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(54) Title: METHOD FOR THE PREPARATION OF CITALOPRAM

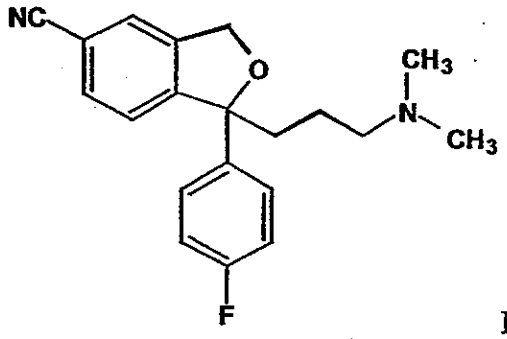
(57) Abstract: The invention provides a new and improved method for the preparation of 5-cyano-phtalid, which is a key intermediate in the preparation of the antidepressant compound citalopram.

Method for the Preparation of Citalopram

The present invention relates to a method for the preparation of key intermediates in the process for the preparation of the well known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

Background of the Invention.

Citalopram is a well known antidepressant drug that has now been on the market for some years and has the following structure:



Formula I

It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982**, *6*, 277-295 and A. Gravem, *Acta Psychiatr. Scand.*, **1987**, *75* , 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A 474580.

Citalopram can be prepared by several disclosed methods. A method and an intermediate for the preparation of citalopram were described in US Patent No 4,650,884. Commercially useful processes are disclosed in International patent application Nos. WO 98019511, WO 98019512 and WO 98019513.

With respect to the above methods for the preparation of citalopram, the process comprising exchange of the 5-bromo group with cyano proved not to be very convenient in commercial scale, since the yield was rather low, the product was impure and, in particular, since it was difficult to separate the resulting citalopram from the corresponding 5-bromo compound.

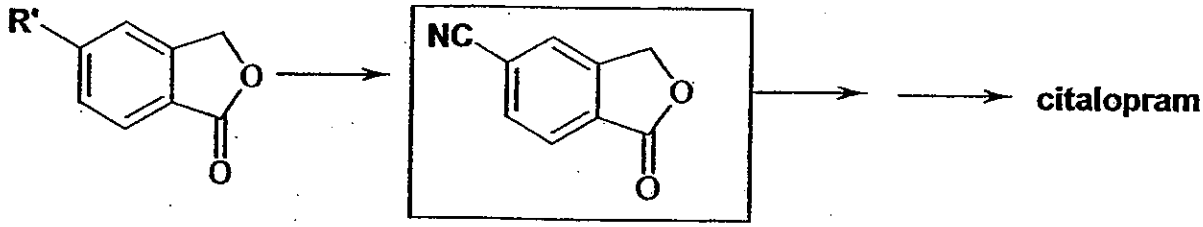
It has now been found that in a new process for the preparation of citalopram, this key intermediate may be obtained in a high yield as a very pure product by a new catalytic

process in which a halogen or a group of the general formula CF_3-$(CF_2)_n$-SO_2- wherein n is any suitable whole number between 0 and 4, situated in the 5-position of a 3-*H*-isobenzofuran-1-one, is exchanged with a cyanide group. By obtaining the correct cyanide substitution at an early stage of the citalopram synthesis, the extensive work up of the old cyanide exchange processes of the previous described processes is avoided. The intermediates of the presently described process are easily purfied and obtained in very high yields. The key intermediate is then subjected to two successive Grignard reactions , *i.e.* with 4-fluorophenyl magnesium halogenide and N.N-dimethylaminopropyl magnesium halogenide, respectively, whereby citalopram is obtained.

The preparation of the key intermediate of the invention is described earlier in J.Chem. Soc., 1931, 867 and by Tiroflet, J. in Bull. Soc. Sci. Betagne, 26, 35, 1951; The process for preparation of the compound is a three step synthesis starting from 5-nitro-phtalimide with low yields, especially in the last step of the synthesis.

Summary of the invention

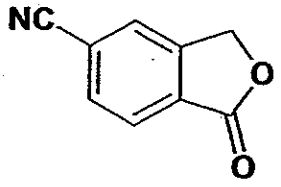
Disclosed herein is a novel method for the preparation of an intermediate in the preparation of citalopram comprising reacting a compound of Formula IV



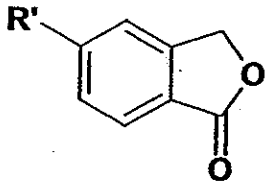
Formula IV

wherein R' is Cl, Br, I or a group of the formula CF_3-$(CF_2)_n$-SO_2- , wherein n is 0-4, with a cyanide source in the presence or absence of a catalyst, whereby 5-cyano-isobenzofuran-1-one is obtained. This intermediate product can be further reacted to citalopram as described above.

In a first aspect of the present invention, there is provided a method for the preparation of a compound of the formula



comprising reacting an isobenzofuran-1-one of the formula



wherein R' represents a halogen or a group of the formula CF_3-$(CF_2)_n$-SO_2- , wherein n is 0-7, with a cyanide source optionally in the presence of a catalyst;

In a second aspect of the present invention, there is provided the process as defined in the first aspect wherein the starting material is an isobenzofuran-1-one with a C1, Br or I in position 5.

The reaction of IV til 5-cyanophtalide may be carried out in more convenient solvents, at a low temperature and at a minimal excess of CN^-. The process has environmental advantages in that it only uses small amounts of heavy metals.

The cyano sources may conveniently be selected from a group consisting of cyanide sources such as $(R''_4N)CN$ wherein each R'' represents C_{1-8}-alkyl optionally two R'' together with the nitrogen form a ring structure; NaCN, KCN, $Zn(CN)_2$ or Cu(CN).

In one embodiment, the reaction of the present invention is performed in the presence or absence of a catalyst. The catalysts may be *i.e.* Ni(O), Pd(O) or Pd(II) catalysts as described by Sakakibara et. al. in Bull. Chem. Soc. Jpn., 61, 1985-1990, (1988). Preferred catalysts are $Ni(PPh_3)_3$ or $Pd(PPh_3)_4$, or $Pd(PPh)_2CI_2$.

In particularly preferred embodiment, a Nickel(O) complex may be prepared *in situ* before the cyanide exchange reaction by reduction of a Nickel(II) precursor such as $NiCl_2$ or $NiBr_2$ by a metal, such as zinc, magnesium or mangan in the presence of excess of complex ligands, preferably triphenylphosphin.

Another embodiment may relate to the process as defined in the first aspect wherein the starting material is an isobenzofuran-1-one with a triflate group of the formula CF_3-$(CF_2)_n$-SO_2-, wherein n is 0, 1, 2, 3 or 4, in position 5.

Still another embodiment may relate to the process as defined above wherein the cyanide source is selected from $(R''_4N)CN$ wherein each R'' represents C_{1-8}-alkyl optionally two R'' together with the nitrogen form a ring structure; KCN, NaCN, $Zn(CN)_2$ or CuCN or combinations thereof.

The Pd or Ni-catalyst may conveniently be used in an amount of 0.5-10, preferably 2-6, most preferably about 4-5 mol%.

Cu^+ and Zn^{2+} may be added to the reaction mixture in substoichiometric amounts and may function as recycleable cyanide sources, which receives the cyanide from other cyanide sources such as NaCN or KCN. Substoichiometric amounts of Cu^+ and Zn^{2+}, respectively, means 1-20%, preferably 5-10%.

Yet another embodiment may relate to the process as defined above wherein a 5-chloro-isobenzofuran-1-one is subjected to NaCN in the presence of Ni-catalyst.

The reactions may be performed in any convenient solvent as described in Sakakibara et. al. in Bull. Chem. Soc. Jpn., 61, 1985-1990, (1988). Preferred solvents are acetonitril, ethylacetat, THF, DMF or NMP;

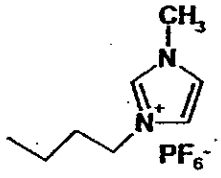
Still yet another embodiment may be a compound of Formula IV wherein R is Cl is reacted with NaCN in the presence of a $Ni(PPh_3)_3$ which is preferably prepared in situ as described above.

Still yet yet another embodiment may be a compound of formula IV, wherein R is Br or I, is reacted with KCN, NaCN, CuCN or $Zn(CN)_2$ in the presence of $Pd(PPh_3)_4$. In a particular aspect of the invention, substoichiometric amounts of Cu(CN) and $Zn(CN)_2$ are added as recycleable cyanide sources.

Another embodiment may be the Cu(CN) is the cyanide source and without catalyst. In a preferred embodiment of this invention, the reaction may be performed at elevated temperature.

A further embodiment may relate to the process according to the above wherein the reaction is performed as a neat reaction *i.e.* without added solvent.

Still another embodiment may relate to the process according to the above wherein the reaction is performed in an ionic liquid of the general formula R_4N^4, X^-, wherein R are alkyl-groups or two of the R groups together form an ring and X^- is the counterion. In one embodiment of the invention, R_4N^4, X^- represents



Another embodiment may relate to the process as defined above wherein the reaction is conducted with a polar solvents such as benzene, xylene or mesitylene and under the influence of microwaves by using *i.e.* Synthewave 1000™ by Prolabo. In a particular aspect of this invention, the reaction is performed without added solvent.

In a third aspect of the present invention, there is provided a method for the preparation of citalopram comprising the preparation of 5-cyano-3H-isobenzofuran-1-one as defined above.

Finally, a further embodiment may relate to a method as defined in the third aspect wherein the 5-cyano-3H-isobenzofuran-1-one is subjected to two successive Griegnard reactions with 4-flourophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide to obtain citalopram.

The temperature ranges may depend upon the reaction type. If no catalyst is present preferred temperatures may be in the range of 100-200°C. However, when the reaction is conducted under the influence of microwaves the temperature in the reaction mixture may raise to above 300 °C. More preferred temperature ranges are between 120-170°C. The most preferred range is 130-150°C.
If catalyst is present, the preferred temperature range is between 0 and 100°C. More preferred are temperature ranges of 40-90°C. Most preferred temperature ranges are between 60-90°C.

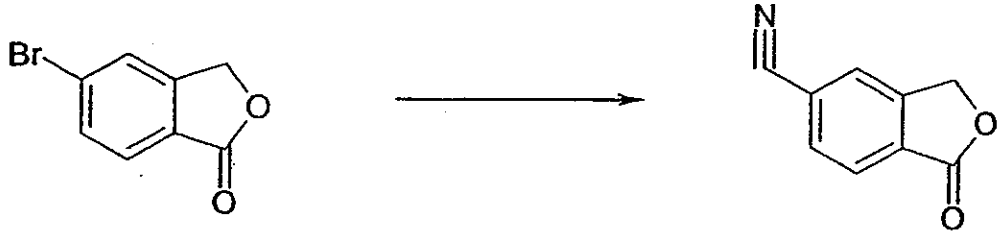
Other reaction conditions, solvents, etc. are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

Examples

The invention is further illustrated by the following examples.

Experimental
Example 1

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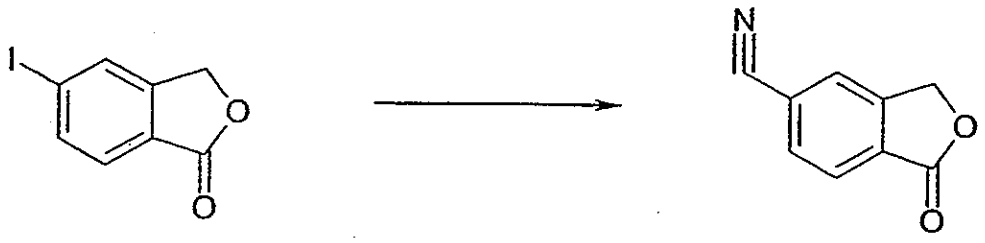
A mixture of $Zn(CN)_2$ (2.4g, 0.02mol) and 5-bromo-3H-isobenzofuran-1-one (4.2g, 0.02mol) in DMF (80mL) were stirred at room temperature under an atmosphere of argon for 30 minutes. Then dissolved oxygen was removed by bubbling argon through the reaction mixture for 10 minutes before the addition of tetrakis(triphenylphosphine)palladium (0) (1.2g, 0.00096mol,) . Then the reaction was heated at 75 °C for 3 hrs, and then the solvent was removed under reduce pressure and the residue poured into water (150mL). Filtration and followed by drying in vaucco give the crude 5-cyano-3H-isobenzofuran-1-one (2.8 g) (HPLC 95%). An analytical sample was obtained by recrystalisation from acetic acid.

Example 2

A mixture of $Zn(CN)_2$ (0.3g, 0.00256mol), NaCN (1g, 0,02mol) and 5-bromo-3H-isobenzofuran-1-one (4.2 g, 0.02mol) in DMF (80mL) were stirred at room temperature under an atmosphere of argon for 30 minutes. Then dissolved oxygen was removed by bubbling argon through the reaction mixture for 10 minutes before the addition of tetrakis(triphenylphosphine)palladium (0) (1.2g, 0.00096mol) . Then the reaction was heated at 75 °C for 3 hrs, and then the solvent was removed under reduce pressure and the residue poured into water (150mL). Filtration and followed by drying in vaucco give the crude 5-cyano-3H-isobenzofuran-1-one (2.7 g) (HPLC 94%). An analytical sample was obtained by recrystalisation from acetic acid.

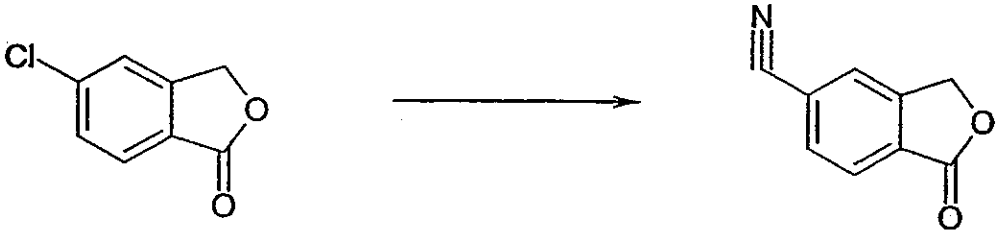
Example 3

A mixture of 5-bromo-3H-isobenzofuran-1-one (4.2 g, 0.02mol) and $Cu(CN)_2$ (2.3g, 0.02mol) in NMP (60mL) were stirred at 140 °C for 3hrs. Then solvent was removed by distilation under reduced pressure and the residue was refluxed in water (150 mL) for 10 minutes and allowed to cool to room temperature. Filtration and followed by drying in vaucco give the crude 5-cyano-3H-isobenzofuran-1-one (2.1g) (HPLC 97%). An analytical sample was obtained by recrystalisation from acetic acid.



Example 4

A mixture of $Zn(CN)_2$ (2.4g, 0.02mol) and 5-iodo-3H-isobenzofuran-1-one (5.24g, 0.02mol) in DMF (80mL) were stirred at room temperature under an atmosphere of argon for 30 minutes. Then dissolved oxygen was removed by bubbling argon through the reaction mixture for 10 minutes before the addition of tetrakis(triphenylphosphine)palladium (0) (1.2g, 0.00096mol). Then the reaction was heated at 75 °C for 3 hrs, and then the solvent was removed under reduce pressure and the residue poured into water (150mL). Filtration and followed by drying in vaucco give the crude 5-cyano-3H-isobenzofuran-1-one (2.4 g) (HPLC 93%). An analytical sample was obtained by recrystalisation from acetic acid.

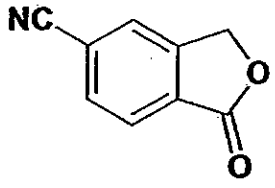


Example 5

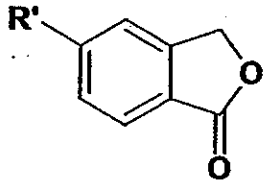
Under a nitrogen atmosphere, a mixture of $NiCl_2$ (0.2g, 0.0015mol) and triphenylphosphine (1.6g, 0.0061 mol) in acetonitrile (80 ml)was heated at reflux for 45 minutes. After cooling to room temperature, zinic powder was added (0.39 g, 0.006 mol) at stirred for 15 minutes before a solution of 5-chloro-3H-isobenzofuran-1-one (3.4g, 0.02mol) in THF (40 mL) was added. After stirring for a further 10 minutes, NaCN (1.1g, 0.021 mol) was added and the reaction heated at 70 °C for 3hrs, cooled , diluted with acetonitrile (50mL) , and then filtered through celite. The filtrate was concentrated under reduced pressure and the residue was was refluxed in water (150 mL) for 10 minutes and allowed to cool to room temperature. Filtration and followed by drying in vaucco give the crude 5-cyano-3H-isobenzofuran-1-one (2.5 g). An analytical sample was obtained by recrystalisation from acetic acid.

CLAIMS

1. A method for the preparation of a compound of the formula



comprising reacting an isobenzofuran-1-one of the formula



wherein R' represents a halogen or a group of the formula CF_3-$(CF_2)_n$-SO_2- , wherein n is 0-7, with a cyanide source optionally in the presence of a catalyst;

2. The process of claim 1 wherein the starting material is an isobenzofuran-1-one with a Cl, Br or I in position 5;
3. The process of claim 1 wherein the starting material is an isobenzofuran-1-one with a triflate group of the formula CF_3-$(CF_2)_n$-SO_2- , wherein n is 0, 1,2,3 or 4, in position 5.
4. The process of claims 1-3 wherein the cyanide source is selected from $(R''_4N)CN$ wherein each R'' represents C_{1-8}-alkyl optionally two R'' together with the nitrogen form a ring structure; KCN, NaCN, $Zn(CN)_2$ or CuCN or combinations thereof.
5. The process of claims 1-4 wherein Zn^{2+} or Cu^+ are added in substoichiometric amounts in combination with another cyanide source.
6. The process of claims 1-4 wherein the catalyst is selected from $Ni(PPh_3)_3$, $Pd(PPh_3)_4$, $Pd(dba)_3$ or $Pd(PPh)_2Cl_2$;
7. The process of claims 1, 2 and 4 wherein a 5-chloro-isobenzofuran-1-one is subjected to NaCN in the presence of Ni-catalyst.
8. The process of claim 7 wherein the Ni-catalyst is $Ni(PPh_3)_3$ prepared *in situ* by subjecting $NiCl_2$ to a reducing agent, such as Zn, in the presence of PPh_3;
9. The process of claim 1, 2 and 4 wherein a 5-bromo- or 5-iodo-isobenzofuran-1-one is subjected to KCN, NaCN, $Zn(CN)_2$, or CuCN or combinations thereof in the presence of $Pd(PPh_3)_4$.

10. The process according to claim 1, 2 and 4 wherein a 5-bromo- or 5-iodo-isobenzofuran-1-one is subjected to KCN, NaCN, $Zn(CN)_2$, or CuCN or combinations thereof and the process is performed without catalysts.
11. The process of claim 10 wherein the reaction is performed in an ionic liquid of the general formula $R_4N^+X^-$ wherein each R represents C_{1-8}-alkyl optionally two R'' together with the nitrogen form a ring;
12. The process of claim 10 wherein the reaction is performed under the influence of microwaves in an apolar solvent;
13. The process according to claim 10 or claim 12 wherein the reaction is performed as a neat reaction.
14. A method for the preparation of citalopram comprising the preparation of 5-cyano-3H-isobenzofuran-1-one according to claim 1-13.
15. A method according to claim 14 wherein the 5-cyano-3H-isobenzofuran-1-one is subjected to two successive Griegnard reactions with 4-flourophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide to obtain citalopram.