonamide and 2-(2,2,2-trifluoroethoxy)benzenesulfonamide are obtained in analogous manner.

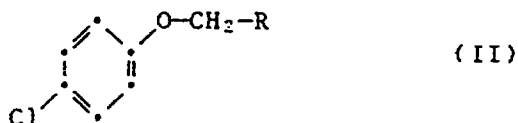


Patent Claims

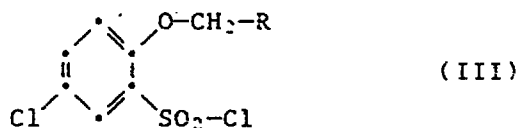
1. A process for the preparation of a 2-alkoxybenzenesulfonamide of formula I



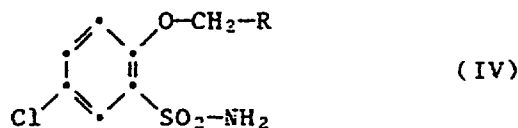
wherein R is chloromethyl, methoxymethyl, C₁-C₄alkyl or trifluoromethyl, which process comprises reacting a 4-alkoxychlorobenzene of formula II



wherein R is as defined for formula I, with chlorosulfonic acid ClSO₃H, converting the resultant sulfonyl chloride of formula III



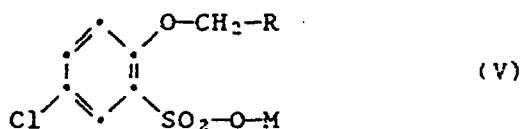
wherein R is as defined for formula I, by reaction with ammonia into the sulfonamide of formula IV



wherein R is as defined for formula I, and hydrogenating said sulfonamide with hydrogen, in the presence of a noble metal catalyst.



2. A process according to claim 1, wherein the reaction of the compound of formula II to give the compound of formula III is carried out in two steps by reacting the compound of formula II with one equivalent of chlorosulfonic acid, neutralising the reaction mixture with an aqueous solution of alkali metal hydroxide and converting the resultant sulfonic acid alkali metal salt of formula V



wherein R is as defined for formula I and M is a sodium or potassium atom, by reaction with a chlorinating agent into the sulfonyl chloride of formula III.

3. A process according to claim 1, wherein the reaction in all its stages is carried out in the temperature range from -10°C to $+100^{\circ}\text{C}$, preferably from -10°C to $+80^{\circ}\text{C}$.

4. A process according to claim 1, wherein the individual reaction steps are carried out in inert solvents.

5. A process according to claim 4, wherein the reaction of the compound of formula II to give the compound of formula III is carried out in methylene chloride, 1,2-dichloroethane or chloroform; the reaction of the compound of formula III to give the compound of formula IV is carried out in water and in the presence of toluene or xylene; and the reaction of the compound of formula IV to give the compound of formula I is carried out in a mixture of 2-butanone and water.



6. A process according to claim 1, wherein the reaction of the compound of formula II to give the compound of formula III is carried out with at least 3 moles of chlorosulfonic acid per mole of the compound of formula II, in an inert solvent and at a temperature in the range from -10°C to $+100^{\circ}\text{C}$.

7. A process according to claim 6, wherein the reaction of the compound of formula II to give the compound of formula III is carried out with at least 5 moles of chlorosulfonic acid per mole of the compound of formula II, at a temperature in the range from -10°C to $+80^{\circ}\text{C}$, in methylene chloride, 1,2-dichloroethane or chloroform.

8. A process according to claim 2, wherein the reaction of the compound of formula III to give the compound of formula IV is carried out in an aqueous solution of ammonia and in the presence of toluene or xylene.

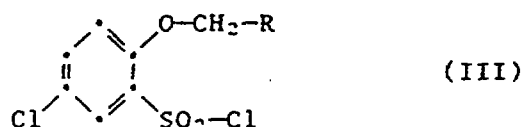
9. A process according to claim 2, wherein the dechlorination of the compound of formula IV to give the compound of formula IV is carried out with hydrogen, in the pressure range from 1 to 5 bar, at a temperature in the range from $+20^{\circ}\text{C}$ to $+70^{\circ}\text{C}$ and in the presence of a 5 % palladium on carbon catalyst in a mixture of 2-butanone, base and water.

10. A process according to claim 2, wherein the compound of formula II is reacted, at a temperature in the range from $+20^{\circ}\text{C}$ to $+60^{\circ}\text{C}$, with 1 equivalent of chlorosulfonic acid in cyclohexane or n-decane; the solution is neutralised with aqueous alkali metal hydroxide, at a temperature in the range from $+50^{\circ}\text{C}$ to $+90^{\circ}\text{C}$; and the sulfonic acid alkali metal salt of formula V is converted, at a temperature in the range from $+60^{\circ}\text{C}$ to $+120^{\circ}\text{C}$, by reaction with phosgene into the sulfonyl chloride of formula III.



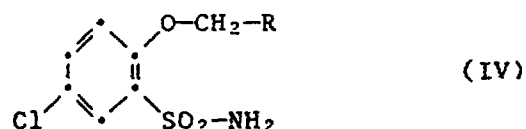
11. A process according to claim 2, wherein a compound of formula II is reacted, at a temperature in the range from +20°C to +60°C and in n-decane, with an equimolar amount of chlorosulfonic acid; the reaction mixture is neutralised with alkali metal hydroxide, at a temperature in the range from +50°C to +90°C; phosgene is added to the resultant sulfonic acid alkali metal salt of formula V, in xylene and at a temperature in the range from +60°C to +120°C; the resultant sulfonyl chloride of formula III is treated with an aqueous solution of ammonia, in the presence of toluene or xylene; and the resultant sulfonamide of formula IV is dechlorinated by catalytic hydrogenation with hydrogen, in a mixture of 2-butanone base and water, under normal pressure, at a temperature in the range from +20°C to +70°C and in the presence of a 5 % palladium on carbon catalyst.

12. A 2-alkoxy-5-chlorobenzenesulfonyl chloride of formula III



wherein R is chloromethyl, methoxymethyl or C₁-C₄ alkyl.

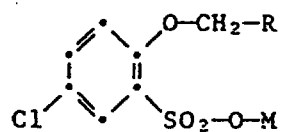
13. A 2-alkoxy-5-chlorobenzenesulfonamide of formula IV



wherein R is chloromethyl, methoxymethyl or C₁-C₄ alkyl.



14. A 2-alkoxy-5-chlorobenzenesulfonic acid alkali metal salt of formula V



(V)

wherein R is chloromethyl, methoxymethyl, C₁-C₄alkyl or trifluoromethyl and M is a sodium or potassium atom.