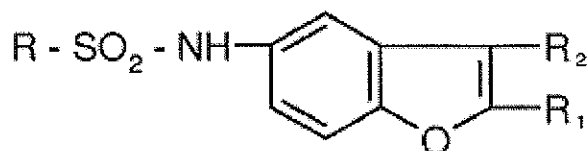


PROCESS FOR PREPARING SULFONAMIDOBENZOFURAN DERIVATIVES

The present invention relates generally to a process for preparing sulfonamidobenzofuran derivatives.

5

More specifically, the invention relates to a process for preparing 5-sulfonamidobenzofuran derivatives of general formula:



I

10

in which R represents an alkyl or aryl group and R_1 and R_2 , which may be identical or different, each represent hydrogen or an alkyl or aryl group.

15

In formula I above, R, R_1 or R_2 represents, in particular, a linear or branched C_1 - C_8 alkyl group, especially a linear or branched C_1 - C_4 alkyl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl or tert-butyl or alternatively a substituted or unsubstituted phenyl group.

20

Among the group R, mention may be made of methyl, and among the group R_1 , mention may be made of n-butyl.

25

In addition, in this formula I, among the group R, mention may be made of methyl, among the group R_1 , mention may be made of n-butyl and among the group R_2 , mention may be made of hydrogen.

30

Among the compounds of formula I above, 2-n-butyl-5-sulfoamidobenzofuran described in patent application WO 02/48132 has proven to be particularly useful as an intermediate product for the final preparation of amino-

alkoxybenzoylbenzofuran derivatives, in particular for the preparation of 2-n-butyl-3-{4-[3-(di-n-butylamino)propoxy]benzoyl}-5-methanesulfonamidobenzofuran, commonly known as dronedarone, and also pharmaceutically acceptable salts thereof. This methanesulfonamidobenzofuran derivative was described in patent EP 047 1 609, along with its therapeutic uses, especially in the cardiovascular field, where it proved to be particularly advantageous, for example, as an antiarrhythmic agent.

A process for synthesizing dronedarone was described in patent application WO 02/48132, mentioned previously, using 2-n-butyl-5-nitrobenzofuran, which is reduced, under pressure with hydrogen in the presence of platinum oxide as catalyst to form 2-n-butyl-5-aminobenzofuran. This benzofuran derivative is then subjected to the action of methanesulfonyl chloride, which gives 2-n-butyl-5-methanesulfonamidobenzofuran, which is treated with 4-[3-(di-n-butylamino)propoxy]benzoyl chloride to obtain dronedarone.

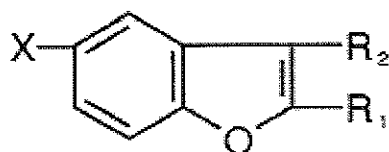
However, this process is not free of inherent drawbacks especially regarding the type of reaction used for the reagents used, namely hydrogenation under pressure, which entails an industrial risk, and also a treatment with methanesulfonyl chloride, a hazardous reagent which may generate genotoxic impurities (methanesulfonates).

The search for a process for preparing 2-n-butyl-5-methanesulfonamidobenzofuran that is capable of overcoming these drawbacks and disadvantages thus remains of fundamental interest.

It has now been found that it is possible to obtain this methanesulfonamidobenzofuran derivative, in good yield, by using reagents and reaction steps that are free of the drawbacks and disadvantages reported previously since it

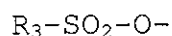
does not make use either of a catalytic hydrogenation reaction under pressure or of methanesulfonyl chloride.

According to the invention, the 5-sulfonamidobenzofuran derivatives of formula I may be prepared by coupling a benzofuran derivative of general formula:



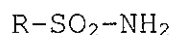
II

in which R_1 and R_2 have the same meaning as previously and X represents chlorine, bromine or iodine or a sulfonate group of general formula:



III

in which R_3 represents a trifluoromethane ($-CF_3$) or imidazolyl group, with a sulfonamide derivative of general formula:



IV

in which R has the same meaning as previously, in the presence of a basic agent and of a catalytic system formed from a complex between a palladium compound and a ligand, which gives the desired compounds.

The palladium complex used in the process of the invention is generally in the form of a palladium (0) compound, for instance:

- tris(dibenzylideneacetone)dipalladium(0), referred to hereinbelow as $Pd_2(dba)_3$ or, advantageously,
- bis(dibenzylideneacetone)palladium(0), referred to hereinbelow as $Pd(dba)_2$

and of a ligand generally chosen from phosphines, usually diarylphosphines.

These diarylphosphines are generally substituted in various ways. Thus, the aryl ring, such as phenyl, not bearing the phosphorus atom, may be mono- or especially polysubstituted, for example with an isopropyl group, while the aryl ring, especially phenyl, bearing the phosphorus atom, may in addition be mono- or polysubstituted. For example, this aryl ring does not comprise any substituents other than the phosphorus atom.

The phosphorus atom may itself be substituted, for example mono- or especially disubstituted, for example with alkyl or cycloalkyl groups such as tert-butyl or cyclohexyl.

By way of example, the following compounds may be used as ligands:

- * 2-(di-tert-butylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl, referred to hereinbelow as ligand L1,
- * 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl, referred to hereinbelow as ligand L2,
- * 2-(dicyclohexylphosphino)-2',6'-dimethoxy-1,1'-biphenyl, referred to hereinbelow as ligand L3,
- * 2-(di-tert-butylphosphino)-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl, referred to hereinbelow as ligand L4.

The ligand L1 is particularly advantageous.

The basic agent used in the process according to the invention may be chosen especially from alkoxides, but more generally from weaker bases such as phosphates or carbonates, for example alkali metal phosphates or alkali metal carbonates such as tripotassium phosphate, potassium carbonate or cesium carbonate.

In general, the coupling reaction is performed hot, for example at a temperature of between 60°C and 120°C, and

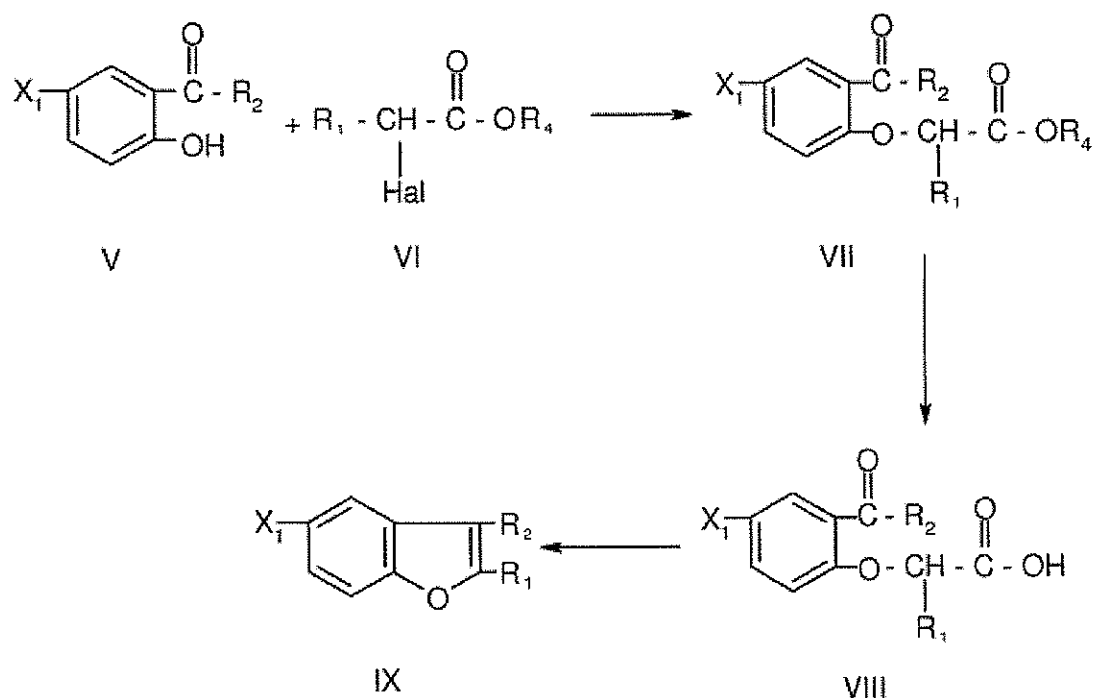
in a suitable solvent. This solvent may correspond to an alcohol, for instance tert-butanol, to an ether, for instance tetrahydrofuran or dioxane, or to a hydrocarbon, preferably an aromatic hydrocarbon, for instance toluene.

5 However, dioxane is a solvent of choice in the context of the present invention.

The starting compounds of formula II may be prepared in various ways according to their chemical structure, as
10 described hereinbelow.

A.- The compounds of formula II in which X represents chlorine, bromine or iodine may be obtained according to the following reaction scheme:

15



i.e. starting with a 2-hydroxyphenyl derivative of the formula V in which R₂ has the same meaning as previously
20 and X₁ represents chlorine, bromine or iodine, which is reacted with a halo ester of formula VI in which R₁ has the same meaning as previously, Hal represents a halogen, preferably bromine, and R₄ represents a C₁-C₄ alkyl group, for instance ethyl, to form an ester of formula VII in

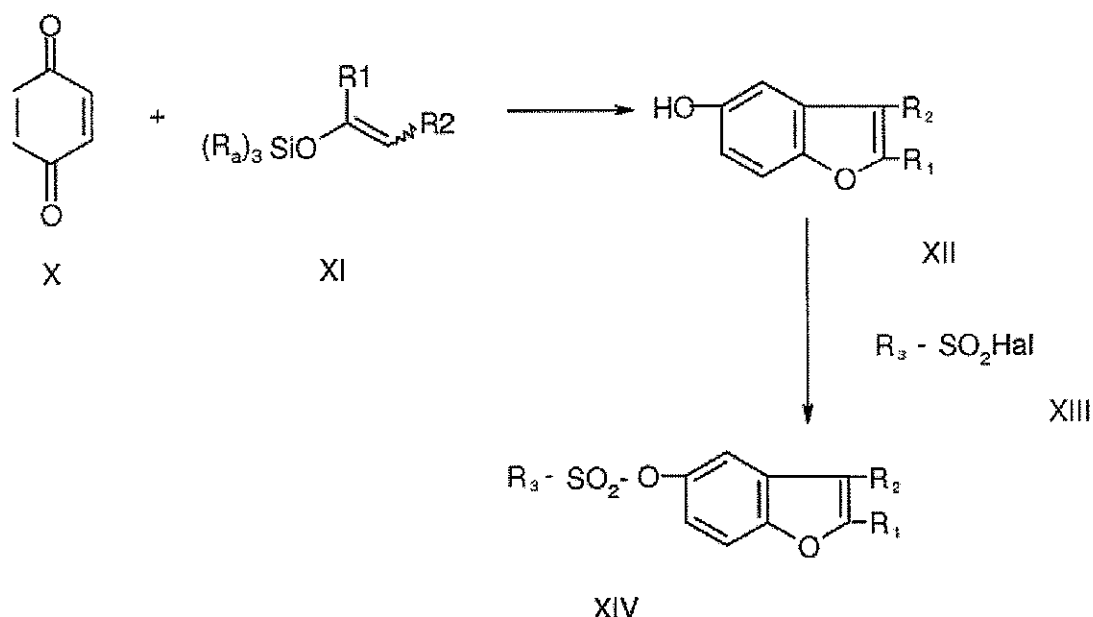
which R_1 , R_2 , R_4 and X_1 have the same meaning as previously.

5 The reaction generally proceeds by heating in a suitable solvent, in particular a polar solvent such as N,N-dimethylformamide and in the presence of a basic agent such as an alkali metal carbonate.

10 The ester of formula VII is then saponified in a solvent, especially an ether, and in the presence of a suitable basic agent such as an alkali metal hydroxide, to form the corresponding salt of a carboxylic acid derivative, which is then treated with a strong acid, in a solvent
15 acid derivative of formula VIII in which R_1 , R_2 and X_1 have the same meaning as previously.

In a subsequent step, the carboxylic acid derivative of formula VIII is then cyclized by heating in the presence
20 of a benzenesulfonyl halide and of an acid acceptor such as a tertiary amine, the reaction generally proceeding by heating in a solvent such as an aromatic hydrocarbon, to give the compounds of formula IX in which X_1 , R_1 and R_2 have the same meaning as previously, i.e. the desired
25 compounds of formula II.

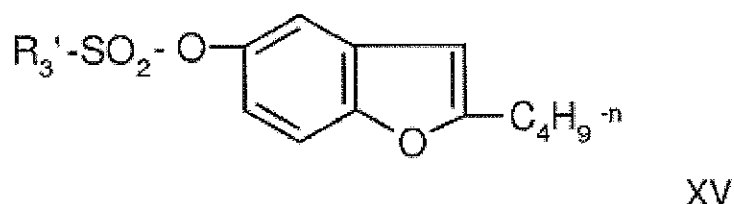
B.- The compounds of formula II in which X represents a sulfonate group may be obtained according to the following reaction scheme:



mainly starting with 1,4-benzoquinone of formula X, which is treated with a silyl enol ether of formula XI in which R_1 and R_2 have the same meaning as previously and R_a represents a linear or branched $\text{C}_1\text{-C}_4$ alkyl group or a phenyl group, to form the 5-hydroxybenzofuran derivatives of formula XII in which R_1 and R_2 have the same meaning as previously.

The compound of formula XII is then coupled with a sulfonyl derivative of formula XIII in which Hal has the same meaning as previously, preferably chlorine, and R_3 has the same meaning as previously, in the presence of an acid acceptor, which gives the sulfonate derivatives of formula XIV in which R_1 , R_2 and R_3 have the same meaning as previously, i.e. the desired compounds of formula II.

The benzofuran derivatives of general formula:



in which R'₃ represents a trifluoromethane or imidazolyl group, represent another subject of the present invention.

5 The non-limiting examples that follow illustrate the invention. In these examples, the abbreviations below are used:

TLC: thin-layer chromatography

HPLC: high-performance liquid chromatography

10 HPTLC: high-performance thin-layer chromatography

NMR: nuclear magnetic resonance

K₃PO₄: tripotassium phosphate

Cs₂CO₃: cesium carbonate

THF: tetrahydrofuran

15

PREPARATIONS

A. Ethyl 2-(4-bromo-2-formylphenoxy)hexanoate (compound
20 VII: R₁ = n-C₄H₉; R₂ = H; R₄ = C₂H₅; X₁ = Br)

8.9 g of potassium carbonate (64.3 mmol) and 45 ml of N,N-dimethylformamide are placed in an equipped reactor and then heated to 55°C with stirring. A solution of 22 g
25 of 2-hydroxy-5-bromobenzeneformaldehyde (compound VIII: X₁ = Br) (107.2 mmol) in 40 ml of N,N-dimethylformamide is then poured in dropwise onto the mixture at 55°C, and the addition funnel is then rinsed with 10 ml of N,N-dimethylformamide. The medium is stirred at 55°C for 30
30 minutes and then heated to 80°C. 20.8 ml of ethyl 2-bromohexanoate (compound IX: R₁ = n-C₄H₉; R₄ = C₂H₅; Hal = Br) (112.6 mmol) are added, and the addition funnel is rinsed with 10 ml of N,N-dimethylformamide. The reaction medium is maintained at 80°C with stirring; the reaction
35 progress is monitored by TLC (eluent: 7/1 methylcyclohexane/ethyl acetate; R_f of compound VIII: 0.53; R_f of compound X: 0.44).

At the end of the reaction, the temperature of the reaction medium is cooled to 20°C, 100 ml of deionized water are then added slowly, leading to the demixing of an oil. This oil is decanted and separated from the aqueous phase, and then washed with 100 ml of water. After decantation and separation, the oil is diluted with 60 ml of toluene, and this organic phase is then washed again with 100 ml of deionized water. This last aqueous phase is back-extracted with 60 ml of ethyl acetate. The organic phases are combined and then concentrated on a rotary evaporator to give 34.9 g of the desired compound X in the form of an orange-yellow oil.

Yield: 95%

^1H NMR (400 MHz, CDCl_3): δ 0.93 (t, $J=7.4$ Hz, 3H, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$); 1.23 (t, $J = 7$ Hz, 3H, $-\text{O}-\text{CH}_2\text{CH}_3$); 1.36-1.43 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$); 1.45-1.54 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$); 1.99-2.05 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}-$); 4.20 (q, $J=7.2$ Hz, 2H, $-\text{O}-\text{CH}_2-\text{CH}_3$); 4.71 (t, $J = 6\text{Hz}$, 1H, $-\text{CH}_2-\text{CH}-\text{O}-$); 6.71 (d, $J=8.8\text{Hz}$, 1H, ArH); 7.56 (dd, $J=9$ and 2.6 Hz, 1H, ArH); 7.94 (d, $J=2.4$ Hz, 1H, ArH); 10.49 (s, 1H, CHO)

^{13}C NMR (CDCl_3): δ 188.3 - 170.6 - 159.3 - 138.1 - 131.1 - 126.9 - 115.2 - 114.5 - 77.4 - 61.6 - 32.3 - 27.3 - 22.3 - 14.2 - 13.9 ppm

In the same manner, but starting with 10 g or 50 g of compound V, the desired compound VII was obtained in yields of 98% and 94%, respectively.

B. 2-(4-Bromo-2-formylphenoxy)hexanoic acid (compound VIII: $\text{R}_1 = n\text{-C}_4\text{H}_9$; $\text{R}_2 = \text{H}$; $\text{X}_1 = \text{Br}$)

60 g of ethyl 2-(4-bromo-2-formylphenoxy)hexanoate (compound X) (0.17 mmol) and 52 ml of methyl tert-butyl ether are placed in an equipped reactor. 78 ml of

deionized water and a solution of 9.37 g of 23% sodium hydroxide (0.23 mmol) in 31.4 g of deionized water are added, at 20°C. The reaction medium is heated to 40°C with stirring and the saponification of the ester is monitored by TLC (eluent: 8/2 methylcyclohexane/ethyl acetate + a few drops of acetic acid; R_f of the compound X = 0.52; R_f of compound XI = 0.08).

At the end of the reaction, the temperature of the reaction medium is returned to 20°C and 25.5 g of sodium chloride (0.43 mol) in 130 ml of deionized water are added, followed by 270 ml of toluene. With stirring, the reaction medium is acidified by slow addition of 20 ml of 37% hydrochloric acid solution, without exceeding 25°C. The two phases are decanted and separated, and the organic phase is then washed with 80 ml of deionized water. After separation of the phases, the organic phase is concentrated under vacuum on a rotary evaporator to give 54.7 g of a red oil, which crystallizes when cold.

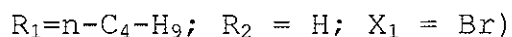
After reslurrying in a diisopropyl ether/heptane mixture, 45.5 g of the desired compound XI are isolated in the form of a yellow-white solid.

Yield: 82%

¹H NMR (400 MHz, CDCl₃): δ 0.93 (t, J=7.2 Hz, 3H, -CH₂-CH₂-CH₃); 1.37-1.44 (m, 2H, -CH₂-CH₂-CH₃); 1.49-1.57 (m, 2H, -CH₂-CH₂-CH₂-); 2.05-2.11 (m, 2H, -CH₂-CH₂-CH-); 4.79 (t, J=6Hz, 1H, -CH₂-CH-CO-); 6.78 (d, J = 8.8 Hz, 1H, ArH); 7.61 (dd, J=8.8 and 2.4 Hz, 1H, ArH); 7.94 (d, J=2.4 Hz, 1H, ArH); 10.39 (s, 1H, CHO)

¹³C NMR (CDCl₃): δ 188.6 - 174.3 - 158.6 - 138.3 - 132.4 - 127.0 - 115.5 - 114.9 - 77.2 - 32.2 - 27.1 - 22.3 - 13.8 ppm

C. 2-n-Butyl-5-bromobenzofuran (compound IX:



25.8 ml of benzenesulfonyl chloride (0.202 mol; 1.4 equivalents) and 40 ml of toluene are placed in an
5 equipped reactor and the mixture is stirred at 80°C.
65 ml of anhydrous triethylamine (0.47 mol) and then
45.2 g of 2-(4-bromo-2-formylphenoxy)hexanoic acid
(compound XI) (0.144 mol) dissolved in 250 ml of toluene
are then added slowly at 80°C. The reaction progress is
10 monitored by TLC (eluent: 80/20 methylcyclohexane/ethyl
acetate; R_f of compound XI = 0.08; R_f of the desired
compound XII = 0.80).

At the end of the reaction, the temperature of the
15 reaction medium is returned to 20°C. The excess
benenesulfonyl chloride is destroyed by addition of
250 ml of aqueous 5% sodium hydroxide solution. The
phases are decanted and separated and the organic phase
is then washed with a mixture of 70 ml of deionized water
20 and 6.8 ml of 37% hydrochloric acid. The phases are
decanted and separated and the organic phase is then
washed with 75 ml of deionized water. The organic phase
is washed with a solution of 7.73 g of sodium hydroxide
dissolved in 67 ml of deionized water. The phases are
25 decanted and separated and the organic phase is then
washed with a solution of 7.53 g of sodium chloride in
70 ml of deionized water. The pH of the aqueous phase is
adjusted to between 5 and 8 with 7% hydrochloric acid
solution. The phases are decanted and separated and the
30 organic phase is then concentrated on a rotary evaporator
to give 37.2 g of a brown oil.

This oil is purified by chromatography on silica gel
(eluent: 80/20 methylcyclohexane/ethyl acetate) to give
35 24.3 g of the desired compound XII in the form of a
yellow oil.

Yield: 67%

^1H NMR (400 MHz, DMSO- d_6): δ 0.91 (t, $J=7.2$ Hz, 3H, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$); 1.30-1.40 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}_3$); 1.61-1.69 (m, 2H, $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$); 2.76 (t, $J=7.4$ Hz, 2H, $-\text{CH}_2-\text{CH}_2-\text{Cq}$);
5 6.57 (s, 1H, ArH); 7.33 (dd, $J=8.8$ and 2Hz, 1H, ArH);
7.46 (d, $J=8.8$ Hz, 1H, ArH); 7.72 (dd, 2Hz, 1H, ArH)

EXAMPLES 1 to 5

2-n-Butyl-5-methanesulfonamidobenzofuran (compound I:

R= CH₃ ; R₁= n-C₄H₉, R₂= H)

5

The following are placed in a 20 ml tube predried in an oven: 2 equivalents of base and 1.5 equivalents of methanesulfonamide, 2 mol% of Pd(dba)₂ and 5 mol% of 2-(di-tert-butylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl (ligand L1). The tube is stoppered with a septum and placed under an inert atmosphere of argon, and 1 equivalent of 2-n-butyl-5-bromobenzofuran (compound IX or III) dissolved in 10 volumes of solvent is then added by syringe. The reaction medium is then stirred and heated to the reflux point of the solvent or at 100°C for 24 hours, while monitoring the reaction progress by TLC (eluent: 20/80 ethyl acetate/methylcyclohexane) or by HPLC. At the end of the reaction, the reaction medium is diluted with ethyl acetate and then filtered while hot. The filtrate is then concentrated to give, when cold, crystallization of the desired compound I.

The following results were obtained:

Example	Base	Solvent	Yield (%)
1	K ₃ PO ₄	tert-butanol	45
2	Cs ₂ CO ₃	dioxane	100
3	Cs ₂ CO ₃	THF	50
4	Cs ₂ CO ₃	toluene	60
5	K ₃ PO ₄	dioxane	81

25

EXAMPLE 62-n-Butyl-5-methanesulfonamidobenzofuran

(compound I: R= CH₃; R₁ = n-C₄H₉, R₂= H)

5

The following are placed in an equipped reactor under an argon atmosphere: 13 g of cesium carbonate (39.9 mmol), 3 g of methanesulfonamide (31.5 mmol), 250 mg of Pd(dba)₂ (0.4 mmol) and 440 mg of 2-(di-tert-butylphosphino)-
10 2',4',6'-triisopropyl-1,1'-biphenyl (ligand L1) (1.04 mmol). 5.5 g of 2-n-butyl-5-bromobenzofuran (compound IX or III) (21.7 mmol) dissolved in 55 ml of dioxane are then added by syringe. The reaction medium is then stirred and heated at 100°C for 24 hours.

15

The reaction medium is then diluted with 40 ml of ethyl acetate and the first crystallization crop is filtered off on a Büchner funnel. After isolation of a second crop, 3.6 g of the desired compound I are isolated in the
20 form of a snow-white powder.

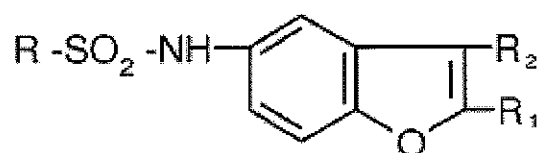
Yield: 68%

¹H NMR (400 MHz, DMSO-d₆): δ 0.91 (t, J=7.4 Hz, 3H, -CH₂-
25 CH₂-CH₃); 1.31-1.40 (m, 2H, -CH₂-CH₂-CH₃); 1.59-1.66 (m, 2H, -CH₂-CH₂-CH₂-); 2.47 (s, 3H, CH₃-SO₂-); 2.66 (t, J=7.4 Hz, 2H, -CH₂-CH₂-Cq-); 6.27 (s, 1H, ArH); 6.61 (dd, J=8.8 and 2Hz, 1H, ArH); 6.94 (d, J=2Hz, 1H, ArH); 7.02 (dd, J=8.8 Hz, 1H, ArH)

30 ¹³C NMR (DMSO-d₆); δ 157.6 - 147.2 - 147.0 - 128.6 - 117.9 - 109.4 - 108.8 - 101.8 - 38.3 - 29.3 - 27.4 - 21.6 - 13.6 ppm

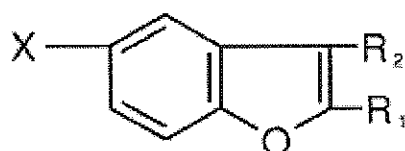
CLAIMS

1. A process for preparing 5-sulfonamidobenzofuran derivatives of general formula:



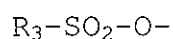
I

in which R represents an alkyl or aryl group and R₁ and R₂, which may be identical or different, each represent hydrogen or an alkyl or aryl group, characterized in that a benzofuran derivative of general formula:



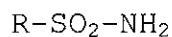
II

in which R₁ and R₂ have the same meaning as previously and X represents chlorine, bromine or iodine or a sulfonate group of general formula:



III

in which R₃ represents a trifluoromethane or imidazolyl group, is coupled with a sulfonamide derivative of general formula:



IV

- 5 in which R has the same meaning as previously, in the presence of a basic agent and of a catalytic system formed from a complex between a palladium compound and a ligand, which gives the desired compounds.
- 10 2. The process as claimed in claim 1, characterized in that R, R₁ or R₂ represents a linear or branched C₁-C₈ alkyl group or a substituted or unsubstituted phenyl group.
- 15 3. The process as claimed in claim 1 or 2, characterized in that R, R₁ or R₂ represents a linear or branched C₁-C₄ alkyl group.
- 20 4. The process as claimed in one of claims 1 to 3, characterized in that R represents methyl, R₁ represents n-butyl and R₂ represents hydrogen.
- 25 5. The process as claimed in one of claims 1 to 4, characterized in that the palladium compound is bis(dibenzylideneacetone)palladium(0).
- 30 6. The process as claimed in one of claims 1 to 4, characterized in that the palladium compound is tris(dibenzylideneacetone)dipalladium (0).
7. The process as claimed in one of claims 1 to 6, characterized in that the ligand is 2-(di-tert-butylphosphino)-2',4',6'-triisopropyl-1,1'-biphenyl.

8. The process as claimed in one of claims 1 to 7, characterized in that the basic agent is an alkali metal phosphate or an alkali metal carbonate.

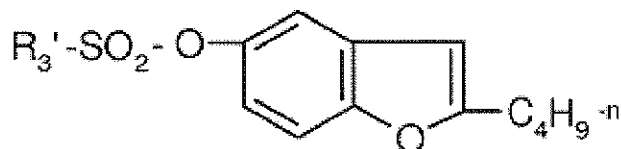
5 9. The process as claimed in claim 8, characterized in that the basic agent is tripotassium phosphate, potassium carbonate or cesium carbonate.

10 10. The process as claimed in one of claims 1 to 9, characterized in that the coupling is performed at a temperature of between 60°C and 120°C.

11. The process as claimed in one of claims 1 to 10, characterized in that the coupling is performed in a solvent chosen from an alcohol, an ether and an aromatic hydrocarbon.

12. The process as claimed in claim 11, characterized in that the solvent is dioxane.

13. A benzofuran derivative of general formula:



XV

25 in which R'_3 represents a trifluoromethane or imidazolyl group.

14. The benzofuran derivative as claimed in claim 13, in which R'_3 represents a trifluoromethane group.

30 15. The benzofuran derivative as claimed in claim 13, in which R'_3 represents an imidazolyl group.