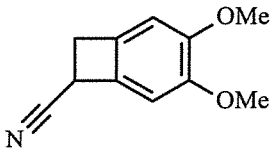
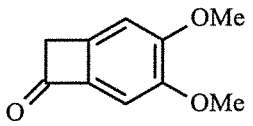
CLAIMS

1. Process for the synthesis of the compound of formula (I):



(I),

characterised in that the compound of formula (VII):



(VII)

is subjected to the action of 1-(isocyanomethylsulphonyl)-4-methylbenzene (TosMIC) in the presence of a base in an organic solvent to yield the compound of formula (I).

2. Process according to claim 1, characterised in that the amount of 1-(isocyanomethylsulphonyl)-4-methylbenzene used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is from 2 to 5 equivalents.

3. Process according to either claim 1 or claim 2, characterised in that the base used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is selected from potassium *tert*-butoxide, sodium *tert*-butoxide, potassium ethoxide, sodium ethoxide, potassium methoxide and sodium methoxide.

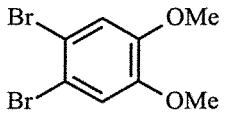
4. Process according to claim 3, characterised in that the base used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is potassium *tert*-butoxide.

5. Process according to any one of claims 1 to 4, characterised in that the organic solvent used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is selected from methanol, ethanol, isopropanol, *tert*-butanol, tetrahydrofuran, ethylene glycol and dimethyl sulphoxide, and a mixture of two from among those solvents.

6. Process according to claim 5, characterised in that the organic solvent used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is a mixture of tetrahydrofuran and methanol.

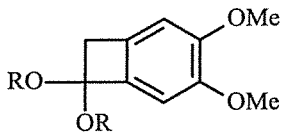
7. Process according to any one of claims 1 to 6, characterised in that the conversion of the compound of formula (VII) to form the compound of formula (I) is carried out at a temperature from -20°C to 50°C.

8. Process according to claim 1, characterised in that the compound of formula (VII) is prepared starting from the compound of formula (VIII):



(VIII),

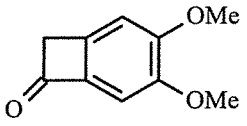
which is converted into a compound of formula (IX):



(IX),

wherein R represents a (C_1-C_4)alkyl group,
in the presence of a 1,1-dialkoxyethene, wherein the alkoxy groups have from 1 to 4 carbon atoms, and an organometallic compound in an organic solvent,

which is hydrolysed in an organoaqueous acidic medium to form the compound of formula (VII):



(VII).

9. Process according to claim 8, characterised in that the 1,1-dialkoxyethene used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is 1,1-diethoxyethene.

10. Process according to claim 9, characterised in that the amount of 1,1-diethoxyethene used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is from 0.8 to 5 equivalents.

11. Process according to any one of claims 8 to 10, characterised in that the organometallic compound used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is selected from *n*-butyllithium, *s*-butyllithium, *t*-butyllithium, phenyllithium and isopropylmagnesium chloride.

12. Process according to claim 11, characterised in that the organometallic compound used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is *n*-butyllithium.

13. Process according to claim 12, characterised in that the amount of *n*-butyllithium used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is from 1 to 3 equivalents.

14. Process according to any one of claims 8 to 13, characterised in that the organic solvent used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is selected from toluene, tetrahydrofuran, dichloromethane and chlorobenzene.

15. Process according to claim 14, characterised in that the organic solvent used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (I) is toluene.

16. Process according to any one of claims 1 to 15, characterised in that the conversion of the compound of formula (VIII) to form the compound of formula (IX) is carried out at a temperature from -20°C to 30°C.

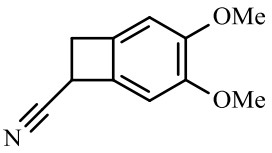
17. Process for the synthesis of ivabradine, pharmaceutically acceptable salts thereof and hydrates thereof, wherein the compound of formula (VII) is converted into the intermediate of formula (I) according to the process of claim 1, and then the intermediate of formula (I) is converted into ivabradine.

No figure.

CLAIMS

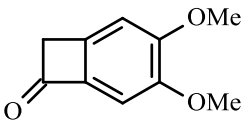
The invention claimed is:

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



(I),

wherein a compound of formula (VII):



(VII)

is subjected to the action of 1-(isocyanomethylsulphonyl)-4-methylbenzene (TosMIC) in the presence of a base in an organic solvent to yield the compound of formula (I).

2. The process according to claim 1, wherein the amount of 1-(isocyanomethylsulphonyl)-4-methylbenzene used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is from 2 to 5 equivalents.

3. The process according to claim 1, wherein the base used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is selected from the group consisting of potassium tert-butoxide, sodium tert-butoxide, potassium ethoxide, sodium ethoxide, potassium methoxide and sodium methoxide.

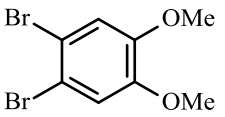
4. The process according to claim 3, wherein the base used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is potassium tert-butoxide.

5. The process according to claim 1, wherein the organic solvent used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is selected from the group consisting of methanol, ethanol, isopropanol, tert-butanol, tetrahydrofuran, ethylene glycol, dimethyl sulphoxide, and a mixture of two from among those solvents.

6. The process according to claim 5, wherein the organic solvent used to carry out the conversion of the compound of formula (VII) to form the compound of formula (I) is a mixture of tetrahydrofuran and methanol.

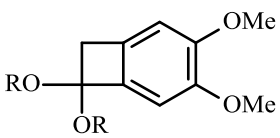
7. The process according to claim 1, wherein the conversion of the compound of formula (VII) to form the compound of formula (I) is carried out at a temperature from −20° C. to 50° C.

8. The process according to claim 1, wherein the compound of formula (VII) is prepared starting from a compound of formula (VIII):



(VIII),

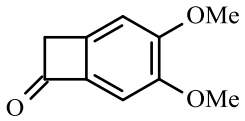
which is converted into a compound of formula (IX):



(IX),

wherein R represents a (C_1-C_4)alkyl group,

in the presence of a 1,1-dialkoxyethene, wherein the alkoxy groups have from 1 to 4 carbon atoms, and an organometallic compound in an organic solvent,
which compound of formula (IX) is hydrolysed in an organoaqueous acidic medium to form the compound of formula (VII):



(VII).

9. The process according to claim 8, wherein the 1,1-dialkoxyethene used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is 1,1-diethoxyethene.

10. The process according to claim 9, wherein the amount of 1,1-diethoxyethene used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is from 0.8 to 5 equivalents.

11. The process according to claim 8, wherein the organometallic compound used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is selected from the group consisting of n-butyllithium, s-butyllithium, t-butyllithium, phenyllithium and isopropylmagnesium chloride.

12. The process according to claim 11, wherein the organometallic compound used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is n-butyllithium.

13. The process according to claim 12, wherein the amount of n-butyllithium used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is from 1 to 3 equivalents.

14. The process according to claim 8, wherein the organic solvent used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (IX) is selected from the group consisting of toluene, tetrahydrofuran, dichloromethane and chlorobenzene.

15. The process according to claim 14, wherein the organic solvent used to carry out the conversion of the compound of formula (VIII) to form the compound of formula (I) is toluene.

16. The process according to claim 8, wherein the conversion of the compound of formula (VIII) to form the compound of formula (IX) is carried out at a temperature from −20° C. to 30° C.

17. A process for the synthesis of ivabradine, pharmaceutically acceptable salts thereof and hydrates thereof, wherein the compound of formula (VII) is converted into the compound of formula (I) according to the process of claim 1, and then the compound of formula (I) is converted into ivabradine.