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(74) Common Representative: **ZAMBON GROUP S.P.A.**;
Industrial Property & Intelligence, via Lillo del Duca, 10,
I-20091 Bresso (IT).

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(71) Applicant (for all designated States except US): **ZAM-
BON GROUP S.P.A.** [IT/IT]; via della Chimica, 9,
I-36100 Vicenza (IT).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **PAIOCCHI, Mau-
rizio** [IT/IT]; via Valsesia, 86/b, I-20152 Milan (IT).
BELLI, Aldo [IT/IT]; via G. Quadri, 2, I-20040 Cor-
nate d'Adda (IT). **PONZINI, Francesco** [IT/IT]; via
Giambellino, 102, I-20146 Milan (IT). **VILLA, Marco**
[IT/IT]; via Riello, 7/A, I-35122 Padova (IT).

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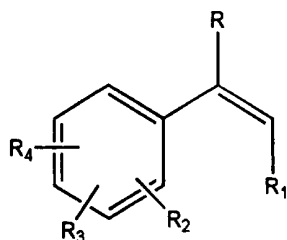
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(54) Title: PROCESS FOR THE PREPARATION OF NITROALKENES



(57) Abstract: A process for the nitration of conjugated alkenes of formula (I) wherein R, R₁, R₂, R₃ and R₄ have the meanings reported in the description, which allows to obtain the corresponding β-nitro-alkenes, characterised in that the nitrating agent is a mixture of an inorganic nitrite and iodine in the presence of an oxidising agent is described.

Process for the preparation of nitroalkenes

The present invention relates to a process for the preparation of nitroalkenes and, more particularly, it relates to a process for the preparation of conjugated β -nitroalkenes by reaction of a conjugated alkene with a nitrite in the presence of iodine and of an oxidising agent.

Conjugated β -nitroalkenes are widely used synthetic intermediates because they can be easily converted into a variety of different compounds. For example, we can cite β -nitrostyrene, useful intermediate for the preparation of several phenylethylamines and fungicides (Chemical Abstracts, vol. 118, no. 38576k), 2-nitro-dihydronaphthalenes, key intermediates for the synthesis of 2-amino-tetrahydronaphthalenes (Debasis Ghosh *et al.*, Synthesis, 1996, pages 195-197) and 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide, an intermediate for the preparation of (*R*)-3-dicyclobutylamino-8-fluoro-chroman-5-carboxylic acid amide, a compound useful in the treatment of disorders of the central nervous system (WO 98/46586 - Astra Aktiebolag).

The nitration of alkenes with nitrites and iodine is known in the literature [Hassner *et al.*, J. Org. Chem., 1969, 34(9), pages 2628-2632].

The method foresees the use of a mixture of silver nitrite and iodine as nitrating agent.

After the paper of Hassner *et al.*, some papers were published with the attempt of improving the nitration conditions.

Wing-Wah Sy *et al.* [Tetr. Lett., 1985, 26(9), pages 1193-1196] describe the nitration of substituted alkenes with silver nitrite and iodine, the only difference from Hassner *et al.* being the use of a higher molar amount of silver nitrite, which is then equimolar with respect to the iodine.

Jew *et al.* [Chemistry Letters, 1986, pages 1747-1748] replace silver nitrite with sodium nitrite and use 2 moles of iodine and 4 moles of nitrite per mole of styrene, respectively.

In the already cited paper published by Debasis Ghosh *et al.* potassium nitrite is used in the presence of a phase transfer catalyst and by treating with ultrasounds in order to increase the solubility of the nitrite ion. Different amounts of iodine were evaluated to optimise the yield and the reported general method foresees the use of 2.6 moles of nitrite and 2.75 moles of

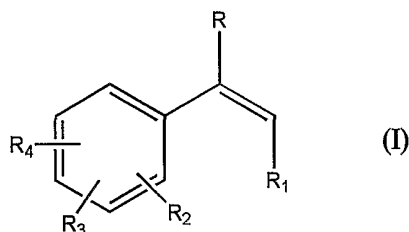
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iodine per mole of alkene, respectively.

Then it is evident that the methods for the nitration of alkenes described in the literature show the relevant drawback of using high amounts of iodine which remarkably decrease the reaction productivity because of the high molecular weight of iodine, make the subsequent treatment with bisulphites, for transforming all the iodine in excess into iodides at the end of the reaction, particularly cumbersome and suffer from the problem of the removal of iodides from the waste waters.

We have now found that the amount of iodine to be used for the nitration of conjugated alkenes can be significantly decreased by adding an oxidizing agent to the reaction mixture containing the alkene, the nitrite and iodine.

Therefore, object of the present invention is a process for the nitration of conjugated alkenes of formula

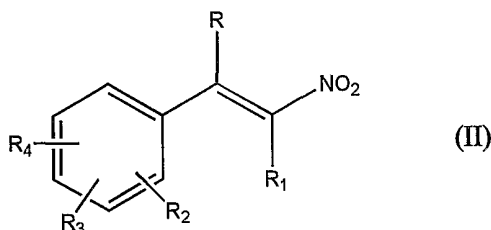


wherein

R is a hydrogen atom, an optionally substituted phenyl, a linear or branched C₁-C₄ alkyl; R₁ is a hydrogen atom or a linear or branched C₁-C₄ alkyl, optionally substituted by an OH or C₁-C₄ alkoxy group; R₂, R₃ and R₄, the same or different, are selected among hydrogen and halogen atoms, linear or branched C₁-C₄ alkyl or alkoxy groups, carboxylic groups, aminocarbonyl groups, alkyloxycarbonyl, alkylcarbonyl, mono- or di-alkylaminocarbonyl, alkylcarbonylamino and alkylcarbonyloxy groups having from 1 to 4 carbon atoms in the alkyl moiety; or two of R₂, R₃ and R₄, in ortho between them, form a methylenedioxy group; or R₁ together with R₂ forms a cyclic system with 5-7 terms condensed with the aromatic ring and optionally containing an oxygen atom; or R₁ together with R forms a cyclic system with 5-7 terms;

which allows to obtain β-nitro-alkenes of formula

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5

wherein R, R₁, R₂, R₃ and R₄ have the already reported meanings;

characterised in that the nitrating agent is a mixture of an inorganic nitrite and iodine in the presence of an oxidising agent.

- 10 The nitration process object of the present invention allows to obtain β-nitroalkenes under mild conditions with good yields.

In the present context, unless otherwise specified, linear or branched C₁-C₄ alkyl means an alkyl selected among methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl and *t*-butyl; linear or branched C₁-C₄ alkoxy means a group selected among methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *sec*-butoxy, isobutoxy and *t*-butoxy; halogen means fluorine, chlorine, bromine and iodine.

15

Substituted phenyl means a phenyl substituted by one or more substituents selected among the meanings of R₂, R₃ and R₄.

It is evident to the man skilled in the art that the substituents on the aromatic ring should be compatible with the used reaction conditions.

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The compounds of formula I used in the nitration process object of the present invention are known.

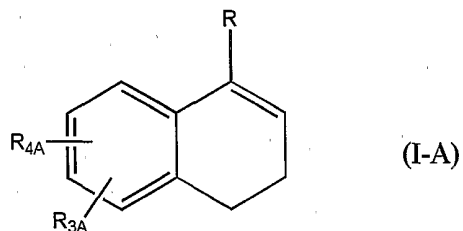
Preferred examples of the compounds of formula I are styrenes optionally substituted on the aromatic ring by from 1 to 3 methoxy groups or by a methylenedioxy group, dihydronaphthalenes optionally substituted by methoxy, methyl, ethyl, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl groups or by a methylenedioxy group or benzopyranes optionally substituted by methoxy, methyl, ethyl, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl, aminocarbonyl or methylaminocarbonyl groups.

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Particularly preferred are the nitration of the compounds of formula

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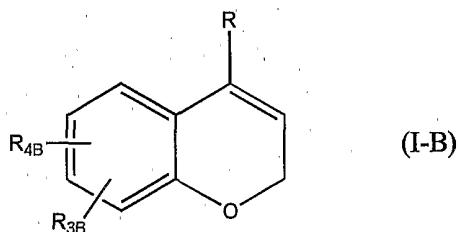


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wherein

R_{3A} and R_{4A} , the same or different, are hydrogen atoms, methoxy, methyl, ethyl, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl groups or, together, form a methylenedioxy group; R has the already reported meanings;

10 and the nitration of the compounds of formula

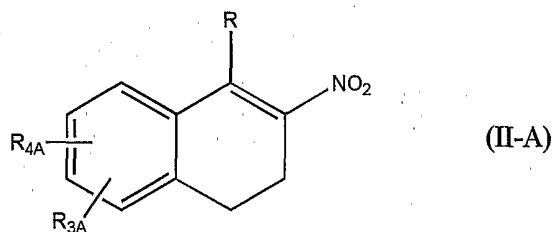


15 wherein

R_{3B} and R_{4B} , the same or different, are hydrogen atoms, methoxy, methyl, ethyl, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl, aminocarbonyl or methylaminocarbonyl groups; R has the already reported meanings;

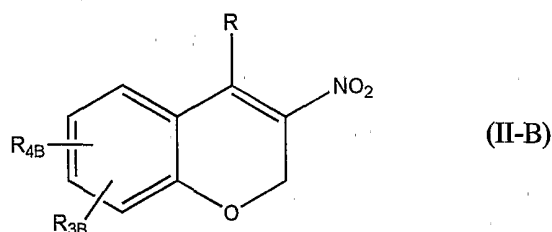
to obtain the corresponding nitroderivatives of formula

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and of formula

25



30 wherein R, R_{3A} , R_{3B} , R_{4A} and R_{4B} have the already reported meanings.

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Examples of inorganic nitrites which can be used in the process object of the present invention are silver nitrite, sodium nitrite and potassium nitrite.

Preferably sodium nitrite is used.

- 5 The amount of nitrite is in excess with respect to the compound of formula I, generally not lower than 2 moles per mole of compound to be nitrated.

Preferably an amount of nitrite from 2 and 4 moles per mole of compound of formula I is used.

- 10 The most characterising feature of the present process is represented by the amount of iodine which is used.

In fact, the presence of an oxidising agent allows to significantly decrease the amount of iodine up to an amount generally equal or lower than 1 mole per mole of compound of formula I, preferably from 0.1 and 0.8 moles per mole of substrate to be nitrated.

- 15 As already underlined, the remarkable decrease of the amount of iodine necessary to carry out the nitration gives to the process object of the present invention the advantages related to the increased productivity and to the higher simplicity of the work-up of the reaction mixture. This is mainly in the final treatment to remove the iodine still present, which is generally carried out with bisulphite, but which can be also avoided in the process object of the present invention.

- 20 The advantages of the process object of the present invention are particularly evident by comparing the nitration reported in example 2 and the nitration carried out according to the prior art on the same substrate, as reported in the already cited WO 98/46586 (see in particular the example on page 12).

- 25 In fact, by working according to the method object of the present invention the nitroderivative is obtained with a practically triplicate yield.

Generally, the oxidation agent is slowly added, usually in 3-4 hours, to the reaction mixture containing the nitrite, iodine and the compound of formula I.

A hypothesis on the role of the oxidant is that of oxidising the iodides formed in the reaction mixture according to the following scheme

- 30
$$\text{AlkH} + \text{NaNO}_2 + \text{I}_2 \rightarrow \text{AlkNO}_2 + \text{HI} + \text{NaI}$$

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wherein AlkH represents the compound of formula I,

so forming an amount of iodine which is sufficient to go on with the nitration reaction.

A further advantage is represented by the fact that, by using an oxidising agent, the iodine can

5 also be prepared *in situ* by oxidation of iodides. Iodides which can be used for such purposes are generally alkali metal iodides, preferably potassium iodide.

Specific examples of oxidising agents which can be used in the process object of the present invention are peracids such as peracetic acid and *m*-chloroperbenzoic acid, oxygen peroxide and inorganic nitrites, optionally in admixture each other.

10 It is evident that when an inorganic nitrite is used as oxidant agent, the same inorganic nitrite which is present in the nitrating mixture will be preferably used.

The oxidising agent must be used in an acid environment, preferably at a pH lower than 5.

Then, depending on the selected oxidant, it could be necessary also the addition of an acidifying agent to bring the pH up to the desired value.

15 Then, when peracids such as peracetic acid which is not sufficiently acid are used, it will be suitable to use the oxidant in solution with an acid solvent, preferably acetic acid. In a similar way, when oxygen peroxide or an inorganic nitrite are used as oxidising agent, acetic acid will be preferably used.

The use of a mixture of peracetic acid, oxygen peroxide, acetic acid and water, already
20 available on the market (Oxistrong® - Ausimont) is particularly advantageous.

It is evident that the amount of oxidant will be in relation to the used amount of iodine, preferably in slight excess. When the iodides are used to form iodine directly in the reaction medium, a higher amount of oxidant will be needed to allow the initial oxidation of the iodides.

The process object of the present invention is carried out in the presence of a suitable organic
25 solvent which is selected in relation to the solubility of the compound of formula I but which is not a critical parameter for the achievement of the process.

Examples of suitable solvents are esters such as ethyl acetate, isopropyl acetate and isobutyl acetate, aromatic hydrocarbons such as toluene and xylene, chlorinated hydrocarbons such as methylene chloride and 1,2-dichloropropane and ethers such as *tert*-butyl methyl ether.

30 When the reaction mixture contains water, the addition of a phase transfer catalyst can be

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useful.

Also the temperature is not a critical parameter. Preferably temperatures from 20°C to 70°C are used. A still more preferred temperature range is from 40°C to 50°C.

- 5 A preferred embodiment of the process object of the present invention is the following.

Iodine and then, slowly, a solution of the oxidising agent are added to a mixture of the alkene of formula I and of sodium nitrite in a suitable organic solvent. At the end of the addition and at the completion of the reaction, an aqueous solution of sodium metabisulphite is optionally added up to decoloration of the iodine and the compound of formula II is separated according to usual techniques.

10

In order to better illustrate the present invention the following examples are now given.

Example 1

Preparation of 2-nitro-3,4-dihydronaphthalene

Into a three-necks flask equipped with a reflux condenser and a mechanic stirrer, at room temperature and under inert gas, 1,2-dihydronaphthalene (3.9 g; 30 mmoles), sodium nitrite (6.2 g; 90 mmoles) and isopropyl acetate (40 ml) were charged. The mixture was kept under stirring and heated at 50°C. Iodine (3.8 g; 15 mmoles) and then, through a rubber separator, a solution of peracetic acid in acetic acid (8.5 ml - solution 39% w/w) were added in 4 hours. At the end of the addition, the mixture was kept under stirring for further 30 minutes, cooled to 20°C, then a freshly prepared 10% sodium metabisulphite solution was slowly (15 minutes) added up to decoloration of iodine (about 30 ml). The phases were separated and the aqueous phase was washed with isopropyl acetate (2x10 ml). The collected organic phases were washed with a saturated sodium chloride aqueous solution (10 ml). After separation of the phases, the organic phase was dried on sodium sulphate, filtered and the solvent was removed under reduced pressure obtaining crude 2-nitro-3,4-dihydronaphthalene (4.7 g; 73% yield) as a brown oil.

20

25

$M^+ = 175$

Example 2

Preparation of 8-fluoro-3-nitro-2H-chromene-5-carboxylic acid amide

30 Into a reactor, equipped with a reflux condenser and under inert gas, 8-fluoro-2H-chromene-5-

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carboxylic acid amide (4.94 g; 25.6 mmol), sodium nitrite (4.4 g; 64 mmol) and isopropyl acetate (40 ml) were charged. The mixture was kept under mechanic stirring and heated at 50°C. In one portion iodine (1.9 g; 7.5 mmol) and then, in 3 hours, Oxistrong 15® (6 ml) were added. At the end of the addition the reaction mixture was kept under stirring for 1 hour and cooled to 20°C. After addition of water (30 ml), the mixture was further cooled at 5°C for 1 hour. The solid was filtered and washed with isopropyl acetate (3x10 ml), pre-cooled at 0°C, and with water (2x10 ml). After drying in oven under vacuum at 50°C overnight, 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide (4.7 g; HPLC titre 90%; 70% yield) was obtained. The mother liquors of the reaction were treated with a 15% solution of sodium metabisulphite (20 ml) up to decoloration. The phases were separated, the organic phase was dried and the organic solvent was removed under reduced pressure obtaining a solid (0.8 g) containing 49% of 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide. Overall yield: 76.4%.

Example 3

Preparation of 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide

Into a reactor, equipped with a mechanic stirrer and a reflux condenser, 8-fluoro-2*H*-chromene-5-carboxylic acid amide (3.1 g; 15 mmol), sodium nitrite (3.1 g; 45 mmol) and toluene (30 ml) were charged at room temperature and under inert gas. The mixture was heated under stirring at 50°C, then iodine (1.9 g; 7.5 mmol) and, slowly in 4 hours, Oxistrong 15® (3.7 ml) were added. At the end of the addition the reaction mixture was kept under stirring for a further hour, then cooled to 0°C. A 20% solution of sodium metabisulphite (about 15 ml) was added and the mixture was kept under stirring for 1 hour. After filtration the solid was washed with water (2x10 ml) and with toluene (10 ml) and dried in oven under vacuum at 50°C overnight obtaining 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide (3.4 g; titre 78%; 74% yield).

Example 4

Preparation of 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid methyl ester

Into a reactor, equipped with mechanic stirrer and reflux condenser, 8-fluoro-2*H*-chromene-5-carboxylic acid methyl ester (6.6 g; 30 mmol), sodium nitrite (6.2 g; 90 mmol) and ethyl

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acetate (60 ml) were added at room temperature and under inert gas. The mixture was heated under stirring at 50°C, then iodine (2.6 g; 10 mmoles) and, slowly in 4 hours, Oxistrong 15[®] (7.4 ml) were added. At the end of the addition the reaction mixture was kept under stirring
5 for a further hour, then cooled at 0°C. A 20% solution of sodium metabisulphite (about 25 ml) was added and the mixture was kept under stirring for 1 hour. After filtration the solid was washed with water (2x10 ml). The mother liquors were separated and, the previously filtered solid was added to the organic phase. The solvent was removed under reduced pressure and the semisolid residue was taken up with methanol (about 10 ml) and kept under stirring at 0°C
10 for 1 hour. After filtration and wash of the panel with methanol pre-cooled at 0°C (3 ml), the resultant solid was dried in oven under vacuum at 40°C overnight obtaining 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid methyl ester (4.6 g; titre 92%; 55% yield). The mother liquors were evaporated to dryness obtaining an oil (2.7 g) containing 55% of 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid methyl ester. Overall yield 75%.

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Example 5

Preparation of 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide

Into a reactor, equipped with a mechanic stirrer and a reflux condenser, 8-fluoro-2*H*-chromene-5-carboxylic acid amide (2 g; 10 mmoles), sodium nitrite (1.4 g; 20 mmoles), potassium iodide (0.33 g; 2 mmoles) and ethyl acetate (20 ml) were charged at room
20 temperature and under inert gas. The mixture was heated at 40°C, then Oxistrong 15[®] (4 ml) was added in 4 hours. At the end of the addition the reaction mixture was kept under stirring for 1.5 hours, then cooled at 20°C and diluted with ethyl acetate up to complete dissolution (about 150 ml). After washing with a 20% sodium metabisulphite solution, the phases were separated. The organic phase was washed with a saturated sodium chloride solution, dried and
25 the solvent was removed under reduced pressure, obtaining 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide (1.8 g; titre 88%; 66% yield).

Example 6

Preparation of 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide

Into a reactor, equipped with a mechanic stirrer and a reflux condenser, 8-fluoro-2*H*-chromene-5-carboxylic acid amide (120 g; 0.609 moles), sodium nitrite (96.6 g; 1.4 moles),
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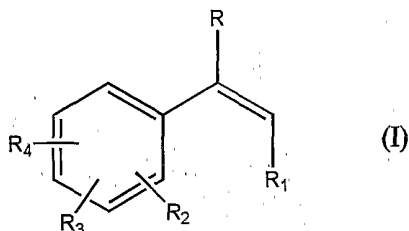
iodine (31.2 g; 0.123 moles) and ethyl acetate (720 ml) were charged at room temperature and under inert gas. The mixture was heated under stirring at 40°C, then Oxistrong 15[®] (173.4 g) was added in 4 hours. At the end of the addition the reaction mixture was kept under stirring
5 for 1 hour, then cooled at 20°C. Water (480 ml) was added and the mixture was kept under stirring for 1 hour. After filtration and wash of the panel with isopropyl acetate pre-cooled at 0°C (2x120 ml) and then with water (150 ml), the solid was dried in oven under vacuum at 50°C overnight obtaining 8-fluoro-3-nitro-2*H*-chromene-5-carboxylic acid amide (112.7 g; titre 91%; 70% yield).

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Claims

- 1) A process for the nitration of conjugated alkenes of formula

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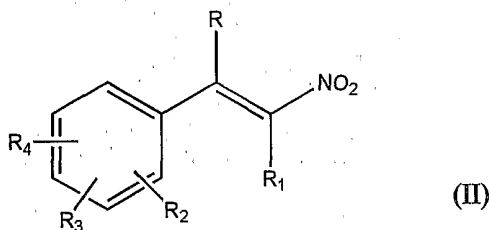


wherein

- R is a hydrogen atom, an optionally substituted phenyl, a linear or branched C₁-C₄ alkyl; R₁ is a hydrogen atom or a linear or branched C₁-C₄ alkyl, optionally substituted by an OH or C₁-C₄ alkoxy group; R₂, R₃ and R₄, the same or different, are selected among hydrogen and halogen atoms, linear or branched C₁-C₄ alkyl or alkoxy groups, carboxylic groups, aminocarbonyl groups, alkyloxycarbonyl, alkylcarbonyl, mono- or di-alkylaminocarbonyl, alkylcarbonylamino and alkylcarbonyloxy groups having from 1 to 4 carbon atoms in the alkyl moiety; or two of R₂, R₃ and R₄, in ortho between them, form a methylenedioxy group; or R₁ together with R₂ forms a cyclic system with 5-7 terms condensed with the aromatic ring and optionally containing an oxygen atom; or R₁ together with R forms a cyclic system with 5-7 terms;

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which allows to obtain β-nitro-alkenes of formula



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wherein R, R₁, R₂, R₃ and R₄ have the already reported meanings;

characterised in that the nitrating agent is a mixture of an inorganic nitrite and iodine in the presence of an oxidising agent.

- 2) A process according to claim 1 wherein the iodine is in an amount from 0.1 to 0.8 moles per mole of the compound of formula I.

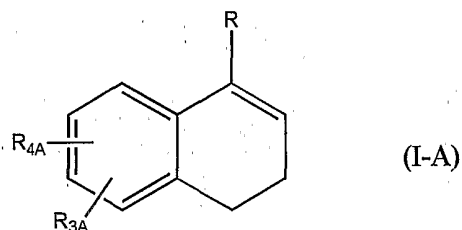
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- 3) A process according to claim 1 wherein the inorganic nitrite is selected among silver

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nitrite, sodium nitrite and potassium nitrite.

- 4) A process according to claim 3 wherein the inorganic nitrite is sodium nitrite.
- 5) A process according to claim 1 wherein the inorganic nitrite is in an amount from 2 to 4 moles per mole of the compound of formula I.
- 6) A process according to claim 1 wherein the oxidant agent is selected among peracids, oxygen peroxide and inorganic nitrites.
- 7) A process according to claim 6 wherein the oxidant agent is a mixture of peracetic acid, oxygen peroxide and water.
- 8) A process according to claim 1 wherein the iodine is formed *in situ* from alkaline iodides.
- 9) A process according to claim 1 wherein the temperature is from 40°C to 50°C.
- 10) A process according to claim 1 for the nitration of styrenes, optionally substituted on the aromatic ring by from 1 to 3 methoxy groups or by a methylenedioxy group.
- 11) A process according to claim 1 for the nitration of dihydronaphthalenes, optionally substituted by methoxy, methyl, ethyl, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl groups or by a methylenedioxy group.
- 12) A process according to claim 11 for the nitration of dihydronaphthalenes of formula



wherein

- 25 R_{3A} and R_{4A} , the same or different, are hydrogen atoms, methoxy, methyl, ethyl, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl groups or, together, form a methylenedioxy group;

R is a hydrogen atom, an optionally substituted phenyl, a linear or branched C_1 - C_4 alkyl.

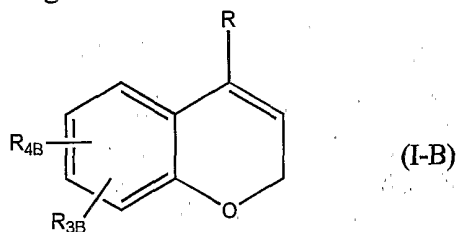
- 13) A process according to claim 1 for the nitration of benzopyranes optionally substituted by methoxy, methyl, ethyl, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl,

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aminocarbonyl or methylaminocarbonyl groups.

14) A process according to claim 13 for the nitration of the benzopyrans of formula

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wherein

R_{3B} and R_{4B} , the same or different, are hydrogen atoms, methoxy, methyl, ethyl, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl, aminocarbonyl or methylaminocarbonyl groups;

10

R is a hydrogen atom, an optionally substituted phenyl, a linear or branched C_1 - C_4 alkyl.

15) A process according to claim 13 for the nitration of the compound 8-fluoro-2H-chromene-5-carboxylic acid amide.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 01/06902

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07B43/02 C07C201/08 C07C205/04 C07C205/05 C07D311/58

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)

IPC 7 C07B C07C C07D

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, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 46586 A (ASTRA AB) 22 October 1998 (1998-10-22) cited in the application example 6	1,3,4,9, 13-15
A	GHOSH, DEBASIS ET AL: "An improved method for the preparation of cyclic conjugated nitroolefins" SYNTHESIS (1996), (2), 195-7 , XP002179766 cited in the application the whole document	1,3,11, 12

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Date of the actual completion of the international search

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Name and mailing address of the ISA

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

Authorized officer

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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