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Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

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(54) **Title:** PROCESS FOR THE SEPARATION OF 4-BROMOMETHYL-2'-SUBSTITUTED BIPHENYLS FROM 4,4,-DIBROMOMETHYL-2'-SUBSTITUTED BIPHENYLS

(57) **Abstract:** Disclosed herein is process for the separation of 4-bromomethyl-2'-substituted biphenyls of Formula (II) from 4,4-dibromomethyl-2'-substituted biphenyls of Formula (III) and 4-methyl-2'-substituted biphenyl of Formula (I) by stirring a crude reaction mixture comprising compounds of Formula (I), (II) and (III) in suitable organic solvents at a temperature above 50°C; and gradually cooling the reaction mixture below 20°C to obtain pure crystals of Formula (II) with purity of more than 97%.

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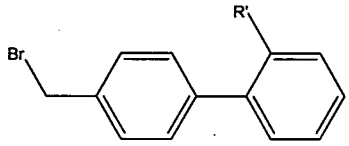
"PROCESS FOR THE SEPARATION OF 4-BROMOMETHYL-2'-SUBSTITUTED BIPHENYLS FROM 4,4,-DIBROMOMETHYL-2'-SUBSTITUTED BIPHENYLS"

Field of invention:

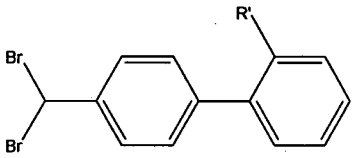
The present invention relates to a novel process for the separation of 4-bromomethyl-2'-substituted biphenyls of Formula II



Formula II

wherein R' is cyano, 1-H tetrazole or N-protected 1-H tetrazole

from 4,4,-dibromomethyl-2'-substituted biphenyls of Formula III

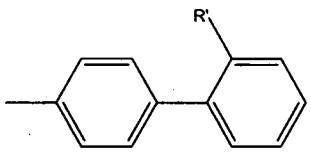


Formula III

wherein R' is same as specified above.

Background of the invention:

4-Bromomethyl-2'-substitutedbiphenyls are known as useful intermediates for pharmaceutical products, such as a compound having an angiotensin II antagonist action. The compound was first disclosed in EP0253310. The bromomethyl biphenyls are prepared from the corresponding methyl biphenyls of Formula I by bromination reaction.



Formula I

wherein R' is same as above.

Various brominating agents have been reported in the literature to carry out this bromination.

US 5621134 discloses the use of economical bromine as brominating agent.

US 2003/0233009 describes the use of bromine as a brominating agent with an oxidizing agent like sodium bromate in the presence of a radical initiator.

Patent applications JP 63-23868, EP 553879, and US 6177587 describe the bromination of o-tolylbenzonitrile (referred to herein below as OTBN) using brominating agents such as N-bromosuccinimide (referred to herein below as NBS), dibromodimethylhydantoin (DDH), N-bromophthalimide or bromine, in the presence of chemical initiator such as benzoyl peroxide, t-butyl peroxide, t-butyl perbenzoate or 2,2'-azobis(isobutyronitrile) (referred to herein below as AIBN) in solvents like C_5-C_7 alkane, halogentated C_1-C_4 aliphatic hydrocarbons such as dicholoromethane or carbon tetrachloride, a C_1-C_4 alkyl ester such as ethyl acetate, or a halogenated aromatic hydrocarbon such as chlorobenzene.

US 2002/0095042 describes bromination of compound of Formula I using brominating agents such as N-bromoimides, or DDH or N,N'-dibromo-5,5-diphenylhydantoin in a suitable solvent like an ester of a carboxylic acid.

However, bromination of compound of Formula I, by various methods as described above, results in a mixture in which major compounds are those represented by compound of Formula II & compound of Formula III with varying quantity of unreacted starting compounds represented by Formula I. Impurity of Compound of Formula III always get formed simultaneously by dibromination of compound of Formula I.

None of the above mentioned processes describes the separation of compound of formula II from compound of formula III and unreacted compound of formula I. It has been observed that contamination of the said impurity causes,

1. Unwanted parallel reactions at subsequent stages

2. Lowering the yield of final product
3. Lowering the purity of final product
4. Consumption of expensive reagents in large quantity.
5. Difficulty in purifying the final product
6. Difficulty in handling the process at large scale
7. Overall process expensive, thus uneconomical

It is therefore very essential to develop a process for the separation of compound of Formula II from compound of Formula III in order to get compound of Formula II substantially free from compound of Formula III.

The present inventors have surprisingly found out a simple process for obtaining compound of Formula II, substantially free from compound of Formula III. Thus, increasing the yield and purity of the final product and reducing overall cost of production. Also, compound of formula II separated during the process can be further used to obtain OTBN or can be converted to aldehyde compound which is also a useful intermediate.

Object of the invention:

An object of the invention is to provide a process for the separation of 4-bromomethyl-2'-substituted biphenyls from 4,4,-dibromomethyl-2'-substituted biphenyls.

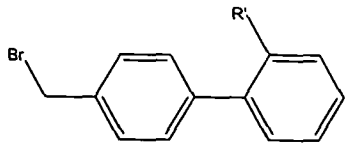
Another object of the invention is to provide an economical process to obtain 4-bromomethyl-2'-substituted biphenyls, substantially free from other impurities.

Yet another object of the invention is to provide a process for obtaining 4-bromomethyl-2'-substituted biphenyls in high purity.

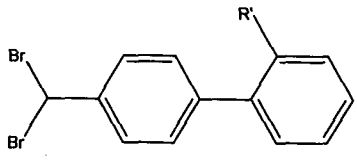
Summary of the invention:

According to an aspect of the invention there is provided a process for the separation of 4-bromomethyl-2'-substituted biphenyls of Formula II from 4,4-dibromomethyl-2'-

substituted biphenyls of Formula III and to get substantially pure 4-bromomethyl-2'-substituted biphenyls of Formula II.



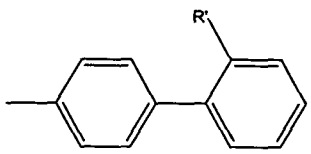
Formula II



Formula III

Wherein, R' is cyano, 1-H tetrazole or N-protected 1-H tetrazole.

The present invention particularly describes a process for the separation of 4-bromomethyl-2'-substitued biphenyl of Formula II from 4,4-dibromo-2'-substitued biphenyls of Formula III in a crude reaction mixture obtained after brominating compounds of Formula I



wherein R' is as specified above

comprising:

a) stirring the crude reaction mixture with an organic solvent at above 50°C;

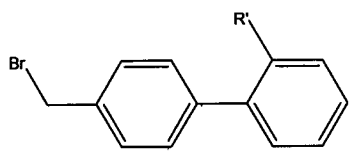
b) gradually cooling below 20°C and stirring; and

c) filtering the crystals to obtain compound of Formula II with >97% purity.

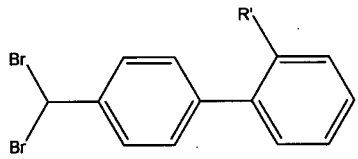
Detailed description of the invention:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.

4-Bromomethylbiphenyl derivatives of Formula II substituted in the 2'position are very valuable as intermediate products in the production of pharmaceutically active substances, especially for the production of drugs, which are useful as angiotensin-II-antagonists.



Formula II

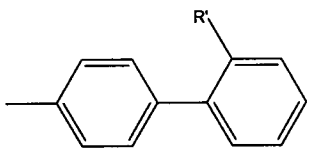


Formula III

wherein R' is cyano , 1-H tetrazole or N-protected 1-H tetrazole

The present inventors have surprisingly found out a process for obtaining compound of Formula II substantially free from compound of Formula III.

Accordingly, the present invention particularly describes a process for the separation of 4-bromomethyl-2'-substitued biphenyl of Formula II from 4,4-dibromo-2'-substitued biphenyls of Formula III in a crude reaction mixture obtained after brominating compounds of Formula I



Formula I

wherein R' is cyano, 1-H tetrazole or N-protected 1-H tetrazole

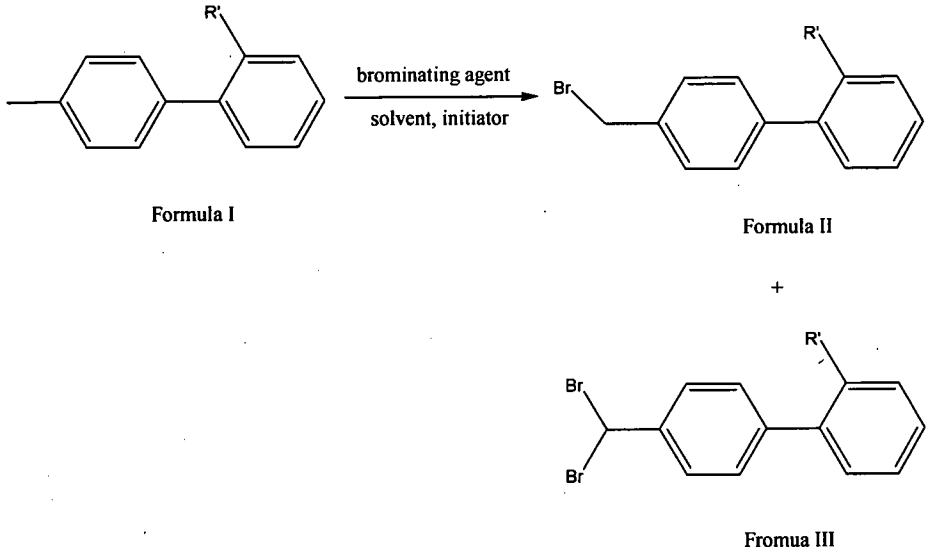
comprising;

a) stirring the crude reaction mixture with an organic solvent at above 50° C;

b) gradually cooling below 20°C and stirring; and

c) filtering the crystals to obtain compound of Formula II with >97% purity.

4-Bromomethyl-2'- substituted biphenyls of Formula II can be prepared from 4-methyl-2'-substituted biphenyls of Formula I by bromination with brominating agents well-known in the literature. The reaction is as shown in the scheme below.



Formula I

Formula II

+

Fromua III

There are many references, which describe the above bromination procedure. The crude reaction mixture obtained after bromination is a mixture of the compounds of Formula II, Formula III and Formula I. It has been observed that after the reaction gets completed, the usual work up procedure yields the product in the form of a cake having general HPLC (Unquantified area %) composition: 70-87% (II), 6-12% (III), and 5-20% (I).

Accordingly, the bromination of compound of Formula I can be carried out by any of the methods reported in the prior art such as using N-bromoimides or DDH as brominating agent in a suitable solvent in the presence of a chemical initiator like benzoyl peroxide or AIBN or without the chemical initiator. The product was obtained as a cake with the composition as Compound of Formula II – 84%+ Compound of Formula III – 11% + Compound of Formula I – 5%

According to present invention, the crude reaction mixture containing a mixture of compounds of Formula II, compounds of Formula III and compounds of Formula I, obtained as a cake is further stirred with an organic solvent at a temperature of above 50° C.

Stirring temperature varies between 50° to 90°C, preferably between 60°C to 90°C, more preferably between 60° to 70°C.

Stirring time varies from 10 to 90 minutes, preferably for 10 to 60 minutes, more preferably for 10 to 45 minutes.

The organic solvent is selected from esters and ethers; preferably esters, more preferably alkyl ester of C_1-C_4 carboxylic acid.

The solvent used is 1 to 5 times with respect to the crude reaction mixture, preferably 2 to 4 times.

The slurry obtained in step (a) is then cooled gradually to less than 20°C, preferably between 0°C to 15°C, more preferably between 0°C to 10°C and maintained the temperature with stirring. Stirring is continued for 1-3 hours, preferably for 1 hour.

Crystals thus obtained are collected by filtration and dried under vacuum to obtain compounds of the Formula II with HPLC purity >97%.

Purity of the compounds of Formula II can be further enhanced by repeating the above mentioned treatment.

According to the present invention compounds of Formula II are obtained in 91-95% yield.

Bromination of compounds of Formula I is carried out by methods known in the literature.

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather

than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

Examples

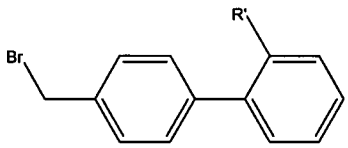
Example-1
Bromination of 4-methyl-2'-cyanobiphenyl (OTBN)

100 g OTBN was added to 500 ml dichloromethane, 100 g NBS and 5 g AIBN were added to the reaction mixture. The mixture was then stirred at 40°C to 45°C for 4 to 5 hours and then monitored by HPLC. After cooling to room temperature, the organic layer was washed with water (2 x 100 ml). Dichloromethane was stripped off. The residue was dried under vacuum to get 140 g of cake (Composition by HPLC (Unquantified area%)- Br-OTBN– 84%+ dibromo-OTBN – 11% + OTBN – 5%)

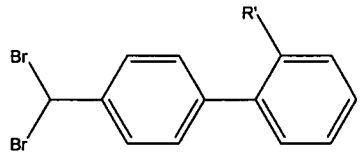
Example-2
Separation of 4-Bromomethyl-2'- cyano biphenyls
The cake obtained in Example-1 was transferred to a flask and slurried with 300 ml ethyl acetate. The reaction mixture was heated to 60° to 70° C. After stirring for 15 minutes, the mixture was gradually cooled to 3° to 5°C, maintained for 1 hour with stirring and filtered. Additional quantity of the product was obtained by concentrating the mother liquor, cooling it to 0°C to 5°C and filtration.
Yield – 129 g (91.5%); HPLC > 97.5% purity.

We claim,

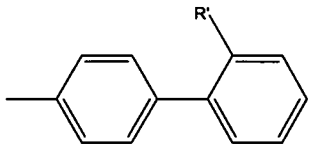
1. A process for the separation of 4-bromomethyl-2'-substituted biphenyls of Formula II from 4,4-dibromomethyl-2'-substituted biphenyls of Formula III and 4-methyl-2'-substituted biphenyl of Formula I



Formula II



Formula III



Formula I

wherein R' is cyano, 1-H tetrazole or N-protected 1-H tetrazole;

comprising;

a) stirring the crude reaction mixture in an organic solvent at above 50° C;

b) gradually cooling below 20°C and stirring; and

c) filtering the crystals to obtain compound of Formula II with >97% purity.

2. The process as claimed in claim 1, wherein the organic solvent is selected from esters and ethers, preferably esters, more preferably alkyl esters of C1-C4 carboxylic acids.

3. The process as claimed in claims 1 or 2, wherein the solvent used is 1 to 5 times with respect to the crude reaction mixture, preferably 2 to 4 times.

4. The process as claimed in claim 1, wherein the stirring temperature varies between 50° to 90°C, preferably between 60° to 90°C, most preferably between 60°C to 70°C.

5. The process as claimed in claim 1(a), wherein the stirring time varies from 10 to 90 minutes, preferably for 10 to 45 minutes.

6. The process as claimed in claim 1, wherein the slurry obtained in step (a) is cooled gradually to less than 20°C, preferably between 0°C to 15°C, more preferably between 0°C to10°C.

7. The process as claimed in claims 1 (b) or claim 6, wherein the stirring is continued for 1 to 3 hours, preferably for 1 hour.

8. The process as claimed in any of the preceding claims, wherein the compound of formula II obtained with purity of >97%.

9. A process for the separation of 4-bromomethyl-2'-substituted biphenyls of Formula II from 4,4-dibromomethyl-2'-substituted biphenyls of Formula III and 4-methyl-2'-substituted biphenyl of Formula I as substantially described herein with reference to the foregoing examples 1 to 2.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2007/000613

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C253/34 C07C255/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ULRICH BEUTLER ET AL: "A High-Throughput Process for Valsartan" ORGANIC PROCESS RESEARCH AND DEVELOPMENT, vol. 11, 28 July 2007 (2007-07-28), pages 892-898, XP002479424 First paragraph of the experimental section	1-9
X	US 2002/095042 A1 (SCHNEIDER HEINRICH [DE] ET AL) 18 July 2002 (2002-07-18) cited in the application examples 1-5	1-9
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 May 2008	26/05/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cooper, Simon

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2007/000613

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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