BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICH
Faculty of Chemical and Bioengineering

ELABORATION OF NEW SUNSCREEN AGENTS

Ph.D. Thesis

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1 INTRODUCTION

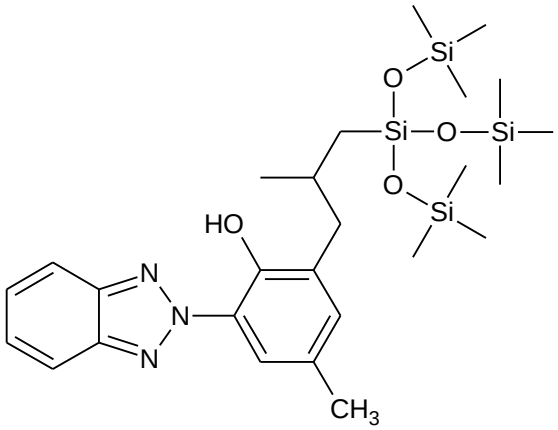
Sunlight is essential for us in many biological processes, but overexposure to sunlight brings the negative effects more into focus. In particular, UV radiation may cause unpleasant skin and eye problems. On top of its short-term effects there are also longer term harmful impacts, like the formation of malignant tumors.

Unfortunately measurements reveal that in the last 20 years UV radiation reaching the Earth's surface has risen by 6-14%. Therefore it is imperative to keep the rules of sunbathing and to use a sunscreen agent according to our skin type.

Many leading pharmaceutical and cosmetic companies discovered that the usage of proper sunscreen products can prevent a number of skin-related diseases, so these research studies have gained more attention lately.

I joined the research group lead by Professor Lajos Novák in 2004, at the Department of Organic Chemistry at the Budapest University of Technology and Economics. In cooperation with the Spanish pharmaceutical company ESTEVE, we set aimed to develop new sunscreen agents.

As the compounds consisting of benzotriazoles proved to be the most successful agents on the basis of a number of parameters, we have chosen Mexoryl XL (**1**) as a lead compound.



1

In our research we aimed at developing a method for elaborating new aryl-benzotriazole derivatives with photo stability and protection against both UV-A and UV-B radiation, as well as preparing them in the amounts and purity required for biological tests.

2 LITERARY BACKGROUND

The habit of sunbathing is barely 100 years old.

In the early 1900's, an increasing number of scientists addressed the beneficial effects of sunlight, which made sunbathing an increasingly popular therapy. The first sunscreen cream came to market, developed by Franz Greiter in 1938[1].

Sunscreen products can be divided into 2 groups, based on their operating mechanism: *physical* and *chemical filters*[2].

The two most common types of *physical filters* are the natural mineral titanium dioxide and zinc oxide, both of which are able to reflect the full spectrum (visible, ultraviolet, infrared) of sunlight. However, cosmetic application of them is difficult. They are prone to uneven wetting and lumping, leaving uncovered areas that are vulnerable to harmful effects of sunlight. They are heavily blocking the skin from the environment, they get washed off due to water contact and sweating and they give the skin a whiter than normal shade.

Chemical filters work in the upper epithelial layers by absorbing light. They emit the absorbed energy in a form of light or heat. They are suitable for protecting against UV-A and UV-B or both radiations. They are the most effective and most widely used sunscreen agents today.

2-(2′-Hydroxyphenyl)benzotriazoles also operate on the principle of absorption. They are widely used as UV stabilizers in the plastics industry; however, their human application only came to foreground in 1986[3].

Due to their structure, hydroxyphenyl-benzotriazole derivatives are able to establish an intramolecular hydrogen bond, which is essential for molecular photostability[4]. They are non-allergenic. They have strong absorption bands in the UV-A and UV-B range, and their excited-state lifetime is negligibly short. The absorbed energy gets emitted in a non-radiating way[5,6].

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1. *The New York Times,* June 24, **2010**, E3.
2. Dévay Attila, Antal István: *A gyógyszeres biofarmácia alapjai*, Budapest, **2009**, 291-292.
3. L'Oreal, S.A.: 3,700,531, **1986**.
4. Otterstedt A. J.-E.: *J. Chem. Phys.*, **1973,** *58*, 5716-5725.
5. Chodoba C., Riedle E., Pfeiffer M., Elsasser T., *Chem. Phys. Lett.*, **1996,** *263*, 622.
6. Forurnier T., Pommert S., Mialocq J.-C., Deflandre A., Rozot R., *Chem Phys. Lett.*, **2000,** *325*, 171.

3 EXPERIMENTAL METHODS

In the course of my synthetic work I applied the preparative and separation methods of organic chemistry. I used thin layer chromatography with silica gel for monitoring the reactions. For the purification of the crude products preparative thin layer and column chromatography were used, as well as recrystallization. The new compounds were characterized by chromatographic R_f values and melting points. The purity of the compounds was checked by microanalytical data and their structures were identified by spectroscopic methods (IR, ^{1}H- and ^{13}C-NMR, MS).

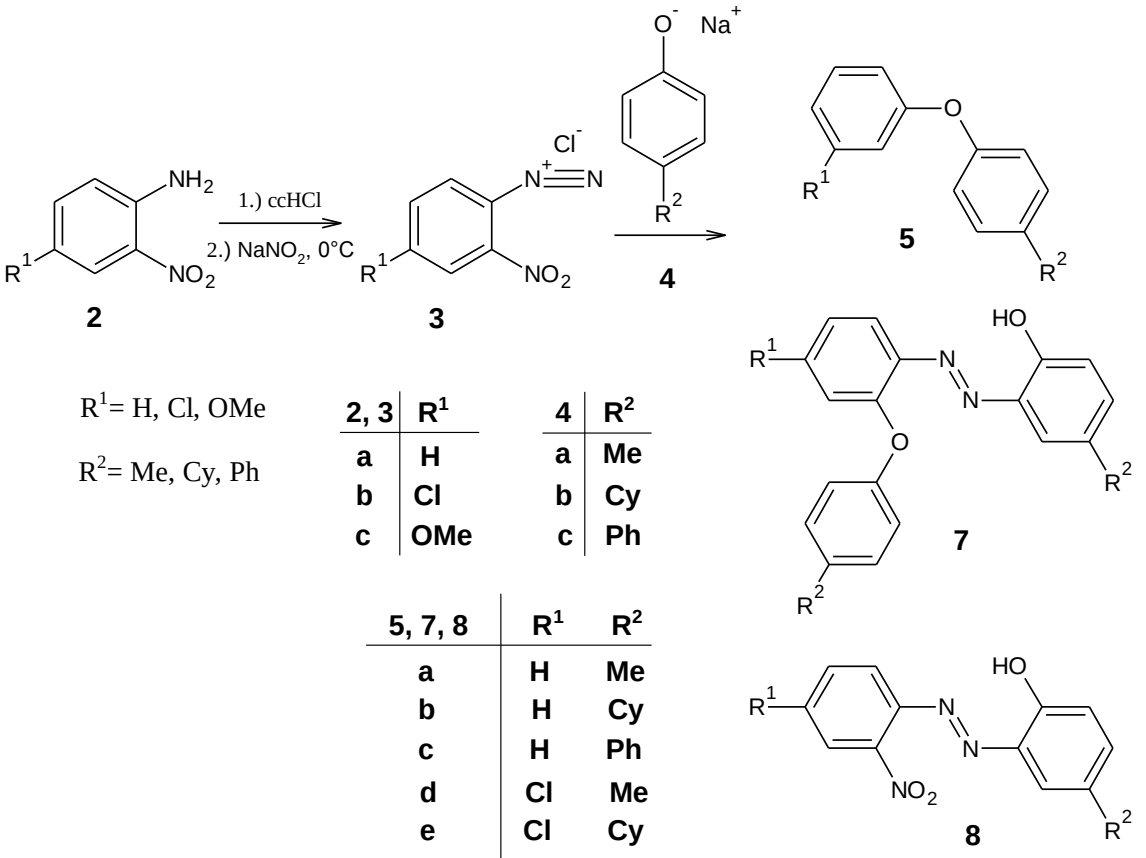
The photochemical properties of the prepared phenylbenzotriazole substances were measured for UV-absorption, fluorescence and photostability.

4 RESULTS

The lead molecule (**1**) was disassembled into its synthons by retrosynthetic analysis and we elaborated a method to create compounds based on benzotriazole skeletons.

The first step was an *azo coupling*.

We used 2-nitroaniline (**2a**) and its 4-substituted derivatives (**2b,c**) as starting substances. After the azo coupling reaction we isolated a significant amount of non-expected side-product (**7**) and a trace amount of compound **5**.



R^1= H, Cl, OMe

R^2= Me, Cy, Ph

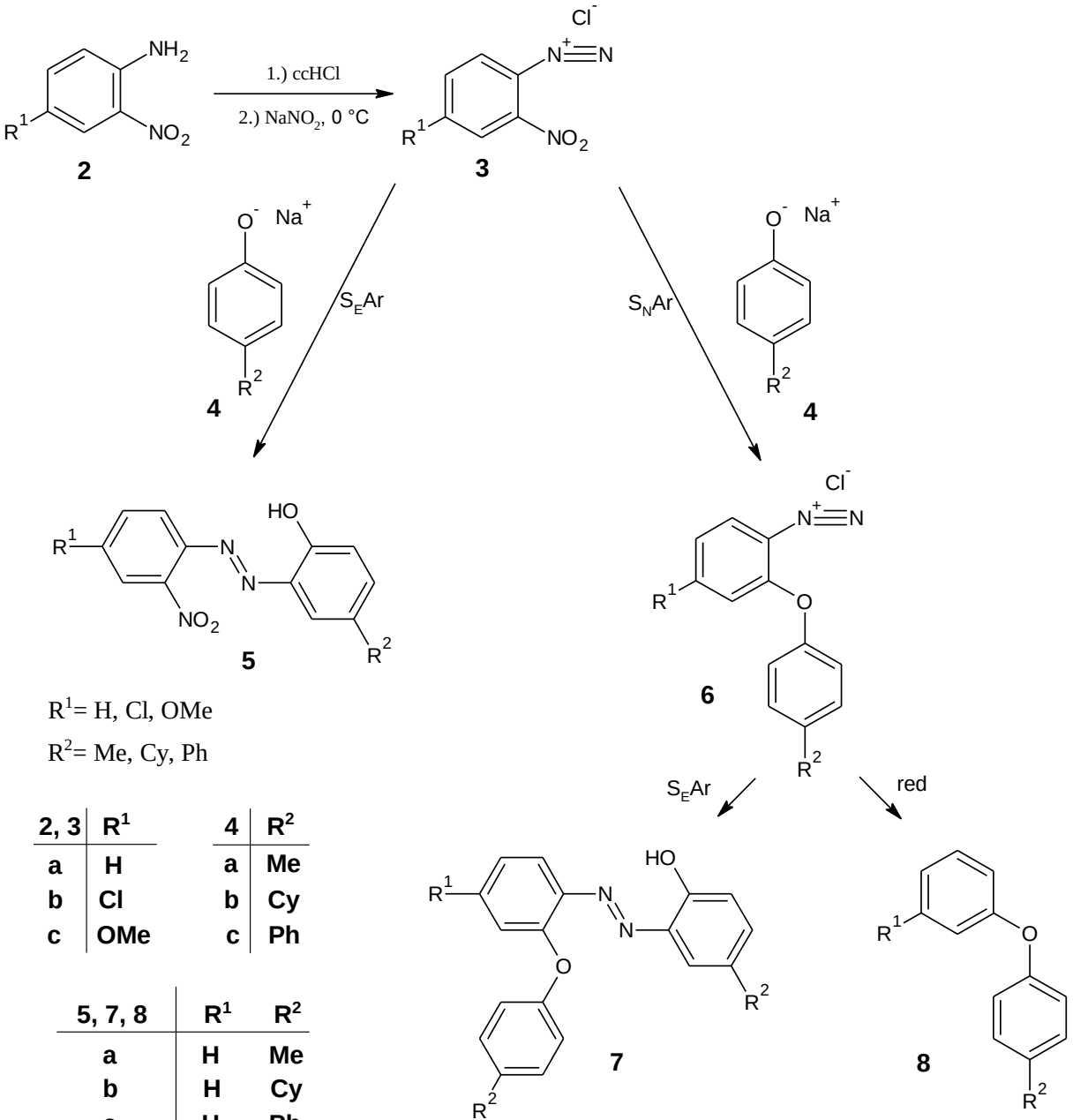
2, 3	R^1
a	H
b	Cl
c	OMe

4	R^2
a	Me
b	Cy
c	Ph

5, 7, 8	R^1	R^2
a	H	Me
b	H	Cy
c	H	Ph
d	Cl	Me
e	Cl	Cy
f	Cl	Ph
g	OMe	Me
h	OMe	Ph

We suggest the creation mechanism of the formation of these new substances.

We can gain the products of two parallel S_EAr and S_NAr reactions from the crude products. The side reaction most probably starts with the nucleophilic aromatic substitution of nitro group, and then the electrophilic substitution occurs, out of which product **7** derive. We can get compound **8** out of compound **6** with reductive dediazotization (*Figure 1*).



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2, 3	R^1
a	H
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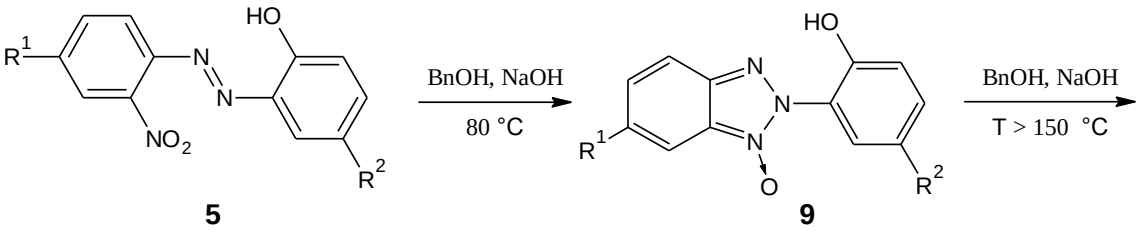
a	Me
b	Cy
c	Ph

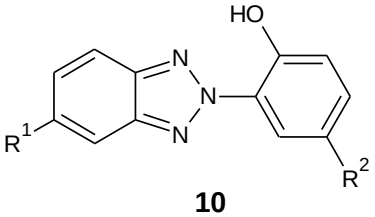
5, 7, 8	R^1	R^2
a	H	Me
b	H	Cy
c	H	Ph
d	Cl	Me
e	Cl	Cy
f	Cl	Ph
g	OMe	Me
h	OMe	Ph

Figure 1: The mechanism of azo coupling and its side reactions

In the next step we have formed the benzotriazole ring out of the azo compound (**5**) by *reductive cyclization*. The reaction was performed by benzyl alcohol in the presence of sodium hydroxide for 1-1,5 hours.



5 **9**



10

R^1= H, Cl, OMe

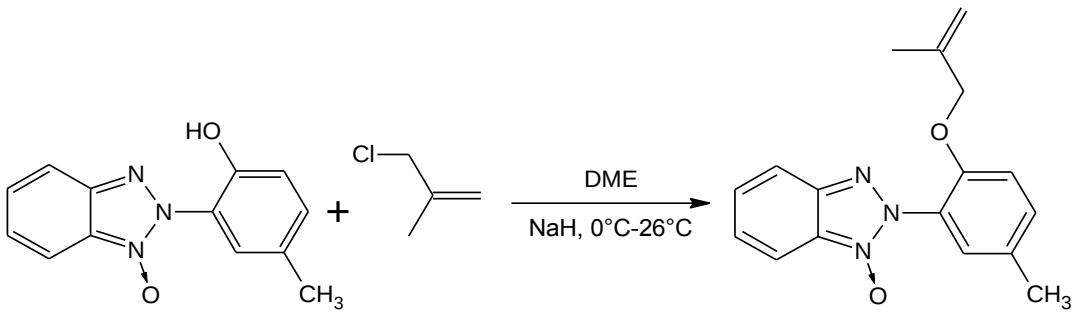
R^2= Me, Cy, Ph

5, 9, 10	R^1	R^2
a	**H**	**Me**
b	**H**	**Cy**
c	**H**	**Ph**
d	**Cl**	**Me**
e	**Cl**	**Cy**
f	**Cl**	**Ph**
g	**OMe**	**Me**
h	**OMe**	**Ph**

The corresponding *N*-oxide (**9**) was an intermediate of the above reaction. This is a stable compound that can also be prepared with appropriate conditions. Product **9** is the first product but **10** is thermodynamically more stable substance. On this basis, we developed a procedure where only by controlling the temperature we can control the production of end products from a pure *N*-oxide compound (**9**) up to – on a higher temperature – a pure benzotriazole substance (**10**).

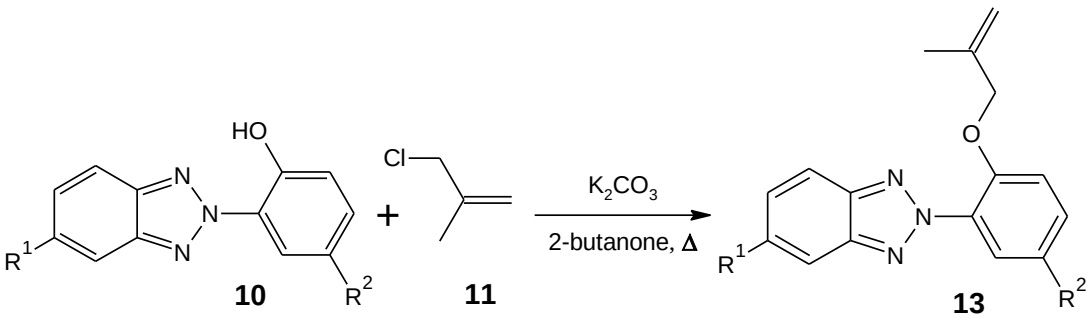
The third step is the *alkylation of phenolic hydroxyl group*.

In the case of the *N*-oxide derivative (**9a**) we used sodium hydride as a base in dimethoxyethane solvent (DME), with dropping methallyl chloride at low temperature.



9a **11** **12**

In the case of the benzotriazole derivative (**10**) we used potassium carbonate as base in 2-butanone solvent in the presence of potassium iodide and methallyl chloride (**11**) at higher temperature to obtain the desired product (**13**).



10 **11** **13**

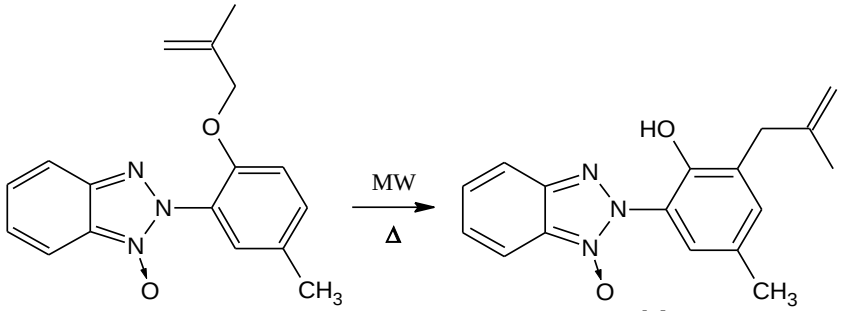
R^1= H, Cl

R^2= Me, Cy, Ph

10, 13	**R^1**	**R^2**
a	**H**	**Me**
b	**H**	**Cy**
c	**H**	**Ph**
e	**Cl**	**Cy**
f	**Cl**	**Ph**

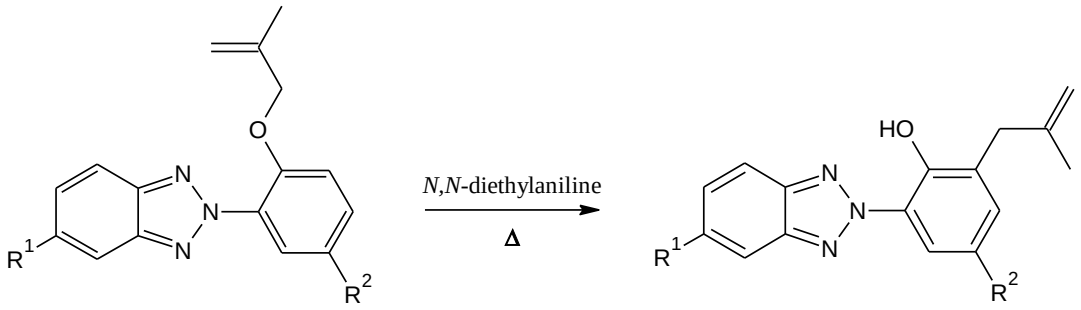
The next step is the *thermal rearrangement of the allyl group*.

In the case of the *N*-oxide derivative (**12**) microwave reactor was used to perform the rearrangement. The reaction was carried out without solvent at 150°C in 2 hours.



12 **14**

The product **13** was treated in *N*, *N*-diethylaniline for 3 hours on 210°C, giving a good yield for molecule **15**. This substance crystallized very well from non-polar solvents after processing.



13 **15**

R^1= H, Cl

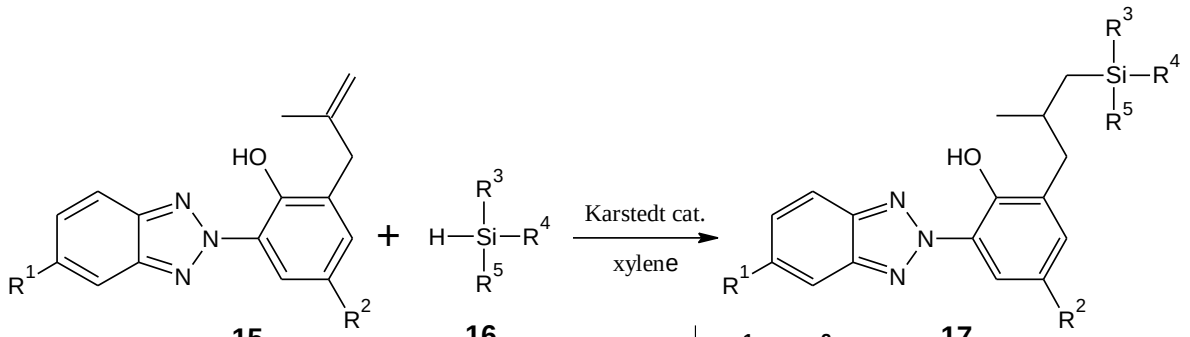
R^2= Me, Cy, Ph

13, 15	**R^1**	**R^2**
a	**H**	**Me**
b	**H**	**Cy**
c	**H**	**Ph**
e	**Cl**	**Cy**
f	**Cl**	**Ph**

We also tried the rearrangement of benzotriazoles (**13**) in a microwave reactor. The reaction took place without solvents, on a lower temperature (150°C) in a shorter reaction time (2 hours).

A great advantage of the microwave reactor is simplifying the reaction as it does not require solvents and it's also faster.

As a *final step* I treated siloxane derivatives (**16**) with the double bond of the allyl group in the presence of Karstedt catalyst in xylene and isolated compound **17** in acceptable to good yields.



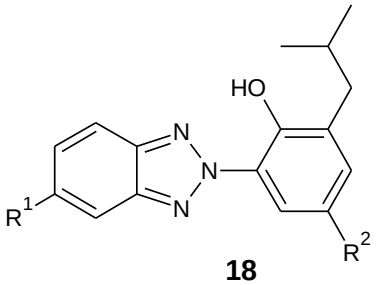
15 **16** **17**

R^1= H, Cl

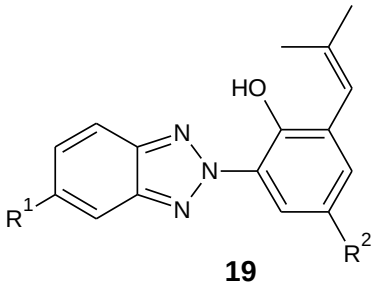
R^2= Me, Cy, Ph

15, 17-19	**R^1**	**R^2**
a	**H**	**Me**
b	**H**	**Cy**
c	**H**	**Ph**
e	**Cl**	**Cy**
f	**Cl**	**Ph**

We were able to isolate two side-products (**18, 19**) from this reaction.



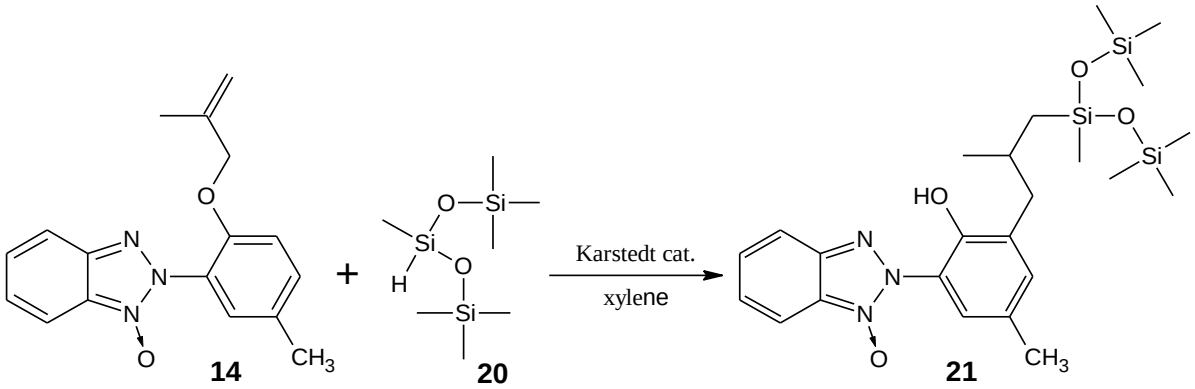
18



19

These (**18**, **19**) are the typical side products of hydrosilylation.

The method can also be used for the synthesis of sylilated benzotriazole *N*-oxide (**21**).



14 **20** **21**

With this procedure we prepared a number of Mexoryl XL analogues (**17**) substituted on the benzotriazole ring. The photochemical properties of these were examined by our Spanish partner.

5 THESES

1. We developed a rational synthesis route for aryl-benzotriazole derivatives that provide protection against both UV-A and UV-B radiation, similar to our lead compound (Mexoryl XL (1)). [1-4]
2. We proposed a mechanism for the formation of side products that occur in the substitution reaction during the azo coupling. [2]
3. We produced better yields than current literature for both the N-oxide and the benzotriazole derivatives during the reductive cyclization reaction with benzyl alcohol in the presence of sodium hydroxide. [3]
4. We improved yields and made the process of Claisen-rearrangement simpler by successfully achieving the reaction in a microwave reactor without the usage of solvents.

5. A number of new sunscreen compounds were synthesized based on this method and their photochemical properties showed excellent results, proving to be potential UV-filter candidates. [1]

6 PUBLICATIONS

6.1 Publications containing the results of the dissertation

1. **Renáta Farkas**, Virginie Lhiaubet-Vallet, Jordi Corbera, Mercédesz Tőrincsi, Olga Gorchs, Carles Trullas, Oscar Jiménez, Miguel A. Miranda, Lajos Novák: Synthesis of New 2-(2′-Hydroxyaryl)benzotriazoles and Evaluation of Their Photochemical Behavior as Potential UV-Filters,
   Molecules, **2010**, *15*, 6205-6216. [IF: 1.738]
2. **Renáta Farkas**, Mercédesz Tőrincsi, Pál Kolonits, Jenő Fekete, Oscar Jimenez Alonso, Lajos Novák: Simultaneous displacement of nitro group during coupling of diazotized *o*-nitroaniline with phenols,
   Cent. Eur. J. Chem., **2010**, *8* (2), 300-307. [IF: 0,991]
3. **Renáta Farkas**, Mercédesz Tőrincsi, Pál Kolonits, Oscar Jimenez Alonso, Lajos Novák: One-pot Synthesis of Benzotriazols and Benzotriazol-1-Oxides by Reductiv Cyclization of *o*-Nitrophenylazo Compounds with Benzyl Alcohol,
   Heterocycles, **2009**, *78* (10), 2579-2588. [IF: 1,165]
4. **Renáta Farkas**, Mercédesz Tőrincsi, Pál Kolonits, Lajos Novák: Synthesis of new potential UV-filters,
   Periodica Polytechnica, **2012,** accepted for publication.

6.2 Further publications

Keglevich György, **Farkas Renáta**, Ludányi Krisztina, Hanusz Miklós, Kálmán Simon: New P-ligands: The aromaticity and reactivity of 2,4,6-trialkylphenylphospholes: *Heteroatom Chemistry*, **2005**, *16* (2) 104-110.

Keglevich György, **Farkas Renáta**, Imre Tímea, Ludányi Krisztina, Szöllősy Áron, Tőke László: 2,4,6-Trialkylphenyl-2H-phospholes from slightly aromatic 1H-phospholes and their use in [4+2] cycloaddition reactions: *Heteroatom Chemistry*, **2003**, *14* (4) 316-319.

6.3 Lectures in connection with the dissertation

Farkas Renáta, Kolonits Pál, Novák Lajos:

Fényvédő hatású molekulák kifejlesztése. (Presentation)

XII. Nemzetközi Vegyészkonferencia, Csíkszereda (Romania), 2006.

Farkas Renáta, Kolonits Pál, Novák Lajos:

Developing Light Protecting Molecules. (Poster)

I. Europian Chemistry Congress, Budapest, 2006.

Farkas Renáta, Kolonits Pál, Novák Lajos:

Fényvédő hatású molekulák kifejlesztése. (Presentation)

IV. Doktoráns Konferencia, 2006.

Farkas Renáta, Kolonits Pál, Novák Lajos:

Fényvédő hatású molekulák kifejlesztése. (Poster)

XI. Nemzetközi Vegyészkonferencia, Kolozsvár (Romania), 2005.