Diastereoselective synthesis of novel tetrahydroquinoline derivatives *via tert*-amino effect

Doctoral thesis

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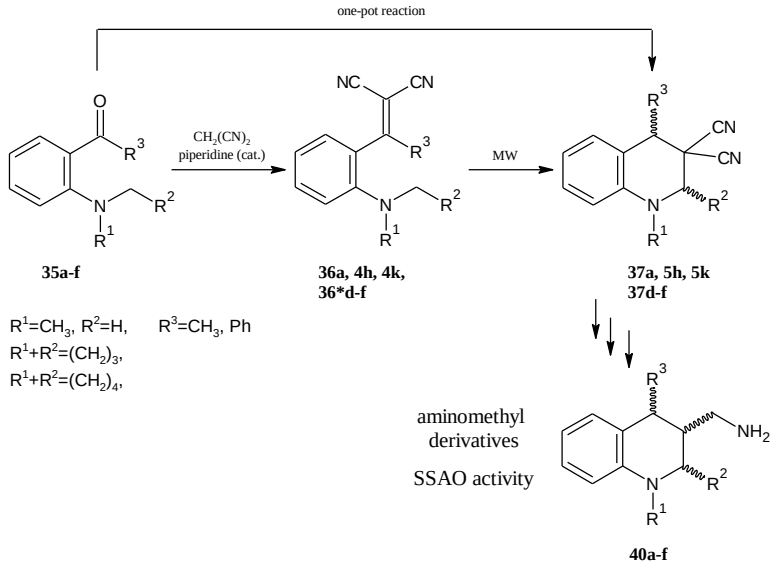
Introduction

Within the framework of the ongoing research project focusing on the *tert*-amino effect at the Department of Organic Chemistry, Semmelweis University, we have synthesized various tetrahydroquinoline compounds starting from simple starting materials, such as 2-dialkyl-amino acetophenone and 2-dialkylamino benzophenone derivatives by performing ring-closure reactions following the previous Knoevenagel condensation step (Scheme 1).



Scheme 1: Synthesis of tetrahydroquinoline compounds

The obtained novel stereogenic centers and the substituents eligible for further transformation gave an opportunity to produce substances with potential biological activity.

Aims

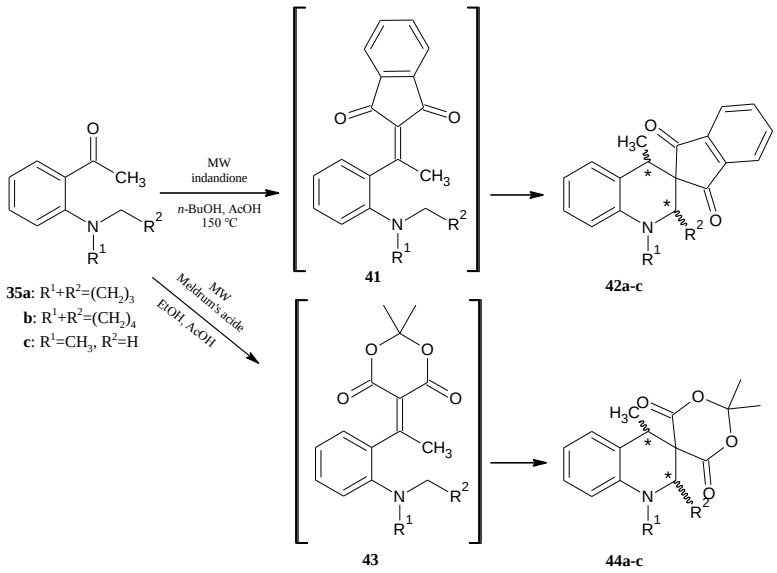
1) The primary aim of our research was to investigate the *tert*-amino effect with respect to the synthesis of condensed heterocycles containing nitrogen:

a) the investigation of the ring-closure reactions of 2-vinyl-*N*,*N*-dialkylanilines supported by microwaves from the aspect of diastereoselectivity, and to study the diastereomers formed including their ratios, giving an accurate description of the experimental findings.

b) studying the stereochemical outcome of the cyclized products obtained in the chemical reactions performed, in the respect of the relationship between the substituent size and the diastereomeric ratios,

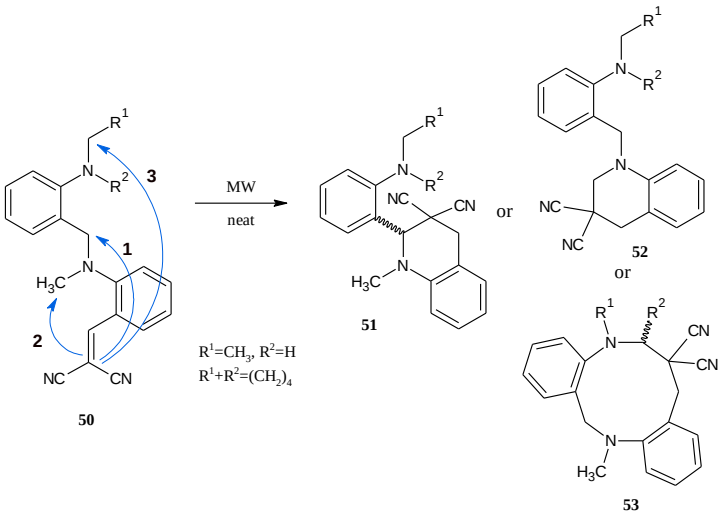
c) the confirmation and/or amendment of the earlier descriptions of the mechanism of the *tert*-amino effect,

d) studying the reactions accomplished in the presence of highly electron withdrawing groups (indan-1,3-dione and Meldrum's acid) in order to understand the impact of these compounds on the rate of ring formation (Scheme 2).



Scheme 2: Synthesis of new spirocyclic compounds
via the *tert*-amino effect

2) One of the ongoing research programs at the Department led by P. Mátyus relates to the study of inhibitors and substrates of semicarbazide sensitive amine oxidase (SSAO) enzyme. As a part of the project, transformation of some dinitrile products into aminomethyl compounds (**40a-f**) was also aimed.



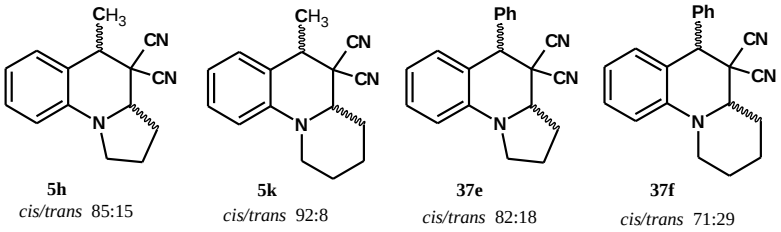
Scheme 3: Extension of the *tert*-amino effect to the bridged biaryl systems

3) Extension of the *tert*-amino effect to biaryls, bridged with a methylamino-*N*-methyl group between the phenyl rings, was studied in the course of my PhD work, as well. Performing ring closure reactions on these skeletons may give rise to medium-sized or macrocyclic entities (Scheme 3).

Methods

First, the ring closed products were prepared under one-pot reaction condition, furnishing the Knoevenagel reaction and the ring closure step sequentially, employed by our group previously. Compounds, which are substituted with methyl moiety (R^3=CH_3), were formed with relatively good yields and in a stereoselective manner, giving rise solely to the *cis* isomers.

Second, the ring-closed products were synthesized in a two steps procedure under microwave-assisted solvent-free condition from previously prepared 2-vinyl-*N*,*N*-dialkylaniline intermediates, as well. The isomeric ratios in the crude products were determined in all the cases, by using NMR and/or HPLC (Figure 1).

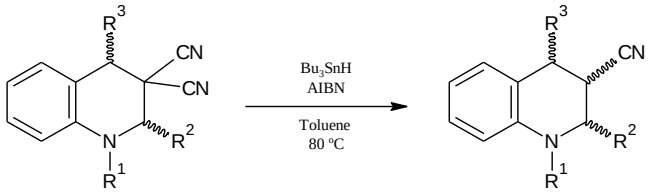


5h *cis/trans* 85:15 **5k** *cis/trans* 92:8 **37e** *cis/trans* 82:18 **37f** *cis/trans* 71:29

Figure 1: Ratio of the diastereomers in the crude product

In order to determine the relative configuration of the *trans* isomer, the diastereomers were separated by column chromatography or semi-preparative HPLC and the structures of all the obtained isomers were elucidated using 1D and 2D NMR spectroscopy methods.

The decyanation reactions of dinitrile compounds were carried out by radical reduction driven by tributyltin hydride in the presence of azobisisobutyronitrile (AIBN) in toluene (Scheme 5). As the R^3 substituent is either methyl or phenyl, the anticipated number of diastereomers are four, yet only two diastereomers were formed during the reaction, as proved by NMR. Column chromatography allowed the separation of the diastereomers, which were employed for the subsequent steps in pure form.

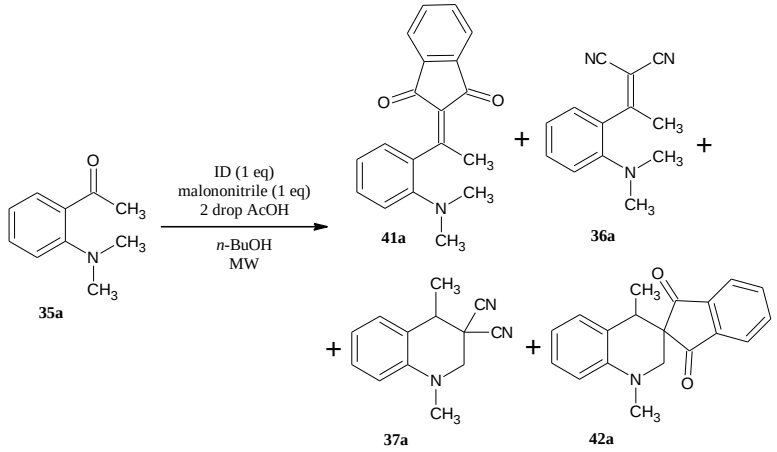


37a, 5h, 5k 37d-f **38a-f**

Scheme 5: Chemoselective reductive elimination of the cyano group of the geminal dinitrile

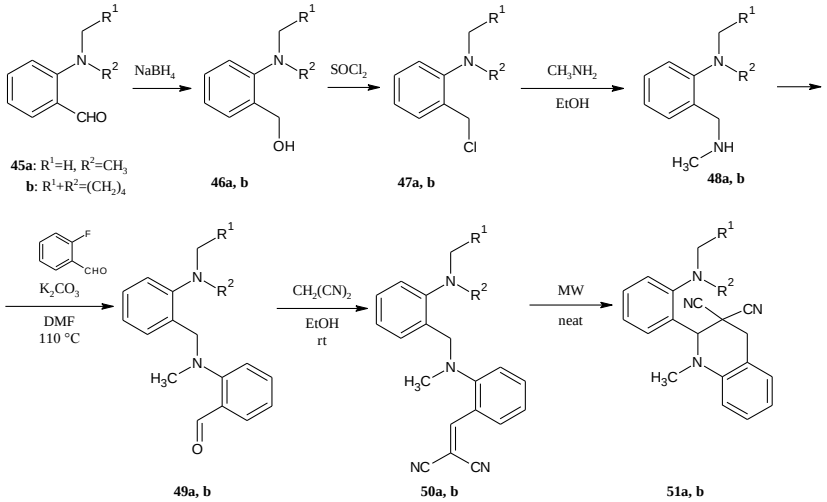
To the synthesis of aminomethyl derivatives, the nitrile group was reduced with sodium borohydride in the presence of a catalytic amount of $NiCl_2$, followed by protection with di-*tert*-butyl dicarbonate (Boc_2O) in methanol, furnishing the Boc protetcted product. In the second step, the carbamate product was treated with HCl/EtOAc at room temperature for 17-48 hours to afford the final product.

Furthermore, starting from 2-dialkylamino acetophenone and 2-dialkylamino benzophenone derivatives, we studied the effects of the respective substituents on the rate of the ring closure reaction (Scheme 6). Employing indan-1,3-dione (ID) and Meldrum's acid, the stereochemical outcomes of which are described in my dissertation, led to the formation of novel spirocyclic compounds (**42a-c**, **44a-c**).



Scheme 6: Competition experiment with malononitrile and ID

Finally, we studied the perspectives of the extension of the *tert*-amino effect to biaryl systems bridged with methylamino-*N*-methyl group (Scheme 7).



Scheme 7: Extension of the *tert*-amino effect to biaryl systems

Theoretically, these substances can be transformed into three different ring-closed products, however, only one route, allowing a tetrahydroquinoline product with a six-

membered ring, involved exclusively and regioselectivity. The thermochemical features of the ring closure reactions, using computations (PM3, DFT) and experiments (DSC), were evaluated and then confirmed the experimental findings.

Results

Cis-diastereoselectivity of the cyclizations was observed in all the cases, by the analysis of the crude products. The separation of the diastereomers by column chromatography or semi-preparative HPLC enabled the characterization of the relative configuration of both diastereomers by NOE interactions and the analysis of the vicinal coupling constans.

The ring-closed dinitrile derivatives were suitable precursors of various aminomethyl derivatives known to act as substrates to SSAO. An additional stereogenic center was formed by a chemoselective denitrilation.

The SSAO activity of aminomethyl derivatives was tested on the microsomal fraction of rat aorta. 4-Phenylbutylamine (4-PBA) was used as the reference substrate, while 2-bromoethylamine (2-BEA) was used as selective, irreversible inhibitor. According to the hydrogen peroxide formation assay, two compounds (**40**: R^3=CH_3, R^1=CH_3, R^2=H and R^3=Ph, R^1+R^2=$(CH_2)_3$) act as inhibitors of moderate potency as compared to 2-BEA, while one of them (**40**: R^3=CH_3 and R^1+R^2=$(CH_2)_3$) behaves as a substrate.

Regarding the stereochemical outcome of the synthesized spirocyclic compounds - with ID as well as with Meldrum's acid, - the *cis* isomer was formed predominantly. The cyclization reactions with ID and Meldrum's acid are faster than with malononitrile, based on the experimental results - we were not able to isolated the vinyl compounds - and the competition experiments followed by ^{1}H NMR spectroscopy.

The cyclization of biaryl systems bridged with methylamino-*N*-methyl group, based on our microwave assisted solvent-free protocol, exclusively took place *via* the first route, affording the six-membered ring products in excellent yield. Exclusively formation of tetrahydroquinoline products can be explained by the thermochemical and kinetic point of view.

Conclusion

1) A facile microwave-assisted diastereo-selective cyclization reaction was exploited for the preparation of condensed tetrahydroquinoline derivatives *via* the *tert*-amino effect.

a) The first, diastereoselective cyclizations step providing selectively the *cis* isomers in all the cases, irrespectively to the two types of R^3 substituents (CH_3 or Ph).

b) The rate of the ring closure reaction is greater in structures containing the more reactive cyclic secondary amino groups (pirrolidino and piperidino) than in those containing aliphatic (eg. dimethylamino) substituents. Diastereomers were separated by chromatography then the relative configuration was elaborated by NOE interactions and vicinal coupling constans.

c) Summarizing our present and the earlier Reinhoudt's results, we were led to the assumption that the *cis*/*trans* diastereomeric ratio depends not only on the steric hindrance in the starting vinil compounds, but also the difference between the activation energy of the transition state leading to the *cis* and the *trans* isomer - based on the Curtin-Hammet principle.

d) From the sum of the competition experiments, one can conclude that the formation of the vinyl compound substituted with malononitrile is faster than the formation of the vinyl compound substituted with ID. However, if the vinyl compound formed in the reaction mixture, the ring closure reaction could be faster in the case of ID, due to the stronger electron withdrawing effect of that group, compared to malononitrile.

2) The further transformation of the dinitrile compounds, including the chemoselective reductive elimination of the cyano group, resulted two diastereomers, which were separated and fully characterized. Reduction of the nitrile group afforded SSAO active aminomethyl derivatives. One of them showed enzyme substrate activity, while two other compounds inhibit this enzyme with a moderate potential, compared to that of the irreversible reference inhibitor 2-bromoethylamine, on the microsomal fraction of rat aorta.

3) Extension of the *tert*-amino effect to biaryls, bridged with a methylamino-*N*-methyl group between the phenyl rings, proceeded along the one route of three possible pathways. Exclusively formation of tetrahydroquinoline products can be explained by the thermochemical and kinetic point of view.

In the present work, we aimed to develop a facile, short synthesis for a novel, small presumably reversible inhibitor library designed for SSAO, represented by few relevant examples. Regarding the pharmacological results, these compounds proved to be hit molecules for the further biological experiments.

Publication

Publications of the author related to the present work

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Arkivoc (V) 164-196 (**2016**) *IF 1.177 (2015)*

Publications of the author outside the scope of the present work

Énzsöly A., Dunkel P., Czompa A., **Deme R.**, Gyires K., Magyar K., Németh J., Mátyus P.: Szemikarbazid-szenzitív amin oxidáz gátlók mint új hatóanyagok gyulladásos szembetegségek kezelésére: Szelektív inhibitoroktól új típusú több-támadáspontú gyulladás-gátló gyógyszerjelöltig.
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