(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 461 331 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
08.03.2006 Bulletin 2006/10

(21) Application number: **02793596.4**

(22) Date of filing: **09.12.2002**

(51) Int Cl.:
C07D 319/06 *(2006.01)*

(86) International application number:
PCT/NL2002/000876

(87) International publication number:
WO 2003/059901 (24.07.2003 Gazette 2003/30)

(54) **PROCESS FOR THE PREPARATION OF 2-(6-SUBSTITUTED-1,3-DIOXANE-4-YL) ACETIC ACID DERIVATIVES**

PROZESS FÜR DIE HERSTELLUNG VON 2-(6-SUBSTITUIERTEN-1,3-DIOXAN-4-YL) ESSIGSÄURE DERIVATEN

PROCEDE DE PREPARATION DE DERIVES D'ACIDE 2-(6-SUBSTITUE-1,3-DIOXANE-4-YL) ACETIQUE

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SI SK TR
Designated Extension States:
AL LT LV MK RO

(30) Priority: **27.12.2001 EP 01000794**

(43) Date of publication of application:
29.09.2004 Bulletin 2004/40

(60) Divisional application:
05014484.9

(73) Proprietor: **AstraZeneca UK Limited**
London,
Greater London W1K 1LN (GB)

(72) Inventor: **HOF, Robert, Patrick**
NL-5981 GD PAnningen (NL)

(74) Representative: **Bill, Kevin**
AstraZeneca
R&D Headquarters
Global Intellectual Property, Patents
SE-151 85 Södertälje (SE)

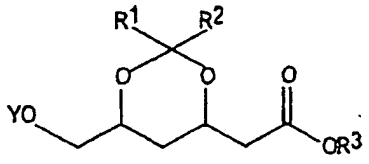
(56) References cited:
EP-A- 1 024 139

EP 1 461 331 B1

Printed by Jouve, 75001 PARIS (FR)

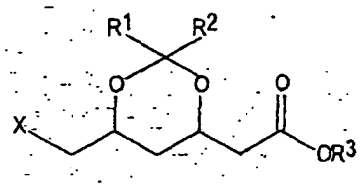
Description

[0001] The invention relates to a process for the preparation of a 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 1,



(1)

wherein R^1, R^2 and R^3 are each independently a C1-4 alkylgroup or wherein R^1 and R^2 together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl and wherein Y stands for R^A-CO- or for R^B-SO_2- with R^A, R^B are chosen from the group of alkyl or aryl with 1-12 C-atoms, from its corresponding 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 2,



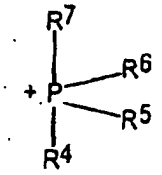
(2)

wherein R^1, R^2 and R^3 are as defined above and wherein X stands for a halogen, in the presence of a phase transfer catalyst and an oxylating agent.

[0002] Such a process is known from EP 1 024 139, wherein the preparation of a compound according to formula 1 from a compound according to formula 2 is achieved in the presence of a quaternary ammonium salt (phase transfer catalyst) and a carboxylic acid salt (acyloxylafing agent).

[0003] It is the object of the invention to provide an alternative process for the preparation of a 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 1 from its corresponding 2-(6-substituted-1,3-dioxane-4-yl) acetic acid derivative according to formula 2.

[0004] This is achieved according to the invention by using a quarternary phosphonium ion according to formula 3 as a phase transfer catalyst,



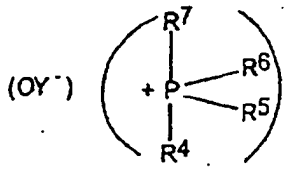
(3)

wherein R^4, R^5, R^6, R^7 each independently stand for an alkyl, cycloalkyl, aralkyl or aryl with 1 to 12 C-atoms, and an ion according to formula 4,

$$OY^- \qquad (4)$$

wherein Y is as defined above, as an oxylating agent. The reaction has a high yield.

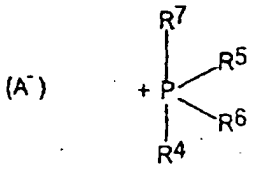
[0005] The quarternary phosphonium ion according to formula 3 used as a phase transfer catalyst and the ion according to formula 4 used as an oxylating agent may be present in a quarternary phosphonium salt according to formula 5,



(5)

wherein Y, R^4, R^5, R^6 and R^7 are as defined above. The phosphonium salt according to formula 5 can be used as both a phase transfer catalyst and as an oxylating agent. The quarternary phosphonium salt according to formula 5 can be prepared according to methods known to the person skilled in the art (e.g. analogous to the preparation of tetra-n-butylammoniumacetate as described in US 5 278 313).

[0006] In a preferred embodiment of the invention, the phase transfer catalyst and the oxylating agent are not present in the same molecule. In this embodiment, a quarternary phosphonium salt according to formula 3a,



(3a)

wherein R^4, R^5, R^6 and R^7 are as defined above and wherein A stands for the anion of the quarternary phopshoniumsalt and is selected from the group of halogens, for example Cl, Br, I is used as a phase transfer catalyst and the acid salt according to formula 4a,

$$(OY^-)_n\ M^{n+} \qquad (4a)$$

wherein Y is as defined above, wherein M stands for alkali metal or an alkaline metal, for example Li, K, Na, Mg, Ca, Ba and wherein n represents an integer of 1 or 2, depending on the valence of M is used as an oxylating agent. Preferred is M is K or Na.

[0007] In the process according to the invention, halogens X are preferably Cl, Br or I, more preferably Cl.

[0008] In the process according to the invention, R^1, R^2 and R^3 are preferably a C1-4 alkyl group, more preferably R^1 and R^2 are a methyl or an ethyl group, more preferably a methyl group. R^3 is preferably a methyl or a butyl, most preferably a t-butyl.

[0009] In the process according to the invention Y groups are preferably represented by R^A-CO- or R^B-SO_2-, wherein R^A, R^B are chosen from the group of C_1-C_4 alkyl or aryl with 6-10 C-atoms. In a preferred embodiment, Y is chosen from the group of acyl, more preferably acetyl (with R^A is CH_3), benzenesulphonyl (with R^B is benzene), more preferably nitro substituted benzenesulphonyl (with R^B is p-nitrobenzene), tosyl (with R^B is p-methyl-benzene) or mesyl (with R^B is methyl).

[0010] In the process according to the invention, preferably a phosphonium salt according to formula 3a or according to formula 5, with at least three out of four R groups are the same (e.g. R^4, R^5, R^6 are butyl and R^7 is methyl or R^4, R^5, R^6 are phenyl and R^7 is butyl), more preferably a phosphonium salt with all four R groups are the same, is used.

[0011] R^A and R^B and R^4, R^5, R^6, R^7, -in case R^4, R^5, R^6, R^7 are aryl or aralkyl-, may be substituted for example with substituents chosen from the group of halogens, alkoxy (e.g. methoxy or ethoxy) with 1-6 C-atoms, alkyl with 1-6 C atoms, (e.g. methyl if R^B is toluene) or nitro, preferably only R^A or R^B are substituted.

[0012] The quarternary phosphonium salt according to formula 3a is preferably used in a molar equivalent amount of 0.01 to 1.0, more preferably 0.05 to 0.7, most preferably 0.1 to 0.5 relative to the amount of compound according to formula 2.

[0013] The quarternary phosphonium salt according to formula 5 is preferably used in a molar equivalent amount of 0.8 to 5, preferably 1 to 3, most preferably 1 to 1.5.

[0014] The acid salt according to formula 4a is preferably used in a molar equivalent amount of 1 to 5 relative to the amount of compound according to formula 2 present. More preferably, a molar equivalent amount of acid salt according to formula 4a of 1 to 4, most preferably 2 to 3, is used.

[0015] The solvents suitable for use in the present invention are a various number of organic solvents, which are known to the person skilled in the art. Organic solvents, which may be used are hydrocarbon series solvents, for example benzene, toluene, cyclohexane, etc; ether series solvents, for example diethyl ether tetrahydrofuran, 1,4-dioxane, methyl-

t-butyl ether, dimethoxyethane, etc.; ester series solvents, for example ethyl acetate, butyl acetate, etc.; halogen containing solvents, for example methylene chloride, chloroform, 1,1,1-trichloroethane, etc.; nitrogen-containing solvents, for example acetamide, formamide, acetonitrile etc.; and aprotic polar solvents, for example dimethyl sulfoxide, N, N-dimethylformamide, N-methylpyrrolidone, hexamethylphosphoric triamide etc. Preferably, the solvent used is an aprotic polar solvent, more preferably the solvent used is N-methylpyrrolidone or N.N-dimethylformamide. The solvent can be used alone or in combination with one or more other solvent species, for example N-methylpyrrolidone in combination with toluene.

[0016] The temperature, by which the process of the invention is preferably carried out, is between 80 and 200°C, more preferably between 100 and 160°C, most preferably between 110 and 150°C.

[0017] The reaction product can be isolated from the reaction medium, if desired, according to methods known to the person skilled in the art (e.g. the method as described in US 5 278 313).

[0018] The invention will be illustrated by way of the following examples. However, these examples are not meant to restrict the invention.

Examples

Example 1

[0019] 0.5 molar equivalents tetrabutylphosphoniumbromide (TBPB) and 2.5 molar equivalents potassiumacetate were added to a solution of I (tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate) in the solvent N-methylpyrrolidone (1g/3ml) at 100°C. The conversion of I in the presence of TBPB was 87.6% after 20 hours reaction time, the conversion af I into II (tert-butyl 2-{(4R,6S)-2,2-dimethyl-6-[(methyl-carbonyloxy)methyl]-1 , 3-dioxan-4-yl) acetate) thereof being 90.3%.

Example 2

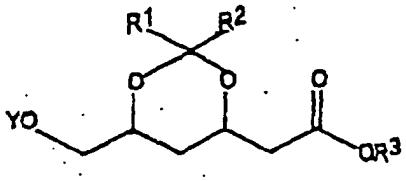
[0020] Example I was repeated whereby the reaction temperature for the conversion of I into II was kept at 115°C. The conversion of I in the presence of TBPB was 95.1% after 3 hours reaction time, the conversion of I into II thereof being 91%.

Example 3

[0021] 0.1 molar equivalents tetraphenylphosphoniumbromide (TTB) and 2.5 molar equivalents potassiumacetate were added to a solution of I (tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate) in the solvent N-methylpyrrolidone (1g/3ml) at 140°C. After 20 hours, the conversion of I was 97%, the conversion of I into II thereof being 77.2%.

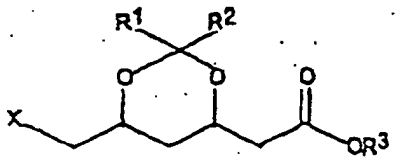
Claims

1. Process for the preparation of a 2-(6-substituted-1,3-dioxana-4-yl) acetic acid derivative according to formula 1,



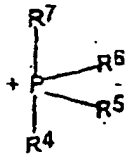
(1)

wherein R^1, R^2 and R^3 are each independently a C1-4 alkylgroup or wherein R^1 and R^2 together with the C-atom to which they are bound form a 5- or 6-membered cycloalkyl and wherein Y stands for R^A-CO- or for R^B-SO_2- with R^A,R^B are chosen from the group of alkyl or aryl with 1-12 C-atoms, from its corresponding 2-(6-substitured-1,3-dioxane-4-yl) acetic acid derivative according to formula 2,



(2)

wherein R^1, R^2 and R^3 are as defined above and wherein X stands for a halogen, in the presence of a phase transfer catalyst and an oxylating agent, **characterized in that** a quarternary phosphonium ion according to formula 3,



(3)

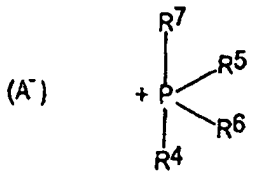
wherein R^4, R^5, R^6, R^7 each independently stand for an alkyl, cycloalkyl, aralkyl or aryl with 1 to 12 C-atoms, is used as a phase transfer catalyst and an ion according to formula 4,

$$OY^- \qquad (4)$$

wherein Y is as defined above, is used as an oxylating agent;
wherein R^A and R^B and R^4, R^5, R^6, R^7, -in case R^4, R^5, R^6, R^7 are aryl or aralky-, may be substituted with substituents chosen from the group of halogens, alkoxy with 1-6 C-atoms, alkyl with 1-6 C atoms, or nitro.

2. Process according to claim 1, **characterized in that** R^A, R^B are chosen from the group of C_1-C_4 alkyl or aryl with 6-10 C-atoms.

3. Process according to any of claims 1-2, **characterized in that** as a phase transfer catalyst a quarternary phosphonium salt according to formula 3a,



(3a)

wherein R^4, R^5, R^6 and R^7 are as defined above and wherein A stands for a halogen, is used and **in that** an acid salt according to formula 4a,

$$(OY^-)_n M^{n+} \qquad (4a)$$

wherein Y is as defined above, wherein M stands for alkali metal or an alkaline metal, is used as an oxylating agent.

4. Process according to claim 3, **characterized in that** the quarternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.05 to 0.7 relative to the amount of compound according to formula 2.

5. Process according to claim 4, **characterized in that** the quarternary phosphonium salt according to formula 3a is used in a molar equivalent amount of 0.1 to 0.5 relative to the amount of compound according to formula 2.

6. Process according to any of claims 1-5, **characterized in that** the process is carried out at a temperature between 100 and 160°C.

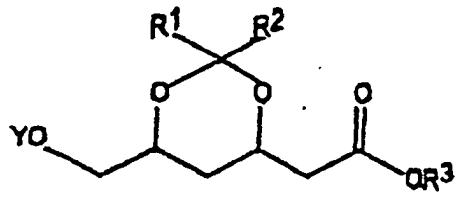
7. Process according to any of claims 1-6, **characterized in that** the process is carried out at a temperature between

110 and 150°C.

8. Process according to any of claims 1-7, **characterized in that** the compound according to formula 1 is tert-butyl 2-{(4R,6S)-2,2 dimethyl-6-[(methylcarbonyloxy)methyl]-1,3-dioxan-4-yl} acetate and **in that** the compound according to formula 2 is tert-butyl 2-[(4R,6S)-6-(chloromethyl)-2,2-dimethyl-1,3-dtoxan-4yt]acetate.

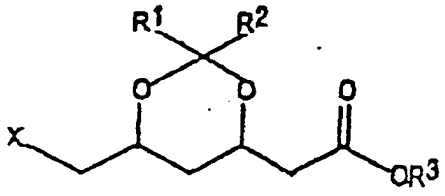
Patentansprüche

1. Verfahren zur Herstellung eines 2-(1,3-Dioxan-4-yl)essigsäurederivats mit 6-substituierter Dioxanylgruppe gemäß Formel 1



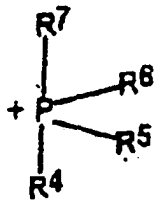
(1)

worin R^1, R^2 und R^3 jeweils unabhängig voneinander für eine C_{1-4}-Alkylgruppe stehen oder R^1 und R^2 gemeinsam mit dem C-Atom, an das sie gebunden sind, 5- oder 6-gliedriges Cycloalkyl bilden und Y für R^A-CO- oder R^B-SO_2- steht, wobei R^A und R^B aus der Gruppe bestehend aus Alkyl oder Aryl mit 1-12 C-Atomen ausgewählt sind, aus dem entsprechenden 2-(1,3-Dioxan-4-yl)essigsäurederivat mit 6-substituierter Dioxanylgruppe gemäß Formel 2



(2)

worin R^1, R^2 und R^3 die oben angegebene Bedeutung besitzen und X für Halogen steht, in Gegenwart eines Phasentransferkatalysators und eines Oxylierungsmittels, **dadurch gekennzeichnet, daß** man als Phasentransferkatalysator ein quaternäres Phosphoniumion gemäß Formel 3



(3)

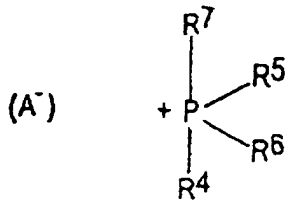
worin R^4, R^5, R^6 und R^7 jeweils unabhängig voneinander für Alkyl, Cycloalkyl, Aralkyl oder Aryl mit 1 bis 12 C-Atomen stehen, und als Oxylierungsmittel ein Ion gemäß Formel 4

$$OY^- \qquad (4)$$

worin Y die oben angegebene Bedeutung besitzt, verwendet;
wobei R^A und R^B und R^4, R^5, R^6 und R^7- in dem Fall, daß R^4, R^5, R^6 und R^7 für Aryl oder Aralkyl stehen - durch Substituenten aus der Gruppe bestehend aus Halogenen, Alkoxy mit 1-6 C-Atomen, Alkyl mit 1-6 C-Atomen oder Nitro substituiert sind.

2. Verfahren nach Anspruch 1, **dadurch gekennzeichnet, daß** man R^A und R^B aus der Gruppe bestehend aus C_1-C_4-Alkyl oder Aryl mit 6-10 C-Atomen auswählt.

3. Verfahren nach einem der Ansprüche 1-2, **dadurch gekennzeichnet, daß** man als Phasentransferkatalysator ein quaternäres Phosphoniumsalz gemäß Formel 3a



(3a)

worin R^4, R^5, R^6 und R^7 die oben angegebene Bedeutung besitzen und A für Halogen steht, und als Oxylierungsmittel ein Säuresalz gemäß Formel 4a

$$(OY^-)_n\ M^{n+} \qquad (4a)$$

worin Y die oben angegebene Bedeutung besitzt und M für Alkalimetall oder ein alkalisches Metall steht, verwendet.

4. Verfahren nach Anspruch 3, **dadurch gekennzeichnet, daß** man das quaternäre Phosphoniumsalz gemäß Formel 3a in einer Moläquivalentmenge von 0,05 bis 0,7, bezogen auf die Menge an Verbindung der Formel 2, verwendet.

5. Verfahren nach Anspruch 4, **dadurch gekennzeichnet, daß** man das quaternäre Phosphoniumsalz gemäß Formel 3a in einer Moläquivalentmenge von 0,1 bis 0,5, bezogen auf die Menge an Verbindung der Formel 2, verwendet.

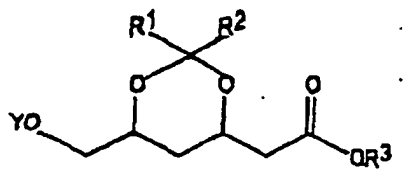
6. Verfahren nach einem der Ansprüche 1-5, **dadurch gekennzeichnet, daß** man es bei einer Temperatur zwischen 100 und 160°C durchführt.

7. Verfahren nach einem der Ansprüche 1-6, **dadurch gekennzeichnet, daß** man es bei einer Temperatur zwischen 110 und 150°C durchführt.

8. Verfahren nach einem der Ansprüche 1-7, **dadurch gekennzeichnet, daß** es sich bei der Verbindung gemäß Formel 1 um 2-{(4R,6S)-2,2-Dimethyl-6-[(methylcarbonyloxy)methyl]-1,3-dioxan-4-yl}essigsäure-tert.-butylester und bei der Verbindung gemäß Formel 2 um 2-[(4R,6S)-6-(Chlormethyl)-2,2-dimethyl-1,3-dioxan-4-yl]essigsäure-tert.-butylester handelt.

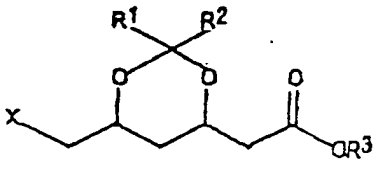
Revendications

1. Procédé pour la préparation d'un dérivé d'acide 2-((6-substituant)-1,3-dioxane-4-yl)acétique selon la formule 1,



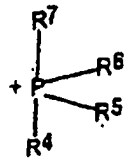
(1)

dans laquelle R^1, R^2 et R^3 sont chacun indépendamment un groupe alkyle en C1-4 ou dans laquelle R^1 et R^2 avec l'atome C auquel ils sont liés forment un cycloalkyle à 5 ou 6 éléments et dans laquelle Y représente R^A-CO- ou R^B-SO_2-, R^A et R^B étant choisis entre un alkyle ou un aryle ayant 1-12 atomes de C, à partir de son dérivé d'acide 2-((6-substituant)-1,3-dioxane-4-yl)acétique correspondant selon la formule 2,



(2)

dans laquelle R^1, R^2 et R^3 sont tels que définis ci-dessus et dans laquelle X représente un halogène, en présence d'un catalyseur de transfert de phase et d'un agent oxylant, **caractérisé en ce que** qu'on utilise comme catalyseur de transfert de phase un ion phosphonium quaternaire selon la formule 3,



(3)

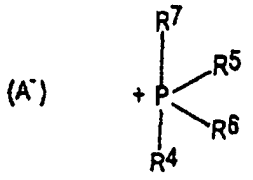
dans laquelle R^4, R^5, R^6, R^7 représentent chacun indépendamment un alkyle, un cycloalkyle, un aralkyle ou un aryle ayant 1 à 12 atomes de C et **en ce qu'**on utilise comme agent oxylant un ion selon la formule 4,

$$OY^- \qquad (4)$$

dans laquelle Y est tel que défini ci-dessus ;
dans lequel R^A et R^B et R^4, R^5, R^6, R^7, -dans le cas où R^4, R^5, R^6, R^7 sont un aryle ou un aralkyle-, peuvent être substitués par des substituants choisis entre des halogènes, un alcoxy ayant 1-6 atomes de C, un alkyle ayant 1-6 atomes de C ou un nitro.

2. Procédé selon la revendication 1, **caractérisé en ce que** R^A, R^B sont choisis entre un alkyle en C_1-C_4 ou un aryle ayant 6-10 atomes de C.

3. Procédé selon l'une quelconque des revendications 1-2, **caractérisé en ce qu'**on utilise comme catalyseur de transfert de phase un sel de phosphonium quaternaire selon la formule 3a,



(3a)

dans laquelle R^4, R^5, R^6 et R^7 sont tels que définis ci-dessus et dans laquelle A représente un halogène et **en ce qu'**on utilise comme agent oxylant un sel d'acide selon la formule 4a,

$$(OY^-)_n\, M^{n+} \qquad (4a)$$

dans laquelle Y est tel que défini ci-dessus, dans laquelle M représente un métal d'un alcali ou un métal alcalin.

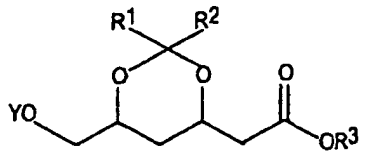
4. Procédé selon la revendication 3, **caractérisé en ce que** le sel de phosphonium quaternaire selon la formule 3a est utilisé en quantité en équivalent molaire de 0,05 à 0,7 par rapport à la quantité de composé selon la formule 2.

5. Procédé selon la revendication 4, **caractérisé en ce qu'**on utilise le sel de phosphonium quaternaire selon la formule 3a en quantité en équivalent molaire de 0,1 à 0,5 par rapport à la quantité de composé selon la formule 2.

6. Procédé selon l'une quelconque des revendications 1-5, **caractérisé en ce qu'**on effectue le procédé à une température comprise entre 100 et 160'C.

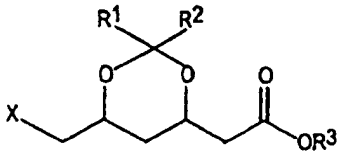
7. Procédé selon l'une quelconque des revendications 1-6, **caractérisé en ce qu'**on effectue le procédé à une température comprise entre 110 et 150°C.

8. Procédé selon l'une quelconque des revendications 1-7, **caractérisé en ce que** le composé selon la formule 1 est le 2-{(4R,6S)-2,2-diméthyl-6-[(méthylcarbonyloxy)méthyl]-1,3-dioxan-4-yl}acétate de tert-butyle et **en ce que** le composé selon la formule 2 est le 2-[(4R,6S)-6-(chlorométhyl)-2,2-diméthyl-1,3-dioxan-4-yl]acétate de tert-butyle.



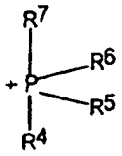
(1)

Formula 1



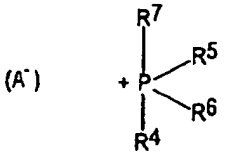
(2)

Formula 2



(3)

Formula 3

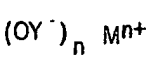


(3a)

Formula 3a

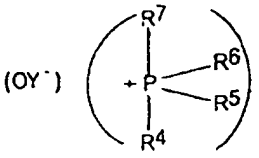
(4)

Formula 4



(4a)

Formula 4a



(5)

Formula 5