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RESEARCH ARTICLE

Rearrangement Reactions for the Synthesis of Some Oxa- and Aza-tricyclic Rings Heterocyclic Compounds

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Abstract

This review article describes the main results of our research during the last 5-6 years. A series of new rearrangement reactions was discovered and used for the synthesis of novel heterocyclic compounds: furo[2,3-f]isoquinolines, furo[3,2 -f] quinolines, benzo[c]xanthene, benzo[h]chromene, benzo[a] xanthene, benzo[f]chromene, furo[2,3-f]isoquinoline, spiro-furo[3,2-f]quinoline, cycloalkanoindoles, and benzotriazines.

Keywords

Claisen rearrangements, aza-Claisen rearrangements, Alder-ene reaction , furo[2,3-f]isoquinolines, furo[3,2-f]quinolones, furo[3,2-h]quinolones, cycloalkano[b]indole, benzotriazoles, UV-filters

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1 Introduction

Since their discovery, sigmatropic rearrangements have been widely studied and have stimulated the interest of organic chemists. These reactions followed by other transformation are among the most efficient and useful strategies for constructing complex organic compounds.

Among the rearrangement reactions Claisen rearrangement got special attention, because of its simplicity, the predictable stereochemical outcome, and the products could be converted into a wide variety of commercially valuable chemicals [1-3]. Among the different types of Claisen rearrangements aza-Claisen rearrangement was considered as a more complicated variant [4]. Owing to the more forcing conditions – the process needed about 25 kJ/mol more activation energy than its oxy-analogue – it was rare applied in the synthesis of heterocycles. However, after the discovery of the catalysis of Claisen rearrangements, the aza-Claisen rearrangement got significant attention, too [5,6].

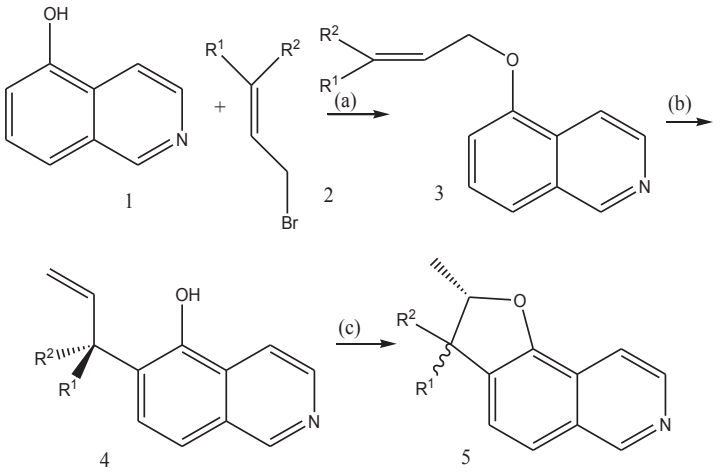
In a continuation of our work on the synthesis of biologically active compounds, we have focused our attention on the application of new rearrangement reactions in the synthesis of novel heterocycles. We also examined the microwave-accelerated Claisen and aza-Claisen rearrangements. These reactions coupled with acid-catalyzed cyclization were used for the synthesis of a series of new three and four fused heterocycles and the preparation of the carba analogs of physostigmine. One of the crucial reaction steps was also a rearrangement reaction in our synthesis of potential UV-filters.

The present brief review summaries the results of our work in the past five to six years.

2 New rearrangement reactions

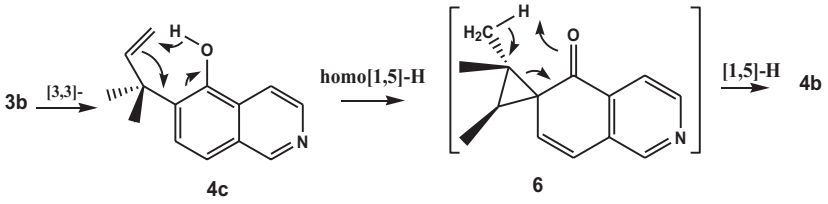
2.1 Rearrangement of allyloxyisoquinolines. Preparation of furo[2,3-*f*]isoquinolines

The furo[3,2-*f*]isoquinolines were found to possess phosphodiesterase IV inhibitory activity and are considered to be anti-arteriosclerotic agents [7]. The structural isomer furo[2,3-*f*]isoquinolines have not received as much attention – only one synthetic method has so far been reported for their preparation [8].



2-5	R^1	R^2
a	H	H
b	Me	Me

Scheme 1 Synthesis of furo[2,3-*f*]isoquinolines. Reagents and conditions: NaH, DME, r.t.; (b) microwave irradiation, 120°C, 6 h; (c) H_2SO_4, 100°C, 1 h.



Scheme 2 Plausible mechanism for the formation of compound **4b.**

Our interest in the preparation of new heterocyclic compounds which might be promising in the treatment of psychiatric disorders prompted us to elaborate a novel method for the preparation of new furo[2,3-*f*]isoquinolines and their cycloalkano derivatives [9].

Our synthesis is depicted in Scheme 1. Treatment of isoquinolin-5-ol (**1**) with NaH afforded the corresponding anion which was reacted with allyl bromide (**2a**). The allyl isoquinolinyl ether (**3a)** formed was subjected to microwave irradiation assisted [3,3] rearrangement to give **4a.** Acid-catalyzed intramolecular cyclization of the latter yielded furo[2,3-*f*]isoquinoline (**5a).**

Likewise, reaction between the sodium salt of **1** and methallyl chloride (**2b**) afforded an ether (**3b**). However, thermal rearrangement of this ether (**3b**) yielded an unexpected product (**4b**). The formation of this compound could be the following: the initial step a [3,3]-sigmatropic rearrangement of the ether (**3b**) afforded intermediate **4c** which then underwent a homo[1,5]-H shift to yield compound **6** [Scheme 2]. A [1,5]-H shift on compound **6** led to the formation of compound **4b** which by intermolecular cyclization furnished **5b** in excellent yield.

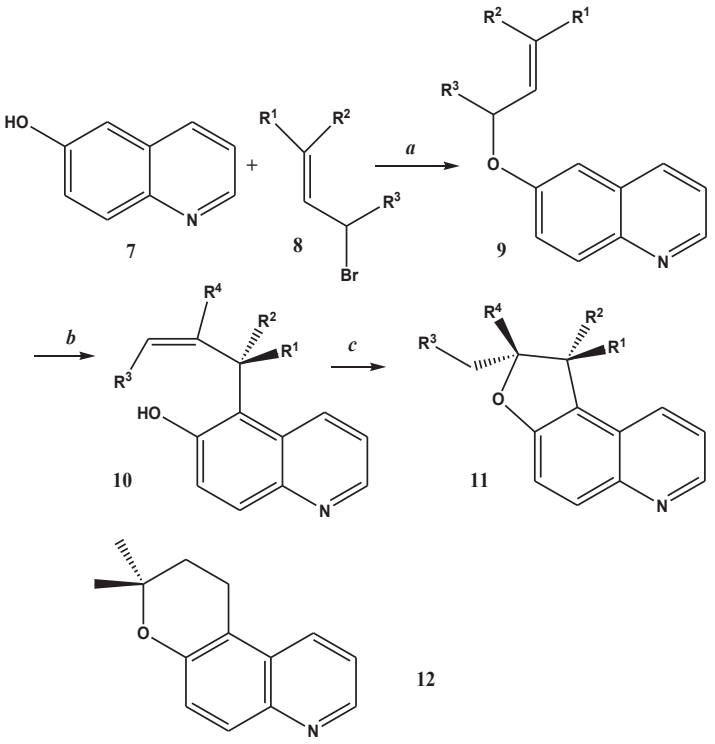
2.2 Rearrangement of allyloxyquinolines. Preparation of furo[3,2 -*f*]quinolines

Furo[3,2-*f*]quinolines have not received much attention. So far only three papers have been published dealing with the preparation of this ring system [10-12]. Following our synthetic efforts toward the preparation of new heterocyclic compounds which might be useful intermediates for the developments of molecules of pharmaceutical or biological interest, we elaborated new synthesis generally applicable for the preparation of furo[3,2-*f*]quinolines [13].

Here, we used essentially the same synthetic strategy as was applied for the preparation of the isomeric furo-isoquinolines (Cf. 2.1). Namely, ethers of quinolin-6-ol (**9,** Scheme 3) were prepared by the reaction of the sodium salt of quinolin-6-ol (**7**) with the appropriate allyl bromide (**8**). The allyl ether (**9a**) was then subjected to thermal [3,3] rearrangement in a microwave oven to give compound **10a**. Acid-catalyzed intramolecular cyclization of this rearrangement product afforded a furo[3,2-*f*]quinoline (**11a**).

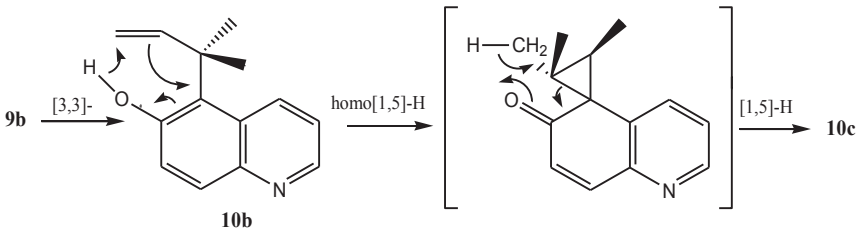
Starting with compound **9b**, the microwave assisted rearrangement gave two products **10b** and **10c** in a ratio 3:1. Compound **10b** was formed in the normal Claisen rearrangement and it afforded the wanted furo[3,2-*f*]quinoline (**11b**) by acid promoted ring closure.

Compound **10c** took its origin from three consecutive reaction steps (Scheme 4). A Claisen rearrangement of ether **9c** yielded intermediate **10b** which then underwent a homo[1,5]-H shift to give compound **12.** Further [1,5-]-H migration on the intermediate led to the formation of **10c** which afforded furo[3,2-*f*]quinoline (**11c**) by acid-catalyzed ring closure.



10,11	R¹	R²	R³	R⁴
a	H	H	H	H
b	Me	Me	H	H
c	Me	H	H	Me

Scheme 3 Preparation of furo[3,2-*f*]quinolines. Reagents and conditions: (a) NaH, DME, r.t.; (b) microwave irradiation, 175°C, 10 h; (c) H_2SO_4, 100°C, 1 h.



Scheme 4 Plausible mechanism for the formation of compound **10c.**

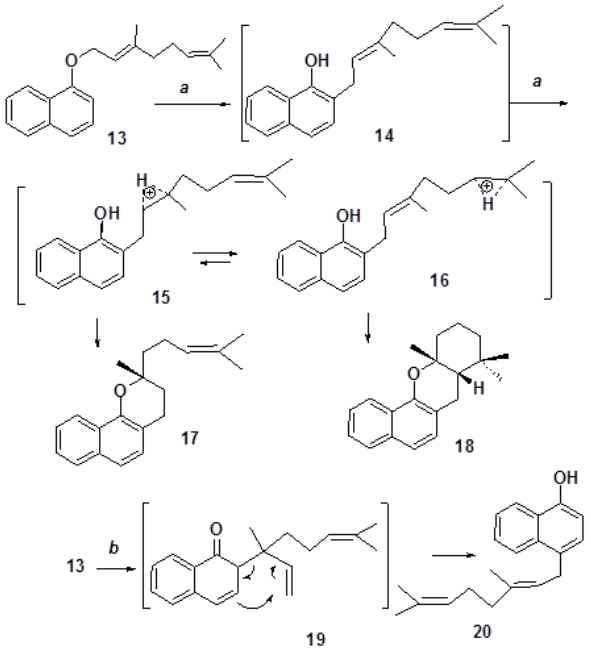
2.3 Rearrangement of aryl geranyl ethers. Preparation of benzo[*c*]xanthene, benzo[*h*]chromene, benzo[*a*]xanthene, benzo[*f*]chromene, furo[2,3-*f*] isoquinoline, and spiro-furo[3,2-*f*]quinoline

Aryl geranyl ethers were isolated from the New Zealand liverwort (*Trichocolea molissima*) and showed cytotoxic effects against kidney cells and in AIDS-related lymphoma screens [14,15]. Several geranyl phenyl ethers were prepared and tested for inhibition of insect growth. The epoxide of these compounds showed significant insect juvenile hormone activity [16]. Furanone, coumarine and naphthol derivatives containing a geraniol-like fragment have been shown to process significant in vitro cytostatic activity [17]. These interesting biological effects of aryl geranyl ethers prompted us to prepare a series of these compounds and to elaborate short and efficient method for the conversion them into new heterocyclic compounds [18].

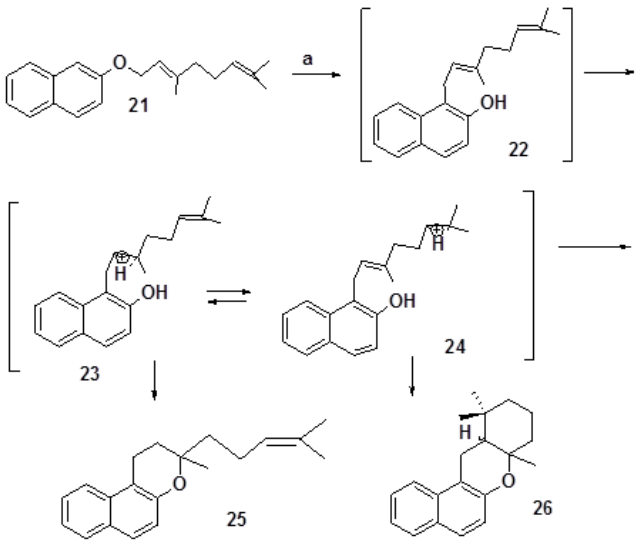
Geranyl naphth-1-yl ether (**13**, Scheme 5) was prepared from naphthalene-1-ol and geranyl bromide using the usual method. In the presence of PTSA, the thermal rearrangement of this ether afforded two unexpected products **17** and **18.** A plausible reaction path for the formation of benzo[*h*]chromene and benzo[*c*]xanthene (**17** and **18**, respectively) may be a [1,3]-alkyl shift, followed by acid catalyzed intramolecular cyclization (**15** → **17** and **16** →**18**).

At higher temperature the rearrangement of ether **13** led to a *para*-substituted naphthalene derivative **20.** Here, a [3,3]-sigmatropic rearrangement afforded intermediate **19,** which then underwent an another [3,3]rearrangement (Cope rearrangement) to give compound **20**. In microwave oven at higher temperature (170 °C) ether **13** decomposed and only naphthalene-1-ol was isolated.

Similar results were obtained with geranyl naphth-2-yl ether (**21**, Scheme 6). In toluene solution, the acid-initiated rearrangement reaction yielded intermediate **22**, which underwent subsequent acid-catalyzed cyclizations (**22** →**23**→**25** and **22** →**24**→**26**) to afford benzo[*f*]chromene **25** and benzo[*a*]xanthene **26** (in a ratio 1:3).



Scheme 5 Rearrangement of naphtha-1-yl geranyl ether. Reagents and conditions: (a) *p*-toluenesulfonic acid, toluene, r.t., 7 days; (b) reflux in chlorobenzene, 24 h.



Scheme 6 Rearrangement of naphth-2-yl geranyl ether. Reagent and conditions: (a) *p*-toluenesulfonic acid, toluene, r.t., 7 days.

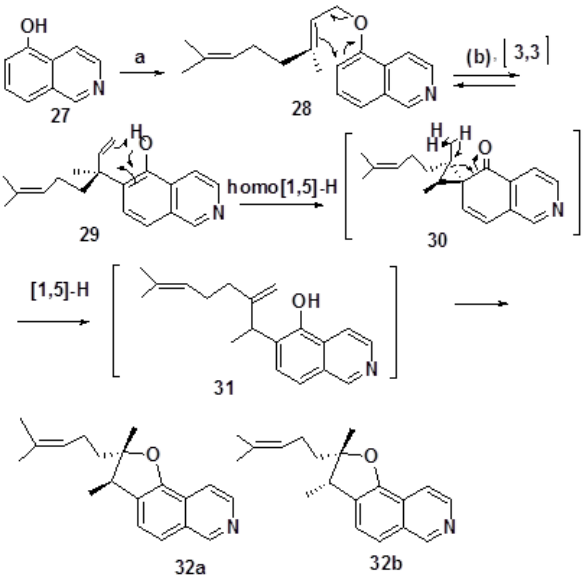
Attempted thermal rearrangement in boiling chlorobenzene or under microwave irradiation resulted only the decomposition of ether **13**, and naphthalene-2-ol was isolated.

Geranyl isoquinolinyl ether was prepared by the reaction between isoquinolin-5-ol (**27)** and geranyl bromide. The product **28** underwent rearrangement in a microwave oven to furnish furo[2,3-*f*]isoquinoline as a mixture of stereoisomers (**32a** and **32b**, Scheme 7). A plausible mechanism for the formation of compound **32** was based on an abnormal Claisen rearrangement depicted in Scheme 7. A [3,3]-sigmatropic rearrangement of ether **28** afforded intermediate **29,** which then underwent a homo[1,5]-H shift to yield intermediate **30**. Further [1,5]-H migration on the latter led to the formation of compound **31**, which by intramolecular cyclization furnished compound **32** as a 3:2 mixture of *cis* and *trans*-isomers.

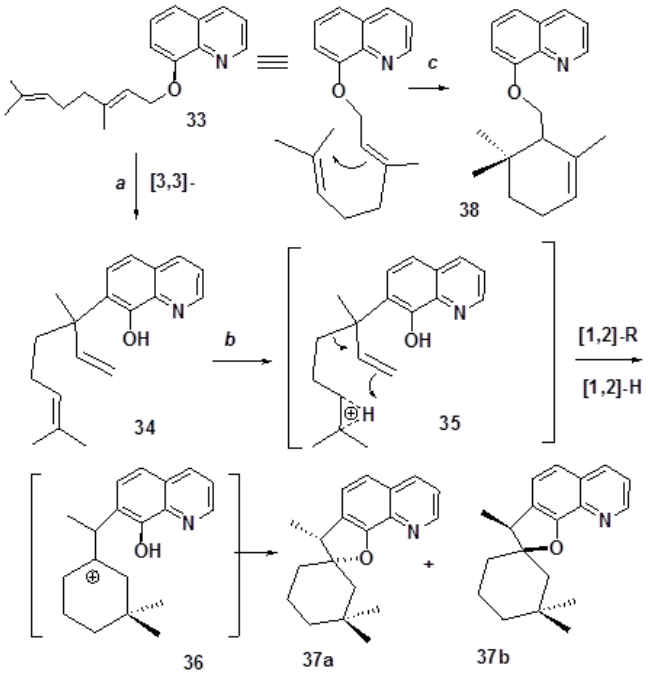
Geranyl quinolin-8-yl ether (**33**, Scheme 8) was prepared from quinolin-8-ol and geranyl bromide according to the published procedure [19]. Thermal rearrangement of **33** in boiling toluene led to the formation of the Claisen product **34** in moderate yield (28%). The microwave assisted reaction gave better result and compound **34** was isolated in 61% yield.

Surprisingly, acid-catalyzed intramolecular cyclization of compound **34** afforded a stereoisomeric mixture of spiro compounds (**37a** and **37b**). These unexpected products took their origin from consecutive [1,2]-alkyl migration, [1,2]-H shift, and cyclization reaction (**34→ 35 →36→37).**

Reaction of ether **33** with sulfuric acid at elevated temperature resulted only in the formation of compound **38** as the result of acid-catalyzed ring closure of the geranyl moiety.



Scheme 7 Rearrangement of isoquinolin-5-yl geranyl ether. Reagents and conditions: (a) NaH, geranyl bromide; (b) microwave irradiation, 180°C, 20 h.



Scheme 8 Rearrangement of quinolin-8-yl geranyl ether. Reagents and conditions: (a) microwave irradiation, 160 °C, 8 h; (b) H_2SO_4, 100 °C, 1 h; (c) PTSA, toluene, r.t., 40 h

3 Aza-Claisen rearrangement of *N*-(cycloalkenylmethyl)benzeneamines. Synthesis of cycloalkanoindoles, the carba analogs of physostigmine

Alzheimer's disease is a progressive dementia associated with the chlorinerg system [19,20]. Acetylcholinesterase enzyme rapidly metabolizes the naturally released acetylcholine causing a lack in this neurotransmitter [21]. An alkaloid of the African Calabar bean (*Physostigma venenosum),* (-)-physostigmine, inhibits the acetylcholinesterase by transcarbamylation [22,23]. This inhibition reduces the rate of acetylcholine's hydrolysis in the brain and increases its cholinerg activity. Physostigmine (eserine) and its phenylcarbamoyl derivative have been used medically to improve memory and relief in Alzheimer's disease [24-26].

Nowdays, cholinesterase inhibitors –donepezil (aricept), rivastigmine (exelon, an aryl carbamate derivative), and galantamine (nivalin) are also used for the treatment in the mild to moderate stages of Alzheimer's disease.

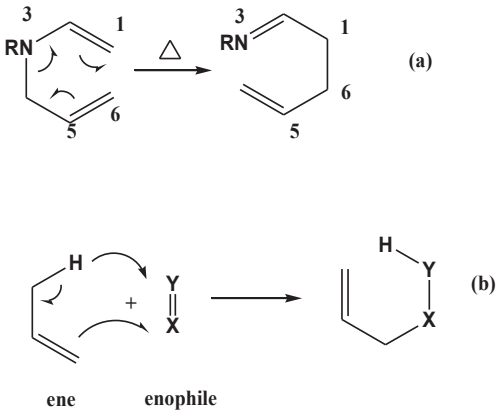
The growing need for new acetylcholinesterase inhibitors in clinical trials and application had focused interest on the preparation of physostigmine congeners. For instance, the pyrrolo[2,3-*b*] indole skeleton was replaced by furo[2,3]indole. However, the carba analogs in which one of the nitrogen-containing ring had been substituted by cycloalkano skeleton, have not got attention.

Our general interest in the preparation of new heterocyclic compounds, which might be promising in the treatment of mental disease, prompted us to elaborate methods for the synthesis of the carba analogs of physostigmine [27-30].

In our synthesis the key step was an aza-Claisen rearrangement followed by an Alder-ene reaction of the intermediate. Aza-Claisen rearrangement is also a thermal [3,3]sigmatropic rearrangement which shows a suprafacial reaction pathway (Scheme 9) [3-6,31,32]. The aza-Claisen rearrangement can be efficiently catalyzed with acid and Lewis-acids.

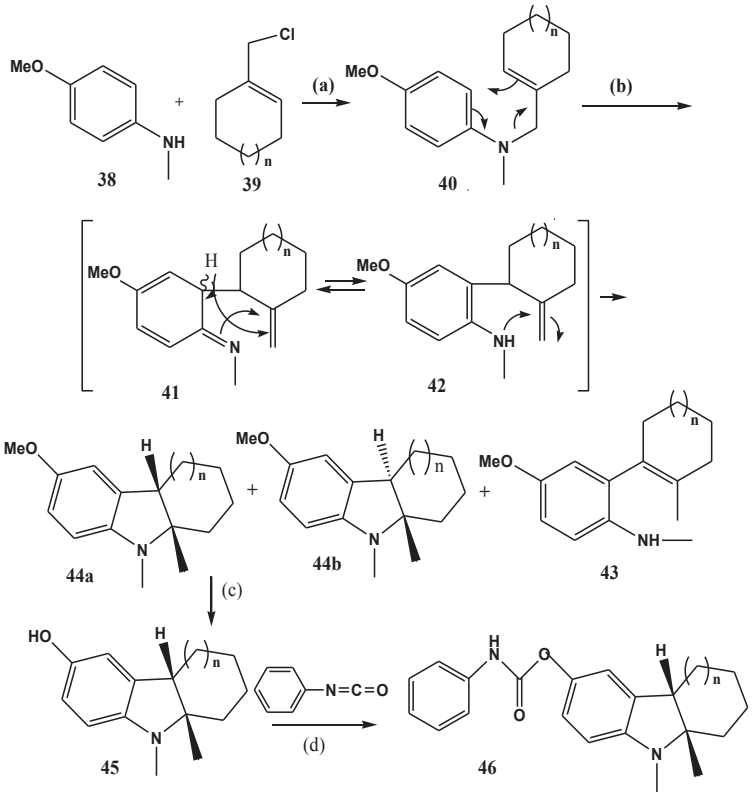
In Alder-ene reaction a four electron system including an alkene π-bond and an allylic C-H bond react with an enophilic olefin in a [4+2]-addition reaction. In this pericyclic reaction a double bond is shifted and new C-H and C-C σ-bonds are formed (Scheme 9) [33,34]. Alder-ene reaction can also be catalyzed by Lewis-acid.

Synthesis of the carba analogs of physostigmine is depicted in Scheme 10. The reaction of aniline derivative (**38**) with 1-(chloromethyl)-cycloalkan-1-ene (**39**) gave the expected amine (**40**), which was subjected to thermal rearrangement using BF_3OEt_2 as a catalyst. The aza-Claisen rearrangement



X=Y may be C=C, C=O, C=N, etc.

Scheme 9 aza-Claisen rearrangement (a) and Alder-ene reaction (b).



Scheme 10 Preparation of the carba analogs of physostigmine. Reagents and conditions: (a) Et_3N; (b) $BF_3 \cdot Et_2O$, sulfolane, 170°C; (c) BBr_3, $CHCl_3$, r.t.; (d) phenyl isocyanate, THF, reflux, 30h.

followed by a ring closure reaction afforded two products: compound **44** and side product **43.** In case of cyclopent-1-ene (**39a**, $n = 0$), only the *cis*-isomer was formed. However, cyclohex-1-ene and cyclohept-1-ene derivatives (**39b**, $n = 1$ and **39c**, $n = 2$, respectively) afforded a 3:1 mixture of *cis*- and *trans*-stereoisomers, which was separated by column chromatography. Side product **43** was formed by the migration of the carbon-carbon double bond.

For the preparation of the carba analog of physostigmine the *cis*-**44a-c** was treated with BBr_3 and the hydroxy derivatives **45a-c** formed were then reacted with phenyl isocyanate to afford the carba analog of physostigmine **46a** and its congeners **46b,c**.

Earlier we had considered the mechanism of the key step as aza-Claisen rearrangement followed by aromatic stabilization and nucleophilic attact of the nitrogen on the exo-double bond. But further investigation revealed another possible mechanism. Especially the *ab initio* DFT calculation on the transition states leading from **40c** to **44c.**

In the transition state of the first step (**40c → 41c**), there was a rather large difference between the energies of the chair and the boat geometry ($\Delta\Delta E$ = -17.3 kJ mol^{-1}), showing improbable boat conformation of the transition state in the aza-Claisen rearrangement. The *cis*-diastereoselectivity of the reaction can be rationalized on the above finding (Table 1 and Figs. 1 and 2).

Table 1 Calculation on the formation of compound **44c.**

Reagent	ΔE(kJ mol^{-1})	Reagent	ΔE(kJ mol^{-1})
Starting compound **40c**	0	Starting compound **40c**	0
Chair-TS-**41c**	234	Boat-TS-**41c**	251
Intermediate (*R,R;S,S*) **41c**	122	Intermediate (*R,R;S,S*) **41c**	133
TS-**42c**	358	TS-**42c**	361
Intermediate **42c**	-2,7	Intermediate **42c**	-2,7
TS-*cis*-**44c**	211		
TS-*trans*-**44c**	235		
TS-aza-Alder-ene reaction	288		

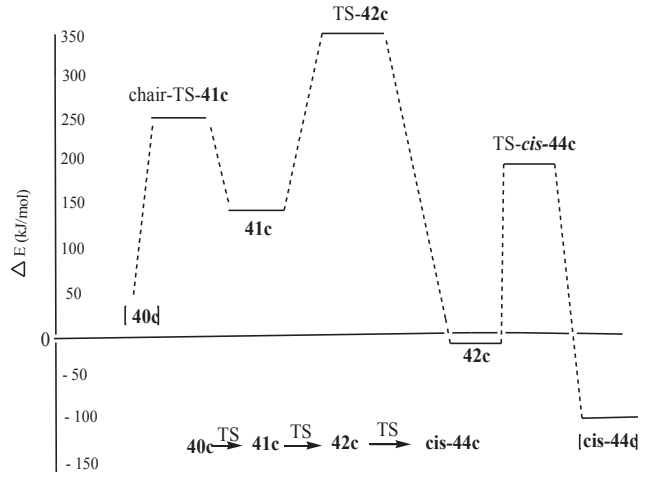


Fig. 1 Energy diagram of the formation of compound **44c.**

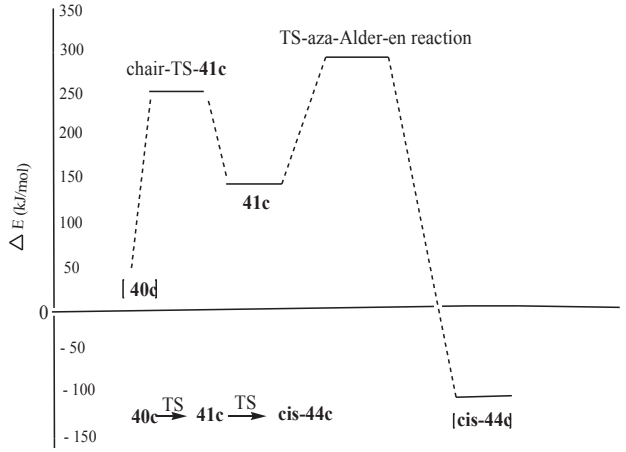


Fig. 2 Energy diagram of the aza-Claisen rearrangement followed by aza-Alder-ene reaction.

Surprisingly, the calculation for the transition state of the second step, aromatization, showed high energy (ΔE = 358 kJ mol^{-1}). For the closing step the transition state leading to the *cis*-product (**44c**) had lower energy than the corresponding "*trans"* (ΔΔE = -23.5 kJ mol^{-1}), suggesting that the "*trans"* reaction pathway was unfavorable, in accordance with experiment. We got also lower energy for the *cis*-product (**44c**) than for the *trans*-isomer (ΔΔE = -7.5 kJ mol^{-1}).

Due to the calculated high activation energy of intermediate **42**, we considered another possible mechanism for this reaction. We found that an intramolecular aza-Alder-ene reaction on the intermediate **41c** might also take place. The calculated activation energy (**41c → TS-41c→44**) was significantly lower then that calculated for the **TS-42** (ΔΔE = 147 kJ mol^{-1}). Therefore, this two-step pathway with its low activation barrier may be regarded as the mechanism of the formation of compounds **44c**. We had further evidence for this mechanism. We treated the isolated side product **43c** with BF_3 OEt_2 at 170°C for longer time, but no ring closured product **44c** could be isolated. We observed only some degradation.

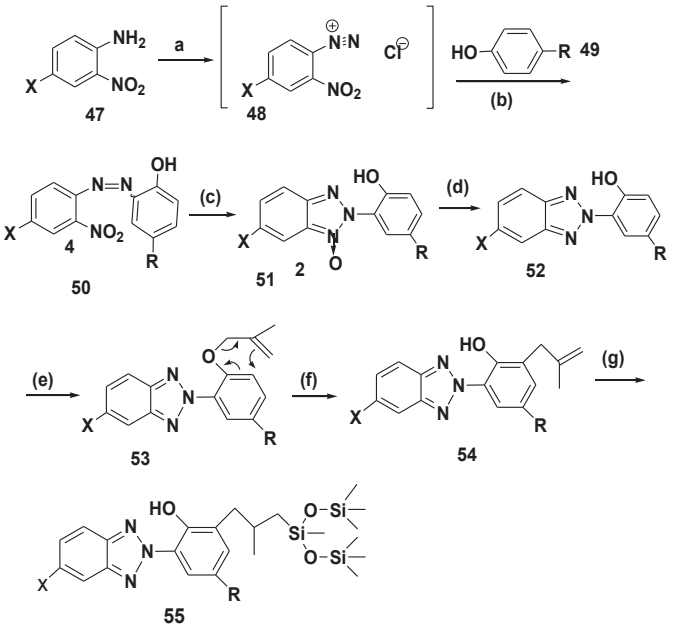
4 Synthesis of new potential UV-filters

As the result of the decreasing of the protective ozone layer, the exposure to ultraviolet light (UV) is increasing worldwide. UVA light (320- 400 nm), which is approximately 90% of the UV light, can pass through window glass, penetrates into the dermis, and may cause tanning, wrinkling, and skin cancer. Malignant melanoma is the most harmful of all skin cancers. Recently, it has been increasing faster than any other cancer and regarding the number of cases it has more than doubled in the last five years. Therefore, protection against the UV light has been growing and is of crucial significance [35-41].

A number of molecules are employed as UV light protecting agents. Among them compounds having intramolecular H-bond are strong UV absorbers and show proper photostability. Mexoryl XL, a benzotriazole derivative, is widely used as UV stabilizers. In this molecule the photoinduced excited state returns to the ground state by a proton transfer and rapid non-radiative dissipation of the harmful UV energy. The relaxation mechanism involves intramolecular proton transfer (ESIPT) from the S_1 state occurring in the femtosecond timescale, then radiative decay of the excited molecule (fluorescence emission with a large shift, $\lambda_{em} \approx 640$ nm) is followed by back proton transfer, causing a return to the ground state (back ESIPT) [42-45].

Recently we have elaborated new economical method for the preparation of 2-(2'-hydroxylphenyl)benzotriazoles (**51**, **52**, Scheme 11) by the reduction of compounds **50** with benzyl alcohol [46]. These important building blocks were then used for the preparation of new potential UV-filters. The synthesis followed is shown in Scheme 11.

Treatment of the aniline derivatives (**47**) with $NaNO_2$ and HCl afforded compounds **48**, which was coupled with phenols (**49**). The products (**50**) were treated with benzyl alcohol at 100°C to yield N-oxide (**51**) and at higher temperature benzotriazole derivatives (**52**) were isolated in excellent yield. Compounds **52** were heated with methallyl chloride in the presence of K_2CO_3 and KI to give ethers **53.** Thermal rearrangement of the products in *N,N*-dimethylaniline afforded compounds **54**,



47,48	X
a	H
b	Cl
c	OMe

50-55	X	R
a	H	Ph
b	H	cyclohexyl
c	Cl	Me
d	Cl	Ph
e	Cl	cyclohexyl
f	OMe	Me
g	OMe	Ph
h	OMe	cyclohexyl

Scheme 11 Preparation of potential UV-filters. Reagents and conditions: (a) $NaNO_2$, HCl, 0°C; (b) NaOH, isopropanol; (c) NaOH, benzyl alcohol, 100°C; (d) NaOH, benzyl alcohol, 120°C; (e) K_2CO_3, KI, methallyl chloride, butan-2-one, reflux, 12 h; (f) *N,N*-dimethylaniline, 160°C, 6 h; (g) $HSiCH_3[OSi(CH_3)_3]_2$, Karstedt catalyst.

which were then silylated using heptamethyltrisiloxane and Karlstedt catalyst [Pt_2(divinyltetramethyldisiloxane)$_3$] to give the desired products **55** in good yield [47-49].

Compounds **55** were evaluated for their photochemical behavior as potential UV-filters. The results are shown by the example of compound **55a**. The absorption spectra of compound **55a** showed two maxima, λ_1 at *ca.* 300 nm and λ_2 at *ca.* 350 nm, in ethanol, and after excitation a new emission spectra was observed at λ_1 at 590 nm. Moreover, steady state photolysis showed that this compound exhibits a potential applicability as UV-filter due to its UVA-absorption capability and its photostability.

5 Concluding remarks

New methods have been elaborated for the economical preparation of novel heterocyclic compounds, the carba analogs of physostigmine, and potential UV-filters. The key step of these syntheses was a rearrangement reaction: Claisen rearrangement, "abnormal" Claisen rearrangement, and aza-Claisen rearrangement. These rearrangement reactions are excellent tools in the preparation of complex heterocyclic compounds.

Acknowledgements

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