BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLAH DOCTORAL SCHOOL

SYNTHESIS AND REACTIONS OF FORMYLATED *N*-PIVALOYL PHENYLETHYL- AND BENZYLAMINES

PhD Theses

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1. Introduction and review of the literature

Isoquinolines and their partly saturated congeners (dihydro- and tetrahydroisoquinolines) constitute an important class of natural and synthetic compounds exhibiting biological activity. Among benzylisoquinoline alkaloids papaverine is used as an antispasmodic agent,[1] and berberine is used in medicine for its antibacterial effect and cytotoxicity against human cancer cells.[2]

Synthetic isoquinoline derivatives have diverse biological activities. Drotaverine is the most commonly used medication for smooth muscle spasms and biliary tract disorders.[3] Trabectedin, which is used to treat sarcomas of soft tissues, is considered a milestone in cancer research.[4] Nomifensine inhibits the reuptake of noradrenaline and dopamine in the body, resulting in a sedative, antidepressant effect.[5]

1,8-Disubstituted *N*-acylated drug candidate derivatives (**7a**,**b** and **8**; Fig. 1), which are structurally most similar to the subject of this dissertation, are calcium channel blockers and may play a role in the alleviation of chronic pain.[6, 7]

The numbering of the compounds is identical in these PhD theses and in the PhD dissertation.

1 S. Mussa, T. J. Guzik, E. Black, M. A. Dipp, K. M. Channon, D. P. Taggart, *J. Thorac. Cardiovasc. Surg.*, **2003**, *126*, 1798−1805.

2 K. Zou, Z. Li, Y. Zhang, H. Zhang, B. Li, W. Zhu, J. Shi, Q. Jia, Y. Li, *Acta Pharmacol. Sin.*, **2016**, *38*, 157−167.

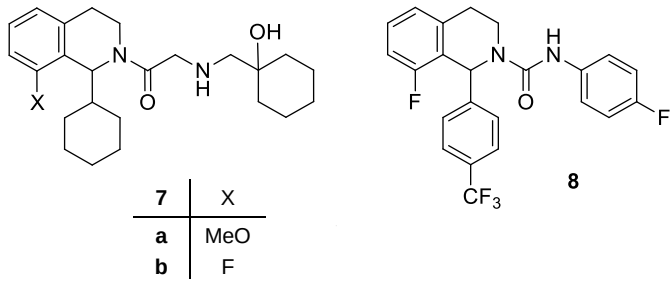
3 D. Tomaszewski, M. Balkota, *J. Biomed. Res. Int.*, **2015**, 1–7.

4 I. P. Singh, P. Shah, *Expert Opin. Ther. Pat.*, **2017**, *27*, 17−36.

5 R. N. Brogden, R. C. Heel, T. M. Speight, G. S. Avery, *Drugs*, **1979**, *18*, 1−24.

6 T. Ogiyama, K. Yonezawa, M. Inoue, N. Katayama, T. Watanabe, S. Yoshimura, T. Gotoh, T. Kiso, A. Koakutsu, S. Kakimoto, J. Shishikura, *J. Bioorg. Med. Chem.*, **2015**, *23*, 4638–4648.

7 N. A. Tamayo, Y. Bo, V. Gore, V. Ma, N. Nishimura, P. Tang, H. Deng, L. Klionsky, S. G. Lehto, W. Wang, B. Youngblood, J. Chen, T. L. Correll, M. D. Bartberger, N. R. Gavva, M. H. Norman, *J. Med. Chem.*, **2012**, *55*, 1593–1611.



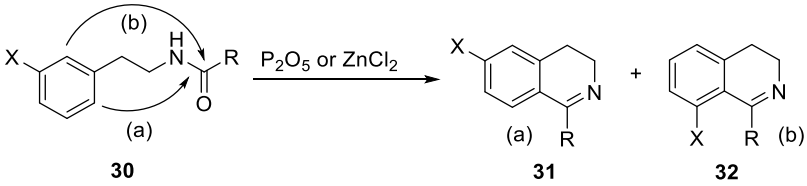
7	X
a	MeO
b	F

Figure 1. 1,8-Disubstituted 1,2,3,4-tetrahydroisoquinoline derivatives (**7a**,**b** and **8**)

Classical methods for the synthesis of isoquinolines are Bischler-Napieralski (B-N), Pictet-Gams (P-G), Pictet-Spengler (P-S) and Pomeranz-Fritsch (P-F) syntheses, the latter is not described herein in detail.[8] B-N reactions give 3,4-dihydroisoquinolines, P-G ring closures lead to isoquinolines, while P-S method results in tetrahydroisoquinolines.

In the case of the starting compound containing a substituent in the *meta* position of the aminoalkyl side chain (**30**, **33**, **36**, Scheme 1), if both *ortho* positions of the aromatic ring are unsubstituted, regioisomers can be formed. Their ratio and the reaction conditions necessary for ring closure are determined by the electronic and steric properties of the substituents on the benzene ring. In B-N, P-G and P-S reactions, the formation of the 8-substituted isomers (**32**, **35**, **38**) shown in Scheme 1 are usually sterically unfavored.

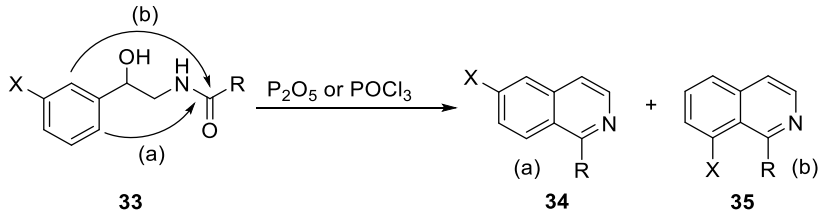
Bischler-Napieralski synthesis:



30 **31** **32**

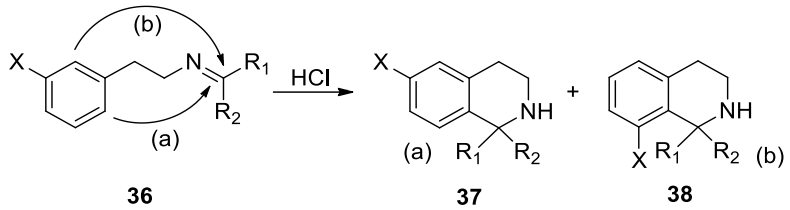
[8] Győző Bruckner: Szerves Kémia III/1, 520–528. p., Tankönyvkiadó, Budapest, 1964.

Pictet-Gams synthesis:



33 **34** **35**

Pictet-Spengler synthesis:

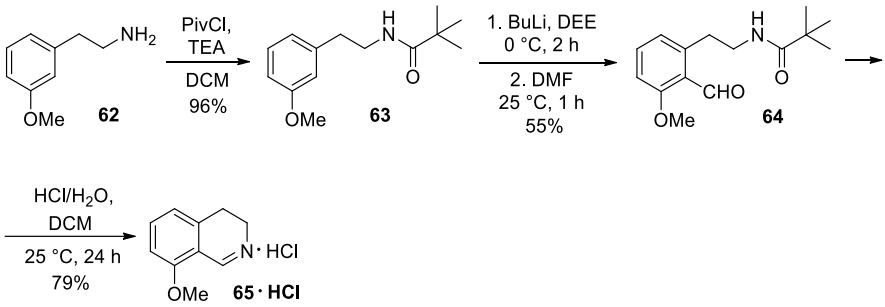


36 **37** **38**

Scheme 1. Application of classical isoquinoline syntheses on derivatives containing a substituent in the *meta* position of the aminoalkyl side chain (**30**, **33**, **36**)

Schlosser és Simig have published a short, simple synthesis that is more advantageous than the aforementioned isoquinoline preparations. The starting material (**62**, Scheme 2) was first protected with a pivaloyl group. In the next step of the synthesis, 3-methoxy-*N*-pivaloylphenylethylamine (**63**) was reacted with butyllithium in diethyl ether at 0 °C, followed by treatment with *N*,*N*-dimethylformamide. The reaction resulted in the formation of derivative **64** formylated in the common *ortho* position of substituents on the aromatic ring. The aldehyde thus obtained (**64**) was next converted to target compound **65** · **HCl** under acidic conditions.[9] This process does not require vigorous conditions and no regioselectivity problems occur.

[9] M. Schlosser, Gy. Simig, *Tetrahedron Lett.*, **1991**, *32*, 1965–1966.

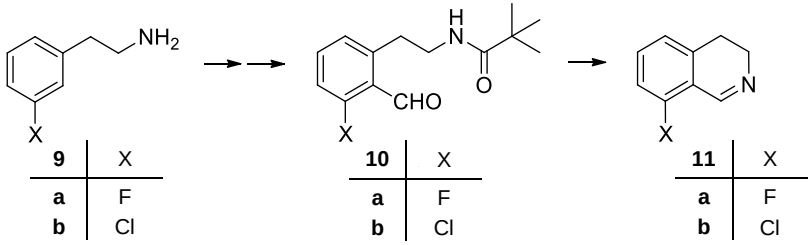


Scheme 2. Preparation of 8-methoxy-3,4-dihydroisoquinoline (**65** · **HCl**) by Schlosser-Simig synthesis

2. Aims

The aims of my research on the synthesis and reactions of formylated *N*-pivaloylphenylethyl- and benzylamines at the Directorate Drug Substance Development of Egis Pharmaceuticals Plc. were as follows:

1. synthesis of 8 fluoro- and chloro-substituted 3,4-dihydroisoquinolines (**11a**,**b**) starting from the corresponding 3-halogenated phenylethylamines (**9a**,**b**) *via* intermediates **10a**,**b** formylated in the common *ortho* position;

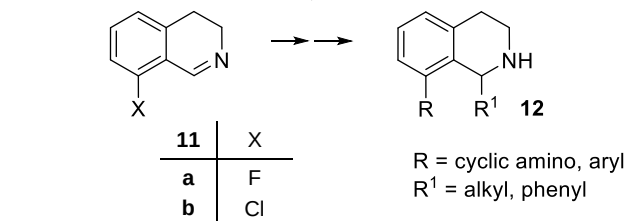


9	X
a	F
b	Cl

10	X
a	F
b	Cl

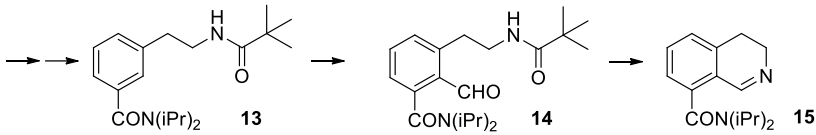
11	X
a	F
b	Cl

2. synthesis of 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines (**12**) from 8-fluoro- or 8-chloro-substituted 3,4-dihydroisoquinolines (**11a**,**b**);

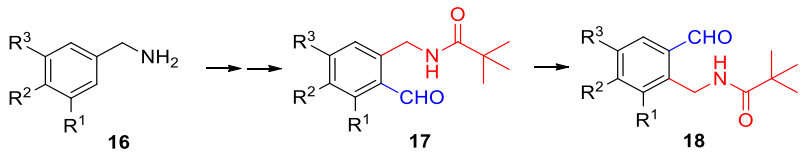


11	X
a	F
b	Cl

3. investigation of the lithiation reaction of *N*-pivaloylphenylethylamine (**13**) containing a diisopropylcarbamoyl group in the *meta* position and synthesis of the corresponding 8-diisopropylcarbamoyl-3,4-dihydroisoquinoline (**15**) *via* formyl intermediate **14**;



4. synthesis of *ortho*-(pivaloylaminomethyl)benzaldehydes (**17**) from the corresponding benzylamines (**16**) and investigation of their rearrangement reactions to compounds **18**.



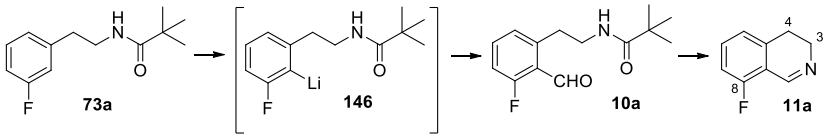
3. Experimental methods

Our compounds were prepared by using standard procedures of preparative organic chemistry. The reactions were followed by thin-layer chromatography (TLC) and HPLC-MS. Purification of the crude products was carried out by column or flash chromatography, recrystallization, salt formation and preparative HPLC. The products were identified and characterized by ^{1}H and ^{13}C NMR, IR, HRMS, and in many cases by elemental analysis, two-dimensional NMR and single-crystal X-ray measurement.

4. New scientific results

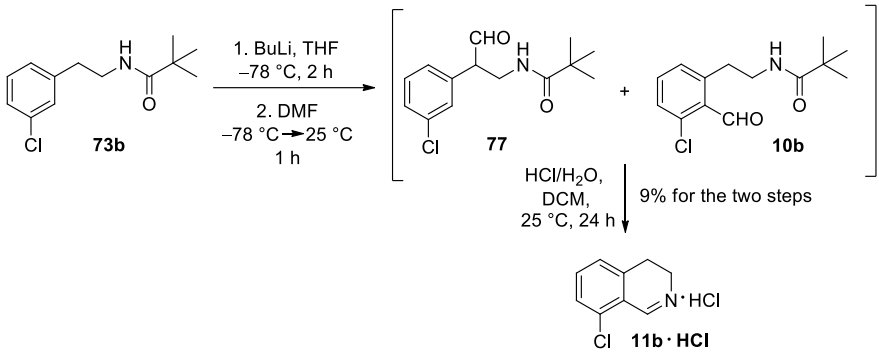
4.1. Synthesis of 8-halogen-substituted 3,4-dihydroisoquinolines

In the first part of my doctoral research, on the topic of formylated *N*-pivaloyl phenylethylamines, 8-fluoro-3,4-dihydroisoquinoline (**11a**, Scheme 3) was prepared by Schlosser-Simig synthesis. This key intermediate was sythesized from the corresponding 3-fluoro-*N*-pivaloylphenylethylamine (**73a**) by formylation *via* lithiation in the common *ortho* position of **73a**, followed by acidic ring closure. The synthesis was carried out with good yields.



Scheme 3. Synthesis of 8-fluoro-3,4-dihydroisoquinoline (**11a**)

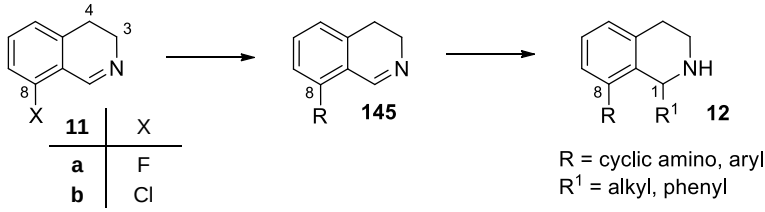
Similar lithiation and formylation of 3-chloro-*N*-pivaloylphenylethylamine (**73b**, Scheme 4) resulted in the regioisomer formylated in the benzyl position (**77**) as the major isomer. The compound formylated in the common *ortho* position (**10b**) was formed as the minor product. As the key intermediate **11b** · **HCl** could only be prepared in poor yields after acidic treatment of the crude mixture, the compound was also prepared by a significant optimization of a literature process.



Scheme 4. Lithiation and formylation of 3-chloro-*N*-pivaloylphenylethylamine (**73b**)

4.2. Preparation of 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines

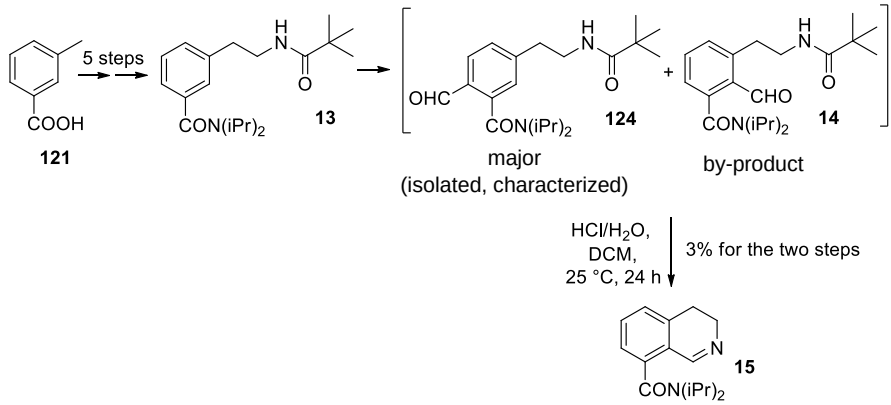
We successfully carried out the preparation of potential biologically active 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines (**12**, Scheme 5) containing cyclic amino or aryl substituensts in the C(8) position and alkyl or phenyl substituent in the C(1) position. The target compounds were synthesized from 8-fluoro- and 8-chloro-3,4-dihydroisoquinoline (**11a**,**b**) key intermediates. 8-Amino derivatives were prepared by a fluoro-amine exchange, while 8-aryl derivatives were obtained from 8-chloro-3,4-dihydroisoquinoline by Suzuki reaction. Subsequently, the substituent was introduced into the C(1) position by addition of lithium organic compounds.



Scheme 5. Synthesis of 1,8-disubstituted 1,2,3,4-tetrahydroisoquinoline target compounds (**12**)

4.3. Investigation of the lithiation reaction of *N*-pivaloylphenylethylamine containing a diisopropylcarbamoyl group in the *meta* position

Experiments were carried out to sythesize 8-diisopropylcarbamoyl-3,4-dihydroisoquinoline (**15**, Scheme 6) by Schlosser-Simig synthesis which was successfully applied in the case of 8-fluoro analogue. We prepared 3-diisopropylcarbamoyl-*N*-pivaloylphenylethylamine (**13**) in 5 steps starting from 3-methylbenzoic acid (**121**). After lithiation and formylation of compound **13**, we isolated aldehyde **124** as the major product which contained the formyl moiety in the sterically less hindered position of the diisopropylcarbamoyl group. However, the formation of a small amount of **14** regioisomer was confirmed by the isolation of 3,4-dihydroisoquinoline **15** after acidic treatment of the crude isomeric mixture.

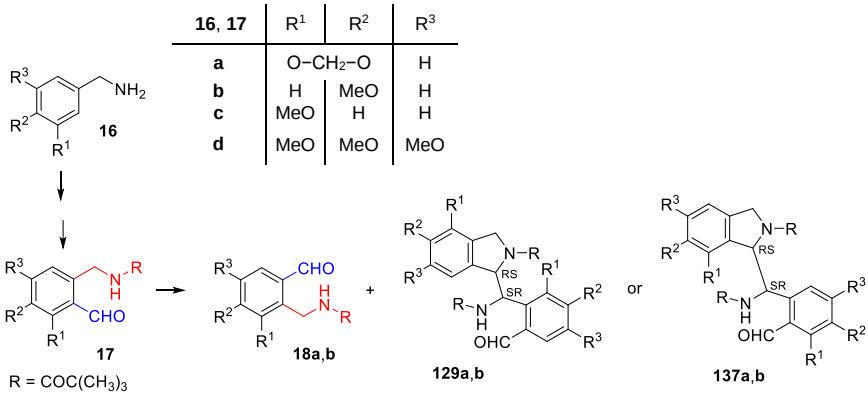


Scheme 6. Lithiation and formylation of 3-diisopropylcarbamoyl-*N*-pivaloylphenylethylamine (**13**)

4.4. Investigation of the rearrangement reactions of *ortho*-(pivaloylaminomethyl)benzaldehydes

In the second part of my doctoral research, we investigated the acid-catalyzed rearrangement reactions of formylated *N*-pivaloylbenzylamines (**17**, Scheme 7) with different substitution patterns. Compounds **17** were prepared starting from the corresponding

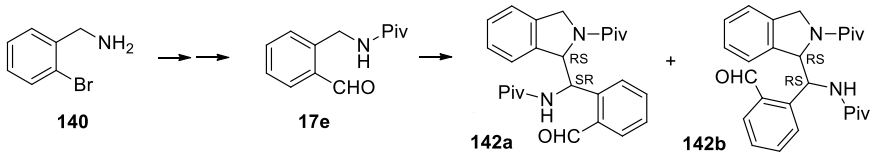
benzylamines (**16**) by acylation with pivaloyl chloride followed by formylation *via* directed *ortho*-lithiation. In case of *ortho*-(pivaloylaminomethyl)benzaldehydes containing a methylenedioxy substituent on the benzene ring (**17a**) or a methoxy substituent in the *para* position of the pivaloylaminomethyl side chain (**17b**), besides the rearranged aldehydes (**18a**,**b**) dimer-like compounds **129a**,**b** were also isolated. In the similar reaction of **17c** and **17d**, only dimer-like aldehydes **137a**,**b** were isolated. Theoretically, when starting from substituted *ortho*-(pivaloylaminomethyl)benzaldehydes (**17a**–**d**), four dimer-like regioisomers can be expected, each of them as the mixture of two diastereomeric racemates. In our experiments, the dimer-like aldehyde formed in the highest amount (**129a**,**b**; **137a**,**b**) was isolated. In the dissertation, a proposed mechanism for the rearrangement and the formation of dimer-like products is also given.



Scheme 7. Synthesis and rearrangement of variously substituted *ortho*-(pivaloylaminomethyl)benzaldehydes (**17**)

Unsubstituted *ortho*-(pivaloylaminomethyl)benzaldehyde (**17e**, Scheme 8) was also prepared from the corresponding benzylamine (**140**) by acylation with pivaloyl chloride followed by formylation *via* directed *ortho*-lithiation. In the absence of substituents,

rearrangement cannot be investigated on this model compound, but the formation of dimer-like aldehydes is simplified in this case, since only two diastereomeric racemate can be formed in the reaction. In the acid-catalyzed tranformation of *ortho*-(pivaloylaminomethyl)benzaldehyde (**17e**), beside the *RS-SR* main product (**142a**), the diastereomeric *RR-SS* type dimer-like aldehyde (**142b**) was isolated, as well.



Scheme 8. Preparation and acid-catalyzed tranformation of *ortho*-(pivaloylaminomethyl)benzaldehyde (**17e**)

Stereochemistry of the dimer-like aldehydes (**129a**,**b**; **137a**,**b**; **142a**,**b**) was determined by single crystal X-ray diffraction and NOE measurements. The proposed mechanism of the rearrangement and the formation of dimer-like compounds was investigated in detail by DFT level quantum chemical computations. The results obtained were consistent with the experimental findings.

5. Theses

1. An efficient method was elaborated for the preparation of 8-fluoro-3,4-dihydroisoquinoline which is hardly accessible by classical isoquinoline syntheses. The target compound was synthesized from 3-fluoro-*N*-pivaloylphenylethylamine by formylation *via* lithiation in the common *ortho* position followed by an acidic ring closure. [I]
2. Starting from 8-fluoro-3,4-dihydroisoquinoline a synthesis was elaborated for the preparation of 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines containing a cyclic amino group in the C(8) position and an alkyl or phenyl substituent in the C(1) position. 8-Amino derivatives were obtained by fluoro-amine exchange, the introduction of alkyl and phenyl substituents into the C(1) position was carried out by addition of lithium organic compounds. [I]

3. It was observed that unlike the corresponding 3-fluoro compound, the lithiation and formylation of 3-chloro-*N*-pivaloyl-phenylethylamine mainly occur in the benzyl position instead of the common *ortho* position. As by this method 8-chloro-3,4-dihydroisoquinoline could only be prepared in poor yield, the compound was also prepared by a significant optimization of a literature process. [II]
4. Starting from 8-chloro-3,4-dihydroisoquinoline a synthesis was elaborated for the preparation of 1,8-disubstituted 1,2,3,4-tetrahydroisoquinolines containing an aryl substituent in the C(8) position and an alkyl or phenyl substituent in the C(1) position. 8-Aryl derivatives were obtained by Suzuki reaction, the introduction of the alkyl and phenyl substituents into the C(1) position was carried out by addition of lithium organic compounds. [II]
5. Starting from 3-methylbenzoic acid 3-diisopropylcarbamoyl-*N*-pivaloylphenylethylamine was synthesized in 5 steps. It was observed that lithiation and formylation of the latter compound mainly occur in the sterically less hindered *ortho* position of the diisopropylcarbamoyl group instead of the common *ortho* position. [III]
6. We have observed that methylenedioxy-substituted *ortho*-(pivaloylaminomethyl)benzaldehyde rearranged to its regioisomer under acidic conditions and a dimer-like aldehyde by-product was isolated, as well. A proposed mechanism was given for the rearrangement and the "dimer formation". [IV]
7. The acid-catalyzed rearrangement reaction of *ortho*-(pivaloylaminomethyl)benzaldehydes was also investigated using three other derivatives, which were variously substituted on the aromatic ring, and in the case of unsubstituted *ortho*-(pivaloylaminomethyl)benzaldehyde, as well. Stucture of the isolated dimer-like aldehydes was also confirmed by single crystal X-ray diffraction and two-dimensional NMR measurements. This allowed for a more accurate understanding of the mechanism of the rearrangement and "dimer formation", which was also supported by DFT calculations.

6. Application of the scientific results

Isoquinolines and their partly saturated congeners (dihydro- and tetrahydroisoquinolines) constitute an important class of natural and synthetic compounds exhibiting biological activity. During my PhD research, new synthetic methods were elaborated which can be easily extended to the preparation of many new compounds with potential biological effects. A wide variety of 1,8-substituted 1,2,3,4-tetrahydroisoquinolines can be synthesized starting from 8-halogen-substituted 3,4-dihydroisoquinolines by changing the substituents at positions 8 and 1.

7. Publications

7.1. Full scientific publications related to the PhD dissertation

I. Csilla Hargitai, Tamás Nagy, Judit Halász, Gyula Simig, Balázs Volk. Synthesis of 8-fluoro-3,4-dihydroisoquinoline and its transformation to 1,8-disubstituted tetrahydroisoquinolines. *Molecules*, **2018**, *23*, 1280−1290; *doi: 10.3390/molecules23061280*. IF (2018): 3,060 [HCS: 100 %]

II. Csilla Hargitai, Tamás Nagy, Judit Halász, Györgyi Koványi-Lax, Gábor Németh, Gyula Simig, Balázs Volk. Synthesis and further transformations of 8-chloro-3,4-dihydroisoquinoline. *Tetrahedron*, **2018**, *74*, 7009−7017; *doi: 10.1016/j.tet.2018.10.016*. IF (2018): 2,379 [HCS: 100 %]

III. Csilla Hargitai, Tamás Nagy, Judit Halász, Gyula Simig, Balázs Volk. Study on the lithiation reaction of 3-diisopropylcarbamoyl-*N*-pivaloylphenylethylamine. *Periodica Polytechnica Chemical Engineering*, **2019**, *63*, 629−635; *doi: 10.3311/PPch.13770*. IF (2018): 1,382 [HCS: 100 %]

IV. Csilla Hargitai, Györgyi Koványi-Lax, Tamás Nagy, Péter Ábrányi-Balogh, András Dancsó, Judit Halász, Gábor Tóth, Gyula Simig, Balázs Volk. Interesting transformations of methylenedioxy-substituted *ortho*-(pivaloylaminomethyl)-benzaldehyde. *Monatshefte für Chemie - Chemical Monthly*, **2019**, *150*, 1121−1125; *doi: 10.1007/s00706-019-02395-6*. IF (2018): 1,501 [HCS: 100 %]

7.2. Further publication

Bence Szilágyi, Csilla Hargitai, Ádám A. Kelemen, Anita Rácz, György G. Ferenczy, Balázs Volk, György M. Keserű. Synthesis and biochemical evaluation of lid-open D-amino acid oxidase inhibitors. *Molecules*, **2019**, *24*, 290−297; *doi: 10.3390/molecules24020290*. IF (2018): 3,060 [HCS: 25 %]

7.3. Oral presentations

- Csilla Hargitai, Tamás Nagy, Gyula Simig, Balázs Volk. 8-Szubsztituált di- és tetrahidroizokinolinok szintézise. *Alkaloid- és Flavonoidkémiai Munkabizottság ülése*. Mátrafüred, 6–7 Apr 2017
- Csilla Hargitai, Tamás Nagy, Gyula Simig, Balázs Volk. 8-Szubsztituált di- és tetrahidroizokinolinok szintézise. *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*. Balatonszemes, 15–17 May 2017
- Csilla Hargitai, Tamás Nagy, Györgyi Koványi-Lax, Gyula Simig, Balázs Volk. 1,8-Diszubsztituált tetrahidroizokinolinok előállítása. *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*. Balatonszemes, 6–8 Jun 2018