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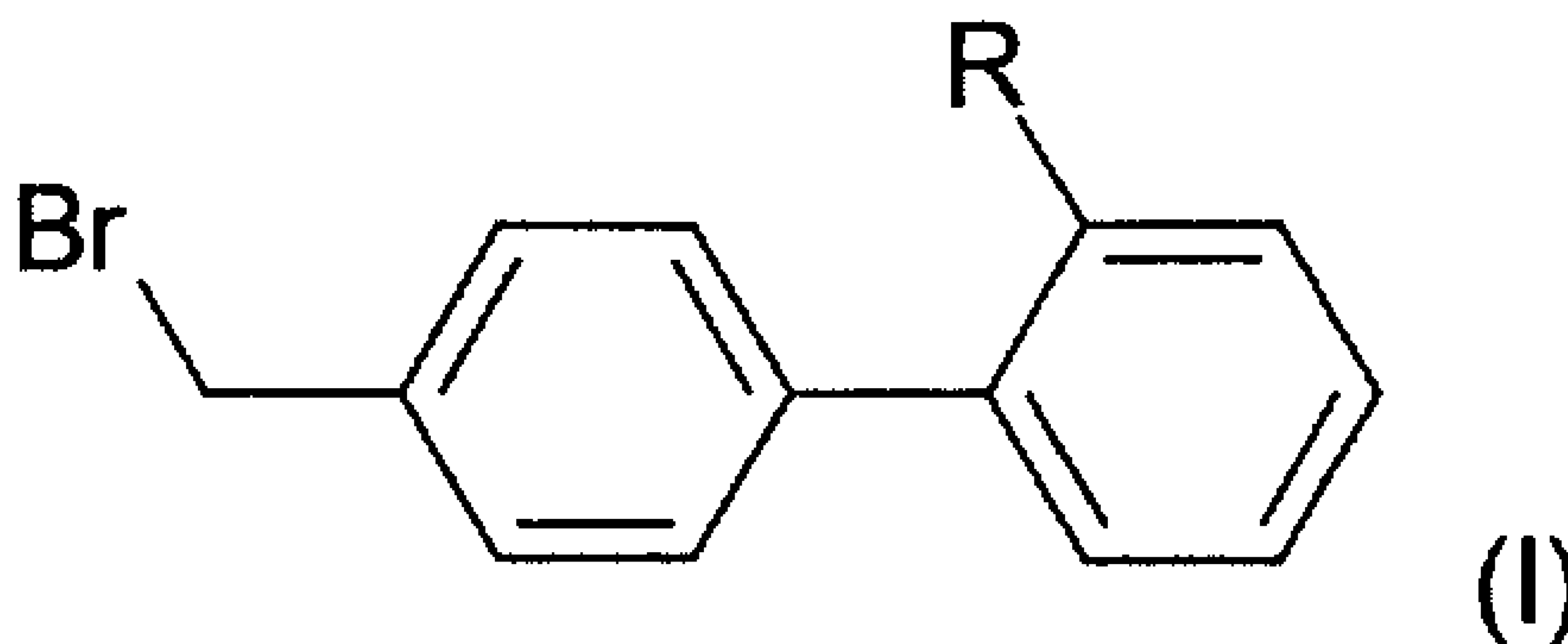
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(54) Titre : PROCEDE DE BROMATION DE CHAÎNE LATÉRALE DE DÉRIVÉS DE 4-METHYLBIPHENYLE
SUBSTITUÉS EN POSITION 2'

(54) Title: PROCESS FOR BROMINATING THE SIDE CHAIN OF 4-METHYLBIPHENYL DERIVATIVES SUBSTITUTED
IN THE 2' POSITION



(57) **Abrégé/Abstract:**

The invention relates to a method, which can be applied in industrial scale, for carrying out the side chain bromination of 4-methyl biphenyl derivatives substituted at the 2'-position with N-bromoimides or N-bromoamides in order to form 4-bromomethyl biphenyl derivatives which are substituted at the 2'-position and which are of general formula (I), wherein R can have the meaning cited in the description and in the claims.

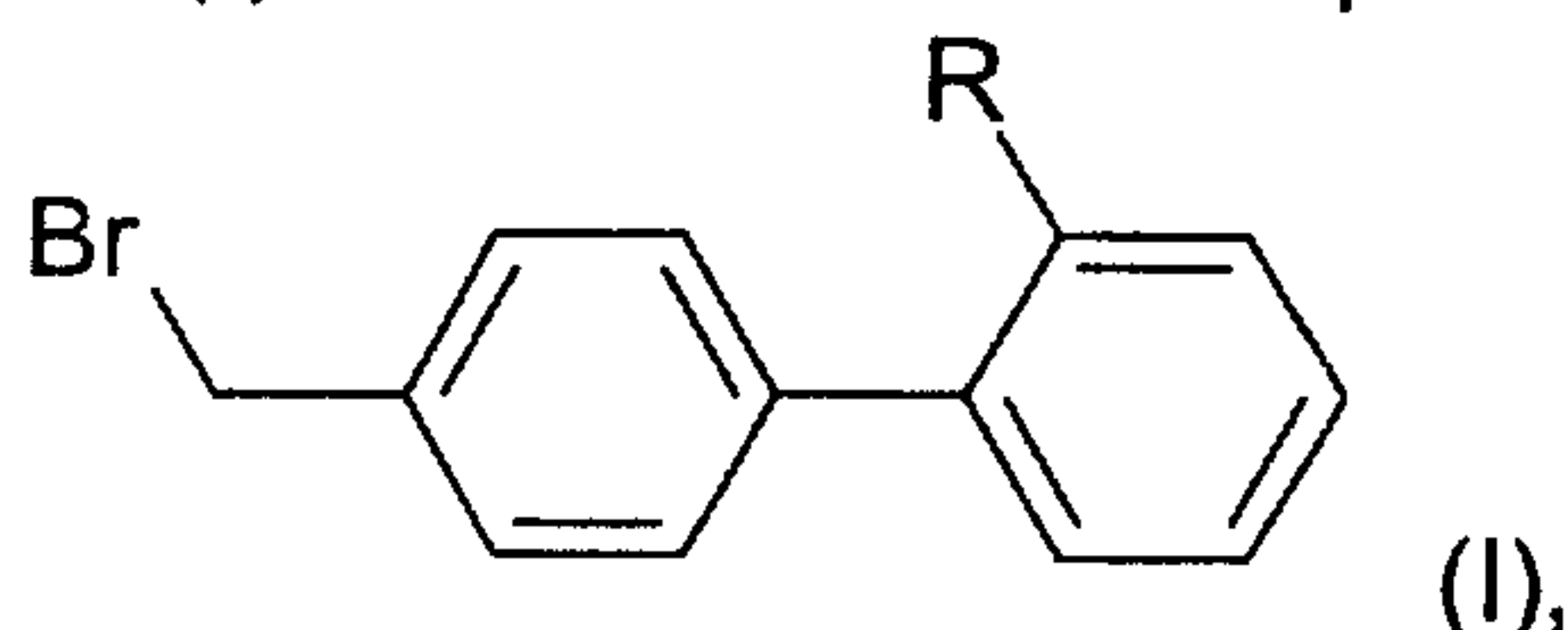
(57) Abstract

The invention relates to a method, which can be applied in industrial scale, for carrying out the side chain bromination of 4-methyl biphenyl derivatives substituted at the 2'-position with N-bromoimides or N-bromoamides in order to form 4-bromomethyl biphenyl derivatives which are substituted at the 2'-position and which are of general formula (I), wherein R can have the meaning cited in the description and in the claims.

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**Process for brominating the side chain of 4-methylbiphenyl derivatives
substituted in the 2' position**

- 5 The invention relates to a process which can be used on an industrial scale for brominating the side chain of 4-methylbiphenyl derivatives substituted in the 2' position with N-bromo-imides or -amides to obtain 4-bromomethylbiphenyl derivatives of general formula (I) substituted in the 2' position



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wherein R may have the meanings given in the specification and in the claims.

Background of the invention

- 4-Bromomethylbiphenyl derivatives of general formula (I) substituted in the 2' position are very valuable as intermediate products in the production of pharmaceutically useful active substances, particularly in the production of active substances for drugs which may be used as angiotensin-II-antagonists.

- Processes for preparing biphenyl derivatives of general formula (I) are known from the prior art. EP-A-253310 proposes using N-bromosuccinimide (NBS hereinafter) in the presence of the radical forming agent azo-bis-isobutyronitrile (AIBN hereinafter) in carbon tetrachloride at the boiling point of the solvent in order to react 4-methyl-2'-methoxycarbonylbiphenyl to obtain the corresponding bromomethyl derivative. For preparing 4-bromomethylbiphenyl derivatives, EP-A-553879 discloses bromination of the corresponding methyl-biphenyls using NBS or N-bromo-phthalimide in the presence of a radical-forming agent in a halogenated solvent. EP-A-595150 discloses a method of preparing, for example, 4-bromomethyl-2'-cyanobiphenyl by bromination with NBS in the presence of benzoylperoxide in chlorobenzene as solvent.

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- The methods of brominating 4-methylbiphenyl derivatives substituted in the 2' position known from the prior art do, however, have a number of drawbacks when attempts are made to carry out synthesis on an industrial scale. Thus, they generally use chlorinated hydrocarbons, which are known to be capable of causing liver and kidney damage, as solvents. Moreover, they are usually characterised by long reaction times when reactions are carried out on an industrial scale. However,

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lengthy reaction times lead to an increased formation of the bis-bromo products, which has a detrimental effect on the yield and purity of the desired mono-bromo derivatives.

- 5 The aim and objective of the present invention is therefore to provide an industrial-scale process for preparing 4-methylbiphenyl derivatives substituted in the 2' position which overcomes the disadvantages encountered in the processes known from the prior art.

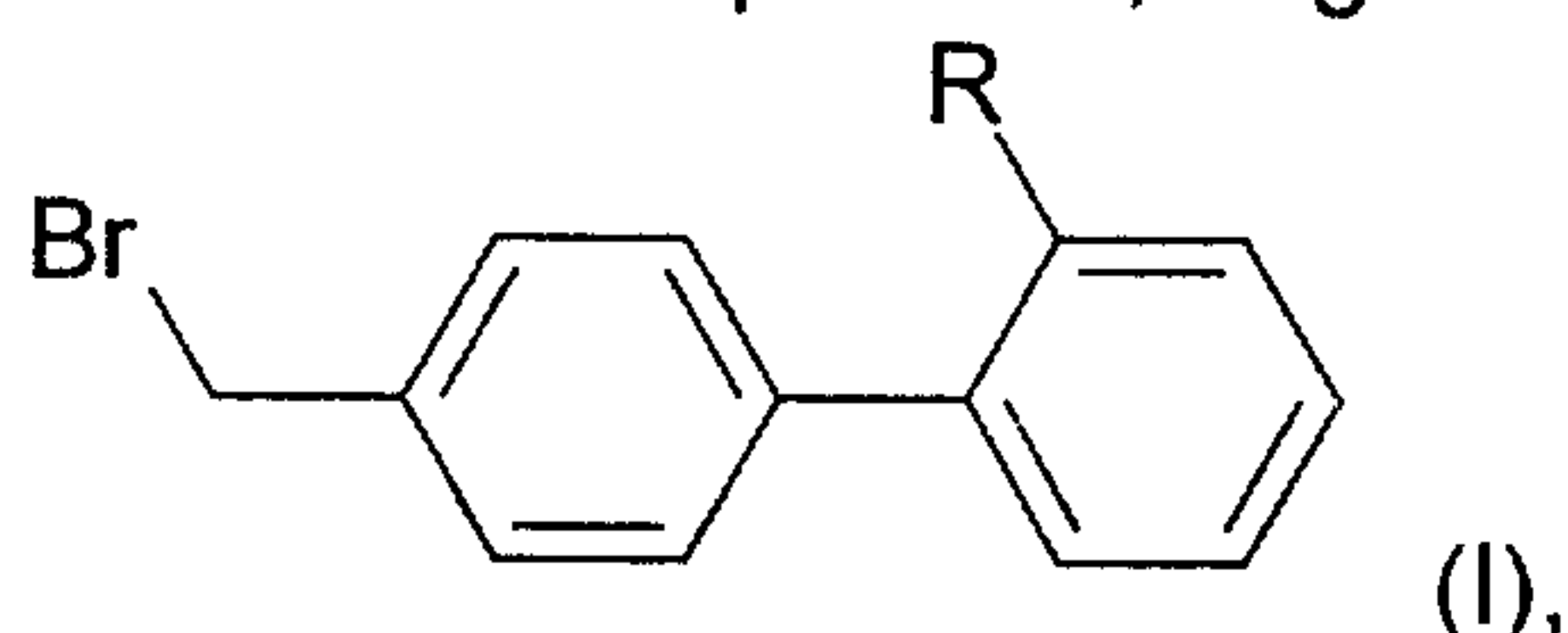
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Detailed description of the invention

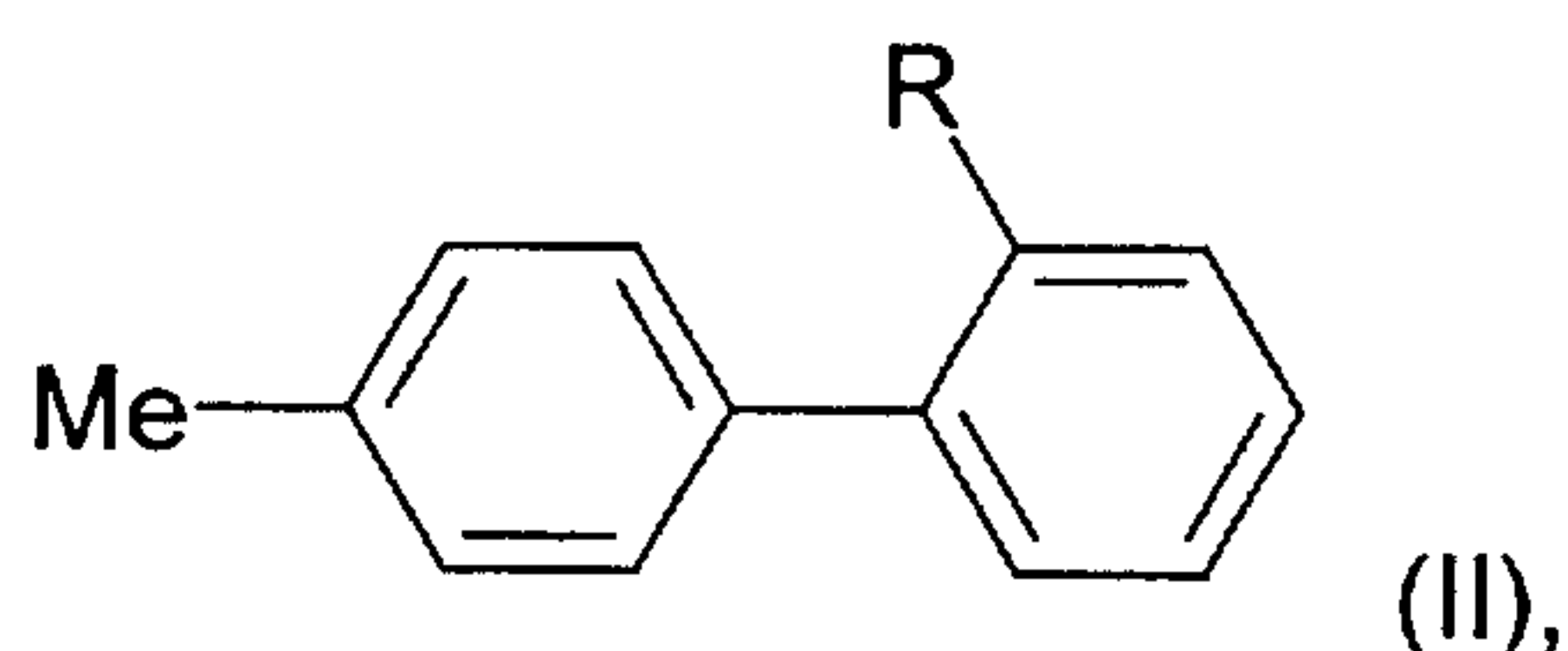
It has been found that, surprisingly, the abovementioned disadvantages of the bromination methods known from the prior art can be avoided if organic carboxylic acid esters are used as the solvents during bromination with N-bromo-imides or -amides.

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The present invention consequently relates to the preparation of 4-bromomethylbiphenyl derivatives, substituted in the 2' position, of general formula (I)



by reacting 4-methylbiphenyl derivatives, substituted in the 2' position, of general
20 formula (II)



wherein

- R denotes CN, COOR¹, CONR¹R² or C(OR³)=NR⁴, or 5-tetrazolyl optionally substituted by benzyl, methyloxycarbonyl, ethyloxycarbonyl,
25 9-fluorenylmethyloxycarbonyl, 2,2,2-trichloroethyloxycarbonyl, benzyloxycarbonyl, tert.butyloxycarbonyl, allyloxycarbonyl, trichloroacetyl, trifluoroacetyl or trityl;
- R¹, R² which may be identical or different denote hydrogen or C₁-C₆-alkyl, preferably C₁-C₄-alkyl;
- 30 R³ and R⁴ together denote a C₂-C₃-alkylene bridge optionally mono-, di-, tri- or tetra-substituted by one or more of the groups methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert.-butyl, phenyl or naphthyl,

characterised in that bromination is carried out by means of N-bromo-imides or -amides in the presence or absence of a radical-forming agent in organic carboxylic acid esters as solvent.

- 5 A preferred process according to the invention is a process for preparing compounds of general formula (I) wherein
- R denotes CN, COOR¹, CONR¹R² or C(OR³)=NR⁴, or 5-tetrazolyl optionally substituted by benzyl, 9-fluorenylmethyloxycarbonyl, benzyloxycarbonyl, tert. butyloxycarbonyl, allyloxycarbonyl or trityl;
- 10 R¹, R² which may be identical or different denote hydrogen or C₁-C₄-alkyl; R³ and R⁴ together denote a C₂-C₃-alkylene bridge optionally mono- or disubstituted by methyl.

It is also preferred according to the invention to synthesise compounds of general
15 formula (I) wherein R denotes CN, COOR¹ or 5-tetrazolyl and R¹ denotes hydrogen or C₁-C₄-alkyl.

It is particularly preferred to synthesise compounds of general formula (I) wherein R denotes CN or COOR¹ and R¹ denotes hydrogen, methyl, ethyl, n-propyl, iso-propyl,
20 n-butyl, iso-butyl, 2-butyl or tert.-butyl.

Of particular interest according to the invention is the synthesis of compounds of general formula (I) wherein R denotes CN, COOH or COO-tert.-butyl.

- 25 Suitable brominating agents include, in particular, the standard commercial N-bromo-imides and -amides such as N-bromosuccinimide (NBS), N-bromophthalimide, N-bromo-acetamide, N,N'-dibromo-5,5-dimethylhydantoin (DDH) or N,N'-dibromo-5,5-diphenylhydantoin. According to the invention it is preferable to use the brominating reagents NBS and DDH.

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Suitable solvents include, in particular, organic carboxylic acid esters with 3-6 carbon atoms. It is preferable to use as the solvent a carboxylic acid ester selected from the group comprising methyl acetate, ethyl acetate, dimethyl carbonate or diethyl carbonate. It is particularly preferable to use methyl acetate and ethyl acetate as
35 solvent. According to the invention, methyl acetate is of particular importance as the solvent.

The process according to the invention may be carried out in the presence or absence of a radical forming agent. If radical forming agents are used, according to

the invention, standard commercial compounds of the azo-bis series may be used, e.g. AIBN or organic peroxides such as bis-benzoylperoxide. Preferably, AIBN is used as the radical forming agent.

- 5 The following method is used according to the invention to prepare 4-bromomethyl-biphenyl derivatives substituted in the 2' position of general formula (I).
In a reaction apparatus of suitable dimensions, 100-120 mol%, preferably 100-110 mol%, most preferably about 105 mol% of brominating reagent and optionally 0 - 2 mol% of radical forming agent, per 100 mol of methylbiphenyl derivative of general
10 formula (II), are added to the solvent, the organic carboxylic acid ester, and the mixture is heated to boiling. In the course of the reaction (after about 70-80 % of the reaction time) the brominating reagent goes into solution. As soon as the solution has become practically colourless, the solvent is mainly (about 50-90%) distilled off. The residue remaining is taken up in a mixture of an at least partially water-miscible
15 solvent and the product is precipitated by the addition of water, while at the same time the imide or amide formed goes into solution. In the case of acid-sensitive products decomposition can be largely prevented by the addition of basic substances. Excesses of brominating reagent can be deactivated by the addition of reducing substances. After crystallisation, the product is centrifuged, preferably
20 washed with the same mixture of solvent and water and dried.

The reaction times are generally in the range from 10 minutes to 8 hours. It has been found that the particular reaction time is strongly dependent on the purity of the compound of formula (II) used. Moreover, it has been found that the reaction times
25 observed exhibit a strong dependency on concentration. To carry out the methods of synthesis according to the invention, the applicants normally used 30-100 l of carboxylic acid ester, preferably 40-90 l of carboxylic acid ester, most preferably about 50-80 l of carboxylic acid ester per 100 mol of methylbiphenyl derivative of general formula (II). Depending on the amount of solvent used, which may also be
30 outside the range specified above if it is desirable for the reaction to be faster or slower, it is possible to influence the reaction time decisively.

In addition to the advantages of the process according to the invention mentioned earlier, such as the absence of halogenated solvents, the short reaction times and
35 the reduced tendency to form the dibromo adducts, the process is characterised by a high space-time yield.

Moreover, the procedure according to the invention achieves a technically important improvement over other bromination processes with N-bromo-imides or -amides

known from the prior art. Since the solvent used according to the invention is partially water-miscible and the imides or amides formed in the course of bromination with N-bromo-imides or -amides remain in solution in the mother liquor during the working up according to the invention in a mixture of water and another water-miscible solvent, laborious filtering of the mother liquor is no longer necessary.

The Examples which follow serve to illustrate methods of synthesis carried out by way of example for preparing 4-bromomethylbiphenyl derivatives substituted in the 2' position. They should be regarded simply as possible procedures described by way of example, without restricting the invention to their content.

Example 1

241.2 kg of tert.-butyl 4-methylbiphenyl-2'-carboxylate, 168.2 kg of NBS, 0.3 kg of AIBN and 724 l of methyl acetate are placed in a 1200 litre enamel stirring apparatus and the mixture is heated to 60 – 65°C. The reaction mixture begins to boil and after about 80 % of the reaction time the NBS goes into solution. As soon as the solution has become practically colourless, 603 l of solvent are distilled off under normal pressure and then 482 l of isopropanol, 121 l of water and 14.8 kg of sodium acetate (anhydrous) are added. The resulting mixture is cooled to 15 – 25°C and stirred for a further 1 h. The product precipitated is separated by centrifugation, washed with a mixture of 482 l of isopropanol and 121 l of water and dried.

Yield : 250 kg of tert.-butyl 4-bromomethylbiphenyl-2'-carboxylate
(80 % of theory)

Example 2

241.2 kg of tert.-butyl 4-methylbiphenyl-2'-carboxylate, 168.2 kg of NBS, 0.3 kg of AIBN and 724 l of methyl acetate are placed in a 1200 l enamel stirring apparatus and the mixture is heated to 60 – 65°C. The reaction mixture begins to boil and after about 80% of the reaction time the NBS goes into solution. As soon as the solution has become practically colourless, 603 l of solvent are distilled off under normal pressure and then 482 l of acetone, 121 l of water and 14.8 kg of sodium acetate (anhydrous) are added. The resulting mixture is cooled to 15 – 25°C and stirred for a further 1 h. The product precipitated is separated by centrifugation, washed with a mixture of 482 l of acetone and 121 l of water and dried.

Yield : 250 kg of tert.-butyl 4-bromomethylbiphenyl-2'-carboxylate
(80 % of theory)

Example 3

173.7 kg of 4-methyl-2'-cyanobiphenyl, 168.2 kg of NBS and 695 l of methyl acetate are placed in a 1200 l enamel stirring apparatus and the mixture is heated to 60 – 65°C. The reaction mixture begins to boil and after about 80% of the reaction time the NBS goes into solution. As soon as the solution has become practically colourless, 608 l of solvent are distilled off under normal pressure and then 434 l of methanol and 174 l of water are added. The resulting mixture is cooled to 15 – 25°C and stirred for a further 1 h. The product precipitated is separated by centrifugation, washed with a mixture of 434 l of methanol and 174 l of water and dried.

Yield : 205 kg of 4-bromomethylbiphenyl-2'-cyanobiphenyl
(83.7 % of theory)

Example 4

268.0 kg of tert.-butyl 4-methylbiphenyl-2'-carboxylate, 157.3 kg of DDH, 1.6 kg of AIBN and 572 l of methyl acetate are placed in a 1200 l enamel stirring apparatus and the mixture is heated to 60 – 65°C. As soon as the solution has become practically colourless, 458 l of solvent are distilled off under normal pressure and then 530 l of isopropanol, 148 l of water and 16.4 kg of sodium acetate (anhydrous) are added. The resulting mixture is cooled to 15 – 25°C and stirred for a further 1 h. The product precipitated is separated by centrifugation, washed with a mixture of 530 l of acetone and 148 l of water and dried.

Yield : 295 kg of tert.-butyl 4-bromomethylbiphenyl-2'-carboxylate
(85 % of theory)

Example 5

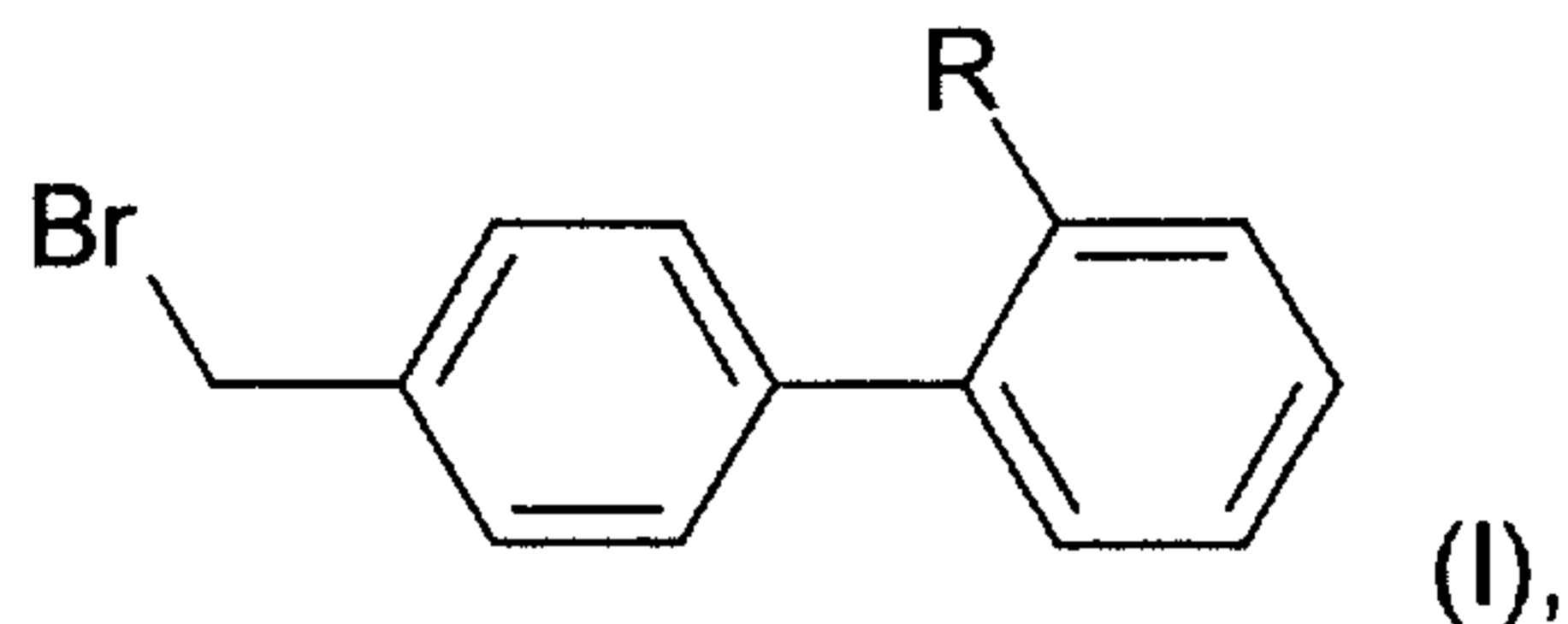
212 kg of 4-methylbiphenyl-2'-carboxylic acid, 195.8 kg of NBS, 1.6 kg of AIBN and 530 l of methyl acetate are placed in a 1200 l enamel stirring apparatus and the mixture is heated to 60 – 65°C. The reaction mixture begins to boil and after about 80% of the reaction time the NBS goes into solution. As soon as the solution has become practically colourless, 424 l of solvent are distilled off under normal pressure and then 424 l of methanol and 106 l of water are added. The resulting mixture is cooled to 15 – 25°C and stirred for a further 1 h. The product precipitated is separated by centrifugation, washed with a mixture of 424 l of methanol and 106 l of water and dried.

Yield : 240 kg of 4-bromomethylbiphenyl-2'-carboxylic acid
(82.5 % of theory)

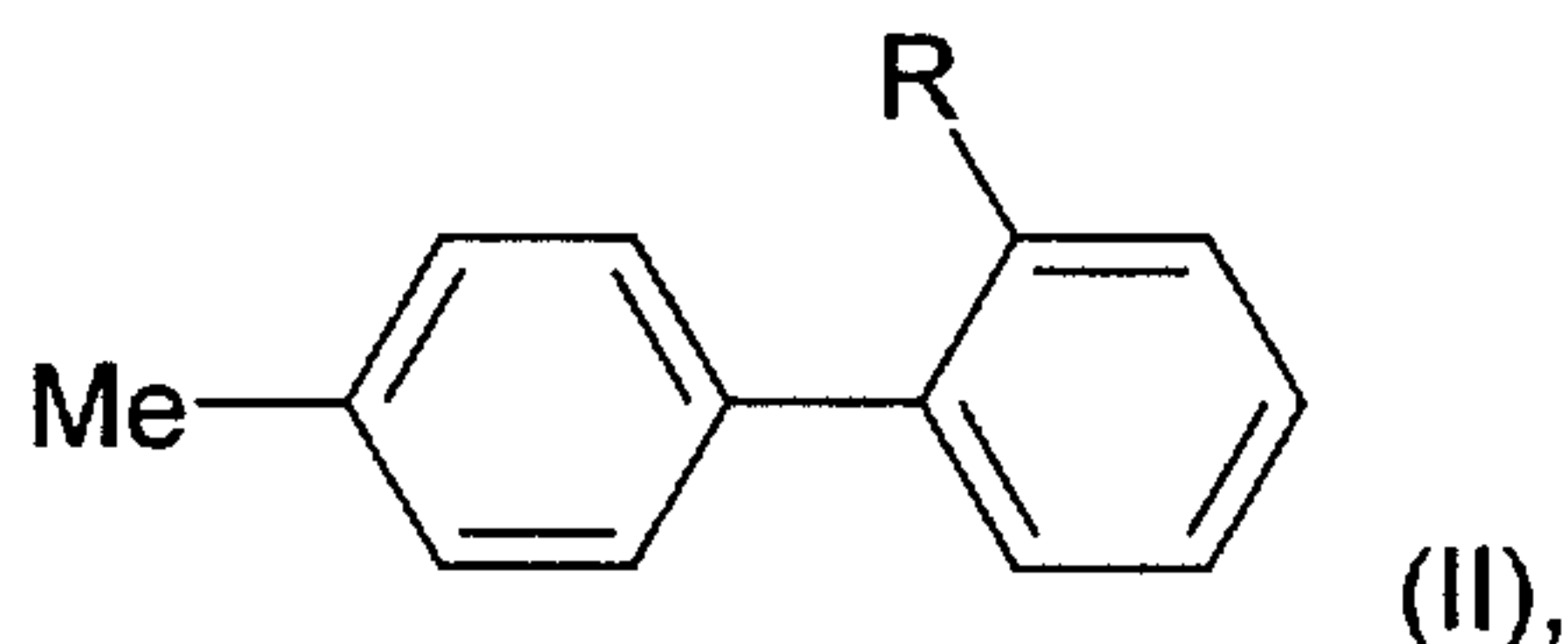
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New Patent Claims

- 1) Industrial-scale process for preparing 4-bromomethyl-biphenyl derivatives
5 substituted in the 2' position of general formula (I)



by reacting 4-methylbiphenyl derivatives substituted in the 2' position of general formula (II)



10 wherein

R denotes CN, COOH or COO-tert. butyl,

characterised in that bromination is carried out by means of NBS or DDH in
the presence of a radical forming agent selected from AIBN or benzoyl
15 peroxide in methyl acetate.

- 2) Process according to claim 1, wherein R denotes COO-tert. butyl.
- 3) Process according to one of claims 1 or 2, characterised in that, during working
20 up, the imide or amide formed is dissolved in a mixture of water and another
water-miscible solvent in the mother liquor.

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