6-chloro-3-(phenyl-d_5)-inden-1-one and use thereof

FIELD OF THE INVENTION

The present invention relates to 6-chloro-3-(phenyl-d_5)-inden-1-one, use of the compound as well as processes for preparation of the compound.

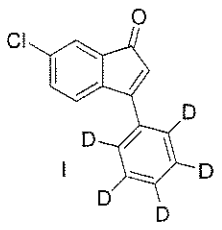
BACKGROUND OF THE INVENTION

Deuterated 1-piperazino-3-phenyl-indanes for treatment of schizophrenia have been disclosed in US Application No. 13/527,364. US Application No. 13/527,364 also discloses how specific deuterated 1-piperazino-3-phenyl-indanes can be obtained via 6-chloro-3-(phenyl-d_5)-indan-1-one. However, the disclosed routes for synthesis of both racemic and enantiomerically pure 6-chloro-3-(phenyl-d_5)-indan-1-one rely on the uneconomical use of high loading of either a chiral rhodium catalyst or a chiral palladium catalyst. Accordingly, new processes for the synthesis of racemic and enantiomerically pure 6-chloro-3-(phenyl-d_5)-indan-1-one are desirable, and are herein described proceeding via the compound 6-chloro-3-(phenyl-d_5)-inden-1-one (I).

Clark, W. M. et al in *Organic Letter,* **1999**, Vol. 1, No. 11, pp. 1839-1842 attempted the preparation of 3-arylindenones, such as 6-chloro-3-(phenyl-d_5)-indan-1-one (I), with electron-withdrawing groups (Cl, Br, NO_2) at the C(5)- or C(6)-position of the indenone ring using a Suzuki methodology, but failed to obtain appreciable amounts of the desired products. In contrast, the present invention describes the successful preparation of such 3-arylindenones, e.g. 6-chloro-3-(phenyl-d_5)-indan-1-one (I), via a Suzuki methodology.

SUMMARY ~~OF THE INVENTION~~

One aspect of ~~T~~the present invention discloses the compound 6-chloro-3-(phenyl-d_5)-inden-1-one (I)



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and routes of synthesis to obtain (I). In ~~a~~ further ~~aspect~~ embodiments, ~~the present invention discloses~~ the use of 6-chloro-3-(phenyl-d_5)-inden-1-one (I) to obtain racemic 6-chloro-3-(phenyl-d_5)-indan-1-one (VIII) or (*S*)-6-chloro-3-(phenyl-d_5)-indan-1-one (IX) is disclosed.

Further the ~~present invention discloses~~ use of 6-chloro-3-(phenyl-d_5)-inden-1-one (I) to obtain 4-((1*R*,3*S*)-6-chloro-3-(phenyl-d_5)-indan-1-yl)-1(d_3),2,2-trimethyl-piperazine and pharmaceutically acceptable salts thereof is disclosed.

In another aspect, there is disclosed a process for production of compound (I), wherein compound (I) is obtained via reaction of 3-bromo-6-chloro-inden-1-one with an arylboronic acid or an arylboronic ester.

Another aspect relates to a process comprising the steps a) Compound (I) as defined herein is reduced to obtain 6-chloro-3-(phenyl-d5)-1H-inden-1-ol (VIa); b) Compound (VIa) is converted to 6-chloro-3-(phenyl-d5)-indan-1-one (VIIIa) via base-induced rearrangement.

Another aspect relates to a process comprising the steps a) Compound (I) as defined herein is converted to (S)-6-chloro-3-(phenyl-d5)-1H-inden-1-ol (VII) via enantioselective reduction in the presence of enantioselective catalyst and reductant; b) Compound (VII) is converted to (S)-6-chloro-3-(phenyl-d5)-indan-1-one (IX) via base-induced rearrangement.

Another aspect relates to a process comprising conversion of Compound (I) as defined herein to obtain 6-chloro-3-(phenyl-d5)-indan-1-one (VIIIa) via hydrogenation in the presence of a suitable catalyst, such as tris(triphenylphosphine)rhodium(I) chloride, in a suitable solvent, such as ethyl acetate.

Another aspect relates to a process comprising conversion of Compound (I) as defined herein to obtain (S)-6-chloro-3-(phenyl-d5)-indan-1-one (IX) via asymmetric hydrogenation in the presence of a suitable catalyst, such as a rhodium salt, and a chiral phosphine ligand and a suitable solvent, such as ethyl acetate.

Another aspect relates to a process wherein the compounds obtained in any of the processes described above are converted to 3,5-dichloro-1-(phenyl-d5)-indan, in particular (±)-cis-3,5-dichloro-1-(phenyl-d5)-indan or (1S,3S)-3,5-dichloro-1-(phenyl-d5)-indan, the process comprising the following steps:

a) Reduction of (±)-6-chloro-3-(phenyl-d5)-indan-1-one (VIII), 6-chloro-3-(phenyl-d5)-indan-1-one (VIIIa) or (S)-6-chloro-3-(phenyl-d5)-indan-1-one (IX) to obtain the corresponding indanol: (±)-cis-6-chloro-3-(phenyl-d5)-indan-1-ol (X), 6-chloro-3-(phenyl-d5)-

indan-1-ol (Xb) or (1S,3S)-6-chloro-3-(phenyl-d5)-indan-1-ol (Xa) in the presence of a suitable reduction agent, such as NaBH4;

b) Chlorination, e.g. in the presence thionyl chloride, of any of the compounds obtained in step a) to obtain the corresponding chlorinated indan compound (±)-cis-3,5-dichloro-1-(phenyl-d5)-indan (XI), 3,5-dichloro-1-(phenyl-d5)-indan (XIb) or (1S,3S)-3,5-dichloro-1-(phenyl-d5)-indan (XIa)

Yet another aspect relates to a process wherein the (±)-cis-3,5-dichloro-1-(phenyl-d5)-indan (XI), 3,5-dichloro-1-(phenyl-d5)-indan (XIb) or (1S,3S)-3,5-dichloro-1-(phenyl-d5)-indan (XIa) as obtained above are converted to a pharmaceutically acceptable salt of (±)-trans-1-(6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine, 1-(6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine or 1-((1R, 3S)-6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine, the process comprising the following steps:

a) reaction with 2,2-dimethylpiperazine or a compound that subsequently can be transformed to to the 3,3-dimethylpiperazine moiety of (±)-trans-1-(6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine, 1-(6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine or 1-((1R, 3S)-6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine;

b) formation and optionally precipitation of the pharmaceutically acceptable salt by addition of the corresponding acid.

Another aspect relates to a process wherein the pharmaceutically acceptable salt of (±)-trans-1-(6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine, 1-(6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine or 1-((1R, 3S)-6-chloro-3-(phenyl-d5)-indan-1-yl)-3,3-dimethyl-piperazine as obtained above is converted to a pharmaceutically acceptable salt of 4-((1R,3S)-6-chloro-3-(phenyl-d5)-indan-1-yl)-1(d3),2,2-trimethyl-piperazine, the process comprising the following steps:

a) alkylation in the presence of an active methyl-d3 donor, such as methyl-iodide-d3, and a base, such as potassium hydroxide, and

b) precipitation and optionally of the pharmaceutically acceptable salt by addition of the corresponding acid.

Another aspect relates to a process wherein the 3,5-dichloro-1-(phenyl-d5)-indan, in particular (±)-cis-3,5-dichloro-1-(phenyl-d5)-indan or (1S,3S)-3,5-dichloro-1-(phenyl-d5)-indan, obtained as described above is converted to a pharmaceutically acceptable salt of 4-((1R,3S)-6-chloro-3-(phenyl-d5)-indan-1-yl)-1(d3),2,2-trimethyl-piperazine, the process comprising the following steps:

a) nucleophile substitution of 3,5-dichloro-1-(phenyl-d5)-indan with 1(d3),2,2-trimethylpiperazine bis-2,2,2-trifluoroacetate or a compound that subsequently can be transformed to the 1(d3),2,2-trimethyl-piperazine moiety of 4-((1R,3S)-6-chloro-3-(phenyl-d5)-indan-1-yl)-1(d3),2,2-trimethyl-piperazine

b) precipitation and optionally of the pharmaceutically acceptable salt by addition of the corresponding acid.

DETAILED DESCRIPTION OF THE INVENTION

Compound list

(I): 6-chloro-3-(phenyl-d_5)-inden-1-one

(II): 6-chloro-1-indanone

(III): 3-bromo-6-chloro-inden-1-one

(IV): 6-chloro-3-(phenyl-d_5)-1*H*-indene

(V): 5-chloro-1-indanone

(VI): (±)-6-chloro-3-(phenyl-d_5)-1*H*-inden-1-ol

(VIa) 6-chloro-3-(phenyl-d_5)-1*H*-inden-1-ol

(VII): (*S*)-6-chloro-3-(phenyl-d_5)-1*H*-inden-1-ol

(VIII): (±)-6-chloro-3-(phenyl-d_5)-indan-1-one

(VIIIa): 6-chloro-3-(phenyl-d_5)-indan-1-one

(IX): (*S*)-6-chloro-3-(phenyl-d_5)-indan-1-one

(X): (±)-*cis*-6-chloro-3-(phenyl-d_5)-indan-1-ol

(Xa): (1*S*,3*S*)-6-chloro-3-(phenyl-d_5)-indan-1-ol

(Xb): 6-chloro-3-(phenyl-d_5)-indan-1-ol

(XI): (±)-*cis*-3,5-dichloro-1-(phenyl-d_5)-indan

(XIa): (1*S*,3*S*)-3,5-dichloro-1-(phenyl-d_5)-indan