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FACULTY OF CHEMICAL AND BIOENGINEERING
GEORGE OLAH DOCTORAL SCHOOL

SYNTHESIS AND FURTHER TRANSFORMATIONS OF OXINDOLE AND 1,3-DIAZAOXINDOLE DERIVATIVES

Summary of PhD Thesis

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1. Introduction and review of the literature

The biological activity of 1,3-dihydro-2*H*-indol-2-one (oxindole, **1**, Fig. 1) derivatives render these compounds important targets in medicinal and synthetic organic chemistry. The interest in the structurally related 5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-one derivatives (1,3-diazaoxindoles, **2**, Fig. 1) increased in the last few years due to their biological relevance.

1, oxindole **2**, 1,3-diazaoxindole

Figure 1. Oxindole (**1**) and 1,3-diazaoxindole (**2**) skeletons[1]

Launched drugs possessing an oxindole skeleton are as follows: the dopamine agonist ropinirole[2] for the treatment of Parkinson's disease and restless leg syndrome (RLS) or fibromyalgia; the atypical antipsychotic ziprasidone[3] for the treatment of bipolar disorder and two oncology drugs from the tyrosine kinase inhibitor family, sunitinib[4] and nintedanib. [5]

Several patent applications claim pharmaceutical compositions containing 1,3-diazaoxindole derivatives as the active ingredients for the treatment and/or prophylaxis of diseases, and cardiovascular disorders.[6] Furthermore the protein kinase inhibitor effects of certain 1,3-diazaoxindole derivatives is also described.[7] Nevertheless, there is no launched drug with 1,3-diazaoxindole (**2**) skeleton yet.

At Egis Pharmaceuticals Plc., the elaboration of a new manufacturing process of the anti-inflammatory drug tenidap (**18**) initiated further studies on the functionalizations of oxindole (**1**, Fig. 1) derivatives (Scheme 1).[8] In the reaction of the oxindole (**1**) and a base, deprotonation can take place on both the *N* and *C*(3) atoms due to the ambident nucleophile character of the

[1] The numbering of the compounds is identical in this summary of PhD thesis and in the PhD dissertation.

[2] S. Murayama, H. Narabayashi, H. Furukazu, N. Yanagisawa, Y. Mizuno, M. Nakajima, I. Kanazawa *Jap. Pharmacol. Ther.* **1996**, *24*, 221.

[3] C. Prakash, A. Kamel, J. Gummerus, K. Wilner *Drug Metab. Dispos.* **1997**, *25*, 863−872.

[4] A.-M. O'Farrell, T. J. Abrams, H. A. Yuen, T. J. Ngai, S. G. Louie, K. W. Yee, L. M. Wong, W. Hong, L. B. Lee, A. Town, B. D. Smolich, W. C. Manning L. J. Murray, M. C. Heinrich, J. M. Cherrington *Blood* **2003**, *101*, 3597−3605.

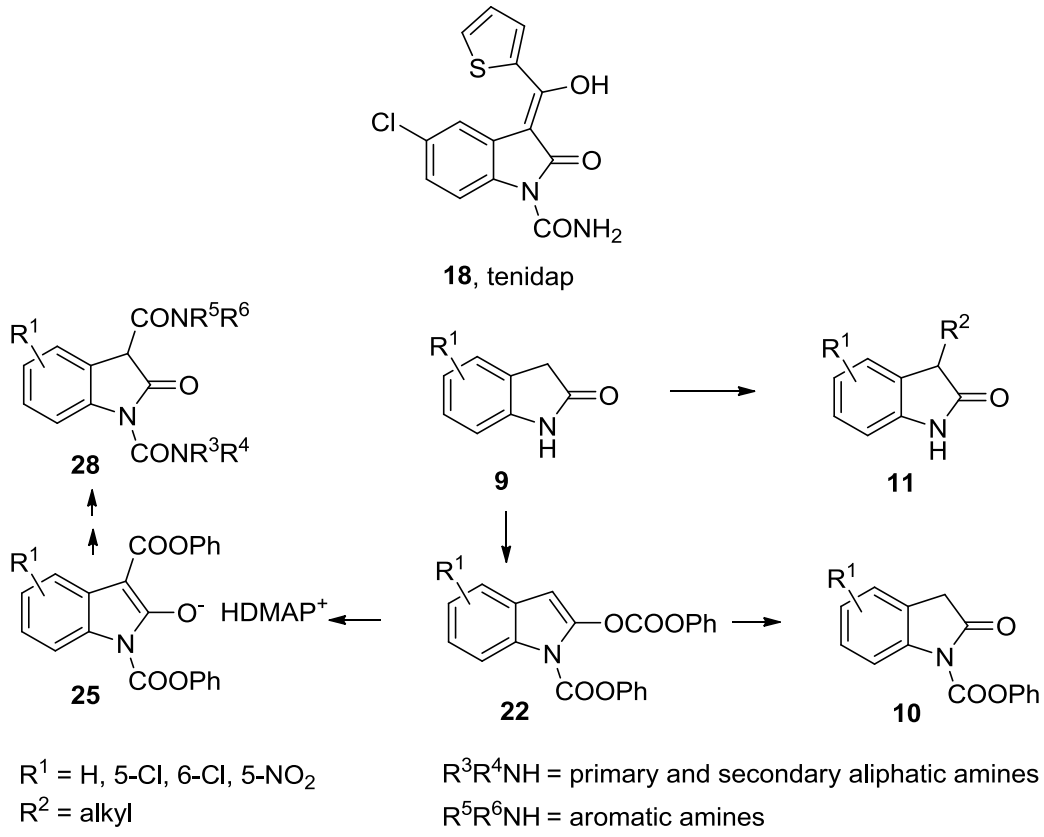
[5] C. Dallinger et al. *J. Clin. Pharmacol.* **2016**, *56*, 1387−1394.

[6] (a) M. Follmann et al. *US* 2014249168 U.S. Pat. Appl.; *Chem. Abstr.* **2014**, *161*, 404656.

[7] T. A. Shepherd et al. *US* 2010120801 U.S. Pat. Appl.; *WO* 2010056563 PCT Intern. Pat. Appl.; *Chem. Abstr.* **2010**, *152*, 568154.

[8] M. Porcs-Makkay, Gy. Simig *Org. Proc. Res. Dev*. **2000**, *4*, 10–16.

oxindole anion. Based on the results, they found that oxindole (**1**) and its derivatives substituted on the aromatic ring could not be acylated selectively. However *N*,*O*-diacylated compounds **22** were prepared in good yields. Starting from these (**22**), the *N*-acylated (**10**) and *N*,*C*(3)-diacylated (**25**) oxindole derivatives were easily prepared in good yields.[9] This finding made also the versatile synthesis of oxindole-1,3-carboxamides (**28**) possible, starting from compounds **25** using an amidation reaction.[10] An efficient method for the regioselective synthesis of *N*-unprotected 3-alkyloxindoles **11**, based on the Raney nickel (Ra-Ni) induced 3-alkylation of oxindoles **9** with primary and secondary alcohols was also elaborated at Egis (Scheme 1).[11]

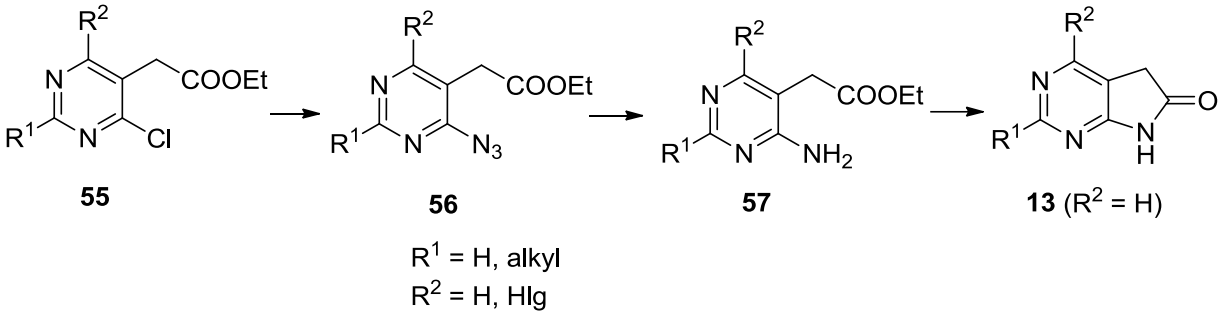


Scheme 1. Studies on the functionalization of oxindole derivatives at Egis

Due to the encouraging pharmacological results of some oxindole derivatives as new central nervous system drug candidates, the synthesis and further functionalization of the structurally

[9] M. Porcs-Makkay et al. *Tetrahedron* **2000**, *56*, 5893–5903.
[10] M. Porcs-Makkay et al. *Tetrahedron* **2010**, *66*, 7017–7027.
[11] B. Volk et al. *Synthesis* **2002**, 595–597.

related 1,3-diazaoxindole (**2**, Fig. 1) derivatives also became of interest. The most applied method for the synthesis of 1,3-diazaoxindole skeleton is the "azide route" (Scheme 2).[12]



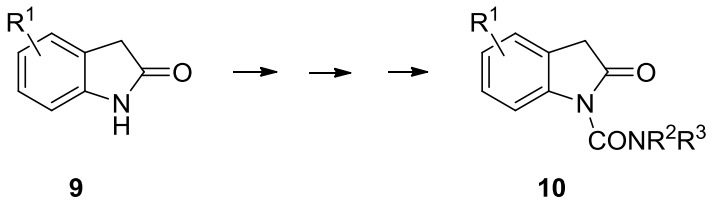
Scheme 2. Synthesis of 1,3-diazaoxindole (**13**) via the "azide route"

There is no systematic study in the literature on the *C*(5)-mono- and/or dialkylation of 1,3-diazaoxindoles. The alkylation of the unsubstituted skeleton (**2**, Fig. 1) is unprecedented in the literature. A few special studies are described using lithium, cesium or sodium bases for the deprotonation step.[13]

2. Aims

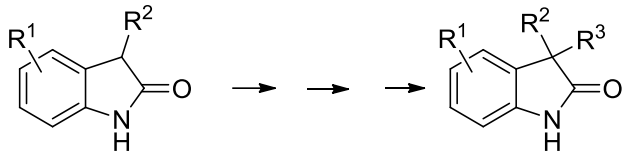
During my PhD work I joined the research project aiming at the synthesis and functionalization of oxindole and 1,3-diazaoxindole derivatives. We set ourselves the following tasks:

1. Elaboration of a new synthesis of 3-unsubstituted oxindole-1-carboxamides (**10**) starting from the corresponding oxindoles substituted on the aromatic ring (**9**),



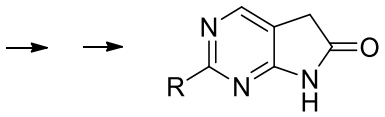
2. Elaboration of selective *C*(3) alkylation reactions of *N*-unsubstituted 3-alkyloxindoles (**11**) and preparation of *N*-unsubstituted 3,3-dialkyloxindoles (**12**),

[12] J. T. Hunt et al. *WO* 0071129 PCT Intern. Pat. Appl.; *Chem. Abstr.* **2000**, *134*, 17506.
[13] T. A. Shepherd et al. *US* 2010120801 U.S. Pat. Appl.; *WO* 2010056563 PCT Intern. Pat. Appl.; *Chem. Abstr.* **2010**, *152*, 568154.



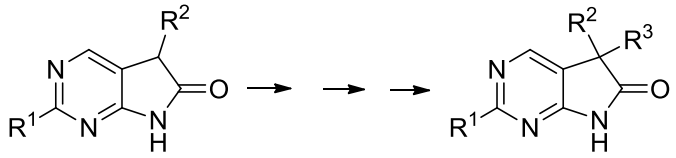
11 **12**

3. Elaboration of a new, efficient synthesis of 2-substituted 1,3-diazaoxindoles (**13**),



13

4. Study the regioselectivity of *C*(5) alkylation of *N*-unsubstituted 1,3-diazaoxindoles, focusing on the regioselective preparation of 5,5-dialkyl-1,3-diazaoxindoles (**15**) starting from 5-alkyl-1,3-diazaoxindoles (**14**).



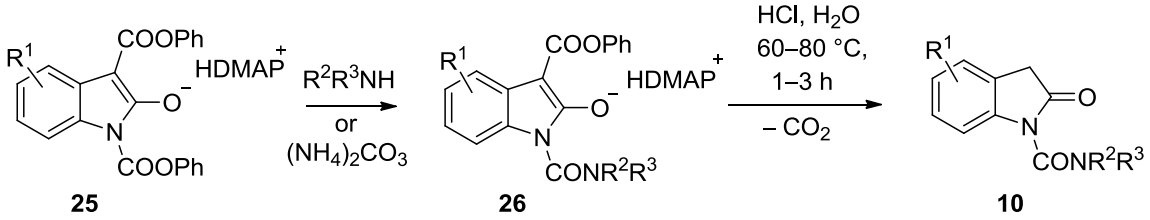
14 **15**

3. Experimental methods

The reactions and work-up procedures were carried out using conventional organic chemistry equipment. The reaction mixtures were analyzed by thin layer chromatography (TLC) and HPLC-MS. Laboratory autoclaves were used in catalytic hydrogenations and in the reactions carried out using ammonia as the reagent. Purification of the crude products was carried out by column chromatography, flash chromatography (Isco CombiFlash Rf), recrystallization or vacuum distillation. The products were identified and characterized by ^{1}H and ^{13}C NMR, MS and/or HRMS and/or elemental analysis. The structure of one new compound (**100a**) was confirmed by single-crystal X-ray diffraction.

4. New scientific results

4.1. Convenient synthesis of 3-unsubstituted oxindole-1-carboxamides[14]



R^1 = H, 5-NO_2, 5-MeO, 5-Cl, 5-F, 6-F, 6-Cl
R^2R^3NH = aliphatic and aralkyl amines

Scheme 3. Synthesis of new oxindole-1-carboxamides **10**

DMAP salts of 3-(phenoxycarbonyl)oxindole-1-carboxamides (**26**) seemed to be appropriate starting compounds for the synthesis of 3-unsubstituted oxindole-1-carboxamides (**10**, Scheme 3). Treatment of compounds **26** with aqueous hydrochloric acid resulted in the removal of the 3-phenoxycarbonyl group via hydrolysis and decarboxylation, leading to 3-unsubstituted oxindole-1-carboxamides (**10**) in good yields.

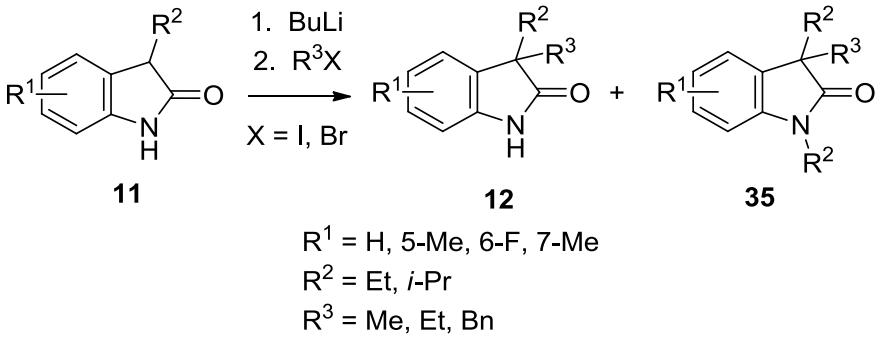
At the beginning, 5-chloro substituted oxindole derivatives were used as model compounds. Later on, we inquired whether this methodology could be extended by varying the character and the position of the substituent on the aromatic ring. Thus, we investigated the analogous synthesis of 6-chloro, 5-nitro, 5-methoxy, 5-fluoro, 6-fluoro and unsubstituted oxindole derivatives, using piperidine as the amine reagent. We made further investigations on the amidation reaction of diesters **25** and applied various amines successfully: primary and secondary amines, aralkyl amines and ammonium carbonate. It was concluded that in each case the desired oxindole-1-carboxamides (**10**) could be prepared using the new procedure, in medium to good yields. We prepared four new diesters **25** (R^1 = H, 5-F, 6-F, 5-MeO) and five new amines were applied to synthetize oxindole derivatives **26**. Furthermore, the synthesis of several oxindole-1-carboxamides **10** was also carried out in one-pot procedures.

[14] M. Porcs-Makkay, B. Volk, E. Kókai, Gy. Simig *Tetrahedron* **2012**, *68*, 1427–1435.

4.2. Regioselective *C*(3)-alkylation of *N*-unsubstituted 3-alkyloxindoles and subsequent transformations on the aromatic ring of 3,3-dialkylated oxindoles[15]

Several papers and patent applications deal with the *C*(3) alkylation reactions of 3-alkyloxindoles, but none of these can be generally applied for the regioselective *C*(3)-alkylation of 3-alkyloxindoles.

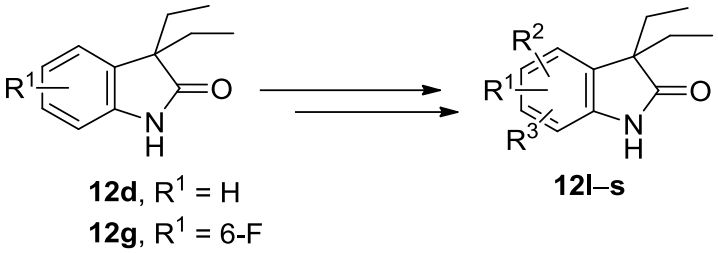
During our experiments, 3-ethyloxindole (**11**, R^1 = H, R^2 = Et) was first used as the model compound for the introduction of a second alkyl group. 3-Ethyloxindole was reacted with 2.5 eq BuLi and 1.2–2.5 eq MeI. The reaction performed with 2.5 eq MeI led to a mixture of *C*(3)-alkylated and *C*(3),*N*-dialkylated oxindoles, while using 1.2 eq. MeI the reaction was regioselective at the *C*(3) position (Scheme 4). Other alkylating agents (EtI, BnBr) and variously substituted 3-alkyloxindoles on the aromatic ring were successfully used in the optimized regioselective alkylation (yields of the 3,3-dialkylated oxindoles were 56–90%). No by-products (**35**) were detected in the optimized alkylation reactions.



Scheme 4. Alkylation reactions of 3-alkyloxindoles **11**

Several moieties on the aromatic ring (e.g., Br, NO_2, *ortho*-directing groups, etc.) can be incompatible with BuLi-mediated deprotonation and 3-alkylation. Therefore, aromatic substitution reactions were carried out, starting from 3,3-diethyloxindoles **12** (R^2 = R^3 = Et), aiming at the introduction of BuLi-incompatible aromatic moieties. Moreover, further modifications of the primarily prepared 5-nitro and 5-chlorosulfonyl derivatives were also carried out, thus several new oxindole derivatives were prepared (**12l–s**, Scheme 5)

[15] E. Kókai, Gy. Simig, B. Volk *Molecules* **2017**, *22*, 1–18.



12d, R^1 = H
12g, R^1 = 6-F

12l–s

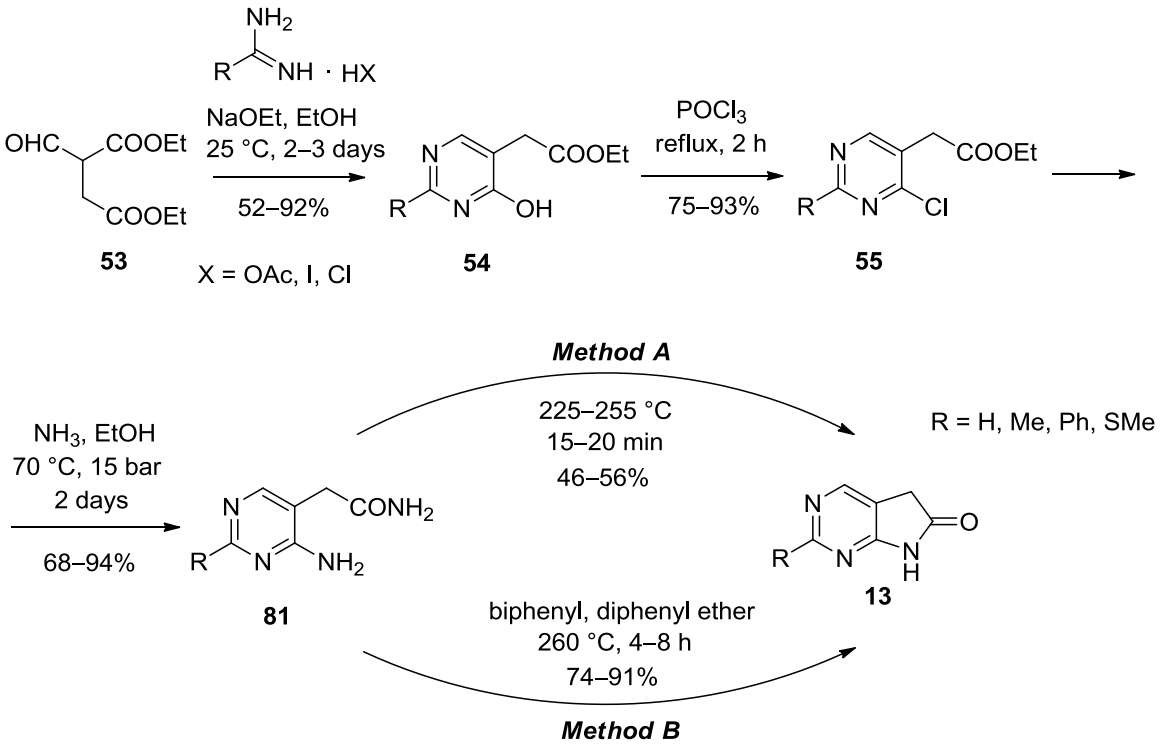
R^2, R^3 = 5-Cl, 5-Br, 5-NO_2, 5-NH_2, 5,7-diCl,
5,7-diCl-6-F, 5-SO_2Cl, 5-SO_2NH_2 etc.

Scheme 5. Various functionalizations on the aromatic ring of 3,3-diethyloxindoles (**12d,g**)

4.3. Synthesis of *N*(7)-unsubstituted *C*(2)-substituted 5,7-dihydro-6*H*-pyrrolo-[2,3-*d*]pyrimidine-6-ones (2-substituted 1,3-diazaoxindoles)[16]

We checked the feasibility of the synthetic routes leading to 1,3-diazaoxindoles described in the literature. Motivated by the published high-yielding "azide route" synthesis, first we tried to synthesize the 2-unsubstituted 1,3-diazaoxindole (**13**, R = H, Scheme 6) by this method, but the reactions gave unsatisfactory yields. Next, we turned our attention to the direct amination reaction of chloro ester **55** with ammonia. In our preliminary experiments a mixture of products was obtained with amino-amide **81** being the major product. We optimized the amination reaction to give **81** as the only product, and finally amino-amides **81** were successfully cyclized in melt to 1,3-diazaoxindoles **13** (Scheme 6). When the ring closure was carried out by heating in a mixture of diphenyl ether and biphenyl, the target compounds **13** were obtained in even higher yields.

[16] (a) E. Kókai, J. Nagy, T. Tóth, J. Kupai, P. Huszthy, Gy. Simig, B. Volk *Monatsh. Chem. (Chem. Monthly)* **2016**, *147*, 767−773. (b) Kókai E., Nagy J., Huszthy P., Simig Gy., Volk B. *Tavaszi Szél 2016 Tanulmánykötet* **2016**, Pirrolopirimidinon származékok szintézise 121–131.



Scheme 6. Synthesis of 1,3-diazaoxindoles **13**

4.4. Study on the alkylation reactions of *N*(7)-unsubstituted 1,3-diazaoxindoles[17]

Systematic studies on the *C*(5)-mono or dialkylation of *N*(7)-unsubstituted 1,3-diazaoxindoles cannot be found in the literature.

During our research, the alkylation reactions of 5-isopropyl-1,3-diazaoxindoles **14** were studied (Scheme 7). In our first experiments, NaOH (2.5 eq) was used as the base and the alkylation reactions resulted in *C*(5),*N*(7)-dialkyloxindoles **96**.

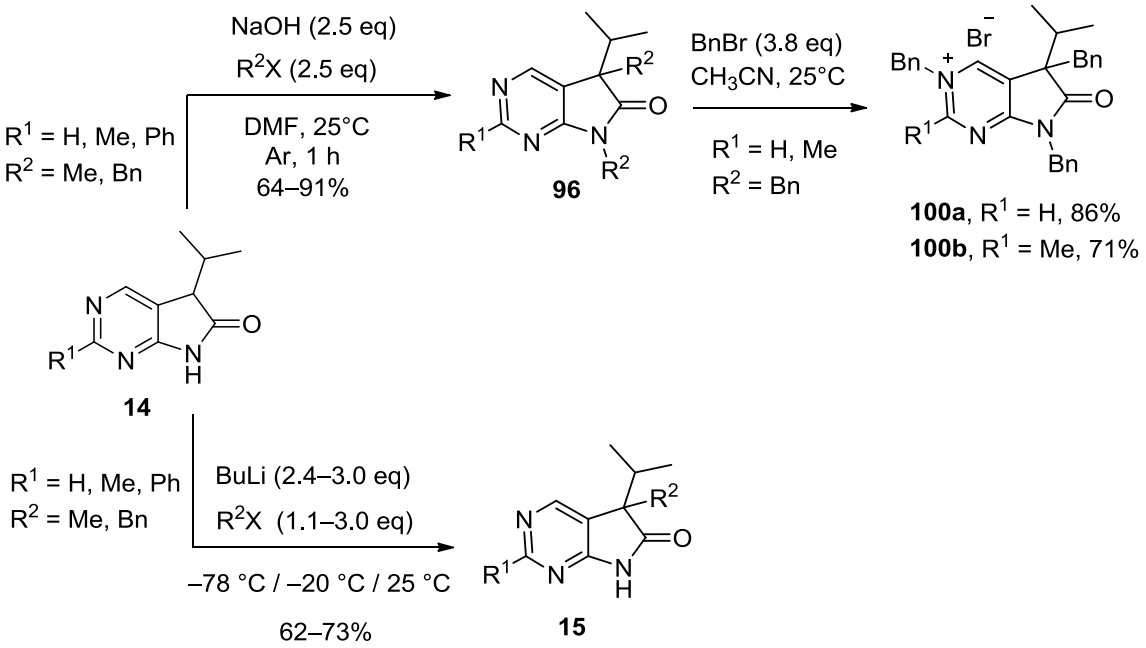
We continued our efforts by applying BuLi as the base in the *C*(5)-alkylation reactions of 5-isopropyl-1,3-diazaoxindoles **14**, which proved to be the optimal base in the analogous regioselective *C*(3)-alkylation reactions of *N*-unprotected oxindoles. It was observed that the optimal excess of the base and the alkylating agent depended on the substituent (H, Me, Ph) in the *C*(2) position (**15**, Scheme 7).

3,5,7-*N*(3),*C*(5),*N*(7)-Tribenzylated quaternary bromide salts **100a**,**b** – isolated first as minor products in the reactions performed with 3.0 eq BuLi and 3.0 eq BnBr – were synthesized from the 5,7-dibenzylated compounds (Scheme 7). The reaction was carried out with 3.8 eq BnBr in

[17] E. Kókai, J. Halász, A. Dancsó, J. Nagy, Gy. Simig, B. Volk *Molecules* ***2017****, 22, 846; doi: 10.3390/molecules22050846*

acetonitrile at room temperature. The quaternary salts **100a** and **100b** were obtained in good yields (86 and 71%, respectively). The structure of **100a** was also confirmed by single-crystal X-ray diffraction.

If pre-inertization with argon was incomplete, 5-hydroxy by-products were also isolated in some cases during our preliminary experiments. The targeted synthesis of the 5-hydroxy derivatives was carried out with BuLi (2.5 eq) without alkylating agent and under non-inert conditions with good yields.



Scheme 7. Alkylation reactions from **14** 5-isopropyl-1,3-diazaoxindoles

5. Theses

1. A conveniently applicable reaction sequence has been elaborated for the synthesis of 3-unsubstituted oxindole-1-carboxamides starting from the easily available 1,3-bis(phenoxycarbonyl)oxindoles. Selective amidation of the *N*-phenoxycarbonyl moiety and subsequent removal of the *C*(3)-phenoxycarbonyl moiety were carried out. The synthesis of 3-unsubstituted oxindole-1-carboxamides was also carried out successfully in a one-pot procedure. [I]
2. An optimized method for the 3-alkylation of *N*-unsubstituted 3-alkyloxindoles was elaborated by applying butyllithium as the base. We determined the optimal excess of buthyllithium and the alkylating agent. The method has been extended to derivatives variously substituted on the aromatic ring. [II]

3. The synthesized *N*-unsubstituted 3,3-dialkyloxindoles were used for aromatic substitution reactions of the aromatic ring. Several moieties on the aromatic ring can be incompatible with BuLi-mediated deprotonation and 3-alkylation. Aromatic substitution reactions were carried out, starting from 3,3-diethyloxindoles prepared by the above method, aiming at the introduction of BuLi-incompatible aromatic moieties. [II]

4. A new synthetic route was elaborated providing a convenient access to *N*-unsubstituted 1,3-diazaoxindoles. Treatment of the easily available ethyl 2-(4-chloropyrimidin-5-yl)acetate derivatives with alcoholic ammonia afforded the corresponding 2-(4-aminopyrimidin-5-yl)acetamides, which were finally cyclized to the *N*-unsubstituted 1,3-diazaoxindoles. [III]

5. The alkylation reactions of *N*(7)-unsubstituted 5-isopropyl-1,3-diazaoxindoles have been studied in order to determine the optimal conditions of the introduction of a second *C*(5)-substituent. When using sodium hydroxide as the base and methyl iodide or benzyl bromide as the alkylating agent, 5,7-dialkylated 1,3-diazaoxindoles were obtained. Buthyllithium was the optimal base in this case, too. The optimal rate of the substrate, base and alkylating agent has been determined for the regioselective *C*(5)-alkylation reactions. [IV]

6. Application of the scientific results

The oxindole skeleton is of a common motif in drugs and drug candidates, while the biological importance of 1,3-diazaoxindoles is demonstrated by patent applications describing representatives of this latter family of compounds as potential drugs. During my PhD research new, versatile synthetic methods were elaborated and several new compounds were prepared in these two compound families. The elaborated synthesic methods can easily be extended to the preparation of further derivatives. 3-Alkyl-3-hydroxyoxindoles and 5-alkyl-5-hydroxy-1,3-diazaoxindoles described in the dissertation render the synthesis of further novel derivatives possible.

7. Publications

7.1. Full scientific publications related to the PhD thesis

[I.] M. Porcs-Makkay, B. Volk, **E. Kókai**, Gy. Simig. Convenient synthesis of 3-unsubstituted oxindole-1-carboxamides. *Tetrahedron* **2012**, *68*, 1427−1435. IF: 2,817; C: 1 [KE: 100%]

[II.] **E. Kókai**, Gy. Simig, B. Volk. Literature survey and further studies on the 3-alkylation of *N*-unprotected 3-monosubstituted oxindoles. Practical synthesis of *N*-unprotected 3,3-

disubstituted oxindoles and subsequent transformations on the aromatic ring. *Molecules* **2017**, *22*, 24−41. IF (2015): 2,465 [KE: 100%]

[III.] (a) **E. Kókai**, J. Nagy, T. Tóth, J. Kupai, P. Huszthy, Gy. Simig, B. Volk. Convenient synthesis of 2-substituted 5,7-dihydro-6*H*-pyrrolo[2,3-*d*]pyrimidin-6-ones. *Monatshefte für Chemie (Chemical Monthy)* **2016**, *147*, 767−773. IF (2015): 1,131 [KE: 100%]

(b) **Kókai E.**, Nagy J., Huszthy P., Simig Gy., Volk B. Pirrolopirimidinon származékok szintézise. *Tavaszi Szél 2016 Tanulmánykötet, II. kötet* (ISBN: 978-615-5586-09-5) **2016**, 121–131, Doktoranduszok Országos Szövetsége, 2016. IF: 0 [KE: 100%]

[IV.] **E. Kókai**, J. Halász, A. Dancsó, J. Nagy, Gy. Simig, B. Volk. Study on the alkylation reactions of *N*(7)-unsubstituted 1,3-diazaoxindoles. *Molecules* **2017**, *22*, 846*; doi: 10.3390/molecules22050846.* IF (2015): 2,465 [KE: 100%]

7.2. Other publications not related to the PhD thesis

1. Gyűjtő I., **Kókai E.**, Hegedűs L., Nagy J. Aktív metilcsoportot tartalmazó heteroaromás vegyület alfa-aminosavvá történő átalakítása *XXXVII. Kémiai Előadói Napok, Konferenciakötet* (ISBN: 978-963-9970-53-3) **2014**, 169. IF: 0 [KE: 20%]

2. Z. Weltsch, J. Hlinka, **E. Kókai**. Wetting Properties of Silver Based Alloys. *World Academy of Science Engineering and Technology* (ISSN: 2010-376X) **2015**, *9*, 402–405. IF: 0 [KE: 25%]

3. D. Weiser, L. C. Bencze, G. Bánóczi, F. Ender, R. Kiss, **E. Kókai**, A. Szilágyi, B. G. Vértessy, Ö. Farkas, C. Paizs, L. Poppe. Phenylalanine ammonia-lyase catalyzed deamination of an acyclic amino acid - Enzyme mechanistic studies aided by a novel microreactor filled with magnetic nanoparticles. *ChemBioChem* **2015**, *16*, 2283–2288. IF: 2,850; C: 1 [KE: 5%]

4. Gyűjtő I., **Kókai E.**, Hegedűs L., Sátorhelyi P., Poppe L., Nagy J. *Pc*PAL fermentációja és új heteroaromás szubsztrátanalogonok előállítása biokatalízishez. *Tavaszi Szél 2016 Tanulmánykötet, II. kötet* (ISBN: 978-615-5586-09-5) **2016**, 111–120, Doktoranduszok Országos Szövetsége, 2016. IF: 0 [KE: 20%]

7.3. Oral presentations

1. Porcs-Makkay Márta, **Kókai Eszter**. A 3-as helyzetben szubsztituálatlan oxindol-1-karboxamidok előállítása aminolízissel. *XXXIV. Kémiai előadói Napok*, Szeged, 2011. 11. 2–4.

2. Porcs-Makkay Márta, **Kókai Eszter**. A 3-as helyzetben szubsztituálatlan oxindol-1-karboxamidok előállítása aminolízissel. *BME Tudományos Diákköri Konferencia*, Budapest, 2011. 11. 16. Szerves Kémia Szekció, I. helyezés.

3. Porcs-Makkay Márta, Volk Balázs, **Kókai Eszter**, Simig Gyula. A 3-as helyzetben szubsztituálatlan és 3-alkilezett oxindol-1-karbamidok előállítása. *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése*. Balatonszemes, 2012. 06. 06–08.

4. **Kókai Eszter**, Nagy József, Poppe László. Vizsgálatok nem-természetes alfa- és béta-aminosavak előállításához, *XVIII. Nemzetközi Vegyészkonferencia*, Félixfürdő, Románia, 2012. 11. 22–24.

5. Farkas Emese, **Kókai Eszter**, Nagy József, Kovács Péter, Hornyánszky Gábor, Poppe László. Enantiomerek enzimatikus elválasztása click-kémia segítségével. *XXXVI. Kémiai Előadói Napok*, Szeged, 2013. 10. 28-30.

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7.4. Poster presentations

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2. **Kókai E.**, Volk B., Nagy J. A pirrolopirimidin váz szintézise tandem-gyűrűzárási reakcióval. *Oláh György Doktori Iskola XI. konferenciája*, Budapest, 2014. 02. 06.

3. **E. Kókai**, E. Farkas, Z. Boros, J. Nagy, P. Kovács, G. Hornyánszky, L. Poppe. Separation of secondary alcohol enantiomers aided by click chemistry. *5th EuCheMS Chemistry Congress*, Istanbul, Törökország, 2014. 08. 31.- 09. 04.