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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3:
C07C 41/01, 43/295, 79/355;
C07D 213/64, 239/34, 241/44

A1

(11) International Publication Number: WO 82/00638

(43) International Publication Date: 4 March 1982 (04.03.82)

(21) International Application Number: PCT/AU81/00104

(22) International Filing Date: 6 August 1981 (06.08.81)

(31) Priority Application Numbers: PE 5252
PE 8172

(32) Priority Dates: 26 August 1980 (26.08.80)
27 March 1981 (27.03.81)

(33) Priority Country: AU

(71) Applicant *(for all designated States except US)*: ICI AUSTRALIA LIMITED [AU/AU]; 1 Nicholson Street, Melbourne, Vic. 3001 (AU).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: WATSON, Keith, Geoffrey [AU/AU]; 36 Medway Street, Box Hill North, Vic. 3129 (AU).

(74) Agent: FRECKLETON, Douglas, Arthur; P.O. Box 4311, Melbourne, Vic. 3001 (AU).

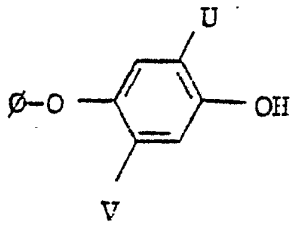
(81) Designated States: AU, CH (European patent), DE (European patent), FR (European patent), GB (European patent), JP, US.

Published
With international search report

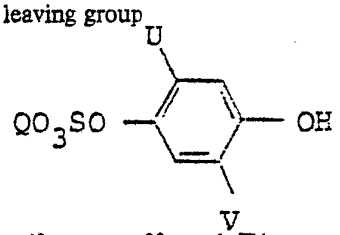
(54) Title: PROCESS FOR THE SYNTHESIS OF ARYLOXY DERIVATIVES

(57) Abstract

Process for the synthesis of compounds of formula I

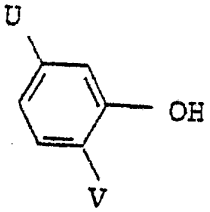


wherein Q, is a substituted or unsubstituted aryl or heteroaryl group and U and V may be chosen from a range of substituents including hydrogen, halogen, alkyl and alkoxy; the process comprising reacting a sulfate ester of formula II, wherein Q is a cation, with a compound of formula III, wherein L is a leaving group



Ø–L

and hydrolysing the sulfate ester formed. Preferably the sulfate ester of formula II is prepared by the oxidation of a phenol of formula IV with a persulfate.



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Process for the Synthesis of Aryloxy Derivatives

TECHNICAL FIELD

This invention relates to a process for the synthesis of organic compounds and in particular to a process for the synthesis of 4-(aryloxy)phenol derivatives.

BACKGROUND ART

4-(Aryloxy)phenol derivatives are useful intermediates for the synthesis of a wide range of [4-(aryloxy)phenoxy]alkane derivatives which have been shown to have herbicidal activity. In the past the required 4-(aryloxy)phenol derivatives have been prepared either:

i) by condensing the appropriate 4-alkoxyphenol with the appropriate aryl derivatives to give a [4-(alkoxy)phenoxy]aryl derivative and then cleaving the alkyl residue from the 4-alkoxy group; or

ii) by condensing the appropriate hydroquinone with the appropriate aryl derivative.

However, both of these processes suffer the disadvantage of using relatively expensive hydroquinone

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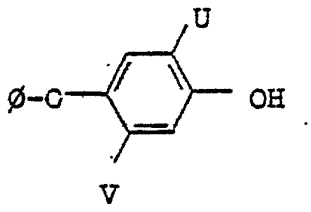
(derivatives) and the first process suffers the additional disadvantage of requiring the use of relatively expensive reagents to cleave the alkyl residue from the 4-alkoxy group.

DISCLOSURE OF INVENTION

It has now been found that 4-(aryloxy)phenol derivatives may be prepared from the appropriate phenol obviating the need to use a hydroquinone or a 4-alkoxyphenol.

Accordingly the invention provides a process for the synthesis of a compound of formula I



I

wherein Ø is an aryl group, a heteroaryl group, a substituted aryl group, or a substituted heteroaryl group; and

U and V are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, thiocyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_2 to C_6 haloalkenyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, carboxy, (C_1 to C_6 alkoxy)carbonyl, phenyl, phenoxy, phenylthio and the groups substituted phenyl, substituted phenoxy and substituted phenylthio wherein in each group the phenyl ring is substituted with from 1 to 3 substituents chosen from the group consisting of halogen, nitro, cyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy;

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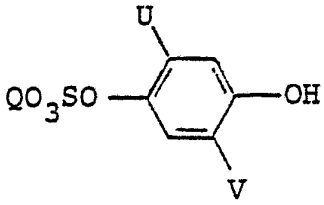
which process is characterised in that it comprises the following steps in sequence:

a) reacting a sulfate ester of formula II,



II

wherein Q is a cation, with a compound of formula III,

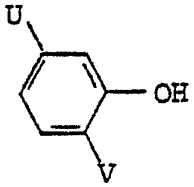
$$Ø\text{-}L \qquad \text{III}$$

wherein L is a leaving group; and

b) hydrolysing the sulfate ester formed in step a) to give a compound of formula I.

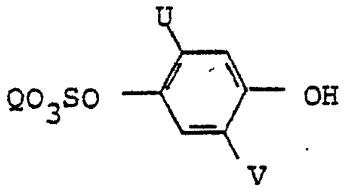
The sulfate ester of formula II may be readily formed by oxidation of a phenol with persulfuric acid or a salt thereof. Accordingly, in a preferred embodiment the invention provides a process for the synthesis of a compound of formula I as hereinbefore defined which process comprises:

i) oxidizing a compound of formula IV



IV

with persulfuric acid or a salt thereof to form a sulfate ester of formula II,



II

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wherein Q is a cation; and

ii) which process is characterised by the following steps in sequence:

a) reacting the sulfate ester of formula II with a compound of formula III,

$$\text{Ø-L} \qquad \text{III}$$

wherein L is a leaving group; and

b) hydrolysing the sulfate ester formed in step a) to give a compound of formula I.

The nature of the cation Q in the compound of formula II is not critical. Suitable Q include the hydrogen ion, the alkali and alkaline earth metal ions and the ammonium ion.

The nature of the leaving group L in the compound of formula III is not critical. For example, suitable leaving groups may be chosen from halogen, nitro, C_1 to C_6 alkylthio, C_1 to C_6 alkylsulfonyl, C_1 to C_6 haloalkylsulfonyl, aryloxy such as phenoxy, arylthio such as phenylthio, arylsulfonyl such as benzenesulfonyl, aralkylsulfonyl such as benzylsulfonyl, alkarylsulfonyl such as p-toluenesulfonyl, C_1 to C_6 alkylsulfonyloxy, C_1 to C_6 haloalkylsulfonyloxy, arylsulfonyloxy such as benzenesulfonyloxy, aralkysulfonyloxy such as benzylsulfonyloxy, alkarylsulfonyloxy such as p-toluenesulfonyloxy, C_1 to C_6 alkylsulfonamido, C_1 to C_6 haloalkylsulfonamido and the group $-\overset{\oplus}{N}R^{10}R^{11}R^{12}X^{\ominus}$ wherein R^{10}, R^{11} and R^{12} are chosen from C_1 to C_6 alkyl, phenyl and benzyl or $-\overset{\oplus}{N}R^{10}R^{11}R^{12}$ is a heterocyclic group such as, for example, 1-methyl-1-pyrrolio, 1-methyl-1-imidazolio, 1-methyl-1-pyrrolidinio, 1-methyl-1-pyrrolinio, 1-methyl-1-imidazolinio, 1-methyl-1-piperidinio, 4-methyl-4-morpholinio, 1-pyridinio, 1-pyrazinio, 1-pyrimidinio and 1-pyridazinio, and $X^{\ominus}$ is a

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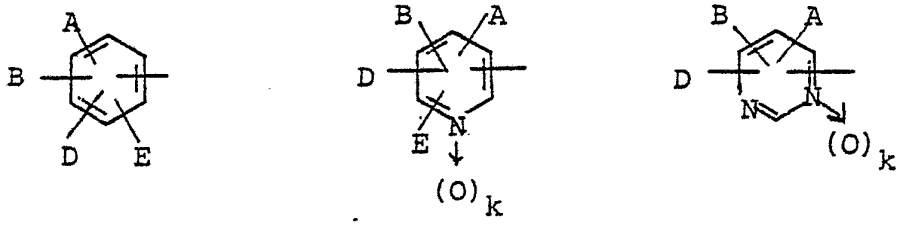
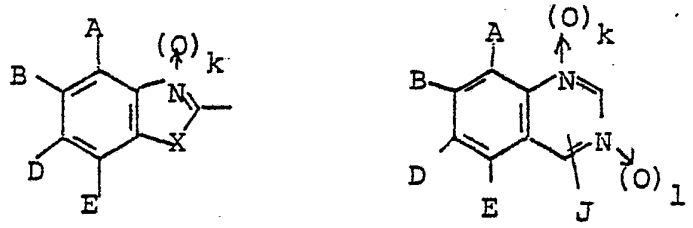
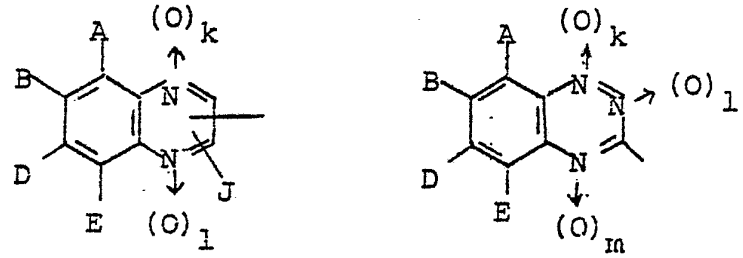
suitable anion including the anions of strong acids such as, for example, hydrochloric acid, hydrobromic acid, hydriodic acid, tetrafluoroboric acid, hexafluorophosphoric acid, hexafluoroantimonoic acid, methanesulfonic acid, fluorosulfonic acid, fluoromethanesulfonic acid and trifluoromethanesulfonic acid.

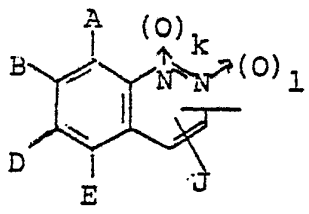
In the compound of formula I:

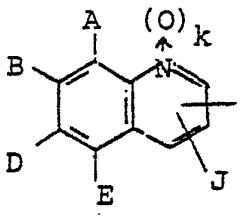
Preferred Ø include aryl and heteroaryl groups of the formula:











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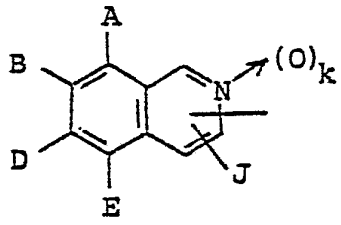

wherein A, B, D, E and J are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, thiocyano, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_3 to C_7 cycloalkyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, C_1 to C_6 alkylsulfinyl, C_1 to C_6 alkylsulfonyl, C_1 to C_6 haloalkylsulfinyl, C_1 to C_6 haloalkylsulfonyl, sulfo, C_1 to C_6 alkoxysulfonyl, sulfamoyl, N-(C_1 to C_6 alkyl)-sulfamoyl, N,N-di(C_1 to C_6 alkyl)sulfamoyl, carboxy, (C_1 to C_6 alkoxy)carbonyl, carbamoyl, N-(C_1 to C_6 alkyl)carbamoyl, N,N-di(C_1 to C_6 alkyl)carbamoyl, phenyl, phenoxy, phenylthio, and the groups substituted phenyl, substituted phenoxy and substituted phenylthio wherein in each group the phenyl ring is substituted with from 1 to 3 substituents chosen from the group consisting of halogen, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_1 to C_6 alkoxy, nitro and cyano;

X is chosen from the group consisting of oxygen, sulfur and NR^1 wherein R^1 is chosen from hydrogen and C_1 to C_6 alkyl;

k, l and m are independently chosen from 0 and 1 provided that k + l + m is 0, 1 or 2.

Preferred A, B, D and E include hydrogen, halogen, nitro, cyano, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, carboxy and C_1 to C_6 alkoxycarbonyl. More preferred A, B, D and E include

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hydrogen, halogen, nitro and trifluoromethyl.

Preferred J include hydrogen, halogen, nitro, cyano, C_1 to C_6 alkyl and C_1 to C_6 haloalkyl. More preferred J include hydrogen and halogen.

Preferred X include oxygen, sulfur and NR^1 wherein R^1 is hydrogen or methyl. More preferred X include oxygen and sulfur.

Preferred k, l and m are 0 or 1 wherein k + l + m is 0 or 1. More preferred k, l and m are 0.

Preferred U and V include hydrogen, halogen, nitro, cyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, and C_1 to C_6 alkoxy. More preferred U and V include hydrogen and halogen.

In the compound of formula II preferred Q include the alkali metals such as, for example, sodium and potassium, and ammonium.

In the compound of formula III preferred L include the halogen atoms chlorine, bromine and iodine, methanesulfonyl, trifluoromethanesulfonyl, p-toluenesulfonyl, methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethanesulfonamido and 1-pyrimidino p-toluenesulfonate.

Step a) of the process of the invention may be carried out under a wide range of operating conditions. Preferably the reaction is carried out in the presence of an alkaline material.

Suitable alkaline materials include the alkali metal and alkaline earth metal hydroxides and carbonates such as, for example, sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate.

Step a) of the process of the invention is also preferably carried out in the presence of an organic solvent. Suitable solvents include: alcohols such as, for example, methanol, ethanol, n-propanol and iso-propanol; ketones such as, for example, acetone, methyl

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ethyl ketone and methyl isobutyl ketone; and dipolar aprotic solvents such as, for example, dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methylpyrrolidone, hexamethylphosphoramide and sulfolan.

The specific reaction conditions required to effect the reaction in step a) of the process of the invention will vary with the specific reactants and solvent used. In general the reaction is facilitated by the application of heat and usually a reaction temperature in the range of from 40 to 150°C and a reaction time of between 0.5 and 20 hours is satisfactory. However, higher or lower reaction temperatures and/or shorter or longer reaction times may be employed if desired.

On completion of the reaction in step a) of the process of the invention the compound of formula I may be formed by hydrolysis of the sulfate ester according to step b) of the process of the invention. The sulfate ester formed in step a) of the process of the invention may be hydrolysed without isolation from the reaction mixture, or alternatively the sulfate ester may be isolated from the reaction mixture and then hydrolysed.

If step b) of the process of the invention is carried out without the isolation of the sulfate ester, conveniently, the compound of formula I may be formed in situ by acid hydrolysis. For example, the reaction mixture formed in step a) of the process of the invention may be acidified, for example with a mineral acid, for example, acetic acid, to hydrolyse the sulfate ester. In general the hydrolysis reaction is facilitated by the application of heat.

Alternatively, the sulfate ester formed in step a) of the process of the invention may be isolated from the reaction mixture before hydrolysis. Conveniently, the sulfate ester may be isolated by removing the

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solvent from the reaction mixture formed in step a) of the process of the invention. For example, if step a) of the process of the invention was carried out in aqueous solution the reaction mixture may be extracted with a water-immiscible organic solvent, optionally after acidification of the reaction mixture, to remove any unreacted compound of formula III from the reaction mixture. The solvent may then be removed from the aqueous solution, for example by distillation, distillation under reduced pressure, evaporation or freeze-drying, and the sulfate ester may be purified as required. The sulfate ester may then be hydrolysed to form a compound of formula I, for example, by hydrolysis with an aqueous mineral acid such as hydrochloric acid or an organic acid such as acetic acid.

Preferably, the sulfate ester of formula II which is used in step a) of the process of the present invention is formed by the oxidation of a phenol of formula IV with persulfuric acid or a salt thereof. The oxidation may be carried out under a wide range of operating conditions. However, preferably the oxidation is carried out in aqueous alkaline solution using a salt of persulfuric acid. Suitable bases include the alkali metal and alkaline earth metal oxides, hydroxides and carbonates. Suitable salts of persulfuric acid include the ammonium salt and the alkali metal salts such as sodium persulfate and potassium persulfate. Conveniently, the compound of formula IV is dissolved in an aqueous alkaline solution and the oxidizing agent is added slowly to the solution which is maintained at or below ambient temperature during the addition.

On completion of the oxidation process the sulfate ester of formula II may be reacted directly, without isolation, with the compound of formula III or alternatively the sulfate ester may be isolated from the

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reaction mixture and then reacted with the compound of formula III.

If the step a) of the process of the invention is carried out without isolation of the sulfate ester, conveniently, the compound of formula III may be simply added to the oxidation reaction mixture and step a) of the process may be carried out in the reaction mixture formed in the oxidation process. If desired, any unreacted compound of formula IV may be removed from the oxidation reaction mixture before carrying out step a) of the process of the invention by, for example, acidifying the aqueous reaction mixture formed (eg by the addition of an acid or carbon dioxide) and extracting the aqueous acid solution with a relatively polar, water-immiscible organic solvent. Any unreacted compound of formula IV extracted into the organic solvent may be recovered and recycled.

Alternatively, the sulfate ester of formula II formed in the oxidation process may be isolated before reaction with the compound of formula III. Conveniently, the sulfate ester may be isolated by removing the solvent from the reaction mixture formed in the oxidation process and extracting the sulfate ester from the residue. For example, the aqueous reaction mixture formed may be acidified (eg by the addition of an acid or carbon dioxide) and extracted with a relatively polar, water-immiscible organic solvent to remove any unreacted compound of formula IV from the reaction mixture. The aqueous phase may then be made basic, for example made alkaline to litmus with sodium hydrogen carbonate. The solvent may then be removed from the alkaline solution, for example by distillation, distillation under reduced pressure, evaporation or freeze-drying, and the sulfate ester may then be extracted from the residue. The solvent used to extract

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the sulfate ester from the residue will depend to a large extent on the solubility properties of the sulfate ester. However, in general the solvent used will be a polar organic solvent, such as, for example, ethanol or acetone, in order to effect maximum recovery of the sulfate ester combined with as small an amount of inorganic salts as possible. After extraction of the sulfate ester, the sulfate ester containing solution may be used directly in step a) of the process of the invention or the sulfate ester may be separated for example by removal of the solvent, and further purified as required.

The process of the invention may be used for the preparation of a wide range of 4-(aryloxy)phenols of formula I. For example:

4-[(5-chloropyrimid-2-yl)oxy]phenol may be prepared by reacting a 4-hydroxyphenylsulfate salt with a 2-substituted-5-chloropyrimidine, such as 5-chloro-2-methanesulfonylpyrimidine, and hydrolysing the sulfate ester formed;

4-(2-nitro-4-trifluoromethylphenoxy)phenol may be prepared by reacting a 4-hydroxyphenylsulfate salt with a 4-substituted-3-nitrobenzotrifluoride, such as 4-chloro-3-nitrobenzotrifluoride, and hydrolysing the sulfate ester formed;

4-[(6-chloroquinoxalin-2-yl)oxy]phenol may be prepared by reacting a 4-hydroxyphenylsulfate salt with a 2-substituted-6-chloroquinoxaline, such as 2,6-dichloroquinoxaline, and hydrolysing the sulfate ester formed;

4-[(5-trifluoromethylpyridin-2-yl)oxy]phenol may be prepared by reacting a 4-hydroxyphenylsulfate salt with a 2-substituted-5-trifluoromethylpyridine, such as 2-chloro-5-trifluoromethylpyridine, and hydrolysing the sulfate ester formed;

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4-(2,4-dichlorophenoxy)phenol may be prepared by reacting a 4-hydroxyphenylsulfate salt with a 2-substituted-2,4-dichlorobenzene such as 1-bromo-2,4-dichlorobenzene, and hydrolysing the sulfate ester formed; and

4-(4-trifluoromethylphenoxy)phenol may be prepared by reacting a 4-hydroxyphenylsulfate salt with a 4-substituted-benzotrifluoride, such as 4-chlorobenzotrifluoride, and hydrolysing the sulfate ester formed.

In the preferred process of the invention the 4-hydroxyphenylsulfate salt used in the foregoing reactions is prepared by the oxidation of phenol using a salt of persulfuric acid.

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MODES OF CARRYING OUT THE INVENTION

The invention is now illustrated by, but in no way limited to, the following Examples.

Example 1

Preparation of 4-/(5-chloropyrimid-2-yl)oxy/phenol

A solution of ammonium persulfate (8.0 g; 35 mmole) in water (30 ml) was added dropwise to a stirred solution of phenol (3.2 g; 35 mmole) in aqueous 10% sodium hydroxide (70 ml) which was maintained at or below a temperature of 20°C throughout the addition. On completion of the addition the solution was allowed to stand overnight at a temperature of 15 to 20°C. 5-Chloro-2-methanesulfonylpyrimidine (6.0 g; 30 mmole) was added and the reaction mixture was heated under reflux for a period of 1.5 hours. After cooling the reaction mixture was extracted with diethyl ether (2 x 100 ml). The aqueous phase was then made acidic to litmus by the addition of concentrated hydrochloric acid (10 ml). The reaction mixture was heated under reflux for a period of 1 hour. After cooling the reaction mixture was extracted with ethyl acetate (4 x 100 ml), the combined organic extracts were dried (over anhydrous magnesium sulfate), and the solvent was removed by distillation under reduced pressure. The residue was purified by chromatography over silica gel (eluent ethyl acetate) to give 4-/(5-chloropyrimid-2-yl)oxy/phenol (2.0 g).

The product was characterised by comparison with an authentic sample of 4-/(5-chloropyrimid-2-yl)-oxy/phenol. The pmr spectrum of the product was identical with the pmr spectrum of the authentic sample and the chromatographic behaviour of the product on thin-layer chromatography was identical with that of the authentic sample.

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Example 2

Preparation of 4-(2-nitro-4-trifluoromethylphenoxy)-phenol

A solution of ammonium persulfate (8.0 g; 35 mmole) in water (30 ml) was added dropwise to a stirred solution of phenol (3.2 g; 35 mmole) in aqueous 10% sodium hydroxide (70 ml) which was maintained at or below a temperature of 20°C throughout the addition. On completion of the addition the solution was allowed to stand overnight at a temperature of 15 to 20°C. The solution was made acidic (to Congo red) by the addition of concentrated hydrochloric acid and the acidic solution was extracted with diethyl ether (2 x 500 ml). The aqueous phase was separated, made alkaline to litmus with aqueous sodium hydroxide solution and the water was removed by evaporation under reduced pressure. The residue was acidified and extracted with aqueous 90% ethanol (200 ml). The aqueous ethanolic solution was made alkaline and was heated under reflux while 4-chloro-3-nitobenzotrifluoride (8.0 g; 35 mmole) was added dropwise. After heating under reflux for a period of 2 hours the hot solution was made acidic by the addition of concentrated hydrochloric acid and stirred overnight at room temperature. The solvent was removed by distillation under reduced pressure and the residue was partitioned between water and dichloromethane. The organic phase was separated, dried over anhydrous magnesium sulfate, and the solvent was removed by distillation under reduced pressure. The residue was chromatographed over silica gel (eluent dichloromethane) to give 4-(2-nitro-4-trifluoromethylphenoxy)phenol (0.6 g) as a pale yellow oil.

The product was characterised by comparison with an authentic sample of 4-(2-nitro-4-trifluoromethylphenoxy)phenol. The pmr spectrum of the product

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was identical with the pmr spectrum of the authentic sample and the chromatographic behaviour of the product on thin-layer chromatography was identical with that of the authentic sample.

Example 3

Preparation of 4-/(6-chloroquinoxalin-2-yl)oxy/phenol

a) Potassium 4-hydroxyphenylsulfate

A solution of potassium persulfate (27.0 g) in water (500 ml) was added dropwise over a period of 2 hours to a stirred solution of phenol (9.4 g) and sodium hydroxide (20.0 g) in water (200 ml) the reaction mixture being maintained at a temperature of 20±2°C throughout the addition. On completion of the addition the reaction mixture was stirred for a further period of 24 hours at a temperature of 20°C. An excess of carbon dioxide was passed through the reaction mixture to neutralize the base. The mixture was then extracted with diethyl ether (2 x 200 ml) and the unreacted phenol (2.7 g) was recovered from the ethereal extracts. The aqueous solution was evaporated to dryness under reduced pressure and the solid residue was extracted with an ethanol (20 parts)/water (1 part) mixture (3 x 500 ml). The combined aqueous ethanolic extracts were evaporated to dryness to give potassium 4-hydroxyphenylsulfate as a pale brown powder (10.5 g), mp 210-220°C. (Found: C, 31.7; H, 2.65; S, 13.9. $C_6H_5O_5SK$ requires: C, 31.6; H, 2.2; S, 14.0%.)

b) 4-/(6-Chloroquinoxalin-2-yl)oxy/phenol

A mixture of potassium 4-hydroxyphenylsulfate (1.14 g; prepared as described in part a) above) 2,6-dichloroquinoxaline (0.90 g), anhydrous potassium carbonate (0.70 g), dimethylformamide (5 ml) and xylene (5 ml) was heated and stirred at a temperature of 110°C for a period of 5 hours. The solvents were removed by

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distillation under reduced pressure, acetic acid (20 ml) was added to the solid residue and the mixture was heated under reflux for a period of 2 hours. The acetic acid was removed by distillation under reduced pressure and the solid residue was partitioned between water (100 ml) and ethyl acetate (2 x 200 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent was removed by distillation under reduced pressure to give the crude product (1.8 g). The product was chromatographed over silica gel with chloroform elution to give recovered 2,6-dichloroquinoxaline (0.1 g), 2-/(6-chloroquinoxalin-2-yl)oxy/phenol (0.75 g; 64% based on 2,6-dichloroquinoxaline used) as a colourless crystalline solid, mp 204-205°C.

The product was characterised by comparison with an authentic sample of 4-/(6-chloroquinoxalin-2-yl)oxy/phenol. The pmr spectrum of the product was identical with the pmr spectrum of the authentic sample and the melting points and mixed melting point of the product and the authentic sample were the same.

Example 4

Preparation of 4-/(5-trifluoromethylpyridin-2-yl)oxy/-phenol

A mixture of potassium 4-hydroxyphenylsulfate (1.14 g; prepared as described in Example 3 part a)), 2-chloro-5-trifluoromethylpyridine (0.93 g), anhydrous potassium carbonate (0.75 g), dimethylformamide (5 ml) and xylene (5 ml) was heated and stirred at a temperature of 85-90°C for a period of 4 hours. The solvents were removed by distillation under reduced pressure, acetic acid (15 ml) was added to the solid residue and the mixture was heated under reflux for a period of 2 hours. The acetic acid was removed by distillation under reduced

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pressure and the residue was partitioned between aqueous 1M sodium bicarbonate solution (100 ml) and chloroform (2 x 100 ml). The combined chloroform extracts were dried over anhydrous magnesium sulfate and the solvent was removed by distillation under reduced pressure to give the product as a pale brown oil. Chromatography over silica gel with chloroform elution gave 4-[(5-trifluoromethylpyridin-2-yl)oxy]phenol as an oil (0.35 g; 28%). Mass spectrum (m/e, %): 255 (M^+, 100); 254 (76); 227 (94).

Example 5

Preparation of 4-(2,4-dichlorophenoxy)phenol

A mixture of potassium 4-hydroxyphenylsulphate (2.0 g; prepared as described in Example 3 part a)), bromo-2,4-dichlorobenzene (2.0 g), anhydrous potassium carbonate (1.4 g), cuprous oxide (0.1 g) and pyridine (10 ml) was stirred and refluxed under an atmosphere of nitrogen for 16 hours. The pyridine was removed under reduced pressure, acetic acid (20 ml) was added to the residue and the mixture was heated under reflux for a period of 2 hours. The acetic acid was removed by distillation under reduced pressure and the residue was partitioned between 2 M aqueous sodium hydroxide (100 ml) and chloroform (50 ml). The aqueous layer was separated and acidified with hydrochloric acid and then extracted with chloroform (2 x 50 ml). The chloroform extracts were dried over anhyhdrous magnesium sulphate and the solvent was removed by distillation under reduced pressure to give the product as a brown oil (0.1 g). The 4-(2,4-dichlorophenoxy)phenol was identified by its pmr and mass spectra.

Proton magnetic resonance spectrum: ($CDCl_3$; δ in ppm) 6.7, d, 1H; 6.8, s, 4H; 7.1, d of d, 1H; 7.4, d, 1H.

Mass spectrum (m/e, %): 256 (70); 254 (M^+, 100); 220

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(25), 184 (60).

Example 6

4-(4-Trifluoromethylphenoxy)phenol was prepared from 4-trifluoromethylchlorobenzene and potassium 4-hydroxyphenylsulphate following essentially the same procedure as that described in Example 5. The product a pale brown oil was characterized by its mass spectrum (m/e, %): 254 (M^+).

INDUSTRIAL APPLICABILITY

The 4-(aryloxy)phenols which may be prepared according to the process of the invention are useful intermediates for the synthesis of a wide range of herbicidal, (aryloxyphenoxy)alkane derivatives. In particular, the 4-(aryloxy)phenol derivatives which may be prepared according to the process of the invention are useful intermediates in the preparation of a number of herbicidal 2-(4-aryloxyphenoxy)propionic acid derivatives.

The process of the present invention offers a number of advantages over the prior art processes which have been used for the synthesis of such 4-(aryloxy)-phenol derivatives. In the past the required 4-(aryloxy)phenol derivatives have been prepared either:

i) by condensing the appropriate 4-alkoxyphenol with the appropriate aryl derivatives to give a /4-(alkoxy)phenoxy/aryl derivative and then cleaving the alkyl residue from the 4-alkoxy group; or

ii) by condensing the appropriate hydroquinone with the appropriate aryl derivative.

However, both of these processes suffer the disadvantage of using relatively expensive hydroquinone (derivatives). Moreover, the first process suffers the additional disadvantage of requiring the use of

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relatively expensive reagents to cleave the alkyl residue from the 4-alkoxy group while the second process suffers the additional disadvantage of possible reaction at both hydroxyl groups to give bis(aryloxy) derivatives of hydroquinones.

It will be evident to those skilled in the art that the process of the present invention offers the advantage of the utilization of relatively inexpensive phenol (derivatives) and does not suffer the disadvantages of either the use of relatively expensive reagents or the possible formation of bis(aryloxy) derivatives of hydroquinones.

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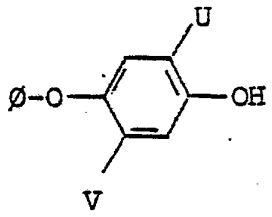
CLAIMS

1. A process for the synthesis of a compound of formula I



I

wherein Ø is an aryl group, a heteroaryl group, a substituted aryl group, or a substituted heteroaryl group; and

U and V are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, thiocyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_2 to C_6 haloalkenyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, carboxy, (C_1 to C_6 alkoxy)carbonyl, phenyl, phenoxy, phenylthio and the groups substituted phenyl, substituted phenoxy and substituted phenylthio wherein in each group the phenyl ring is substituted with from 1 to 3 substituents chosen from the group consisting of halogen,

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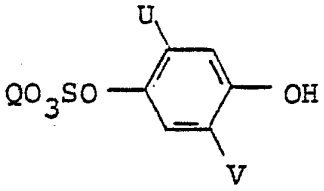
nitro, cyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy;

which process is characterised in that it comprises the following steps in sequence:

a) reacting a sulfate ester of formula II,



II

wherein Q is a cation, with a compound of formula III,

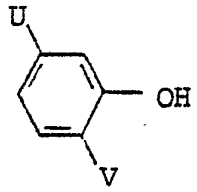
Ø-L III

wherein L is a leaving group; and

b) hydrolysing the sulfate ester formed in step a) to give a compound of formula I.

2. A process for the synthesis of a compound of formula I as defined according to claim I which process comprises:

i) oxidizing a compound of formula IV



IV

with persulfuric acid or a salt thereof to form a sulfate ester of formula II,

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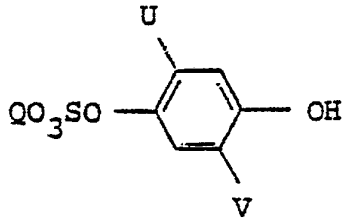

II

wherein Q is a cation; and

ii) which process is characterised by the following steps in sequence:

a) reacting the sulfate ester of formula II with a compound of formula III,

Ø-L III

wherein L is a leaving group; and

b) hydrolysing the sulfate ester formed in step a) to give a compound of formula I.

3. A process according to claim 1 wherein: step a) is carried out in the presence of a solvent and an alkaline material; and step b) is carried out using a mineral acid or an organic acid to hydrolyse the sulfate ester.

4. A process according to claim 2 wherein:

i) the oxidation of the compound of formula IV is carried out in aqueous alkaline solution using a salt of persulfuric acid as oxidant; and

ii) step a) is carried out in the presence of a solvent and an alkaline material; and step b) is carried out using a mineral acid or an organic acid to hydrolyse the sulfate ester.

5. A process according to claim 1 wherein:

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step a) is carried out in the presence of an organic solvent and an alkaline material chosen from the alkali metal and alkaline earth metal hydroxides and carbonates; and step b) is carried out using a mineral acid or an organic acid to hydrolyse the sulfate ester.

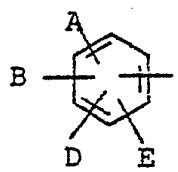
6. A process according to claim 2 wherein:

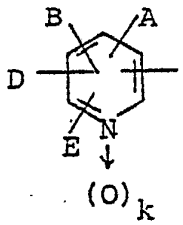
i) the oxidation of the compound of formula IV is carried out by the slow addition of a salt of persulfuric acid to an aqueous alkaline solution of the compound of formula IV; and

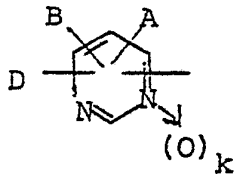
ii) step a) is carried out in the presence of an organic solvent and an alkaline material chosen from the alkali metal and alkaline earth metal hydroxides and carbonates; and step b) is carried out using a mineral acid or an organic acid to hydrolyse the sulfate ester.

7. A process according to claim 1 wherein:
in the compound of formula I

Ø is chosen from aryl and heteraryl groups of the formulae







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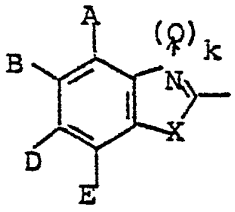

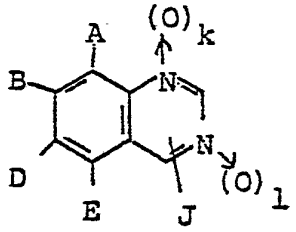

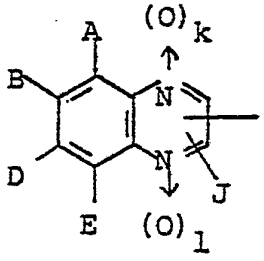

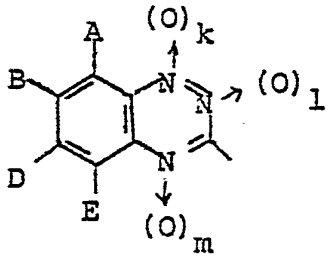

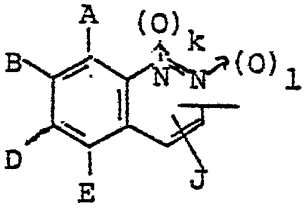

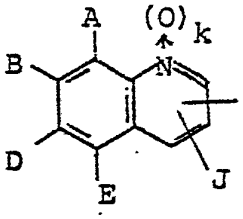

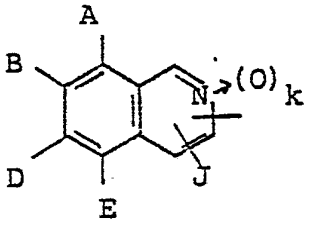

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wherein A, B, D, E and J are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, thiocyano, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_3 to C_7 cycloalkyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, C_1 to C_6 alkylsulfinyl, C_1 to C_6 alkylsulfonyl, C_1 to C_6 haloalkylsulfinyl, C_1 to C_6 haloalkylsulfonyl, sulfo, C_1 to C_6 alkoxysulfonyl, sulfamoyl, N-(C_1 to C_6 alkyl)-sulfamoyl, N,N-di(C_1 to C_6 alkyl)sulfamoyl, carboxy, (C_1 to C_6 alkoxy)carbonyl, carbamoyl, N-(C_1 to C_6 alkyl)carbamoyl, N,N-di(C_1 to C_6 alkyl)carbamoyl, phenyl, phenoxy, phenylthio, and the groups substituted phenyl, substituted phenoxy and substituted phenylthio wherein in each group the phenyl ring is substituted with from 1 to 3 substituents chosen from the group consisting of halogen, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_1 to C_6 alkoxy, nitro and cyano;

X is chosen from the group consisting of oxygen, sulfur and NR^1 wherein R^1 is chosen from hydrogen and C_1 to C_6 alkyl;

k, l and m are independently chosen from 0 and 1 provided that k + l + m is 0, 1 or 2; and

U and V are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, thiocyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_2 to C_6 haloalkenyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, carboxy, (C_1 to C_6 alkoxy)carbonyl, phenyl, phenoxy, phenylthio and the groups substituted phenyl, substituted phenoxy and substituted phenylthio wherein in each group the phenyl ring is substituted with from 1 to 3 substituents chosen from the group consisting of halogen

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nitro, cyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy;

in the compound of formula II -

Q is a cation; and

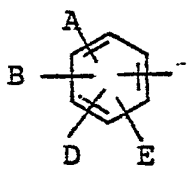
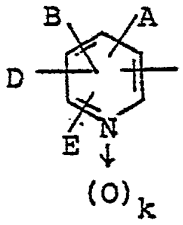
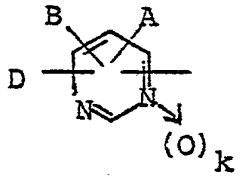
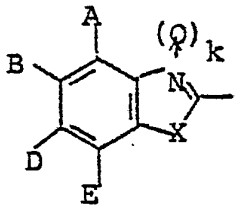
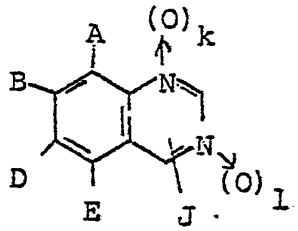
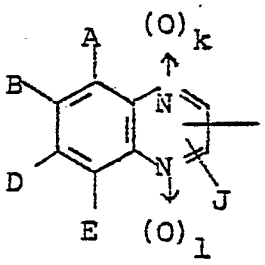
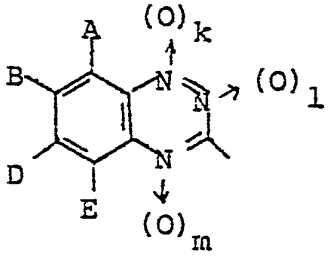
in the compound of formula III -

L is a leaving group.

8. A process according to claim 2 wherein:

in the compound of formula I -

Q is chosen from aryl and heteroaryl groups of the formulae

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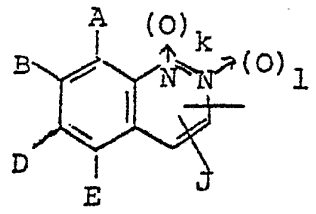
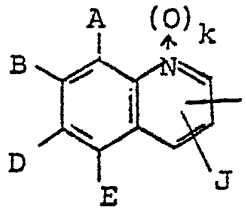

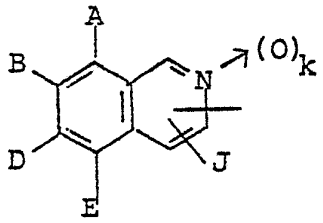

wherein A, B, D, E and J are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, thiocyano, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_3 to C_7 cycloalkyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, C_1 to C_6 alkylsulfinyl, C_1 to C_6 alkylsulfonyl, C_1 to C_6 haloalkylsulfinyl, C_1 to C_6 haloalkylsulfonyl, sulfo, C_1 to C_6 alkoxysulfonyl, sulfamoyl, N-(C_1 to C_6 alkyl)-sulfamoyl, N,N-di(C_1 to C_6 alkyl)sulfamoyl, carboxy, (C_1 to C_6 alkoxy)carbonyl, carbamoyl, N-(C_1 to C_6 alkyl)carbamoyl, N,N-di(C_1 to C_6 alkyl)carbamoyl, phenyl, phenoxy, phenylthio, and the groups substituted phenyl, substituted phenoxy and substituted phenylthio wherein in each group the phenyl ring is substituted with from 1 to 3 substituents chosen from the group consisting of halogen, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_1 to C_6 alkoxy, nitro and cyano;

X is chosen from the group consisting of oxygen, sulfur and NR^1 wherein R^1 is chosen from hydrogen and C_1 to C_6

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alkyl;

k, l and m are independently chosen from 0 and 1 provided that k + l + m is 0, 1 or 2; and

U and V are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, thiocyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_2 to C_6 haloalkenyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, carboxy, (C_1 to C_6 alkoxy)carbonyl, phenyl, phenoxy, phenylthio and the groups substituted phenyl, substituted phenoxy and substituted phenylthio wherein in each group the phenyl ring is substituted with from 1 to 3 substituents chosen from the group consisting of halogen, nitro, cyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy;

in the compound of formula II -

Q is a cation; and

in the compound of formula III -

L is a leaving group.

9. A process according to claim 7 or claim 8 wherein:

in the compound of formula I -

A, B, D and E are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl, C_2 to C_6 alkenyl, C_1 to C_6 alkoxy, C_1 to C_6 haloalkoxy, C_1 to C_6 alkylthio, carboxy and C_1 to C_6 alkoxycarbonyl;

J is chosen from the group consisting of hydrogen, halogen, nitro, cyano, C_1 to C_6 alkyl and C_1 to C_6 haloalkyl;

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X is chosen from the group consisting of oxygen, sulfur, and NR^1 wherein R^1 is hydrogen or methyl;

k, l and m are chosen from 0 and 1 wherein k + l + m is 0 or 1; and

U and V are independently chosen from the group consisting of hydrogen, halogen, nitro, cyano, C_1 to C_6 alkyl, C_1 to C_6 haloalkyl and C_1 to C_6 alkoxy;

in the compound of formula II -

Q is chosen from hydrogen, the alkali and alkaline earth metals and ammonium; and

in the compound of formula III -

L is chosen from the group consisting of chlorine, bromine, iodine, methanesulfonyl, trifluoromethanesulfonyl, p-toluenesulfonyl, methanesulfonyloxy, trifluoromethanesulfonyloxy, p-toluenesulfonyloxy, trifluoromethane sulfonamido and 1-pyrimidino p-toluenesulfonate.

10. A process according to claim 7 or claim 8 wherein:

in the compound of formula I -

A, B, D and E are independently chosen from the group consisting of hydrogen, halogen, nitro and trifluoromethyl;

J is chosen from hydrogen and halogen;

X is chosen from oxygen and sulfur;

k, l and m are 0; and

U and V are independently chosen from hydrogen and halogen;

in the compound of formula II -

Q is an alkali metal or ammonium; and

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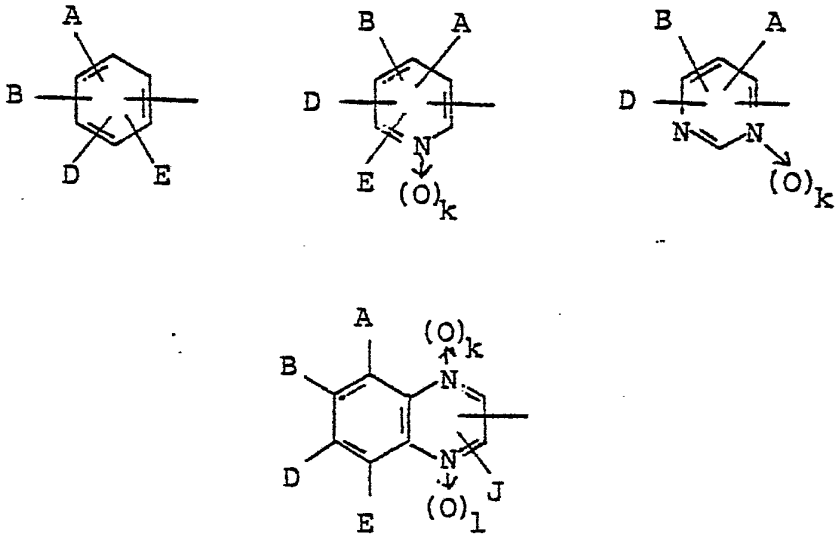
in the compound of formula III -

L is chosen from the group consisting of chlorine bromine or iodine.

11. A process according to claim 7 or claim 8 wherein:

in the compound of formula I -

Ø is chosen from



wherein A, B, D and E are independently chosen from the group consisting of hydrogen, halogen, nitro and trifluoromethyl;

J is hydrogen;

k, l and m are 0; and

U and V are hydrogen;

in the compound of formula II -

Q is chosen from sodium, potassium and ammonium; and

in the compound of formula III -

L is chosen from the group consisting of chlorine, bromine and iodine.

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12. A process according to claim 1 or claim 2 for the synthesis of a compound of formula I selected from the group consisting of 4-[(5-chloropyrimid-2-yl)oxy]-phenol, 4-(2-nitro-4-trifluoromethylphenoxy)phenol, 4-[(6-chloroquinoxalin-2-yl)oxy]phenol, 4-[(5-trifluoromethylpyridin-2-yl)oxy]phenol, 4-(2,4-dichlorophenoxy)phenol and 4-(4-trifluoromethylphenoxy)-phenol.

13. A compound of formula I synthesised according to the process of claim 1 or claim 2.

DATED this day of 1981

ICI AUSTRALIA LIMITED

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INTERNATIONAL SEARCH REPORT

International Application No PCT/AU 81/00104

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[3] C07C 41/01, 43/295, 79/355
C07D 213/64, 239/34, 241/44

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC	C07C 41/00, 41/01, 43/28, 43/295, 79/355, C07D 213/64, 239/34, 241/44
US Cl.	544/315, 354; 546/290, 303 ; 568/586, 588, 637

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

AU:IPC as above; Australian Classification 09.18, 09.62

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	E.E. Gilbert, "Sulphonation and Related Reactions" published 1965, by Interscience Publishers, (New York), see pages 379 to 381, especially page 380 lines 19 to 22.	1-13
X	The Merck Index, 9th Edition, published 1976 (Merck & Co.Inc., N.J.), see page ONR-27, "Elbs persulfate oxidation".	1-13
X	Tetrahedron, Volume 26, 1970 (Pergamon Press) pages 5945 to 5951, Ogata et al, "Kinetics and Orientation in the Peroxydisulfate Oxidation of Phenol".	1-13
A	WO, A, 79/00094, published 1979, March 8, Imperial Chemical Industries Ltd., see pages 15 to 20 (& AU, A, 38596/78)	12
P	EP, A, 0017767, published 1980, October 29, The Dow Chemical Company, (& AU, A, 63039/80)	12
A	US, A, 3966826, published 1976, June 29, Trosken (& CH, B, 611588)	12

* Special categories of cited documents: [15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
28 September 1981 (28.09.81)	30 SEPTEMBER 1981 (30-09-81)
International Searching Authority [1]	**Signature of Authorized Officer [20]**
Australian Patent Office	A.S. Moore A S Moore

Form PCT/ISA/210 (second sheet) (October 1977)