Abstract: The invention relates to an improved process for the manufacture of novel benzotriazoles as well as novel benzotriazoles obtained by the novel process. This novel economical process provides products in high purity and yields.
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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. This is reflected by novel regulations e.g. the EU recommendation 2006 which require the UVA protection to be at least one third of the UVB protection provided by the sun-care product or the FDA monograph proposal 2007 which introduces a star rating for UVA protection.

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 C12-15 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 an alkali metal and/or alkaline earth metal carbonate or bicarbonate base to form the respective ether as exemplified below:

![Chemical structure](image)

The inventive process results in less coloured reaction mixtures which makes additional purification steps dispensable. Furthermore, the products are obtained in high yields.

Thus, the invention relates to a process for the preparation of benzotriazole derivatives of formula (Ia)
R¹ is hydrogen; C₁₋₃ alkyl; C₁₋₅ alkoxy; C₁₋₅ alkoxy carbonyl; C₅₋₇ cycloalkyl; C₆₋₁₀ aryl or aralkyl;
R² is hydrogen; C₁₋₃ alkyl; C₁₋₅ alkoxy; C₁₋₅ alkoxy carbonyl; C₅₋₇ cycloalkyl; C₆₋₁₀ aryl or aralkyl;
R³ is hydrogen; C₁₋₅ alkyl; C₁₋₅ alkoxy or halogen, preferably hydrogen, Cl or hydroxy;
R⁴ is hydrogen or C₁₋₅ alkyl;
R⁵ is C₁₋₃ alkyl or C₅₋₁₀ cycloalkyl.

said process comprising the step of reacting a 2-(2H-benzotriazol-2-yl)-6-chloromethylphenol derivative (lla) with an alcohol R⁵-OH in the presence of an alkali metal and/or alkaline earth metal carbonate or bicarbonate.

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

wherein
R² is hydrogen; C₁₋₃ alkyl; C₁₋₅ alkoxy; C₁₋₅ alkoxy carbonyl; C₅₋₇ cycloalkyl; C₆₋₁₀ aryl or aralkyl;
R³ is hydrogen; C₁₋₅ alkyl; C₁₋₅ alkoxy or halogen, preferably hydrogen or Cl, most preferably hydrogen;
R⁴ is hydrogen or C₁₋₅ alkyl; and
R⁵ is C₁₋₃ alkyl or C₅₋₁₀ cycloalkyl,
said process comprising the step of reacting a 2-(2H-benzotriazol-2-yl)-6-chloromethylphenol derivative (lib) with an alcohol R⁵-OH in the presence of alkali metal and/or alkaline earth metal carbonate or bicarbonate.
In a particular embodiment the invention relates to for the preparation of benzotriazole derivatives of formula (lc)

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 $C_{1-2}$ alkyl or $C_{5-7}$ cycloalkyl, preferably $C_{5-10}$ alkyl or $C_{6}$ cycloalkyl such as most preferably $C_{5-10}$ alkyl or $C_{6}$ cycloalkyl,

said process comprising the step of reacting a 2-(2H-benzotriazol-2-yl)-6-chloromethylphenol derivative (lie) with an alcohol $R_5^5$-OH in the presence of alkali metal and/or alkaline earth metal carbonate or bicarbonate

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

$R_2$ is methyl;

$R_4$ is hydrogen and
R₅ is C₅-ioalkyl or C₆-cycloalkyl such as C₆-ioalkyl or C₆-cycloalkyl 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 R₄CHO as exemplified below.

Suitable aldehydes R₄CHO are in particular formaldehyde and acetaldehyde and sources of formaldehyde such as paraformaldehyde or hexamethylenetetramine.

Particular suitable benzotriazoles for the chloroalkylation are 2-(2H-benzotriazol-2-yl)-4-methylphenol [CAS 2440-22-4], 2-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)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 R₄ 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 (la-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_{1-30}alkyl (encompassing C_{1-2}alkyl, C_{5-10}alkyl, C_{6-10}alkyl, C_{3-12}alkyl) denotes to straight-chain or branched alkyl radicals like 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_{12-18}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, 2-ethylhexyl or 3,3,5-trimethyl-cyclohexyl.

The term cycloalkyl denotes to unsubstituted or C_{1-10}alkyl, in particular C_{5-10}alkyl substituted cyclic, bicyclic or tricyclic hydrocarbon residues such as in particular cyclopentyl, cyclohexyl, cycoheptyl or decahyronaphtyl. Preferably, the term cycloalkyl denotes to unsubstituted or C_{1-2}alkyl substituted cyclopentyl, cyclohexyl or cycoheptyl such as in particular 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.
Suitable alkali metal and/or alkaline earth metal carbonates or bicarbonates encompass sodium carbonate, potassium carbonate, lithium carbonate, calcium carbonate, magnesium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, lithium hydrogen carbonate and magnesium hydrogen carbonate.

The amount of the alkali metal and/or alkaline earth metal carbonates or bicarbonates used in the process according to the invention is generally selected in the range of 0.9 to 1.5 mol-% such as particularly in the range of 1 to 1.1 mol-%, based on the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative.

Advantageously alkali metal carbonates such as in particular sodium carbonate, potassium carbonate or lithium carbonate are used in the process according to the invention. Particular good results are obtained if lithium carbonate is used as base in the processes according to the invention as this, next to a decreased discoloration, furthermore leads to a decreased formation of unwanted side products such as in particular of the respective 2-(2H-Benzotriazol-2-yl)-6-hydroxymethylphenol derivative compared to other alkali metal carbonates.

Suitable alcohols $R^\delta\text{OH}$ 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-butylcyclohexanol, 4-tert-amylcyclohexanol, cyclohexanemethanol, 2-cyclohexylethanol, 3-cyclohexyl-1-propanol, 4-methyl-1-cyclohexanemethanol, 2-cyclohexylecyclohexanol,
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 C₅₋₁₂ alcohols, in particular branched C₅₋₁₀ alcohols or even branched C₆₋₁₀ 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.

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 R⁵-OH (in the absence of any further solvents) or in the presence of an inert solvent.

If no inert solvent is present in the process according to the invention, then the alcohol R⁵-OH is preferably used in a large excess. Advantageously the molar ratio of alcohol R⁵-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 R⁵-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 acetone, acetonitrile, N,N-dimethylformamide, tetrahydrofuran, dioxane, benzene 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 5:1 and at least 1:1, such as from about 3:1 to 1:1 and in particular from about 2:1 to 1.1:1.

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 10 times the amount of R^5-OH [g/g].

A particular suitable inert solvent is toluene as the water released in the reaction medium can be removed by azeotropic co-evaporation.

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.

If a solvent such as in particular toluene is used in the process according to the invention and the molar excess of the alcohol R^5-OH to the respective 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative is at most 5:1 and at least 1:1, such as from about 3:1 to 1:1 and in particular from about 2:1 to 1.1:1 based on the amount of the respective 2-(2H-
benzotriazol-2-yl)-6-chloromethyl-phenol derivative advantageously a catalyst such as in particular lithium bromide is used as this significantly decreases the reaction times respectively increases the time of turnover.

Particular advantageous results are obtained if the reaction is carried out in toluene, the alkali metal and/or alkaline earth metal carbonate or bicarbonate is lithium carbonate and the catalyst is lithium bromide as this significantly increases the time of turnover. Thus, in a particular embodiment the process according to the present invention is carried out in toluene, the alkali metal and/or alkaline earth metal carbonate or bicarbonate is lithium carbonate, 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 5:1 and at least 1:1, such as from about 3:1 to 1:1 and in particular from about 2:1 to 1:1, the catalyst is lithium bromide used in an amount ranging from about 5 to 20 mol-% such as in an amount ranging from about 8 to 15 mol-% based on the respective 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative. 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: Synthesis of 2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol

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), cone. 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).

Example 2: Comparison of various bases

2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methylphenol (1.0 g, 3.7 mmol) 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

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>Turnover*</th>
<th>side products*</th>
<th>Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Na₂CO₃</td>
<td>100%</td>
<td>4.4% benzylalcohol derivative</td>
<td>slightly yellow</td>
</tr>
<tr>
<td>2</td>
<td>Li₂CO₃</td>
<td>100%</td>
<td>0.4%</td>
<td>slightly yellow</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃</td>
<td>100%</td>
<td>3.0%</td>
<td>slightly yellow</td>
</tr>
<tr>
<td>4</td>
<td>Na</td>
<td>100%</td>
<td>-0.5 - 1% oligomers</td>
<td>orange</td>
</tr>
</tbody>
</table>
As can be retrieved from table 1, only the use of alkali metal carbonates leads to slightly colored products whereas the use of other bases such as Na, NaOME, NaH or tBuOK results in a strong discoloration. Furthermore, the use of lithium carbonate further reduces the formation of side products.

Example 3: Comparison of sodium carbonate and lithium carbonate in an inert solvent

A suspension of 2-(2H-benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol (50.0 g, 183 mmol), 2-ethylhexan-1-ol (50.0 g, 384 mmol), lithium bromide (1.6 g, 18 mmol), and 1.1 equivalent of the carbonate in toluene (150.0 g) is stirred under reflux for 3 hours, while generated water is continuously removed by azeotropic distillation. The turnover and impurity profile is determined after 3 hours by means of HPLC analysis. The colour is analysed visually.

Table 2

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>cat.</th>
<th>turnover</th>
<th>side products</th>
<th>colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li₂CO₃</td>
<td>LiBr</td>
<td>98.7%</td>
<td>0.0%</td>
<td>Slightly yellow</td>
</tr>
<tr>
<td>2</td>
<td>Na₂CO₃</td>
<td>LiBr</td>
<td>44.1%</td>
<td>8.6%</td>
<td>Slightly yellow</td>
</tr>
</tbody>
</table>

As can be retrieved from table 2, the time of turnover in an inert solvent, i.e. toluene is significantly increased if lithium carbonate instead of sodium carbonate is used as a base in the presence of a lithium bromide as catalyst. Furthermore, the side product formation is significantly lower.

The lithium carbonate batch has been further worked up by addition of heptane (100 ml.) and extraction of the reaction mixture with water (100 ml.) at 80°C. The aqueous phase is washed with heptane (50 ml.). The combined organic phases are washed with 0.1 M HCl (100 ml.), filtered and heptane is removed by evaporation. Residual alcohol is removed at
60°C under high vacuum and recovered. The resulting product is obtained in 93% yield with an HPLC purity of 98%.

Example 4: 2-(2H-Benzotriazol-2-yl)-6-(3-methyl-butoxymethyl)-4-methyl-phenol

2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol (10.0 g, 33 mmol) is suspended in a mixture of isoamyl alcohol (35 g, 0.4 mol) and acetone (5 g) and stirred at 80°C for 30 minutes. Sodium carbonate (4.7 g, 44 mmol) is added and the slightly yellow reaction mixture is stirred at 80°C for 30 minutes. Acetone is removed under vacuum, salts are filtered off and the reaction mixture is evaporated to dryness. The residue is dissolved in ethyl acetate and extracted with aqueous citric acid (5%) and brine. The organic layer is dried over sodium sulphate, filtered and evaporated to dryness. The crude product is purified by column chromatography (ethyl acetate/heptane 1:12) to yield 7.0 g of 2-(2H-Benzotriazol-2-yl)-6-(3-methyl-butoxymethyl)-4-methyl-phenol.

Example 5: 2-(5-Chloro-benzotriazol-2-yl)-6-(2-ethylhexyloxymethyl)-4-methyl-phenol

2-(5-Chloro-2H-benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol (5.0 g, 16 mmol) is suspended in a mixture of 2-ethylhexanol (20.0 g, 154 mmol) and acetone (5 g) and stirred at 80°C for 15 minutes. Sodium carbonate (3.4 g, 32 mmol) is added. The slightly yellow reaction mixture is stirred at 80°C for 3 hours and evaporated to dryness. The residue is dissolved in ethyl acetate and extracted with aqueous citric acid (5%) and brine. The organic layer is dried over sodium sulphate, filtered and evaporated to dryness. The crude product is purified by column chromatography (ethyl acetate/heptane 1:12) to yield 4.9 g of 2-(5-Chloro-benzotriazol-2-yl)-6-(2-ethylhexyloxymethyl)-4-methyl-phenol.
Example 6: 2-(5-Chloro-2H-benzotriazol-2-yl)-4-methyl-6-(3-methyl-butoxymethyl)-phenol

![Chemical structure](image)

2-(5-Chloro-2H-benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol (5.0 g, 16 mmol) is suspended in a mixture of isoamyl alcohol (20.0 g, 227 mmol) and acetone (5 g) and stirred at 80°C for 15 minutes. Sodium carbonate (2.1 g, 20 mmol) is added. The slightly yellow reaction mixture is stirred at 80°C for 2 hours and evaporated to dryness. The residue is dissolved in ethyl acetate and extracted with aqueous citric acid (5%) and brine. The organic layer is dried over sodium sulphate, filtered and evaporated to dryness. The crude product is purified by column chromatography (ethyl acetate/heptane 1:12) to yield 4.7 g of 2-(5-Chloro-2H-benzotriazol-2-yl)-4-methyl-6-(3-methyl-butoxymethyl)-phenol.

Example 7: 2-Ethyl-hexanoic acid 3-(2H-benzotriazol-2-yl)-2-hydroxy-5-methyl-benzyl ester

![Chemical structure](image)

2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol (10.0 g, 33 mmol) is suspended in a mixture of 2-ethylhexanoic acid (11.9 g, 82 mmol) and tetrahydrofuran (75 g) and stirred at 70°C for 30 minutes. Sodium carbonate (10.5 g, 99 mmol) is added. The reaction mixture is stirred at 60°C for 15 minutes and evaporated to dryness. The residue is dissolved in ethyl acetate and extracted with an aqueous potassium carbonate solution (10%) and brine. The organic layer is dried over sodium sulphate, filtered and evaporated to dryness. The crude product is purified by column chromatography (ethyl acetate/heptane 1:12) to yield 11.2 g of 2-Ethyl-hexanoic acid 3-(2H-benzotriazol-2-yl)-2-hydroxy-5-methyl-benzyl ester.
**Example 8:** 3-Methyl-butyric acid 3-(2H-benzotriazol-2-yl)-2-hydroxy-5-methyl-benzyl ester

![Chemical structure]

2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol (10.0 g, 33 mmol) is suspended in a mixture of 2-isovaleric acid (8.4 g, 82 mmol) and tetrahydrofuran (75 g) and stirred at 70°C for 30 minutes. Sodium carbonate (10.5 g, 99 mmol) is added. The reaction mixture is stirred at 60°C for 15 minutes and evaporated to dryness. The residue is dissolved in ethyl acetate and extracted with an aqueous potassium carbonate solution (10%) and brine. The organic layer is dried over sodium sulphate, filtered and evaporated to dryness. The crude product is purified by column chromatography (ethyl acetate/heptane 1:12) to yield 11.5 g of 3-Methyl-butyric acid 3-(2H-benzotriazol-2-yl)-2-hydroxy-5-methyl-benzyl ester.

**Example 9:** 3,3’-Bis(2H-benzotriazol-2-yl)-2,2’-dihydroxy-5,5’-dimethylbenzyl ether

![Chemical structure]

To a suspension of 2-(2H-Benzotriazol-2-yl)-6-chloromethyl-4-methyl-phenol (1.1 g, 3.9 mmol) and 2-(2H-benzotriazol-2-yl)-6-hydroxymethyl-4-methyl-phenol (1.1 g, 3.9 mmol) in toluene (50 mL) sodium carbonate (456 mg, 4.3 mmol) is added. The reaction mixture is stirred at 100°C for 4 hours. The precipitated product is filtered off, washed with water and tetrahydrofuran, and dried at 70°C under vacuum to yield 1.3 g of 3,3’-Bis(2H-benzotriazol-2-yl)-2,2’-dihydroxy-5,5’-dimethylbenzyl ether.

**Example 10:** Determination of the solubility in cosmetic solvents

1.5 g of a cosmetic solvent (Capric/Caprylic Triglyceride (Mygliol 318) and Alkylbenzoate (Finsolv TN)) is saturated with the respective Benzotriazol-derivative by adding 0.2 g portions while stirring at room temperature. The saturated solution is stirred for 7 days at room temperature. 1 ml of the supernatant is centrifuged and filtered in order
to obtain a clear solution. The concentration of the Benzotriazol-derivative is determined by means of HPLC.

Table 3

<table>
<thead>
<tr>
<th>Compound of example</th>
<th>Benzotriazole of formula (lb) wherein</th>
<th>Derivative</th>
<th>solubility</th>
</tr>
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<tbody>
<tr>
<td>R³</td>
<td>R⁵</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>-CH₂CH(C₂H₆)C₄H₉</td>
<td>Ether</td>
<td>66%</td>
</tr>
<tr>
<td>(2-Ethylhexyl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>-C⁶H⁴CH(CH₃)₂</td>
<td>Ether</td>
<td>36%</td>
</tr>
<tr>
<td>(Isoamyl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>-CO₂H₄CH(CH₃)₂</td>
<td>Ester</td>
<td>6%</td>
</tr>
<tr>
<td>(Isoamylcarbonyl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>-C₂H₄CH(CH₃)₂</td>
<td>Ether</td>
<td>12%</td>
</tr>
<tr>
<td>(Isoamyl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>-CH₂OH</td>
<td>Bis-Ether</td>
<td>0.01%</td>
</tr>
</tbody>
</table>

As can be retrieved from table 3 the alkyl-ether derivatives show a significantly higher solubility compared to the corresponding ester derivatives or the bis-ether of example 9.
Claims:

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

\[
\begin{array}{c}
\text{R}^3 \quad \text{N} \\
\text{HO} \quad \text{OR}^5 \\
\text{R}^4 \quad \text{R}^2
\end{array}
\]

(lb)

wherein

- \( \text{R}^2 \) is hydrogen; \( \text{C}_{1-3} \)-alkyl; \( \text{C}_{1-5} \)-alkoxy; \( \text{C}_{5-7} \)-cycloalkyl; \( \text{C}_{6-10} \)-aryl or aralkyl;
- \( \text{R}^3 \) is hydrogen; \( \text{C}_{1-5} \)-alkyl; \( \text{C}_{1-5} \)-alkoxy or halogen, preferably hydrogen or Cl, most preferably hydrogen;
- \( \text{R}^4 \) is hydrogen or \( \text{C}_{1-5} \)-alkyl; and
- \( \text{R}^6 \) is \( \text{Cl}_{1-3} \)-alkyl or \( \text{C}_{5-10} \)-cycloalkyl.

said process comprising the step of reacting a 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative of formula (lib) with an alcohol \( \text{R}^2 \)-OH in the presence of an alkali metal and/or alkaline earth metal carbonate or bicarbonate

\[
\begin{array}{c}
\text{R}^3 \quad \text{N} \\
\text{HO} \quad \text{Cl} \\
\text{R}^4 \quad \text{R}^2
\end{array}
\]

(lib).

2. The process according to claim 1 wherein \( \text{R}^2 \) is hydrogen or \( \text{C}_{1-12} \)-alkyl, preferably \( \text{C}_{1-5} \)-alkyl, most preferably methyl; \( \text{R}^3 \) is hydrogen; \( \text{R}^4 \) is hydrogen or \( \text{C}_{1-2} \)-alkyl, preferably hydrogen; and \( \text{R}^6 \) is \( \text{C}_{1-12} \)-alkyl or \( \text{C}_{5-7} \)-cycloalkyl, preferably \( \text{C}_{5-10} \)-alkyl or \( \text{C}_{6} \)-cycloalkyl.

3. The process according to claim 1 or 2 wherein \( \text{R}^5 \) is a branched alkyl or a methyl substituted cyclohexyl radical.
4. 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.

5. The process according to any one of claims 1 to 4 wherein the alkali metal and/or alkaline earth metal carbonate or bicarbonate is used in an amount of 0.9 to 1.5 mol-%, preferably in an amount of 1 to 1.1 mol-% based on the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative.

6. The process according to any one of claims 1 to 5 wherein the alkali metal and/or alkaline earth metal carbonate or bicarbonate is an alkali metal carbonate, preferably lithium carbonate.

7. The process according to any one of claims 1 to 6 wherein the reaction temperature is selected in the range of 70 to 90 °C.

8. The process according to any one of claims 1 to 7 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.

9. The process according to any one of claims 1 to 7 wherein the reaction is carried out in the presence of an inert solvent.

10. The process according to claim 9, wherein the inert solvent is toluene.

11. The process according to claim 9 or 10 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 5:1 to 1:1.

12. The process according to any one of claims 9 to 11 wherein an additional amount of lithium bromide is present.
13. The process according to claim 12 wherein the amount of lithium bromide is selected in the range of 5 to 20 mol-%, preferably in the range of 8 to 15 mol-% based on the 2-(2H-benzotriazol-2-yl)-6-chloromethyl-phenol derivative.

14. Benzotriazole derivatives obtained by a process according to any one of claims 1 to 13.
INTERNATIONAL SEARCH REPORT

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

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C08K A61K

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>A</td>
<td>CN 1 727 338 A (HUATAI CHEMICAL CO LTD CHANGZH [CN]) 1 February 2006 (2006-02-01) compounds on pages 14-18 featuring acylated hydroxymethyl groups in 6-positions of the phenyl ring;</td>
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<td>A</td>
<td>&amp; DENG A ET AL: &quot;COMPOUND BENZOTRIAZOLE CATEGORY POSSESS ALKENYL ESTER TYPE STRUCTURE PREPARATION METHOD&quot;, WPI/THOMSON, 1 February 2006 (2006-02-01), XP007911427, the whole document</td>
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<td>X</td>
<td>JP 8 208628 A (OSAKA SEIKAI KOGYO KK) 13 August 1996 (1996-08-13) pages 9-10; compounds 12-13, 16-17 Table on page 11, entries 1, 3, 4;</td>
<td>14</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

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  "A" document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search
7 February 2011

Date of mailing of the international search report
15/02/2011

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

Authorized officer
Lange, Tim
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<td>- &amp; HONMARU H ET AL: &quot;New benzotri azole derivative vs. absorb UV radiation - useful in mfr. of e.g. UV-absorbing resins, paints and cosmetics&quot;, WPI/THOMSON, 13 August 1996 (1996-08-13), XP007911428, the whole document ****</td>
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<td>X, P</td>
<td>WO 2010/053917 Al (ALCON INC [CH]; LAREDO WALTER R [US]) 14 May 2010 (2010-05-14) example 7 Use for UV absorbance; page 7, line 5 - line 6 ****</td>
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