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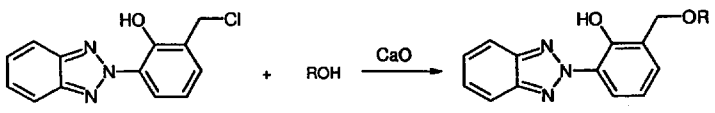
(54) **Title**: PROCESS FOR THE SYNTHESIS OF BENZOTRIAZOLES USEFUL AS UV-FILTERS



(57) **Abstract**: The invention relates to an improved process for the manufacture of novel benzotriazoles as well to novel benzotriazoles obtained by the novel process. This novel economical process provides products in high purity and yields.

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PROCESS FOR THE SYNTHESIS OF BENZOTRIAZOLES USEFUL AS UV-FILTERS

The invention relates to a process for the manufacture of novel benzotriazoles as well to novel benzotriazoles obtained by the novel process. This novel economical process provides products in high purity and yields.

Sun care products have evolved considerably over the years. Earlier formulations were intended to protect the user from UV-B radiation (UVB) as was once thought that UV-B rays were the most important contributors to wrinkling, skin disease, and skin cancer. However, more recent studies have shown that UV-A radiation (UVA) is equally or even more important in the development of solar damage and skin diseases, such as lupus erythematosus and melanoma and non-melanoma skin cancers. Thus, today's focus is toward eliminating as much of UVA (320-400 nm) and / or UVB (280-320 nm) light as possible.

Due to the increasing demand for high SPF sun care products with a UVA protection complying with the above mentioned regulations, more UV-filter substances at elevated levels have to be incorporated into the sun care products;

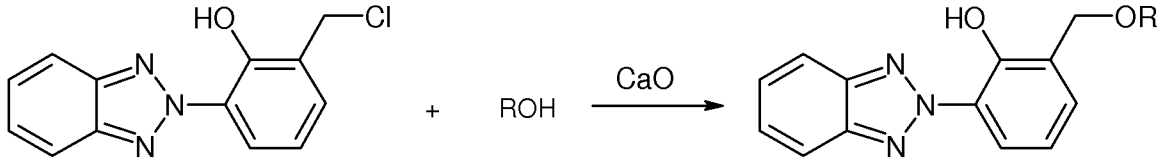
In order to achieve the UVA protection required by the novel regulations today's sun-care products often contain Butyl Methoxydibenzoylmethane (BMDBM), the only globally approved UVA screening agent.

BMDBM, however, exhibits only a limited solubility in the conventional cosmetic oils used for the solubilisation of solid UV-filter substances in order to enable their incorporation into cosmetic preparations (such as e.g. the cosmetic oils C_{12-15} alkyl benzoate or diisopropyl sebaceate), which is typically less than 20%. As a consequence sun-care products containing high amounts BMDBM require high amounts of such cosmetic oils in order to solubilize BMDBM and avoid a re-crystallization in the product, which in turn, however, often results in an unpleasant oily gritty and/ or tacky skin feel of the final products and a reduction in UV protection performance.

Furthermore, BMDBM is photoinstable i.e. it is degraded relatively quickly under the action of sunlight and, as a result, loses its protective action.

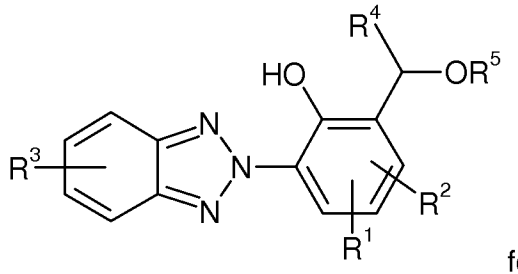
Thus, there is an ongoing need for compounds which are able to efficiently stabilize BMDBM and furthermore act as solubilizer for BMDBM in order to reduce the total amount of cosmetic oils used in sun care products. Furthermore, such compounds should be well soluble itself in such cosmetic oils or even be liquid and be accessible via a simple, economically attractive and environmentally benign method in order to be competitive in the market.

It has now surprisingly be found that novel benzotriazoles which are able to efficiently stabilize BMDBM are obtainable in simple, economically attractive and environmentally benign manner by reaction of a (2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative with an alcohol in the presence of Calcium oxide (CaO) as base to form the respective ether as exemplified below:



The inventive process results in less coloured reaction mixtures which makes additional purification steps dispensable. Furthermore, the reaction proceeds quickly and the products are obtained in high yields. In addition the use of Calcium oxide avoids the formation of the respective benzylalcohol side product which is highly unwanted in the final product.

Thus, the invention relates to a process for the preparation of benzotriazole derivatives of formula (Ia)



formula (Ia)

wherein

R^1 is hydrogen; C_{1-30}alkyl; C_{1-5}alkoxy; C_{1-5}alkoxycarbonyl; C_{5-7}cycloalkyl; C_{6-10}aryl or aralkyl;

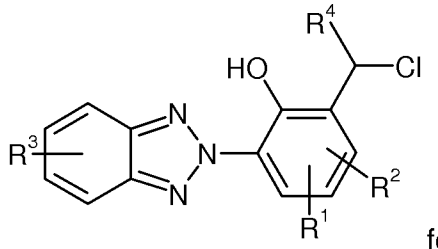
R^2 is hydrogen; C_{1-30}alkyl; C_{1-5}alkoxy; C_{1-5}alkoxycarbonyl; C_{5-7}cycloalkyl; C_{6-10}aryl or aralkyl;

R^3 is hydrogen; C_{1-5}alkyl; C_{1-5}alkoxy or halogen, preferably hydrogen or Cl;

R^4 is hydrogen or C_{1-5}alkyl;

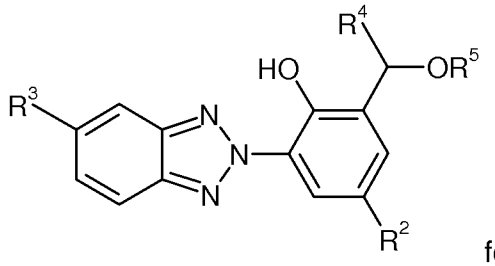
R^5 is C_{1-30}alkyl or C_{5-10}cycloalkyl.

said process comprising the step of reacting a 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative (IIa) with an alcohol R^5-OH in the presence of Calcium oxide



formula (IIa)

In another aspect, the invention relates to a process for the preparation of benzotriazole derivatives of formula (Ib)



formula (Ib)

wherein

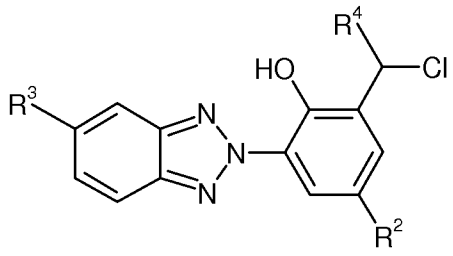
R^2 is hydrogen; C_{1-30}alkyl; C_{1-5}alkoxy; C_{1-5}alkoxycarbonyl; C_{5-7}cycloalkyl; C_{6-10}aryl or aralkyl;

R^3 is hydrogen; C_{1-5}alkyl; C_{1-5}alkoxy or halogen, preferably hydrogen or Cl, most preferably hydrogen;

R^4 is hydrogen or C_{1-5}alkyl; and

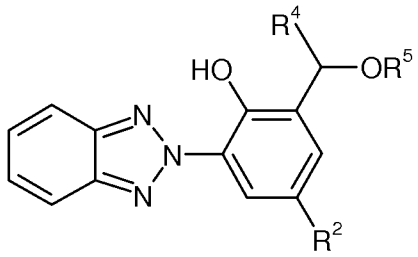
R^5 is C_{1-30}alkyl or C_{5-10}cycloalkyl,

said process comprising the step of reacting a 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative (IIb) with an alcohol R^5-OH in the presence of Calcium oxide



formula (IIb)

In a particular embodiment the invention relates to for the preparation of benzotriazole derivatives of formula (Ic)



formula (Ic)

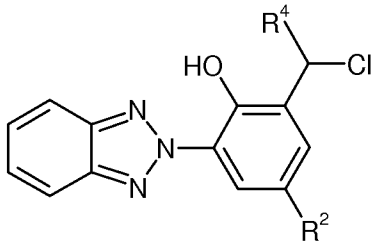
wherein

R_2 is hydrogen or C_{1-12}alkyl, preferably C_{1-4}alkyl, most preferably methyl;

R_4 is hydrogen or C_{1-2}alkyl; preferably hydrogen and

R_5 is C_{1-12}alkyl or C_{5-7}cycloalkyl, preferably C_{5-10}alkyl or C_6cycloalkyl such as most preferably C_{6-10}alkyl or C_6cycloalkyl,

said process comprising the step of reacting a 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative (IIc) with an alcohol R^5-OH in the presence of Calcium oxide.



formula (IIc)

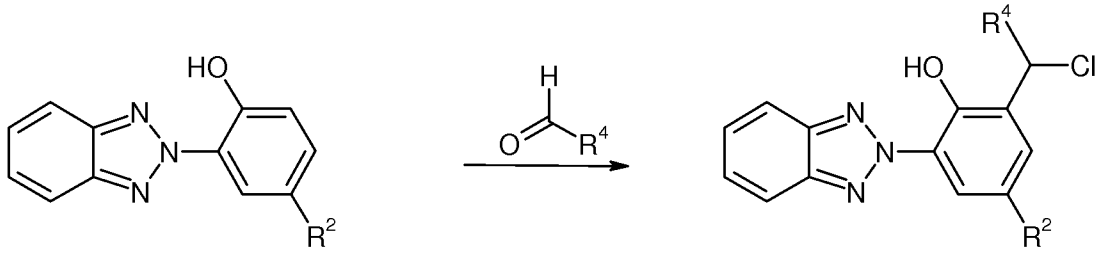
In another particular embodiment the invention relates to a process for the preparation of benzotriazol derivatives of formula (Ic) wherein

R_2 is methyl;

R_4 is hydrogen and

R_5 is C_{5-10}alkyl or C_6cycloalkyl such as C_{6-10}alkyl or C_6cycloalkyl such as in particular 2,5,5-trimethylhexyl, 3,5,5-trimethylhexyl, isoamyl, 2-ethylhexyl or 3,3,5-trimethyl-cyclohexyl.

The 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivatives according to the invention can be prepared by known methods in the art and as illustrated in the examples such as e.g. by chloroalkylation of a benzotriazole with an aldehyde R^4CHO as exemplified below



Suitable aldehydes R^4CHO are in particular formaldehyde and acetaldehyde and sources of formaldehyde such as paraformaldehyde or hexamethylenetetramine.

Particular suitable benzotriazoles for the chloralkylation are 2-(2H-benzotriazol-2-yl)-4-methylphenol [CAS 2440-22-4], 2-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethyl-butyl)phenol [CAS 3147-75-9], and 2-(2H-benzotriazol-2-yl)-4-tert-butyl-phenol [CAS 3846-71-7].

The chloroalkylation can be performed according to known methods for reacting aromatic compounds with hydrogen chloride and an appropriate aldehyde in the presence of a Lewis acid or a proton acid as a catalyst or mixtures thereof. The amount of aldehyde employed in the chloroalkylation reaction may be the stoichiometric amount, i.e., the amount which provides one R^4 group per benzotriazole. Preferably a slight excess is used in order to achieve full conversion and good yields. Particularly, zinc chloride is used as catalyst and the reaction is carried out in acetic acid. The reaction temperature may vary from about 70°C to 130°C. Preferably, the reaction temperature ranges from about 70°C to 100 °C, even more preferably from about 65-85°C. The amount of hydrogen chloride used in the reaction is usually at least about one mol equivalent, based on the amount of the benzotriazole; and it is generally introduced by bubbling it through the reaction mixture or by pressurizing the reaction vessel with it.

If the benzotriazole derivatives (Ia-c) according to the invention exhibit one or more stereocenter the present invention encompasses the optically pure isomers or pure enantiomers as well as mixtures of different isomers, e.g. racemates, and/or mixtures of

rotamers. If applicable, mixtures of different isomers, e.g. racemates, and/or mixtures of rotamers are preferred.

The term "C_{x-y}-alkyl", refers to straight-chain or branched alkyl radicals comprising x to y carbon atoms such as e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec.butyl, tert.butyl, amyl, isoamyl or tert.amyl, hexyl, 2-ethylhexyl, heptyl, octyl, isooctyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl or eicosyl without being limited thereto. Particularly advantageous are branched alkyl radicals such as particularly branched C_{5-12}alkyl radicals, more particularly branched C_{5-10}alkyl radicals such as branched C_{6-10}alkyl radicals such as e.g. 2,5,5-trimethylhexyl, 3,5,5-trimethylhexyl, isoamyl or 2-ethylhexyl as the respective benzotriazoles exhibit a particularly good solubility in the cosmetic oils Myritol 318 [INCI: Capric/Caprylic Triglyceride] respectively Finsolv TN [INCI: C_{12-15} Alkylbenzoate].

Therefore, in a specific embodiment the invention also relates to a process according to the invention, wherein R^2 is methyl; R^4 is hydrogen and R^5 is a branched alkyl radical such as in particular a branched C_{5-10}alkyl radical such as most in particular 2,5,5-trimethylhexyl, 3,5,5-trimethylhexyl, isoamyl or 2-ethylhexyl.

The term cycloalkyl denotes to unsubstituted or C_{1-10}alkyl, in particular C_{1-5}alkyl substituted cyclic, bicyclic or tricyclic hydrocarbon residues such as in particular cyclopentyl, cyclohexyl, cycoheptyl or decahydronaphtyl. Preferably, the term cycloalkyl denotes to unsubstituted or C_{1-2}alkyl substituted cyclopentyl, cyclohexyl or cycoheptyl such as in particular to unsubstituted or methyl substituted cyclohexyl such as most in particular cyclohexyl or 3,3,5-trimethyl-cyclohexyl. Particularly advantageous are methyl substituted cyclohexyl radicals such as particularly 3,3,5-trimethylcyclohexyl.

The term C_{1-5}alkoxy refers for example to methoxy, ethoxy, propoxy, butyloxy or pentyloxy.

The term C_{6-10}aryl refers for example to naphthyl or phenyl, preferably to phenyl.

Calcium oxide (CaO) [CAS 1305-78-8] is e.g. commercially available at Sigma Aldrich.

The amount of the Calcium oxide used in the process according to the invention is generally selected in the range of 0.1 to 2 mol-% such as particularly in the range of 0.2 to 1.5 mol-% such as in the range of 0.3 to 1 mol-% based on the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative.

Suitable alcohols R^5OH according to the present invention are e.g. methanol, ethanol, n-propanol, i-propanol, 1-butanol, 2-butanol, tert.-butanol, 2-ethyl-1-butanol, 2-methyl-1-butanol, 1-pentanol, 2-pentanol, 3-pentanol, 4-methyl-2-pentanol, 3-methyl-1-pentanol, 2-methyl-1-pentanol, 1- hexanol, 2-hexanol, 3-hexanol, 2-methyl-3-hexanol, 5-methyl-2-hexanol, 5-methyl-1-hexanol, 2,2-dimethyl-3-hexanol, 4-ethyl-3-hexanol, 3-methyl-1-hexanol, 2,5-dimethyl-3-hexanol, 1- heptanol, 2- heptanol, 3-heptanol, 5-methyl-3-heptanol, 2,4-dimethyl-3-heptanol, 6-methyl-2-heptanol, 4-methyl-3-heptanol, 2,6-dimethyl-4-heptanol, 2,6-dimethyl-2-heptanol, 1-octanol, 2-octanol, 3-octanol, 4-octanol, 2-butyl-1-octanol, 3,7-dimethyl-1-octanol, 1-nonanol, 2-nonanol, 3-nonanol, 4-nonanol, 5-nonanol, 2,6,8-trimethyl-4-nonanol, 1-decanol, 2-decanol, 4-decanol, 1-undecanol, 2-undecanol, 3-undecanol, 6-undecanol, 1-dodecanol, cyclohexanol, 4-ethylcyclohexanol, 4-methylcyclohexanol, 3-methylcyclohexanol, 2-methylcyclohexanol, 2,3-dimethylcyclohexanol, 4-butylcyclohexanol, 2-tert-butylcyclohexanol, 4-tert-butyl-cyclohexanol, 4-tert-amylcyclohexanol, cyclohexanemethanol, 2-cyclohexylethanol, 3-cyclohexyl-1-propanol, 4-methyl-1-cyclohexanemethanol, 2-cyclohexylcyclohexanol, 1-cyclohexyl-1-butanol, cyclooctanol, cyclopentanol, cycloheptanol, decahydro-2-naphthol, borneol, isoborneol, isopinocampheol, menthol, isomenthol, neomenthol, myrtanol, tetrahydrolavandulol, 2-norboranemethanol, 1-adamantanol, 2-adamantanol, isoamylalcohol such as in particular hexanol, isoamylalcohol, 2,5,5-trimethylhexan-1-ol, 2-ethylhexanol, 3,3,5-trimethylcyclohexanol or 3,5,5-trimethylhexan-1-ol as well as mixtures thereof.

It is particularly advantageous to use branched alkyl alcohols in the processes according to the invention, such as branched C_{5-12} alcohols, in particular branched C_{5-10} alcohols or even branched C_{6-10} alcohols such as e.g. isoamylalcohol, 2,5,5-trimethylhexan-1-ol, 2-ethylhexanol or 3,5,5-trimethylhexan-1-ol as this leads to particularly well suitable benzotriazoles in the cosmetic oils selected from Myritol 318 [INCI Capric/Caprylic Triglyceride] and Finsolv TN [INCI C12-15 Alkylbenzoate]. Further advantageous is the use of methyl substituted cyclohexanols such as e.g. 3,3,5-trimethylcyclohexanol.

The process according to the present invention is typically conducted at 50–100 °C and is completed in about 1–15 hours. It is particularly advantageous to add the CaO after the reaction temperature has been reached as this reduces significantly the reaction times making the process more economical.

Pressure is not critical to the present process, except to the extent that the selection of a particular pressure may facilitate rapid removal of the water released in the reaction medium.

If the reaction is carried out at normal pressure, the reaction temperature is preferably chosen in the range of about 70 to 90 °C.

The reaction can either be carried out in an excess of the corresponding alcohol R^5-OH (in the absence of any further solvents) or in the presence of an inert solvent.

The term inert solvent refers to any solvent that does not react or interact in any way with the reagents of the process of the present invention. Such solvents are well known to and can be easily selected by a person skilled in the art and encompass e.g. hydrocarbon solvents (i.e. organic solvents, molecules of which consist only of hydrogen and carbon atoms such as e.g. benzene, kerosene, xylene, hexane, cyclohexane, methylcyclohexane or other petroleum derivatives).

If no inert solvent is present in the process according to the invention, then the alcohol R^5-OH is preferably used in a large excess. Advantageously the molar ratio of alcohol R^5-OH to the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is at least 5:1. Preferably, in the absence of an inert solvent, the molar ratio of alcohol R^5-OH to the respective 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is selected in the range of about 5:1 to 100:1 such as particularly in the range of about 10:1 to 15:1.

The reaction, however, can also be carried out in a wide range of inert solvents such as in particular in hydrocarbon solvents such as e.g. cyclohexane, methylcyclohexane, benzene, xylene or toluene. In the presence of an inert solvent, the alcohol R^5-OH is preferably used in a small excess. Advantageously the molar ratio of the alcohol R^5-OH to the respective 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is selected in the

range of at most 6:1 and at least 1:1, such as from about 5:1 to 1:1 and in particular from about 4:1 to 2:1.

The presence of an inert solvent is in particular advantageous if the alcohol R^5-OH has a high boiling point such as e.g. a boiling point above 100°C or even above 150°C (such as e.g. 2-ethylhexanol) since it takes extra work-up efforts and costs to remove high boiling alcohols.

The amount of solvent can easily be adjusted by a person skilled in the art and is e.g. selected in the range of 0.25 to 10 times the amount of R^5-OH [g/g] such as e.g. 2 to 6 times the amount of R^5-OH [g/g].

A particular suitable inert solvent is methylcyclohexane as the dimeric by-product generated during the preparation of the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivatives can easily be removed by filtration. Another particular suitable inert solvent is toluene.

In a particular advantageous embodiment a mixture of the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative and an inert solvent is heated to reflux at ambient pressure (about 1013mbar) before CaO suspended in the alcohol R^5-OH is added as this leads to a significant reduction of the reaction times. Preferably, the inert solvent is methylcyclohexane or toluene such as most preferably toluene.

Catalysis is not generally necessary in the process according to the present invention however, if deemed appropriate, the reaction rate (i.e. time of turnover) can be further improved by the addition of a catalyst such as a soluble iodide salt, a phase transfer catalysts such as tetrabutylammonium phosphate (TBAP), triethylammonium bicarbonate (TEAB) or lithium bromide (LiBr).

If a catalyst is present, the amount of the catalyst is preferably chosen in the range of 5 to 20 mol-% such as in the range of 8 to 15 mol-% based on the respective 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative.

Particular advantageous results are obtained if the reaction is carried out in methylcyclohexane. Thus, in a particular embodiment the process according to the present invention is carried out in methylcyclohexane and the molar ratio of the alcohol R^5-OH to the respective 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is selected in the range of at most 6:1 and at least 1:1, such as from about 5:1 to 2:1 and in particular from about 4:1 to 2:1. Even more preferably, the alcohol R^5-OH is a branched alkyl alcohol such as most in particular 2-ethylhexanol and the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is 2-(2H-benzotriazol-2-yl)-6-chloromethyl-4-methylphenol.

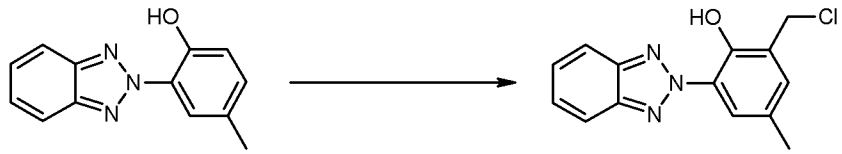
In another embodiment of the invention, the invention relates to benzotriazole derivatives obtained according to a process of the present invention.

The process according to the invention can in principle be carried out in any reactor suitable for the respective reaction type. Without restricting generality, the following are mentioned by way of example: suspension reactor, stirred tank, stirred tank cascade, tubular reactor, shell-type reactor, shell and tube reactor, fixed-bed reactor, fluidized-bed reactor, reactive distillation column.

The following examples are provided to further illustrate the processes of the present invention. These examples are illustrative only and are not intended to limit the scope of the invention in any way.

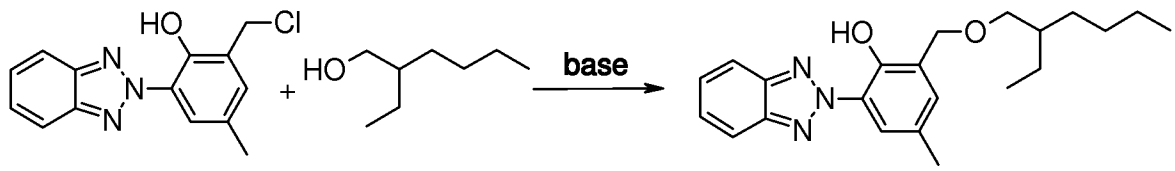
Example 1: Comparison of various bases

Step a.)



A mixture of 2-(2H-benzotriazol-2-yl)-4-methyl-phenol (100.0 g, 0.44 mol), paraformaldehyde (26.4 g, 0.88 mol), sulphuric acid (10.9 g, 110 mmol), conc. HCl (200 mL), and acetic acid (500 mL) is heated to 90°C for six hours. The precipitated product is isolated by filtration and washed subsequently with AcOH, AcOH:heptane (1:1), and heptane and dried at 45°C (95 % yield).

Step b.)



2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methylphenol (1.0 g, 3.7 mmol) obtained as outlined in step a.) is suspended in 2-ethylhexan-1-ol (4.0 g, 31 mmol) at 80°C. 1.1 equivalent of the respective base is added and the mixture is stirred for 15 minutes at 80°C. The turnover and impurity profile is determined by means of HPLC analysis. The colour is analysed visually.

In case of sodium methoxide (NaOMe, entry 5) the base is first combined with 2-ethylhexan-1-ol and methanol is removed by distillation under vacuum at 80°C. Subsequently 2-benzotriazol-2-yl-6-chloromethyl-4-methyl-phenol is added and the reaction mixture is stirred 15 minutes at 80°C.

Table 1

entry	base	Turnover*	side products#	Colour
1	Na_2CO_3	100%	4.4% benzylalcohol derivative	slightly yellow
2	Na	100%	~0.5 - 1% oligomers	orange
3	NaOMe	100%	0.5% benzylalcohol derivative & ~0.5 - 1% oligomers	orange
4	NaH	100%	~0.5 - 1% oligomers	orange
5	tBuOK	100%	1.0%	orange
6	CaO	100%	4.75%	slightly yellow

* i.e. total consumption of 2-(2H-benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol

i.e. amount of side products detected

As can be retrieved from table 1, only the use of Na_2CO_3 as well as of Calcium oxide leads to slightly coloured products whereas the use of other bases such as Na, NaOMe, NaH or tBuOK results in a strong discoloration. Furthermore, the use of Calcium oxide

does not result in the formation of the benzylalcohol derivative (i.e. 2-(2H-Benzotriazol-2-yl)-6-hydroxymethyl-4-methylphenol).

Example 2: Preparation of 2-(2H-Benzotriazol-2-yl)-6-(2-ethylhexyloxymethyl)-4-methylphenol in methylcyclohexane

60 g (1 eq) 2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methylphenol obtained as outlined in example 1, step a.), 7.38 g (0.6 eq) Calcium oxide, 85.6 g (3 eq 2-ethylhexanol) and 300 ml methylcyclohexane were mixed under a nitrogen blanket. The pale yellow suspension was heated to 80°C. After 4h at 80°C the reaction was checked by HPLC and no starting material as well as no benzylalcohol derivative was detected. After the reaction mixture was cooled to 20°C, 10 ml aqueous (25%) ammonia was added followed by 150ml 1M HCl with gentle stirring. The heterogeneous mixture was filtered. The organic layer was separated and extracted with 3 x 60 ml water. The solution was then treated with 6 g activated charcoal and filtered. The solvents were removed in the rotary evaporator followed by high vacuum at 60°C. Isolated yield: 74.4 g (92%).

Example 3: Preparation of 2-(2H-Benzotriazol-2-yl)-6-(2-ethylhexyloxymethyl)-4-methylphenol in toluene

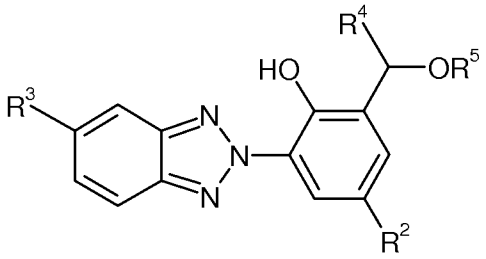
100 g (1 eq) 2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methylphenol obtained as outlined in example 1, step a.), 20.5 g (1.0 eq) Calcium oxide, 100 g (2.1 eq) 2-ethylhexanol and 250 ml toluene were mixed under a nitrogen blanket. The pale yellow suspension was heated to reflux (inner temperature approx. 117°C). After 1, 2, and 4 hours at reflux the reaction was checked by HPLC and 45%, 25%, and 7% starting material was detected. After 7h at reflux a turnover of 99.9% was reached and no benzylalcohol derivative was detected. The reaction mixture was cooled to 25°C and extracted with 25% HCl (96 g). The organic layer was separated and washed with an aqueous bicarbonate solution (1 w%, 2 X 200 ml). The toluene was distilled of the residue diluted with 150 g heptane and filtered. The solvents were removed in the rotary evaporator followed by high vacuum at 60°C. Isolated yield: 153.9 g (94%).

Example 4: Preparation of 2-(2H-Benzotriazol-2-yl)-6-(2-ethylhexyloxymethyl)-4-methyl-phenol in toluene with CaO addition at reflux

100 g (1 eq) 2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methylphenol obtained as outlined in example 1 in 250 ml toluene were heated under a nitrogen blanket to reflux (inner temperature approx. 117°C). Then 20.5 g (1.0 eq) Calcium oxide suspended in 100 g (2.1 eq) 2-ethylhexanol where added. After 2h at reflux a turnover of 99.9% was reached and 0.3% benzylalcohol derivative was detected. The reaction mixture was cooled to 25°C and extracted with 25% HCl (96 g). The organic layer was separated and washed with an aqueous bicarbonate solution (1 w%, 2 X 200 ml). The toluene was distilled of the residue diluted with 150 g heptane and filtered. The solvents were removed in the rotary evaporator followed by high vacuum at 60°C. Isolated yield: 143.7 g (88%).

Claims:

1. A process for the manufacture of benzotriazole derivatives of formula (Ib)



(Ib)

wherein

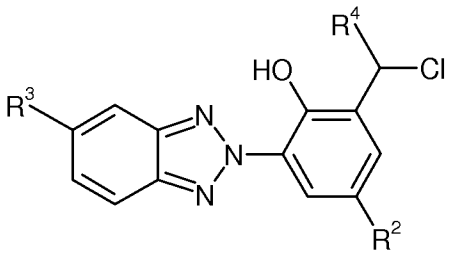
R^2 is hydrogen; C_{1-30}alkyl; C_{1-5}alkoxy; C_{1-5}alkoxycarbonyl; C_{5-7}cycloalkyl; C_{6-10}aryl or aralkyl;

R^3 is hydrogen; C_{1-5}alkyl; C_{1-5}alkoxy or halogen, preferably hydrogen or Cl, most preferably hydrogen;

R^4 is hydrogen or C_{1-5}alkyl; and

R^5 is C_{1-30}alkyl or C_{5-10}cycloalkyl.

said process comprising the step of reacting a 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative of formula (IIb) with an alcohol R^5-OH in the presence of calcium oxide



(IIb).

2. The process according to claim 1 wherein R^2 is hydrogen or C_{1-12}alkyl; R^3 is hydrogen; R^4 is hydrogen or C_{1-2}alkyl; and R^5 is C_{1-12}alkyl or C_{5-7}cycloalkyl.

3. The process according to claim 1 wherein R^2 is C_{1-4} alkyl; R^3 and R^4 are hydrogen; and R^5 is C_{5-10}alkyl or C_6cycloalkyl.

4. The process according to any one of claims 1 to 3 wherein R^5 is a branched alkyl or a methyl substituted cyclohexyl radical.

5. The process according to claim 1 wherein R^2 is methyl, R^3 and R^4 are hydrogen and R^5 is 2,5,5-trimethylhexyl, 3,5,5-trimethylhexyl, isoamyl, 2-ethylhexyl or 3,3,5-trimethyl-cyclohexyl.

6. The process according to any one of claims 1 to 5 wherein the calcium oxide is used in an amount of 0.1 to 2 mol-% based on the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative.

7. The process according to any one of claims 1 to 5 wherein the calcium oxide is used in an amount of 0.3 to 1 mol-% based on the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative.

8. The process according to any one of claims 1 to 7 wherein the reaction temperature is selected in the range of 70 to 90 °C.

9. The process according to any one of claims 1 to 8 wherein the reaction is carried out in the absence of an inert solvent and the molar ratio of alcohol R^5-OH to the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is at least 5:1.

10. The process according to any one of claims 1 to 9 wherein the reaction is carried out in the presence of an inert solvent.

11. The process according to claim 10 wherein the inert solvent is methylcyclohexane or toluene.

12. The process according to claim 10 or 11 wherein the amount of the inert solvent is selected in the range of 0.25 to 10 times the amount of R^5-OH [g/g].

13. The process according to any one of claims 10 to 12 wherein the molar ratio of the alcohol R^5-OH to the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is selected in the range of 6:1 to 1:1.

14. The process according to any one of claims 10 to 13 wherein in a first step the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is heated together with the inert

solvent at ambient pressure to reflux followed by the addition of a suspension of CaO in R^5-OH.

15. The process according to any one of claims 1 to 14 wherein an additional amount of lithium bromide is present.

16. The process according to claim 15 wherein the amount of lithium bromide is selected in the range of 5 to 20 mol-% based on the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/060086

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D249/20 A61K31/4192 C08K5/3475 A61Q17/04
ADD.

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)
C07D A61K C08K A61Q

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 practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/053917 A1 (ALCON INC [CH]; LAREDO WALTER R [US]) 14 May 2010 (2010-05-14) the whole document -----	1-16

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 July 2012	08/08/2012

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2012/060086

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