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APPLICATION OF MICROWAVES IN ORGANIC SYNTHESIS

Summary of Doctoral Theses

Supervisor

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Introduction

During the last decade microwave heating has become a convenient and widely used tool in organic synthesis. In the microwave environment chemical reactions usually proceed faster, in higher yields and with less byproducts. Microwave technologies have found especially extensive application in medicinal chemistry in the field of drug discovery, where speed and automatization is matter of high importance. The demand for new chemical compounds is continually growing in medicinal chemistry, thereby promoting the development of new technologies, which are designed for fast synthesis of large number of compounds (so called „compound libraries”). Well-known are methods of combinatorial chemistry – parallel synthesis, application of polymer supported reagents and catalysts, etc. Acceleration of chemical reactions by microwave irradiation enables both the intensification of already existing methods and the development of new processes in medicinal chemistry.

Synthesis of heterocycles is one of the most widely used area in the microwave chemistry, due to the high temperatures commonly employed in heterocycle condensation reactions. Furthermore, heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. Because of the drug-like character and considerable range of structural diversity, large collections or libraries of diverse heterocycles are routinely employed in high-throughput screening at early stages of drug discovery programs. A heterocyclic core is propitious for variations of substitution patterns during structure-activity relationship studies. Due to potential of automatization, microwave technology has become one of the most suitable methods for synthesis of large heterocycle libraries. However, the use of purpose-built automatized microwave synthesizers in the synthesis of compound libraries introduces additional requirements, mostly related to automatized reagent addition and isolation of products. Therefore, the development of new microwave assisted methods suited for synthesis of heterocyclic libraries is very important.

Dielectric microwave heating frequently features specific effects, which are not observed under conventional heating conditions, such as superheating, selective heating of reactants or catalysts, etc. Despite the wide application of microwave

technology in organic chemistry many of specific microwave effects still are not fully explored. For example, suspension of metal particles

in organic solvents has long been considered incompatible with microwave irradiation, because of the perception that metal powders necessarily cause electrical discharge (arcing) in the microwave field. However, examination of this phenomenon demonstrated that one can avoid arcing by proper choice of reaction conditions, thus giving new opportunities for application of microwaves to organic reactions, which proceeds with participation of metals. Metals are heated in the microwave field by far better than organic solvents. Different conduction properties of materials apparently results in the selective heating of metal particles under microwave conditions. The interaction of electromagnetic field with the metal occurs predominantly on the surface of the metal. Therefore selective microwave heating of metals in organic solvents potentially could be beneficial for activation of the metal surface in such chemical reactions as synthesis of magnesium and zinc organometallic reagents.

The activation of metal surface is critical for the successful preparation of both Grignard and organozinc reagents from the corresponding metal and organic halides. The most commonly employed are various chemical activation methods, mechanical activation or sonification. To carry out the oxidative addition of zinc to aryl halides, a suspension of highly active „Rieke zinc” is often used. Preparation of the Rieke zinc is laborious and its handling requires inert conditions. Microwave irradiation as metal activation method in preparation of organometallic reagents has not been studied up to now, though microwave application would be technologically simple procedure suitable for automatization. Furthermore, microwave irradiation could also accelerate the formation of organometallic compounds in the case of unreactive halides, for example, aryl bromides and aryl chlorides. Finally, microwave dielectric heating can be applied to the subsequent reactions of synthesized organometallic compounds. For example, organozinc reagents are widely utilized in palladium or nickel catalyzed C-C bond formation reactions (Negishi cross-coupling), which usually proceeds at elevated temperatures. Not only would microwave heating facilitate the formation of organozinc reagents, but also it could accelerate the following subsequent cross-coupling reaction. Sequential multistep reactions certainly are advantageous for preparation of compound libraries in the automatized synthesis systems.

Aims of the work

The main goal of the present work is to develop new microwave assisted methods suited for automatized synthesis of compound libraries.

1. Analysis of the recent literature should be made to evaluate the main criteria of such methods.
2. According to the conclusions made from the literature analysis, new method for synthesis of coumarin derivatives should be developed and applied to the synthesis of the coumarin library using automatized microwave heating device.
3. Reactions of metallic zinc and magnesium with organic halides in the microwave field should be studied to examine the possible metal surface activation by microwaves.
4. Microwave irradiation should be applied to accelerate the synthesis of magnesium and zinc organometallic compounds from unreactive substrates such as aryl and heteroaryl halides.
5. A new method for widely used transition metal catalyzed cross-coupling reaction of organozinc reagents (Negishi reaction) should be developed, that would be based on microwave-assisted preparation of organozinc reagents and sequential cross-coupling reaction with aryl halides.

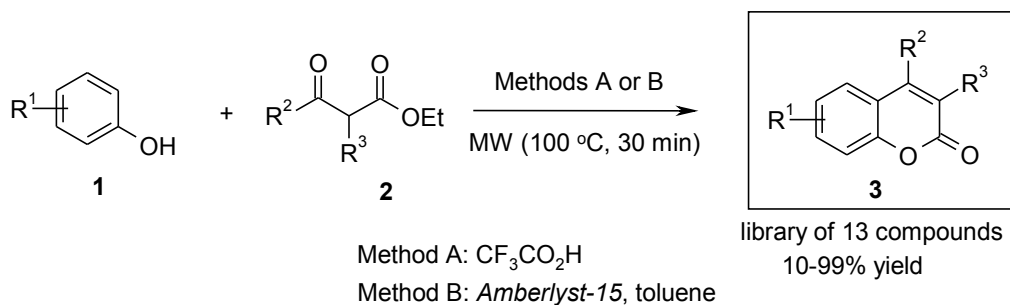
Results

Analysis of microwave-assisted synthesis of heterocyclic compounds that have been published in literature over a period of last 5 years, indicated the criteria, which can be used to evaluate the suitability of methods for synthesis of compound libraries. The main criteria are as follows:

- Short reaction times and possibility of automatization;
- Suitability for parallel synthesis;
- Possibility to carry out multistep reactions without isolation of the intermediate products ("one pot", "domino" reactions);
- Multicomponent reactions for synthesis of wide diversity of compounds in one step;
- Simple procedure for isolation of final products without using the chromatography method.

These findings have been applied in the development of new methods suitable for synthesis of coumarin library. One of the most frequently used ways to obtain coumarins is the Pechmann reaction – condensation of phenols and β -ketoesters in the presence of Brønsted or Lewis acid. Acceleration of the Pechmann reaction under microwave conditions is well examined. At the same time, most of the methods of microwave assisted coumarin synthesis are designed for domestic microwave ovens and can not be applied to automatized processes. Furthermore, microwave-assisted Pechmann reaction is carried out mostly without solvent, by mixing neat reagents or by using solid supports. For automatized synthesis of coumarin library more convenient would be Pechmann reaction in solution phase, where solutions of reagents could be dispensed by robots.

Two methods were developed for synthesis of coumarin libraries via Pechmann reaction (Scheme 1).



Representative examples:

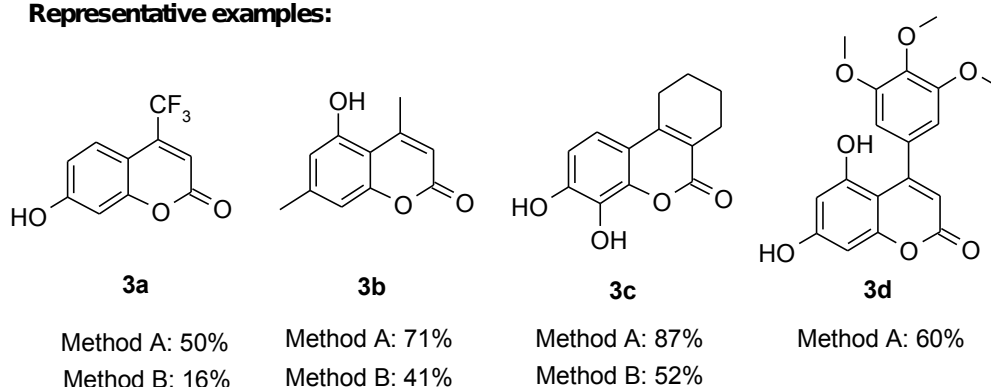


Figure 1. Synthesis of coumarin library under microwave conditions

The first method is based on the use of trifluoroacetic acid both as acid catalyst and solvent, thus providing convenient addition of reagents in automatized systems. Microwave heating (100 °C) reduced the time of synthesis to 30 minutes. Along with acceleration of the reaction, another advantage is a simple isolation procedure: coumarins are precipitated from reaction mixture by adding cold water and then recrystallized. Synthesis of the coumarin library was performed, using focused single-mode microwave synthesizer supplied with automatized solution dispenser.

Other method is based on the application of ion-exchange resin *Amberlyst-15* as acidic catalyst in Pechmann reaction. Reaction was performed in toluene under microwave conditions (100 °C) and completed in 30 minutes. Ion-exchange resin *Amberlyst-15* was separated from reaction mixture by decanting or filtration. Coumarins were isolated by evaporation and recrystallization of the residue.

Both methods utilize easy accessible reagents, are simple in operation and thus, are suitable for automatized microwave assisted synthesis of coumarin libraries. In general, the first method gave better yields of isolated products. Representative library of coumarins was synthesized using both methods.

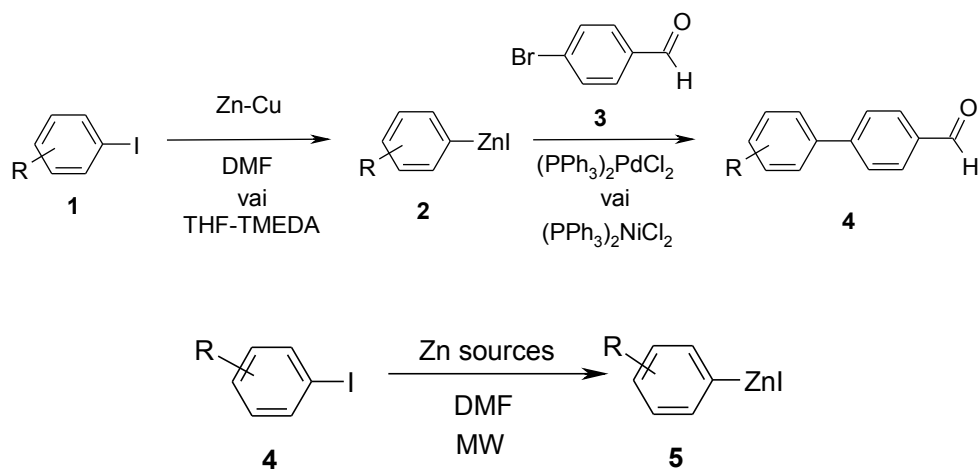
The ability of microwave irradiation to speed up many chemical reactions was utilized not only in intensification of already existing methods, but also in development of new methods. Reactions of organic compounds with metals and possible activation of metal surface in the microwave field were examined. Important prerequisite was study of metal interaction with microwave irradiation. Frequently observed phenomenon of electrical discharge (arcing) between metal particles has held back the application of microwaves in the metal reactions. However, one can avoid destructive arcing by using small-dispersed metal particles (dust, turnings, etc.) and relatively polar high boiling solvents, for example, tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), *N,N*-dimethylformamide (DMF), etc.

To investigate the application of microwave heating in metal reactions, the insertion of zinc into an aryl-iodide bond was studied first, as these reactions traditionally require high temperatures. Attempts to generate arylzinc compound **5a** in the reaction of aryl iodide **4a** with metallic zinc (dust, powder or granules) by heating of the reaction mixture in microwaves up to 160 °C in 1,2-dimethoxyethane were unsuccessful. On the contrary, when DMF was used as a solvent, aryl iodides **4** reacted with zinc dust, giving corresponding arylzinc iodides **5** (yield of arylzinc compound were determined by GC analysis of hydrolysed and idolysed aliquot) (Scheme 2).

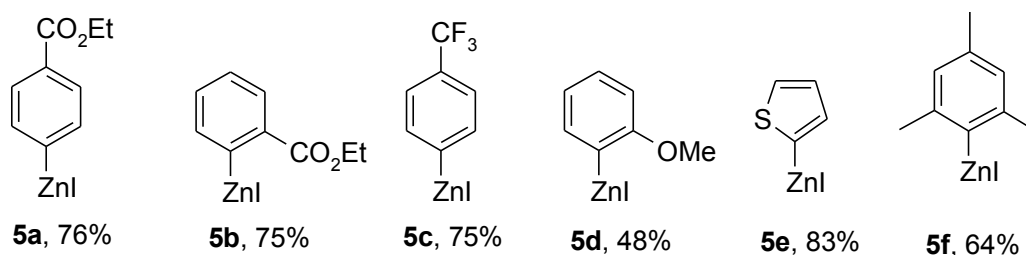
Reaction of zinc dust with iodomesitilene (**4f**) was used to examine the possible activation of zinc surface by microwaves. The formation of mesitylzinc iodide (**5f**) was compared under microwave and conventional conditions. When heating of the reaction mixture was performed in the oil bath (10 min, 160 °C), the yield of organozinc reagent was 69%, which is comparable with the result, obtained by microwave heating (64%). These studies indicatde that thermal activation is essential for the reaction, though there is no evidence of specific microwave activation of the zinc surface.

Aryl iodides react with zinc dust at high temperatures (120-180 °C), which are not suitable for DMF solutions because of the solvent decomposition.

Furthermore, poor reproducibility and moderate yields are substantial drawbacks of the method cutting down its effectiveness in the synthesis of arylzinc reagents.



Representative examples (Zn dust, DMF, MW, 120-180 °C, 5-30 min):



Representative examples (Zn-Cu couple, MW, 60-140 °C, 2-15 min):

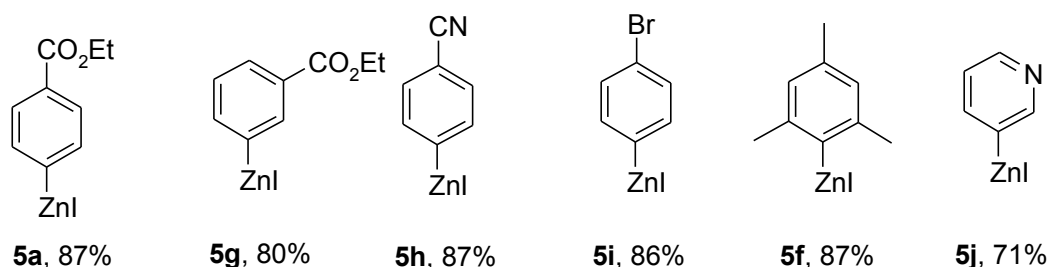
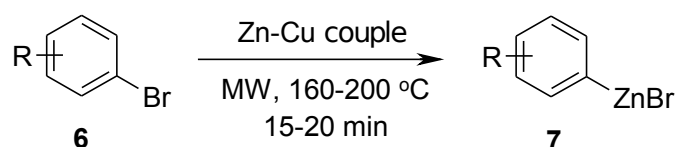


Figure 2. Synthesis of arylzinc iodides **5** under microwave conditions

To improve the reproducibility of the reaction and to reduce the undesired side processes (decomposition of the solvent at high temperatures), chemical activation of the zinc surface was addressed. The routine activation methods (treatment of zinc dust with hydrochloric acid, iodine, 1,2-dibromoethane or trimethylsilyl chloride, as well as addition of copper iodide) proved to be unsuccessful. In the meantime, the use of freshly prepared Zn-Cu couple produced the arylzinc compound **5a** with excellent yield (87%) after microwave heating for 10 minutes at 100 °C. Further investigation

of reactivity of Zn-Cu couple towards aryl iodides showed that the oxidative addition of zinc to the C-I bond readily occurred in polar solvents such as DMF and 1,1,3,3-tetramethylurea (TMU). Reaction proceeded also in less polar ethereal solvents (DME and THF) if *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was added. DMF was the solvent of choice as it provided the fastest reaction. Functionalized aryl- and heteroarylzinc reagents formed quickly (2-15 min) under the developed conditions using microwave heating (60-140 °C) (Figure 2). Several functionalities in aryl iodide, such as carboxylic ester (**5a,g**) and cyano group (**5h**) were tolerated. Aryl bromides (**5i**) do not react with Zn-Cu under the reported reaction conditions.

To accomplish the reaction of aryl bromides with Zn-Cu couple, higher temperatures were employed. At 160-200 °C zinc inserted into C-Br bond in the case of several aryl and heteroaryl bromides (**6a-d**), however yields were moderate (25-74%) and the number of reactive substrates were limited (Figure 3).



Representative examples of arylzinc bromides:

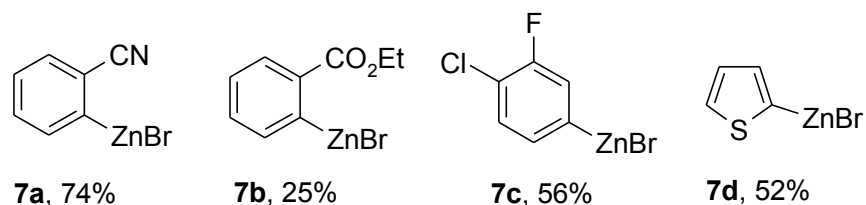


Figure 3. Synthesis of arylzinc bromides **7** under microwave conditions

Since the use of Zn-Cu couple in the synthesis of organozinc reagents has not been reported so far, the developed method can be considered as novel. Furthermore, microwave heating had substantial advantage in cases when high temperatures were necessary.

To study the possible acceleration of arylzinc formation by microwaves, the rates of the formation of mesitylzinc iodide **5f** were compared under microwave and conventional conditions (Figure 4). Initial acceleration of the reaction rate under microwave heating conditions was observed (after 2 min 56% of **5f** under microwave conditions vs. 10% in oil bath; after 5 min 79% and 52% respectively). In the longer period yields of mesitylzinc iodide **5f** produced under both heating conditions became comparable. Therefore, the initial acceleration of the reaction can be attributed to the more rapid dielectric heating process.

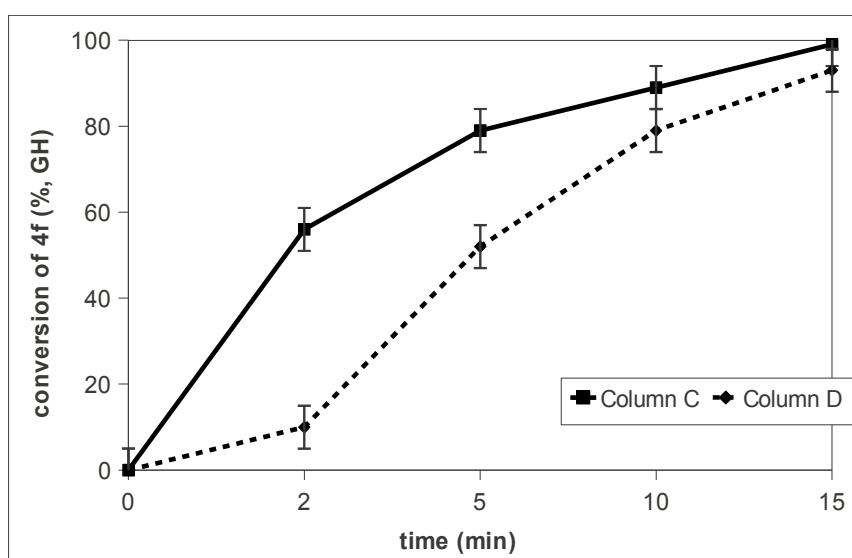


Figure 4. Reaction of Zn-Cu couple with iodomesitylene **4f** under microwave and conventional conditions

To demonstrate the suitability of the developed method for the generation of compound libraries, the obtained arylzinc iodides **5** were employed in the Negishi cross-coupling protocol. 4-Bromobenzaldehyde (**8**) was used as a coupling partner and reaction was promoted by microwave heating (120 °C, 5 min). Among the various catalysts tested, $(PPh_3)_2PdCl_2$ was the most efficient in DMF solution, while $(PPh_3)_2NiCl_2$ was the catalyst of choice for the Negishi coupling in THF.

The developed sequential arylzinc formation - Negishi cross-coupling protocol allowed to obtain biaryl aldehydes **9** in 57-96% yield in a short period of time (7-35 min) (Figure 5).

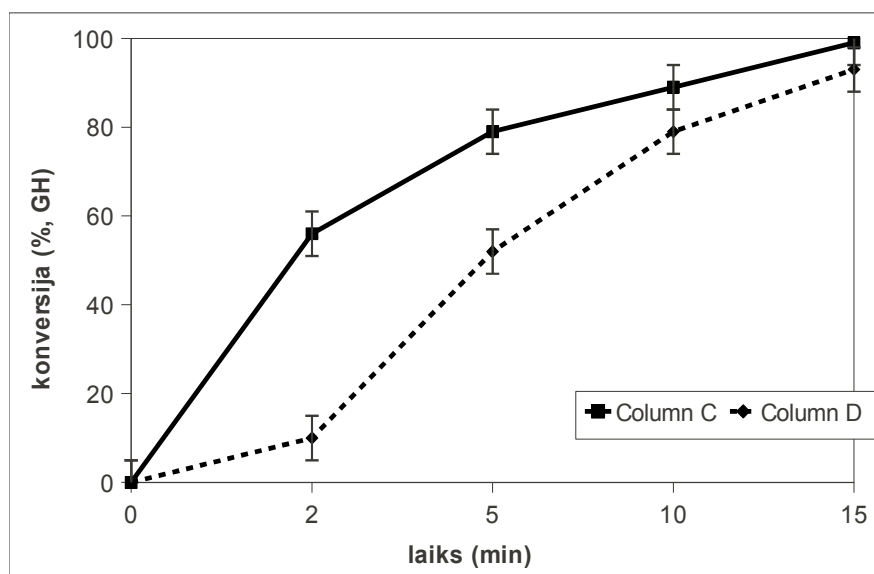
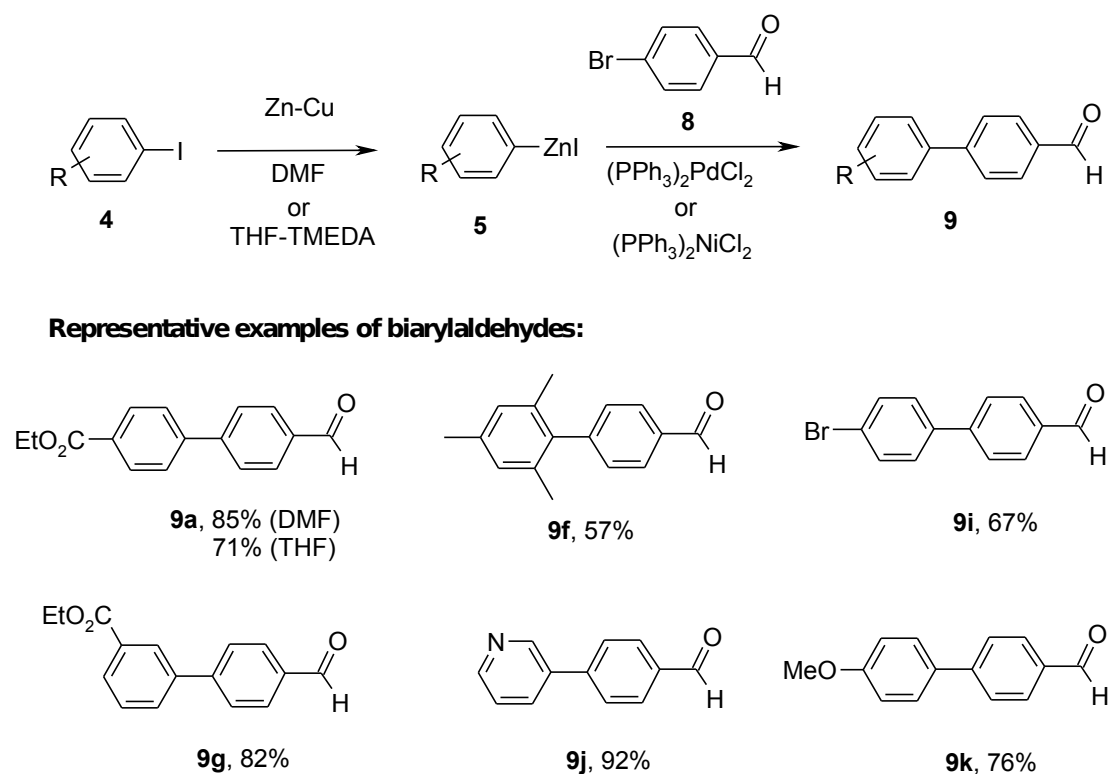
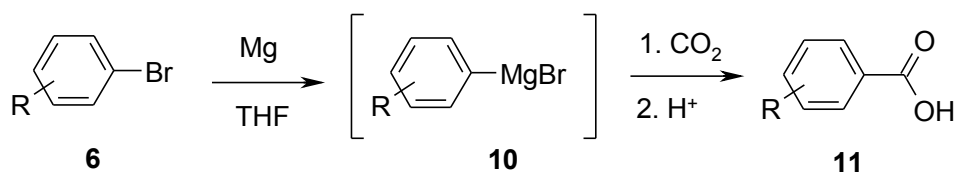


Figure 5. Microwave assisted preparation of arylzinc iodides and Negishi cross-coupling

To expand the scope of substrates to less reactive compounds such as aryl bromides and aryl chlorides more active metal – magnesium was employed. Subsequent transmetallation using zinc salts afforded the corresponding arylzinc compounds.

Grignard species were readily formed from aryl bromides without prior activation of magnesium. Thus, Grignard reagents **10** were obtained in 71-88% yield in the reaction of aryl bromides **6** with non-activated magnesium turnings under microwave conditions (80-120 °C, 10-30 min) (Figure 6). Carbon dioxide was used as a quenching agent to obtain the corresponding aryl carboxylic acids **11** and thus establish yields of the formed Grignard reagents **10**.



Representative examples of arylmagnesium bromides:

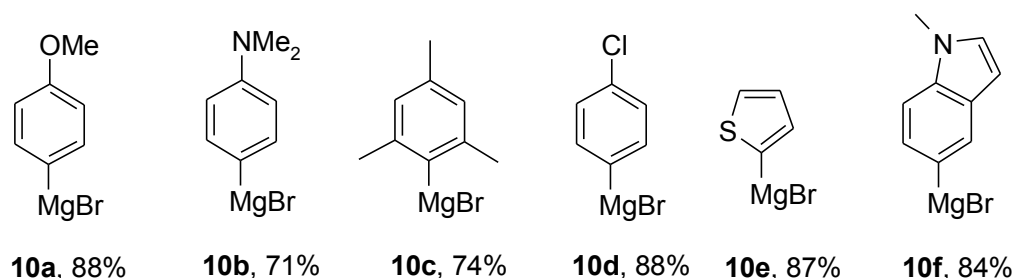
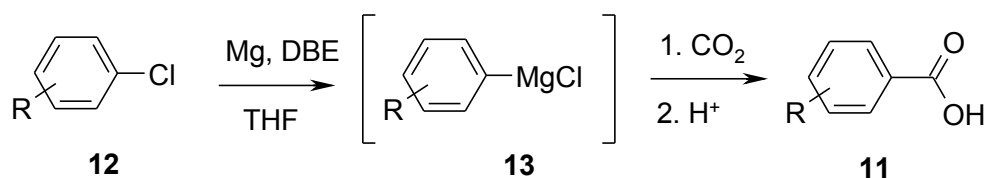


Figure 6. Microwave assisted preparation of arylmagnesium bromides **10**.

On the contrary, considerably less reactive aryl chlorides did not react with non-activated magnesium turnings even at 180 °C. Among various chemical activation methods examined, the use of 1,2-dibromoethane (DBE) was the most appropriate, as addition of DBE resulted in both the activation of magnesium surface and *in situ* formation of MgBr₂ solution.

The presence of magnesium salts substantially improved the absorption of microwaves by the relatively nonpolar reaction media (THF), thus enabling to perform reactions at high temperatures (180-200 °C). Formation of Grignard reagents **13** under the developed reaction conditions proceeded in 10-30 min with moderate to good yields (48-82%) (Scheme 7).



Representative examples of arylmagnesium chlorides:

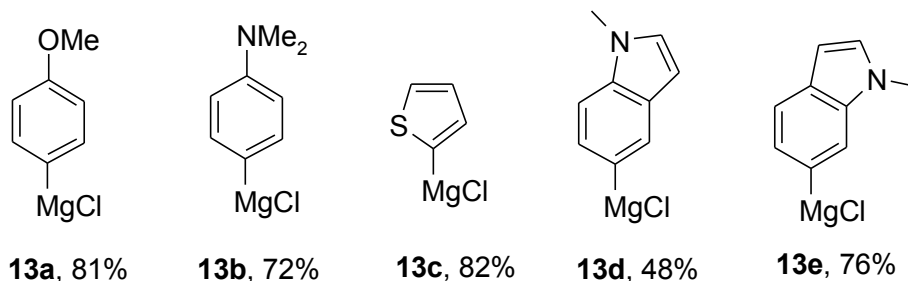
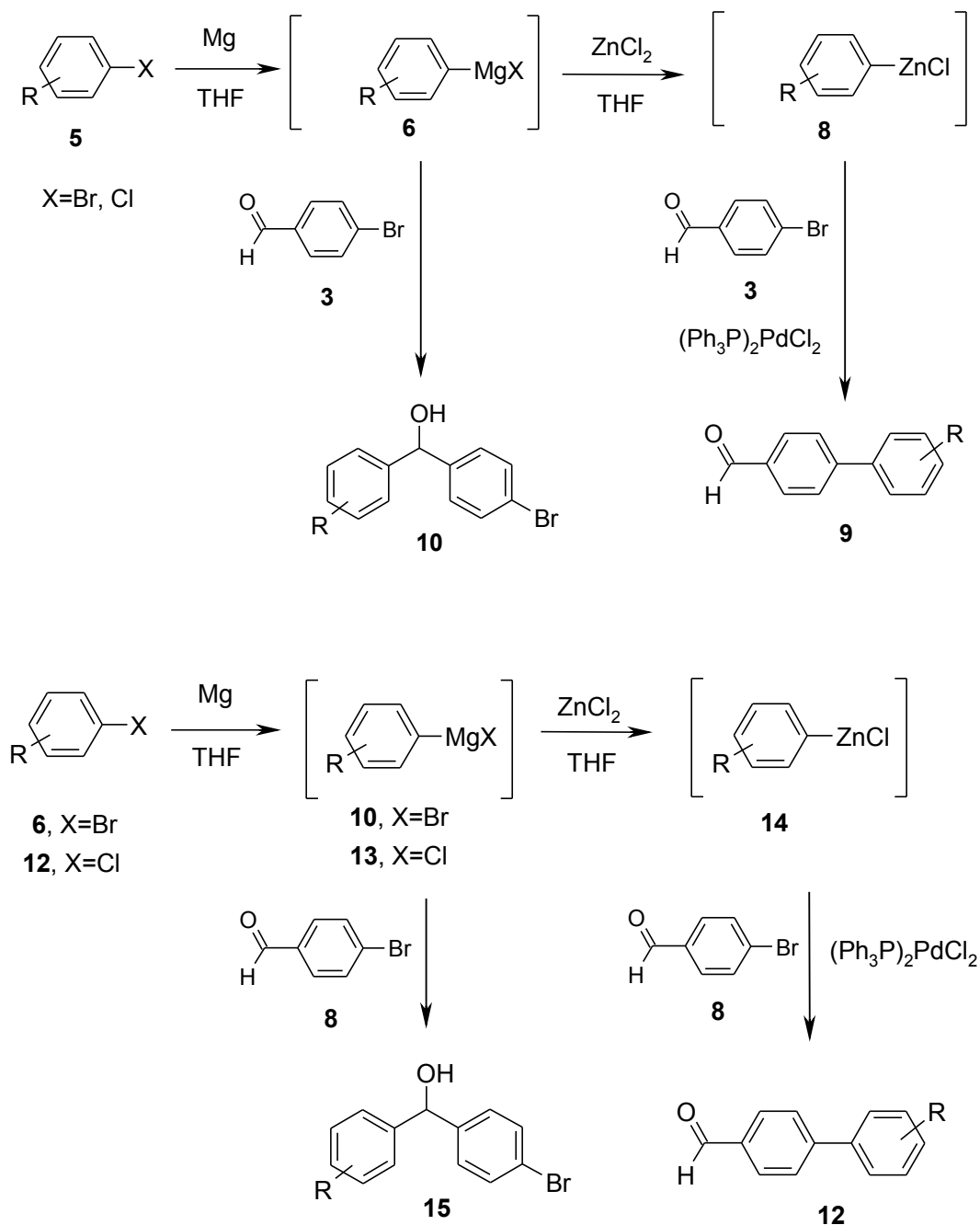


Figure 7. Microwave assisted preparation of arylmagnesium chlorides **13**

The transmetalation of Grignard reagents to the corresponding arylzinc species was achieved by using the ZnCl₂-TMEDA complex under microwave conditions (15 min, 80 °C). To follow the progress of the transmetalation, the chemoselective reaction of 4-bromobenzaldehyde (**8**) with organozinc reagents **14** in the presence of (PPh₃)₂PdCl₂ was employed.

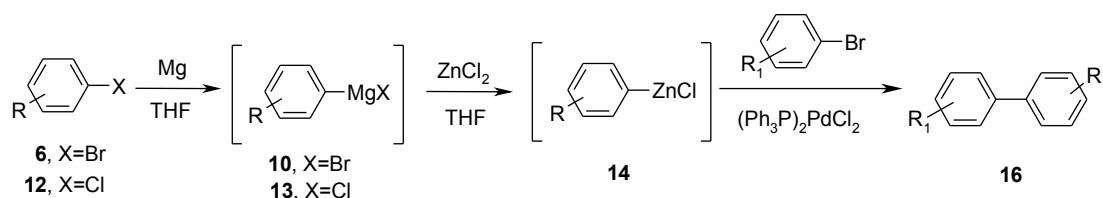
Thus, unreacted Grignard species **10** and **13** reacted with an aldehyde moiety of benzaldehyde **8** to give alcohol **15**, while organozinc compound **14** participated in Negishi cross-coupling reaction providing the biphenyl aldehyde **12** (Figure 8).



Scheme 8. Study of the transmetalation reaction of Grignard reagents **10** and **13**.

Negishi cross-coupling of transmetalated arylzinc chloride **14** proceeded at room temperature, while the same $(\text{PPh}_3)_2\text{PdCl}_2$ catalyzed reaction of arylzinc iodides **5** (prepared from aryl iodide and Zn-Cu couple, Figure 2) required microwave heating (120°C , 5 min). The difference in the reactivity could be attributed to the presence of

magnesium salts in the solution of arylzinc chloride, which could possibly promote the Negishi cross-coupling. The assumption was proved by the experiment, where phenylzinc iodide (prepared from Zn-Cu couple in the 0.5 M MgCl₂ solution of THF) was converted into biaryl compound in 5 min at room temperature.



Representative examples:

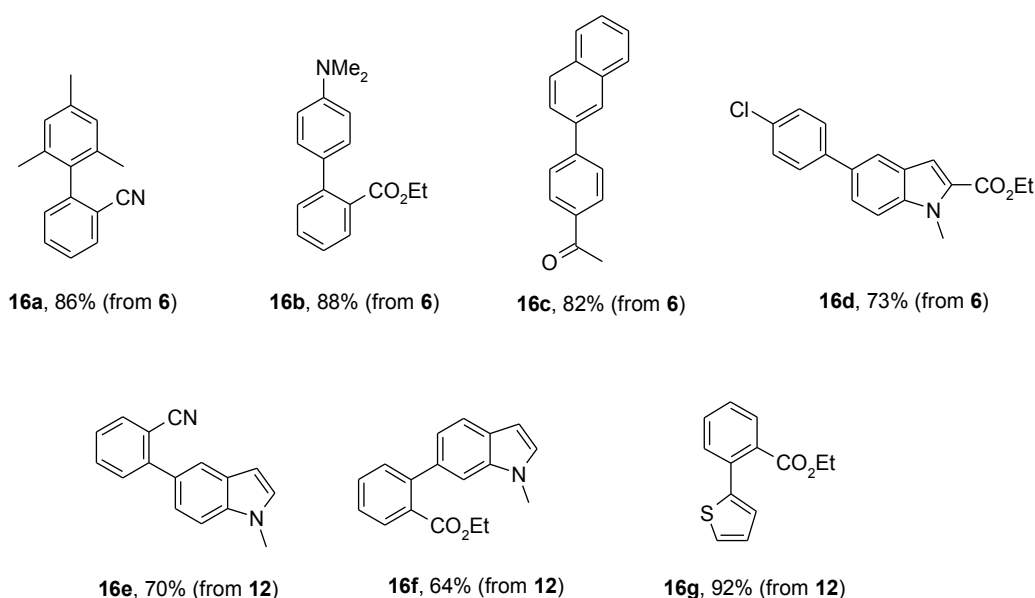


Figure 9. Microwave assisted sequence of Grignard reagent preparation – transmetalation – Negishi coupling reactions

The Negishi cross-coupling with other aryl bromides required elevated temperatures. Thus, a series of cross-coupled compounds **16** was obtained under microwave heating conditions (80-120 °C) in 2-30 min (Figure 9). As aryl chlorides did not react under employed Negishi reaction conditions, 4-chloro-1-bromobenzene was selectively coupled with indolylzinc **10f** to produce chloro – substituted compound **16d**.

Conclusions

1. Analysis of microwave-assisted methods for synthesis of heterocyclic compounds was based on the latest literature data. The main criteria were identified to evaluate the suitability of methods for the synthesis of heterocycle libraries. Literature analysis was published as a review.

2. Two new methods for microwave-assisted synthesis of coumarin library via Pechmann reaction were developed. One of them was based on the use of trifluoroacetic acid both as an acidic catalyst and solvent. The acidic ion exchange resin Amberlyst-15 in toluene provided an alternative method of heterogeneous catalysis. Microwave heating (100 °C) was applied in both methods to reduce the reaction time to 30 minutes. The developed methods were used in the synthesis of a representative library of coumarins.

3. Reactions of metals with aromatic halides under microwave heating conditions were examined. It was established that microwave dielectric heating generally is not sufficient for activation of the metal surface and additional chemical activation is often necessary to bring about the formation of organometallic compounds:

- Nonactivated zinc dust reacted with aryl iodides under microwave conditions in DMF solution at 120-180 °C temperature to produce the arylzinc iodides. The use of zinc-copper couple as a source of chemically activated zinc enabled to perform the reactions at lower temperatures (60-140 °C). In addition, reaction reproducibility and yields of the products were improved. Zn-Cu couple was found to be the most efficient source of activated zinc for synthesis of organozinc reagents from aryl- and heteroaryl iodides as well as from electronically poor aryl- and heteroaryl bromides under microwave heating conditions. Zn-Cu couple hitherto has not been used in the synthesis of aromatic organozinc compounds and therefore the developed method can be considered as novel.
- Nonactivated magnesium turnings reacted with aryl bromides at 80-120 °C in the microwave field. On the other hand, microwave thermal activation is not sufficient in the case of less reactive aryl chlorides. Therefore additional *in*

situ chemical activation with 1,2-dibromoethane and higher temperatures (180-200°C) were required to generate the Grignard reagents.

4. The formation of organozinc species from aryl iodides and Zn-Cu couple was faster under microwave conditions in comparison with conventional heating. Presumably, the reason for the acceleration is more efficient heating of the reaction mixture in the microwave field.

5. Two-step procedure for fast generation of biaryl compounds was developed. The method was based on synthesis of organozinc compounds from aryl iodides and Zn-Cu couple and sequential Negishi cross-coupling reaction under microwave conditions. Total time for two sequential reactions was 7-20 minutes. Microwave assisted generation of Grignard reagents and subsequent transmetallation to organozinc compounds were employed to obtain the arylzinc reagents from more easily available aryl bromides and chlorides. Three-step procedure was developed for Pd catalyzed C-C bond formation reaction using microwave dielectric heating. The procedure comprising Grignard formation, transmetallation and Negishi cross-coupling could be performed in 30-75 minutes.

Posters

1. Mutule, I.; Avotina, D.; Suna, E. Microwave assisted preparation of Grignard and organozinc reagents. *Book of Abstracts, Balticum Organicum Syntheticum*, Vilnius, Lithuania, June 23-27, 2002; p. 100.
2. Mutule, I. Microwave-assisted synthesis of aryl- and heteroarylzinc reagents. *Latvijas Ķīmijas Žurnāls*, **2004**, 165. The 3rd Paul Walden Symposium, Riga, Latvia, October 13-14, 2003.
3. Mutule I.; Suna E. Generation of arylzinc species from aryl bromides and aryl chlorides via Grignard reagents under microwave conditions. *Book of Abstracts, Balticum Organicum Syntheticum*, Riga, Latvia, June 27 - July 1, 2004; p. 115 ¹
4. Mutule, I.; Suna, E. Microwave-assisted generation of arylzinc reagents. *Book of Abstracts, 13th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis*, Geneva, Switzerland, July 17-21, 2005; P-255.

Publications

1. Mutule, I.; Suna E. A convenient microwave assisted arylzinc generation-Negishi coupling protocol. *Tetrahedron Lett.* **2004**, *45*, 3909-3912.
2. Mutule, I.; Suna E. Arylzinc species by microwave assisted Grignard formation - transmetallation sequence: application in the Negishi coupling. Mutule, I.; Suna E. *Tetrahedron* **2005**, *61*, 11168-11176.
3. Suna E.; Mutule, I. Microwave-assisted heterocyclic chemistry. In *Microwave Methods in Organic Synthesis*, Larhed, M., Olofsson, K., Eds.; *Topics in Current Chemistry*; Springer: Heidelberg, 2006; *accepted for publication*.
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¹ „Thieme-Verlag” prize for the best poster from Latvia