Copper-catalyzed synthesis of heterocycles *via* oxidative ring closure reactions of aromatic nitriles with diaryliodonium salts

PhD thesis

Klára Aradi

pharmaceutical engineer

Eötvös Loránd University, Doctoral School of Chemistry,
Synthetic Chemistry, Materials Science and Biomolecular Chemistry PhD program

Head of Doctoral School: Dr. György Inzelt
Full Professor

Head of Doctoral program: Dr. András Perczel
Full Professor

Supervisor: Dr. Zoltán Novák
Assistant Professor

Budapest
2016

1. Introduction

In the last decades, the need for efficient and fast syntheses and functionalization of important condensed heterocycles such as indoles, quinolines, carbazoles and other derivatives with the utilization of cheap and commercially available metals such as copper or iron has received great attention in organic chemistry. Hypervalent diaryliodonium salts are efficient reagents of these transformations as they are capable to transfer aryl group, thus in the presence of copper catalysts several C-H arylations[1] were developed in the last few years affording diverse heterocyclic systems. Beside the C-H arylation reactions, a number of cyclizations[2] were reported, for example with the functionalization of unsaturated systems such as alkenes, alkynes or nitriles. With the employment of electron rich nitriles, diaryliodonium salts and copper catalysts the formation of a highly active arylcopper(III) species[1a] can occur providing different heterocyclic products *via* intramolecular and intermolecular arylation-cyclization processes.

The goal of the presented PhD research is to develop novel copper-catalyzed transformations for the construction of condensed heterocyclic skeletons *via* arylation-ring closure procedures from diversely functionalized nitriles and diaryliodonium salts.

2. Results and discussion

2. 1. Synthesis of iminobenzoxazines

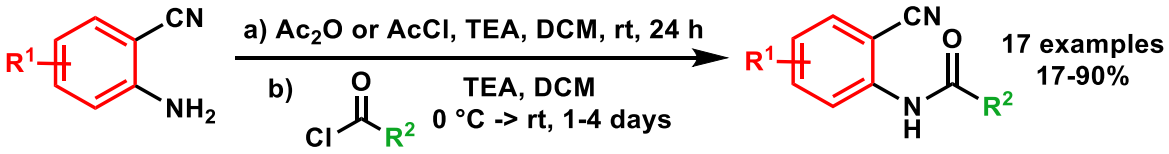
According to the publications of the literature related to the concept of aromatic electrophile generation *via* the intermediacy of Cu(III) species discussed previously by Gaunt et al.[1a], we aimed to examine the reactivity and applicability of electron rich nitrile substrates in arylation-cyclization reactions. Based on the arylation-ring closure strategy of *ortho*-ethynylanilides and diaryliodonium triflates resulting benzoxazine derivatives[2c] developed in our laboratory, we investigated the reactivity and applicability of *ortho*-cyanoanilide substrates with diaryliodonium salts for the construction of iminobenzoxazines through a similar

[1] a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172-8174; b) Qian, X., Han, J., Wang, L. *Tetrahedron Lett.* **2016**, *57*, 607-610; c) Kumar, D.; Pilania, M.; Arun, V.; Pooniya, S. *Org. Biomol. Chem.* **2014**, *12*, 6340-6344; d) Prakash, M.; Muthusamy, S.; Kesavan, V. *J. Org. Chem.* **2014**, *79*, 7836-7843.
[2] a) Zhang, F.; Das, S.; Walkinshaw, A. J.; Casitas, A.; Taylor, M.; Suero, M. G.; Gaunt, M. J. *J. Am. Chem. Soc.* **2014**, *136*, 8851-8854; b) Sinai, Á.; Vangel, D.; Gáti, T.; Bombicz, P.; Novák, Z. *Org. Lett.* **2015**, *17*, 4136-4139; c) Sinai, Á.; Mészáros, Á.; Gáti, T.; Kudar, V.; Palló, A.; Novák, Z. *Org. Lett.* **2013**, *15*, 5654-5657; d) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 5323-5328.

cyclization path. Our target products, iminobenzoxazines, are synthetically useful and biologically active compounds.[3] Most of the syntheses related to the preparation of iminobenzoxazine derivatives employ toxic heavy metals or harsh reaction conditions. Thus, the need for simple and efficient synthesis of this compound class is increasing significantly.

2. 2. Copper-catalyzed ring closure of ortho-cyanoanilides and arylmesityliodonium triflates

For the implementation of these reactions, we prepared the required *N*-(cyanoaryl)amides from the corresponding aminobenzonitriles in the presence of acetic anhydride or acetyl chloride and TEA base in DCM at rt.[4]



Scheme 1. *Synthesis of different N-(2-cyanoaryl)amide derivatives*

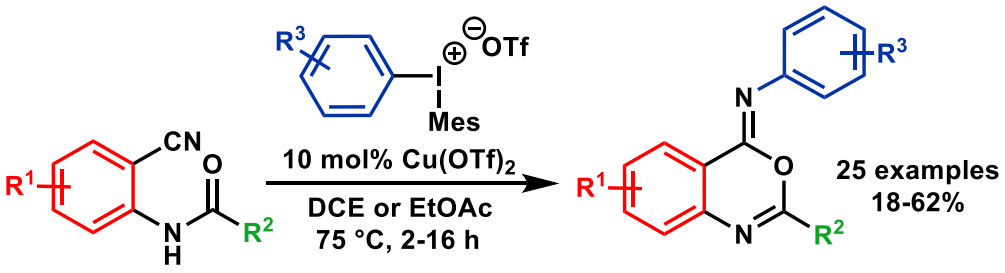
As the coupling partners of the amide derivatives diaryliodonium salts were employed, which prepared previously in our research group according to the modified[2c] one-pot method of Olofsson.[5] Arylmesityliodonium triflates containing both electron-donating and electron-withdrawing substituents were utilized and tested in the cyclizations.

- At 75 °C in 1,2-DCE with 1.2 equiv. of phenylmesityliodonium triflate and 10 mol% of $Cu(OTf)_2$ catalyst *N*-(2-cyanophenyl)acetamide can be completely transformed to the desired iminobenzoxazine in 2 h reaction time.
- We determined, that CuCl, CuBr, $(MeCN)_4CuOTf$ and $Cu(OTf)_2$ are all suitable catalysts for the transformation, whilst in the presence of CuI, CuO, $CuSO_4$ or $Cu(acac)_2$ only poor conversions was reached.
- Both THF, DCM, EtOAc and DCE are suitable solvents for the transformation.
- After determining the optimal reaction conditions, we aimed to explore the applicability of the developed methodology. Implementing the reactions with the different substrates, as a result we have found that a great variety of functionalities are well tolerated in the reaction,

[3] Selby, T. B., Birch, L. D. WO Patent 03/032731 A1, 2003, Chem. Abstr. **2003**, 138:316207.
[4] a) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc*. **2008**, *130*, 16474-16475; b) Ladzita, U.; Koposov, A. Y.; Lo, K. Y.; Willging, J.; Nemykin, V. N.; Zhdankin, V. V. *Angew. Chem. Int. Ed*. **2005**, *44*, 7127-7131; c)Ma, M.; Hou, G.; Wang, J.; Zhang, X. *Tetrahedron Asymmetry* **2011**, *22*, 506-511.
[5] a) Bielawski, M., Olofsson, B. *Chem. Commun*. **2007**, 2521-2523; b) Bielawski, M., Zhu, M.; Olofsson, B. *Adv. Synth. Catal*. **2007**, *349*, 2610-2618.

as we could successfully realized the transformation with the employment of diverse cyanoanilides and iodonium salts.

- During the syntheses we demonstrated, that thiophene and non-aromatic cyclic amide derivatives were also able to transform to the appropriate iminobenzoxazine products.
- Arylmesityliodonium salts equipped with methyl substituents in the *ortho*, *meta* and *para* position of the phenyl group of the iodonium salt provided the desired products in 53-62%, similar efficiency was observed in case of COOEt group in the *ortho* and *para* positions of the aromatic ring.
- Iodonium salts containing halogen atom (F, Cl or Br) *ortho* to the iodine had disadvantageous effect on the ring closing reaction (low GC-MS conversions), however cyclizations with diaryliodonium salts equipped with halogens in the *meta* and *para* positions afforded the appropriate iminobenzoxazines in 47-53%.
- We also gave a plausible mechanism for the copper-catalyzed arylation-ring closure reaction, which is supposed to undergo *via* the formation of arylcopper(III) intermediate.
- The applicability of the transformation was demonstrated on the synthesis of 25 iminobenzoxazine products (out of them 23 are new chemical compounds) in 18-62% yield. Our results were published in *Adv. Synth. Catal.* **2015**, *357*, 371-376 (DOI: 10.1002/adsc.201400763).



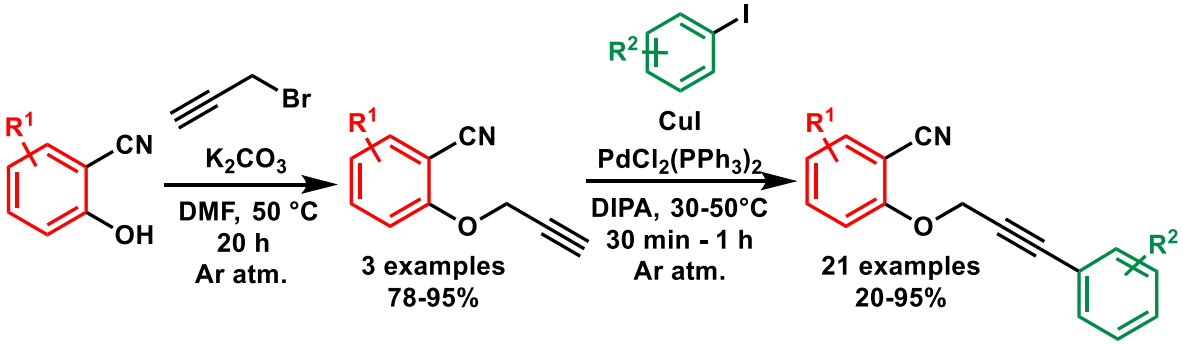
Scheme 2. *Synthesis of iminobenzoxazines via copper-catalyzed arylation-cyclization reaction*

2. 3. Synthesis of quinoline derivatives: examination of the copper catalyzed ring closure reaction of arylpropynyloxybenzonitriles and arylmesityliodonium triflates

Quinoline derivatives can be synthesized with the employment of diaryliodonium salts in the presence of alkynes and nitriles.[6a] On the basis of this transformation, we aimed to develop novel, highly modular catalytic strategies for the construction of complex heterocyclic systems from substrates equipped with nitrile and alkyne functional groups together.

To realize this approach, we designed bifunctional substrates and examined their reactivity in arylation-cyclization reactions in presence of copper catalysts and iodonium salts:

- arylpropynyloxybenzonitrile derivatives as substrates of the copper-catalyzed ring closures were synthesized from the corresponding 2-hydroxybenzonitrile derivatives in a two-step procedure (propargylation followed by Sonogashira coupling) according to the procedure of Lingam[7a] and Kotschy[7b]



Scheme 3. *Synthesis of bifunctional substrates via propargylation and Sonogashira coupling*

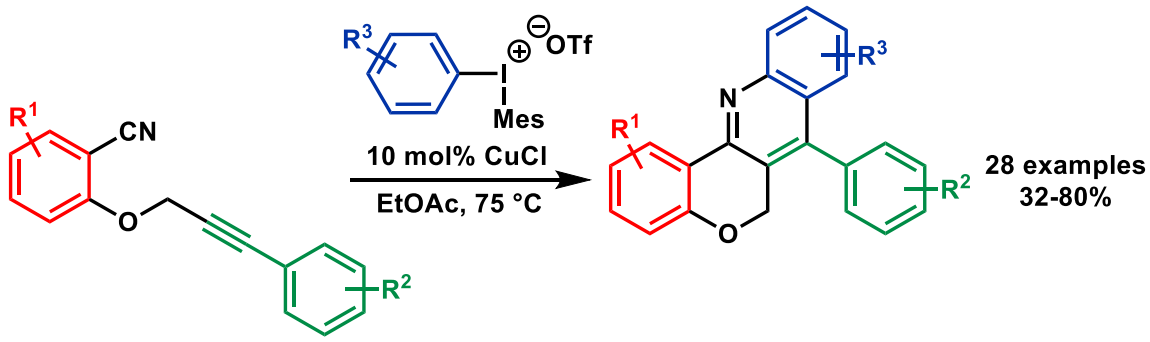
- For the efficient ring closure reactions of the substrates prepared above we aimed to find the optimal conditions of the transformation. Therefore, we determined that the reaction is completed at 75 °C in EtOAc with 1.2 equiv. of phenylmesityliodonium triflate and 10 mol% of CuCl catalyst within 1 h. During our experiments lower conversions were observed if the temperature or the amount of copper source was reduced and if other solvents (DMF, Et_2O, DCM, THF, PhMe, DCE) were utilized.
- We determined that the presence of copper catalyst is required to the transformation, furthermore, the investigation of the different copper sources revealed that both CuCl and

[6] a) Wang, Y.; Chen, C.; Peng, J.; Li, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 5323-5328; b) Wang, Y.; Chen, C.; Zhang, S.; Lou, Z.; Su, X.; Wen, L.; Li, M. *Org. Lett.* **2013**, *15*, 4794-4797.
[7] a) Lingam, V.S. P. R.; Vinodkumar, R.; Mukkanti, K.; Thomas, A.; Gopanal, B. *Tetrahedron Lett.* **2008**, *49*, 4260-4264; Novák, Z.; b) Nemes, P.; Kotschy, A. *Org. Lett.* **2004**, *6*, 4917-4920.

CuBr are suitable catalysts for the transformation, while in case of $Cu(OTf)_2$, $CuSO_4$, $Cu(acac)_2$, or $(MeCN)_4Cu(OTf)$ catalysts full conversion could be reached only if longer reaction time was applied.

- We determined, that implementing the transformation with the optimal reaction conditions, a great variety of functionalities are well tolerated both on the arylpropynyloxybenzonitrile frame and on the arylmesityliodonium salt.
- Bifunctional substrates bearing both halogens, electron-donating and electron-withdrawing groups on the arylpropynyloxy moiety were able to transform to the appropriate chromenoquinoline products, moreover the method was also compatible with halogens on the nitrile moiety, from which further functionalization through Suzuki cross-coupling reaction was also demonstrated on one example.
- We presented, that iodonium salts containing halogen atom (F, Cl or Br) *ortho* to the iodine had disadvantageous effect on the ring closing reaction (low GC-MS conversions), however ring closures with diaryliodonium salts equipped with halogens in the *meta* and *para* positions resulted the appropriate products in 47-65%.
- When *meta* substituted iodonium salts were applied in the reaction, the appropriate chromenoquinolines were obtained as 1:1 mixtures of possible regioisomers.
- Amongst bifunctional substrates containing heteroaromatic system such as thiophene, pyridine or quinoline ring only the thiophene derivative afforded the appropriate chromenoquinoline derivative in 48% yield, in case of other heterocyclic substrates no cyclization occurred.
- Arylpropynyloxybenzonitrile containing strong electron withdrawing nitro group did not result the appropriate chromenoquinoline derivative and lower isolated yield (34%) could be reached in the presence of strong-electron donating methoxy-substituted derivative.
- We also gave a plausible mechanism for the copper-catalyzed arylation-ring closure reaction, which is supposed to undergo *via* the formation of arylcopper(III) intermediate.
- Our proposed mechanism was confirmed by the results observed related to the reactivity of substrate containing amide group in the *ortho* position of the arylpropynyloxy moiety. We determined that the nitrile function has preferential reactivity over the alkyne moiety, affording chromenoquinoline product in 46% yield *via* nitrile activation. The formation of benzoxazines *via* alkyne activation was not observed during our experiments.

- We determined that the aryl group connected directly to the alkyne moiety has remarkable role according to the appropriate reactivity. In the case of benzonitrile derivative equipped with alkylpropargyl substituent instead of arylpropargyl moiety we were not able to detect the formation of the appropriate product, however the utilization of terminal alkyne substrate in the ring closing reaction afforded the corresponding chromenoquinoline derivative in only 28% isolated yield.
- In summary, the applicability of the developed method was demonstrated on the synthesis of 28 chromenoquinoline products (out of them 25 are new chemical compounds) in 32-80 yield. Our results were published in *J. Org. Chem.* **2016**, *81*, 920-931 (DOI: 10.1021/acs.joc.5b02490).



Scheme 4. *Synthesis of chromenoquinolines via copper-catalyzed arylation-cyclization reaction*

2. 4. Single crystal X-ray diffraction mesurements of chromeno[4,3-*b*]quinolines

In a collaboration with the Chemical Crystallography (Research Group Research Centre for Natural Sciences of the Hungarian Academy of Sciences), the conformation of the chromenoquinoline frame was established by single crystal X-ray diffraction in the case of 7-phenyl-*6H*-chromeno[4,3-*b*]quinoline.

- We determined that the chromeno and quinolino moieties are nearly coplanar[8], while the phenyl ring is almost perpendicular to the quinoline moiety, furthermore the triclinic crystal structure is stabilized mostly by a weak C18-H18…O5 interactions.

After that, numerous homologue series of derivatives were included in the structural investigation in order to perform and investigate the steric and electrostatic fine tuning of the system. We aimed to compare the changes occurred in the conformation and the crystal structure (considering the intermolecular interactions) by the modification of the atoms or

[8] Macrae, C. F., Edgington, P. R., McCabe, P., Pidcock, E.; Shields, G. P.; Taylor, Towler, M.; van de Streek, J. *J. Appl. Cryst.* **2006**, *39*, 453-457.

functional groups in the corresponding derivatives of homologue series. Evaluating the result of our investigations we determined the followings:

- Conformational comparison as well as the comparison of the crystal structures considering the intermolecular interactions of the corresponding molecules showed strong similarities for 7-phenyl-*6H*-chromeno[4,3-*b*]quinoline and its methyl derivative.
- Investigation of the halogen series showed that the chloro and bromo derivatives are isostructural, the main stabilizing interactions are C14-H14...N12 and C18-H18…N12.
- In the case of the fluoro derivative, beside the C-H…N interactions, the crystal structure is further strengthened by the C15-H15…F19 interaction.
- In the case of the iodo derivative, beside the C17-H17…N12 interaction, halogen-halogen interaction between I19…I19 is also found.

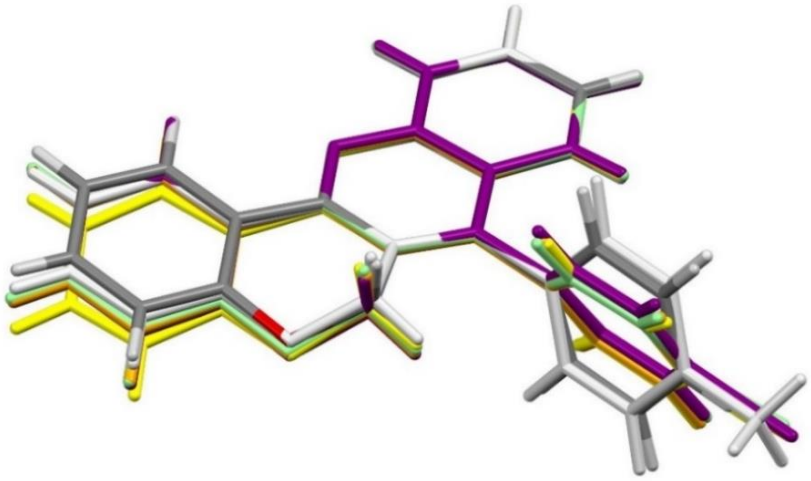


Figure 1. *Conformational comparison between the structure of 7-phenyl-6H-chromeno[4,3-b]quinoline (colored by element) and its methyl (white), fluoro (yellow), chloro (green), bromo (orange) and iodo (purple) derivatives*

3. Publications

3. 1. Papers related to the doctoral thesis

1. „Diaryliodonium salts in organic syntheses: a useful compound class for novel arylation strategies" Aradi, K., Tóth, B. L.; Tolnai, G. L.; Novák, Z. (Review) *Synlett* **2016**, DOI: 10.1055/s-0035-1561369.
2. „Modular copper-catalyzed synthesis of chromeno[4,3-*b*]quinolines with the utilization of diaryliodonium salts" Aradi, K.; Bombicz, P.; Novák, Z. *J. Org. Chem.* **2016**, *81*, 920-931, DOI: 10.1021/acs.joc.5b02490.
3. „Copper-catalyzed oxidative ring closure of *ortho*-cyanoanilides with hypervalent iodonium salts: arylation-ring closure approach to imino-benzoxazines" Aradi, K.; Novák, Z. *Adv. Synth. Catal.* **2015**, *357*, 371-376, DOI: 10.1002/adsc.201400763.

3. 2. Other papers

1. „Optimized synthesis of *N*-heterocyclic dronic acids; closing a black-box era" Aradi, K.; Keglevich, G.; Grün, A.; Garadnay, S.; Greiner, I. *Tetrahedron Lett.* **2011**, *52*, 2744-2746; DOI: 10.1016/j.tetlet.2011.03.093.

3. 3. Lectures

1. „ Azulénszármazékok aranykatalizált alkinilezése" Székely Anna, Péter Áron, Aradi Klára, Tolnai Gergely L., Novák Zoltán; *Annual Meeting of the Working Comittee of Heterocyclic Chemistry of Hungarian Academy of Sciences, Balatonszemes, Hungary, May 18-20, 2016*
2. „Kromeno-kinolinok szintézise diaril-jodónium sók segítségével rézkatalizált gyűrűzárási reakcióban" Aradi Klára, Novák Zoltán; *Annual Meeting of the Working Comittee of Heterocyclic Chemistry of Hungarian Academy of Sciences, Balatonszemes, Hungary, May 27-29, 2015*
3. „Heterociklusok előállítása rézkatalizált oxidatív gyűrűzárási reakcióban" Aradi Klára, Novák Zoltán; *Annual Meeting of the Working Comittee of Heterocyclic Chemistry of Hungarian Academy of Sciences, Balatonszemes, Hungary, May 21-23, 2014*
4. „Secoergoline váz szintézise aszimmetrikus organokatalízissel" Varga Szilárd, Aradi Klára, Szántay Csaba, Soós Tibor; *Annual Meeting of the Working Comittee of*

Heterocyclic Chemistry of Hungarian Academy of Sciences, Balatonszemes, Hungary, June 6-8, 2012

5. „Dronátok előállításának optimálása” *30st Jubilee National Scientific Students' Associations Conference, Pécs, Hungary, 29 April 2011*
6. „Dronátok előállításának optimálása” *Scientific Students' Associations Conference, Budapest University of Technology and Economics, Hungary, 17 November 2010*

3. 4. Posters

1. „A novel synthesis of chromeno[4,3-b]quinolines *via* copper-catalyzed oxidative ring closure reaction of aryl-propynyloxybenzonitriles with diaryliodonium salts” K. Aradi, Z. Novák; *18th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Syntheses (OMCOS 18), Sitges-Barcelona, Spain, June 28 - July 2, 2015*
2. „A novel synthesis of chromeno[4,3-b]quinolines *via* copper-catalyzed oxidative ring closure reaction of aryl-propynyloxybenzonitriles with diaryliodonium salts” K. Aradi, Z. Novák; *16th Blue Danube Symposium on Heterocyclic Chemistry (BDSHC 16), Balatonalmádi, Hungary, 14-17 June, 2015*
3. „A novel synthesis of imino-benzoxazines via copper-catalyzed oxidative ring closure of *ortho*-cyanoanilides” K. Aradi, Z. Novák; *2nd International Symposium on C-H Activation (ISCHA 2), Rennes, France, June 30 - July 3, 2014*
4. „Synthesis of new chiral building blocks with enantioselective organocascade reactions” Sz. Varga, Zs. Dósa, K. Aradi, T. Soós; *18th European Symposium on Organic Chemistry (ESOC 2013), Marseille, France, July 7-12, 2013*
5. „Synthesis of tricyclic indole derivatives *via* asymmetric organocatalysis” Sz. Varga, K. Aradi, Cs. Szántay, T. Soós; *4th EuCheMS Chemistry Congress (4ECC), Prague, Czech Republic, August 26-30, 2012*
6. „Synthesis of tricyclic indole derivatives *via* asymmetric organocatalysis” Sz. Varga, K. Aradi, Cs. Szántay, T. Soós; *Scientific Days of Research Centre, Hungarian Academy of Sciences, Research Centre for Natural Sciences, Budapest, Hungary, November 27-29, 2012*
7. „α-hidroxi-biszfoszfonátok mikrohullámú szintézise” Grün A., Molnár I. G., Aradi K., Bálint E., Greiner I., Keglevich Gy; *Chemistry Conference and 53th Hungarian Spectrochemical Congress of Hungarian Chemical Society, Hajdúszoboszló, Hungary, June 30 - July 2, 2010*