

Influence of microwave irradiation and ionic liquids on multi component reactions

Dissertation zur Erlangung des Doktorgrades
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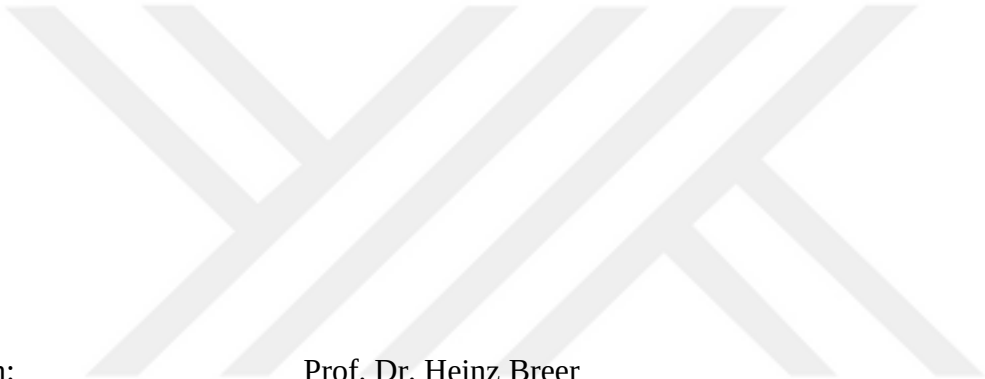
Institut für Chemie

vorgelegt von

Fadime Mert-Balci

**aus Mersin
(Türkei)**

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Dekan: Prof. Dr. Heinz Breer

1. berichtende Person: Prof. Dr. Uwe Beifuss

2. berichtende Person: Prof. Dr. Henry Strasdeit

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PRELIMINARY REMARKS

The work presented in this thesis was carried out under the supervision of Prof. Dr. Uwe Beifuss at the Institute of Chemistry, University of Hohenheim, from June 2006 to December 2008. The results have already been published in international peer reviewed journals.

1. **Fadime Mert-Balci**, Jürgen Conrad, Kathrin Meindl, Thomas Schulz, Dietmar Stalke, and Uwe Beifuss
“Microwave-Assisted Three-Component Reaction for the Synthesis of Pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones”
Synthesis **2008**, 3649-3656
2. **Fadime Mert-Balci**, Jürgen Conrad, and Uwe Beifuss
“Microwave-assisted three-component reaction in conventional solvents and ionic liquids for the synthesis of amino-substituted imidazo[1,2-*a*]pyridines”
ARKIVOC **2012** (iii), 243-256
3. **Fadime Mert-Balci**, Hans-Georg Imrich, Jürgen Conrad, and Uwe Beifuss
“Influence of Guanidinium Salts and other Ionic Liquids on the Three Component aza-*Diels-Alder* reaction”
Helv. Chim. Acta **2013**, 10.1002/hlca.201200655

Concerning the co-authors

Prof. Dr. Uwe Beifuss was the supervisor of this work. He was always available for scientific discussions and made valuable suggestions. He was involved in correcting the manuscripts throughout the whole process of publication. He was responsible for all aspects of publication. He is also the corresponding author of the publications.

Dr. Jürgen Conrad was involved in the interpretation of NMR spectroscopic data. Also, he measured all NMR samples on the 500 MHz Varian ^{Unity}Inova.

Dipl.-Chem. Hans-Georg Imrich has carried out some experiments for the publication “Influence of Guanidinium Salts and other Ionic Liquids on the Three Component *aza-Diels-Alder* reaction” (publication No 3). These experiments are not part of the present thesis.

Dr. Kathrin Meindl, Dr. Thomas Schulz, and Prof. Dr. Dietmar Stalke (Institut für Anorganische Chemie, Universität Göttingen) have carried out the X-ray crystal structure analysis of compound **109n**.

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1. Introduction

The efficient preparation of heterocycles is an important field of synthetic organic chemistry since most heterocycles exhibit biological activities and are therefore of great interest for the development of new drugs, diagnostics, and agrochemicals. Domino reactions^[1] as well as multi component reactions^[2] are among the most valuable tools for the synthesis of heterocycles. In multi component reactions, three or more substrate molecules are reacted in one pot under identical reaction conditions to yield a product in such a way that most of the atoms of the substrates can be found in the product molecule. The advantages of multi component reactions include high synthetic convergency, the generation of structural complexity in one step, high selectivity, high synthetic efficiency, and high atom economy. This is why multi component reactions are particular valuable in combinatorial chemistry and diversity-oriented synthesis. They allow for the synthesis of compound libraries which are of utmost importance for high-throughput screening in the field of drug discovery.

Microwave-assisted reactions^[3] have gained increasing popularity in recent years. In many cases, heating of reaction mixtures with microwaves leads to a decrease of reaction times, an increase of product yields, helps in avoiding the formation of side products, enhances the product purity and improves the reproducibility. It has been demonstrated that not only simple chemical transformations but also many domino- and multi component reactions can be performed successfully under microwave conditions.

Ionic liquids are a new class of non-flammable solvents with a high thermal and chemical stability.^[4] They have an ionic structure and consist of an organic cation and an inorganic anion. Their melting points are below 100°C and their vapor pressure is negligible. Ionic liquids are immiscible with many organic solvents. This means that typical organic reaction products can be extracted from crude reaction mixtures. It means also that the ionic liquids are recyclable. In addition, ionic liquids are considered to be of low-toxicity. Due to these advantages ionic liquids have attracted a great deal of attention among organic chemists. So far, the main interest lies on imidazolium salts, but for a number of reasons guanidinium salts offer a valuable alternative.

With respect to microwave chemistry the most important features of ionic liquids are their high polarity and their stability at high temperatures. Ionic liquids interact very efficiently with microwave irradiation through the ionic conduction mechanism and are rapidly heated at rates easily exceeding 10 °C/s without a significant high pressure build up. This allows the rapid and safe heating of reaction mixtures in closed reaction vessels.

The combination of microwave chemistry and ionic liquids offers a number of opportunities in organic synthesis.^[5] This thesis deals with the influence of microwaves and ionic liquids on two three component reactions, the Groebke reaction and the Povarov reaction.



2. Ionic liquids and their role in organic synthesis

Ionic liquids have increasingly gained importance in organic synthesis as solvents and catalysts and they have been efficiently used in numerous transformations.^[4,6] They are liquid compounds, which are composed entirely of cations and anions. Their melting points are below the boiling point of water.^[7] Ionic liquids exhibit several crucial properties making them very interesting in academia and industry:^[7,8] 1) they are non-volatile, and have a very low vapor pressure, 2) they are non-flammable, 3) they can dissolve both organic and inorganic compounds, 4) they have a high thermal stability (up to 200°C), 5) they have densities greater than the density of water, thus they occur as the lower phase in most biphasic systems, 6) they are non-corrosive, 7) they can be used as electrolytes in electrochemical devices because of their large electrochemical window, i. e. the maximum anodic and cathodic potential that can be applied without decomposition of the ionic liquids, 8) they can be recycled and reused many times without loss of reactivity, and 9) their physical properties such as density, melting point, solvation capability can be adjusted by modification of their cationic or anionic group.

The most widely known and used ionic liquids are *N,N'*-dialkylimidazolium salts, alkylammonium salts, alkylphosphonium salts, *N*-alkylpyridinium salts, and guanidinium salts. The corresponding cations are shown in Figure 1.^[7,8,9] Halides (Cl^- , Br^- , I^-), tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-), nitrate (NO_3^-), perchlorate (ClO_4^-), alkylsulfonate (RSO_3^-), and bis(trifluoromethanesulfonyl)imide (Tf_2N^-) are the most common anions X^- in ionic liquids.^[7,8,9] The positive charge in the guanidinium ions is delocalized over one carbon and three nitrogen atoms. Due to the efficient resonance stabilization of the guanidinium cation, guanidinium salts are very stable even at high temperatures (Figure 2).^[10]

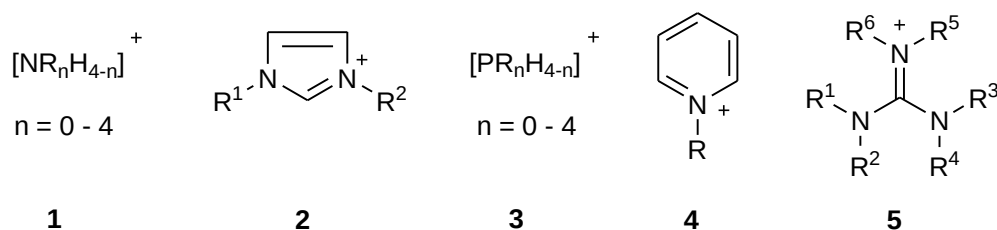


Figure 1. The most commonly used cations of ionic liquids

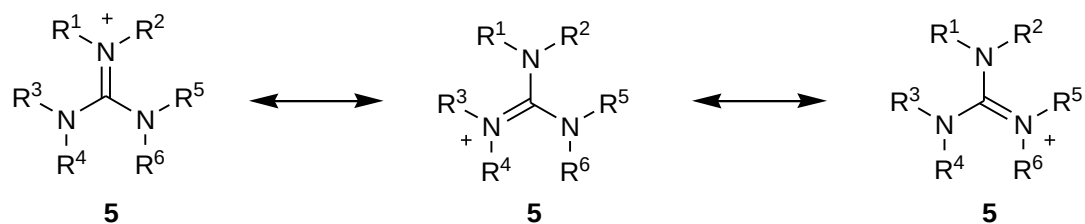
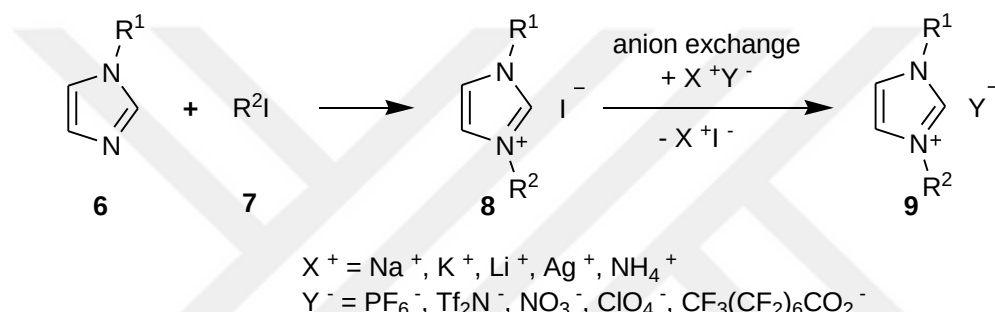


Figure 2. Resonance structures of the guanidinium cation **5**

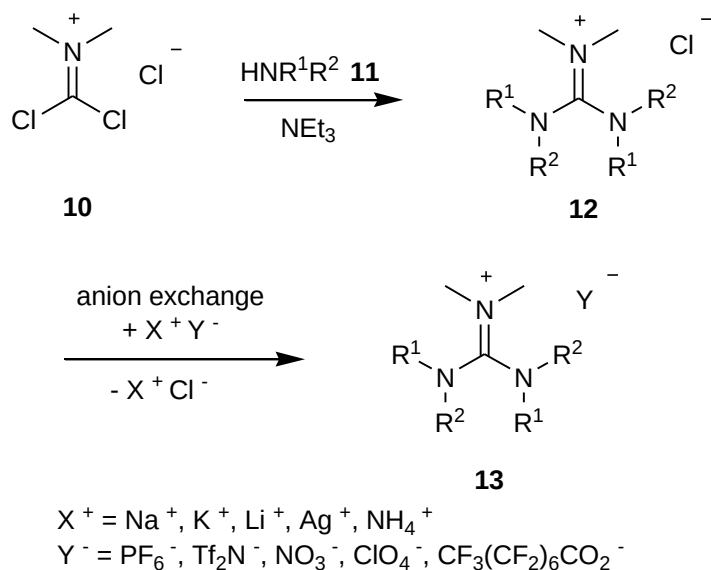
In general, the synthesis of ionic liquids can be divided in two parts. The first step is the preparation of the desired cation, and the second step is the anion exchange reaction to construct the desired ionic liquid.^[4,8b] As an example, the preparation of 1,3-dialkylimidazolium salts **9** is illustrated in Scheme 1.



Scheme 1. Synthesis of 1,3-dialkylimidazolium salts **9** starting from 1-alkylimidazoles **6**^[11]

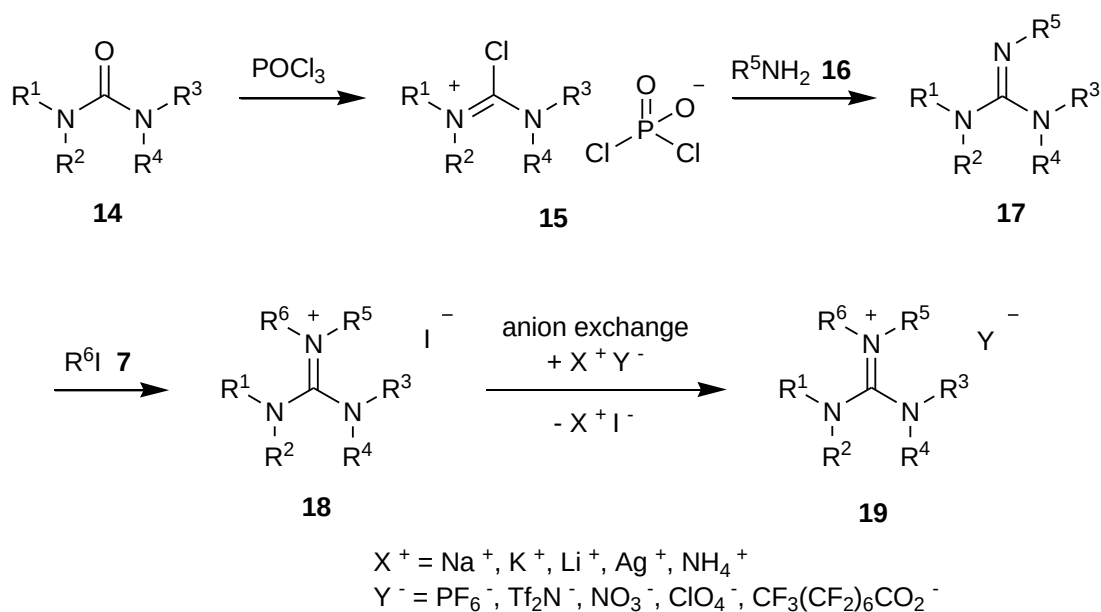
In the first step, the 1,3-dialkylimidazolium iodide **8** is prepared by reaction of the 1-alkylimidazole **6** with a suitable alkyl iodide **7**. In the second step, the imidazolium salt **9** with the desired anion is generated by anion exchange of the 1,3-dialkylimidazolium iodide **8** with X^+Y^- (Scheme 1).^[11]

For the synthesis of guanidinium salts, various methods have been employed. As an example, Carrera et al. have prepared guanidinium salts **13** in two steps (Scheme 2).^[9a] They started with the synthesis of the guanidinium chlorides **12** by reaction of commercially available *N,N*-dimethyl phosgeniminium chloride (**10**) and a secondary amine **11**. In the second step, the chloride anion of the guanidinium chloride **12** was exchanged by reaction of **12** with X^+Y^- to yield the guanidinium salts **13** with the required anion.



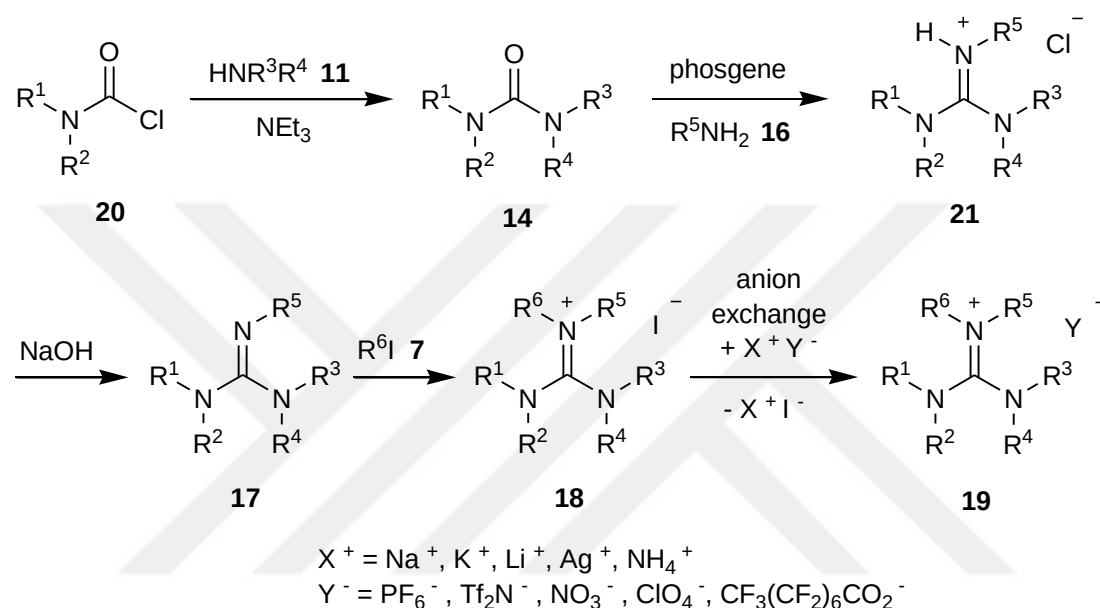
Scheme 2. Synthesis of guanidinium salts **13** starting from *N,N*-dimethyl-phosgeniminium chloride (**10**)^[9a]

Furthermore, guanidinium salts can also be synthesized starting from the corresponding urea **14** (Scheme 3).^[9b,12] Initially, urea **14** is reacted with phosphorus oxychloride (POCl₃) to afford the chloroformamidinium salt **15** (Vilsmeier salt), which is treated with a primary amine **16** to give the guanidine **17**. Treatment of **17** with an alkyl iodide R⁶I **7** produces the guanidinium iodide **18**. The guanidinium salt with the required anion **19** is formed by anion exchange reaction of **18** with X⁺Y⁻.



Scheme 3. Synthesis of guanidinium salts **19** starting from the *N,N,N',N'*-tetraalkyl urea **14**^[9b]

Another useful route for the synthesis of guanidinium salts has been presented by Wang et al. (Scheme 4).^[13] According to this procedure, a secondary amine **11** is reacted with *N,N*-dialkylcarbamoyl chloride **20** in the presence of triethylamine to deliver the required urea **14**. The reaction of **14** with phosgene and a primary amine **16** leads to the guanidinium chloride **21**, which after treatment with a base, such as NaOH, yields the desired guanidine **17**. Reaction of **17** with an alkyl iodide **7** gives the hexaalkylguanidinium iodide **18**. The last step is the anion exchange reaction to furnish the final product **19**.



Scheme 4. Synthesis of guanidinium salts **19** starting from *N,N*-dialkylcarbamoyl chloride **20**^[13]

Imidazolium salts have been successfully applied as solvents and/or catalysts in a variety of organic reactions such as the hydrogenation,^[11c,14] the allylation,^[15] the regioselective alkylation,^[16] and the Diels-Alder reaction.^[17] Imidazolium salts have also been proven to be very efficient as catalysts and/or reaction media in multi component and domino reactions. Examples are the aza-Diels-Alder reaction,^[18] the multi component synthesis of functionalized pyrroles,^[19] and the multi component synthesis of heterocyclic 2,3-dihydroquinazolin-4(1*H*)-ones.^[20]

In recent years, guanidinium salts have also become a valuable alternative to classical organic solvents and to catalysts for organic synthesis. Guanidinium salts have been efficiently employed as solvents for the selective oxidation of benzyl alcohols,^[12] the Knoevenagel condensation reaction,^[21] the catalytic asymmetric dihydroxylation of olefins,^[22] and for the Pd-catalyzed Heck reaction.^[23] The guanidinium salts used in the Heck reaction have played

three major roles; as a ligand to stabilize the activated palladium species, as a base, and as a polar solvent. Moreover, the catalytic activity of various guanidinium salts has been screened in a number of transformations, such as the aldol condensation,^[24] the addition of CO₂ to epoxides,^[25] the Diels-Alder reaction,^[26] the asymmetric phospho-Mannich reaction between phosphine oxides and imines,^[27] the enantioselective α -aminoxylation of carbonyl compounds with nitrosobenzene,^[28] the synthesis of 2-nitroalcohols,^[29] and the hydrogenation of olefins.^[30] They exhibited very high catalytic activities in these processes. Guanidinium salts have also been used successfully in multi component- and domino reactions as solvents and/or catalysts. Examples include the Biginelli reaction between an aldehyde, a β -ketoester and a 2-aminobenzimidazole or a 2-aminobenzothiazole for the construction of 4*H*-pyrimido[2,1-*b*]benzazoles or 4*H*-pyrimido[2,1-*b*]benzothiazoles,^[31] the condensation of carbonyl compounds with two equivalents of an indole to produce bis(indolyl)methanes,^[32] and the condensation of aldehydes with two equivalents of a β -naphthol or a 2-hydroxynaphthalene-1,4-dione or dimedone to generate biologically active xanthene derivatives.^[33]

3. Microwaves in organic synthesis

3.1. Introduction

Microwaves are electromagnetic waves having both electric and magnetic field components, which oscillate in phase perpendicular to each other and perpendicular to the propagation direction of the electromagnetic radiation. The wavelength of microwaves ranges from as long as one meter to as short as one millimeter, and the frequency of the microwaves is in the range between 0.3 GHz and 300 GHz. In a typical microwave oven employed for synthetic applications, microwave radiation with a frequency of 2.540 GHz is used.^[3,34] This energy cannot ionize molecules, since it is lower than their ionization energy, but it causes dipoles to rotate. In the absence of any electromagnetic field, the dipoles behave randomly. If an electromagnetic field is applied in a medium containing polar solvents or compounds, the dipoles are oriented or aligned in only one direction. Due to the oscillation of the electric field, the dipoles try to reorient themselves in the alternating electric field. During the reorientation of the dipoles, collisions and frictions between the dipoles occur. As a result, the microwave energy is transformed to heat energy. The approximate value of the temperature growth that can be achieved in this way is 10°C/s. Therefore, many organic chemical reactions can be performed under such conditions.^[3,34] The heat produced due to the microwave irradiation is generated locally and is not transferred by convection as in the case of thermal heating. Since microwave irradiation results in uniform distribution of the generated heat, in many organic reactions the amount of side products decreases. The energy transfer through microwave irradiation is believed to proceed by dielectric loss. The tendency of chemical compounds to undergo microwave heating depends on their dielectric loss factor (ϵ'') and their dielectric constant (ϵ').^[3,34] The dielectric constant of a substance stands for the ability of a substance to absorb microwave radiation. On the other hand, the dielectric loss factor defines the ability of a chemical compound to transform microwave energy into heat. The susceptibility of a compound towards microwave energy depends on its dissipation factor $\tan \delta$. The dissipation factor is defined as follows (Equation 1).

$$\tan \delta = \epsilon''/\epsilon'$$

$\tan \delta$ = dissipation factor

ϵ'' = dielectric loss factor

ϵ' = dielectric constant

Equation 1.

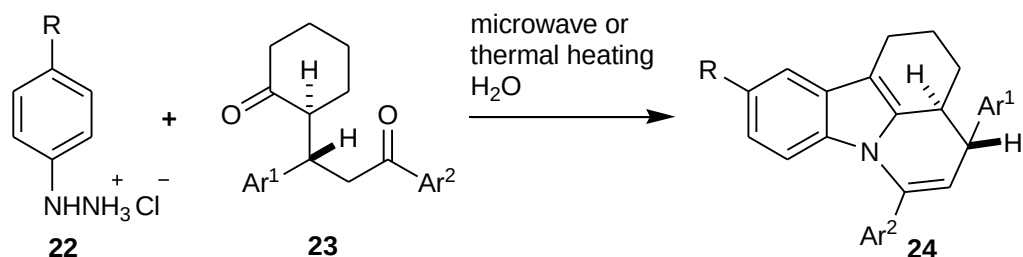
In the case of a high dissipation factor, the susceptibility of a compound to microwave energy is high. For example, the dielectric constants of acetonitrile ($\epsilon' = 36$) and dimethylformamide ($\epsilon' = 36.7$) are very similar, but acetonitrile ($\tan \delta = 0.659$) has a much higher dissipation factor than dimethylformamide ($\tan \delta = 0.062$). This is why acetonitrile can couple much better with microwave irradiation than dimethylformamide. The result is a faster increase of the temperature in acetonitrile. In the case of non polar substrates and/or non polar solvents that do not couple with the microwave irradiation, the use of either a polar solvent or a solid support, such as graphite, may be useful.^[3,34]

Due to the above mentioned reasons, the application of microwave heating technology in the synthesis of organic molecules has attracted great interest in recent years. Among organic synthetic chemists, the use of microwave irradiation technology for simplifying and improving classical organic synthetic reactions has become a very attractive tool. In comparison to conventional thermal heating, the use of microwave irradiation in organic synthesis has several advantages. These include simple operation, efficient control of the reaction conditions, shorter reaction times, higher yields, and better selectivities.^[3,34]

3.2. The use of microwaves in domino- and multicomponent reactions

Meanwhile, microwave heating has been applied successfully in a great number of domino- and multi component reactions.^[3,35] As an example, Chitra et al. have reported the efficient synthesis of carbazole derivatives **24** by reaction between phenylhydrazines **22** and 1,5 diketones **23** under microwave conditions (Scheme 5).^[36] It has been postulated that the synthesis starts with a Fischer indole reaction, which is followed by an intramolecular cyclization. In order to determine the influence of the microwave irradiation on yield and reaction time, the transformations have also been performed under thermal conditions. Under

microwave conditions, the reaction times could be reduced considerably and the yields of the carbazoles could be increased.



thermal heating: 100°C, 2 h

R = H, Ar¹ = C₆H₅, Ar² = C₆H₅, 78%

R = H, Ar¹ = 4-MeC₆H₄, Ar² = C₆H₅, 70%

R = Cl, Ar¹ = 4-MeOC₆H₄, Ar² = C₆H₅, 79%

microwave heating: 120 W, 140°C, 15 min

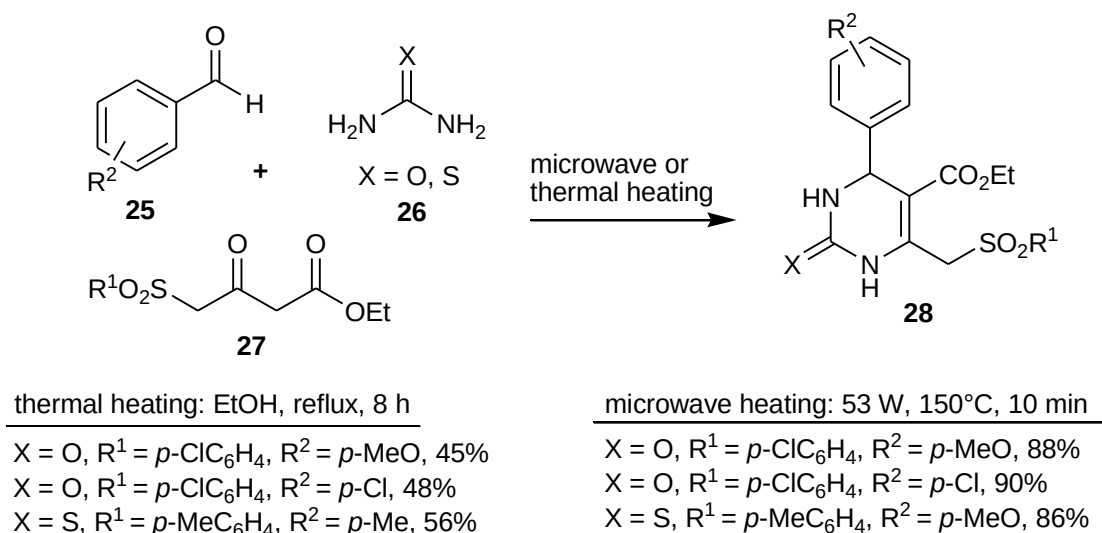
R = H, Ar¹ = C₆H₅, Ar² = C₆H₅, 95%

R = H, Ar¹ = 4-MeC₆H₄, Ar² = C₆H₅, 96%

R = Cl, Ar¹ = 4-MeOC₆H₄, Ar² = C₆H₅, 95%

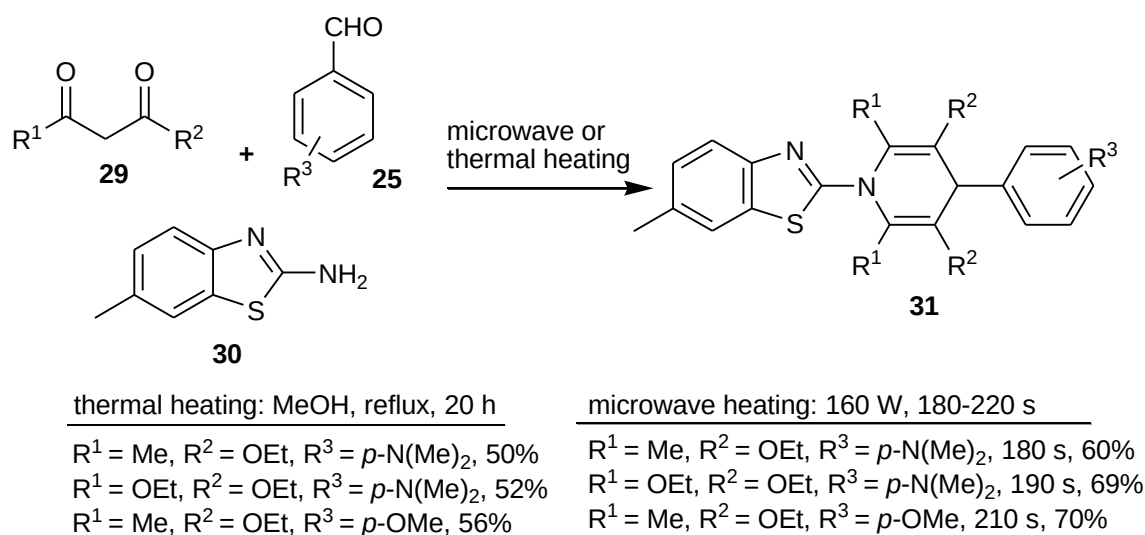
Scheme 5. Domino reaction between phenylhydrazines **22** and 1,5 diketones **23** for the synthesis of carbazole derivatives **24** under thermal and microwave conditions^[36]

Harikrishnan et al. have studied the microwave-assisted Biginelli reaction under solvent-free conditions in the absence of any catalyst (Scheme 6).^[37] Irradiation of a mixture of an ethyl 3-oxo-4-(arylsulfonyl)butanoate **27**, an aromatic aldehyde **25** and urea (**26a**) or thiourea (**26b**) with microwaves for only 10 min delivered the corresponding 2-oxo/thio-1,2,3,4-tetrahydropyrimidines **28** with high yields. When the reactions were run under thermal conditions in EtOH, the yields were considerably lower and the reaction times were much longer.



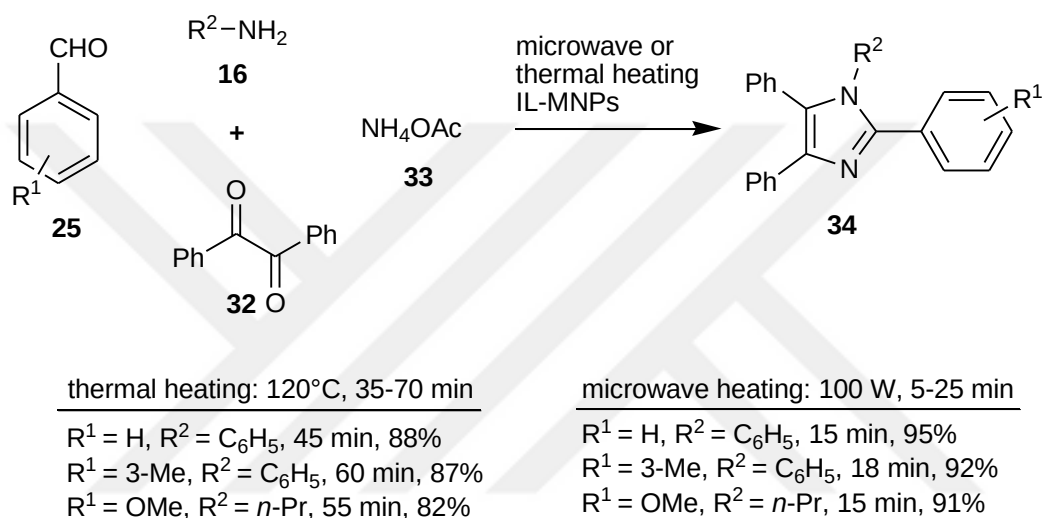
Scheme 6. The Biginelli reaction between an ethyl 3-oxo-4-(arylsulfonyl)butanoate **27**, an aromatic aldehyde **25**, and urea (**26a**) or thiourea (**26b**) under thermal and microwave conditions^[37]

Another classical three component reaction, the Hantzsch 1,4-dihydropyridine synthesis, has also been studied under both thermal and microwave conditions (Scheme 7).^[38] Under microwave conditions, the 1,4-dihydropyridines **31** could be isolated with yields ranging from 60 to 72% after only a few minutes. Under thermal conditions, the reaction time amounted to 20 h and the yields of the 1,4-dihydropyridines **31** were lower. This is another example that clearly demonstrates the advantages of microwave-assisted reactions.



Scheme 7. The Hantzsch reaction for the synthesis of 1,4-dihydropyridine derivatives **31** under thermal and microwave conditions^[38]

Recently, there was a report on the four component reaction between an aldehyde **25**, benzil (**32**), a primary amine **16**, and ammonium acetate (**33**) to give the tetrasubstituted imidazoles **34** (Scheme 8).^[39] The transformation has been carried out under microwave conditions without any solvent in the presence of ionic liquid functionalized magnetic nano particles (IL-MNPs) as a catalyst. The results have been compared with the results from the reactions performed under thermal conditions. The experiments demonstrated that under microwave heating, the reaction times were shorter and the yields were higher.



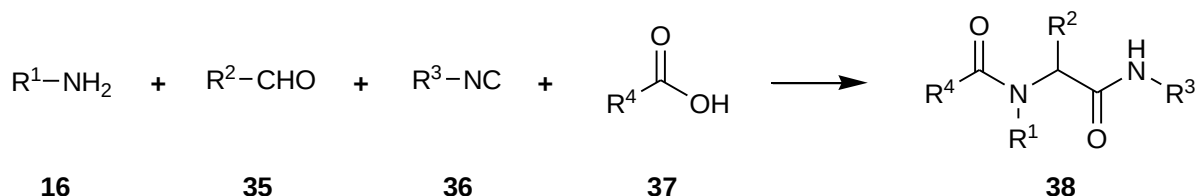
Scheme 8. The four component reaction between an aldehyde **25**, benzil (**32**), a primary amine **16**, and ammonium acetate (**33**) for the synthesis of tetrasubstituted imidazoles **34**^[39]

The few examples discussed here clearly demonstrate that running domino- and multi component reaction under microwave conditions offers numerous advantages.

4. Ugi- and Groebke Reactions

4.1. The Ugi reaction

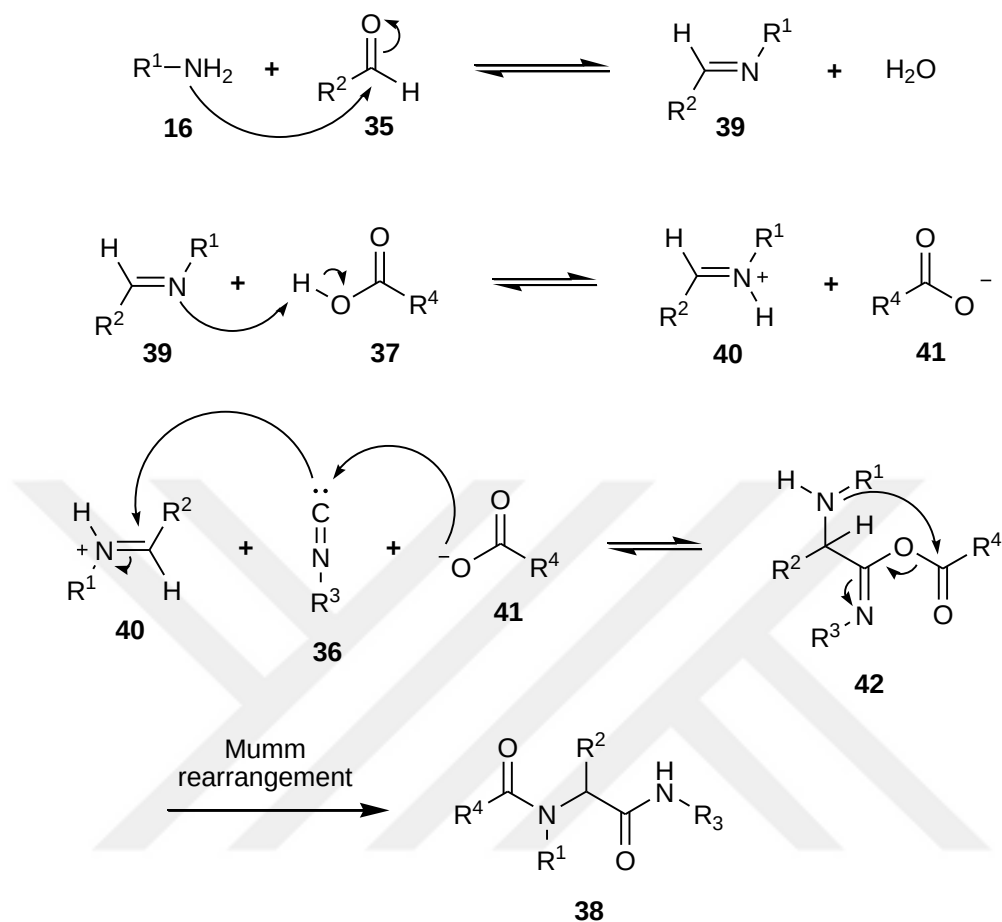
One of the most well-known multi component reactions (MCRs) is the Ugi four component reaction (Ugi-4CR).^[2,40] This powerful transformation was discovered in 1959 by Ivar Ugi and coworkers.^[41] In the Ugi-4CR, an amine **16**, a carbonyl **35**, an isocyanide **36**, and an acid **37** are reacted to form an α -acylamino amide **38** in one synthetic step (Scheme 9). This reaction tolerates the use of a wide variety of amines and acids. Apart from primary amines, ammonia, secondary amines, aromatic amines, hydrazines, and hydroxylamines have been used as an amine moiety. In addition to carboxylic acids, water, hydrogen selenide, hydrogen sulfide, hydrogen cyanate, and hydrogen thiocyanate have been employed as acid components in the Ugi-4CR.^[40c,42] Depending on the structures of the amine and the acid used, structurally very different compounds such as acylamides, carbonamides, thiocarbonamides, selenoamides, amidines, tetrazoles, and iminoimides are obtained.^[40c,42] Therefore, the Ugi-4CR has been extensively studied and used for the synthesis of a multitude of complex organic molecules from simple and commercially available substrates.^[40] By variation of one of the components of the Ugi-4CR, several modifications of the classical Ugi reaction have been developed. As an example, the use of bifunctional components vastly increases the diversity of the Ugi reaction products.



Scheme 9. The Ugi-4CR^[40]

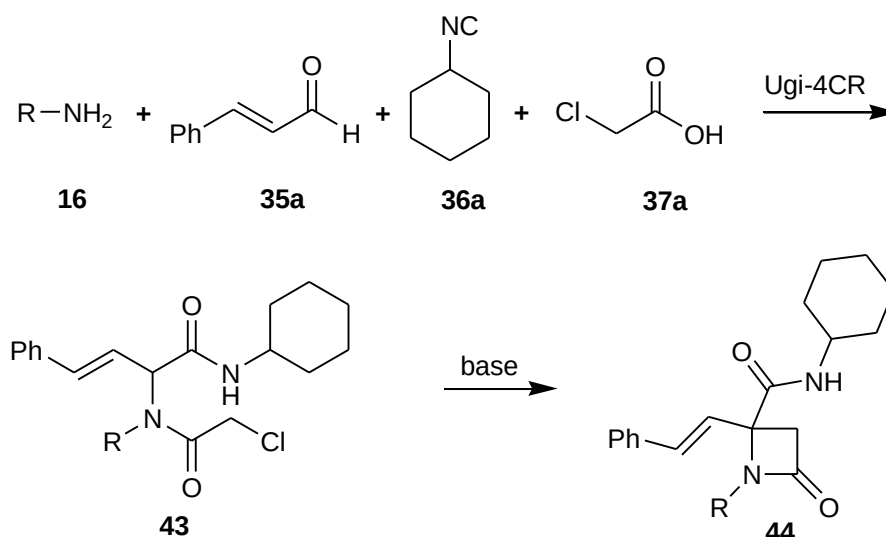
In the first step of the Ugi reaction, the primary amine **16** and the carbonyl compound **35** undergo a condensation to the corresponding imine **39** as an intermediate (Scheme 10). Then, the carboxylic acid **37** protonates the nitrogen atom of the Schiff base **39** which results in an increase of the electrophilicity of the C=N bond. The resulting electrophilic iminium ion **40** and the nucleophilic carboxylate anion **41** react with the isocyanide **36** to deliver the intermediate **42**. After intramolecular acylation and subsequent rearrangement – the so called Mumm rearrangement – the final Ugi-4CR product **38** is obtained. With the exception of the last step, all elementary steps of this reaction are in equilibria. The equilibrium of the last

reaction, the rearrangement of the intermediate **42** to the α -acylamino amide **38** lies on the product side.^[40]



Scheme 10. Mechanism of the Ugi-4CR^[40]

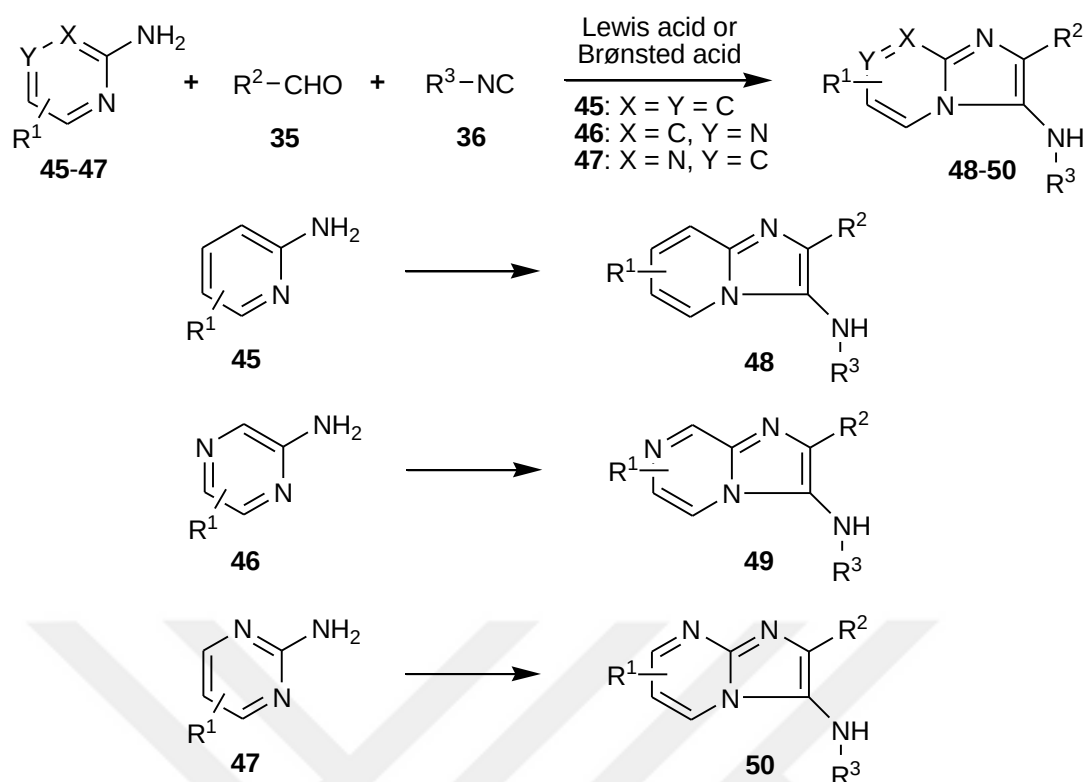
The Ugi four component reaction allows the preparation of a wide range of biological active compounds.^[43] For instance, β -lactams **44** have been successfully synthesized using the Ugi-4CR as the key step (Scheme 11).^[43b]



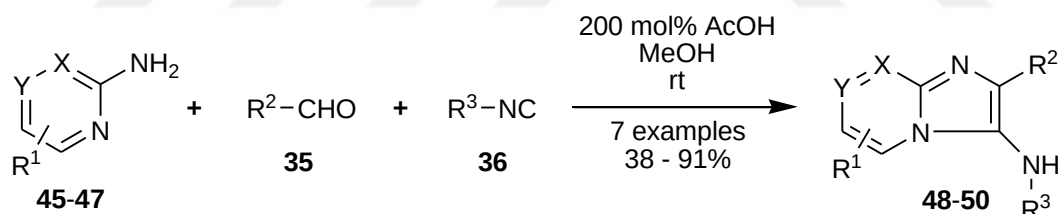
Scheme 11. Synthesis of β -lactams **44** using the Ugi-4CR as the key step^[43b]

4.2. The Groebke reaction

The Groebke reaction is a variant of the Ugi reaction that allows the synthesis of numerous heterobicyclic compounds. In 1998, this reaction has been described independently by Groebke,^[44] Blackburn,^[45] and Bienaymé.^[46] In typical Groebke reactions, 6-membered heteroaromatic amines **45-47** are condensed with aldehydes **35** and isocyanides **36** in the presence of a Lewis or Brønsted acid to give the fused 3-aminoimidazoles **48-50** (Scheme 12).^[44] Depending on the structure of the amine, this reaction allows the synthesis of different imidazo[1,2-*a*] annulated heterobicyclic compounds **48-50** in one pot. The use of 2-aminopyridines **45** results in the formation of imidazo[1,2-*a*]pyridines **48**, with 2-aminopyrazines **46** the corresponding imidazo[1,2-*a*]pyrazines **49** are obtained and with 2-aminopyrimidines **47** the formation of imidazo[1,2-*a*]pyrimidines **50** takes place. Goebke et al. have reported that this three component reaction can be performed using acetic acid as a catalyst and methanol as a solvent at room temperature (Scheme 13).^[44]



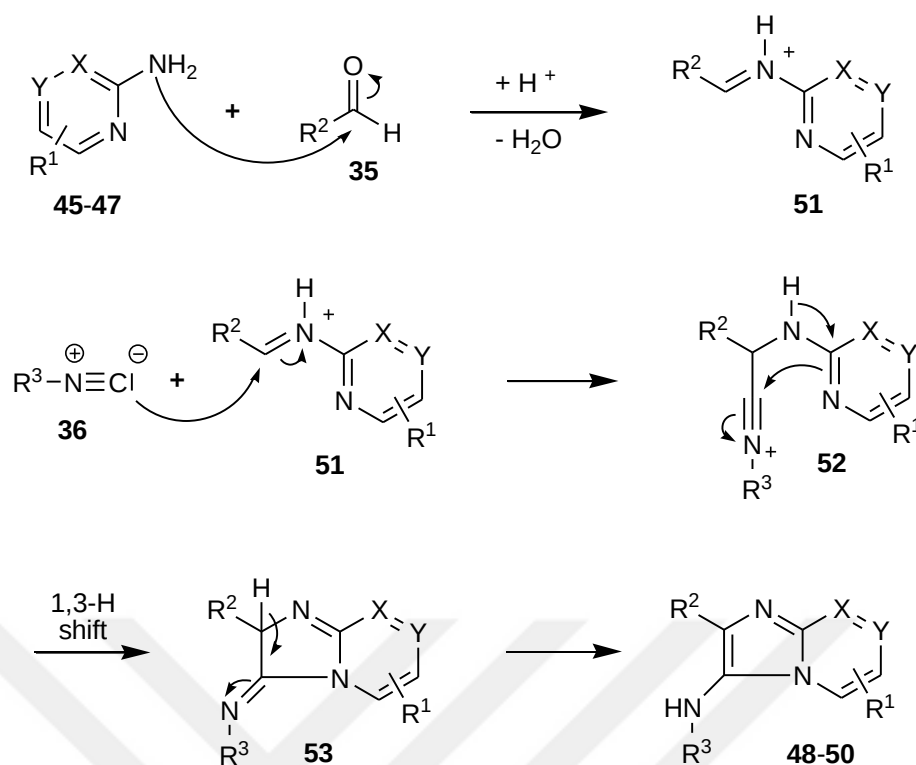
Scheme 12. The classical Groebke reaction^[44]



X = C, Y = C, R¹ = H, R² = CH₂Bn, R³ = Bn, **48a**, 62%
 X = C, Y = C, R¹ = H, R² = CH₂OH, R³ = Bn, **48b**, 44%
 X = C, Y = C, R¹ = H, R² = CH=CH-Ph, R³ = 3,4-(MeO)₂C₆H₃, **48c**, 38%
 X = C, Y = N, R¹ = H, R² = CH₂OH, R³ = Bn, **49a**, 54%
 X = N, Y = C, R¹ = H, R² = 4-MeOC₆H₄, R³ = Bn, **50a**, 48%

Scheme 13. Synthesis of imidazo[1,2-*a*]azines **48-50** according to Groebke et al^[44]

The Groebke reaction starts with the formation of the iminium ion **51** by condensation of aldehyde **35** and amines **45-47**. This is followed by the nucleophilic attack of the isocyanide **36** at the electrophilic iminium ion **51**. An intramolecular nucleophilic attack leads to the formation of the bicyclic intermediate **53**. Aromatization via 1,3-H shift results in the formation of the desired products **48-50** (Scheme 14).^[44]



Scheme 14. Mechanism of the Groebke reaction^[44]

The imidazo[1,2-*a*]azines **48-50** are of considerable interest because they exhibit a wide range of biological activities like antibacterial, antiviral, antifungal, and anti-inflammatory properties.^[47] The imidazo[1,2-*a*]pyridine skeleton is present in several drugs, like zolimidine (**54a**), zolpidem (**54b**), and alpidem (**54c**) (Figure 3).^[48]

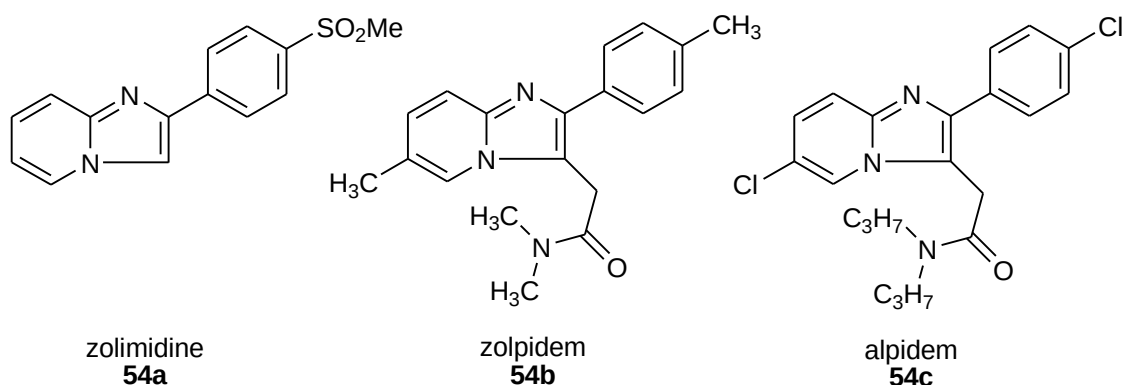
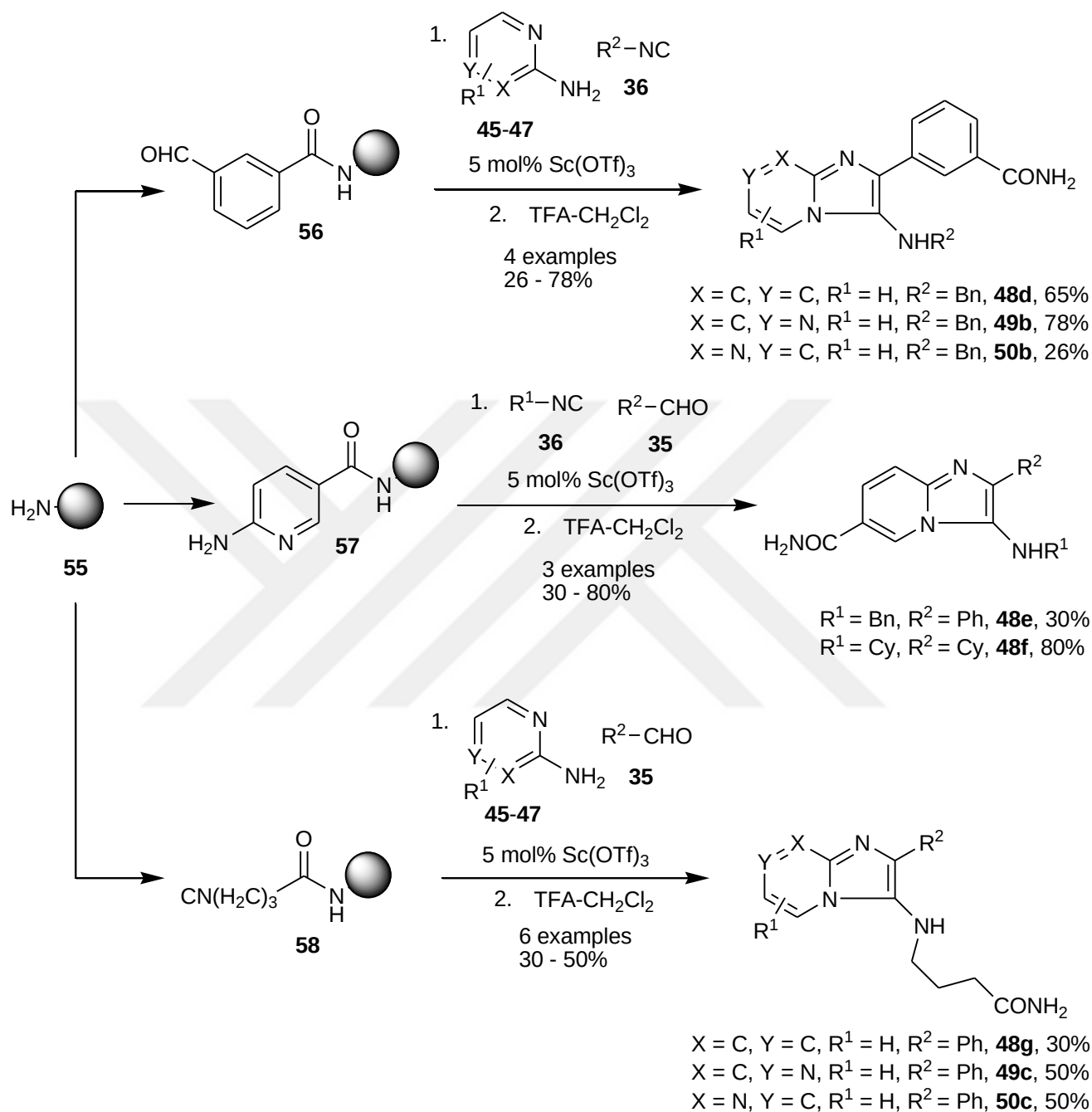


Figure 3. Three drugs with an imidazo[1,2-*a*]pyridine skeleton^[48]

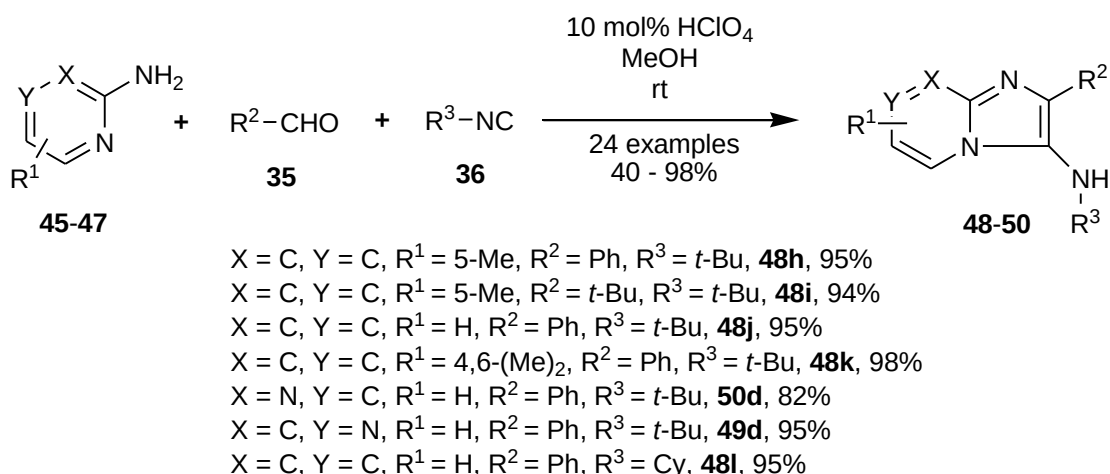
C. Blackburn has used the three component Groebke reaction for the synthesis of 3-aminoimidazo[1,2-*a*]azines using solid phase techniques (Scheme 15).^[45] He started with the preparation of the Rink amide resin (RAM) bound aldehyde **56**, 2-aminoazine **57** and isocyanide **58**. The $\text{Sc}(\text{OTf})_3$ -catalyzed Groebke reaction of any of the three resin bound substrates (**56**, **57** or **58**) with the corresponding reaction partners resulted in the formation of

the heterobicyclic products **48-50**, in reasonable yields and purities after TFA induced cleavage of the resin.^[45]



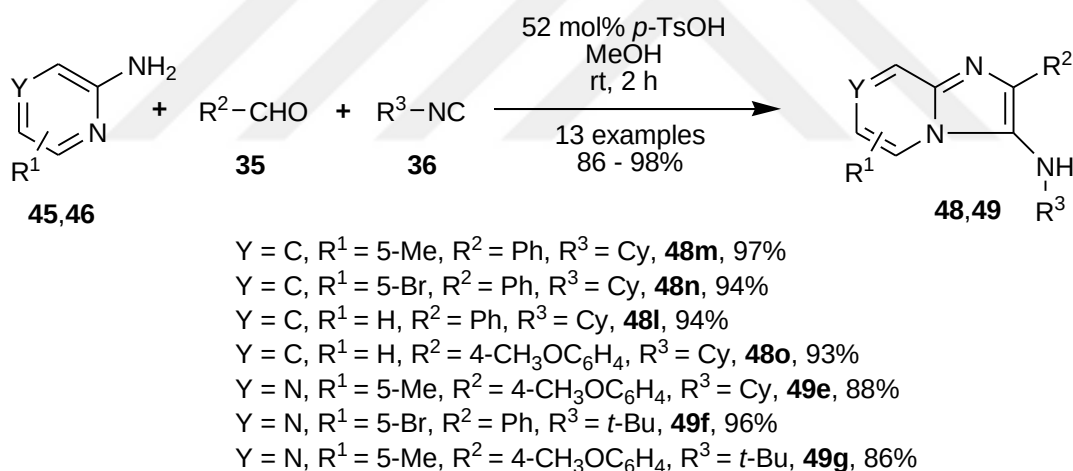
Scheme 15. The Groebke reaction on solid phase^[44]

Perchloric acid has been employed as an efficient catalyst for the Groebke reaction by Bienaymé and Bouzid (Scheme 16).^[46] The three component reaction of a variety of aldehydes **35**, 2-aminoazines **45-47**, and isocyanides **36** in the presence of 10 mol% perchloric acid in methanol at room temperature afforded the corresponding fused 3-aminoimidazoles **48-50** in excellent yields.



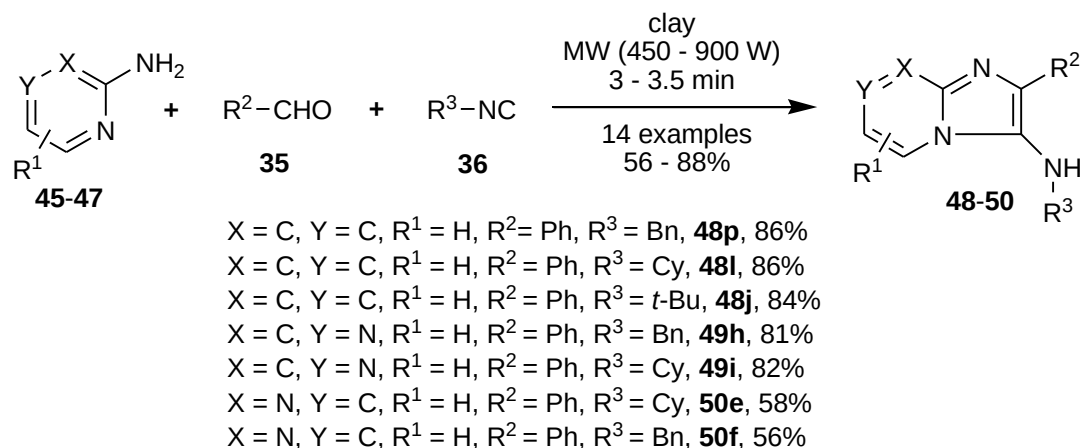
Scheme 16. Synthesis of 3-aminoimidazo[1,2-*a*]azines **48-50** according to Bienaymé and Bouzid^[46]

Another protocol of the Groebke reaction employs cheap *p*-toluenesulfonic acid as a reagent (Scheme 17).^[49] The reaction between **45** or **46**, **35**, and **36** with 52 mol% *p*-TsOH in MeOH at room temperature for 2 h afforded the imidazo[1,2-*a*]azines **48,49** in high yields.



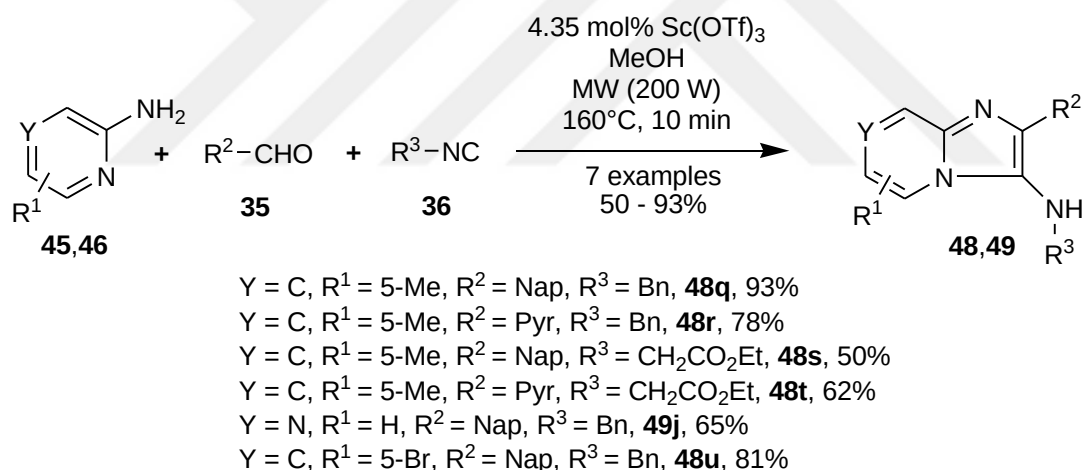
Scheme 17. The Groebke reaction utilizing *p*-toluenesulfonic acid as a reagent^[49]

Microwave technology has also been used for the synthesis of fused 3-aminoimidazoles **48-50** (Scheme 18).^[50] The three component reaction of **45-47**, **35**, and **36** for the preparation of fused 3-aminoimidazoles **48-50** has been carried out with montmorillonite K 10 clay as a catalyst in the absence of any solvent under microwave conditions. The method allowed the preparation of the products within minutes. However, it should be mentioned that this reaction can not be regarded as a true three component reaction, since the authors reacted the 2-aminoazines **45-47** with the aldehydes **35** to the corresponding imine before they added the isocyanide **36** to the reaction mixture.



Scheme 18. Microwave-assisted synthesis of fused 3-aminoimidazoles **48-50** by use of montmorillonite K 10 clay as a catalyst^[50]

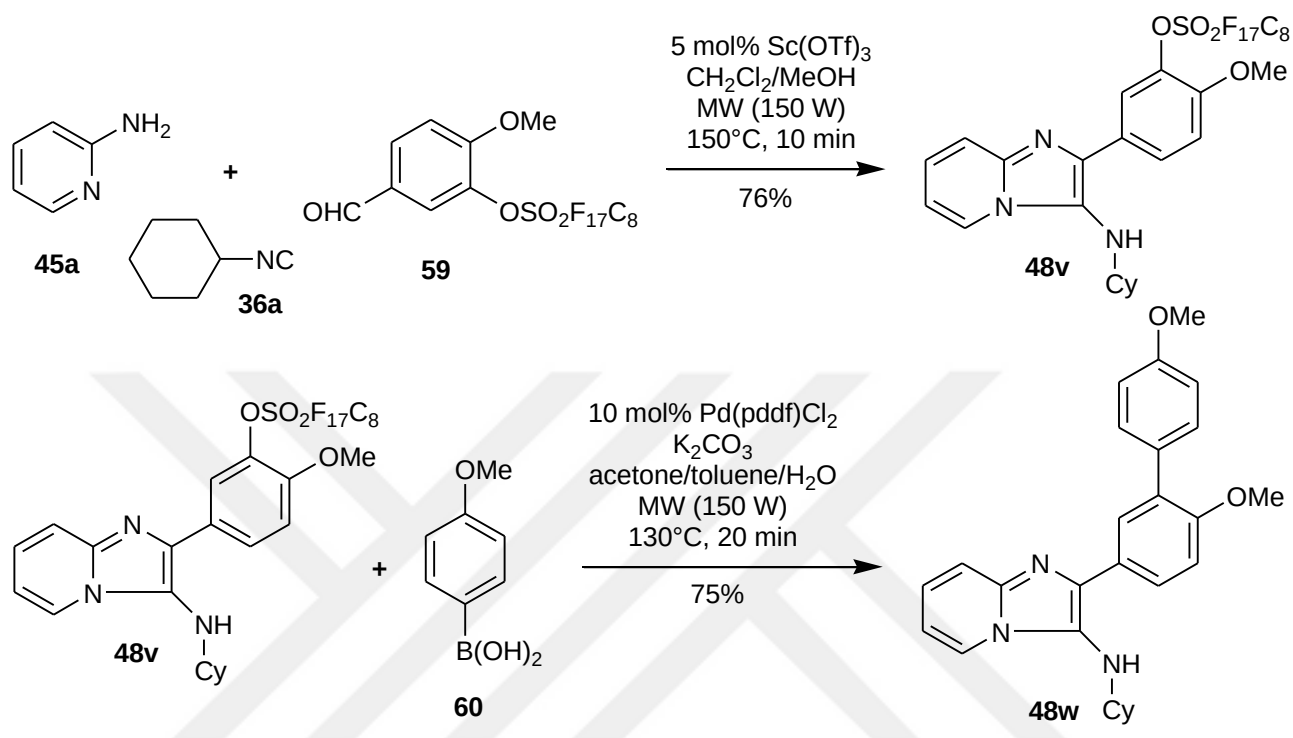
Another efficient protocol of the microwave-assisted Groebke reaction employs $Sc(OTf)_3$ as a catalyst and methanol as a solvent (Scheme 19).^[51] The *N*-heterocycles **48,49** could be isolated in good yields after irradiation with microwaves for only 10 min.



Scheme 19. Microwave-assisted synthesis of imidazo[1,2-*a*]azines **48,49** using $Sc(OTf)_3$ as a catalyst^[51]

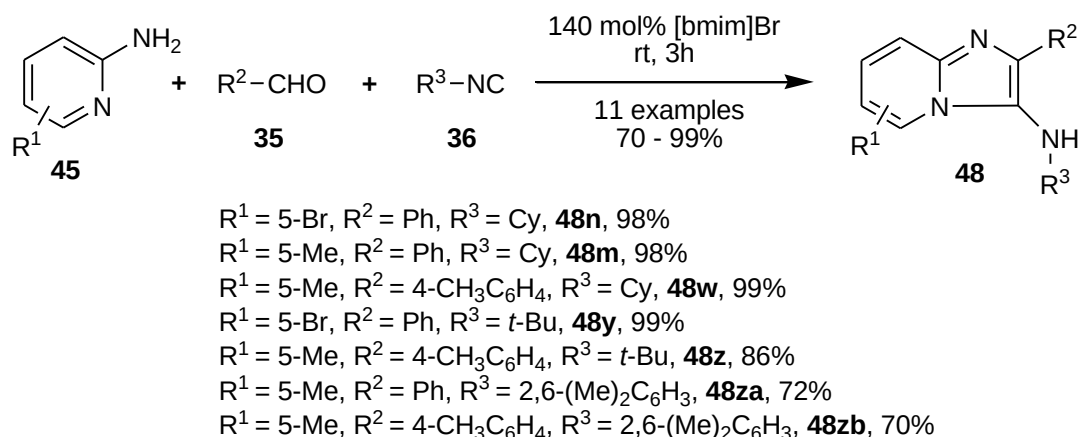
Lu et al. have combined microwave and fluorous technologies for the preparation of 3-aminoimidazo[1,2-*a*]pyridines **48w**.^[52] Fluorous technology, a solid phase extraction technique, has been used to efficiently and quickly separate fluorous reaction products from reaction mixtures. A typical example is illustrated in Scheme 20. The three component reaction of the perfluorooctanesulfonyl-tagged benzaldehyde **59** with 2-aminopyridine (**45a**) and the isocyanide **36a** under microwave conditions is followed by a Pd-catalyzed cross coupling reaction of the resulting **48v** with boronic acid **60** to form product **48w**. The

coupling products were purified by fluorous solid phase extraction (F-SPE). In this approach, the perfluoroalkanesulfonyl tag has three main functions: It acts a) as a phenol protecting group for the condensation reaction, b) as a phase tag during the purification, and c) as an activating group for the Pd-catalyzed cross coupling reaction.^[52]



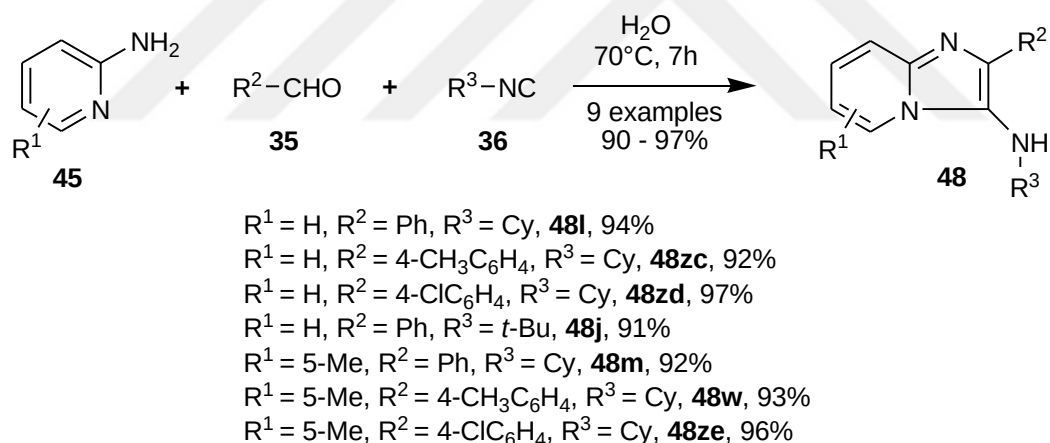
Scheme 20. Fluorous three component reaction and subsequent cross coupling reaction for the synthesis of the fused 3-aminoimidazole **48w**^[52]

Shaabani and co-workers have reported that the ionic liquid 1-butyl-3-methylimidazolium bromide ($[\text{bmim}]\text{Br}$) is an efficient catalyst for the three component Groebke reaction (Scheme 21).^[53] The pharmacological relevant nitrogen containing bicyclic compounds **48** have been obtained in good to excellent yields using $[\text{bmim}]\text{Br}$ as a catalyst and as a solvent at room temperature. The $[\text{bmim}]\text{Br}$ can easily be separated from the reaction mixture by washing with water and can be reused for further transformations.^[53]



Scheme 21. Preparation of nitrogen-containing bicyclic compounds **48** in the presence of [bmim]Br as a catalyst and as a solvent^[53]

And finally, there is also a report on the catalyst-free preparation of fused bicyclic imidazoles **48** via three component reaction between 2-aminopyridines **45**, aldehydes **35**, and isocyanides **36** in water at 70°C (Scheme 22).^[54] The condensation of 2-aminopyridine **45** with various aldehydes **35** and isocyanides **36** delivered the products **48** in excellent yields.



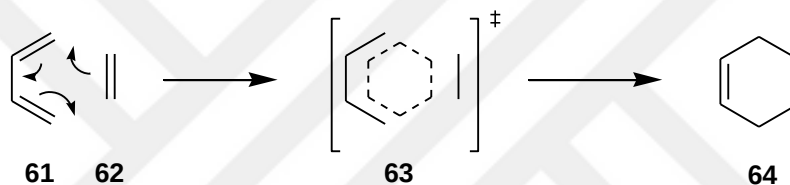
Scheme 22. Catalyst-free preparation of fused bicyclic imidazoles **48** in water^[54]

In summary, the Groebke reaction has been performed using a range of acidic catalysts and a number of reaction conditions.

5. Diels-Alder- and Povarov reactions

5.1. The Diels-Alder reaction

Many processes have been developed for the formation of six-membered carbo- and heterocyclic ring systems; but one of the most popular methods is the Diels-Alder reaction.^[55] The Diels-Alder reaction is a $[4\pi + 2\pi]$ cycloaddition between a *cisoid* conjugated diene (usually a 1,3-butadiene **61**) with 4π electrons and a dienophile (usually an alkene **62**) with 2π electrons to form a six-membered ring (usually a cyclohexene **64**) via an aromatic transition state **63** (Scheme 23). At the expense of three π -bonds in the substrates two new σ -bonds and one new π -bond are formed. The driving force of the Diels-Alder reaction is the formation of the two new σ -bonds which are energetically more stable than the π -bonds in the substrates.



Scheme 23. The Diels-Alder reaction^[55]

According to Woodward and Hoffmann the Diels-Alder reaction is a thermally allowed, orbital-controlled $[4+2]$ cycloaddition with supra-suprafacial arrangement of the reacting π -systems in the transition state.^[55-58] The principle of conservation of orbital symmetry can explain a number of experimental findings related to Diels-Alder reactions:

1. The stereochemistry of the substrates is retained in the product (*cis*-principle).
2. In Diels-Alder reactions with unsymmetrical dienophiles the more stable *endo* transition state is favored over the *exo* transition state (*endo*-rule).
3. The Diels-Alder reaction is accelerated by significantly different electronic properties of the diene and the dienophile.
4. When a substituted dienophile reacts with a diene that has a donor substituent at C-1, there is a preference for the *ortho* product. When the diene has a donor at C-2, the formation of the *para* product is preferred.
5. Solvent effects are small.

- Lewis acid catalysis can increase the rate of the Diels-Alder reaction and improve its regio- and stereoselectivity.

It is widely believed that the Diels-Alder reaction proceeds via a concerted, stereospecific reaction mechanism. However, in a number of cases stepwise reaction mechanisms involving diradical or zwitterionic intermediates have been proposed.

The frontier molecular orbital theory allows to explain the reactivity as well as the regioselectivity of the Diels-Alder reaction.^[55-58] According to this theory, the reactivity of a system results from the energy difference of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reaction partners. Analysis of these molecular orbitals results in a classification of the Diels-Alder reaction into three types. Normal electron demand Diels-Alder reactions are dominated by the interaction of the HOMO of the diene with the LUMO of the dienophile (Figure 4). In the inverse electron demand Diels-Alder reaction, the LUMO of the diene and the HOMO of the dienophile is the lowest energy separation of the frontier orbitals. A Diels-Alder reaction is regarded as neutral Diels-Alder reaction when the energy separations $\text{HOMO}_{\text{diene}}\text{-LUMO}_{\text{dienophile}}$ and $\text{LUMO}_{\text{diene}}\text{-HOMO}_{\text{dienophile}}$ are comparable.

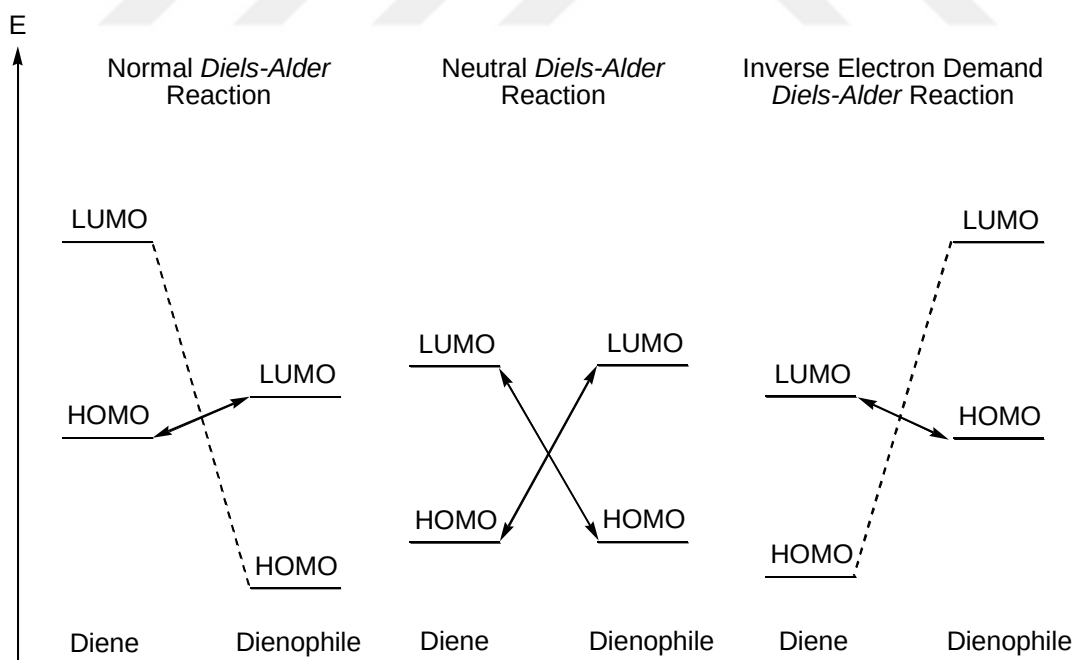


Figure 4. Classification of Diels-Alder reactions

This classification allows a qualitative description of the reactivity pattern in Diels-Alder reactions on the basis of the influence of substituents on the orbital energy.^[55-58] According to K. Houk substituents can be distinguished as follows: A C-substituent raises the energy of the HOMO and lowers the energy of the LUMO. Z-substituents are electron withdrawing groups (EWG). They slightly lower the energy of the HOMO and substantially lower the energy of the LUMO. X-Substituents are electron donating groups (EDG). They substantially raise the energy of the HOMO and slightly raise the energy of the LUMO. This means that the reactivity of a normal electron demand Diels-Alder reaction can be increased by a Z-substituent in the dienophile and an X-substituent in the diene. On the other hand, the reaction rate of inverse electron demand Diels-Alder reactions is increased by a Z-substituent in the diene and an X-group in the dienophile. The reactivity of neutral Diels-Alder reaction is increased by any substituent. While the energies of the frontier orbitals can be used to describe the effect of the substituents on the rate of Diels-Alder reactions, the relative size of the coefficients of the frontier orbitals can be employed to explain the regioselectivity of these transformations.

The Diels-Alder reaction is not restricted to the construction of carbocycles. Using dienes or dienophiles with one or more heteroatoms a great variety of heterocyclic six membered rings is available (Figure 5). Some examples of the Diels-Alder reaction are presented in Figure 5.

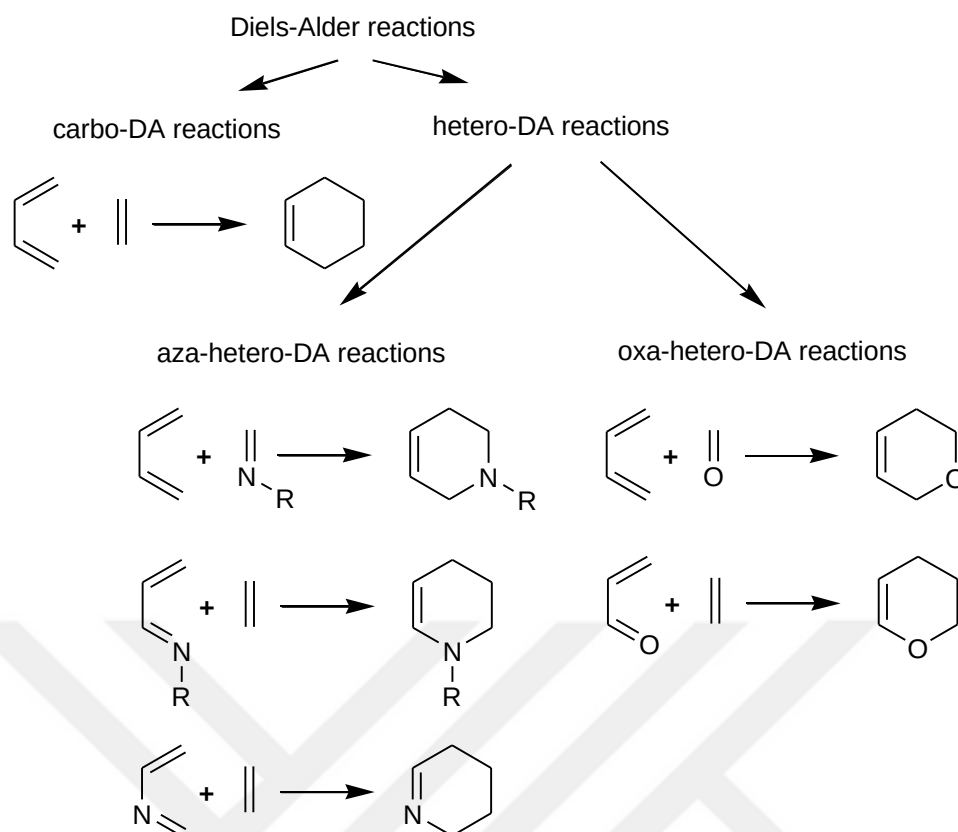
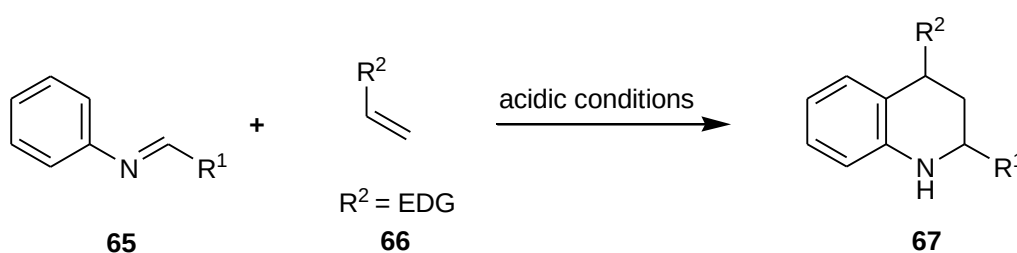


Figure 5. Some variants of the Diels-Alder reaction^[58]

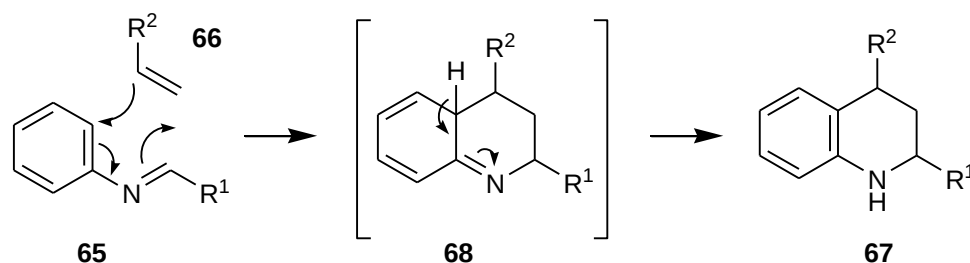
5.2. The Povarov reaction

The aza-DA reaction between an electron poor 2-azadiene moiety of the *N*-aryl imine type **65** (Schiff base) and an electron rich dienophile **66** under acidic conditions that leads to the formation of a tetrahydroquinoline **67** is called the Povarov reaction (Scheme 24).^[58,59] Tetrahydroquinolines constitute an important class of nitrogen heterocycles. Since they have found applications as pharmaceuticals and agrochemicals and since they are useful synthetic building blocks for the preparation of several alkaloids, they are attracting great interest from synthetic and medicinal chemists.^[57,58]



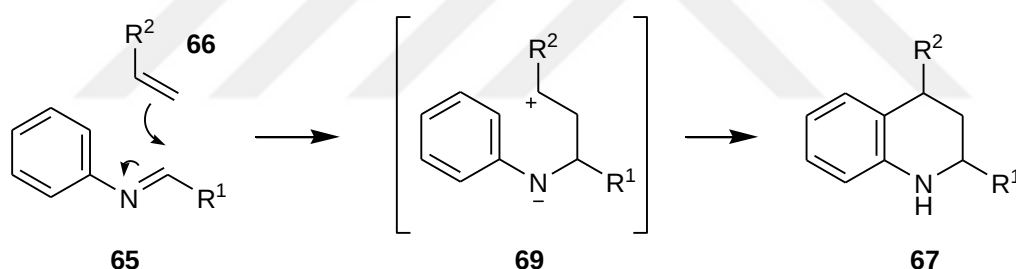
Scheme 24. The intermolecular Povarov reaction^[58]

For the intermolecular Povarov reaction two mechanistic proposals have been presented: 1) The reaction proceeds via a concerted mechanism (Scheme 25),^[60] in which an inverse electron demand, intermolecular [4+2]-cycloaddition is followed by aromatization of **68** to **67**.



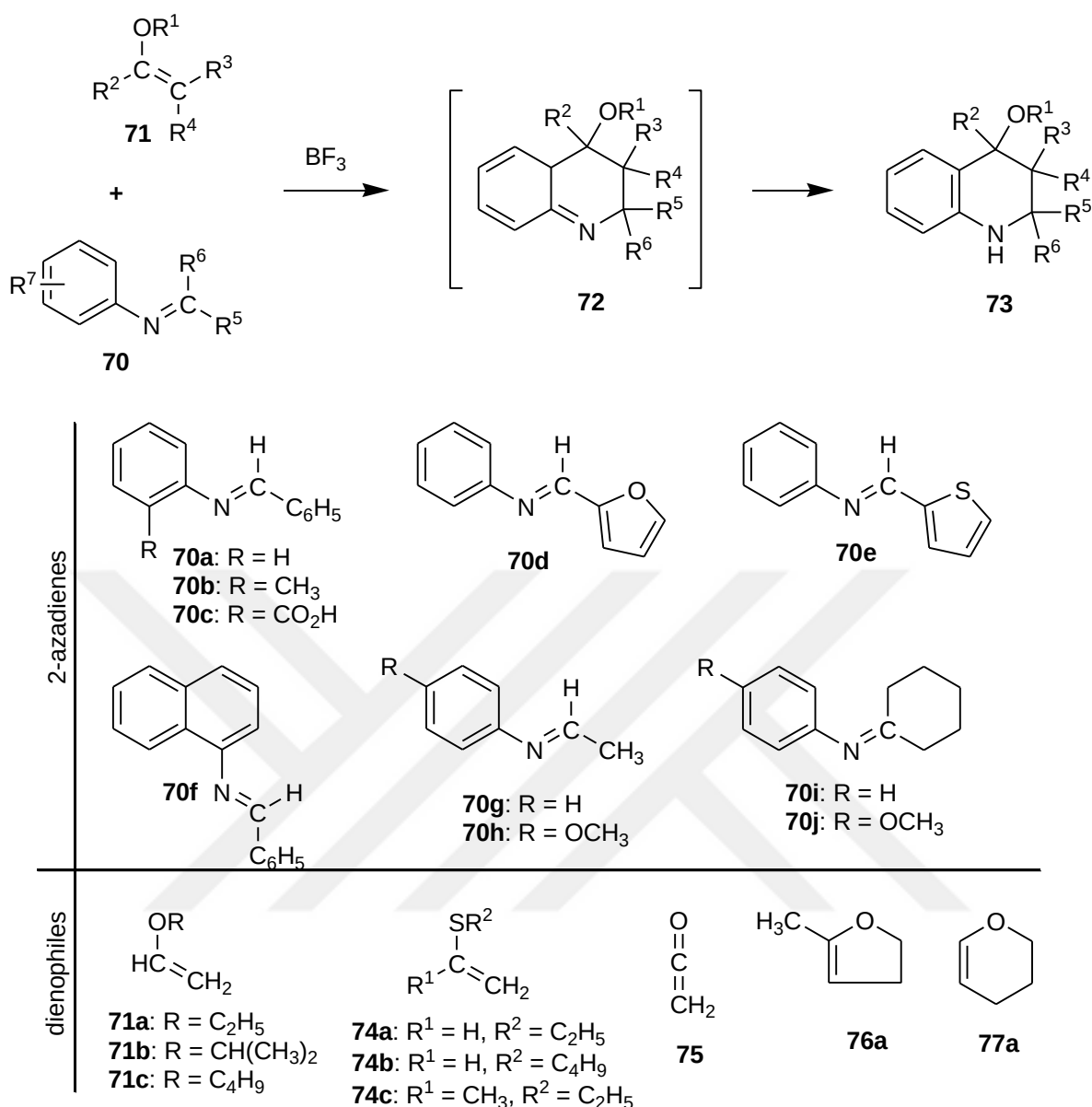
Scheme 25. Concerted reaction mechanism of the intermolecular Povarov reaction^[60]

2) The reaction proceeds via a stepwise mechanism (Scheme 26),^[61] which starts with the reaction between imine **65** and alkene **66** to give the carbenium ion **69** as an intermediate. The carbenium ion **69** undergoes an intramolecular electrophilic substitution reaction (Friedel-Crafts reaction) to the Povarov product **67**.



Scheme 26. Stepwise reaction mechanism of the intermolecular Povarov reaction^[61]

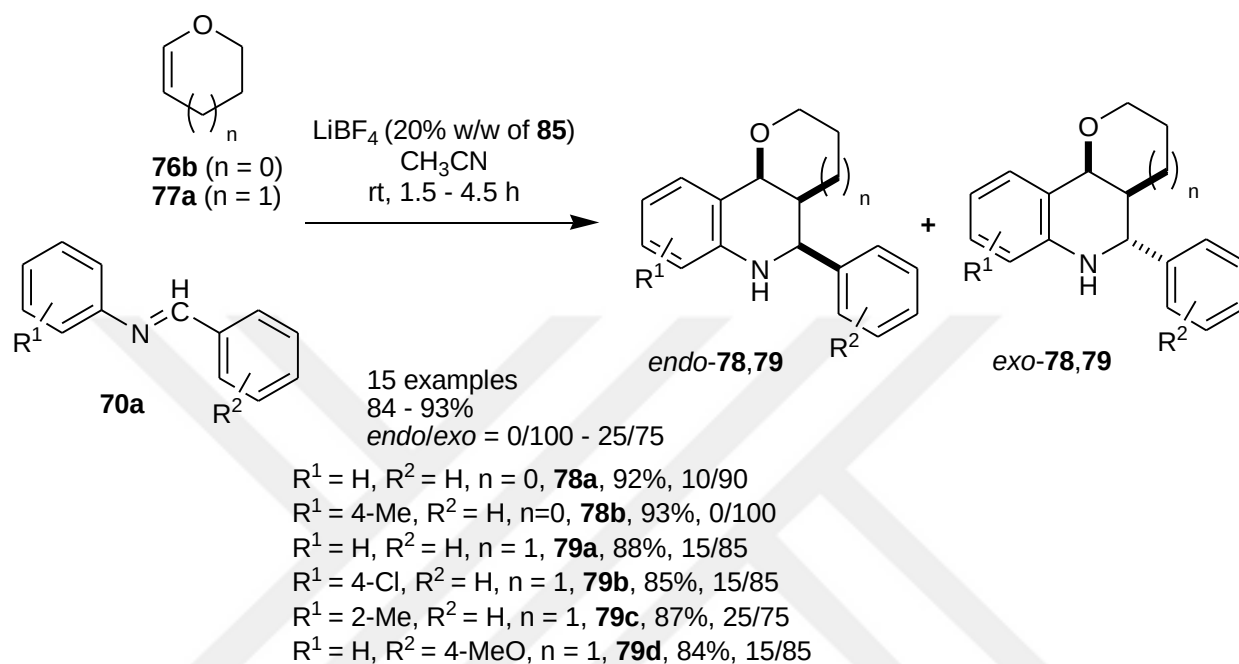
In their studies, Povarov et al. have employed a number of Schiff bases **70**, such as benzylideneanilines **70a-c**, furfurylideneaniline (**70d**), thienylideneaniline (**70e**), benzylidene-1-naphthylamine (**70f**), acetaldehyde anils **70g,h**, and cyclohexanone anils **70i,j** as the 2-azadiene components (Scheme 27).^[59] The Schiff bases could easily be obtained by condensation. Ethyl vinyl ether (**71a**), isopropyl vinyl ether (**71b**), butyl vinyl ether (**71c**), ethyl vinyl sulphide (**74a**), butyl vinyl sulphide (**74b**), ethyl isopropenyl sulphide (**74c**), ketene (**75**), 2-methyl-4,5-dihydrofuran (**76a**), and 2,3-dihydropyran (**77a**) have been used by Povarov et al. as electron rich dienophiles (Scheme 27).^[59] The catalyst Povarov and coworkers employed originally was boron trifluoride (BF₃). In addition to BF₃, they have also used AlCl₃ and AlBr₃ as Lewis acids in their studies. As the solvent ether, benzene, and ethyl acetate have been used by Povarov et al.^[59]



Scheme 27. 2-Azadienes and dienophiles used by Povarov et al.^[59]

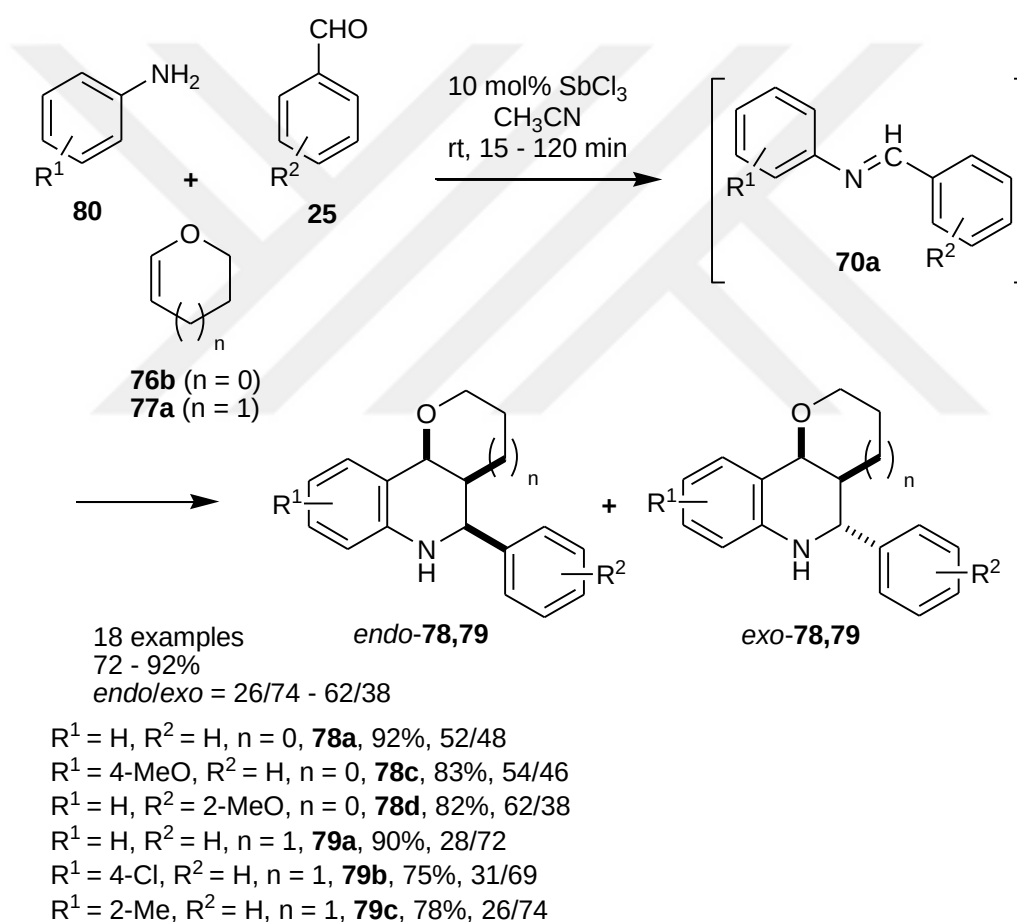
Meanwhile, numerous other 2-azadienes have been employed as substrates for the intermolecular Povarov reaction. The same holds true for the dienophiles. It has also been demonstrated that BF_3 is not the only catalyst that can be used to bring about the Povarov reaction. Typical other Lewis acidic catalysts include LiBF_4 , SbCl_3 , I_2 , Selectfluor, Fe^{3+} -K-10 montmorillonite clay, HY zeolite, fluoroalcohols, $[\text{bmim}]\text{BF}_4$, and InCl_3 .

A typical example is the LiBF_4 -catalyzed intermolecular Povarov reaction between *N*-aryl imines **70a** and the cyclic enol ethers **76b** or **77a** (Scheme 28).^[62] With LiBF_4 (20% w/w of **70a**) as the catalyst the transformation delivers the corresponding heterocycles *exo*-**78,79** and *endo*-**78,79** in high yields and with high diastereoselectivity in favor of the *exo*-products *exo*-**78,79**.



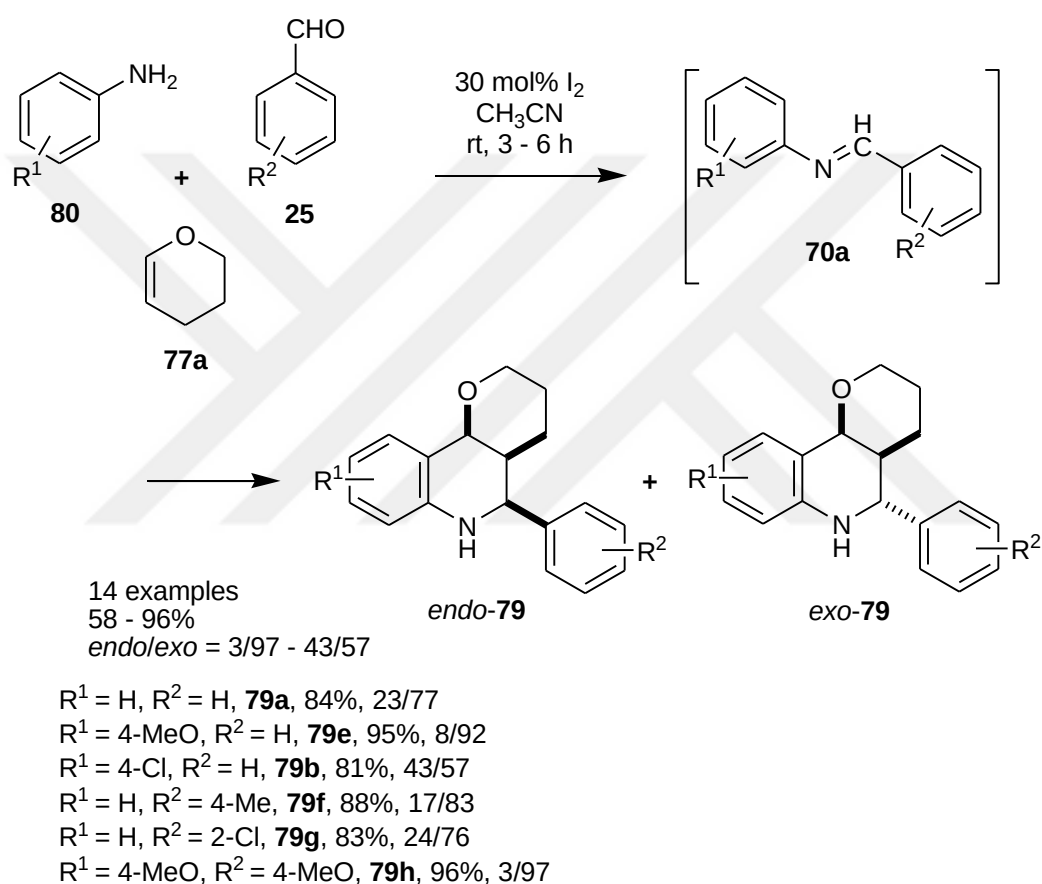
Scheme 28. The LiBF_4 -catalyzed intermolecular Povarov reaction^[62]

The intermolecular Povarov reaction has also been achieved using 10 mol% antimony trichloride (SbCl_3) as a mild, inexpensive and efficient catalyst (Scheme 29).^[63] Here, the authors didn't use a preformed imine, but performed a three component reaction. The sequence starts with the condensation of an aniline **80** with an aromatic aldehyde **25** to give the corresponding imine **70a** which in turn undergoes a Povarov reaction with dienophiles **76b**, **77a**. The SbCl_3 -catalyzed reaction between **70a** and 2,3-dihydrofuran (**76b**) or 2,3-dihhydropyran (**77a**) results in the formation of mixtures of the *endo*- and *exo*-isomers *endo*-**78,79** and *exo*-**78,79** with yields ranging between 72 and 92%. The *exo*-isomers were formed preferentially. Different solvents were employed and acetonitrile was found to give the best results in comparison with dichloromethane, diethylether, tetrahydrofuran, and toluene.^[63]



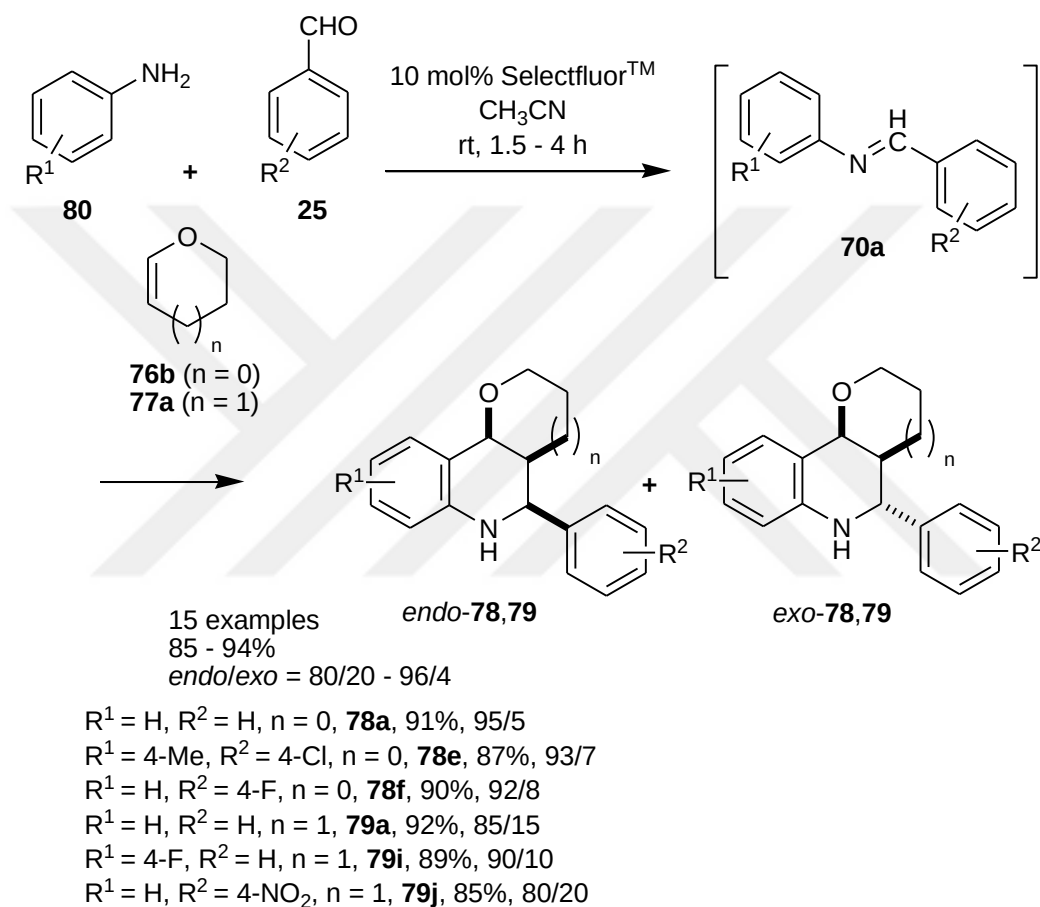
Scheme 29. Synthesis of furano- and pyranoquinolines **78,79** employing SbCl_3 as a catalyst^[63]

Molecular iodine is an inexpensive, readily available reagent with moderate Lewis acidity. It has been used as catalyst for the intermolecular Povarov imino-Diels-Alder reaction of aldehydes **25**, anilines **80**, and 2,3-dihydropyran (**77a**) by Xia et al. (Scheme 30).^[64] Acetonitrile was found to be the most suitable solvent to perform these reactions. The Povarov products, the pyranoquinolines **79**, were obtained as mixtures of the *endo*- and *exo*-isomers *endo*-**79** and *exo*-**79**. The substituents of the aldehydes **25** have no influence on the yield and on the diastereoselectivity. However, the use of anilines **80** with electron-donating substituents leads to an increase of the yields of the cyclization products.



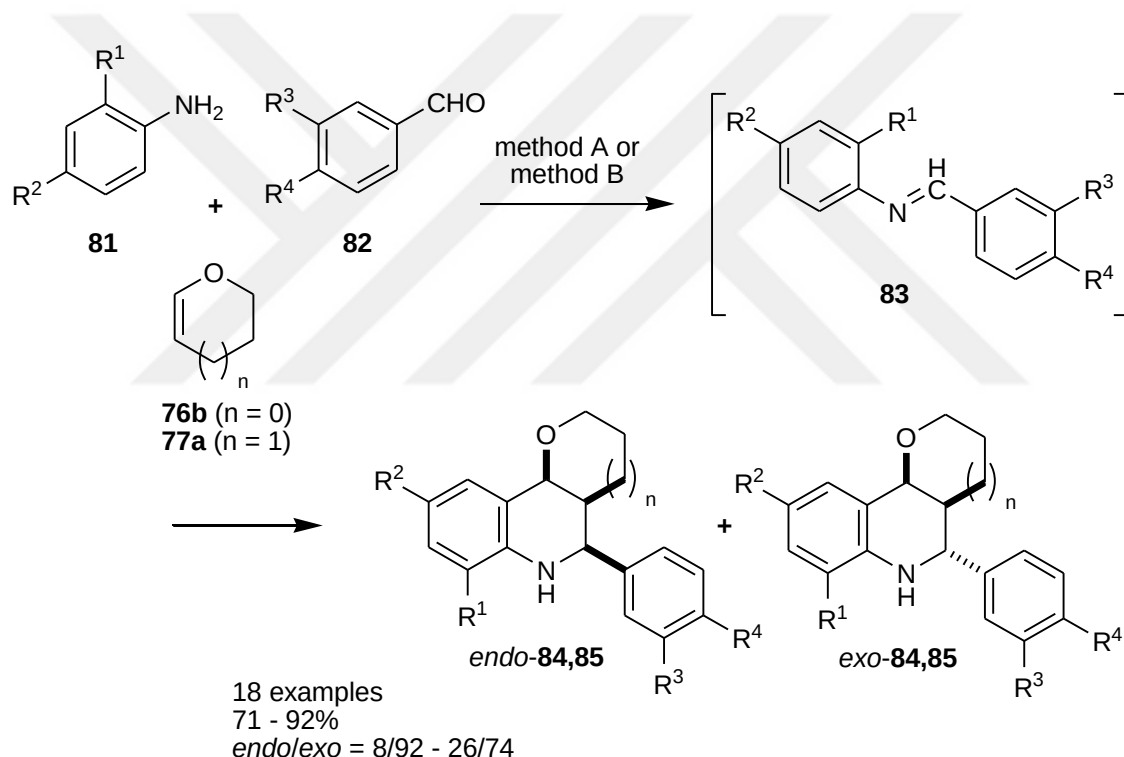
Scheme 30. Preparation of pyranoquinolines **79** utilizing molecular iodine as a catalyst^[64]

[4+2]-Cycloadditions between arylimines **70a** formed *in situ* from benzaldehydes **25** and anilines **80** and cyclic enol ethers **76b,77a** proceed smoothly in presence of the commercially available fluorinating agent selectfluorTM (Scheme 31).^[65] Acetonitrile was found to be the best solvent for this transformations. The products were obtained as mixtures of the *endo*- and *exo*-isomers *endo*-**78,79** and *exo*-**78,79** in favor of the *endo*-diastereomers *endo*-**78,79** with yields ranging from 85% to 94%. No details with regard to the function of SelectfluorTM have been reported.



Scheme 31. Three component Povarov reaction in the presence of SelectfluorTM^[65]

Solid acids such as clays and zeolites have also been employed as catalysts for the three component Povarov reaction. One study deals with the use of a Fe^{3+} -K-10 montmorillonite clay and a HY zeolite for the three component reaction between anilines **81**, aromatic aldehydes **82**, and cyclic enol ethers **76b,77a** for the synthesis of tetrahydroquinolines **84,85** (Scheme 32).^[66] The required products **84,85** have been obtained in high yields and with high deastereoselectivities in favor of the *endo*-products. The Fe^{3+} -K-10 montmorillonite clay catalyzed the reactions at room temperature while the HY-zeolite-catalyzed reactions had to be performed under reflux. The reaction times needed to complete the conversions were shorter when the Fe^{3+} -K-10 montmorillonite clay was used as the catalyst. It seems that the influence of the two different catalysts on yields and diastereoselectivities is not very pronounced.



method A: Fe^{3+} -K-10 clay, CH_3CN , rt, 3 - 4 h

method B: HY-zeolite, CH_2Cl_2 , reflux, 5 - 6 h

$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{H}$, $n = 0$, **84a**, 84% (method A), 18/82

$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{H}$, $n = 0$, **84b**, 79% (method B), 16/84

$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{H}$, $n = 0$, **84c**, 74% (method A), 24/76

$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{H}$, $n = 0$, **84d**, 71% (method B), 25/75

$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{H}$, $n = 1$, **85a**, 86% (method A), 16/84

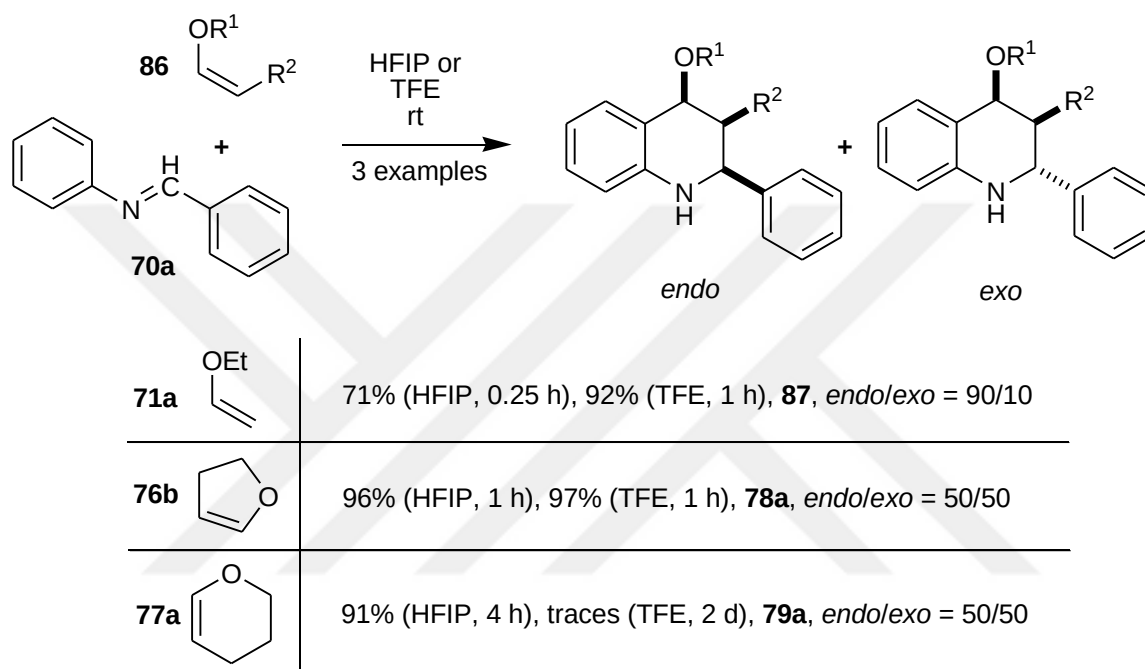
$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{H}$, $n = 1$, **85b**, 82% (method B), 13/87

$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{MeO}$, $n = 1$, **85c**, 90% (method A), 09/91

$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$, $\text{R}^4 = \text{MeO}$, $n = 1$, **85d**, 85% (method B), 12/88

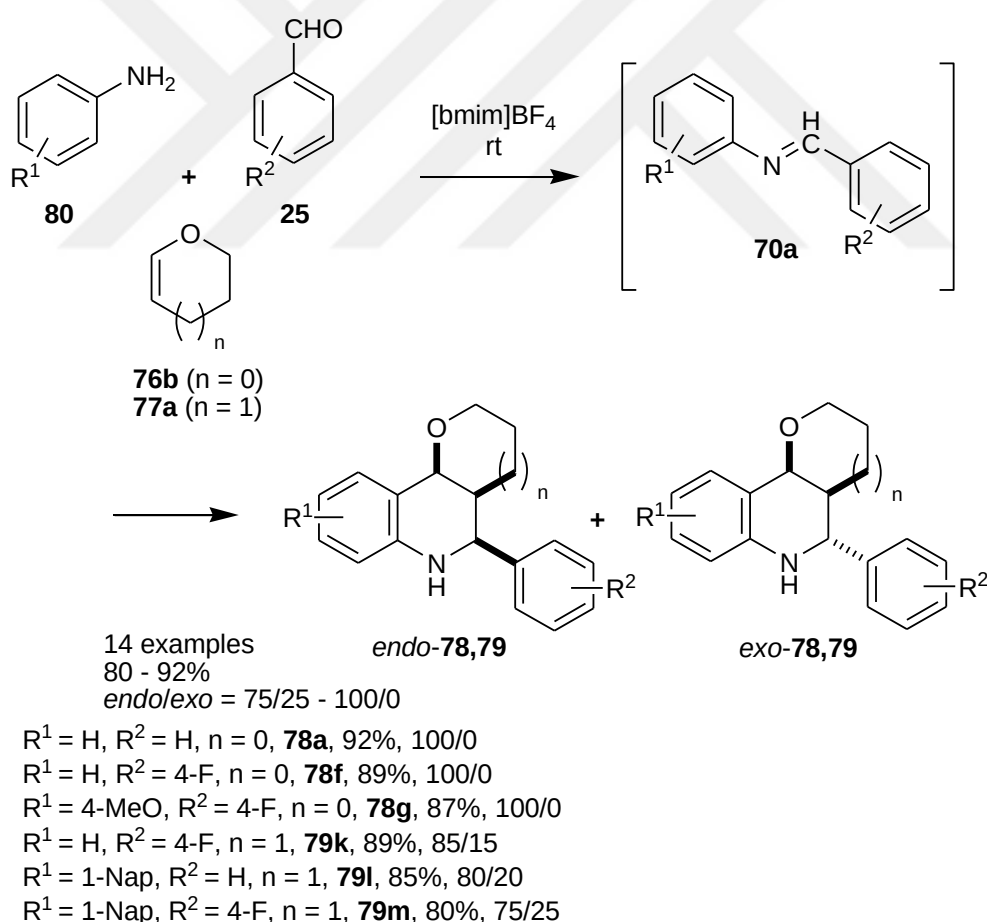
Scheme 32. Synthesis of furano- and pyranoquinolines **84,85** using clays and zeolites^[66]

Aza-Diels-Alder reactions of aldimine **70a** with dienophiles **86** have also been examined in fluoroalcohols, such as hexafluoroisopropanol (HFIP) and trifluoroethanol (TFE) in the absence of any catalyst (Scheme 33).^[67] The reaction of *N*-benzylidene aniline (**70a**) with ethyl vinyl ether (**71a**) in HFIP or TFE at room temperature delivers the tetrahydroquinoline (**87**) in very good yield as a 90:10-mixture of *endo*-**87** and *exo*-**87**. However, when the reactions were performed with **76b** and **77a**, the diastereoselectivity of the Povarov reaction was negligible.^[67]



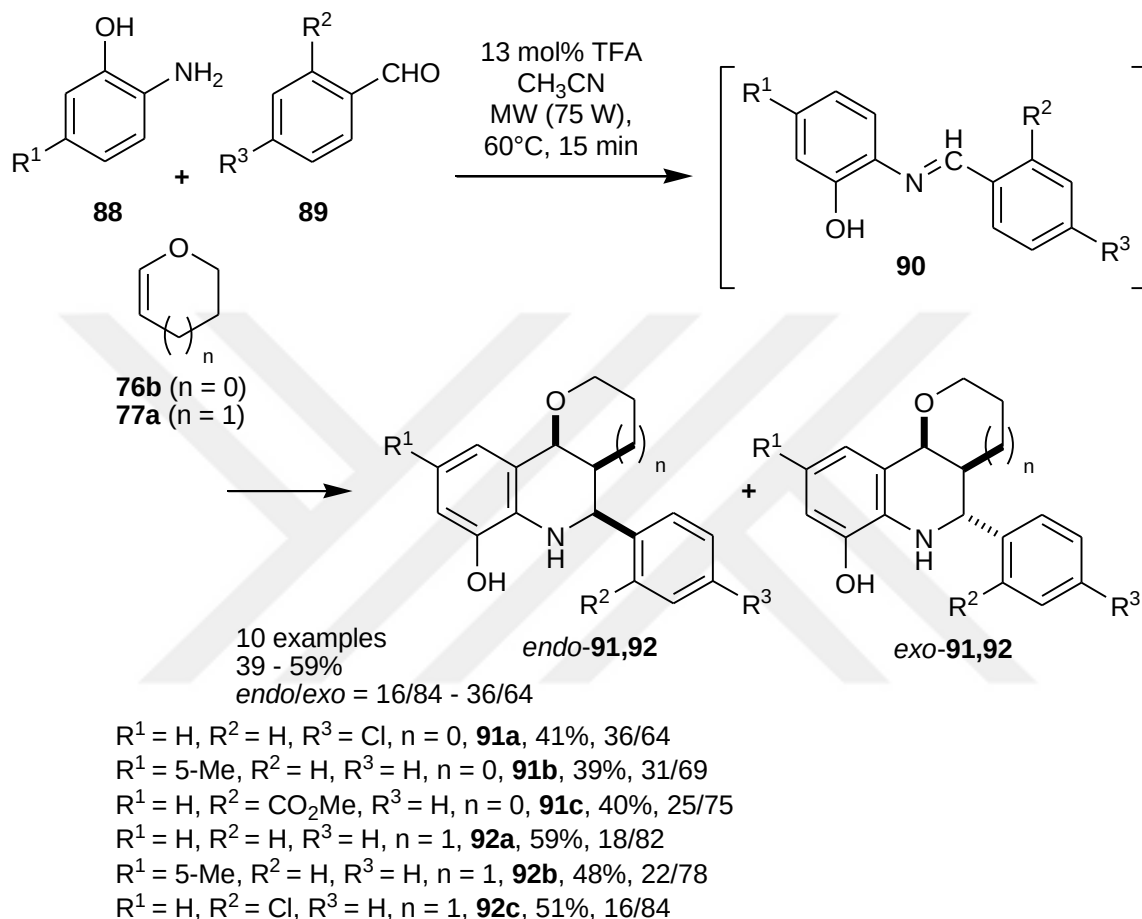
Scheme 33. Aza-Diels-Alder reaction in the presence of fluoroalcohols^[67]

Yadav et al. reported on the successful Povarov reaction between anilines, benzaldehydes, and cyclic enol ethers in the presence of [bmim]BF₄, which served not only as the solvent but also as the catalyst (Scheme 34).^[18] The reactions could be performed at room temperature and delivered the cycloadducts with remarkable high yields and impressing diastereoselectivities. Reaction of different aldimines **70a**, which were generated *in situ* from **80** and **25**, with 2,3-dihydrofuran (**76b**) resulted in the exclusive formation of the *endo*-products *endo*-**78**. In the reactions with 2,3-dihydropyran (**77a**) the *endo*-products *endo*-**79** were formed in excess over the *exo*-products *exo*-**79**. It should be mentioned that the products could easily be separated by simple extraction of the reaction products with diethyl ether, since the solubility of the cycloadducts in the ionic liquid was found to be quite poor. The use of *n*-tetrabutyl ammonium chloride and 1-*n*-butyl-3-methyl imidazolium chloride as ionic liquids for the Povarov reaction was also explored. However, with these ionic liquids no Povarov reaction could be observed.



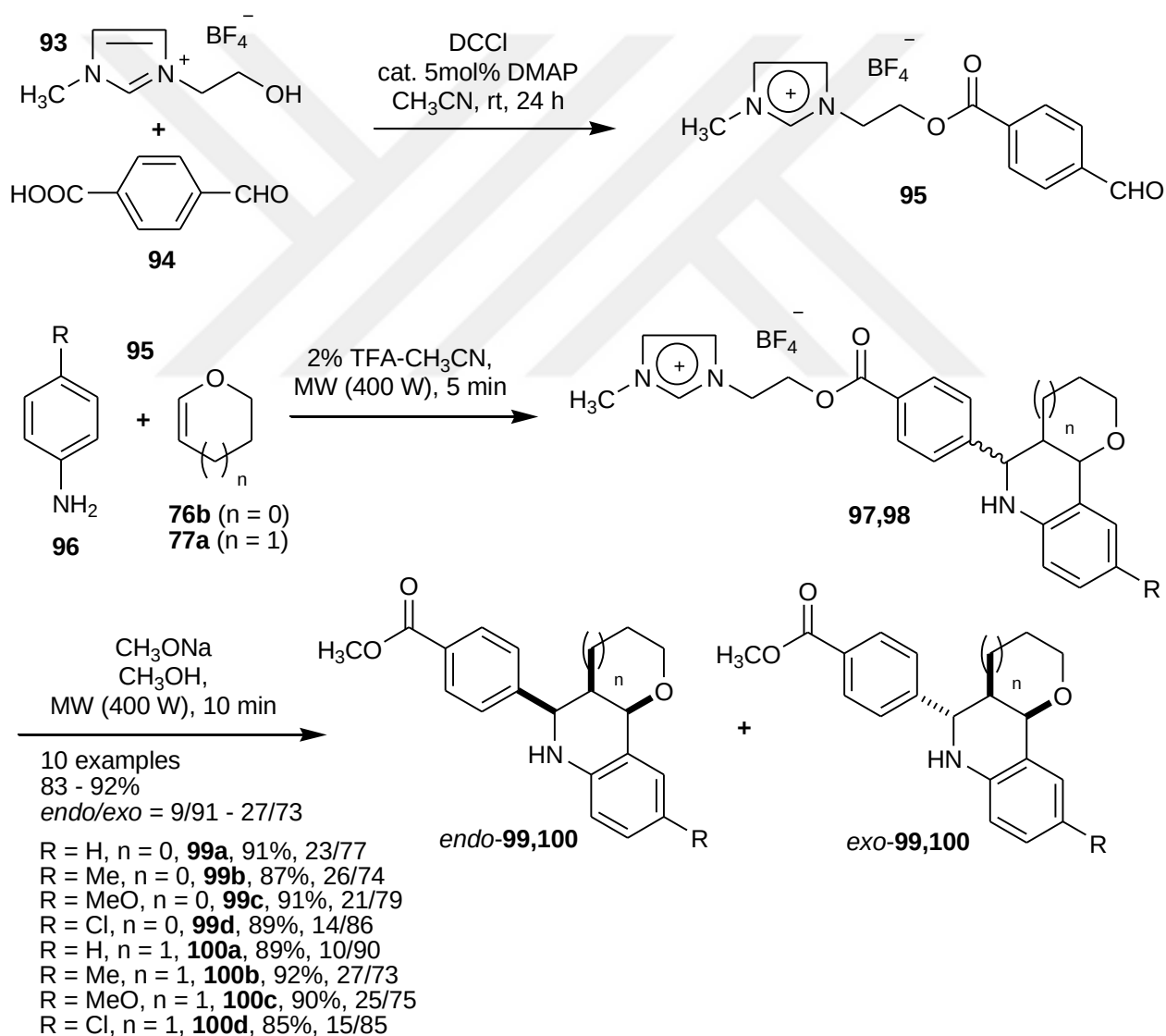
Scheme 34. Synthesis of furano- and pyranoquinolines **78,79** using [bmim]BF₄ as catalyst^[18]

The intermolecular Povarov reaction has also been performed under microwave conditions (Scheme 35).^[68] Reaction between 2-aminophenols **88**, benzaldehydes **89**, and cyclic enol ethers **76b,77a** in the presence of 13 mol% CF₃CO₂H (TFA) in CH₃CN delivered the cycloadducts **91** and **92** after only 15 min irradiation with microwaves (75 W) at 60°C. The *exo*-isomers *exo*-**91,92** were formed in excess over the *endo*-isomers *endo*-**91,92**.



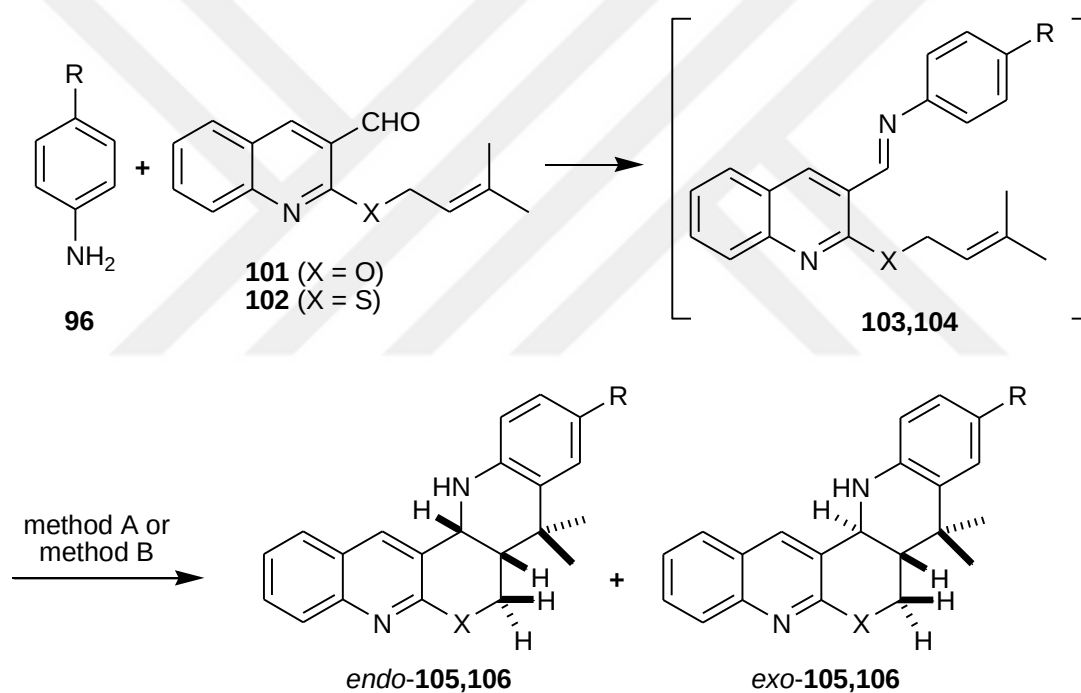
Scheme 35. TFA-catalyzed three component Povarov reaction under microwave conditions^[68]

The scope of the Povarov reaction in ionic liquids has been extended by employing an ionic liquid bound to an aromatic aldehyde (Scheme 36).^[69] The functionalized ionic liquid **95** was prepared by reaction between 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([2-hydemim][BF₄]) (**93**) and 4-formylbenzoic acid (**94**) in the presence of dicyclohexylcarbodiimide (DCCl) and dimethylamino pyridine (DMAP) as a catalyst. The ionic liquid bound aromatic aldehyde **95** was then reacted with aniline **96** and 2,3-dihydrofuran (**76b**) or 2,3-dihydropyran (**77a**) under microwave conditions (400 W) in CH₃CN for 5 min to furnish the heterocycles **97,98**. After cleaving the ionic liquid by treatment of **97,98** under basic conditions the heterocycles **99** and **100** were obtained in favor of the *exo*-isomers *exo*-**99,100** with high yields.



Scheme 36. Ionic liquid-catalyzed synthesis of tetrahydroquinolines **99,100** under microwave conditions^[69]

In addition to the intermolecular Povarov reaction, the intramolecular version of this important transformation has also been studied in detail.^[70] In Scheme 37, a typical example is illustrated. Reaction between anilines **96** and *O*-alkenyl aldehyde (**101**) or *S*-alkenyl aldehyde (**102**) in the presence of 20 mol% InCl₃ in CH₃CN at room temperature (method A) lead to the initial formation of Schiff base **103,104** which underwent an intramolecular [4+2]-cycloaddition (Povarov reaction) to deliver the corresponding pyranoquinolines **105** or thiopyranoquinolines **106** in good yields. When the reaction was performed with InCl₃ impregnated silica gel as the catalyst in the absence of any solvent under microwave conditions (method B) the yields of the cycloadducts increased considerably. However, switching from method A to method B had only little impact on the diastereoselectivity of the cyclization in all cases, the *endo*-isomers were preferentially formed.



12 examples

method A 55 - 87%, *endo/exo* = 65/35 - 83/27

method B 75 - 97%, *endo/exo* = 68/32 - 84/26

method A: 20 mol% InCl₃, CH₃CN, rt, 1 - 3.5 h

method B: 20 mol% silical gel impregnated InCl₃, MW, 1 - 3 min

R = H, X = O, **105a**, 71%, 67/33 (method A)

R = H, X = O, **105b**, 89%, 68/32 (method B)

R = Me, X = O, **105c**, 73%, 70/30 (method A)

R = Me, X = O, **105d**, 93%, 73/27 (method B)

R = H, X = S, **106a**, 73%, 65/35 (method A)

R = H, X = S, **106b**, 92%, 69/31 (method B)

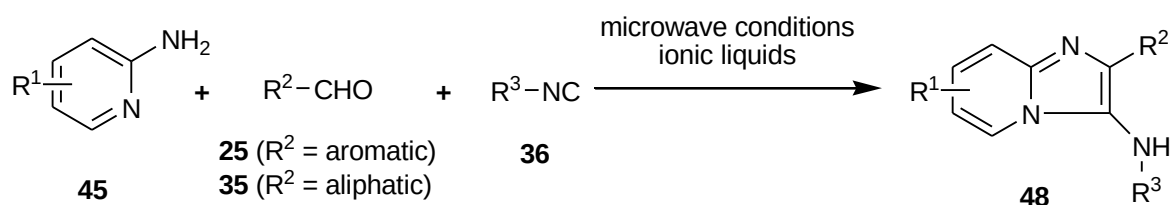
R = Me, X = S, **106c**, 77%, 70/30 (method A)

R = Me, X = S, **106d**, 95%, 74/26 (method B)

Scheme 37. Intramolecular aza-Diels-Alder reaction to generate pyranoquinolines **105** and thiopyranoquinolines **106**^[70]

6. Aim of the study

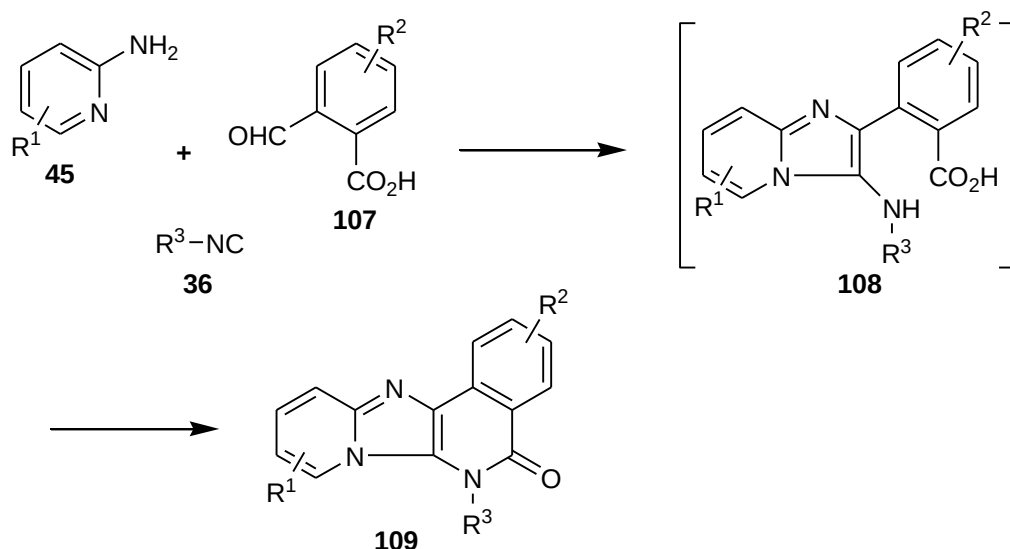
The aim of this work was to evaluate the influence of both microwave irradiation and ionic liquids on several multi component reactions. Of particular interest was to study a) whether guanidinium salts can be employed as solvents and/or catalysts in Groebke and Povarov reactions, and b) the simultaneous influence of microwave irradiation and guanidinium salts on the outcome of these reactions.



Scheme 38. Synthesis of imidazo[1,2-*a*]pyridines **48** under microwave conditions in the presence of ionic liquids

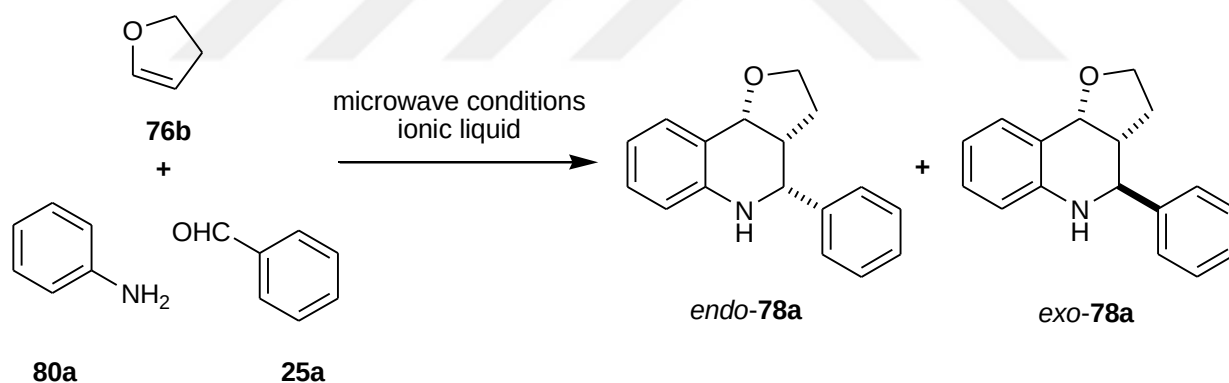
The Groebke reaction between 2-aminopyridines **45**, aldehydes **25,35**, and isocyanides **36** yields imidazo[1,2-*a*]pyridines **48**.^[44] Due to their wide range of biological properties these heterocyclic systems are of great interest in medicinal chemistry. The aim of the first part of this thesis was to develop a simple, rapid and efficient method for the synthesis of 3-amino substituted imidazo[1,2-*a*]pyridines **48** via Groebke reaction under microwave conditions in the presence of ionic liquids (Scheme 38).

The aim of the second part of the thesis was to find out whether the scope of the Groebke reaction can be expanded by using bifunctional substrates like 2-carboxybenzaldehydes **107** as the aldehyde component (Scheme 39).



Scheme 39. Extending the scope of the Groebke reaction

It was envisaged that the nucleophilicity of the amino group in the 3-position of the imidazole moiety in **108** is sufficient to undergo lactam formation with the carboxyl group of the aryl moiety to yield the corresponding pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones **109** (Scheme 39).

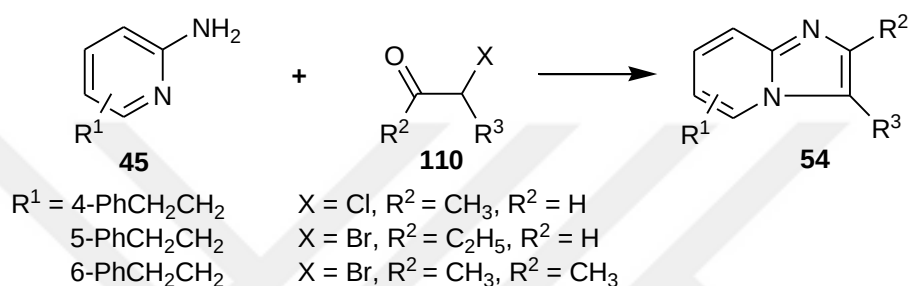


Scheme 40. Povarov reaction under microwave conditions using an ionic liquid as the solvent and/or the catalyst

The third part of this thesis is devoted to the development of a Povarov reaction under microwave conditions using an ionic liquid as the solvent and/or the catalyst (Scheme 40).

7. Synthesis of annulated imidazo[1,2-*a*]pyridines

In recent years, imidazo[1,2-*a*]pyridines have been attracting great interest since they show a wide spectrum of biological activities such as antibacterial, antiviral, antifungal, and anti-inflammatory properties.^[47] In the literature, a number of methods, which are based on two and three component reactions, have been reported for the synthesis of these types of compounds. The classical two component approach to imidazo[1,2-*a*]pyridines **54** is the condensation of α -halo carbonyl compounds **110** with 2-aminopyridines **45** (Scheme 41).^[47c,47e,71]

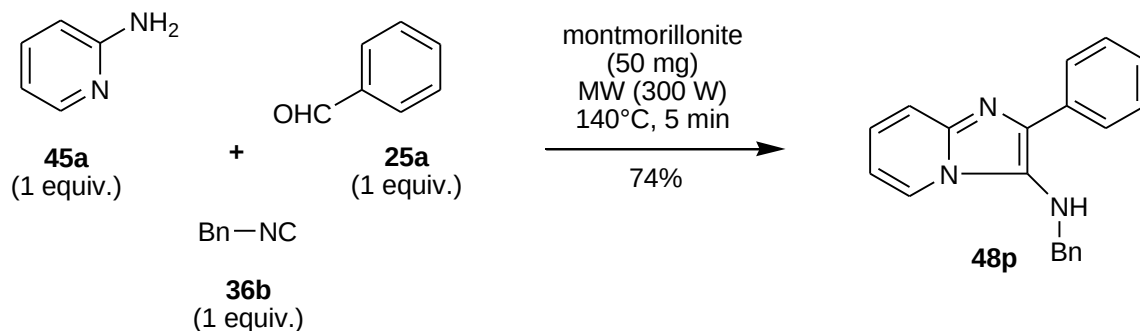


Scheme 41. Synthesis of imidazo[1,2-*a*]pyridines **54** via two component approach^[71b]

However, this method is less suitable for the synthesis of large compound libraries. As already discussed, the most well known three component approach to imidazo[1,2-*a*]pyridines is based on the Groebke reaction between 2-aminopyridines **45**, aldehydes **25,35**, and isocyanides **36** using a Lewis acid or a Brønsted acid as the catalyst. However, most of these methods suffer from several drawbacks, such as long reaction times and/or the application of expensive catalysts. Therefore, our purpose was to develop a simple, rapid and efficient variant of the Groebke reaction for the synthesis of 3-amino substituted imidazo[1,2-*a*]pyridines **48**. Some preliminary experiments revealed that Groebke reactions under microwave conditions can be performed successfully when montmorillonite is used as the catalyst.

On the basis of these preliminary results and the work from Varma's group^[50] the preparation of 3-amino substituted imidazo[1,2-*a*]pyridines **48** under microwave conditions using montmorillonite as a catalyst and imidazolium as well as guanidinium salts as an ionic liquid was studied. The condensation between 2-aminopyridine (**45a**), benzaldehyde (**25a**), and benzylisocyanide (**36b**) was chosen as a model reaction. First, the reaction with montmorillonite as the catalyst was performed under microwave conditions at 140°C in the

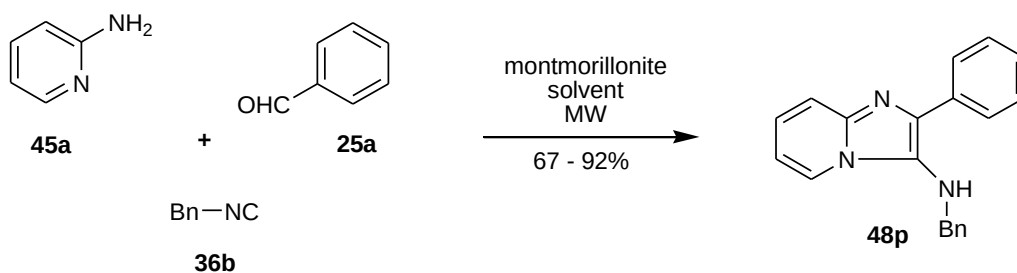
absence of any solvent. The corresponding product **48p** could be isolated in 74% yield (Scheme 42).



Scheme 42. Microwave-assisted synthesis of **48p** in the absence of any solvent

In order to increase the yield, the microwave-assisted model reaction was run under different reaction conditions (Table 1). The yield of **48p** could be improved considerably when the transformation was performed in organic solvents. Optimization with regard to the ratio of the substrates **45a**, **25a**, and **36b**, the reaction time, and the reaction temperature revealed that the highest yield of **48p** could be observed when 1 equiv. **45a**, 1.09 equiv. **25a**, and 1.25 equiv. **36b** were reacted in toluene at 160°C under microwave conditions (Table 1, entry 7). Under these conditions, **48p** could be isolated with 92%. Under thermal conditions (sealed vial, oil bath) the yield of **48p** amounted to only 75%.

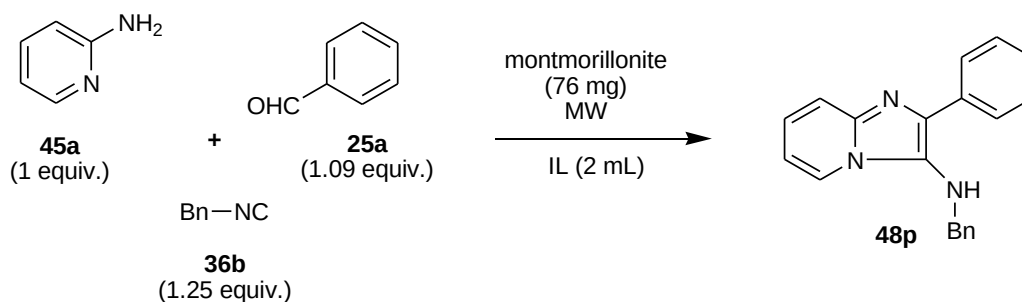
Table 1. Reaction between **45a**, **25a**, and **36b** under different reaction conditions



Entry	45a [equiv.]	25a [equiv.]	36b [equiv.]	t [min]	T [°C]	Solvent [2 mL]	Clay [mg]	Yield [%]
1	1	1.02	1.01	5	140	o- dichlorobenzene	59	71
2	1	1	1.25	7	140	methanol	79	67
3	1.3	1	1.30	5	140	toluene	66	68
4	1	1.04	1.22	7	140	toluene	76	79
5	1	1.07	1.20	5	140	toluene	76	84
6	1	1.09	1.25	7	140	toluene	76	89
7	1	1.09	1.25	7	160	toluene	76	92

Next, the influence of different ionic liquids on the outcome of the microwave-assisted synthesis of 3-amino substituted imidazo[1,2-*a*]pyridines **48** was studied. In a first set of experiments, the model reaction with montmorillonite as the catalyst was run in the presence of different imidazolium salts (Table 2).

Table 2. The use of imidazolium salts as reaction medium for the synthesis of **48p** under microwave conditions

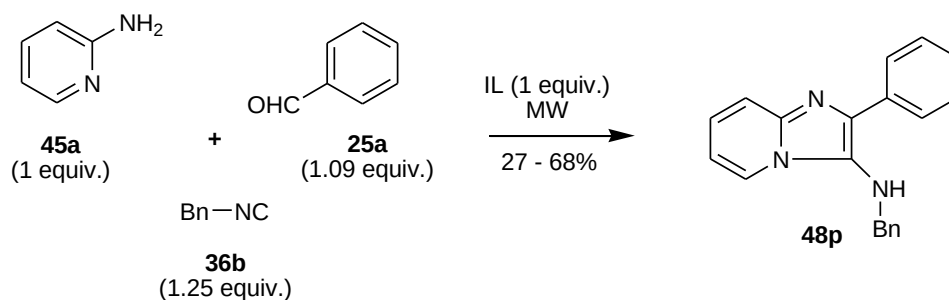


Entry	IL	P [W]	t [min]	T [°C]	Yield [%]
1	[bmim]Cl	10	30	90	66 ^a
2	[bmim]Br	10	30	90	39 ^a
3	[bmim]Br	30	10	160	decomposition
4	[bmim]BF ₄	10	30	90	70
5	[bmim]MeSO ₄	20	7	140	decomposition
6	[bmim]PF ₆	20	7	140	39 ^a

^a The formation of **48p** was accompanied by formation of an unknown by-product

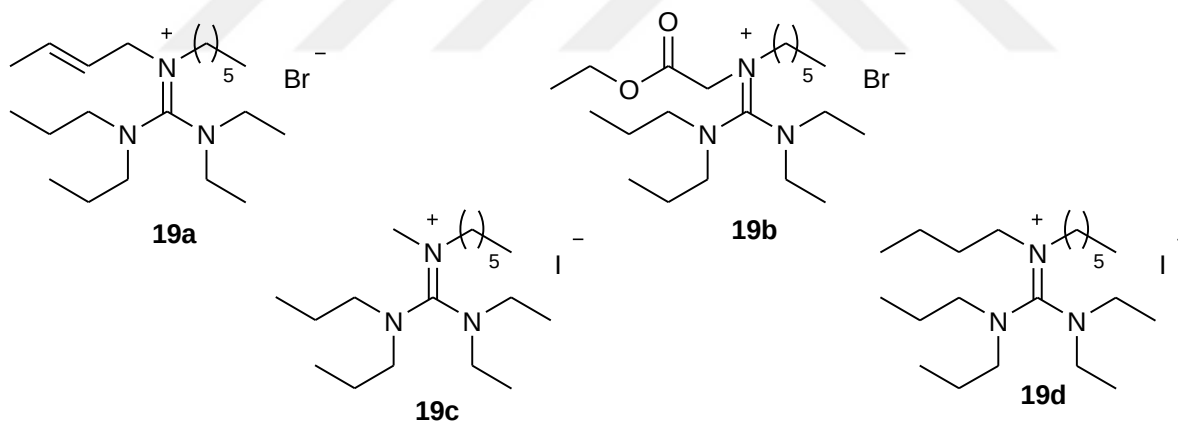
We found that with [bmim]MeSO₄ and [bmim]Br at higher reaction temperatures (140°C and 160°C) only decomposition took place (Table 2, entries 3, 5). When the reaction was run with [bmim]Br or [bmim]Cl at 90°C, the formation of **48p** took place, but it was accompanied by the occurrence of an unknown byproduct (Table 2, entries 1, 2). However, when the transformation was performed in [bmim]BF₄ at 90°C, **48p** was formed exclusively with 70% (Table 2, entry 4). From the results presented in Table 2 it was clear that the yield of **48p** could not be improved by employing imidazolium salts as solvents.

The model reaction, **45a** + **25a** + **36b** → **48p**, could also be performed in the presence of guanidinium salts **19i-l** (Table 3, Figure 6). However, **48p** was isolated with only 43% yield when the microwave-assisted reaction between **45a**, **25a**, and **36b** was run in guanidinium salt **19c** in the presence of montmorillonite as the catalyst (Table 3, entry 5). More interesting, the formation of **48p** could also be accomplished in the absence of montmorillonite. It was found that **48p** was formed with yields ranging from 27 to 68% in the presence of the guanidinium salts **19a-d** (Table 3, entries 1-3, 6, Figure 6). Obviously, the yield of **48p** depends on the structure of the guanidinium salt. When **19b** was employed as the ionic liquid, **48p** could be isolated in 68% yield (Table 3, entry 2). Even if the yield of **48p** could not be improved by employing guanidinium salts, it was clear that in the transformations presented in Table 3 the guanidinium salts **19a-d** act both as a solvent and as a catalyst.

Table 3. The use of guanidinium salts **19** for the synthesis of **48p**

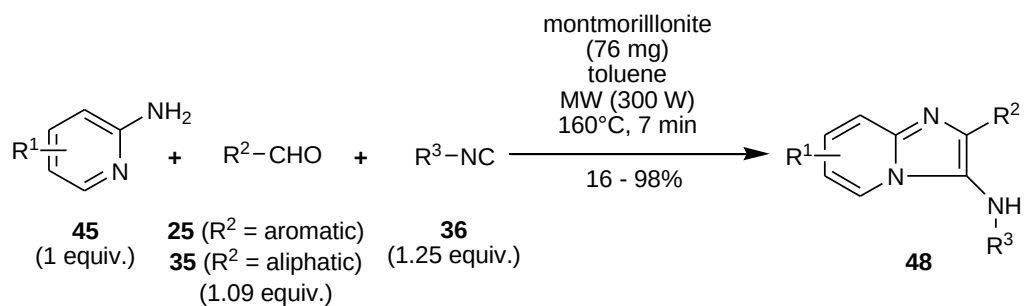
Entry	IL	Montmorillonite	Power [W]	t [min]	T [°C]	Yield [%]
1	19a	-	10	90	90	40
2	19b	-	10	90	90	68
3	19c	-	10	90	90	29
4	19c	-	20	7	160	48 ²
5	19c ¹	76 mg	10	30	90	43
6	19d	-	10	90	90	27

¹ The reaction was performed in 2 mL of **19c**. ² In addition, a side product of unknown structure was observed.

**Figure 6.** Structures of guanidinium salts **19**

To summarize, the highest yield of **48p** was obtained when the microwave-assisted reaction between **45a**, **25a**, and **36b** was performed in toluene using montmorillonite as the catalyst (Table 1, entry 7). With the optimized conditions in hand, the scope of the method was evaluated by reacting the 2-aminopyridines **45** with the aldehydes **25,35** and the isocyanides **36** (Table 4, Figure 7). It was found that in all cases the corresponding imidazo[1,2-*a*]pyridines **48** were obtained exclusively. The yields of the Groebke products were in the range between 16 and 98%.

Table 4. Synthesis of imidazo[1,2-*a*]pyridines **48** from different 2-aminopyridines **45**, aldehydes **25,35**, and isocyanides **36**



Entry	45	R^1	25,35	R^2	36	R^3	48	Yield [%]
1	a	H	25a		b		p	92
2	a	H	25b		b		zf	70
3	a	H	25c		b		zg	80
4	a	H	25d		b		zh	77
5	a	H	25e		b		zi	60
6	a	H	35b		b		zj	53
7	a	H	25a		c		zk	94
8	b	5-Br	25a		b		zl	72
9	b	5-Br	35c		b		zm	16
10	a	H	25b		a		zd	98

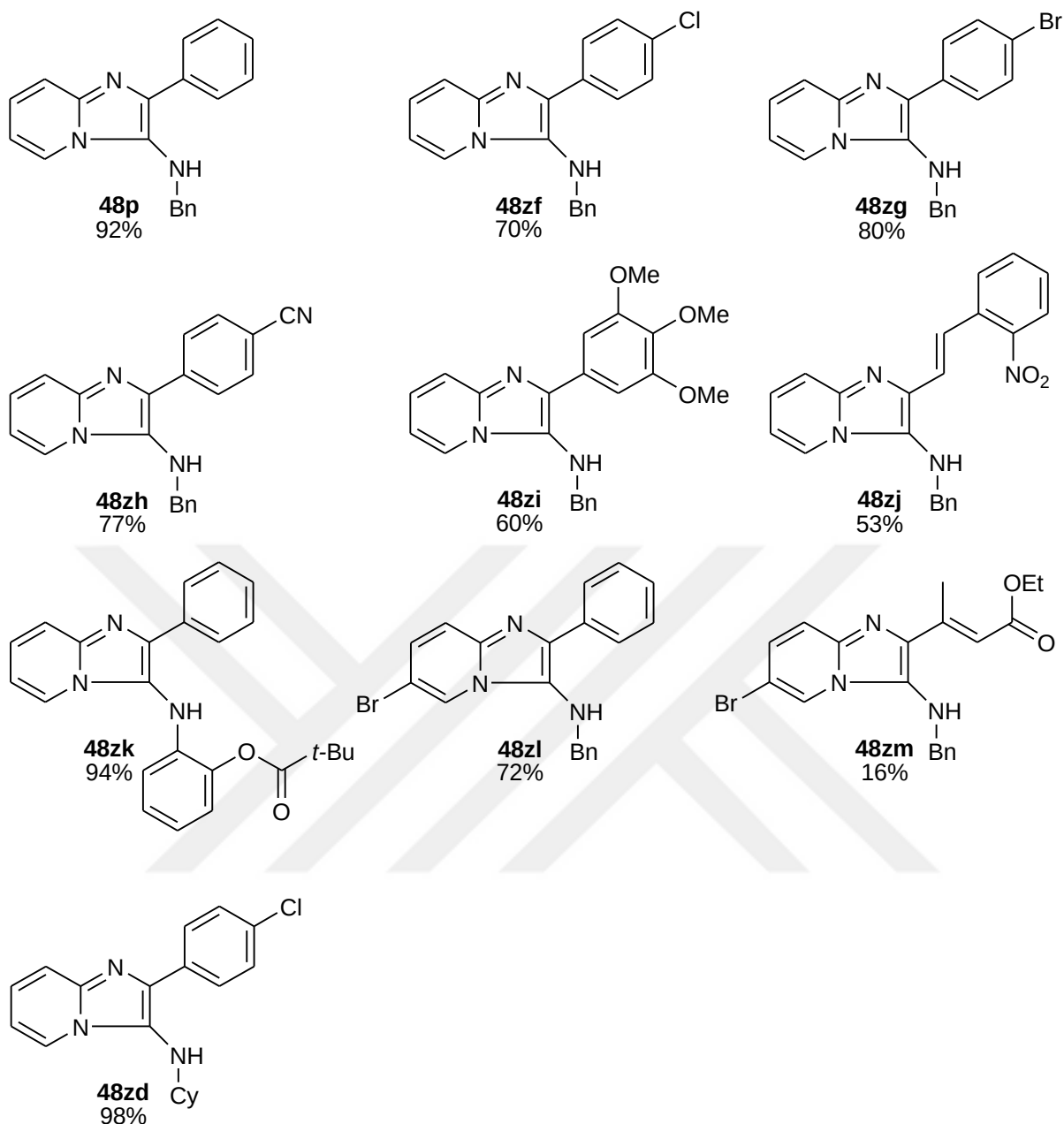
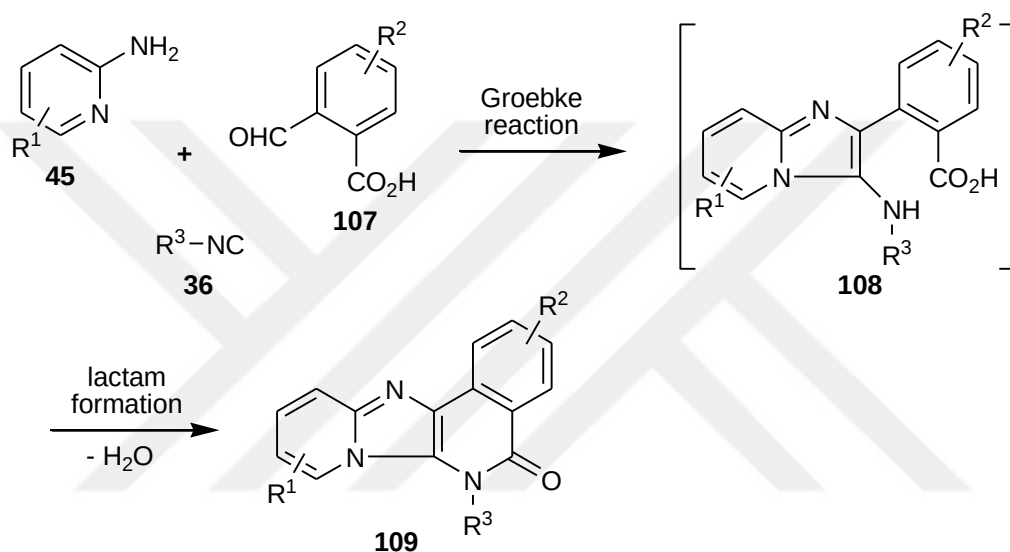


Figure 7. Structures of imidazo[1,2-*a*]pyridines **48**

The structures of all the imidazo[1,2-*a*]pyridines **48** described here have been elucidated by ^1H , ^{13}C , COSY, HSQC, HMBC as well as by mass spectrometric analysis. By means of long-range correlations in the HMBC spectra the quaternary carbons have been identified unambiguously.

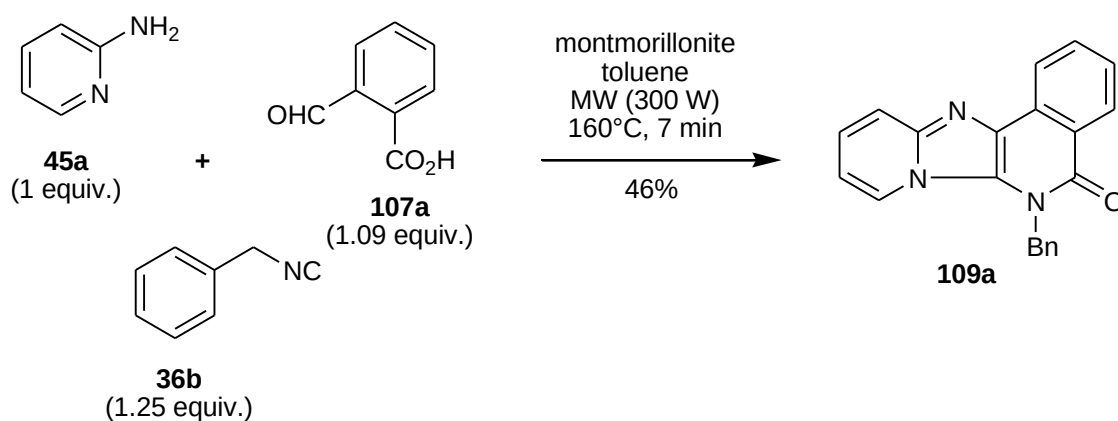
8. Beyond the scope of the classical Groebke reaction: Synthesis of pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-ones in one step

The second part of this thesis is focused on the extension of the scope of the classical Groebke reaction by employing 2-carboxybenzaldehydes **107** as the aldehyde component (Scheme 43). It was speculated that the preliminary product of the Groebke reaction between a 2-aminopyridine **45**, an isocyanide **36**, and a 2-carboxybenzaldehyde **107**, i.e. the imidazo[1,2-*a*]pyridine **108**, could undergo a lactamization under reaction conditions to deliver the corresponding pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-one skeleton **109**.



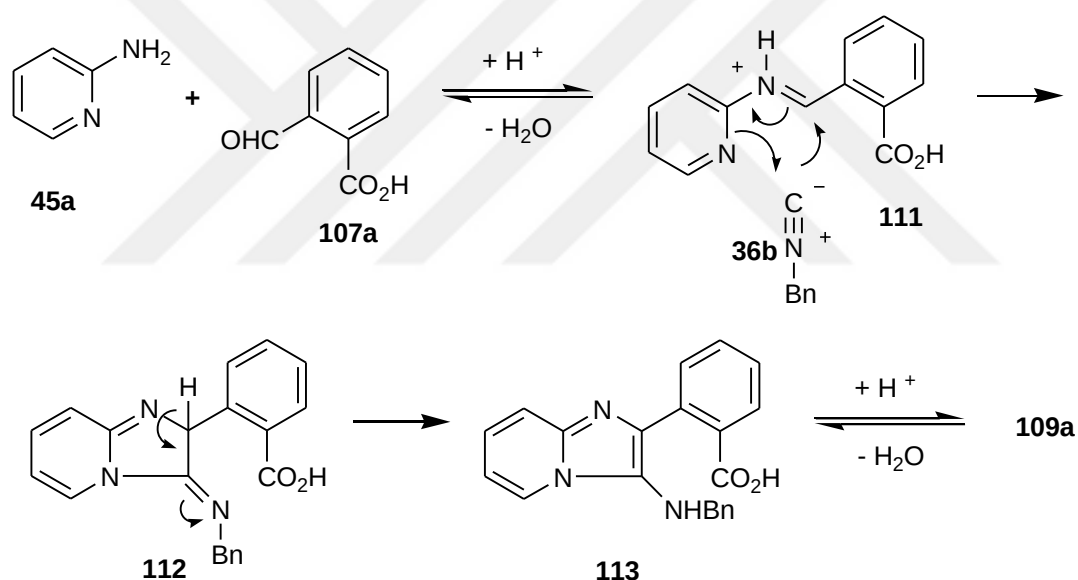
Scheme 43. Synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones **109** in one synthetic step through domino Groebke reaction/lactamization

To check the feasibility of this approach, the reaction between 2-aminopyridine (**45a**), benzylisocyanide (**36b**), and 2-carboxybenzaldehyde (**107a**) was performed under the conditions that had proven successful for the formation of the imidazo[1,2-*a*]pyridines **48** (Scheme 44). When 1 equiv. **45a**, 1.09 equiv. **107a**, and 1.25 equiv. **36b** were reacted with montmorillonite as the catalyst in toluene as the solvent for 7 min under microwave conditions, the expected lactam **109a** was formed exclusively in 46% yield.



Scheme 44. Microwave-assisted synthesis of pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-one **109a**

It should be emphasized that in this transformation four new bonds and two new heterocyclic rings are formed in one synthetic step.



Scheme 45. Proposed mechanism for the formation of pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-ones **109**

A possible reaction mechanism for this three component reaction is shown in Scheme 45. The reaction starts with the initial formation of the protonated Schiff base **111** by condensation of 2-aminopyridine (**45a**) with 2-carboxybenzaldehyde (**107a**). A non-concerted [4+1]-cycloaddition between the protonated Schiff base **111** and the benzyliocyanide (**36b**) results in the formation of intermediate **112**, which after H-shift delivers the product of the classical Groebke reaction, the assumed intermediate **113**. The final step of the reaction sequence is the formation of pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-one **109a** by intramolecular

reaction between the amino nitrogen attached to the imidazole ring and the carboxy group of the aryl moiety. The lactam formation is accompanied by release of H₂O.

Using the reaction of 2-carboxybenzaldehyde (**107a**) with 2-amino-5-bromopyridine (**45b**), and benzylnisocyanide (**36b**) as an example, the reaction conditions were optimized. During the optimization process, it was established that not only montmorillonite, but also several Brønsted acids, such as 4-toluenesulfonic acid, methanesulfonic acid, and trifluoromethanesulfonic acid, can be employed as catalysts for this type of reaction (Table 5). The highest yield of **109b** could be achieved in the presence of 0.2 equiv. methanesulfonic acid as a catalyst when 1 equiv. **45b** was reacted with 2.25 equiv. **36b** and 1.09 equiv. **107a** (Table 5, entry 7).

Table 5. Optimizing the reaction conditions for the reaction of **45b** with **36b** and **107a**

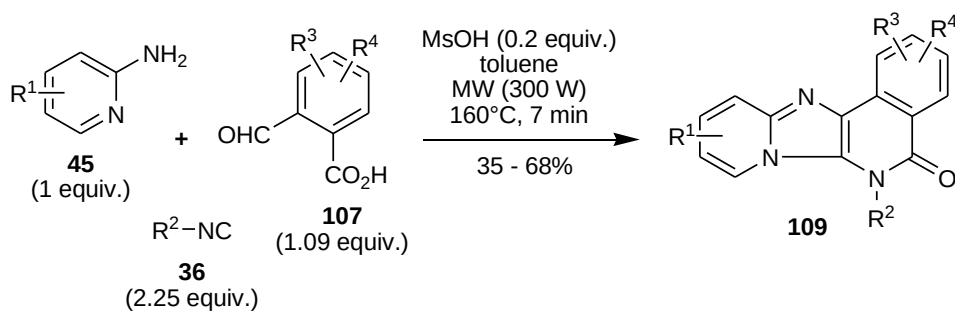
Reaction scheme showing the synthesis of **109b** from **45b**, **36b**, and **107a**. Reagents: toluene, MW (300 W), 160°C, 7 min. Yield: 29 - 66%.

Entry	45b [equiv.]	36b [equiv.]	107a [equiv.]	Reagent	equiv.	Yield [%]
1	1	1.25	1.09	clay	76 mg	29
2	1	1.25	1.09	TsOH	0.1	46
3	1	1.25	1.09	TfOH	0.1	42
4	1	1.25	1.09	MeSO ₃ H	0.1	52
5	1	1.25	1.09	MeSO ₃ H	0.2	54
6	1	1.25	1.09	MeSO ₃ H	0.7	52
7	1	2.25	1.09	MeSO ₃ H	0.2	66

In order to find out whether this new multicomponent reaction is suitable for the library synthesis of the pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones **109**, the reaction was

performed with different substituted 2-aminopyridines **45**, isocyanides **36**, and 2-carboxybenzaldehydes **107** under the optimized conditions (Table 6).

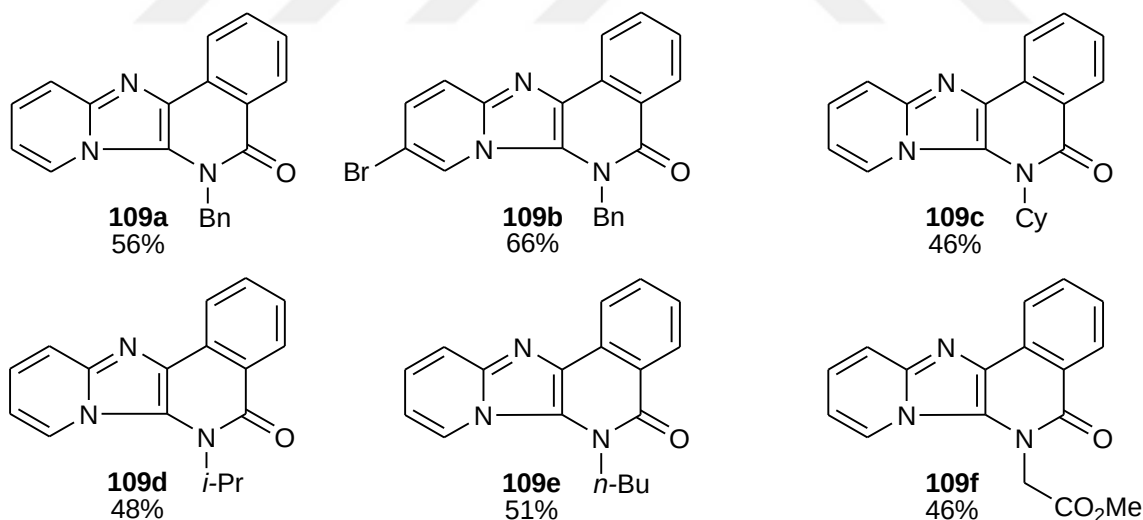
Table 6. Synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones **109** by reaction of different 2-aminopyridines **45**, isocyanides **36**, and 2-carboxybenzaldehydes **107**



Entry	45	R ¹	36	R ²	107	R ³	R ⁴	109	Yield [%]
1	a	H	b	Bn	a	H	H	a	56
2	b	5-Br	b	Bn	a	H	H	b	66
3	a	H	a	Cy	a	H	H	c	46
4	a	H	c	<i>i</i> -Pr	a	H	H	d	48
5	a	H	d	Bu	a	H	H	e	51
6	a	H	e	CH ₂ CO ₂ Me	a	H	H	f	46
7	c	5-Cl	b	Bn	a	H	H	g	64
8	d	3-Me	b	Bn	a	H	H	h	53
9	e	5-Me	b	Bn	a	H	H	i	60
10	f	4-Et	b	Bn	a	H	H	j	50
11	a	H	b	Bn	b	3-OMe	4-OMe	k	35
12	b	5-Br	b	Bn	b	3-OMe	4-OMe	l	43
13	c	5-Cl	b	Bn	b	3-OMe	4-OMe	m	42
14	d	3-Me	b	Bn	b	3-OMe	4-OMe	n	68

15	e	5-Me	b	Bn	b	3-OMe	4-OMe	o	38
16	g	3-OBn	b	Bn	b	3-OMe	4-OMe	p	50

To our delight, the reaction of 2-aminopyridine (**45a**) with 2-carboxybenzaldehyde (**107a**) and different isocyanides **36a-e** delivered the corresponding pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-ones **109a,c-f** with yields ranging from 46 to 56% (Figure 8, Table 6, entries 1, 3-6). In addition, various substituted 2-aminopyridines **45b-f** were successfully reacted with benzylisocyanide (**36b**) and 2-carboxybenzaldehyde (**107a**) to result in the corresponding tetracycles **109b,g-j** in yields between 50 and 66% (Figure 8, Table 6, entries 2, 7-10). Moreover, 2-carboxy-3,4-dimethoxybenzaldehyde (**107b**) was treated with benzylisocyanide (**36b**) and a variety of 2-aminopyridines **45a-e,g**. The expected heterocycles **109k-p** could be isolated with yields ranging from 35 to 68% (Figure 8, Table 6, entries 11-16). It should be noted that a similar approach to pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-ones **109** was published before submission of the results presented here.^[72]



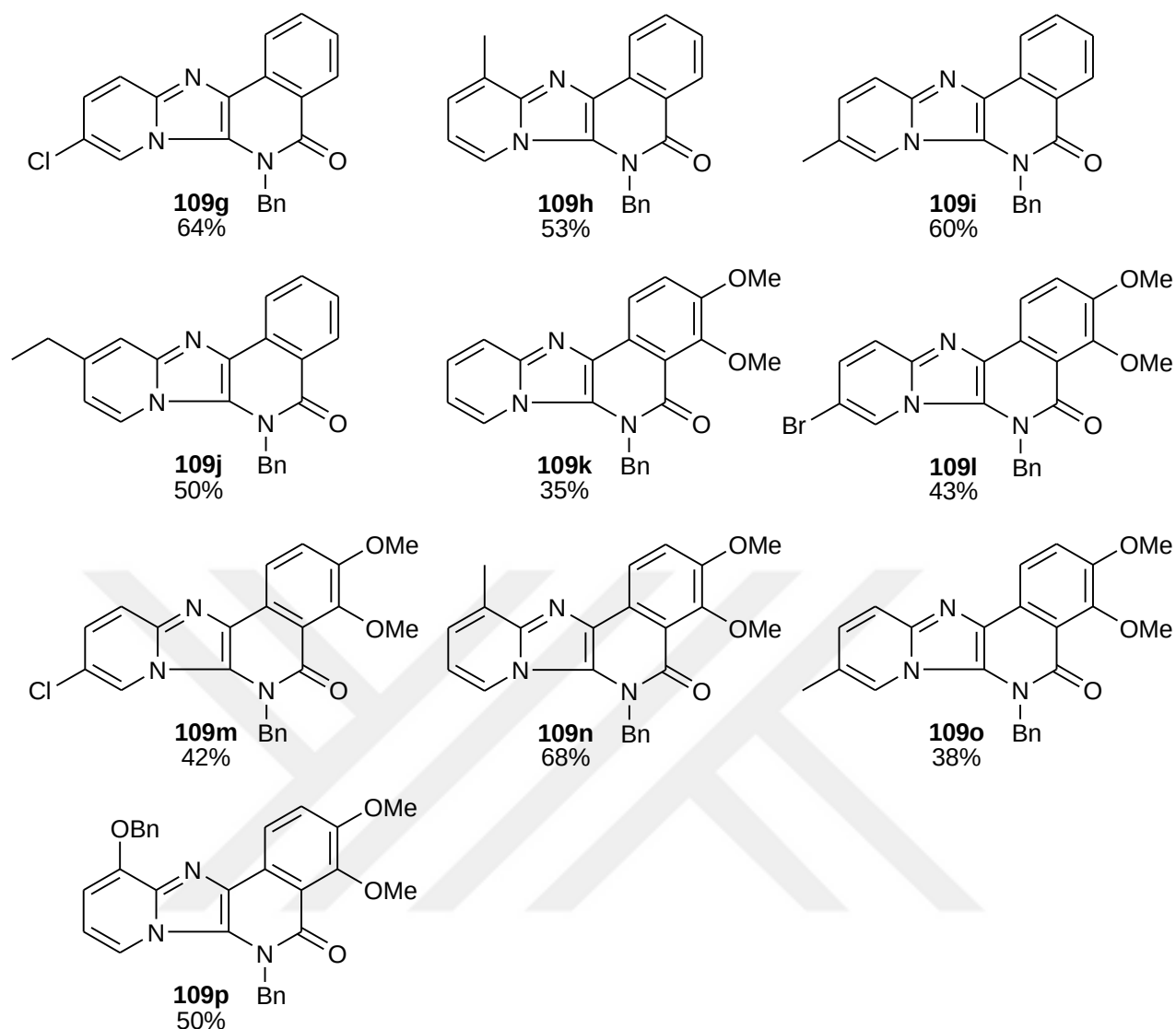


Figure 8. Structures of pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-ones **109a-p**

The structures of all pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-ones **109** prepared in this study have been evaluated by means of mass spectrometry as well as ^1H , ^{13}C , COSY, HSQC, HMBC and INADEQUATE spectroscopic methods. With the help of the long-range correlations in the HMBC spectra and the ^{13}C - ^{13}C correlations in the INADEQUATE spectrum, the signals of the quaternary carbons C-6a, C-11a, and C-11b could be definitely assigned. Important ^1H - ^{13}C - and ^{13}C - ^{13}C correlations of compound **109n** are illustrated in Figure 9.

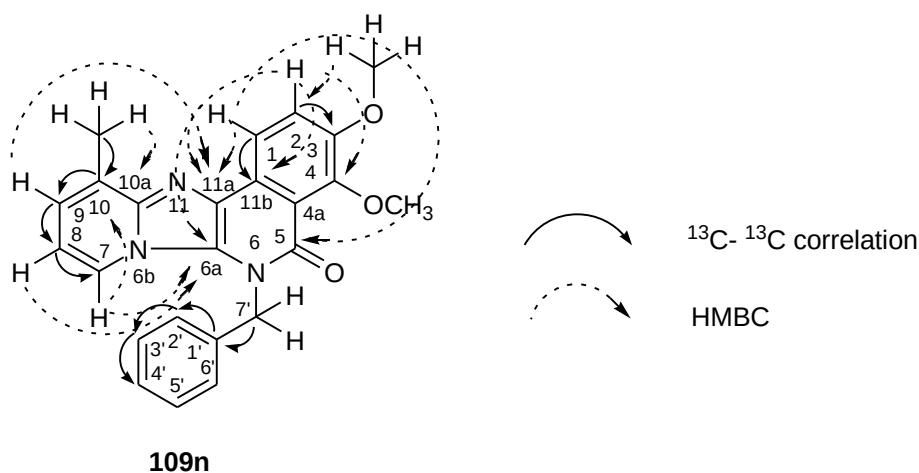


Figure 9. Important ^3J -, ^4J -, ^5J - ^1H ^{13}C - HMBC - and ^{13}C - ^{13}C - correlations in compound **109n**

In addition, the X-ray crystal structure analysis of **109n** has unambiguously proved the NMR structural assignments (Figure 10).^[73]

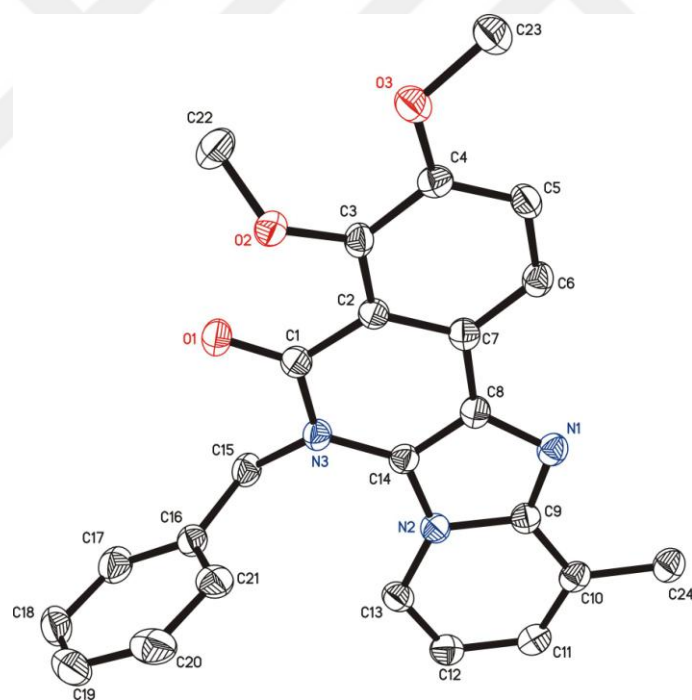
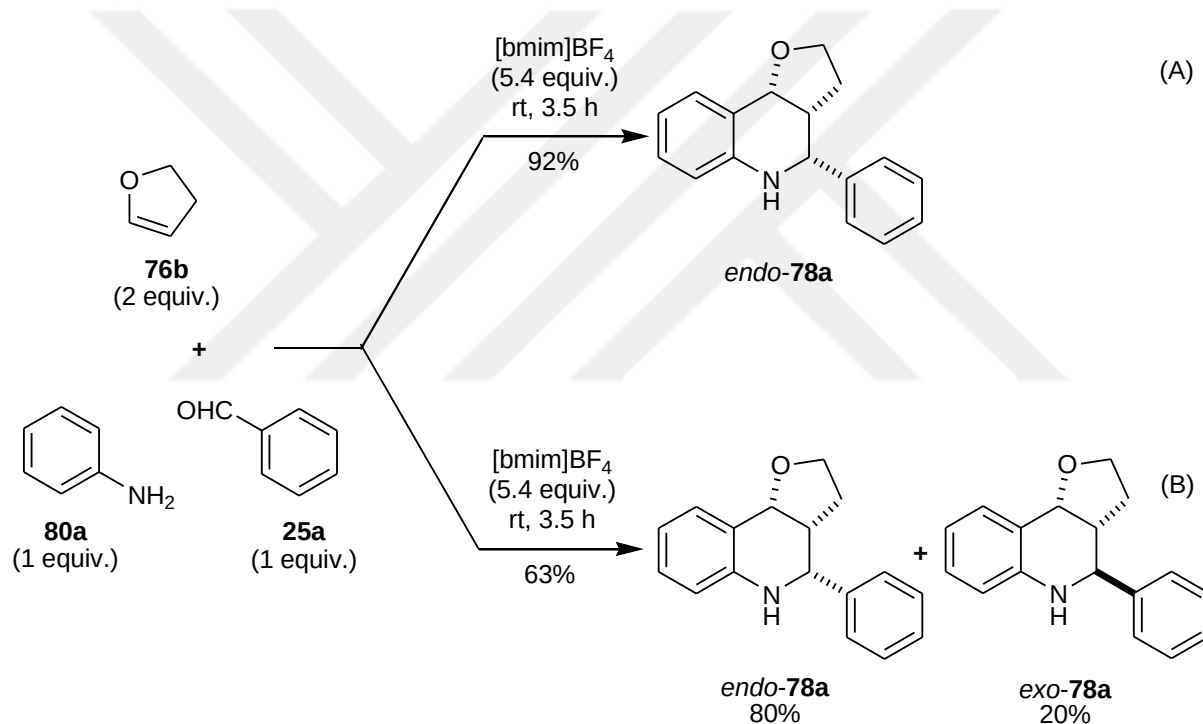


Figure 10. Solid state structure of compound **109n**; anisotropic displacement parameters are depicted at the 50% probability level; the second molecule of the asymmetric unit and H atoms are omitted for reasons of clarity

9. Guanidinium salts as promoters for the one-pot aza-Diels-Alder reaction

In this part of the work, the influence of ionic liquids, such as imidazolium salts and guanidinium salts, on the Povarov reaction was studied under a variety of reaction conditions.

The three component reaction of aniline (**80a**) with benzaldehyde (**25a**) and 2,3-dihydrofuran (**76b**) was selected as a model reaction. To start with, this transformation was performed in the presence of 5.4 equiv. [bmim]BF₄ as an ionic liquid under the conditions reported by Yadav et al. (Scheme 46).^[18] Under these conditions, we obtained 63% of a 80:20-mixture of the *endo*-isomer *endo*-**78a** and the *exo*-isomer *exo*-**78a** (Scheme 46, B). This observation is in contrast to the results of Yadav et al. who reported the exclusive formation of *endo*-**78a** in 92% yield (Scheme 46, A).



Scheme 46. Conflicting results for the Povarov reaction between **80a**, **25a**, and **76b**. (A)

Result according to Yadav et al.,^[18] (B) Result of the present study

This conflicting results prompted us to study the influence of several ionic liquids under different reaction conditions on the Povarov reaction between aniline (**80a**) benzaldehyde (**25a**), and 2,3-dihydrofuran (**76b**) in greater detail.

To start with, the reaction was studied under microwave conditions (Table 7). In the presence of 5.4 equiv. [bmim]BF₄ the microwave-assisted transformation (10 W) at 70°C delivered 69% of a 75:25-mixture of the cyclization products *endo*-**78a** and *exo*-**78a** in only 7 min

(Table 7, entry 1). This is a significant reduction of the reaction time. A decrease of the amount of [bmim]BF₄ from 5.4 to 1.0, and 0.1 equivalents, respectively, resulted in improved *endo/exo*-ratios. However, the yield dropped from 69 to 51% (Table 7, entries 2 and 3).

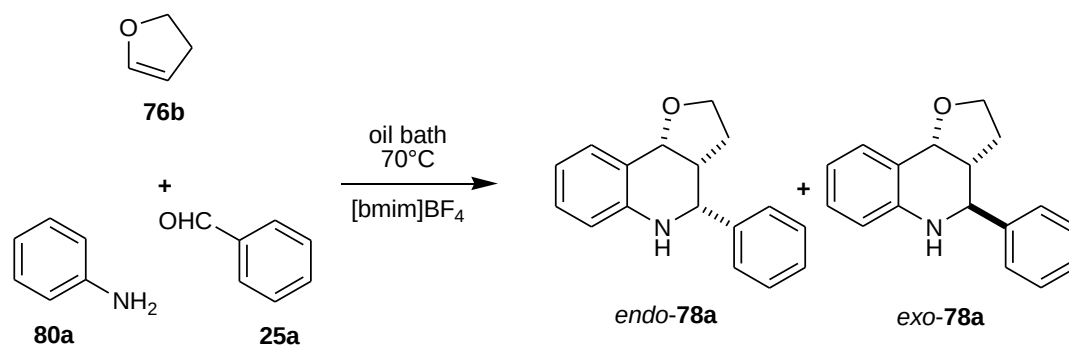
Table 7. The influence of the amount of [bmim]BF₄ on yield and selectivity of the synthesis of **78a** under microwave conditions

Entry	[bmim]BF ₄ [equiv.]	t [min]	Yield [%]	<i>endo/exo</i>
1	5.4	7	69	75/25
2	1.0	10	57	83/17
3	0.1	15	51	84/16

In a control experiment, 1 equiv. of aniline (**80a**), 1 equiv. of benzaldehyde (**25a**), and 2 equiv. of 2,3-dihydrofuran (**76b**) were reacted in the absence of any ionic liquid under microwave conditions (150 W, 70°C, 5 min). Under these conditions, the hexahydrofuro[2,3-*c*]quinolines *endo*-**78a** and *exo*-**78a** were not formed at all. This implies that [bmim]BF₄ acts as a catalyst.

The influence of microwave irradiation on the transformation was studied next. To do so, several reactions of **80a**, **25a**, and **76b** with [bmim]BF₄ were run in a sealed vial under thermal conditions (oil bath, 70°C) (Table 8). The result was that there were no significant differences between the reactions under microwave and thermal conditions (Table 8, entry 1, Table 7, entry 1). Since the yield of *endo*-**78a** and *exo*-**78a** under thermal conditions (Table 8, entry 1) was higher than under microwave conditions (Table 7, entry 1), it was decided to focus on thermal conditions for the rest of the study.

Table 8. Optimization of the reaction conditions of the [bmim]BF₄-catalyzed Povarov reaction under thermal conditions



Entry	80a [equiv.]	25a [equiv.]	76b [equiv.]	[bmim]BF ₄ [equiv.]	t [min]	Yield [%]	<i>endo/exo</i>
1	1	1	2	5.4	5	76	75/25
2	1	1	2	0.1	14	44	84/16
3	1	1	2	0.1	60	43	84/16
4	1.2	1	2	5.4	5	78	75/25
5	1.2	1	2	5.4	7	81	78/22
6	1.2	1	2.2	5.4	7	75	76/24
7	1.2	1	2.4	5.4	7	76	75/25

The highest yield for the reaction under thermal conditions at 70°C with 5.4 equiv. [bmim]BF₄ was achieved when 1.2 equiv. **78a** were reacted with 1.0 equiv. **25a** and 2 equiv. **76b** (Table 8, entry 5). Therefore, all further reactions were conducted using the substrate ratios given in Table 8, entry 5.

In a next set of experiments, the influence of the reaction temperature on reaction time, chemical yield, and the diastereoselectivity of the Povarov reaction between **80a**, **25a**, and **76b** was explored. For this purpose, the transformation was conducted at 0°C, at room temperature, at 70°C, and at 160°C (Table 9). At 160°C, the reaction was completed within three minutes and delivered the products **78a** in quantitative yield in a 67:33-ratio (Table 9, entry 4). It was found that at lower temperatures the chemical yields are lower, the reaction

times are increasing, and the formation of the thermodynamically less stable *endo*-isomer *endo*-**78a** is favored (Table 9).

Table 9. The influence of the reaction temperature on the [bmim]BF₄-catalyzed Povarov reaction

Reaction scheme showing the Povarov reaction of aniline (**80a**, 1.2 equiv.), benzaldehyde (**25a**, 1 equiv.), and furan (**76b**, 2 equiv.) catalyzed by [bmim]BF₄ (5.4 equiv.) in an oil bath. The reaction yields a mixture of *endo*-**78a** and *exo*-**78a** isomers.

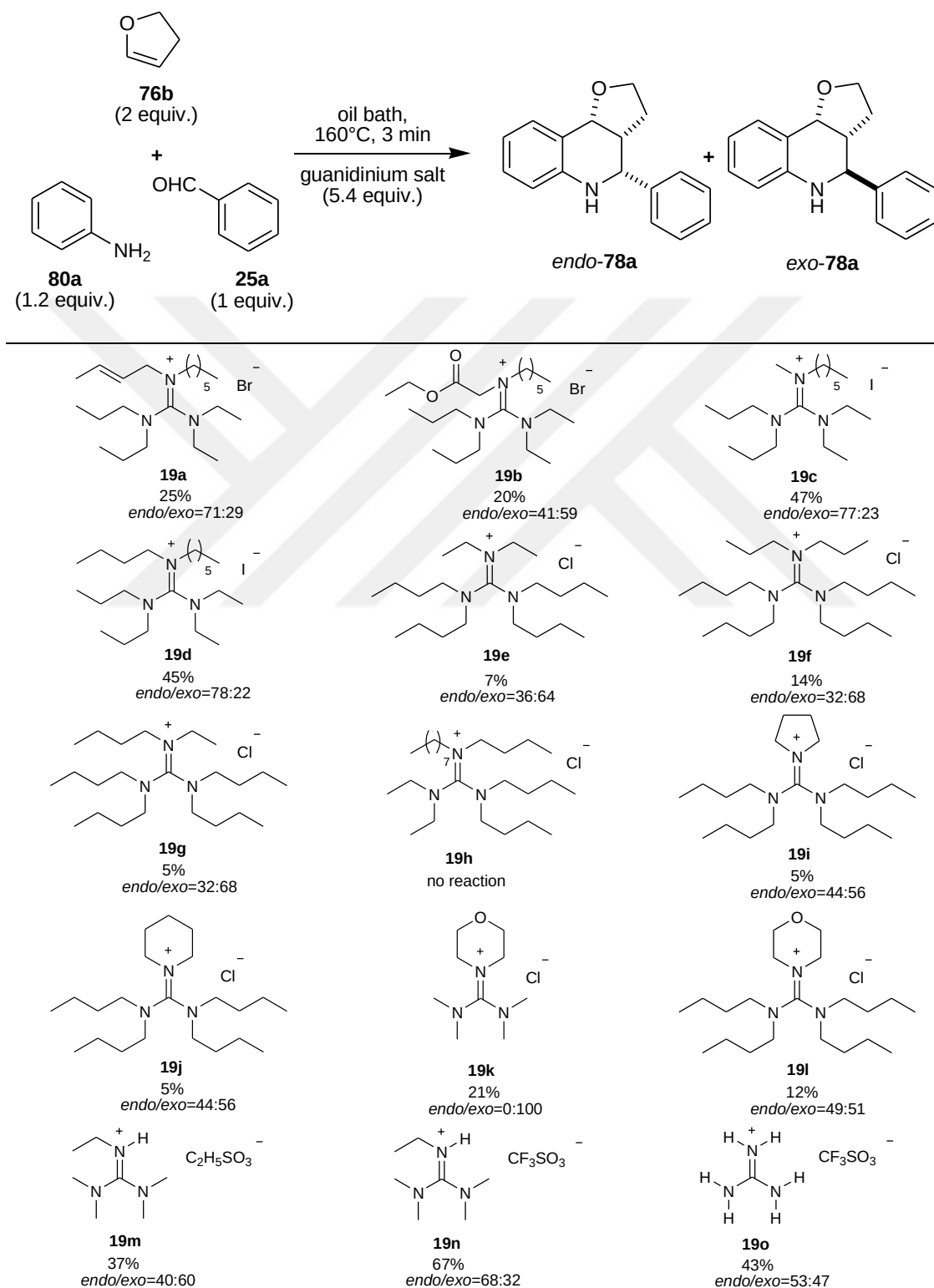
Entry	T [°C]	t [min]	Yield [%]	<i>endo</i> / <i>exo</i>
1	0	1140	79	85/15
2	RT	210	90	81/19
3	70	7	82	77/23
4	160	3	quant.	67/33

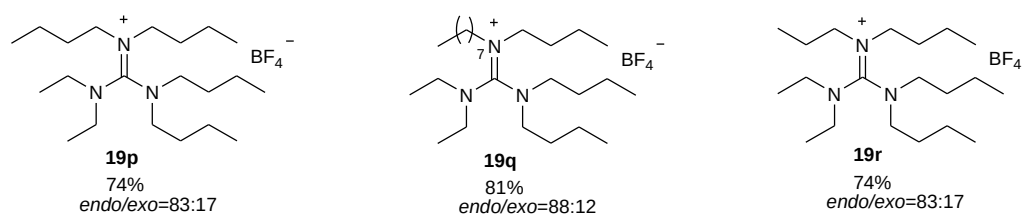
With [bmim]BF₄ as the ionic liquid, the results can be summarized as follows: 1) in all cases, mixtures of the *endo*- and *exo*-isomers *endo*-**78a** and *exo*-**78a** were observed, 2) at lower temperatures, the formation of the *endo*-isomer *endo*-**78a** is favored, 3) running the reactions under microwave conditions offers no advantage over running them under thermal conditions (in a sealed vial).

Since the selective formation of either the *endo*- or the *exo*-isomer could not be achieved with [bmim]BF₄ as the ionic liquid, it was decided to extend the scope of the study to guanidinium salts. For this purpose, the reaction between 1.2 equiv. **80a**, 1 equiv. **25a**, and 2 equiv. **76b** was performed in the presence of a selection of guanidinium salts **19a-r** in a sealed vial under thermal conditions at 160°C (Table 10). The most important result was that both yield and diastereoselectivity depend on the structure of the guanidinium ion as well as the nature of the anion. Guanidinium tetrafluoroborates like **19p**, **19q**, **19r** favored the formation of the *endo*-isomer *endo*-**78a**, whereas guanidinium chlorides favored the formation of the *exo*-isomer

exo-**78a**. A striking example is the guanidinium salt **19k**. With this guanidinium chloride as the ionic liquid, the *exo*-isomer was formed exclusively. However, the yield amounted to only 21%.

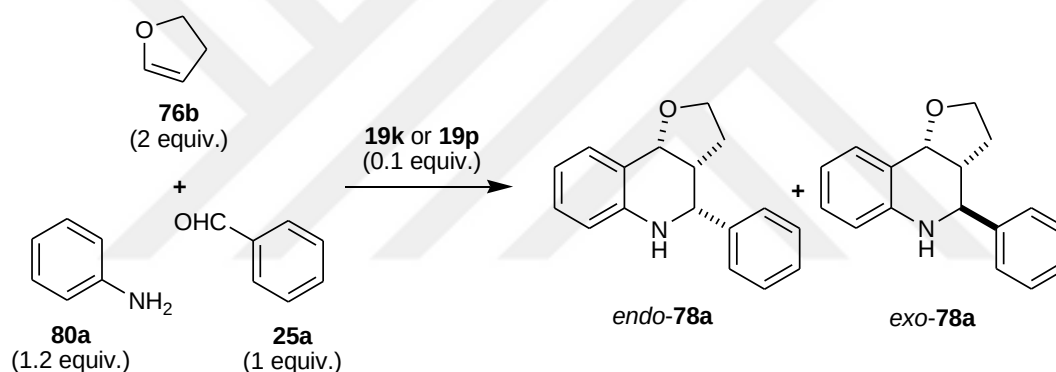
Table 10. Synthesis of furanoquinolines **78a** using various guanidinium salts **19**





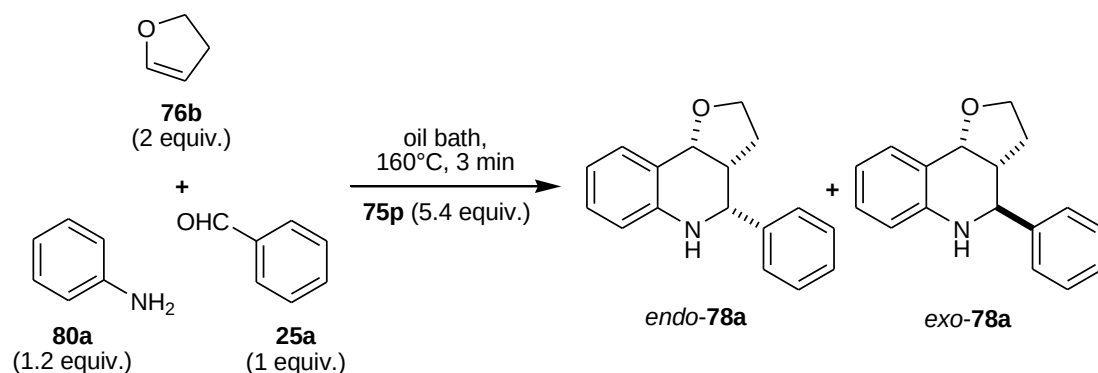
Furthermore, with the guanidinium salts **19k** and **19p** as examples, the influence of the concentration of the guanidinium salts on the results of the aza-Diels-Alder reaction was studied. Most important is that the reaction can be performed with catalytic amounts (0.1 equiv.) of the guanidinium salts in the absence of any further reagent and/or solvent (Table 11). As expected, the reactions could be run under both thermal and microwave conditions. As with [bmim]BF₄, the yields and the *endo/exo*-ratios depend on the reaction temperature.

Table 11. The influence of catalytic amounts (0.1 equiv) of **19k,p** on the synthesis of **78a**

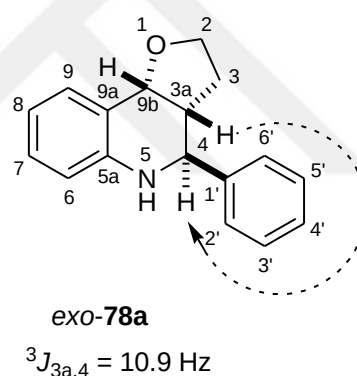
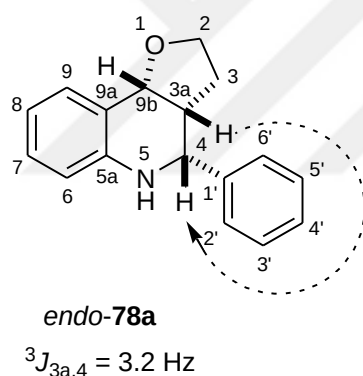


Entry	Ionic liquid	Reaction conditions	Yield [%]	<i>endo/exo</i>
1	19k	160 °C, 3 min	36	35/65
2	19k	MW, 70 °C, 40 min	64	79/21
3	19p	MW, 70 °C, 40 min	86	79/21
4	19k	70 °C, 40 min	72	81/19
5	19p	70 °C, 40 min	97	88/12
6	-	MW, 70 °C, 5 min	-	-

In a last set of experiments, recycling and reuse of guanidinium salts in the Povarov reaction were addressed (Table 12). It was found that the guanidinium salt **19p** could be used for at least four reaction cycles with comparable yields and diastereoselectivities without significant loss of catalytic activity.

Table 12. Recycling and reuse of guanidinium salt **19p**

No. of Runs	1st	2nd	3rd	4th
Yield [%]	70	65	75	74
<i>endo/exo</i>	82/18	80/20	83/17	81/19

**Figure 11.** Structures of **endo-78a** and **exo-78a**

The *endo/exo*-ratios of all transformations were determined by ^1H NMR analysis of the crude reaction mixtures after column filtration. The structures of the *endo*-isomer **endo-78a** – purified by recrystallization (EtOH/H₂O) from the *endo/exo*-mixture – and the *exo*-isomer **exo-78a** were elucidated using mass spectrometry and different NMR spectroscopic methods. The relative stereochemistry of the two diastereomers was established by means of the vicinal coupling constants between 3a-H and 4-H. In the *endo*-isomer, $^3J_{3a,4}$ amounted to 3.2 Hz and is much smaller than $^3J_{3a,4}$ in the *exo*-isomer, which amounts to 10.9 Hz (Figure 11).

10. References

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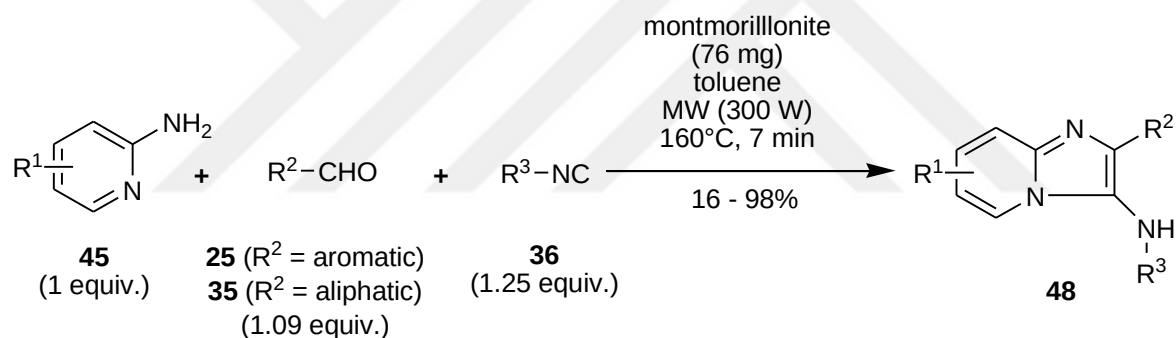
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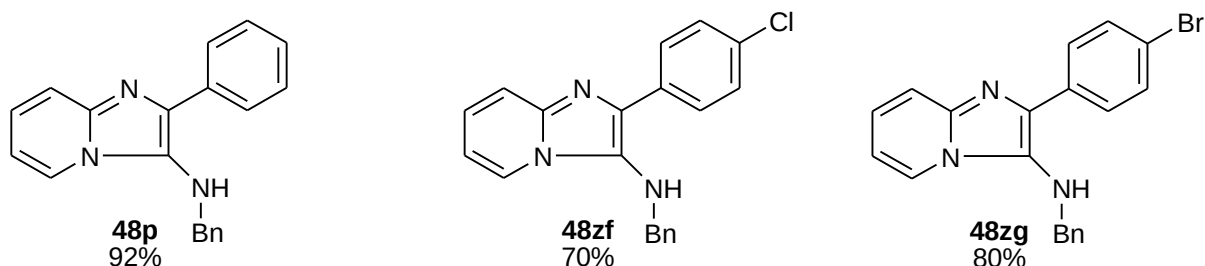
11. Summary

Multi component reactions occupy an important role in the development of new and efficient synthetic approaches to biological active heterocycles. Running reactions under microwave conditions and using ionic liquids as solvents and/or catalysts offers new opportunities for the development of more efficient, “greener” and more sustainable synthetic methods. The present thesis focuses on the influence of microwave irradiation and ionic liquids on the outcome of two well-known three component reactions, the Groebke reaction and the Povarov reaction.

The first part of the thesis deals with the influence of microwaves and ionic liquids on the Groebke reaction. The reaction of 2-aminopyridines **45** with aldehydes **25,35** and isocyanides **36** using montmorillonite as a catalyst in toluene under microwave conditions at 160°C delivers the corresponding imidazo[1,2-*a*]pyridines **48** within only seven minutes with yields ranging from 16 to 98% (Scheme 47, Figure 12).



Scheme 47. Synthesis of imidazo[1,2-*a*]pyridines **48** from different 2-aminopyridines **45**, aldehydes **25,35**, and isocyanides **36**



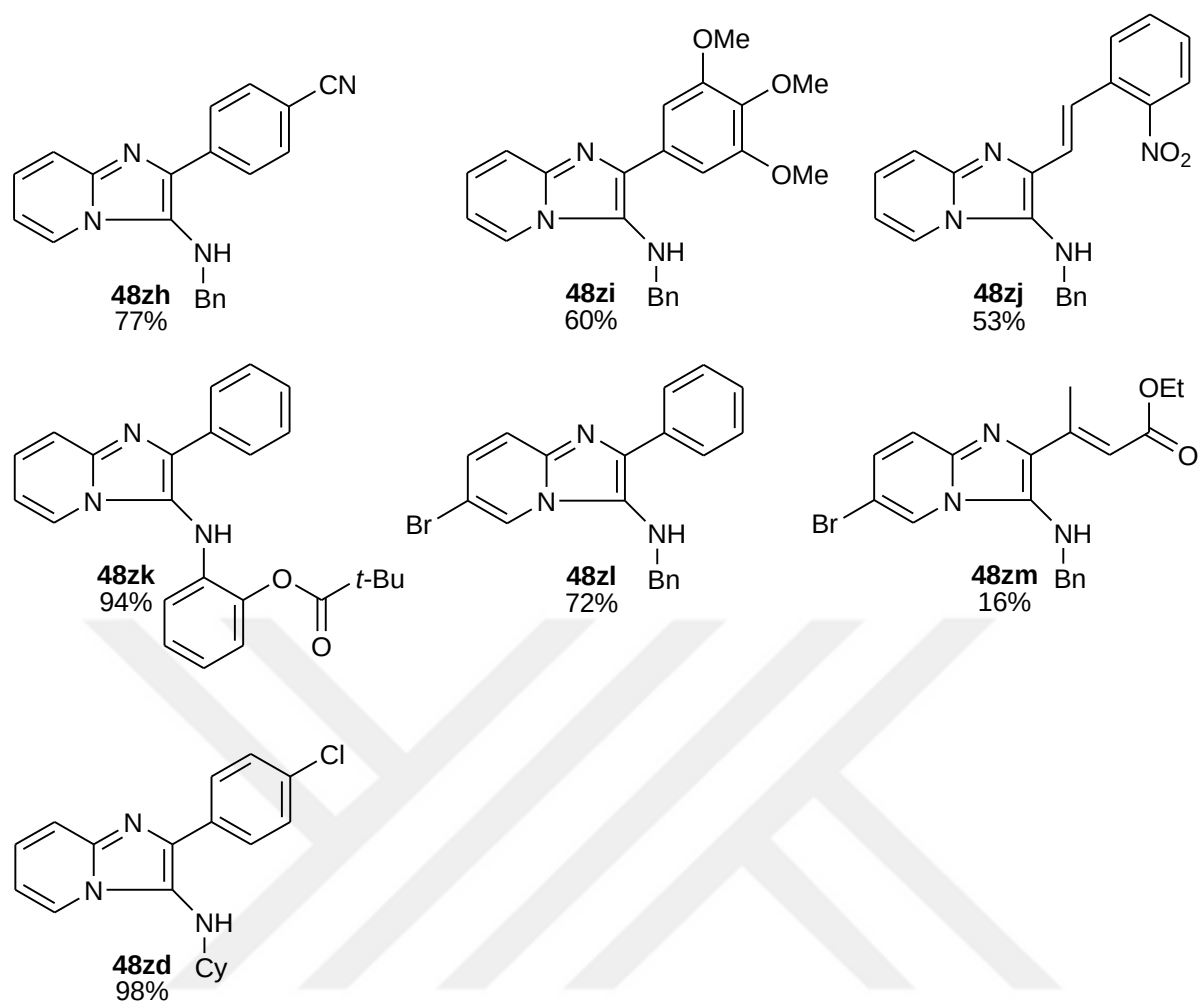
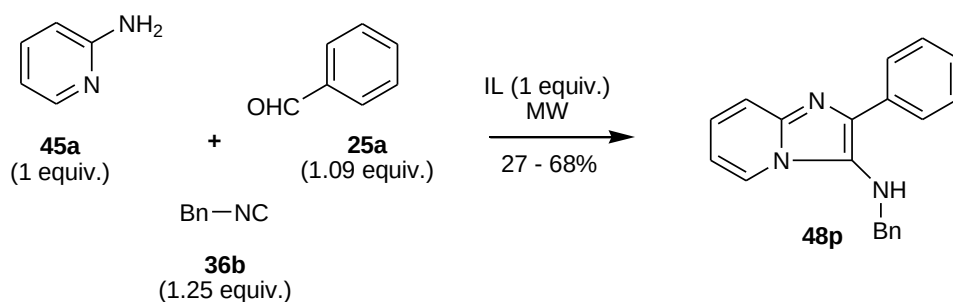


Figure 12. Structures and yields of imidazo[1,2-*a*]pyridines **48**

The organic solvent can be replaced by ionic liquids like imidazolium and guanidinium salts. With guanidinium salts, it is possible to perform the Groebke reaction in the absence of any other catalyst and solvent under microwave conditions (Table 13, Figure 13).

Table 13. The use of guanidinium salts **19a-d** as catalysts for the synthesis of **48p**



Entry	IL	Power [W]	t [min]	T [°C]	Yield [%]
1	19a	10	90	90	40
2	19b	10	90	90	68
3	19c	10	90	90	29
6	19d	10	90	90	27

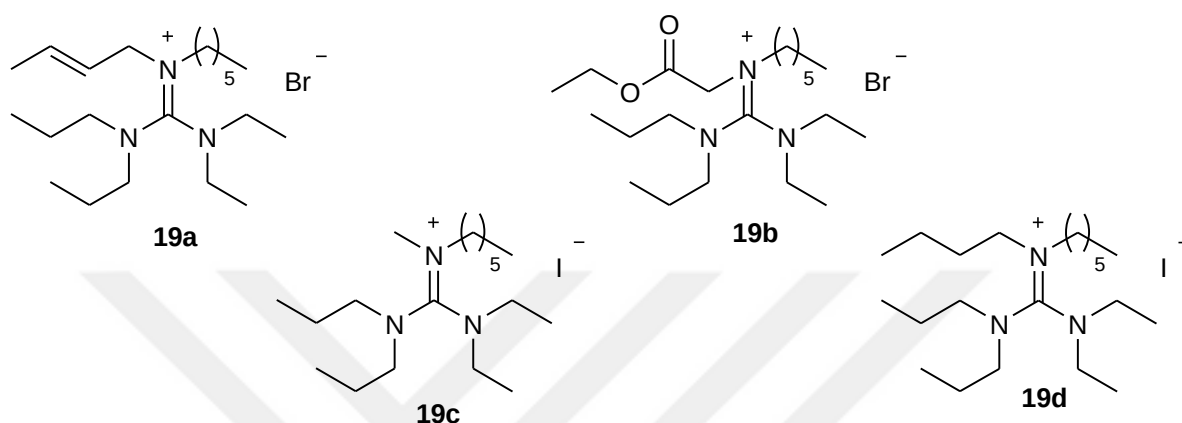
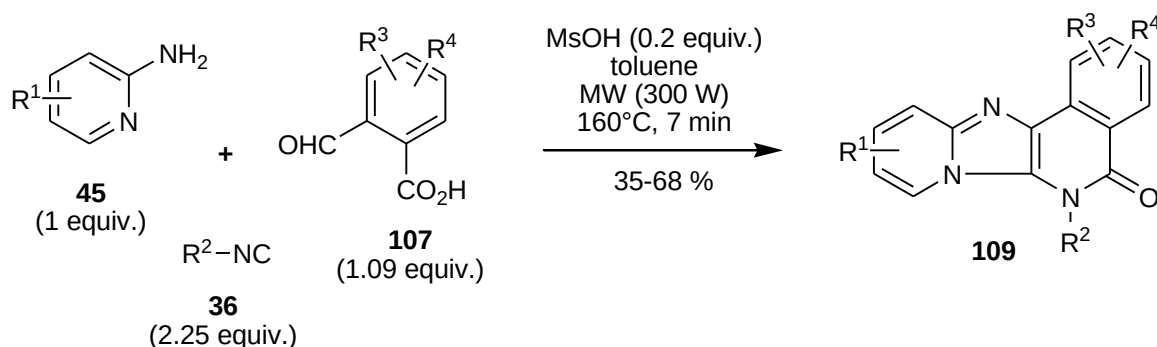


Figure 13. Structures of guanidinium salts **19a-d**

The second part of this work is about the extension of the scope of typical Groebke reactions by replacing the aldehyde component with a bifunctional 2-carboxybenzaldehyde. The reaction of 2-aminopyridines **45** with isocyanides **36** and 2-carboxybenzaldehydes **107** with 20 mol% methanesulfonic acid as a catalyst in toluene under microwave conditions at 160°C affords the corresponding pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-ones **109** with yields ranging between 35 and 68% (Scheme 48, Figure 14). The new method can easily be performed, is robust, and highly efficient.



Scheme 48. Synthesis of pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-ones **109** from different 2-aminopyridines **45**, isocyanides **36**, and 2-carboxybenzaldehydes **107**

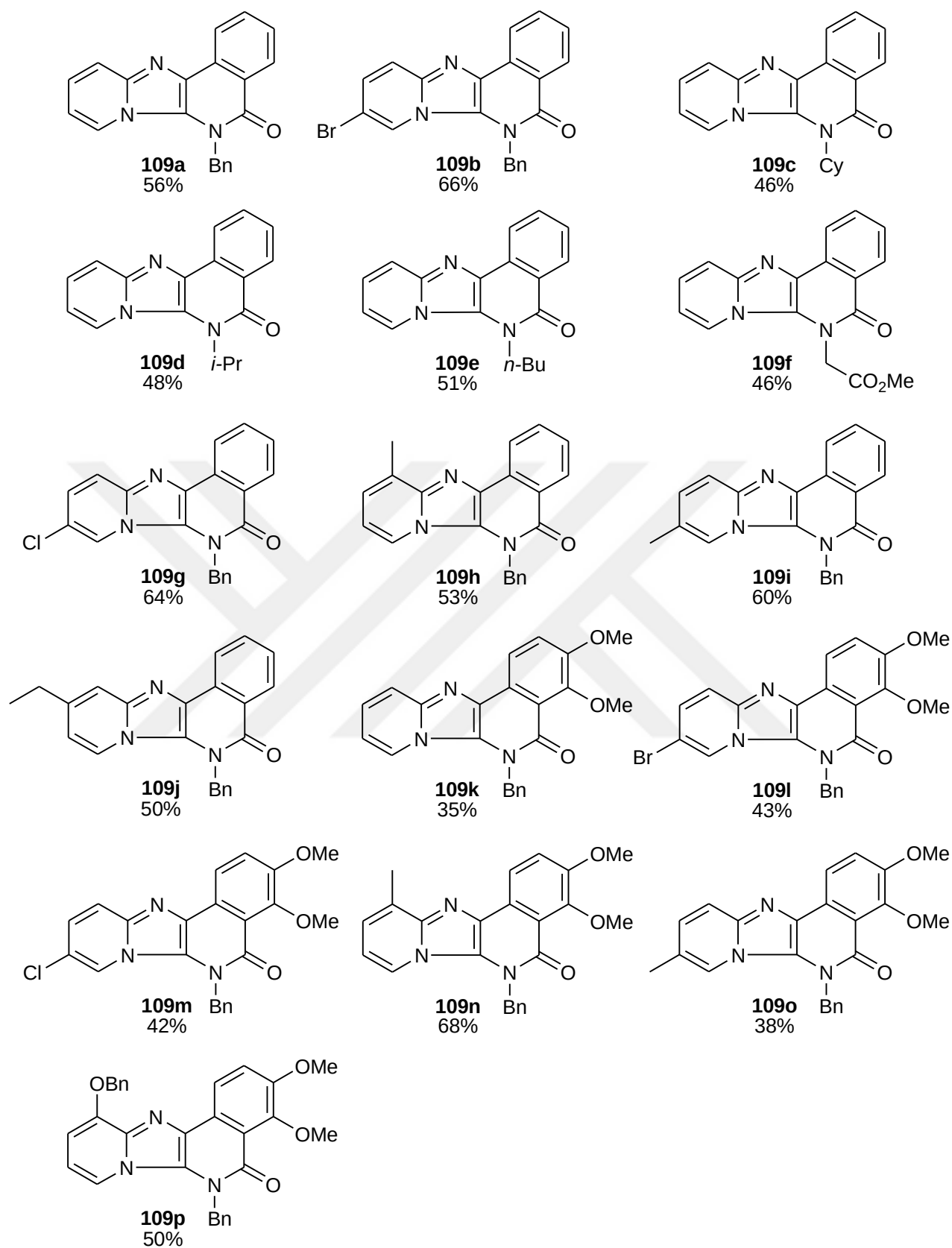
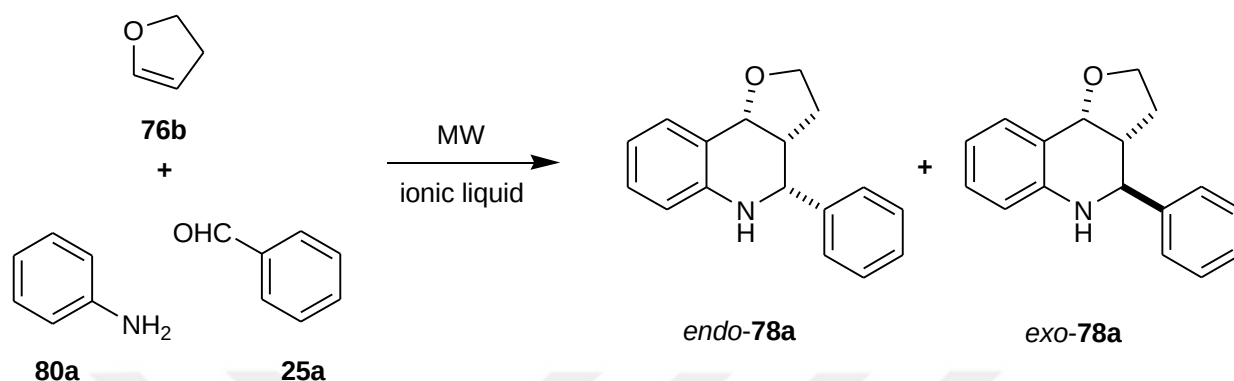


Figure 14. Structures and yields of pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-ones 109a-p

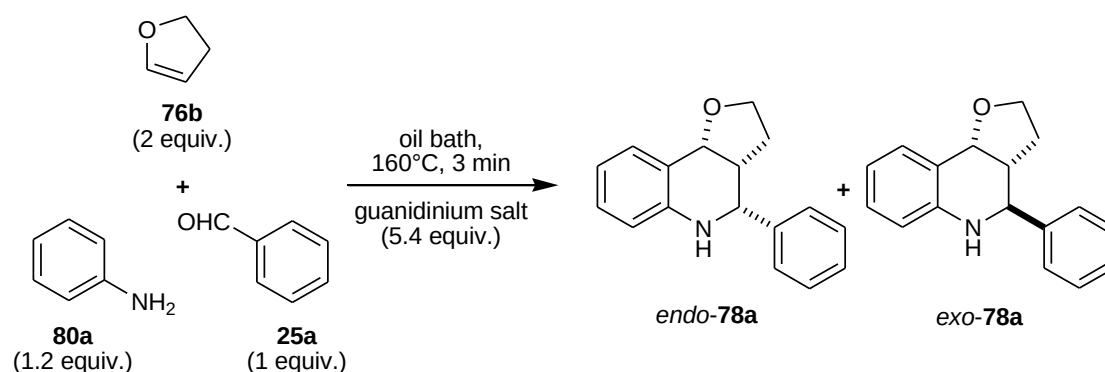
The third part of the thesis is focused on the intermolecular Povarov reaction. Using the reaction between aniline (**80a**), benzaldehyde (**25a**), and 2,3-dihydrofuran (**76b**) to **78a** as a model reaction, the influence of ionic liquids, such as imidazolium and guanidinium salts, and microwaves on the outcome of the Povarov reaction was evaluated (Scheme 49).

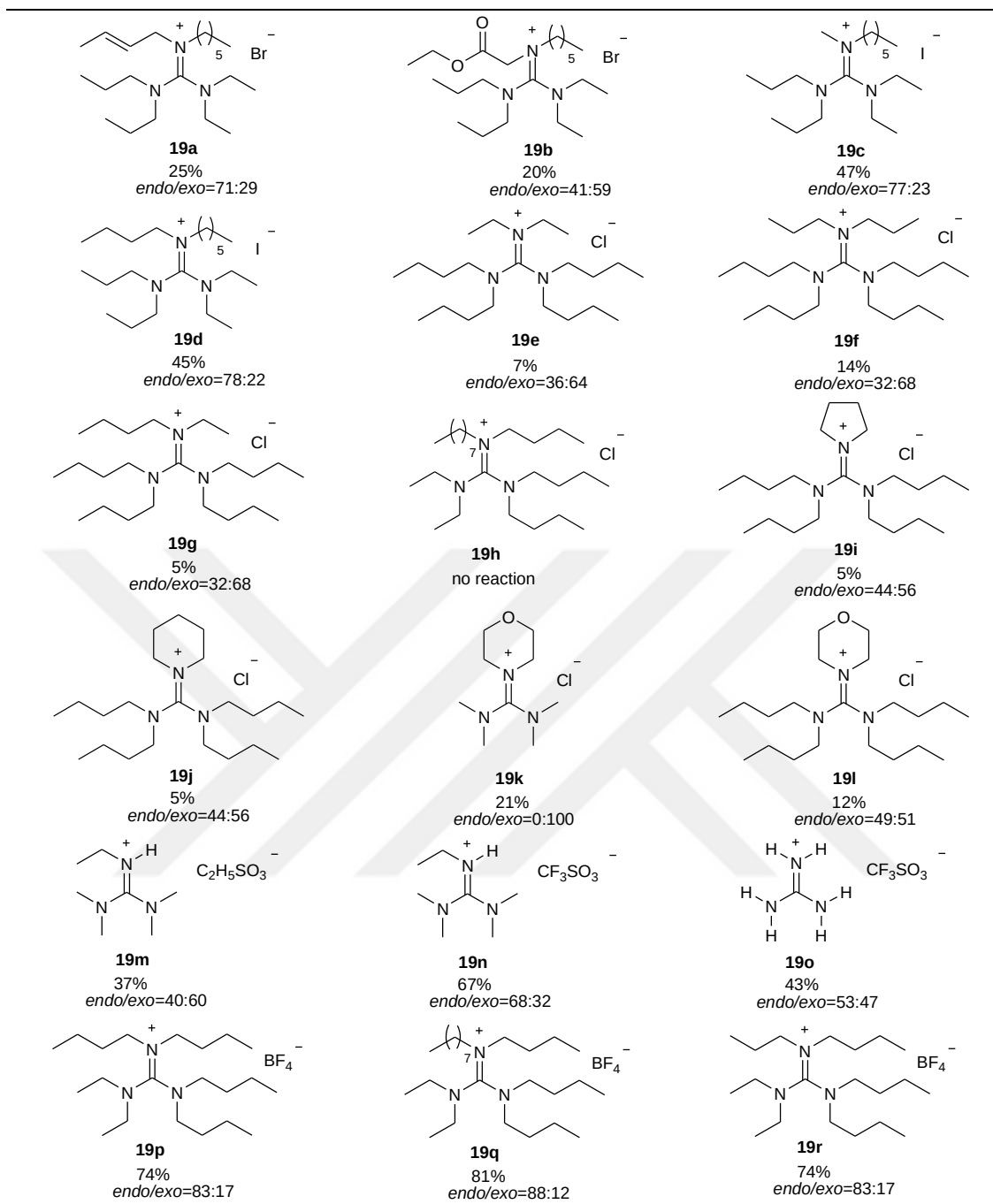


Scheme 49. Microwave-assisted synthesis of furanoquinolines **78a** in the presence of an ionic liquid

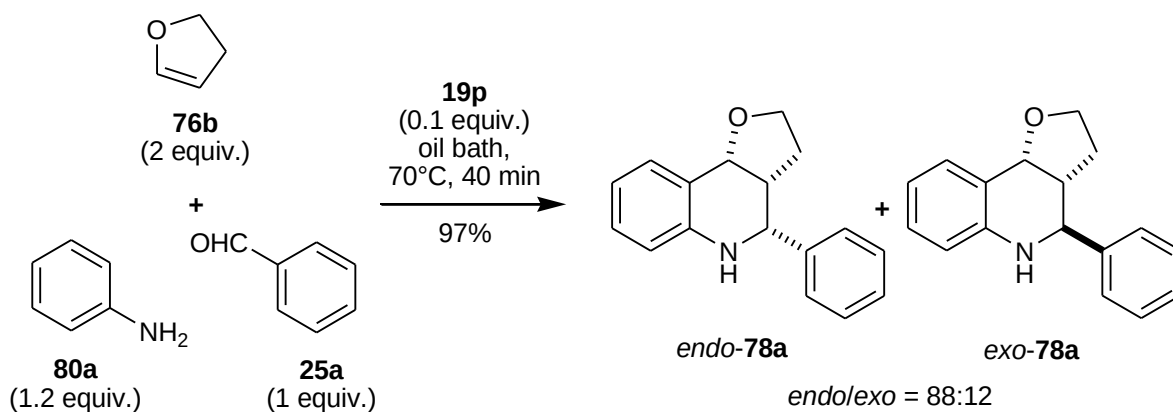
It was established that the model reaction can be promoted by imidazolium salts like [bmim]BF₄ under thermal as well as under microwave conditions. The reaction temperature has a strong impact on the chemical yield and the diastereoselectivity of the model reaction. At lower temperatures the formation of the *endo*-isomer **endo-78a** is favored. However, the influence of microwave irradiation on yield and selectivity is not very pronounced.

Table 14. Synthesis of furanoquinolines **78a** using various guanidinium salts **19a-r**





The Povarov reaction can also be promoted by a great number of guanidinium salts **19a-r** (Table 14). Reactions that were performed under thermal conditions in a sealed vial demonstrated that both the chemical yield and the diastereoselectivity of the reaction are strongly influenced by a) the structure of the guanidinium ion and the nature of the anion of the guanidinium salt, and b) the concentration of the guanidinium salt.



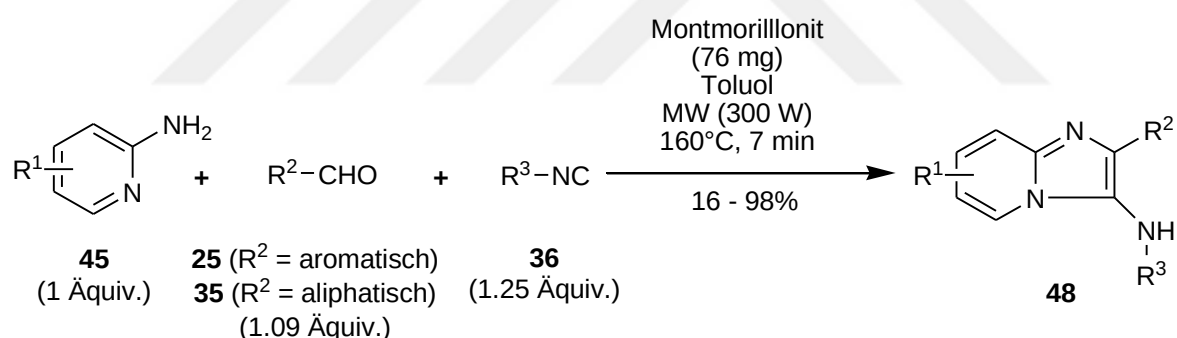
Scheme 50. The influence of catalytic amounts (0.1 equiv) of **19p** on the synthesis of **78a**

Remarkably, the Povarov can also be performed successfully in the presence of only catalytic amounts of a guanidinium salt. When the reaction between **80a**, **25a**, and **76b** was run in the presence of 0.1 equiv. **19p** under thermal conditions at 70°C for 40 min, 97% of an 88:12-mixture of **endo-78a** and **exo-78a** was formed (Scheme 50). Finally, it was demonstrated that the guanidinium salts can be recycled and reused several times without loss of reactivity.

12. Zusammenfassung

Mehrkomponenten-Reaktionen spielen eine wichtige Rolle bei der Entwicklung von neuen und effizienten Synthesemethoden für biologisch aktive Heterocyclen. Die Durchführung der Reaktionen unter Mikrowellenbedingungen und die Verwendung ionischer Flüssigkeiten als Lösungsmittel und/oder Katalysatoren eröffnet neue Perspektiven für die Entwicklung von effizienteren, umweltfreundlicheren und nachhaltigeren Synthesemethoden. Die vorliegende Dissertation beschäftigt sich vor allem mit dem Einfluss von Mikrowellenstrahlung und ionischen Flüssigkeiten auf zwei Dreikomponenten-Reaktionen, die Groebke- und die Povarov-Reaktion.

Im ersten Teil der Dissertation wird der Einfluss von Mikrowellen und ionischen Flüssigkeiten auf die Groebke-Reaktion untersucht. Die Umsetzung von 2-Aminopyridinen **45** mit Aldehyden **25,35** und Isocyaniden **36** mit Montmorillonit als Katalysator in Toluol unter Mikrowellenbedingungen bei 160°C liefert die entsprechenden Imidazo[1,2-*a*]pyridine **48** innerhalb von nur sieben Minuten mit Ausbeuten zwischen 16 und 98% (Schema 47, Abbildung 12).



Schema 47. Synthese von Imidazo[1,2-*a*]pyridinen **48** aus verschiedenen 2-Aminopyridinen **45**, Aldehyden **25,35** und Isocyaniden **36**

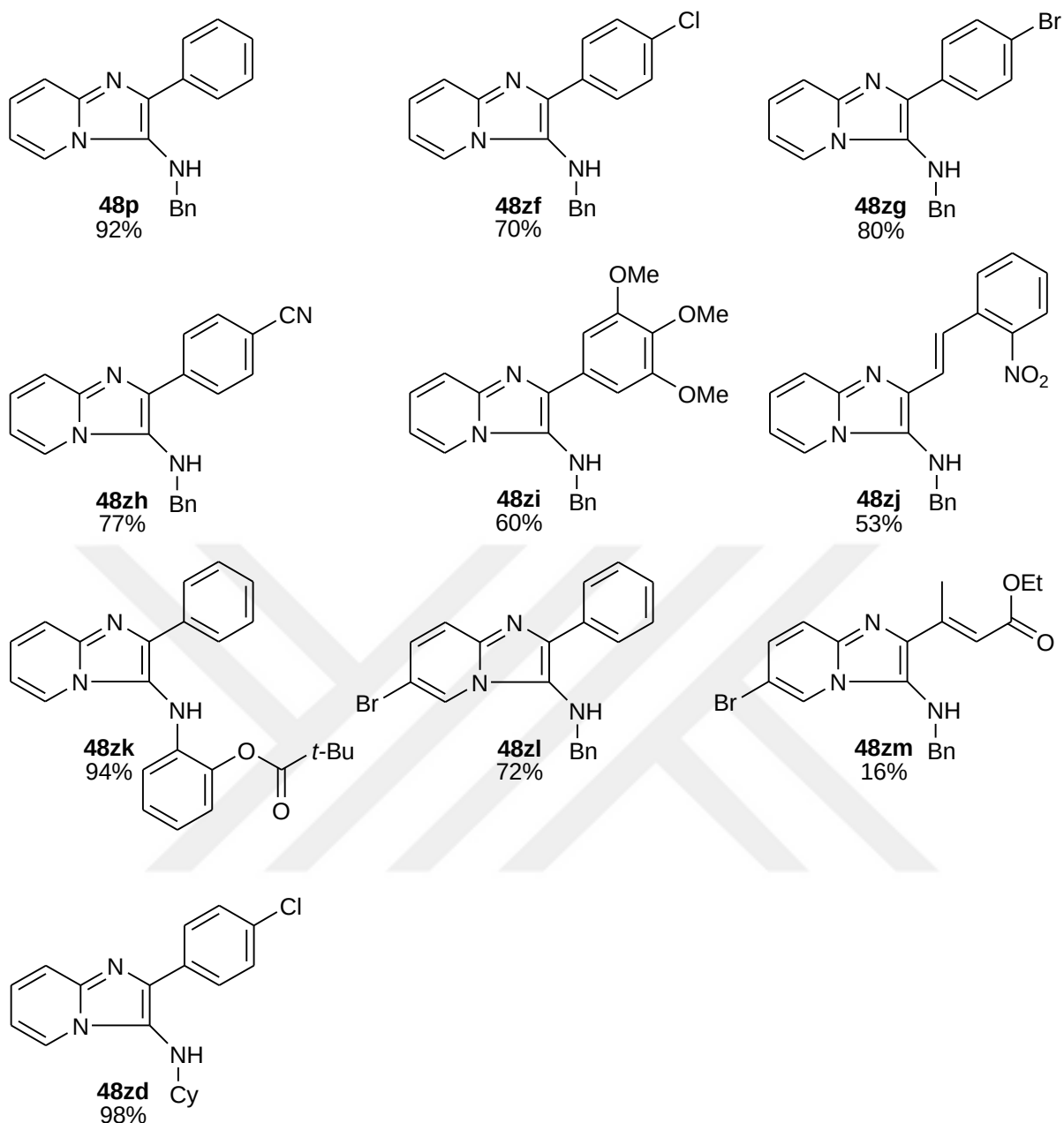
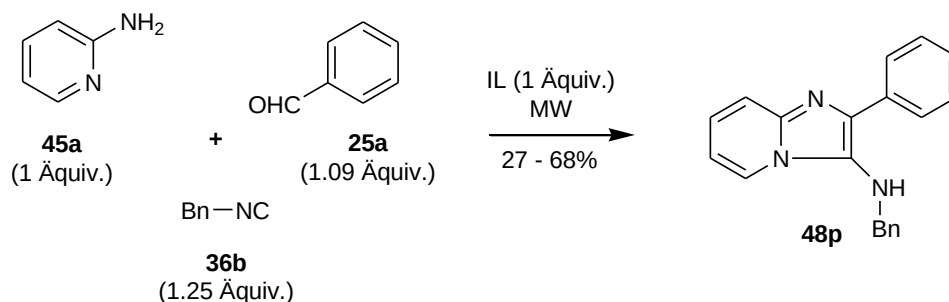


Abbildung 12. Strukturen und Ausbeuten der Imidazo[1,2-*a*]pyridine **48**

Das organische Lösungsmittel kann durch ionische Flüssigkeiten wie Imidazolium- und Guanidiniumsalze ersetzt werden. Mit Guanidiniumsalzen ist es möglich, die Groebke-Reaktion in Abwesenheit irgendeines zusätzlichen Katalysators oder Lösungsmittels unter Mikrowellenbedingungen durchzuführen (Tabelle 13, Abbildung 13).

Tabelle 13. Die Verwendung von Guanidiniumsalzen **19a-d** als Katalysatoren für die Synthese von **48p**



Nr.	IL	Leistung [W]	t [min]	T [°C]	Ausbeute [%]
1	19a	10	90	90	40
2	19b	10	90	90	68
3	19c	10	90	90	29
6	19d	10	90	90	27

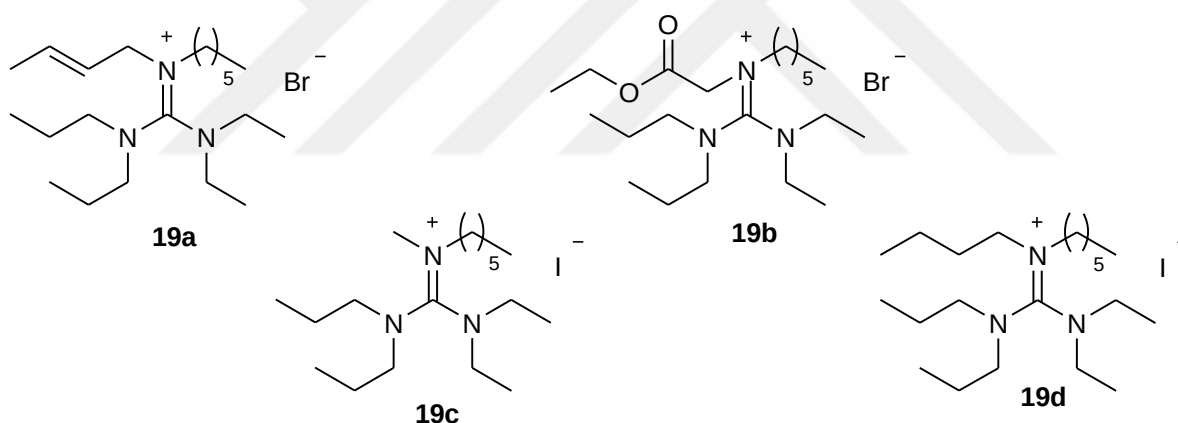
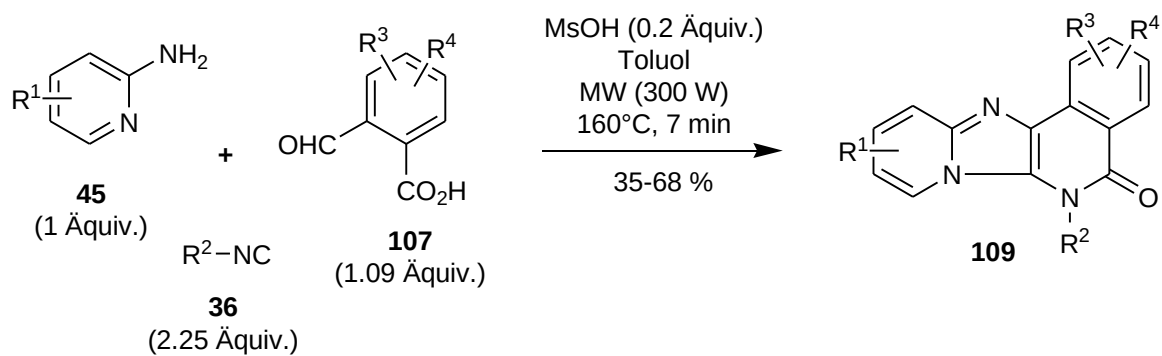
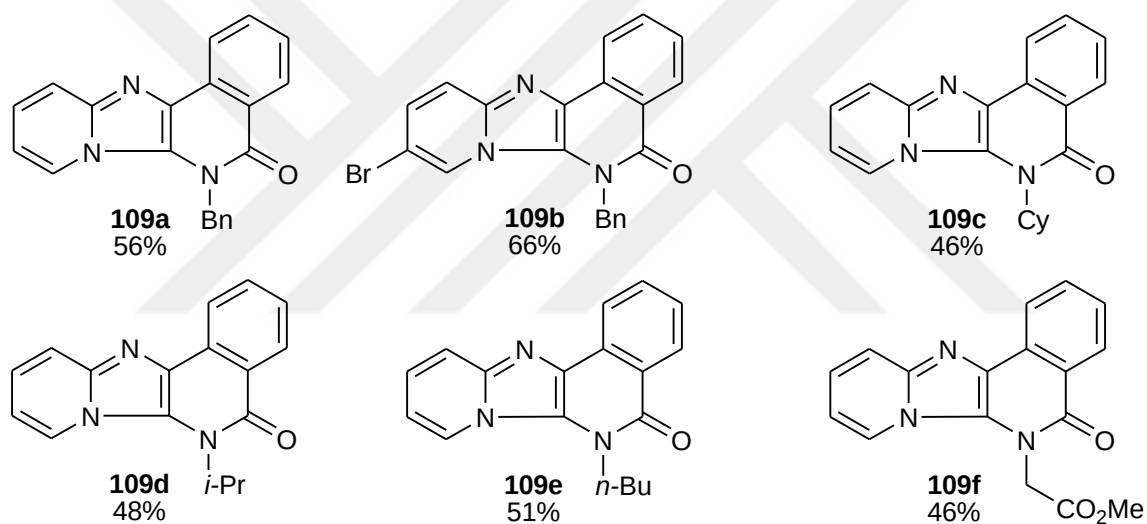


Abbildung 13. Die Strukturen der Guanidiniumsalze **19a-d**

Der zweite Teil dieser Arbeit befasst sich mit der Erweiterung des Anwendungsbereichs der klassischen Groebke-Reaktion durch Ersatz der Aldehydkomponente durch einen bifunktionalen 2-Carboxybenzaldehyd. Die Reaktion von 2-Aminopyridinen **45** mit Isocyaniden **36** und 2-Carboxybenzaldehyden **107** in Gegenwart von 20 mol% Methansulfonsäure als Katalysator in Toluol unter Mikrowellenbedingungen bei 160°C ergibt die entsprechenden Pyrido[2',1':2,3]imidazo[4,5-c]isochinolin-5(6*H*)-one **109** mit Ausbeuten zwischen 35 und 68% (Schema 48, Abbildung 14). Die neue Methode kann leicht durchgeführt werden, ist robust und hoch effizient.



Schema 48. Synthese von Pyrido[2',1':2,3]imidazo[4,5-*c*]isochinolin-5(6*H*)-onen **109** durch Umsetzung verschiedener 2-Aminopyridine **45**, Isocyanide **36** und 2-Carboxybenzaldehyde **107**



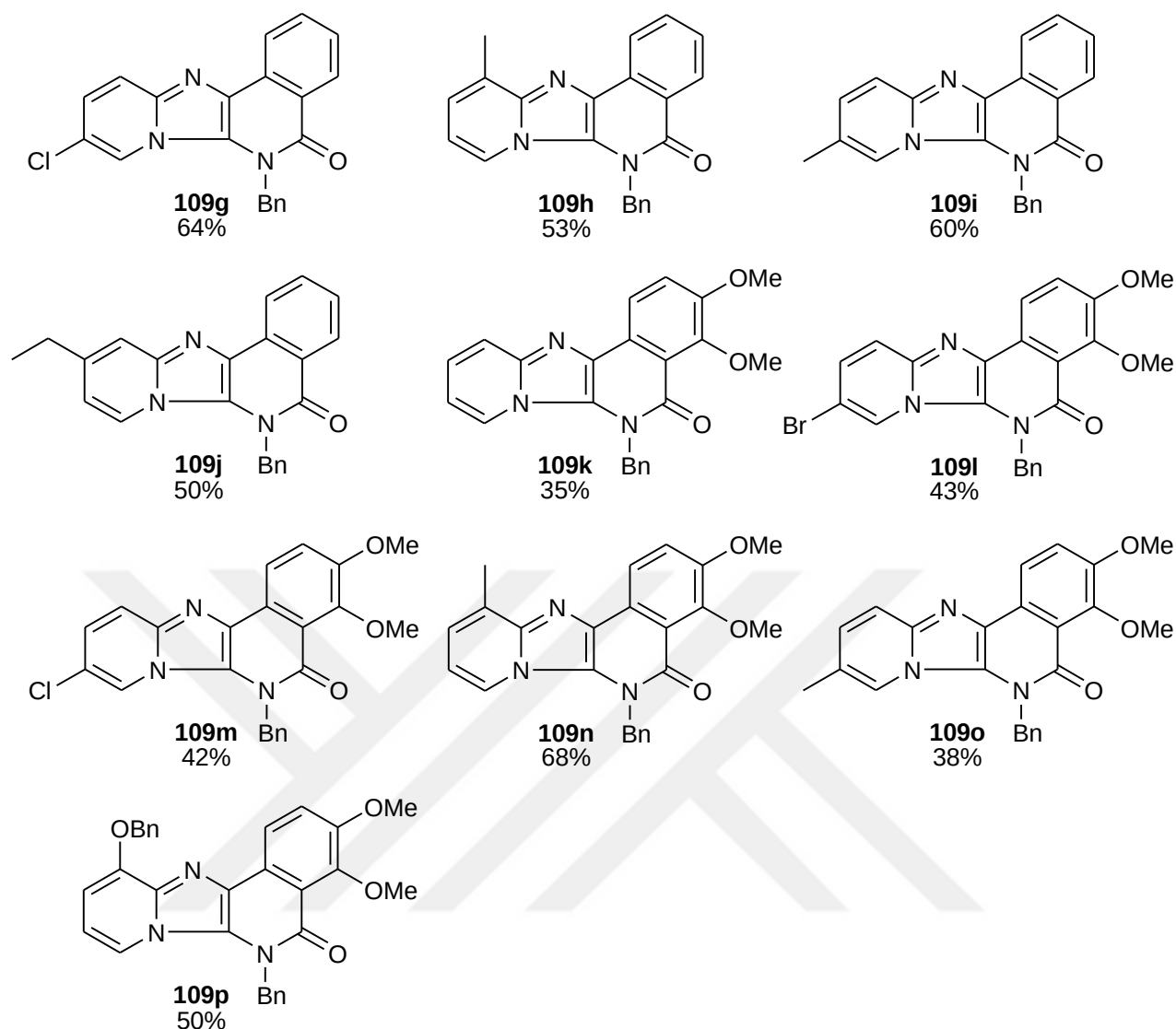
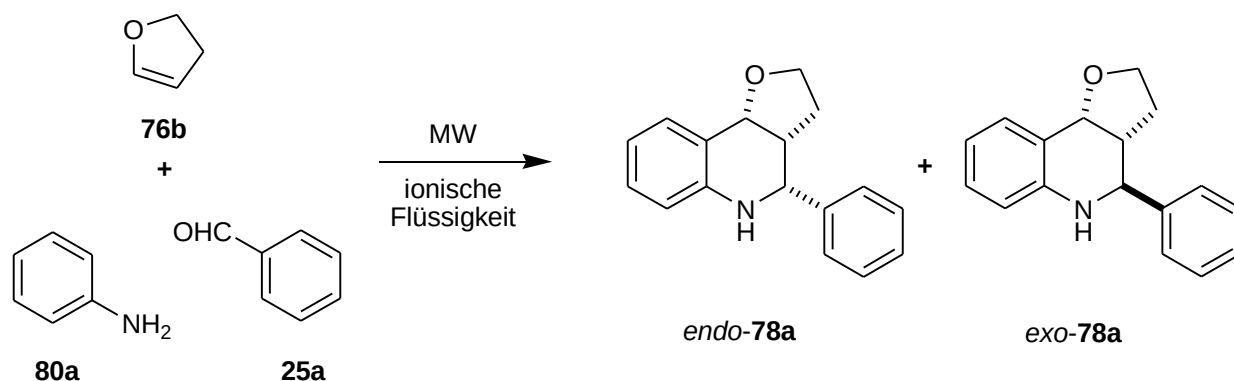


Abbildung 14. Strukturen und Ausbeuten der Pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-one **109a-p**

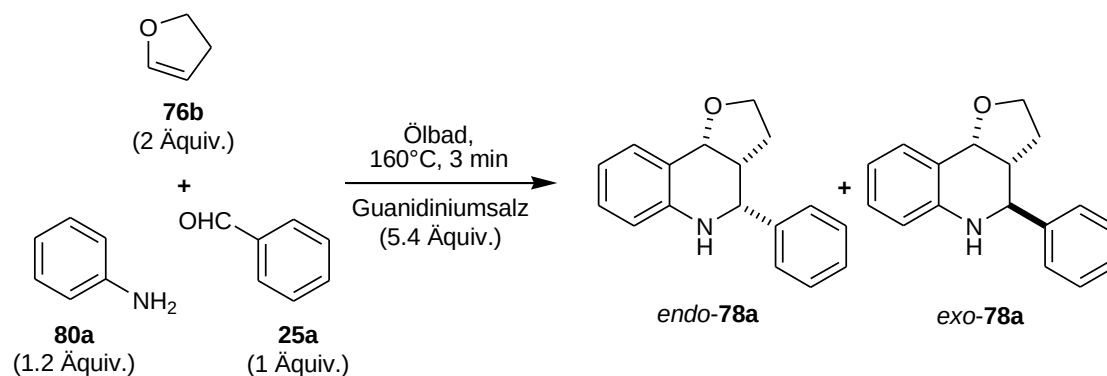
Der dritte Teil dieser Dissertation beschäftigt sich mit der intermolekularen Povarov-Reaktion. Am Beispiel der Umsetzung zwischen Anilin (**80a**), Benzaldehyd (**25a**) und 2,3-Dihydrofuran (**76b**) zu **78a** als Modellreaktion wurde der Einfluss von ionischen Flüssigkeiten wie Imidazolium- und Guanidiniumsalzen sowie von Mikrowellen auf den Verlauf der Povarov-Reaktion untersucht (Schema 49).

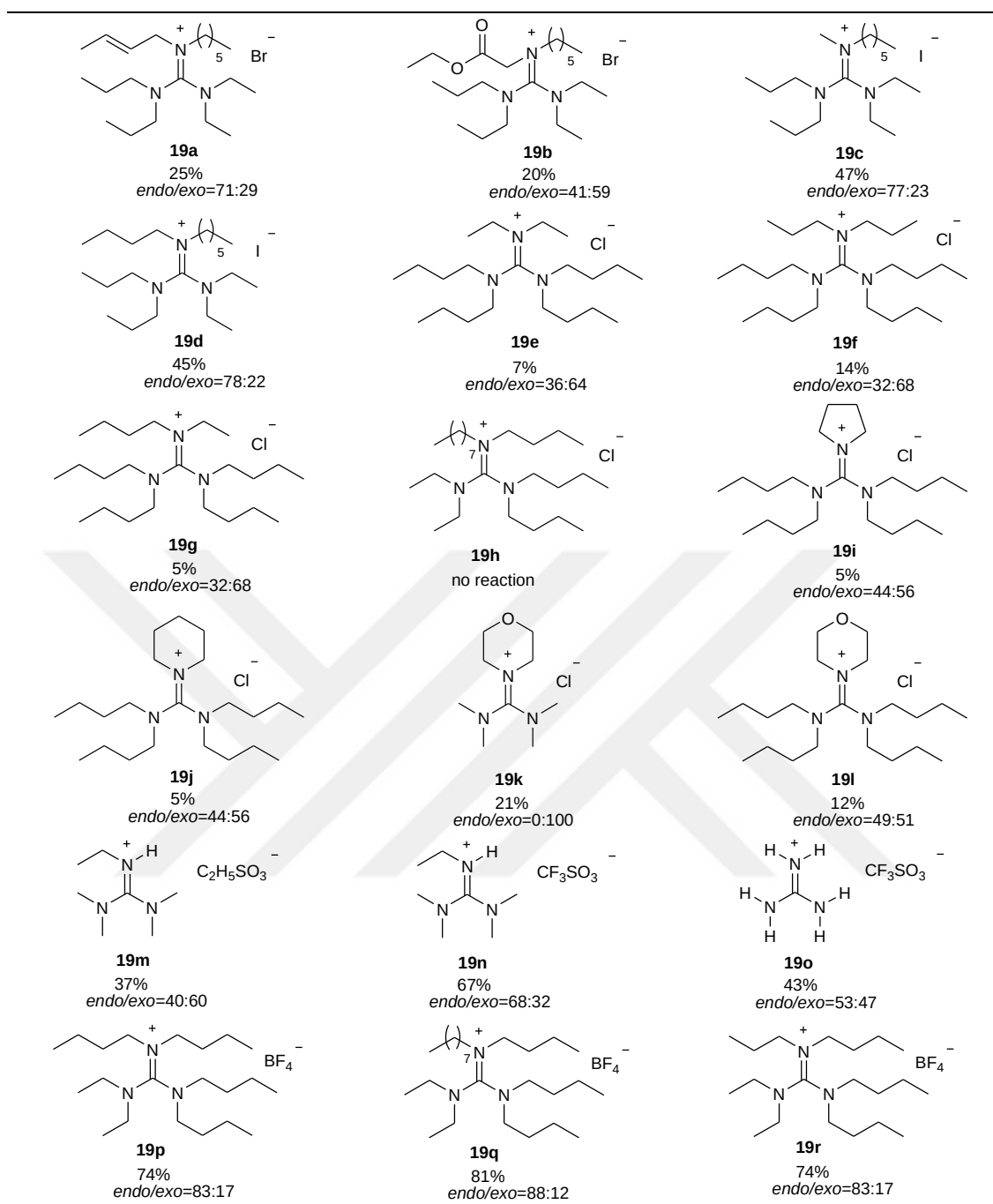


Schema 49. Mikrowellenunterstützte Synthese von Furanochinolinen **78a** in Gegenwart einer ionischen Flüssigkeit

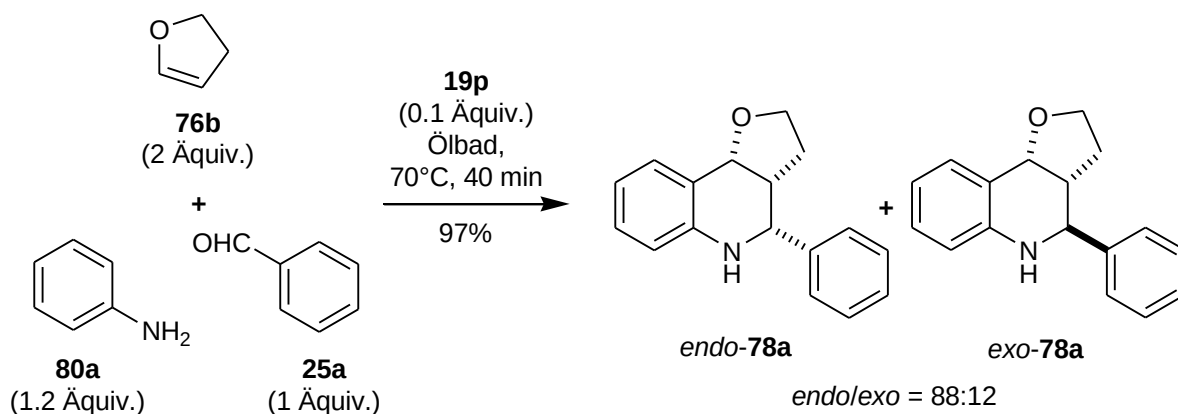
Man fand, dass die Modellreaktion sowohl unter thermischen als auch unter Mikrowellenbedingungen durch Imidazoliumsalze wie [bmim]BF₄ katalysiert werden kann. Die Reaktionstemperatur übt einen starken Einfluss auf die chemische Ausbeute und die Diastereoselektivität der Modellreaktion aus. Bei niedrigen Temperaturen wird die Bildung des *endo*-Isomers *endo*-**78a** bevorzugt. Dagegen ist der Einfluss der Mikrowellenstrahlung auf Ausbeute und Selektivität nicht sehr ausgeprägt.

Tabelle 14. Synthese von Furanochinolinen **78a** in verschiedenen Guanidiniumsalzen **19a-r**





Die Povarov-Reaktion kann auch durch viele Guanidiniumsalze **19a-r** initiiert werden (Tabelle 14). Am Beispiel der Umsetzungen unter thermischen Bedingungen in einem verschlossenen Röhrchen ließ sich zeigen, dass sowohl a) die Struktur des Guanidiniumions und die Art des Anions des Guanidiniumsalzes als auch b) die Konzentration des Guanidiniumsalzes einen starken Einfluss auf die chemische Ausbeute und die Diastereoselektivität ausüben.



Schema 50. Der Einfluss katalytischer Mengen (0.1 Äquiv.) des Guanidiniumsalzes **19p** auf die Synthese von **78a**

Bemerkenswert ist, dass sich die Povarov-Reaktion auch in Gegenwart von nur katalytischen Mengen eines Guanidiniumsalzes erfolgreich realisieren lässt. So isolierte man bei der Umsetzung zwischen **80a**, **25a** und **76b** in Anwesenheit von 0.1 Äquiv. **19p** unter thermischen Bedingungen bei 70°C nach 40 min 97% eines 88:12-Gemisches aus **endo-78a** und **exo-78a** (Schema 50). Abschließend wurde gezeigt, dass die Guanidiniumsalze recycelt und mehrere Male ohne Verlust der Reaktivität wiederverwendet werden können.

13. Publications

13.1. Microwave-assisted three-component reaction in conventional solvents and ionic liquids for the synthesis of amino-substituted imidazo[1,2-*a*]pyridines

13.2. Microwave-assisted three-component reaction for the synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones

13.3. Influence of guanidinium salts and other ionic liquids on the three component aza-*Diels-Alder* reaction



13.1. Microwave-assisted three-component reaction in conventional solvents and ionic liquids for the synthesis of amino-substituted imidazo[1,2-*a*]pyridines

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Microwave-assisted three-component reaction in conventional solvents and ionic liquids for the synthesis of amino-substituted imidazo[1,2-*a*]pyridines

Fadime Mert-Balci, Jürgen Conrad, and Uwe Beifuss*

*Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstr. 30, 70599
Stuttgart, Germany*

E-mail: ubeifuss@uni-hohenheim.de

Dedicated to Professor Rainer Beckert on the occasion of his 60th birthday

Abstract

3-Amino-substituted imidazo[1,2-*a*]pyridines can be prepared with yields up to 98% within a few minutes by microwave-assisted three-component reaction between 2-aminopyridines, aldehydes and isocyanides using montmorillonite as the catalyst and toluene as the solvent. The organic solvent can be replaced by ionic liquids. With guanidinium salts the microwave-assisted reaction can be performed in the absence of any further catalyst.

Keywords: Multicomponent reactions, imidazo[1,2-*a*]pyridines, microwaves, ionic liquids, imidazolium salts, guanidinium salts

Introduction

Recently, the application of microwaves in organic synthesis has become very popular. Microwave-assisted syntheses are a particularly attractive alternative to syntheses under thermal conditions since they often proceed much faster and deliver products with higher yields and higher purity.¹ Upon conventional heating using an external heat source like an oil bath the energy transfer depends on the thermal conductivity of the sample to be penetrated, which is relatively slow and inefficient. In contrast, the energy of the microwaves is directly transferred to the molecules of the reaction mixture *via* dielectric heating. The heating is largely caused by dipolar polarization and ionic conduction.

Currently, the use of ionic liquids (ILs) as solvents and catalysts in organic transformations is receiving a great deal of interest.² ILs have an ionic structure and they consist of an organic cation and an inorganic or organic anion. They have nearly no vapor pressure, are thermally and chemically robust, are non explosive, are convenient to use and can be recycled. Therefore, ILs

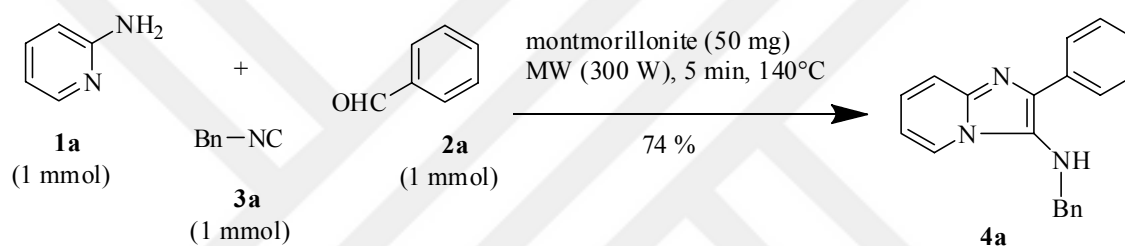
can offer a more sustainable alternative to traditional organic solvents. In a number of reactions performed in ILs both a greatly increased reaction rate and a change in selectivities has been observed. These effects are probably due to polar interactions between the ILs and the substrates. Meanwhile, numerous organic transformations have been performed in ILs,² and many of them from the field of heterocyclic chemistry.³ The significance which ILs have gained in organic synthesis is not only due to their solvent properties but to their catalytic effects as well.⁴ Due to their high polarity and high dielectricity constant ILs can be efficiently heated up by microwave irradiation.⁵ This is why reactions in ILs can benefit tremendously from microwave conditions. The best known ILs are the imidazolium salts which have been successfully used as solvents and/or catalysts in numerous chemical transformations. In addition, there is a large number of other ILs including pyridinium, phosphonium, ammonium and guanidinium salts.

Guanidinium salts, which are easily available by a number of methods, so far have been used in a small number of organic reactions,⁶ including aldol reactions,^{6a,c} Heck reactions,^{6b} and the oxidation of benzylic alcohols.^{6e} Also, guanidinium salts have several properties predisposing them for applications as potential electrolytes in electrochemical devices such as lithium batteries, super capacitors, fuel cells and dye-sensitized solar cells.⁷

Multicomponent reactions are of great importance for the efficient assembly of compound libraries.⁸ The Groebke reaction is a particularly valuable three component reaction as it allows the synthesis of a number of relevant heterocyclic systems. It makes use of the reaction of 2-aminoazines, aldehydes and isocyanides for the preparation of fused 3-aminoimidazoles, including imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyrazines. Due to the marked biological activity of many compounds with an imidazo[1,2-*a*]pyridine skeleton⁹ a number of different protocols for the Groebke reaction have been developed.¹⁰ The synthesis of imidazo[1,2-*a*]pyridines has been achieved in the presence of Brønsted acids^{10h,i} as well as with Lewis acids.^{10b,d,g} The reaction can also be performed in the absence of any catalyst.^{10a} The synthesis has also been performed under microwave conditions in the presence of montmorillonite^{10f} or ZnCl₂.^{10b} There is also a report on the use of [bmim]Br at room temperature to bring about the synthesis of imidazo[1,2-*a*]pyridines.^{10c} However, many of these methods suffer from different drawbacks such as long reaction times and/or the application of expensive catalysts. In order to establish a quick and efficient approach to this class of compounds we decided to study the influence of solvents on the microwave-assisted reaction between 2-aminopyridines, aldehydes and isocyanides in the presence of montmorillonite as the catalyst. It was planned to perform a model reaction in the absence and presence of solvents, including traditional organic solvents as well as ILs. Of particular interest was the use of guanidinium salts as reaction medium.

Results and Discussion

Here we present our results on the microwave-assisted three-component synthesis of 3-amino substituted imidazo[1,2-*a*]pyridines **4** with montmorillonite as the catalyst under a variety of reaction conditions. The reaction between 2-aminopyridine (**1a**), benzaldehyde (**2a**) and benzyliocyanide (**3a**) was used as a model reaction. After some preliminary experiments it was found that the reaction could be run in the absence of any solvent when equimolar amounts of **1a**, **2a** and **3a** were reacted in the presence of montmorillonite in a sealed vial under microwave conditions using a focused single mode microwave reactor for 5 min at 140°C. Under these conditions *N*-benzyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine (**4a**) could be isolated in 74% yield (Scheme 1).



Scheme 1. Microwave-assisted synthesis of **4a** under solvent-free conditions.

Further experiments demonstrated that the yield of **4a** could be improved markedly when the reaction was run in an organic solvent (Table 1). Optimizing the reaction conditions with regard to the amounts of substrates, reaction time and temperature, solvent and the amount of montmorillonite revealed that **4a** could be isolated in 92% yield when 1 mmol **1a**, 1.09 mmol of **2a** and 1.25 mmol of **3a** were reacted with 76 mg montmorillonite in 2 mL toluene at 160 °C for 7 min (Entry 7). When the reaction was run in a sealed vial under thermal conditions (oil bath) the yield of **4a** dropped to 75%.

The microwave-assisted synthesis of **4a** was also studied in different ILs in the presence of montmorillonite. First, the reaction was performed with different imidazolium salts (Table 2). It was found that at higher reaction temperatures mainly decomposition occurs (Entries 3,5). But even at 90°C the formation of **4a** was accompanied with the formation of a side product of unknown structure (Entries 1,2,6). The only IL allowing for the clean formation of **4a** was [bmim]BF₄ at 90°C (Entry 4). Under these conditions **4a** could be isolated with 70% yield. However, in no case did the yield of **4a** exceed that obtained under the conditions given in Table 1, Entry 7.

Table 1. Optimization of the reaction conditions for the synthesis of **4a** in organic solvents

$ \begin{array}{ccccccc} & \text{1a} & + & \text{2a} & + & \text{3a} & \xrightarrow[\text{67 - 92 \%}]{\substack{\text{montmorillonite} \\ \text{organic solvent} \\ \text{MW}}} & \text{4a} \\ \end{array} $								
Entry	1a (mmol)	2a (mmol)	3a (mmol)	t (min)	T (°C)	Solvent (2 mL)	Clay (mg)	Yield 4a (%)
1	1	1.02	1.01	5	140	<i>o</i> -dichlorobenzene	59	71
2	1	1	1.25	7	140	methanol	79	67
3	1.03	1	1.30	5	140	toluene	66	68
4	1	1.04	1.22	7	140	toluene	76	79
5	1	1.07	1.20	5	140	toluene	76	84
6	1	1.09	1.25	7	140	toluene	76	89
7	1	1.09	1.25	7	160	toluene	76	92

Table 2. The use of imidazolium salts as reaction medium in the synthesis of **4a**

$ \begin{array}{ccccccc} & \textbf{1a} & + & \textbf{2a} & + & \textbf{3a} & \xrightarrow[\text{ionic liquid (2 mL)}]{\substack{\text{montmorillonite (76 mg)} \\ \text{MW}}} & \textbf{4a} \\ & (1 \text{ mmol}) & & (1.09 \text{ mmol}) & & (1.25 \text{ mmol}) & & \\ \end{array} $					
Entry	Ionic liquid	Power (W)	t (min)	T (°C)	yield 4a (%)
1	[bmim]Cl	10	30	90	66 ¹
2	[bmim]Br	10	30	90	39 ¹
3	[bmim]Br	30	10	160	Decomposition
4	[bmim]BF ₄	10	30	90	70
5	[bmim]MeSO ₄	20	7	140	Decomposition
6	[bmim]PF ₆	20	7	140	39 ¹

¹ In addition, a side product of unknown structure was observed.

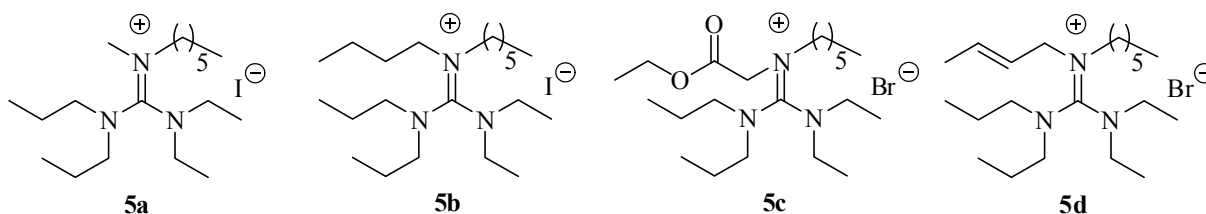
Furthermore, it was studied whether the imidazolium salts can be replaced by guanidinium salts. When the microwave-assisted reaction between **1a**, **2a** and **3a** was run in guanidinium salt **5a** as ionic liquid in the presence of montmorillonite 43% of **4a** could be isolated (Table 3, Entry 1). In a final set of experiments the reaction was studied in the absence of montmorillonite. For this purpose 1 eq **1a**, 1.09 eq **2a** and 1.25 eq **3a** were reacted under microwave conditions in 1 eq

of different guanidinium salts **5a-d** (Table 3, Structure Block 1). The product was formed in each of the ionic liquids employed, but the outcome strongly depends on the structure of the guanidinium salts employed. The highest yield (68%) was obtained with **5c** (Entry 4). However, in no case did the yield of **4a** exceed that obtained under the conditions given in Table 1, Entry 7. The results clearly demonstrate that the three component reaction can be performed in guanidinium salts acting both as solvent and as catalyst. Further studies will be needed to study the influence of the structure of the guanidinium salts.

Table 3. The use of guanidinium salts for the synthesis of **4a**

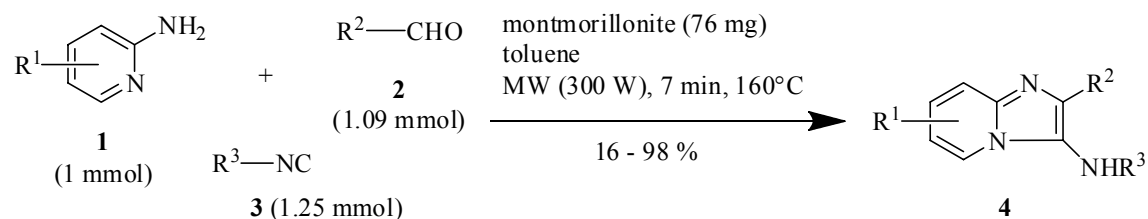
$ \begin{array}{c} \text{1a} \quad + \quad \text{2a} \quad + \quad \text{3a} \\ (1 \text{ mmol}) \quad (1.09 \text{ mmol}) \quad (1.25 \text{ mmol}) \end{array} \xrightarrow[\text{27 - 68 \%}]{\substack{\text{ionic liquid (1 eq)} \\ \text{MW}}} \text{4a} $						
Entry	Ionic liquid	montmorillonite	Power (W)	t (min)	T (°C)	yield 4a (%)
1	5a ¹	76 mg	10	30	90	43
2	5a	-	20	7	160	48 ²
3	5a	-	10	90	90	29
4	5b	-	10	90	90	27
5	5c	-	10	90	90	68
6	5d	-	10	90	90	40

¹ The reaction was performed in 2 mL of **5a**. ² In addition, a side product of unknown structure was observed.

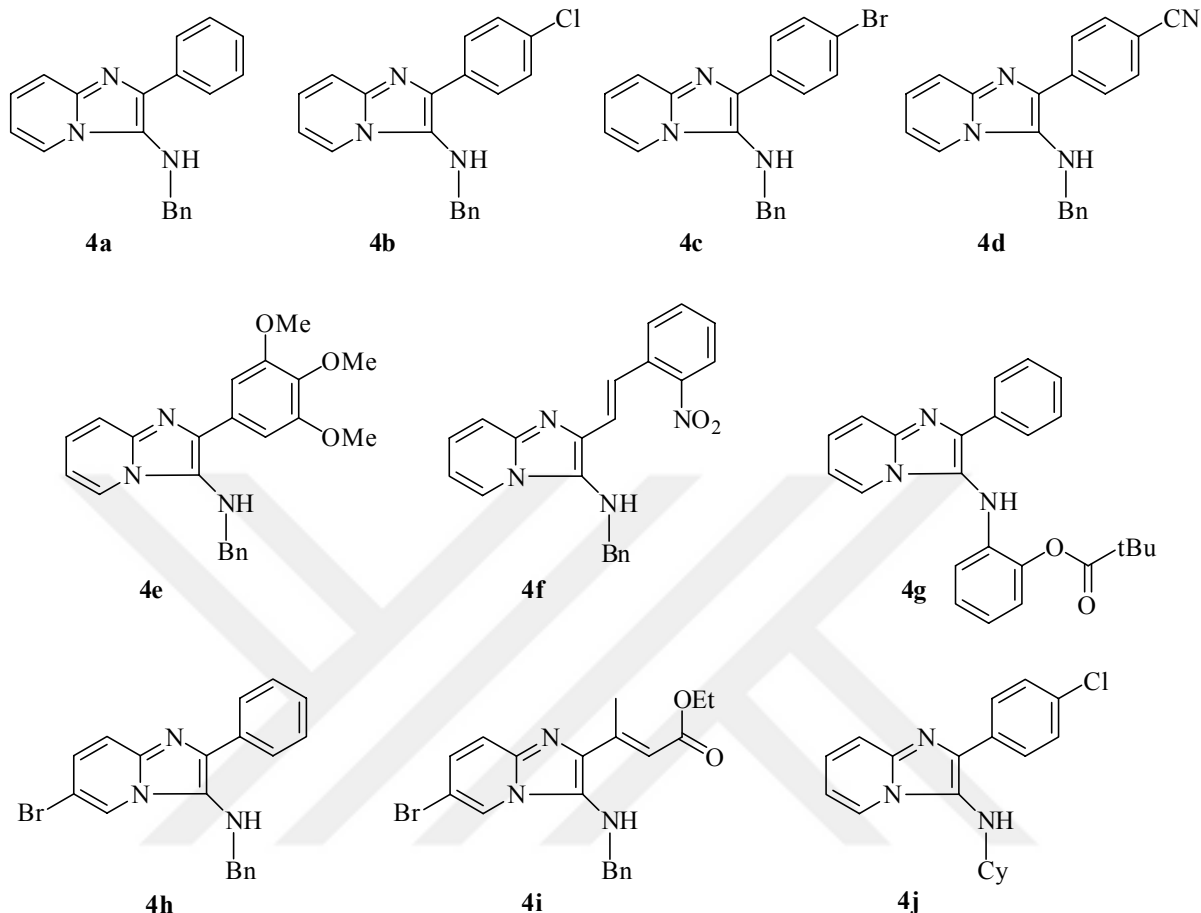


Structure Block 1. Structures of guanidinium salts **5a-d**.

It turned out that the highest yield of **4a** could be obtained when the microwave-assisted reaction between **1a**, **2a** and **3a** using montmorillonite as a catalyst was run in toluene as the solvent. Therefore, the scope of the three-component reaction was studied under these reaction conditions. It was found that 2-aminopyridines **1a,b** can be successfully reacted with different aldehydes **2a-f** and isocyanides **3a-c** to produce a number of imidazo[1,2-*a*]pyridines **4a-j** with yields ranging from 16% to 98% in analytically pure form (Table 4, Structure Block 2).

Table 4. Synthesis of imidazo[1,2-*a*]pyridines **4a-j** from different 2-aminopyridines **1**, aldehydes **2** and isocyanides **3**

Entry	1	R ¹	2	R ²	3	R ³	Product	Yield (%)
1	1a	H	2a		3a		4a	92
2	1a	H	2b		3a		4b	70
3	1a	H	2c		3a		4c	80
4	1a	H	2d		3a		4d	77
5	1a	H	2e		3a		4e	60
6	1a	H	2f		3a		4f	53
7	1a	H	2a		3b		4g	94
8	1b	5-Br	2a		3a		4h	72
9	1b	5-Br	2g		3a		4i	16
10	1a	H	2b		3c		4j	98



Structure Block 2. Structures of imidazo[1,2-*a*]pyridines **4a-j**.

The structures of all imidazo[1,2-*a*]pyridines **4a-j** described here have been elucidated by means of mass, ^1H , ^{13}C , COSY, HSQC and HMBC spectroscopic methods. The assignment of the quaternary carbons relies on long-range correlations in the HMBC spectra.

Conclusions

In summary, the microwave-assisted three-component reaction between 2-aminopyridines, aldehydes and isocyanides with montmorillonite as the catalyst and in toluene as the solvent delivers 3-amino-substituted imidazo[1,2-*a*]pyridines with yields up to 98% within a few minutes. The organic solvent can be replaced by ILs like imidazolium or guanidinium salts. With guanidinium salts the reaction can be performed in the absence of any further catalyst.

Experimental Section

General. Starting materials were purchased from chemical companies and used without purification. Toluene was distilled from sodium. All microwave-assisted reactions were performed using a DiscoverTM single mode cavity microwave synthesizer (CEM Corp.) producing continuous microwave irradiation at 2450 MHz. All experiments were conducted under argon. Thin-layer chromatography (TLC) was performed on TLC aluminum roll silica gel 60 F₂₅₄ (Merck). Compounds were visualized with UV light ($\lambda = 254$ nm) and/or immersion in KMnO₄ solution followed by heating. Column chromatography was performed on silica gel MN 60, 0.063 mm-0.200 mm. Melting points were determined on a Kofler melting point apparatus (Reichert, Austria) and are uncorrected. IR (ATR) spectra were taken on a Spectrum One FT-IR spectrometer (Perkin Elmer). UV spectra were measured using a CARY 4E spectrophotometer (Varian). NMR spectra were recorded on a Varian^{Unity} INOVA spectrometer (300/75 MHz) in CDCl₃; the ¹H and ¹³C chemical shifts were referenced to residual solvent signals at $\delta_H = 7.26$ and $\delta_C = 77.0$ relative to TMS. Mass spectra were recorded on a MAT 90 with 70 eV ionization energy (Finnigan MAT). Elemental analyses were carried out by F. Hambloch, Institute of Organic and Biomolecular Chemistry, University of Göttingen.

General procedure A for the reaction of 1, 2 and 3 under microwave conditions in toluene

1 (1 mmol), **2** (1.09 mmol) and **3** (1.25 mmol) were suspended in toluene (2 mL) and placed in a 10 mL reaction vial heated and cooled under Ar. After addition of montmorillonite (76 mg) the vial was sealed with a septum and irradiated with microwaves (300W) for 7 min at 160°C. The reaction mixture was allowed to cool to r.t. and was then diluted with CH₂Cl₂ (10 mL) and filtered. The residue obtained after concentration *in vacuo* was purified by column chromatography on silica gel to yield **4**.

General procedure B for the reaction of 1a, 2a and 3a under microwave conditions in imidazolium salts

1a (1 mmol), **2a** (1.09 mmol), **3a** (1.25 mmol) and montmorillonite (76 mg) were placed in a 10 mL reaction vial that had been heated and cooled under Ar. After addition of the imidazolium salt (2 mL) the vial was sealed with a septum and irradiated with microwaves. After completion of the reaction, the mixture was allowed to cool to r.t. and washed with EE or TBME (5 × 5 mL). The combined organic extracts were concentrated *in vacuo* and the residue was purified by column chromatography on silica gel to yield **4a**.

General procedure C for the reaction of 1a, 2a and 3a under microwave conditions in guanidinium salts

1a (1 mmol), **2a** (1.09 mmol), **3a** (1.25 mmol) and the guanidinium salt **5** (1 mmol) were placed in a 10 mL reaction vial that had been heated and cooled under argon. The vial was sealed with a

septum and irradiated with microwaves. After completion of the reaction, the mixture was allowed to cool to r.t. and then purified by column chromatography on silica gel to yield **4a**.

***N*-Benzyl-2-phenylimidazo[1,2-*a*]pyridin-3-amine (4a).**^{10f} According to general procedure A 94 mg (1 mmol) **1a**, 116 mg (1.09 mmol) **2a** and 146 mg (1.25 mmol) **3a** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography (TBME/PE = 10/2) 274 mg (0.92 mmol) **4a** (92 %) were isolated as a yellow solid.

mp 122-123°C (Lit.^{10f} mp 112-113°C). IR (ATR): $\tilde{\nu}$ = 3256, 3057, 3020, 1564, 1491, 1472, 1444, 1386, 1348, 1334, 1228, 1192, 1077, 1026, 907, 752, 735, 706, 694. ¹H NMR (300 MHz, CDCl₃): δ = 3.53 (1H, t, *J* = 6.2 Hz, NH), 4.20 (2H, d, *J* = 6.3 Hz, 7''-CH₂), 6.74 (1H, ddd, *J* = 0.9 Hz, *J* = 6.8 Hz, *J* = 6.8 Hz, 5-H), 7.13 (1H, ddd, *J* = 1.3 Hz, *J* = 6.7 Hz, *J* = 9.2 Hz, 6-H), 7.27-7.38 (6H, m, 4'-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 7.45 (2H, t, *J* = 7.6 Hz, 3'-H, 5'-H), 7.56 (1H, bd, *J* = 9.1 Hz, 7-H), 7.90-8.05 (3H, m, 2'-H, 6'-H, 4-H). ¹³C-NMR (75 MHz, CDCl₃): δ = 52.40 (7''-CH₂), 111.79 (5-C), 117.31 (7-C), 122.35 (4-C), 124.20 (6-C), 125.62 (3-C), 127.01 (2'-C, 6'-C), 127.49 (4'-C), 127.65 (4''-C), 128.13 (2''-C, 6''-C), 128.67 (3'-C, 5'-C, 3''-C, 5''-C), 133.90 (1'-C), 135.81 (2-C), 138.90 (1''-C), 141.36 (7a-C). MS (70 eV, EI): *m/z* (%) = 299 (45) [M⁺], 208 (100), 181 (97), 91 (13), 78 (87), 51 (11).

2-(4-Chlorophenyl)-*N*-benzylimidazo[1,2-*a*]pyridin-3-amine (4b). According to the general procedure A 94 mg (1 mmol) **1a**, 153 mg (1.09 mmol) **2b** and 146 mg (1.25 mmol) **3a** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography (TBME/PE = 5/3) 233mg (0.7 mmol) **4b** (70 %) were isolated as a yellow solid.

mp 166-167 °C. IR (ATR): $\tilde{\nu}$ = 3249, 3018, 2919, 1558, 1488, 1454, 1384, 1350, 1332, 1242, 1188, 1090, 1076, 1010, 911, 835, 750, 732, 698. UV (CH₃CN): λ_{max} (lg ϵ) = 339 nm (3.89), 253 (4.58). ¹H-NMR (300 MHz, CDCl₃): δ = 3.42 (1H, t, *J* = 5.9 Hz, NH), 4.17 (2H, d, *J* = 5.9 Hz, 7''-CH₂), 6.74 (1H, ddd, *J* = 1.1 Hz, *J* = 6.7 Hz, *J* = 6.7 Hz, 5-H), 7.13 (1H, ddd, *J* = 1.3 Hz, *J* = 6.6 Hz, *J* = 9.1 Hz, 6-H), 7.28-7.35 (5H, m, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 7.37-7.41 (2H, m, 3'-H, 5'-H), 7.53 (1H, dt, *J* = 1.1 Hz, *J* = 9.1 Hz, 7-H), 7.96 (2H, m, 2'-H, 6'-H), 7.98 (1H, dt, *J* = 1.4 Hz, *J* = 6.7 Hz, 4-H). ¹³C-NMR (75 MHz, CDCl₃): δ = 52.39 (7''-CH₂), 111.85 (5-C), 117.48 (7-C), 122.27 (4-C), 124.28 (6-C), 125.52 (3-C), 127.74 (4''-C), 128.15 (2'-C, 6'-C), 128.20 and 128.74 (2''-C and 6''-C or 3''-C and 5''-C), 128.76 (3'-C, 5'-C), 132.68 (1'-C), 133.17 (4'-C), 135.15 (2-C), 138.78 (1''-C), 141.60 (7a-C). MS (70 eV, EI): *m/z* (%) = 333 (16) [M⁺], 242 (100), 215 (71), 78 (40). Anal. Calcd. for C₂₀H₁₆ClN₃: C, 71.96; H, 4.83; Cl, 10.62; N, 12.59. Found: C, 71.82; H, 4.74; N, 12.80.

***N*-Benzyl-2-(4-bromophenyl)imidazo[1,2-*a*]pyridin-3-amine (4c).** According to the general procedure A 94 mg (1 mmol) **1a**, 202 mg (1.09 mmol) **2c** and 146 mg (1.25 mmol) **3a** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography (TBME/PE = 5/2) 304 mg (0.8 mmol) **4c** (80 %) were isolated as a pale yellow solid.

mp 165-166°C. IR (ATR): $\tilde{\nu}$ = 3242, 1557, 1488, 1443, 1384, 1346, 1331, 1226, 1193, 1070, 1008, 829, 752, 733, 695. UV (CH₃CN): λ_{max} (lg ϵ) = 340 nm (3.93), 255 (4.59). ¹H-NMR (300 MHz, CDCl₃): δ = 3.42 (1H, t, J = 6.0 Hz, NH), 4.17 (2H, d, J = 6.2 Hz, 7'-CH₂), 6.75 (1H, ddd, J = 1.1 Hz, J = 6.8 Hz, J = 6.8 Hz, 5-H), 7.14 (1H, ddd, J = 1.3 Hz, J = 6.7 Hz, J = 9.0 Hz, 6-H), 7.27-7.35 (5H, m, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 7.54 (3H, overlapped, 3'-H, 5'-H, 7-H), 7.87 (2H, d, J = 8.5 Hz, 2'-H, 6'-H), 7.95 (1H, dt, J = 1.2 Hz, J = 6.9 Hz, 4-H). ¹³C-NMR (75 MHz, CDCl₃): δ = 52.32 (7'-CH₂), 112.05 (5-C), 117.28 (7-C), 121.51 (4'-C), 122.35 (4-C), 124.64 (6-C), 125.61 (3-C), 127.76 (4''-C), 128.15 and 128.48 and 128.74 (2'-C and 6'-C or 2''-C and 6''-C or 3''-C and 5''-C), 131.71 (3'-C, 5'-C), 132.76 (1'-C), 134.79 (2-C), 138.73 (1''-C), 141.39 (7a-C). MS (70 eV, EI): m/z (%) = 377 (26) [M⁺], 286 (100), 259 (64), 180 (9), 91 (19), 78 (80). Anal. Calcd. for C₂₀H₁₆BrN₃: C, 63.50; H, 4.26; Br, 21.12; N, 11.11. Found: C, 63.55; H, 4.19; N, 11.02.

***N*-Benzyl-2-(4-cyanophenyl)imidazo[1,2-*a*]pyridin-3-amine (4d).** According to the general procedure A 94 mg (1 mmol) **1a**, 143 mg (1.09 mmol) **2d** and 146 mg (1.25 mmol) **3a** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography (TBME/PE = 10/3) 249 mg (0.77 mmol) **4d** (77 %) were isolated as a yellow solid.

mp 190-191°C. IR (ATR): $\tilde{\nu}$ = 3244, 2225, 1605, 1574, 1454, 1348, 1190, 851, 760, 748, 729, 701. UV (CH₃CN): λ_{max} (lg ϵ) = 350 nm (4.00), 265 (4.53). ¹H-NMR (300 MHz, CDCl₃): δ = 3.54 (1H, t, J = 6.0 Hz, NH), 4.18 (2H, d, J = 6.1 Hz, 7''-CH₂), 6.77 (1H, ddd, J = 1.1 Hz, J = 6.8 Hz, J = 6.8 Hz, 5-H), 7.18 (1H, ddd, J = 1.3 Hz, J = 6.6 Hz, J = 9.0 Hz, 6-H), 7.27-7.31 (5H, m, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 7.54 (1H, dt, J = 1.1 Hz, J = 8.9 Hz, 7-H), 7.65 (2H, d, J = 8.4 Hz, 3'-H, 5'-H), 7.93 (1H, dt, J = 1.2 Hz, J = 6.8 Hz, 4-H), 8.12 (2H, d, J = 8.4 Hz, 2'-H, 6'-H). ¹³C-NMR (75 MHz, CDCl₃): δ = 52.40 (7''-CH₂), 110.43 (4'-C), 112.35 (5-C), 117.62 (7-C), 119.08 (1'-C), 122.36 (4-C), 125.09 (6-C), 126.70 (3-C), 127.11 (2'-C, 6'-C), 127.89 (4''-C), 128.13 (2''-C, 6''-C), 128.80 (3''-C, 5''-C), 132.29 (3'-C, 5'-C), 133.90 (2-C), 138.47 (1''-C), 141.74 (7a-C). MS (70 eV, EI): m/z (%) = 324 (45) [M⁺], 233 (100), 206 (85), 91 (12), 78 (76). HRMS (70 eV, EI) for C₂₁H₁₆N₄: Calcd.: 324.1375; Found: 324.1397.

***N*-Benzyl-2-(3,4,5-trimethoxyphenyl)imidazo[1,2-*a*]pyridin-3-amine (4e).** According to the general procedure A 94 mg (1 mmol) **1a**, 214 mg (1.09 mmol) **2e** and 146 mg (1.25 mmol) **3a** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography (EE/PE = 5/2) 232 mg (0.6 mmol) **4e** (60 %) were isolated as a pale yellow solid.

mp 131-132°C. IR (ATR): $\tilde{\nu}$ = 3189, 2829, 1587, 1495, 1446, 1412, 1391, 1357, 1231, 1120, 1000, 759, 723, 694. UV (CH₃CN): λ_{max} (lg ϵ) = 339 nm (3.89), 261 (4.43), 223 (4.59). ¹H-NMR (300 MHz, CDCl₃): δ = 3.46 (1H, bs, NH), 3.90 (9H, s, 3'-OCH₃, 4'-OCH₃, 5'-OCH₃), 4.23 (2H, d, J = 5.6 Hz, 7'-CH₂), 6.75 (1H, ddd, J = 1.1 Hz, J = 6.7 Hz, J = 6.7 Hz, 5-H), 7.13 (1H, ddd, J = 1.3 Hz, J = 6.6 Hz, J = 9.0 Hz, 6-H), 7.27-7.35 (7H, m, 2'-H, 6'-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 7.55 (1H, dt, J = 1.1 Hz, J = 9.1 Hz, 7-H), 7.95 (1H, dt, J = 1.2 Hz, J = 6.8 Hz, 4-H). ¹³C-

NMR (75 MHz, CDCl₃): δ = 52.40 (7'-CH₂), 56.22 (3'-OCH₃, 5'-OCH₃), 60.91 (4'-OCH₃), 104.26 (2'-C, 6'-C), 111.89 (5-C), 117.23 (7-C), 122.20 (4-C), 124.26 (6-C), 125.28 (3-C), 127.73 (4'-C), 128.02 (2'-C, 6'-C), 128.73 (3'-C, 5'-C), 129.57 (1'-C), 135.67 (2-C), 137.67 (4'-C), 138.88 (1'-C), 141.22 (7a-C), 153.40 (3'-C, 5'-C). MS (70 eV, EI): m/z (%) = 389 (25) [M⁺], 298 (100), 271 (72), 78 (16). HRMS (70 eV, EI) for C₂₃H₂₃N₃O₃: Calcd.: 389.1700; Found: 389.1747.

***N*-Benzyl-2-(2-nitrophenylethenyl)imidazo[1,2-*a*]pyridin-3-amine (4f).** According to the general procedure A 94 mg (1 mmol) **1a**, 193 mg (1.09 mmol) **2f** and 146 mg (1.25 mmol) **3a** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography (EE/PE = 5/3) 195 mg (0.53 mmol) **4f** (53 %) were isolated as an orange solid. mp 152-154°C. IR (ATR): $\tilde{\nu}$ = 3351, 2929, 1514, 1348, 1276, 958, 755, 740, 703. UV (CH₃CN): $\lambda_{\max}$ (lg ϵ) = 375 nm (4.07), 317 (4.14), 261 (4.44). ¹H-NMR (300 MHz, CDCl₃): δ = 3.48 (1H, t, J = 6.8 Hz, NH), 4.22 (2H, d, J = 6.0 Hz, 7'-CH₂), 6.74 (1H, td, J = 1.1 Hz, J = 6.8 Hz, 5-H), 6.87 (1H, d, J = 15.8 Hz, 1'-H), 7.14 (1H, ddd, J = 1.3 Hz, J = 6.7 Hz, J = 9.2 Hz, 6-H), 7.28-7.32 (5H, m, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H), 7.33-7.39 (1H, m, 6'-H), 7.51 (1H, dt, J = 1.1 Hz, J = 9.1 Hz, 7-H), 7.53 (2H, overlapped, 7'-H, 8'-H), 7.85 (1H, d, J = 15.8 Hz, 2'-H), 7.90 (1H, dt, J = 0.9 Hz, J = 8.3 Hz, 5'-H), 7.93 (1H, dt, J = 1.1 Hz, J = 7.0 Hz, 4-H). ¹³C-NMR (75 MHz, CDCl₃): δ = 53.08 (7'-CH₂), 111.75 (5-C), 117.46 (7-C), 122.21 (4-C), 123.93 (2'-C), 124.11 (1'-C), 124.60 (5'-C), 124.70 (6-C), 127.57 (6'-C), 127.69 (4'-C), 127.84 (3-C), 128.00 (8'-C), 128.39 (3'-C, 5'-C), 128.72 (2'-C, 6'-C), 132.67 (7'-C), 133.11 (3'-C), 134.71 (2-C), 139.18 (1'-C), 142.22 (7a-C), 148.01 (4'-C). MS (70 eV, EI): m/z (%) = 370 (42) [M⁺], 279 (100), 252 (46), 234 (16), 205 (10), 145 (7), 128 (6), 91 (7), 78 (41). HRMS (70 eV, EI) for C₂₂H₁₈N₄O₂: Calcd.: 370.1430; Found: 370.1426.

***N*-(2-(2,2-Dimethyl-1-oxopropoxy)phenyl)-2-phenylimidazo[1,2-*a*]pyridin-3-amine (4g).**

According to the general procedure A 94 mg (1 mmol) **1a**, 116 mg (1.09 mmol) **2a** and 254 mg (1.25 mmol) **3b** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography (TBME/PE = 4/3) 362 mg (0.94 mmol) **4g** (94 %) were isolated as a pale gray solid.

mp 216-217°C. IR (ATR): $\tilde{\nu}$ = 2970, 1743, 1519, 1492, 1447, 1391, 1343, 1254, 1172, 1106, 756, 741, 699. UV (CH₃CN): $\lambda_{\max}$ (lg ϵ) = 330 nm (3.83), 245 (4.60), 202 (4.60). ¹H-NMR (300 MHz, CDCl₃): δ = 1.43 (9H, s, 2'-CH₃), 5.63 (1H, s, NH), 6.32 (1H, dd, J = 1.3 Hz, J = 7.9 Hz, 5'-H), 6.80 (1H, t, J = 6.8 Hz, 5-H), 6.88 (1H, td, J = 1.4 Hz, J = 7.6 Hz, 3'-H), 6.98 (1H, td, J = 1.2 Hz, J = 7.8 Hz, 4'-H), 7.11 (1H, dd, J = 1.3 Hz, J = 7.9 Hz, 2'-H), 7.20-7.32 (2H, m, 4'-H, 6-H), 7.38 (2H, t, J = 7.4 Hz, 3'-H, 5'-H), 7.66 (1H, d, J = 9.1 Hz, 7-H), 7.87 (1H, d, J = 6.9 Hz, 4-H), 8.02 (2H, d, J = 7.4 Hz, 2'-H, 6'-H). ¹³C-NMR (75 MHz, CDCl₃): δ = 27.31 (2'-CH₃), 39.44 (2'-C), 112.45 (5-C), 113.79 (5'-C), 116.97 (3-C), 117.65 (7-C), 120.14 (3'-C), 122.67 (2'-C), 122.84 (4-C), 125.18 (6-C), 126.88 (2'-C, 6'-C), 127.09 (4'-C), 127.95 (4'-C), 128.67 (3'-C, 5'-C), 133.15 (1'-C), 136.53 (6'-C), 138.66 (1'-C), 139.46 (2-C), 142.84 (7a-

C), 176.77 (1'''-C). MS (70 eV, EI): m/z (%) = 385 (100) [M^+], 300 (49), 181 (77), 78 (31), 57 (20). Anal. Calcd. for $C_{24}H_{23}N_3O_2$: C, 74.78; H, 6.01; N, 10.90; O, 8.30. Found: C, 74.81; H, 5.87; N, 10.73.

***N*-Benzyl-5-bromo-2-phenylimidazo[1,2-*a*]pyridin-3-amine (4h).** According to the general procedure A 173 mg (1 mmol) **1b**, 116 mg (1.09 mmol) **2a** and 146 mg (1.25 mmol) **3a** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography ($CH_2Cl_2/EE = 12/1$) 270 mg (0.72 mmol) **4h** (72 %) were isolated as a white solid.

mp 173-174°C. IR (ATR): $\tilde{\nu} = 3241, 1474, 1445, 1404, 1323, 1215, 1054, 914, 805, 767, 752, 702, 693$. UV (CH_3CN): λ_{max} (lg ϵ) = 347 nm (3.82), 251 (4.56). ^1H -NMR (300 MHz, $CDCl_3$): $\delta = 3.54$ (1H, t, $J = 5.7$ Hz, NH), 4.18 (2H, d, $J = 5.9$ Hz, 7''-CH₂), 7.16 (1H, dd, $J = 1.8$ Hz, $J = 9.5$ Hz, 6-H), 7.28-7.37 (6H, m, 4'-H, 2''-H, 3''-H, 4''-H, 5''-H, 6''-H), 7.40-7.48 (3H, overlapped, 3'-H, 5'-H, 7-H), 7.95 (2H, d, $J = 7.3$ Hz, 2'-H, 6'-H), 8.03 (1H, dd, $J = 0.8$ Hz, $J = 1.9$ Hz, 4-H). ^{13}C -NMR (75 MHz, $CDCl_3$): $\delta = 52.49$ (7''-CH₂), 106.67 (5-C), 117.96 (7-C), 122.66 (4-C), 125.84 (3-C), 126.99 (2'-C, 6'-C), 127.50 (6-C), 127.80 (4'-C), 127.86 (4''-C), 128.23 (2''-C, 6''-C), 128.74 (3'-C, 5'-C, 3''-C, 5''-C), 133.50 (1'-C), 136.99 (2-C), 138.60 (1''-C), 159.75 (7a-C). MS (70 eV, EI): m/z (%) = 377 (26) [M^+], 286 (99), 259 (100), 180 (9), 156 (33), 103 (9), 91 (22), 76 (12). Anal. Calcd. for $C_{20}H_{16}BrN_3$: C, 63.50; H, 4.26; Br, 21.12; N, 11.11. Found: C, 63.49; H, 4.06; N, 10.95.

***N*-Benzyl-5-bromo-2-(3-ethoxy-1-methyl-3-oxo-1-propen-1-yl)imidazo[1,2-*a*]pyridin-3-amine (4i).**

According to the general procedure A 173 mg (1 mmol) **1b**, 155 mg (1.09 mmol) **2g** and 146 mg (1.25 mmol) **3a** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography ($CH_2Cl_2/TBME = 15/1$) 67 mg (0.16 mmol) **4i** (16 %) were isolated as a yellow solid.

mp 185-186°C. IR (ATR): $\tilde{\nu} = 3303, 1687, 1614, 1451, 1331, 1311, 1197, 1169, 1105, 1048, 881, 812, 698$. UV (CH_3CN): λ_{max} (lg ϵ) = 357 nm (3.84), 261 (4.49). ^1H -NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (3H, t, $J = 7.1$ Hz, 1''-CH₃), 2.65 (3H, s, 1'-CH₃), 3.53 (1H, t, $J = 6.1$ Hz, NH), 4.15 (2H, d, $J = 6.1$ Hz, 7'''-CH₂), 4.22 (2H, q, $J = 7.1$ Hz, 1''-CH₂), 6.53 (1H, s, 2'-H), 7.17 (1H, dd, $J = 1.7$ Hz, $J = 9.5$ Hz, 6-H), 7.29-7.35 (5H, m, 2'''-H, 3'''-H, 4'''-H, 5'''-H, 6'''-H), 7.39 (1H, d, $J = 9.5$ Hz, 7-H), 8.02 (1H, s, 4-H). ^{13}C -NMR (75 MHz, $CDCl_3$): $\delta = 14.34$ (1''-CH₃), 16.86 (1'-CH₃), 52.55 (7'''-CH₂), 59.81 (1''-CH₂), 107.16 (5-C), 117.47 (2'-C), 118.36 (7-C), 122.68 (4-C), 127.54 (3-C), 128.01 (6-C or 4'''-C), 128.12 (6-C or 4'''-C), 128.32 (2'''-C, 6'''-C), 128.81 (3'''-C, 5'''-C), 137.53 (2-C), 138.12 (1'''-C), 139.35 (7a-C), 148.45 (1'-C), 166.89 (3'-C). MS (70 eV, EI): m/z (%) = 413 (41) [M^+], 322 (100), 295 (39), 278 (32), 156 (24), 91 (38). Anal. Calcd. for $C_{20}H_{20}BrN_3O_2$: C, 57.98; H, 4.87; Br, 19.29; N, 10.14; O, 7.72. Found: C, 57.85; H, 4.58; N, 9.88.

2-(4-Chlorophenyl)-N-cyclohexylimidazo[1,2-*a*]pyridin-3-amine (4j).^{10a} According to the general procedure A 94 mg (1 mmol) **1a**, 153 mg (1.09 mmol) **2b** and 136 mg (1.25 mmol) **3c** were reacted with 76 mg montmorillonite in 2 mL toluene. After work up and column chromatography (CH₂Cl₂/TBME = 15/1) 320 mg (0.98 mmol) **4j** (98 %) were isolated as a pale gray solid.

mp 191-192°C (Lit.^{10a} mp 179-181°C). ¹H-NMR (300 MHz, CDCl₃): δ = 1.19 (3H, overlapped, 4''-Ha, 3''-Ha, 5''-Ha), 1.29 (2H, bt, *J* = 11.5 Hz, 2''-Ha, 6''-Ha), 1.61 (1H, bs, 4''-Hb), 1.72 (2H, m, 3''-Hb, 5''-Hb), 1.83 (2H, m, 2''-Hb, 6''-Hb), 2.93-2.95 (1H, m, 1''-H), 3.05 (1H, d, *J* = 4.5 Hz, NH), 6.79 (1H, ddd, *J* = 1.1 Hz, *J* = 6.8 Hz, *J* = 6.8 Hz, 5-H), 7.14 (1H, ddd, *J* = 1.2 Hz, *J* = 6.8 Hz, *J* = 8.9 Hz, 6-H), 7.40 (2H, m, 3'-H, 5'-H), 7.53 (1H, dt, *J* = 0.9 Hz, *J* = 9.0 Hz, 7-H), 8.02 (2H, m, 2'-H, 6'-H), 8.07 (1H, dt, *J* = 1.1 Hz, *J* = 6.8 Hz, 4-H). ¹³C-NMR (75 MHz, CDCl₃): δ = 24.77 (3''-C, 5''-C), 25.65 (4''-C), 34.17 (2''-C, 6''-C), 56.82 (1''-C), 111.98 (5-C), 117.12 (7-C), 122.74 (4-C), 124.61 (6-C), 124.91 (3-C), 128.25 (2'-C, 6'-C), 128.65 (3'-C, 5'-C), 132.44 (1'-C), 133.13 (2-C), 135.06 (4'-C), 141.29 (7a-C). MS (70 eV, EI): *m/z* (%) = 325 (62) [M⁺], 242 (100), 215 (58), 78 (25). HRMS (70 eV, EI) for C₁₉H₂₀ClN₃: Calcd.: 325.1300; Found: 325.1354.

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13.2. Microwave-assisted three-component reaction for the synthesis of pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-ones

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Microwave-Assisted Three-Component Reaction for the Synthesis of Pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones

Fadime Mert-Balci^a, Jürgen Conrad^a, Kathrin Meindl^b, Thomas Schulz^b, Dietmar Stalke^b, Uwe Beifuss^{a*}

^aBioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstr. 30, 70599 Stuttgart, Germany

Fax: (+49)711-459-22951; E-mail: ubeifuss@uni-hohenheim.de

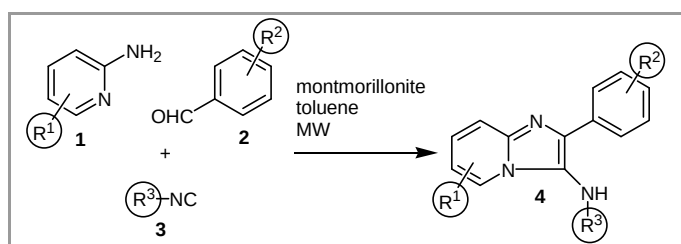
^bInstitut für Anorganische Chemie, Universität Göttingen, Tammannstr. 4, 37077 Göttingen, Germany

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Abstract: Pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones can be obtained by a microwave-assisted three-component reaction between 2-aminopyridines, isocyanides and 2-carboxybenzaldehydes under acidic conditions.

Key words: heterocycles, lactams, multicomponent reactions, Ugi reaction, isocyanide

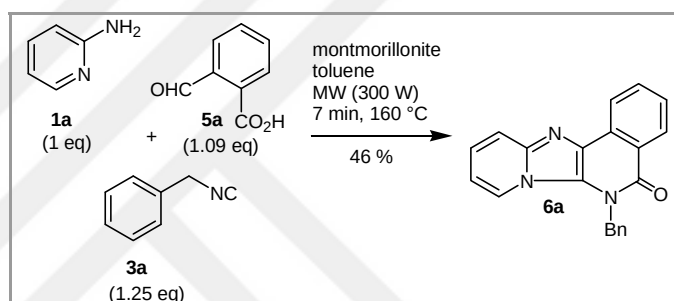
There is no doubt that multicomponent reactions (MCRs) are of central importance to the rapid assembly of large arrays of compounds with diverse substitution patterns.¹ A particularly efficient variant of the Ugi reaction,² the so called Groebke reaction, makes use of the conversion of 2-aminoazines, aldehydes and isocyanides in the presence of a Brønsted acid for the synthesis of fused 3-aminoimidazoles, such as imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines and imidazo[1,2-*a*]pyrazines.³ As these types of heterocycles have proven to be successful in the field of medicinal chemistry,⁴ different reaction conditions have been developed that allow to carry out this three-component reaction (3CR) efficiently.^{3,5}



Scheme 1 Microwave-assisted synthesis of imidazo[1,2-*a*]pyridines **4**

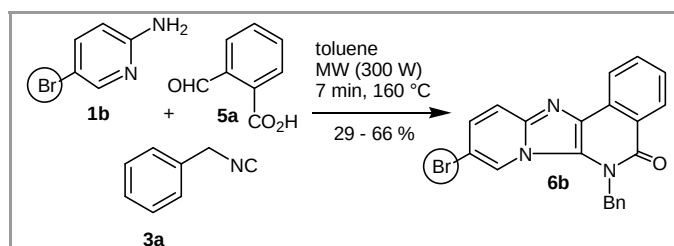
When we performed experiments towards the microwave-assisted synthesis of imidazo[1,2-*a*]pyridines **4** by reaction of different substituted 2-aminopyridines **1**, benzaldehydes **2** and isocyanides **3** it was found that these transformations can be effectively conducted with montmorillonite as a reagent and toluene as a solvent. Under these conditions the corresponding imidazo[1,2-*a*]pyridines **4** could be synthesized successfully (Scheme 1).⁶ Analysis of the studies published so far revealed that the scope of this reaction can be expanded considerably when the nucleophilicity of the amino group in 3-position of the imidazole moiety is employed for further transformations. Here we report on experiments to try out this approach. The reaction between 2-carboxy substituted benzaldehydes, 2-aminopyridines and isocya-

nides was chosen as an example. The spatial proximity of the amino nitrogen of the imidazole moiety and the carboxyl group of the aryl moiety should allow the formation of a lactam and hence provide a new access to pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones in a single synthetic operation.⁷



Scheme 2 Microwave-assisted synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-one **6a**

The model reaction between the 2-aminopyridine (**1a**), the benzylisocyanide (**3a**) and the 2-carboxybenzaldehyde (**5a**) was performed under the conditions that had proven successful for the synthesis of **4**. As a matter of fact, compound **6a** with a pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-one skeleton could be isolated in 46% (Scheme 2). Obviously, this three-component reaction allows the formation of two heterocyclic rings and four new bonds in a single operation. The positive outcome of the model reaction prompted detailed studies about the scope of the new reaction.



Scheme 3 Optimization of the reaction conditions using the synthesis of **6b** as an example

To start with, the reaction conditions were optimized using the example of the transformation of the aminopyridine **1b** with **3a** and **5a**. It was found that not only

montmorillonite but also several Brønsted acids like *p*-TsOH, CH₃SO₃H and CF₃SO₃H (Scheme 3, Table 1) can be used as a reagent. By varying the amount of CH₃SO₃H it could be established that the highest yield of **6b** was obtained with 0.2 equivalents of the acid (Table 1, entry 5). A further increase in **6b** from 54 to 66% was achieved by using the isocyanide **3a** in excess (2.25 equivalents) (Table 1, entry 7). It was also possible to run the reaction of **1b**, **3a** and **5a** in different imidazolium- and guanidinium salts as ionic liquids in the presence as well as in the absence of montmorillonite and CH₃SO₃H, respectively. It should be noted that the synthesis of **6b** can also be achieved in the absence of any reagent and solvent. In no case did the yield of **6b** exceed that obtained under the conditions given in Table 1, entry 7, though.

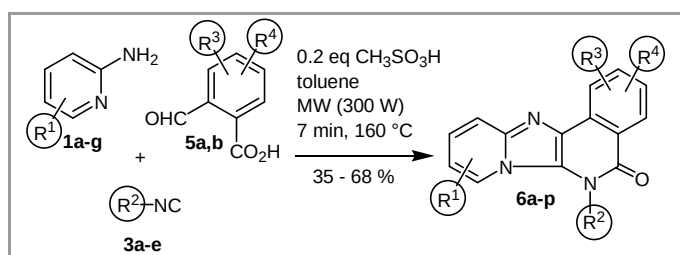
Table 1 Optimizing the reaction conditions for the reaction of **1b** with **3a** and **5a**

Entry	Equiv. of 1b	Equiv. of 3a	Equiv. of 5a	Reagent	Equiv.	Yield of 6b (%) ^{a)}
1	1	1.25	1.09	Clay ^{b)}	76 mg	29
2	1	1.25	1.09	<i>p</i> -TsOH	0.1	46
3	1	1.25	1.09	CF ₃ SO ₃ H	0.1	42
4	1	1.25	1.09	CH ₃ SO ₃ H	0.1	52
5	1	1.25	1.09	CH ₃ SO ₃ H	0.2	54
6	1	1.25	1.09	CH ₃ SO ₃ H	0.7	52
7	1	2.25	1.09	CH ₃ SO ₃ H	0.2	66

^{a)} Isolated yield of product.

^{b)} Montmorillonite was used as clay.

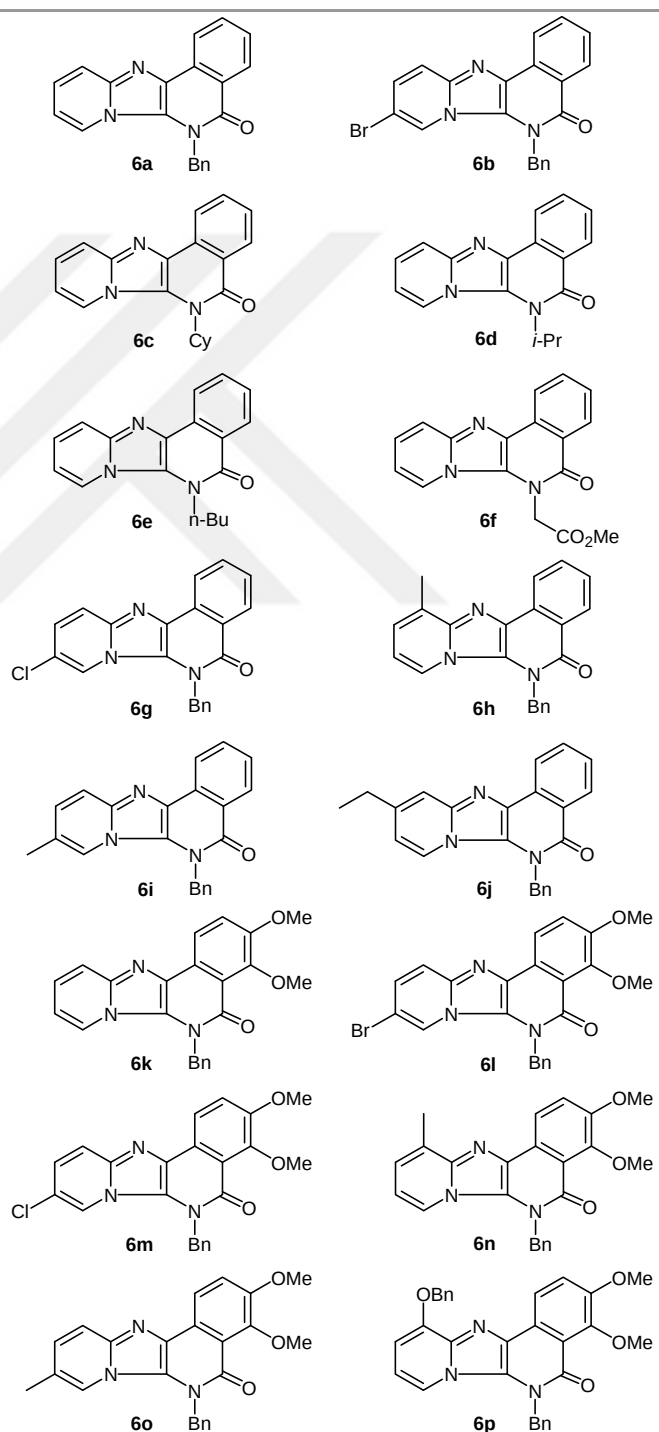
After optimizing the reaction conditions we focussed on the question of whether this domino process could be used for the generation of libraries of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones. To this purpose reactions with different substituted 2-aminopyridines **1**, isocyanides **3** and 2-carboxybenzaldehydes **5** were performed under our optimized reaction conditions (Scheme 4).



Scheme 4 Microwave-assisted synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones **6** under optimized reaction conditions

To start with, reactions of **1a** and **5a** with different isocyanides **3a-e** were conducted. We found that apart from benzyliisocyanide (**3a**), cyclohexyl isocyanide (**3b**), isopropyl isocyanide (**3c**), *n*-butyl isocyanide (**3d**) and methyl isocyanoacetate (**3e**) could be successfully employed. The yields of the tetracycles **6a,c-f** isolated ranged between 46 and 56% (Scheme 5, Table 2, entries 1,3-6). The variation of the aminopyridines also met with success. In the reactions of **3a** and **5a** with the differently substituted aminopyridines **1b-f** the heterocycles **6b,g-j**

were isolated as single products in analytically pure form with yields ranging from 50 to 66% (Scheme 5, Table 2, entries 2,7-10). In addition to the parent molecule **1a** the halogen substituted compounds **1b,c**, the alkyl substituted derivatives **1d-e** and the benzyl ether **1g** could also be reacted. Finally, the reactions of differently substituted aminopyridines **1** with benzyliisocyanide (**3a**) and 2-carboxy-3,4-dimethoxy-benzaldehyde (**5b**) were performed. Here, the products **6k-p** were obtained in analytically pure form as single products in yields of 35 to 68% (Scheme 5, Table 2, entries 11-16).

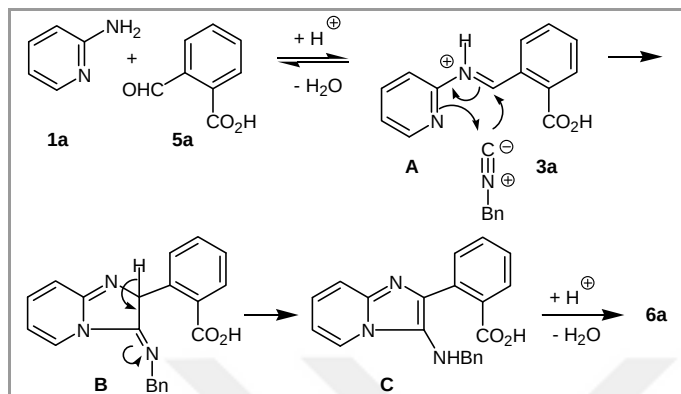


Scheme 5 Structures of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones **6a-p**

Table 2 Synthesis of pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones **6** from different 2-aminopyridines **1**, isocyanides **3** and 2-carboxybenzaldehydes **5**

Entry	1	R ¹	3	R ²	5	R ³	R ⁴	6	Yield of 6
1	a	H	a		a	H	H	a	56
2	b	5-Br	a		a	H	H	b	66
3	a	H	b		a	H	H	c	46
4	a	H	c		a	H	H	d	48
5	a	H	d		a	H	H	e	51
6	a	H	e		a	H	H	f	46
7	c	5-Cl	a		a	H	H	g	64
8	d	3-Me	a		a	H	H	h	53
9	e	5-Me	a		a	H	H	i	60
10	f	4-Et	a		a	H	H	j	50
11	a	H	a		b	3-OMe	4-OMe	k	35
12	b	5-Br	a		b	3-OMe	4-OMe	l	43
13	c	5-Cl	a		b	3-OMe	4-OMe	m	42
14	d	3-Me	a		b	3-OMe	4-OMe	n	68
15	e	5-Me	a		b	3-OMe	4-OMe	o	38
16	g	3-OBn	a		b	3-OMe	4-OMe	p	50

It is assumed that the reaction proceeds according to the mechanism depicted in Scheme 6. The key step of the sequence is the non concerted [4+1]-cycloaddition between the protonated Schiff base **A** and the isocyanide **3a** under formation of **B**. **B** undergoes a proton shift to yield **C**. After elimination of H₂O the lactam **6a** is formed.



Scheme 6 Proposed mechanism for the formation of pyrido[2',1':2,3]imidazo[4,5-c] isoquinolin-5(6H)-ones **6a**

The structures of all the pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-ones **6** described here have been elucidated by mass, ¹H, ¹³C, COSY, HSQC, HMBC and INADEQUATE spectroscopic methods. The complete ¹H, ¹³C spectral assignment, especially of quaternary carbons C-11a, C-11b, and C-6a of compound **6n**, is shown in Figure 1. In the HMBC spectra long-range correlations between the protons 1-H (³J_{CH}), 2-H (⁴J_{CH}), 9-H (⁵J_{CH}) and the carbon signal at δ = 123.66 ppm along with correlations between 7-H (³J_{CH}), 8-H (⁴J_{CH}), 2-H (⁵J_{CH}) and the carbon at δ = 123.62 ppm unambiguously established the C-11a and C-6a positions, respectively. Furthermore, the signal at δ = 126.39 ppm was definitely assigned to the carbon C-11b because of its HMBC correlation to H-2 and its ¹³C connectivity to C-1 in the INADEQUATE spectrum. Unfortunately, strong signal overlap between the aromatic protons 2'-H, 4'-H and 6'-H prevents the ¹³C assignment by HMBC methods. Nevertheless, it was possible to deduce the missing assignment by evaluating the ¹³C-¹³C INADEQUATE (Figure 1).

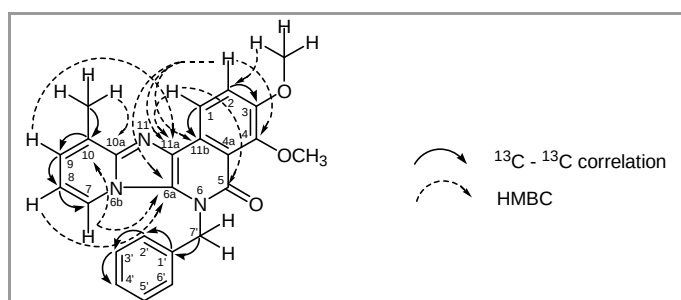


Figure 1 Important ³J-, ⁴J-, ⁵J- ¹H ¹³C - HMBC - and ¹³C - ¹³C - correlations in compound **6n**

The structural assignments based on NMR spectroscopic methods were unambiguously confirmed by the results of the X-ray crystal structure analysis of **6n** (Figure 2).⁸⁻¹³

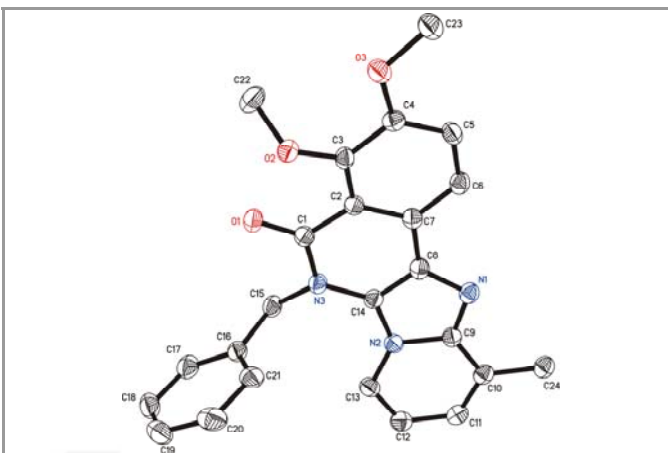


Figure 2 Solid state structure of compound **6n**; anisotropic displacement parameters are depicted at the 50% probability level; the second molecule of the asymmetric unit and H atoms are omitted for clarity reasons.

To summarize, pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-ones can be obtained in a few minutes with yields ranging from 35 to 68% by means of a microwave-assisted three-component reaction between 2-aminopyridines, isocyanides and 2-carboxybenzaldehydes. The transformation is easy to perform, robust and highly efficient, as this process allows the formation of two heterocyclic rings and four new bonds in a single synthetic operation.

Starting materials were purchased from chemical companies and used without purification. Reactions were performed using a Discover™ Explorer microwave synthesizer (CEM Corp.), producing continuous irradiation at 2450 MHz. All experiments were conducted under argon. Anhydrous toluene was distilled from sodium. Thin-layer chromatography (TLC) was performed on TLC aluminum roll silica gel 60 F₂₅₄ (MERCK). Compounds were visualized with UV light (λ = 254 nm) and/or immersion in KMnO₄ solution followed by heating. NMR spectra were recorded in CDCl₃ on 300 MHz and 500 MHz spectrometers. The ¹H and ¹³C chemical shifts were referenced to residual solvent signals at δ_H 7.26 and δ_C 77 relative to TMS. ¹H, ¹³C{¹H}, gDQF-COSY, gHSQC, INADEQUATE (300 MHz, 90 mg of **6n**, 5 mm Shigemi tube) spectra were measured with standard Varian pulse sequences. Adiabatic broadband and band selective gHMBC spectra were recorded using CHEMPACK 4.0 pulse sequences. Melting points were determined on a Kofler melting point apparatus (Reichert, Austria) and are uncorrected. Mass spectra were recorded on a MAT95 with 70 eV ionization energy. IR spectra were taken on a Spectrum One FT-IR Spectrometer. UV spectra were measured using a CARY 4E UV-Visible Spectrophotometer. Elemental analyses were

carried out by F. Hambloch, Institute of Organic and Biomolecular Chemistry, University of Göttingen.

General procedure for the microwave-assisted 3CR of 2-aminopyridines 1, isocyanides 3 and carboxybenzaldehydes 5

1 (1 mmol), **3** (2.25 mmol) and **5** (1.09 mmol) were suspended in toluene (2 mL) and placed in a 10 mL reaction vial heated and cooled under argon. After addition of $\text{CH}_3\text{SO}_3\text{H}$ (0.2 mmol) the vial was sealed with a septum and irradiated with microwaves (Discover™ by CEM; 2450 MHz; 300 W) for 7 min at 160 °C. The reaction mixture was allowed to cool at room temperature, was diluted with CH_2Cl_2 (100 mL), and then washed with NaHCO_3 -solution (2×100 mL). The residue obtained after drying the organic phase over MgSO_4 and after concentration in vacuo was purified by column chromatography on silica gel (EtOAc or EtOAc/ CH_2Cl_2) to yield **6**.

6-Benzyl-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6a)

Pale brown solid; yield: 56%; mp 234–236 °C (lit.^{7d} mp 228–229 °C).

IR (ATR): 1642, 1618, 1559, 1495, 1425, 1385, 1300, 1258, 1153, 1128, 979, 772, 730, 710, 702, 681 cm^{-1} .

UV/Vis (CH_3CN): λ_{max} (log ϵ) = 377 (4.15), 309 (3.61), 259 (4.57), 240 (4.47), 227 nm (4.58).

^1H NMR (300 MHz, CDCl_3): δ = 5.91 (s, 2H, 7'- CH_2), 6.57 (ddd, J = 1.3 Hz, J = 6.7 Hz, J = 7.2 Hz, 1H, 8-H), 7.05 (ddd, J = 1.1 Hz, J = 6.8 Hz, J = 9.4 Hz, 1H, 9-H), 7.20–7.27 (m, 2H, 2'-H, 6'-H), 7.27–7.31 (m, 1H, 4'-H), 7.31–7.39 (m, 2H, 3'-H, 5'-H), 7.62 (ddd, J = 1.4 Hz, J = 7.3 Hz, J = 8.1 Hz, 1H, 3-H), 7.67 (dt, J = 1.3 Hz, J = 9.3 Hz, 1H, 10-H), 7.84 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.1 Hz, 1H, 2-H), 8.13 (dt, J = 1.1 Hz, J = 7.3 Hz, 1H, 7-H), 8.44 (ddd, J = 0.7 Hz, J = 1.3 Hz, J = 8.0 Hz, 1H, 1-H), 8.55 (ddd, J = 0.6 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 4-H).

^{13}C NMR (75 MHz, CDCl_3): δ = 46.8 (C-7'), 112.5 (C-8), 118.7 (C-10), 121.9 (C-1), 123.1 (C-7), 123.7 (C-9), 123.9 (C-4a), 124.7 (C-11a), 125.1 (C-6a), 125.4 (C-2' and C-6'), 127.2 (C-3), 127.8 (C-4'), 129.4 (C-3' and C-5'), 129.5 (C-4), 131.9 (C-11b), 133.3 (C-2), 135.9 (C-1'), 143.0 (C-10a), 161.7 (C-5).

MS (EI, 70 eV): m/z (%) = 325 (37) [M^+], 234 (100), 130 (15), 78 (12), 51 (2).

6-Benzyl-8-bromo-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6b)

Yellow solid; yield: 66%; mp 270–272 °C.

IR (ATR): 3055, 1640, 1618, 1524, 1405, 1340, 1316, 1303, 1267, 933, 796, 765, 732, 713, 698, 660 cm^{-1} .

UV/Vis (CH_3CN): λ_{max} (log ϵ) = 403 (4.02), 383 (4.17), 318 (3.70), 266 (4.52), 245 (4.50), 231 (4.60), 208 nm (4.56).

^1H NMR (300 MHz, CDCl_3): δ = 5.88 (s, 2H, 7'- CH_2), 7.08 (dd, J = 1.3 Hz, J = 9.6 Hz, 1H, 9-H), 7.22–7.29 (m, 2H, 2'-H, 6'-H), 7.29–7.34 (m, 1H, 4'-H), 7.34–7.42 (m, 2H, 3'-H, 5'-H), 7.48 (dd, J = 0.9 Hz, J = 9.7 Hz, 1H, 10-H), 7.60 (ddd, J = 1.2 Hz, J = 7.3 Hz, J = 8.1 Hz, 1H, 3-H), 7.84 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.5 Hz, 1H, 2-H), 8.32 (dd, J = 0.9 Hz, J = 1.7 Hz, 1H, 7-H), 8.40 (ddd, J = 0.6 Hz, J = 1.2 Hz, J = 8.0 Hz, 1H, 1-H), 8.55 (ddd, J = 0.6 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 4-H).

^{13}C NMR (75 MHz, CDCl_3): δ = 46.7 (C-7'), 107.2 (C-8), 119.0 (C-10), 121.9 (C-1), 123.2 (C-7), 124.1 (C-4a), 124.7 (C-11a), 125.5 (C-2' and C-6'), 125.8 (C-6a), 126.9 (C-9), 127.6 (C-3), 128.1 (C-4'), 129.5 (C-3' and C-5'), 129.7 (C-4), 131.6 (C-11b), 133.4 (C-2), 135.7 (C-1'), 141.2 (C-10a), 161.7 (C-5).

MS (EI, 70 eV): m/z (%) = 403 (55) [M^+], 312 (100), 233 (5), 204 (3), 156 (13), 130 (47), 91 (16), 76 (6), 65 (3).

Anal. Calcd. for $\text{C}_{21}\text{H}_{14}\text{BrN}_3\text{O}$: C, 62.39; H, 3.49; N, 10.39. Found: C, 62.65; H, 3.70; N, 10.16.

6-Cyclohexyl-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6c)

Yellow solid; yield: 46%; mp 224–226 °C.

IR (ATR): 2935, 2850, 1645, 1617, 1298, 1268, 1131, 772, 746, 724, 704, 689 cm^{-1} .

UV/Vis (CH_3CN): λ_{max} (log ϵ) = 381 (4.06), 309 (3.52), 261 (4.52), 229 (4.49), 207 nm (4.46).

^1H NMR (300 MHz, CDCl_3): δ = 1.27–2.14 (m, 8H, 2'- H_b , 3'- H_2 , 4'- H_2 , 5'- H_2 , 6'- H_b), 2.81–3.09 (m, 2H, 2'- H_a , 6'- H_a), 4.43 (tt, J = 3.6 Hz, J = 11.9 Hz, 1H, 1'-H), 6.87 (dt, J = 1.2 Hz, J = 7.1 Hz, 1H, 8-H), 7.17 (ddd, J = 1.2 Hz, J = 6.7 Hz, J = 9.2 Hz, 1H, 9-H), 7.53 (ddd, J = 1.3 Hz, J = 7.3 Hz, J = 8.1 Hz, 1H, 3-H), 7.71 (dt, J = 1.2 Hz, J = 9.2 Hz, 1H, 10-H), 7.78 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.1 Hz, 1H, 2-H), 8.14 (bd, J = 7.4 Hz, 1H, 7-H), 8.36 (ddd, J = 0.6 Hz, J = 1.2 Hz, J = 7.8 Hz, 1H, 1-H), 8.43 (ddd, J = 0.6 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 4-H).

^{13}C NMR (75 MHz, CDCl_3): δ = 25.0 (C-4'), 26.4 (C-3' and C-5'), 29.8 (C-2' and C-6'), 60.3 (C-1'), 112.8 (C-8), 119.1 (C-10), 121.8 (C-1), 123.3 (C-7), 123.4 (C-9), 125.3 (C-6a), 125.7 (C-11a), 125.9 (C-4a), 127.1 (C-3), 128.8 (C-4), 131.6 (C-11b), 132.8 (C-2), 142.8 (C-10a), 162.8 (C-5).

MS (EI, 70 eV): m/z (%) = 317 (22) [M^+], 235 (100), 206 (7), 130 (2), 78 (6).

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.43; H, 5.85; N, 13.01.

6-(iso-propyl)-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6d)

Pale green solid; yield: 48%; mp 180–182 °C.

IR (ATR): 1628, 1617, 1574, 1556, 1403, 1302, 1272, 1096, 763, 731, 711, 698, 683 cm^{-1} .

UV/Vis (CH_3CN): λ_{max} (log ϵ) = 380 (4.05), 309 (3.51), 260 (4.50), 228 (4.48), 205 nm (4.44).

^1H NMR (500 MHz, CDCl_3): δ = 1.86 (d, J = 6.8 Hz, 6H, 1'-(CH_3)₂), 5.01 (hept., J = 6.8 Hz, 1H, 1'-H), 6.85 (dt, J = 1.3 Hz, J = 6.9 Hz, 1H, 8-H), 7.17 (ddd, J = 1.2 Hz, J = 6.6 Hz, J = 9.2 Hz, 1H, 9-H), 7.53 (ddd, J = 1.2 Hz, J = 7.1 Hz, J = 8.2 Hz, 1H, 3-H), 7.71 (dt, J = 1.2 Hz, J = 9.2 Hz, 1H, 10-H), 7.77 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.2 Hz, 1H, 2-H), 8.26 (bd, J = 7.3 Hz, 1H, 7-H), 8.37 (ddd, J = 0.6 Hz, J = 1.0 Hz, J = 7.9 Hz, 1H, 1-H), 8.43 (dd, J = 1.7 Hz, J = 8.1 Hz, 1H, 4-H).

^{13}C NMR (125 MHz, CDCl_3): δ = 20.7 (1'- CH_3), 51.3 (C-1'), 112.8 (C-8), 119.0 (C-10), 121.9 (C-1), 123.5 (C-7), 123.6 (C-9), 125.2 (C-6a), 125.6 (C-11a), 125.8 (C-4a), 127.2 (C-3), 128.8 (C-4), 131.6 (C-11b), 132.9 (C-2), 142.8 (C-10a), 162.7 (C-5).

MS (EI, 70 eV): m/z (%) = 277 (34) [M^+], 235 (100), 206 (14), 130 (10), 78 (13), 51 (3).

Anal. Calcd. for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.65; H, 5.16; N, 15.03.

6-(*n*-Butyl)-pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-one (6e)

Yellow solid; yield: 51%; mp 134–135 °C.

IR (ATR): 2950, 2868, 1639, 1617, 1574, 1558, 1498, 1387, 1303, 1262, 773, 734, 703, 682 cm^{-1} .

UV/Vis (CH_3CN): λ_{max} (log ϵ) = 379 (4.12), 309 (3.54), 260 (4.53), 241 (4.40), 227 (4.50), 205 nm (4.46).

^1H NMR (300 MHz, CDCl_3): δ = 1.02 (t, J = 7.4 Hz, 3H, 4'- CH_3), 1.49–1.64 (m, 2H, 3'- CH_2), 1.80–1.96 (m, 2H, 2'- CH_2), 4.56–4.68 (m, 2H, 1'- CH_2), 6.84 (ddd, J = 1.3 Hz, J = 6.7 Hz, J = 7.3 Hz, 1H, 8-H), 7.15 (ddd, J = 1.1 Hz, J = 6.6 Hz, J = 9.2 Hz, 1H, 9-H), 7.53 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.1 Hz, 1H, 3-H), 7.68 (dt, J = 1.2 Hz, J = 9.2 Hz, 1H, 10-H), 7.77 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.1 Hz, 1H, 2-H), 8.31 (dt, J = 1.1 Hz, J = 7.3 Hz, 1H, 7-H), 8.38 (ddd, J = 0.7 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 1-H), 8.46 (ddd, J = 0.7 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 4-H).

^{13}C NMR (75 MHz, CDCl_3): δ = 13.8 (C-4'), 19.9 (C-3'), 32.1 (C-2'), 42.7 (C-1'), 112.9 (C-8), 118.9 (C-10), 121.9 (C-1), 122.8 (C-7), 123.6 (C-9), 124.0 (C-4a), 124.5 (C-6a), 124.8 (C-11a), 127.1 (C-3), 129.2 (C-4), 131.3 (C-11b), 132.9 (C-2), 142.8 (C-10a), 161.2 (C-5).

MS (EI, 70 eV): m/z (%) = 291 (95) [M^+], 235 (100), 206 (15), 130 (23), 78 (27), 51 (6).

Anal. Calcd. for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}$: C, 74.20; H, 5.88; N, 14.42. Found: C, 76.16; H, 5.76; N, 13.89.

6-Methoxycarbonylmethyl-pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-one (6f)

Yellow solid; yield: 46%; mp 221–223 °C.

IR (ATR): 1748, 1736, 1644, 1619, 1558, 1388, 1365, 1318, 1227, 1145, 967, 770, 739, 728, 702 cm^{-1} .

UV/Vis (CH_3CN): λ_{max} (log ϵ) = 376 (4.09), 309 (3.57), 258 (4.52), 240 (4.41), 228 nm (4.51).

^1H NMR (300 MHz, CDCl_3): δ = 3.81 (s, 3H, OCH_3), 5.46 (s, 2H, 2'- CH_2), 6.78 (ddd, J = 1.3 Hz, J = 6.7 Hz, J = 7.2 Hz, 1H, 8-H), 7.13 (ddd, J = 1.2 Hz, J = 6.7 Hz, J = 9.2 Hz, 1H, 9-H), 7.55 (ddd, J = 1.3 Hz, J = 7.3 Hz, J = 8.1 Hz, 1H, 3-H), 7.67 (dt, J = 1.2 Hz, J = 9.2 Hz, 1H, 10-H), 7.81 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.0 Hz, 1H, 2-H), 8.13 (dt, J = 1.0 Hz, J = 7.3 Hz, 1H, 7-H), 8.39 (ddd, J = 0.6 Hz, J = 1.2 Hz, J = 8.0 Hz, 1H, 1-H), 8.46 (ddd, J = 0.7 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 4-H).

^{13}C NMR (75 MHz, CDCl_3): δ = 44.7 (C-2'), 53.2 (OCH_3), 113.0 (C-8), 119.0 (C-10), 121.9 (C-1), 121.9 (C-7), 123.5 (C-4a), 123.7 (C-9), 123.9 (C-6a), 125.0 (C-11a), 127.3 (C-3), 129.4 (C-4), 131.9 (C-11b), 133.5 (C-2), 142.9 (C-10a), 161.3 (C-5), 168.7 (C-1').

MS (EI, 70 eV): m/z (%) = 307 (100) [M^+], 275 (4), 248 (61), 234 (72), 220 (16), 130 (17), 78 (21), 51 (4).

HRMS (ESI): m/z [$\text{M} + \text{H}$]⁺ calcd for $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_3$: 308.1035; found: 308.1030.

6-Benzyl-8-chloro-pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-one (6g)

Yellow solid; yield: 64%; mp 273–274 °C.

IR (ATR): 3057, 1642, 1618, 1515, 1493, 1302, 1266, 1066, 941, 811, 765, 732, 724, 696, 681 cm^{-1} .

UV/Vis (CH_3CN): λ_{max} (log ϵ) = 403 (3.98), 383 (4.13), 317 (3.67), 265 (4.51), 244 (4.45), 230 (4.57), 206 nm (4.55).

^1H NMR (300 MHz, CDCl_3): δ = 5.89 (s, 2H, 7'- CH_2), 7.00 (dd, J = 1.7 Hz, J = 9.6 Hz, 1H, 9-H), 7.22–7.29 (m, 2H, 2'-H, 6'-H), 7.29–7.34 (m, 1H, 4'-H), 7.34–7.42 (m, 2H, 3'-H, 5'-H), 7.55 (dd, J = 1.0 Hz, J = 9.7 Hz, 1H, 10-H), 7.62 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.2 Hz, 1H, 3-H), 7.84 (ddd, J = 1.3 Hz, J = 7.2 Hz, J = 8.1 Hz, 1H, 2-H), 8.21 (bdd, J = 0.8 Hz, J = 2.0 Hz, 1H, 7-H), 8.41 (ddd, J = 0.7 Hz, J = 1.3 Hz, J = 8.0 Hz, 1H, 1-H), 8.55 (ddd, J = 0.6 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 4-H).

^{13}C NMR (75 MHz, CDCl_3): δ = 46.7 (C-7'), 118.8 (C-10), 120.7 (C-8), 121.0 (C-7), 121.9 (C-1), 124.0 (C-4a), 124.9 (C-6a), 124.9 (C-9), 125.5 (C-2' and C-6'), 126.0 (C-11a), 127.6 (C-3), 128.1 (C-4'), 129.5 (C-3' and C-5'), 129.7 (C-4), 131.6 (C-11b), 133.4 (C-2), 135.7 (C-1'), 141.2 (C-10a), 161.7 (C-5).

MS (EI, 70 eV): m/z (%) = 359 (31) [M^+], 268 (100), 130 (21), 112 (9), 91 (9), 76 (4), 65 (2).

Anal. Calcd. for $\text{C}_{21}\text{H}_{14}\text{ClN}_3\text{O}$: C, 70.10; H, 3.92; N, 11.68. Found: C, 69.85; H, 3.79; N, 11.50.

6-Benzyl-10-methyl-pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-one (6h)

Yellow solid; yield: 53%; mp 242–244 °C.

IR (ATR): 1647, 1621, 1557, 1387, 1306, 1269, 1157, 1132, 983, 772, 732, 707, 700, 682 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ϵ) = 373 (4.07), 260 (4.56), 243 (4.42), 229 (4.48), 205 nm (4.60).

¹H NMR (300 MHz, CDCl₃): δ = 2.68 (s, 3H, 10-CH₃), 5.92 (s, 2H, 7'-CH₂), 6.53 (t, J = 7.0 Hz, 1H, 8-H), 6.91 (d, J = 6.7 Hz, 1H, 9-H), 7.22-7.27 (m, 2H, 2'-H, 6'-H), 7.27-7.31 (m, 1H, 4'-H), 7.31-7.39 (m, 2H, 3'-H, 5'-H), 7.59 (ddd, J = 1.2 Hz, J = 7.2 Hz, J = 8.1 Hz, 1H, 3-H), 7.85 (ddd, J = 1.4 Hz, J = 7.2 Hz, J = 7.9 Hz, 1H, 2-H), 8.06 (bd, J = 7.1 Hz, 1H, 7-H), 8.56 (dd, J = 1.5 Hz, J = 8.2 Hz, 1H, 4-H), 8.59 (dd, J = 1.1 Hz, J = 8.1 Hz, 1H, 1-H).

¹³C NMR (75 MHz, CDCl₃): δ = 17.3 (10-CH₃), 46.7 (C-7'), 112.6 (C-8), 121.1 (C-7), 122.2 (C-1), 122.6 (C-9), 123.9 (C-4a), 124.5 (C-11a), 125.1 (C-6a), 125.5 (C-2' and C-6'), 127.1 (C-3), 127.8 (C-4'), 128.5 (C-10), 129.3 (C-3' and C-5'), 129.5 (C-4), 131.9 (C-11b), 133.1 (C-2), 136.0 (C-1'), 143.4 (C-10a), 161.8 (C-5).

MS (EI, 70 eV): m/z (%) = 339 (29) [M⁺], 248 (100), 130 (12), 92 (12), 65 (6).

Anal. Calcd. for C₂₂H₁₇N₃O: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.51; H, 4.82; N, 12.62.

6-Benzyl-8-methyl-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6i)

Pale yellow solid; yield: 60%; mp 257-259 °C.

IR (ATR): 1646, 1616, 1557, 1451, 1407, 1300, 1263, 973, 783, 773, 736, 704 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ϵ) = 377 (4.11), 315 (3.68), 261 (4.54), 244 (4.44), 228 (4.54), 205 nm (4.56).

¹H NMR (300 MHz, CDCl₃): δ = 2.14 (d, J = 1.1 Hz, 3H, 8-CH₃), 5.93 (bs, 2H, 7'-CH₂), 7.01 (dd, J = 1.5 Hz, J = 9.3 Hz, 1H, 9-H), 7.21-7.30 (m, 3H, 2'-H, 4'-H, 6'-H), 7.30-7.39 (m, 2H, 3'-H, 5'-H), 7.61 (dd, J = 1.0 Hz, J = 9.2 Hz, 1H, 10-H), 7.64 (ddd, J = 1.3 Hz, J = 7.1 Hz, J = 8.2 Hz, 1H, 3-H), 7.87 (ddd, J = 1.4 Hz, J = 7.2 Hz, J = 8.2 Hz, 1H, 2-H), 8.02 (q, J = 1.3 Hz, 1H, 7-H), 8.51 (ddd, J = 0.7 Hz, J = 1.3 Hz, J = 8.0 Hz, 1H, 1-H), 8.57 (ddd, J = 0.7 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 4-H).

¹³C NMR (75 MHz, CDCl₃): δ = 18.5 (8-CH₃), 46.9 (C-7'), 117.7 (C-10), 120.7 (C-7), 121.9 (C-1), 122.1 (C-8), 123.8 (C-4a), 124.4 (C-6a), 124.8 (C-11a), 125.5 (C-2' and C-6'), 127.1 (C-9), 127.2 (C-3), 127.8 (C-4'), 129.3 (C-3' and C-5'), 129.5 (C-4), 131.8 (C-11b), 133.2 (C-2), 136.2 (C-1'), 142.1 (C-10a), 161.8 (C-5).

MS (EI, 70 eV): m/z (%) = 339 (27) [M⁺], 248 (100), 130 (13), 92 (9), 65 (6).

Anal. Calcd. for C₂₂H₁₇N₃O: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.62; H, 4.75; N, 12.10.

6-Benzyl-9-ethyl-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6j)

Yellow solid; yield: 50%; mp 222-224 °C.

IR (ATR): 1639, 1623, 1561, 1496, 1448, 1427, 1386, 1307, 1267, 1150, 980, 861, 772, 728, 703, 682 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ϵ) = 378 (4.09), 261 (4.57), 240 (4.43), 227 (4.53), 206 nm (4.60).

¹H NMR (300 MHz, CDCl₃): δ = 1.23 (t, J = 7.5 Hz, 3H, 1''-CH₃), 2.61 (q, J = 7.5 Hz, 2H, 1''-CH₂), 5.89 (s, 2H, 7'-CH₂), 6.43 (dd, J = 1.4 Hz, J = 7.3 Hz, 1H, 8-H), 7.19-7.26 (m, 2H, 2'-H, 6'-H), 7.26-7.30 (m, 1H, 4'-H), 7.30-7.38 (m, 2H, 3'-H, 5'-H), 7.39 (bs, 1H, 10-H), 7.56 (ddd, J = 1.4 Hz, J = 7.1 Hz, J = 8.1 Hz, 1H, 3-H), 7.82 (ddd, J = 1.4 Hz, J = 7.2 Hz, J = 8.3 Hz, 1H, 2-H), 8.02 (dd, J = 0.8 Hz, J = 7.3 Hz, 1H, 7-H), 8.42 (ddd, J = 0.6 Hz, J = 1.2 Hz, J = 8.0 Hz, 1H, 1-H), 8.54 (ddd, J = 0.6 Hz, J = 1.3 Hz, J = 8.1 Hz, 1H, 4-H).

¹³C NMR (75 MHz, CDCl₃): δ = 13.8 (1''-CH₃), 28.1 (C-1''), 46.8 (C-7'), 114.3 (C-8), 115.3 (C-10), 121.8 (C-1), 122.5 (C-7), 123.8 (C-4a), 124.4 (C-6a), 124.9 (C-11a), 125.5 (C-2' and C-6'), 126.9 (C-3), 127.8 (C-4'), 129.4 (C-3' and C-5'), 129.5 (C-4), 132.1 (C-11b), 133.2 (C-2), 135.9 (C-1'), 140.8 (C-9), 143.8 (C-10a), 161.6 (C-5).

MS (EI, 70 eV): m/z (%) = 353 (23) [M⁺], 262 (100), 130 (10), 106 (7).

Anal. Calcd. for C₂₃H₁₉N₃O: C, 78.16; H, 5.42; N, 11.89. Found: C, 77.97; H, 5.19; N, 12.13.

6-Benzyl-3,4-dimethoxy-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6k)

Yellow solid; yield: 35%; mp 281-286 °C.

IR (ATR): 1641, 1615, 1577, 1385, 1294, 1252, 1232, 1080, 1072, 1043, 1030, 988, 943, 852, 811, 732, 718, 691 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ϵ) = 389 (4.13), 266 (4.36), 229 nm (4.61).

¹H NMR (300 MHz, CDCl₃): δ = 3.99 (s, 3H, 3-OCH₃), 4.01 (s, 3H, 4-OCH₃), 5.86 (s, 2H, 1'-CH₂), 6.59 (t, J = 6.8 Hz, 1H, 8-H), 7.08 (dd, J = 6.9 Hz, J = 8.8 Hz, 1H, 9-H), 7.22-7.31 (m, 3H, 2'-H, 4'-H, 6'-H), 7.31-7.40 (m, 2H, 3'-H, 5'-H), 7.51 (d, J = 8.9 Hz, 1H, 2-H), 7.65 (bd, J = 9.1 Hz, 1H, 10-H), 8.10 (bd, J = 7.2 Hz, 1H, 7-H), 8.25 (d, J = 8.9 Hz, 1H, 1-H).

¹³C NMR (75 MHz, CDCl₃): δ = 46.4 (C-7'), 56.7 (3-OCH₃), 61.5 (4-OCH₃), 112.7 (C-8), 118.1 (C-10), 118.2 (C-1), 118.6 (C-4a), 119.1 (C-2), 123.1 (C-7), 123.7 (C-6a), 123.9 (C-9), 124.1 (C-11a), 125.5 (C-2' and C-6'), 126.1 (C-11b), 127.8 (C-4'), 129.3 (C-3' and C-5'), 136.1 (C-1'), 142.5 (C-10a), 150.9 (C-4), 152.9 (C-3), 159.5 (C-5).

MS (EI, 70 eV): m/z (%) = 385 (56) [M⁺], 294 (100), 279 (18), 251 (14), 190 (7), 91 (6), 78 (18).

Anal. Calcd. for C₂₃H₁₉N₃O₃: C, 71.67; H, 4.97; N, 10.90. Found: C, 71.39; H, 4.70; N, 11.18.

6-Benzyl-8-bromo-3,4-dimethoxy-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6l)

Yellow solid; yield: 43%; mp 262–264 °C.

IR (ATR): 1651, 1399, 1274, 1258, 1246, 1083, 1074, 1031, 990, 976, 810, 798, 786, 780, 747, 697 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ε) = 416 (4.14), 394 (4.25), 274 (4.39), 234 nm (4.69).

¹H NMR (300 MHz, CDCl₃): δ = 3.99 (s, 3H, 3-OCH₃), 4.02 (s, 3H, 4-OCH₃), 5.83 (s, 2H, 7'-CH₂), 7.08 (dd, *J* = 1.3 Hz, *J* = 9.5 Hz, 1H, 9-H), 7.23–7.29 (m, 2H, 2'-H, 6'-H), 7.29–7.33 (m, 1H, 4'-H), 7.33–7.42 (m, 2H, 3'-H, 5'-H), 7.48 (dd, *J* = 0.8 Hz, *J* = 9.6 Hz, 1H, 10-H), 7.51 (d, *J* = 8.8 Hz, 1H, 2-H), 8.19 (d, *J* = 8.7 Hz, 1H, 1-H), 8.27 (dd, *J* = 0.9 Hz, *J* = 1.8 Hz, 1H, 7-H).

¹³C NMR (75 MHz, CDCl₃): δ = 46.3 (C-7'), 56.7 (3-OCH₃), 61.5 (4-OCH₃), 107.2 (C-8), 118.2 (C-1), 118.5 (C-10), 118.7 (C-4a), 119.1 (C-2), 123.1 (C-7), 123.7 (C-6a), 125.1 (C-11a), 125.6 (C-2' and C-6'), 125.8 (C-11b), 126.8 (C-9), 127.9 (C-4'), 129.5 (C-3' and C-5'), 135.9 (C-1'), 140.8 (C-10a), 150.9 (C-4), 153.2 (C-3), 159.5 (C-5).

MS (EI, 70 eV): *m/z* (%) = 463 (51) [M⁺], 372 (100), 357 (28), 344 (22), 329 (18), 190 (11), 158 (17), 91 (24), 76 (9), 65 (6).

Anal. Calcd. for C₂₃H₁₈BrN₃O₃: C, 59.50; H, 3.91; N, 9.05. Found: C, 59.35; H, 3.94; N, 8.75.

6-Benzyl-8-chloro-3,4-dimethoxy-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6m)

Yellow solid; yield: 42%; mp 278–279 °C.

IR (ATR): 3082, 1652, 1462, 1400, 1291, 1276, 1259, 1247, 1083, 1053, 1035, 991, 976, 953, 810, 799, 787, 748, 698 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ε) = 415 (4.13), 394 (4.25), 273 (4.39), 234 nm (4.69).

¹H NMR (300 MHz, CDCl₃): δ = 4.00 (s, 3H, 3-OCH₃), 4.02 (s, 3H, 4-OCH₃), 5.83 (s, 2H, 7'-CH₂), 7.01 (dd, *J* = 1.5 Hz, *J* = 9.6 Hz, 1H, 9-H), 7.23–7.29 (m, 2H, 2'-H, 6'-H), 7.29–7.33 (m, 1H, 4'-H), 7.33–7.42 (m, 2H, 3'-H, 5'-H), 7.50 (d, *J* = 8.7 Hz, 1H, 2-H), 7.56 (bd, *J* = 9.8 Hz, 1H, 10-H), 8.17 (bd, *J* = 2.1 Hz, 1H, 7-H), 8.21 (d, *J* = 8.7 Hz, 1H, 1-H).

¹³C NMR (75 MHz, CDCl₃): δ = 46.3 (C-7'), 56.7 (3-OCH₃), 61.6 (4-OCH₃), 118.2 (C-10), 118.3 (C-1), 118.7 (C-4a), 119.1 (C-2), 120.8 (C-8), 120.9 (C-7), 123.9 (C-6a), 124.9 (C-9), 125.2 (C-11a), 125.5 (C-2' and C-6'), 125.8 (C-11b), 128.0 (C-4'), 129.5 (C-3' and C-5'), 135.9 (C-1'), 140.8 (C-10a), 150.9 (C-4), 153.2 (C-3), 159.5 (C-5).

MS (EI, 70 eV): *m/z* (%) = 419 (54) [M⁺], 328 (100), 312 (29), 285 (21), 190 (7), 112 (19), 91 (16), 76 (7), 65 (4).

Anal. Calcd. for C₂₃H₁₈ClN₃O₃: C, 65.79; H, 4.32; N, 10.01. Found: C, 65.44; H, 4.18; N, 9.85.

6-Benzyl-3,4-dimethoxy-10-methyl-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6n)

Yellow solid; yield: 68%; mp 202–204 °C.

IR (ATR): 1650, 1470, 1418, 1385, 1297, 1271, 1249, 1077, 1046, 999, 828, 722, 715, 696 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ε) = 386 (4.13), 266 (4.44), 230 (4.59), 219 nm (4.60).

¹H NMR (500 MHz, CDCl₃): δ = 2.67 (s, 3H, 10-CH₃), 3.99 (s, 3H, 3-OCH₃), 4.02 (s, 3H, 4-OCH₃), 5.85 (s, 2H, 7'-CH₂), 6.50 (t, *J* = 7.0 Hz, 1H, 8-H), 6.87 (d, *J* = 6.7 Hz, 1H, 9-H), 7.21–7.29 (m, 3H, 2'-H, 4'-H, 6'-H), 7.29–7.38 (m, 2H, 3'-H, 5'-H), 7.50 (d, *J* = 8.7 Hz, 1H, 2-H), 7.98 (d, *J* = 7.2 Hz, 1H, 7-H), 8.34 (d, *J* = 8.8 Hz, 1H, 1-H).

¹³C NMR (125 MHz, CDCl₃): δ = 16.9 (10-CH₃), 45.9 (C-7'), 56.3 (3-OCH₃), 61.1 (4-OCH₃), 111.8 (C-8), 117.7 (C-1), 118.0 (C-4a), 118.4 (C-2), 120.5 (C-7), 121.8 (C-9), 123.6 (C-6a), 123.7 (C-11a), 125.2 (C-2' and C-6'), 126.4 (C-11b), 127.2 (C-4'), 127.6 (C-10), 128.8 (C-3' and C-5'), 136.1 (C-1'), 142.7 (C-10a), 150.3 (C-4), 152.1 (C-3), 159.0 (C-5).

MS (EI, 70 eV): *m/z* (%) = 399 (47) [M⁺], 308 (100), 293 (14), 265 (12), 190 (6), 92 (15), 65 (8).

Anal. Calcd. for C₂₄H₂₁N₃O₃: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.85; H, 4.97; N, 10.39.

6-Benzyl-3,4-dimethoxy-8-methyl-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6o)

Dark yellow solid; yield: 38%; mp 241–245 °C.

IR (ATR): 1639, 1578, 1400, 1292, 1263, 1240, 1070, 1040, 1029, 985, 850, 813, 788, 712, 693 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ε) = 389 (4.17), 267 (4.40), 253 (4.40), 230 nm (4.65).

¹H NMR (300 MHz, CDCl₃): δ = 2.07 (d, *J* = 1.0 Hz, 3H, 8-CH₃), 3.98 (s, 3H, 3-OCH₃), 4.01 (s, 3H, 4-OCH₃), 5.84 (s, 2H, 7'-CH₂), 6.88 (dd, *J* = 1.5 Hz, *J* = 9.3 Hz, 1H, 9-H), 7.22–7.30 (m, 3H, 2'-H, 4'-H, 6'-H), 7.30–7.40 (m, 2H, 3'-H, 5'-H), 7.47 (d, *J* = 8.8 Hz, 1H, 2-H), 7.50 (d, *J* = 9.3 Hz, 1H, 10-H), 7.85–7.92 (m, 1H, 7-H), 8.19 (d, *J* = 8.6 Hz, 1H, 1-H).

¹³C NMR (75 MHz, CDCl₃): δ = 18.5 (8-CH₃), 46.5 (C-7'), 56.7 (3-OCH₃), 61.5 (4-OCH₃), 117.3 (C-2), 117.9 (C-1), 118.5 (C-4a), 119.1 (C-10), 120.7 (C-7), 121.9 (C-8), 123.5 (C-6a), 124.3 (C-11a), 125.6 (C-2' and C-6'), 126.5 (C-11b), 126.9 (C-9), 127.7 (C-4'), 129.2 (C-3' and C-5'), 136.5 (C-1'), 141.8 (C-10a), 150.9 (C-4), 152.7 (C-3), 159.6 (C-5).

MS (EI, 70 eV): *m/z* (%) = 399 (45) [M⁺], 308 (100), 393 (13), 265 (13), 190 (6), 92 (13), 65 (9).

Anal. Calcd. for C₂₄H₂₁N₃O₃: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.06; H, 5.57; N, 10.30.

6-Benzyl-10-benzoyloxy-3,4-dimethoxy-pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6H)-one (6p)

Yellow solid; yield: 50%; mp 215–217 °C.

IR (ATR): 1647, 1545, 1535, 1394, 1268, 1254, 1236, 1195, 1068, 1049, 999, 970, 818, 752, 725, 699 cm⁻¹.

UV/Vis (CH₃CN): λ_{max} (log ε) = 381 (4.09), 269 (4.52), 219 (4.64), 210 nm (4.65).

¹H NMR (300 MHz, CDCl₃): δ = 3.98 (s, 3H, 3-OCH₃), 4.00 (s, 3H, 4-OCH₃), 5.38 (s, 2H, 7''-CH₂), 5.81 (bs, 2H, 7'-CH₂), 6.32 (dd, *J* = 1.3 Hz, *J* = 7.6 Hz, 1H, 9-H), 6.37 (dd, *J* = 6.6 Hz, *J* = 7.5 Hz, 1H, 8-H), 7.19–7.25 (m, 2H, 2'-H, 6'-H), 7.28–7.41 (m, 6H, 3'-H, 4'-H, 5'-H, 3''-H, 4''-H, 5''-H), 7.48 (d, *J* = 8.9 Hz, 1H, 2-H), 7.47–7.52 (m, 2H, 2''-H, 6''-H), 7.70 (dd, *J* = 1.3 Hz, *J* = 6.7 Hz, 1H, 7-H), 8.40 (d, *J* = 8.6 Hz, 1H, 1-H).

¹³C NMR (75 MHz, CDCl₃): δ = 46.4 (C-7''), 56.7 (3-OCH₃), 61.5 (4-OCH₃), 70.8 (C-7''), 101.9 (C-9), 112.2 (C-8), 116.2 (C-7), 118.5 (C-4a), 118.6 (C-1), 118.9 (C-2), 123.8 (C-11a), 124.5 (C-6a), 125.5 (C-2' and C-6'), 126.5 (C-11b), 127.1 (C-2'' and C-6''), 127.6 (C-4'), 128.1 (C-4''), 128.6 and 129.2 (C-3' and C-5' and C-3'' and C-5''), 136.0 and 136.2 (C-1' and C-1''), 137.3 (C-10a), 147.9 (C-10), 150.7 (C-4), 152.6 (C-3), 159.6 (C-5).

MS (EI, 70 eV): *m/z* (%) = 491 (57) [M⁺], 400 (100), 309 (37), 283 (9), 91 (43), 65 (3).

Anal. Calcd. for C₃₀H₂₅N₃O₄: C, 73.30; H, 5.13; N, 8.55. Found: C, 73.03; H, 4.90; N, 8.32.

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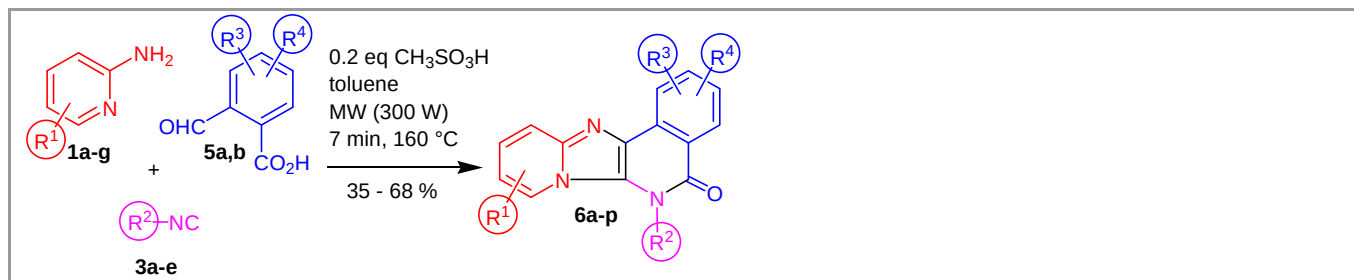
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- (8) (a) X-ray crystal structure analysis for **6n**: formula C₂₄H₂₁N₃O₃, *M* = 399.44, orange crystal 0.10×0.03×0.02 mm³, *a* = 22.673(2), *b* = 7.2566(7), *c* = 24.348(2) Å, β = 107.4740(19)°, *V* = 3821.1(6) Å³, ρ_{calcd} = 1.389 Mg/m³, absorption coefficient μ = 0.093 mm⁻¹, *Z* = 8, monoclinic, space group *P* 2₁/n, reflections collected 41880, θ_{max} = 28.49°, independent reflections 9106 [*R*_{int} = 0.0678], final *R*₁[*I* > 2σ(*I*)] = 0.0454, *wR*₂[*I* > 2σ(*I*)] = 0.0977, *R*₁(all data) = 0.1016, *wR*₂(all data) = 0.1172, GOF = 1.016, extinction parameter = 0.0012(2), largest diff. peak and hole 0.252 and -0.249 eÅ⁻³. (b) X-ray data were collected at 100(2) K on an INCOATEC Microsource device with mirror-monochromated Mo-Kα radiation (λ = 0.71073 Å). The device is equipped with a SMART APEX II area detector. The data were integrated with SAINT⁹ and an empirical absorption correction (SADABS)¹⁰ was applied. The structure was solved by using direct methods with SHELXS-97 and refined by full-matrix least-squares on *F*² for all data with SHELXL-97.^{11–13} All non-hydrogen atoms were refined with anisotropic displacement parameters. A riding model with idealized geometry was employed for all hydrogen atoms. CCDC-674626 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Short title: Three-Component Reaction for the Synthesis of Pyrido[2',1':2,3]imidazo[4,5-*c*]isoquinolin-5(6*H*)-ones



Graphical abstract

Prof. Dr. Uwe Beifuss
 Bioorganische Chemie
 Institut für Chemie
 Universität Hohenheim
 Garbenstr. 30
 D-70599 Stuttgart
 Tel.: (+49)(711)45922171; Sekretariat: Int (+49)(711)45923571
 Fax: (+49)(711)45922951
 E-Mail: ubeaufuss@uni-hohenheim.de

13.3. Influence of guanidinium salts and other ionic liquids on the three component aza-*Diels-Alder* reaction

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Influence of Guanidinium Salts and other Ionic Liquids on the Three Component aza-*Diels-Alder* reaction

by **Fadime Mert-Balci**, **Hans-Georg Imrich**, **Jürgen Conrad**, and **Uwe Beifuss***

Bioorganische Chemie, Institut für Chemie, Universität Hohenheim, Garbenstr. 30, 70599 Stuttgart,
Germany

(phone: +49-711-459-22171; fax: +49-711-459-22951; e-mail: ubeifuss@uni-hohenheim.de)

Abstract: The three component reaction of aniline, benzaldehyde and dienophiles like 2,3-dihydrofuran, ethyl vinyl ether, 2,3-dihydropyran and cyclopentadiene can be promoted by ionic liquids like imidazolium salts and guanidinium salts under thermal as well as under microwave conditions. The chemical yield as well as the diastereoselectivity of the *Povarov* reaction strongly depend on the ionic liquid employed. The guanidinium salts can be recycled and reused several times without loss of reactivity.

Keywords: aza-*Diels-Alder* reaction, ionic liquids, domino reactions, *N*-heterocycles

Introduction. - The inverse electron-demand aza-*Diels-Alder* reaction of an electron poor, positively charged or neutral 2-azabutadiene with an electron-rich alkene, the so-called *Povarov* reaction, is one of the most efficient and flexible routes for the synthesis of tetrahydroquinolines [1]. Two methods - the use of preformed 2-azabutadienes and the *in situ* preparation of 2-azabutadienes - have been developed to supply the required 2-azabutadienes. Many aza-*Diels-Alder* reactions reported so far make use of a preformed *N*-arylimine as the heterodiene, which can be generated by condensation of an aromatic amine with a carbonyl compound [2]. However, the use of preformed imines as heterodienes is often hampered by their instability. In fact, many imines are unstable at higher temperatures and rapidly hydrolyze upon

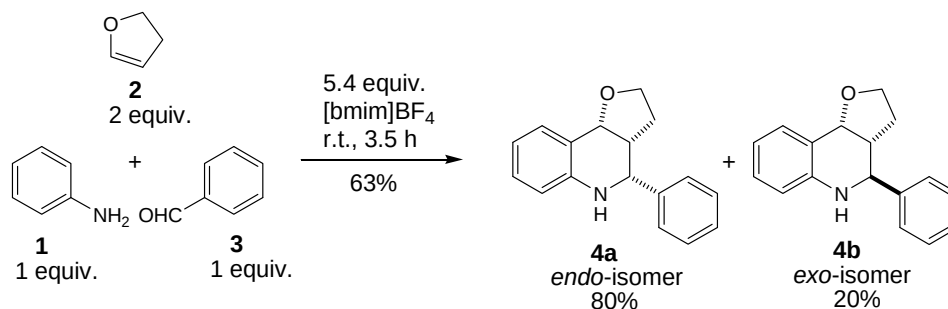
contact to water. Their purification by distillation or chromatography can sometimes be difficult [3]. The *in situ* generation of 2-azabutadienes by reaction of an amine with a carbonyl compound in the presence of a dienophile not only circumvents the problems encountered with the instability of preformed 2-azabutadienes. It also allows for the synthesis of tetrahydroquinolines and related heterocycles in one pot [4]. This type of three component reaction can be promoted by numerous reagents such as SmI_2 [4a], SbCl_3 [4b], phosphomolybdic acid [4c], TMSCl [4d], I_2 [4e], sulfamic acid [4f], InCl_3 [4g,4j], $\text{Sc}(\text{OTf})_3$ [4g], selectfluorTM [4h], fluorinated alcohols [4i], $\text{Dy}(\text{OTf})_3$ [4k,4m], GdCl_3 [4l], $\text{Ln}(\text{OTf})_3$ [4n] and $\text{CF}_3\text{CO}_2\text{H}$ [4o,4p].

Recently, the application of ionic liquids as solvents and catalysts in organic transformations has become very popular [5]. Ionic liquids have negligible vapor pressure, are thermally and chemically stable, have a wide operating temperature range and can be reused. This is why they represent a more sustainable, environmentally safe alternative to volatile traditional organic solvents. However, the attention which ionic liquids have received in organic synthesis is not only due to their solvent properties but also to their catalytic effects. It has been demonstrated that ionic liquids exert a strong influence on the kinetics or the stereoselectivity of reactions [5c,5f,6]. These effects probably can be attributed to polar interactions between the ionic liquids and the substrates, the transition states or the intermediates. Apart from the well-studied imidazolium salts there are a number of other ionic liquids such as pyridinium, phosphonium and ammonium salts [5]. Recently, guanidinium salt based ionic liquids have received considerable attention. Guanidinium salts can easily be synthesized using a number of efficient and reliable methods [7]. They have been used as solvents or catalysts for a number of

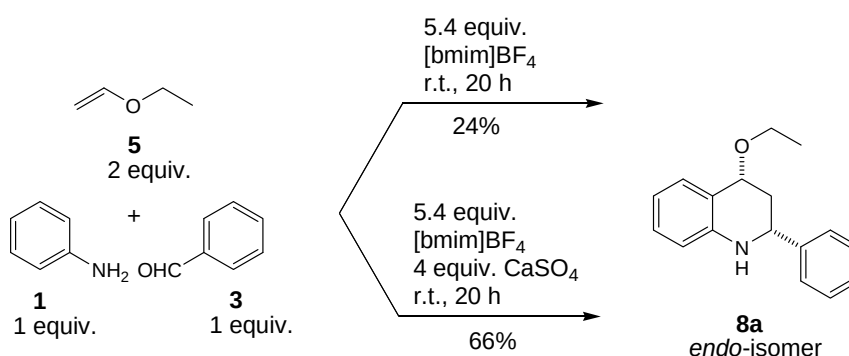
transformations such as the aldol reaction [8], the condensation of indoles with aldehydes to produce bis(indolyl)methanes [9], the *Knoevenagel* reaction [10], the *Mannich* reaction [11], the asymmetric α -aminoxylation of carbonyls [12], the *Henry* reaction [13], the fixation of CO₂ by epoxides [14], the *Heck* reaction [15], the hydrogenation [16], the hydroformylation [17], the oxidation of benzylic alcohols [18] and the *Sharpless* dihydroxylation [19].

Ionic liquids have also been employed to promote *aza-Diels-Alder* reactions [20,21]. *Yadav et al.* reported the three component synthesis of pyrano- and furoquinolines using [bmim]BF₄ as ionic liquid [20d]. *Wilhelm et al.* have shown that *aza-Diels-Alder* reactions between preformed 2-azabutadienes and alkenes can be catalyzed by an imidazolium hexafluorophosphate as the ionic liquid [20c]. *Li et al.* reported the synthesis of pyrano- and furoquinolines via the three component reaction between an imidazolium tetrafluoroborate bound benzaldehyde, an aniline and a cyclic enol ether [20b]. In addition, it has been established that *aza-Diels-Alder* reactions with imines as the dienophile can be performed in the presence of ionic liquids [20c,21].

Results and Discussion. - Close inspection of the results published suggested the assumption that yields and stereoselectivities of the *aza-Diels-Alder* reaction for the synthesis of furoquinolines depend on the ionic liquid and the reaction conditions. This prompted us to study the influence of different ionic liquids on the outcome of a typical *aza-Diels-Alder* reaction under different reaction conditions. As part of a program devoted to the development of new ionic liquids for applications in organic synthesis, we were particularly interested whether guanidinium salts can be used as solvents and/or catalysts for the *aza-Diels-Alder* reaction.

Scheme 1. *[bmim]BF₄* promoted reaction between **1**, **2** and **3**

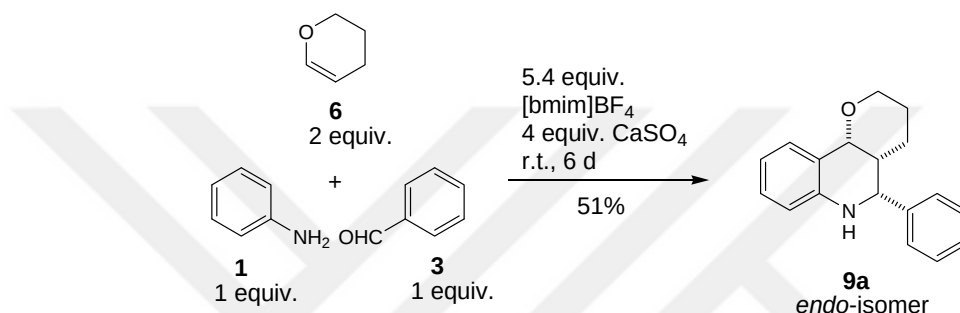
The three component reaction between aniline (**1**), 2,3-dihydrofuran (**2**) and benzaldehyde (**3**) was studied first. For comparison, this reaction was performed initially in the presence of an imidazolium salt. When 1 equiv. **1**, 2 equiv. **2**, and 1 equiv. **3** were reacted in *[bmim]BF₄* under *Yadav*'s conditions [20d], *i.e.* at room temperature for 3.5 h, 63% of a 4:1-mixture of the *endo*- and the *exo*-furoquinolines **4a** and **4b**, respectively, was formed (Scheme 1). The *endo/exo* ratio was determined by ¹H-NMR analysis of the reaction mixture after column filtration on SiO₂. This result is in contrast to the findings of *Yadav et al.* who reported the exclusive formation of the *endo*-isomer **4a** in 92% yield.

Scheme 2. *[bmim]BF₄* promoted reaction between **1**, **3** and ethyl vinyl ether (**5**)

Apart from 2,3-dihydrofuran (**2**) as the dienophile, the *Povarov* reaction in *[bmim]BF₄* was also performed with ethyl vinyl ether (**5**), 2,3-dihydropyran (**6**) and cyclopentadiene (**7**) as dienophiles. When 1 equiv. **1**, 2 equiv. ethyl vinyl ether (**5**)

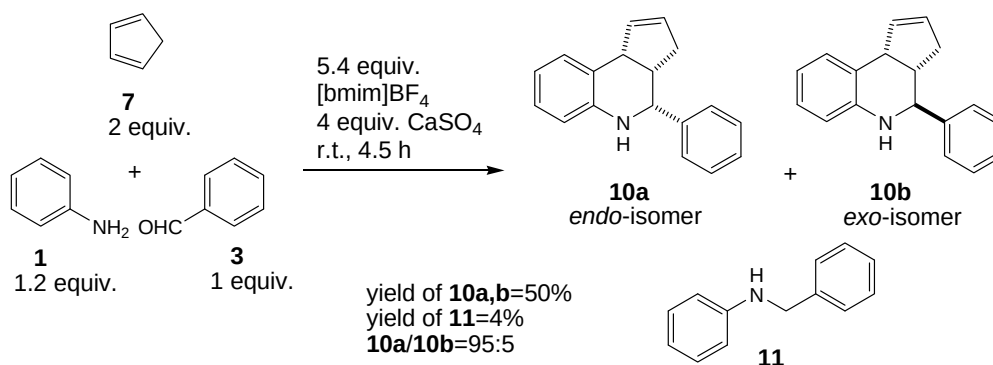
and 1 equiv. **3** were reacted in 5.4 equiv. [bmim]BF₄ for 20 h at room temperature, 24% of the *endo*-isomer **8a** (4-ethoxy-1,2,3,4-tetrahydro-2-phenylquinoline) were isolated (Scheme 2). It should be noted that the yield of **8a** could be improved to 66% when the experiment was repeated in the presence of CaSO₄ to remove the water formed during the condensation of aniline (**1**) and benzaldehyde (**3**).

Scheme 3. [bmim]BF₄ promoted reaction between **1**, **3** and 2,3-dihydropyran (**6**)



The highly diastereoselective *Povarov* reaction between 1 equiv. **1**, 2 equiv. 2,3-dihydropyran (**6**) and 1 equiv. **3** in the presence of 5.4 equiv. [bmim]BF₄ and 4 equiv. CaSO₄, delivered 51% of the *endo*-isomer **9a** after 6 d at room temperature (Scheme 3).

Scheme 4. [bmim]BF₄ promoted reaction between **1**, **3** and cyclopentadiene (**7**)



The *Povarov* reaction was also performed with cyclopentadiene (**7**) as the dienophile. When 1.2 equiv. **1**, 2 equiv. **7** and 1 equiv. **3** were reacted with 5.4 equiv.

[bmim]BF₄ and 4 equiv. CaSO₄, 50% of a 95:5-mixture of *endo/exo*-**10a,b** were formed (Scheme 4). In addition to the cycloadducts **10a,b**, 4% of *N*-benzylaniline (**11**) were obtained. Firstly, the *endo*-isomer **10a** could be separated by recrystallization of the product mixture. *N*-benzylaniline (**11**) and the *exo*-isomer **10b** were volatile enough to be separated via Kugelrohr distillation. The *exo*-isomer **10b** could be obtained in pure form by flash chromatography of the distillate.

Table 1. Influence of the Amount of [bmim]BF₄ on Yield and Selectivity of the Synthesis of **4a,b** under Microwave Conditions^{a)}

$\text{1 (1 equiv.)} + \text{2 (2 equiv.)} + \text{3 (1 equiv.)} \xrightarrow[\text{70}^\circ]{\text{[bmim]BF}_4 \text{ Microwave (10 W)}} \text{4a} + \text{4b}$				
Entry	[bmim]BF ₄ (equiv.)	t (min)	Yield (%)	<i>endo/exo</i>
1	5.4	7	69	75:25
2	1.0	10	57	83:17
3	0.1	15	51	84:16

^{a)} The reactions were performed in a sealed vial.

The three component reaction between aniline (**1**), 2,3-dihydrofuran (**2**) and benzaldehyde (**3**) was selected as a model reaction to study the influence of different ionic liquids and microwave irradiation on the outcome of the *Povarov* reaction. First, the [bmim]BF₄ promoted reaction was studied under microwave conditions (Table 1) [22]. It was found that the reaction with 5.4 equiv of the ionic liquid could be brought to completion within 7 min to yield 69% of **4a,b** with an *endo/exo* ratio of 75:25 (Table 1, Entry 1). Reduction of the amount of [bmim]BF₄ was associated with longer reaction times, decreasing yields, but an improved *endo/exo* ratio of **4a,b** (Table 1, Entries 2,3). When the reaction was performed in the absence of any ionic

liquid under microwave conditions (150 W, 70°, 5 min) not a trace of the aza-Diels Alder product was formed. This control experiment clearly underlines the importance of the ionic liquid for this transformation.

Table 2. [bmim]BF₄ Promoted Synthesis of **4a,b** under Thermal Conditions^{a)}

	1	+	2	+	3	[bmim]BF₄ oil bath 70° →	4a	+	4b
<i>Entry</i>	1	2	3		[bmim]BF ₄	t (min)	Yield		<i>endo</i>
	(equiv.)	(equiv.)	(equiv.)		(equiv.)		(%)		/exo
1	1	2	1		5.4	5	76		75:25
2	1	2	1		0.1	14	44		84:16
3	1	2	1		0.1	60	43		84:16
4	1.2	2	1		5.4	5	78		75:25
5	1.2	2	1		5.4	7	81		78:22
6	1.2	2.2	1		5.4	7	75		76:24
7	1.2	2.4	1		5.4	7	76		75:25

^{a)} The reactions were performed in a sealed vial.

To determine the influence of the microwave irradiation on the outcome of this reaction, it was also studied under thermal conditions in a sealed vial at 70° (Table 2). Interestingly, in terms of diastereoselectivity there was no difference between the reactions under thermal and microwave conditions (Table 1, Entries 1,3 and Table 2, Entries 1-3). However, the yield of **4a,b** under thermal conditions was slightly better than under microwave conditions (Table 1, Entry 1 and Table 2, Entry 1). This is why all further experiments were performed in a sealed vial in an oil bath. Variation of the amounts of the substrates revealed that best yields were obtained when 1.2 equiv. **1**, 2 equiv. **2** and 1 equiv. **3** were reacted in 5.4 equiv. [bmim]BF₄ under the conditions given in Table 2, Entry 5.

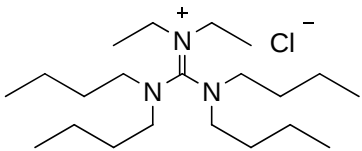
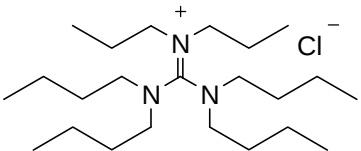
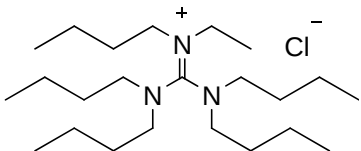
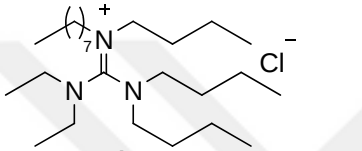
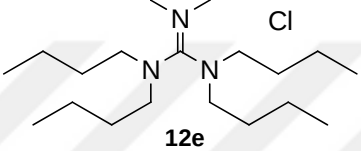
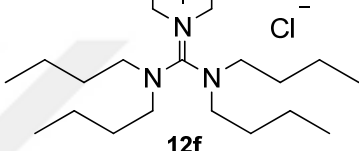
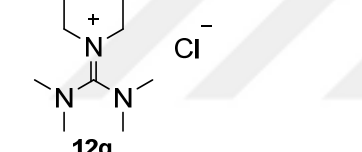
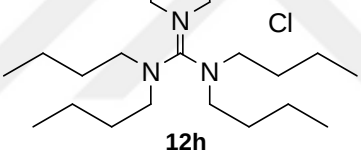
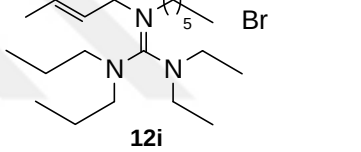
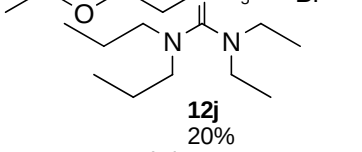
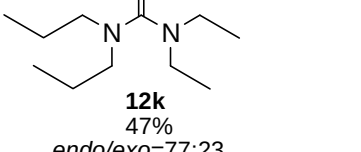
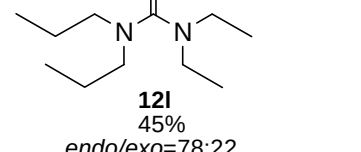
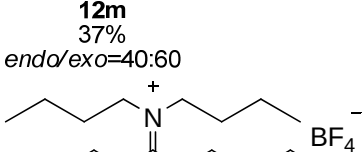
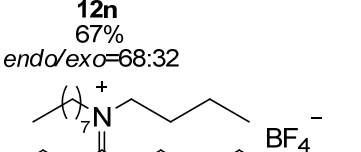
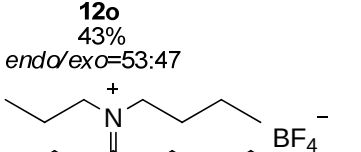
Table 3. Influence of the Reaction Temperature on the Formation of **4a,b** in the Presence of [bmim]BF₄^{a)}

$\begin{array}{c} \text{1} \\ (1.2 \text{ equiv.}) \end{array} + \begin{array}{c} \text{2} \\ (2 \text{ equiv.}) \end{array} + \begin{array}{c} \text{3} \\ (1 \text{ equiv.}) \end{array} \xrightarrow[\text{oil bath}]{5.4 \text{ equiv. [bmim]BF}_4} \text{4a} + \text{4b}$				
Entry	T (°)	t (min)	Yield (%)	endo/exo
1	0	1140	79	85:15
2	r.t.	210	90	81:19
3	70	7	81	78:22
4	160	3	quant.	67:33

^{a)} The reactions were performed in a sealed vial.

In further experiments, the influence of the reaction temperature on the reaction time, the chemical yield and the *endo/exo* selectivity was studied by reacting **1**, **2** and **3** in [bmim]BF₄ as the ionic liquid in a sealed vial under thermal conditions (Table 3). It was found that the reaction time could be reduced substantially when the reaction temperature was changed from 0° to 160°. Simultaneously, the amount of the *exo*-isomer **4b** increased. At 160°, it took only 3 min to obtain a 67:33 mixture of **4a** and **4b** in quantitative yield (Table 3, Entry 4). To summarize, using [bmim]BF₄ as the ionic liquid led under all reaction conditions to mixtures of the *endo*- and the *exo*-isomers **4a** and **4b**. Interesting to note that lower reaction temperatures favored the formation of the *endo*-isomer. The influence of microwave irradiation on yield and selectivity seems to be negligible.

Table 4. Influence of Different Guanidinium Salts on the Synthesis of **4a,b**^{a)}

1 (1 equiv.) + 2 (2 equiv.) + 3 (1 equiv.)			5.4 equiv. 12 oil bath 160°, 3 min	4a + 4b endo + exo	
 12a 7% endo/exo=36:64	+	 12b 14% endo/exo=32:68	→	 12c 5% endo/exo=32:68	
 12d no reaction	+	 12e 5% endo/exo=44:56	→	 12f 12% endo/exo=41:59	
 12g 21% endo/exo=0:100	+	 12h 12% endo/exo=49:51	→	 12i 25% endo/exo=71:29	
 12j 20% endo/exo=41:59	+	 12k 47% endo/exo=77:23	→	 12l 45% endo/exo=78:22	
 12m 37% endo/exo=40:60	+	 12n 67% endo/exo=68:32	→	 12o 43% endo/exo=53:47	
 12p 74% endo/exo=83:17	+	 12q 81% endo/exo=88:12	→	 12r 74% endo/exo=83:17	

^{a)} The reactions were performed in a sealed vial.

During the search for ionic liquids favoring the formation of either the *endo*-isomer **4a** or the *exo*-isomer **4b** we came across guanidinium salts. These ionic liquids are easily available as they can be prepared efficiently using well elaborated synthetic protocols [7]. Another advantage is that guanidinium salts are known to be highly stable [7]. Therefore, the synthesis of **4a,b** was studied in different guanidinium salts **12**. We began with the reaction between 1.2 equiv. **1**, 2 equiv. **2** and 1 equiv. **3** with 5.4 equiv. of the corresponding guanidinium salts **12a-r** under thermal conditions (160°, 3 min; *Table 4*). It was found that the yield as well as the *endo/exo* ratio of **4a,b** strongly depend on the structure of the guanidinium cation as well as that of the counter ion. With the guanidinium chlorides the *exo*-product **4b** was formed preferentially while the guanidinium tetrafluoroborates delivered the *endo*-isomer **4a** in excess. A particularly striking example is the reaction in **12g**, which results in the exclusive formation of the *exo*-isomer **4b**, albeit at low yields (*Table 4*).

Table 5. Influence of Catalytic Amounts (0.1 equiv.) **12g** and **12p** on the Synthesis of **4a,b**^{a)}

$$\begin{array}{c}
 \text{1} \quad + \quad \text{2} \quad + \quad \text{3} \\
 (1.2 \text{ equiv.}) \quad (2 \text{ equiv.}) \quad (1 \text{ equiv.})
 \end{array}
 \xrightarrow{0.1 \text{ equiv. ionic liquid}}
 \text{4a} + \text{4b}$$

Entry	Ionic liquid	Reaction conditions	Yield 4 (%)	<i>endo/exo</i>
1	12g	160°, 3 min	36	35:65
2	12g	microwave, 70°, 40 min	64	79:21
3	12p	microwave, 70°, 40 min	86	79:21
4	12g	70°, 40 min	72	81:19
5	12p	70°, 40 min	97	88:12
6	-	microwave, 70°, 5 min	-	-

^{a)} The reactions were performed in a sealed vial.

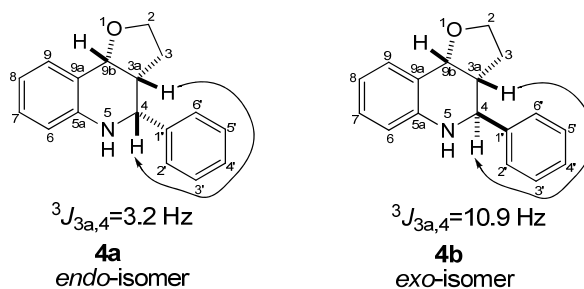
Using the guanidinium salts **12g** and **12p** as examples, it could be demonstrated that the chemical yield as well as the *endo/exo* ratio depend on the concentration of the guanidinium salt (Table 5). It was particularly interesting to note that the transformation can be performed with catalytic amounts of the guanidinium salts (0.1 equiv.) in the absence of any solvent (Table 5, Entries 1-5). It turned out that the reactions can be run under thermal (Table 5, Entries 1,4,5) as well as under microwave conditions (Table 5, Entries 2,3). In addition, the chemical yields as well as the *endo/exo* ratio depend on the reaction temperature. It should also be emphasized that no cycloadducts **4** were formed when the microwave assisted reaction between **1**, **2** and **3** was run in the absence of an ionic liquid (Table 5, Entry 6). These results underline that ionic liquids can not only be used as solvents but can also be employed as catalysts for this chemical transformation.

Table 6. Recycling and Reuse of Guanidinium Salt **12p**^{a)}

	1 (1.2 equiv.)	+	2 (2 equiv.)	+	3 (1 equiv.)	5.4 equiv. 12p oil bath 160°, 3 min →	4a	+	4b
No. of Runs	1st				2nd		3rd		4th
Yield (%)	70				65		75		74
<i>endo/exo</i>	82:18				80:20		83:17		81:19

^{a)} The reactions were performed in a sealed vial.

And finally, it was demonstrated that guanidinium salts can be used for several successive cycles with comparable yields and diastereoselectivities and without significant loss of catalytic activity (Table 6). The results presented here clearly demonstrate the potential of guanidinium salts as solvents and catalysts for the *Diels-Alder* reaction.

Figure 1. Structures of the *endo*-isomer **4a** and the *exo*-isomer **4b**

The structures of isomers **4a** and **4b** were elucidated by mass spectrometry and NMR spectroscopic methods, including ^1H , ^{13}C , COSY, HSQC and HMBC measurements. The relative configuration of the products was established based on the coupling constants between H-C(3a) and H-C(4). In *endo*-**4a** the vicinal coupling

constant $J_{3a,4}$ amounts to 3.2 Hz and is significantly smaller than the corresponding coupling constant in *exo*-**4b**, which amounts to 10.9 Hz (*Figure 1*).

Conclusions. - In summary, it has been demonstrated that the three component reaction between aniline, benzaldehyde and 2,3-dihydrofuran can be catalyzed by ionic liquids like imidazolium salts and guanidinium salts under thermal as well as under microwave conditions. The chemical yield as well as the diastereoselectivity of the one-pot *aza-Diels-Alder* reaction strongly depend on the ionic liquid employed. The guanidinium salts can be used for several successive cycles without significant loss of yield, diastereoselectivity, and loss of activity.

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Experimental Part

General. Aniline was distilled from KOH, benzaldehyde from $MgSO_4$ and 2,3-dihydrofuran from CaH_2 . Cyclopentadiene was obtained by heating of dicyclopentadiene. Reactions were performed using a Discover™ Explorer microwave synthesizer (CEM Corp.), producing continuous irradiation at 2450 MHz. All experiments were conducted under argon. Thin-layer chromatography (TLC) was performed on TLC aluminum roll silica gel 60 F₂₅₄ (MERCK). Compounds were visualized with UV light ($\lambda = 254$ nm). NMR spectra were recorded in $CDCl_3$ on 300 MHz and 500 MHz spectrometers. The ^1H - and ^{13}C -chemical shifts were referenced to residual solvent signals at δ_H 7.26 and δ_C 77 relative to TMS. Melting points were determined on a Kofler melting point apparatus (Reichert, Austria) and are uncorrected. Mass spectra were recorded on a MAT95 at 70 eV. IR spectra were taken on a Spectrum One FT-IR Spectrometer (Perkin Elmer). UV spectra were measured using a Varian Cary 50.

General procedure for the three component reaction between aniline (1), 2,3-dihydrofuran (2) and benzaldehyde (3): 1.2 equiv. of **1** (0.6 mmol), 2.0 equiv. of **2** (1 mmol), 1.0 equiv. of **3** (0.5 mmol), and 5.4 equiv. of a guanidinium salt **12** (2.7 mmol) were placed in a 10 mL microwave reaction vial that had been heated and cooled under argon. The vial was sealed with a septum and heated in an oil bath at 160° for 3 min. After completion of the reaction (TLC), the mixture was allowed to cool to r.t. and extracted with Et₂O (5×5 mL). The combined extracts were concentrated *in vacuo* and the resulting crude product was purified by flash chromatography (silica gel; CH₂Cl₂/petroleum ether 10:3) to afford a mixture of the furoquinolines **4a,b** in analytically pure form (for the ratio of **4a/4b**, see Table 4).

(3aRS,4RS,9bRS)-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline (4a): *R*_f (petroleum ether/AcOEt 8 : 2) 0.48. M.p. 98-100°. ¹H-NMR (500 MHz): 1.53 (*dd*, *J* = 11.7 and 6.8, 1H, H_B-C(3)); 2.22 (*dd*, *J* = 11.8 and 9.5, 1H, H_A-C(3)); 2.80 (*dddd*, *J* = 9.4, 8.0, 7.0 and 3.2, 1H, H-C(3a)); 3.70 – 3.75 (*m*, 1H, H_A-C(2)); 3.80 – 3.86 (*m*, 1H, H_B-C(2)); 3.84 (*br. s*, 1H, NH); 4.71 (*d*, *J* = 3.2, 1H, H-C(4)); 5.29 (*d*, *J* = 8.0, 1H, H-C(9b)); 6.61 (*dd*, *J* = 7.9 and 0.7, 1H, H-C(6)); 6.82 (*ddd*, *J* = 7.5, 7.5 and 1.0, 1H, H-C(8)); 7.10 (*ddd*, *J* = 7.6, 6.9 and 1.5, 1H, H-C(7)); 7.30 – 7.34 (*m*, 1H, H-C(4')); 7.36 (*d*, *J* = 7.4, 1H, H-C(9)); 7.38 – 7.42 (*m*, 2H, H-C(3') and H-C(5')); 7.46 – 7.49 (*m*, 2H, H-C(2') and H-C(6')). ¹³C-NMR (125 MHz): 24.64 (C(3)); 45.75 (C(3a)); 57.50 (C(4)); 66.79 (C(2)); 75.94 (C(9b)); 114.89 (C(6)); 119.15 (C(8)); 122.69 (C(9a)); 126.49 (C(2') and C(6')); 127.63 (C(4')); 128.32 (C(7)); 128.63 (C(3') and C(5')); 130.10 (C(9)); 142.16 (C(1')); 144.93 (C(5a)). EI-MS: 251 (75, *M*⁺), 232 (36), 218 (82), 206 (100), 174 (31), 146 (19), 130 (29), 115 (30), 91 (45), 77 (42), 65 (17), 51 (26).

(3aRS,4SR,9bRS)-4-phenyl-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]quinoline (4b): *R*_f (petroleum ether/AcOEt 8 : 2) 0.41. ¹H-NMR (500 MHz): 1.73 (*dd*, *J* = 13.5 and 1.0, 1H, H_B-C(3)); 2.02 (*dd*, *J* = 13.1 and 7.5, 1H, H_A-C(3)); 2.47 (*dddd*, *J* = 10.9, 7.6, 5.1 and 1.0, 1H, H-C(3a)); 3.81 (*d*, *J* = 10.9, 1H, H-C(4)); 3.82 – 3.87 (*m*, 1H, H_A-C(2)); 4.01 – 4.07 (*m*, 1H, H_B-C(2)); 4.14 (*br. s*, 1H, NH); 4.61 (*d*, *J* = 5.1, 1H, H-C(9b)); 6.63 (*dd*, *J* = 8.1 and 0.7, 1H, H-C(6)); 6.81 (*ddd*, *J* = 7.5, 7.5 and 1.1, 1H, H-C(8)); 7.13 (*ddd*, *J* = 7.8, 7.8 and 1.5, 1H, H-C(7)); 7.33 – 7.37 (*m*, 1H, H-C(4')); 7.38 – 7.41 (*m*,

2H, H-C(3') and H-C(5')); 7.39 – 7.42 (m, 1H, H-C(9)); 7.44 – 7.46 (m, 2H, H-C(2') and H-C(6')). ¹³C-NMR (125 MHz): 28.80 (C(3)); 43.36 (C(3a)); 57.76 (C(4)); 65.18 (C(2)); 76.18 (C(9b)); 114.66 (C(6)); 118.37 (C(8)); 120.04 (C(9a)); 128.12 (C(4')); 128.25 (C(2') and C(6')); 128.65 (C(3') and C(5')); 128.92 (C(7)); 131.20 (C(9)); 141.67 (C(1')); 145.38 (C(5a)). EI-MS: 251 (85, *M*⁺), 220 (17), 206 (100), 182 (27), 174 (18), 144 (16), 130 (18), 115 (15), 91 (29), 77 (16).

Three component reaction between aniline (1), ethyl vinyl ether (5) and benzaldehyde (3): A mixture of 1 equiv. of **1** (1 mmol), 2 equiv. of **5** (2 mmol) and 1 equiv. of **3** (1 mmol) in 5.4 equiv. [bmim]BF₄ (5.4 mmol) was stirred under argon at r.t. for 20 h. After completion of the reaction (TLC), the mixture was extracted with TBME (6×7 mL). The combined organic phases were washed with NaCl solution (3×10 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The resulting crude product was purified by preparative layer chromatography (silica gel; petroleum ether/acetone 100:1) to afford **8a**.

(2*RS*,4*RS*)-2-phenyl-4-ethoxy-1,2,3,4-tetrahydroquinoline (**8a**): *R*_f (petroleum ether/TBME 10:1) 0.51. M.p. 76-78°. UV (CH₃CN): 207 (4.15), 255 (4.20), 322 (3.49). IR (ATR): 2923, 1597, 1553, 1507, 1489, 1446, 1422, 1319, 1283, 1124, 1023, 828, 792, 730, 689. ¹H-NMR (300 MHz): 1.26 (t, *J* = 6.9, 3H, H-C(3'')); 2.08 (ddd, *J* = 11.5, 11.5 and 11.5, 1H, H_{ax}-C(3)); 2.42 (ddd, *J* = 12.3, 5.6 and 5.6, 1H, H_{eq}-C(3)); 3.58 (dq, *J* = 9.2 and 7.0, 2H, H-C(2'')); 3.94 (br. s, 1H, NH); 4.54 (dd, *J* = 11.5 and 2.5, 1H, H-C(2)); 4.82 (dd, *J* = 10.5 and 5.6, 1H, H-C(4)); 6.50 – 6.55 (m, 1H, H-C(8)); 6.72 – 6.79 (m, 1H, H-C(6)); 7.03 – 7.10 (m, 1H, H-C(7)); 7.27 – 7.49 (m, 6H, H-C(5), H-C(2'), H-C(3'), H-C(4'), H-C(5') and H-C(6')). ¹³C-NMR (75 MHz): 15.63 (C(3'')); 37.06 (C(3)); 55.91 (C(2)); 63.48 (C(1'')); 73.96 (C(4)); 114.01 (C(8)); 117.78 (C(6)); 122.58 (C(4a)); 126.60 (C(2') and C(6')); 127.23 (C(5)); 127.77 (C(4')); 128.21 (C(7)); 128.67 (C(3') and C(5')); 143.66 (C(2'')); 144.56 (C(8a)). EI-MS: 253 (<1, *M*⁺), 205 (100), 176(7), 149(6), 128(2), 102.5(10), 102(18), 88(5), 57(3), 28(24).

Three component reaction between aniline (1), 2,3-dihydropyran (6) and benzaldehyde (3): A mixture of 1 equiv. of **1** (1 mmol), 2 equiv. of **6** (2 mmol), 1 equiv. of **3** (1 mmol) and 4 equiv. anhydrous calcium sulfate (4 mmol) in 5.4 equiv. [bmim]BF₄ (5.4 mmol) was stirred under argon at

r.t. for 6 d. After completion of the reaction (TLC), the mixture was extracted with TBME (7×7 mL). The combined organic phases were washed with NaCl solution (3×10 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The resulting crude product was purified by flash chromatography (silica gel; petroleum ether/AcOEt 40:1) to afford **9a**.

(4aRS,5RS,10bRS)-5-phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline (**9a**): R_f (petroleum ether/AcOEt 8:2) 0.48. M.p. 126-128°. UV (CH₃CN): 214 (4.33), 249 (4.00), 304 (3.34). IR (ATR): 3330, 2942, 1606, 1482, 1352, 1317, 1273, 1144, 1084, 1071, 1033, 970, 929, 840, 774, 700, 704. ¹H-NMR (500 MHz): 1.29 – 1.34 (*m*, 1H, H–C(4)); 1.40 – 1.49 (*m*, 1H, H–C(3)); 1.50 – 1.60 (*m*, 1H, H–C(4)); 1.50 – 1.60 (*m*, 1H, H–C(3)); 2.13 – 2.22 (*m*, 1H, H–C(4a)); 3.44 (*dt*, *J* = 11.4 and 2.1, 1H, H_{ax}–C(1)); 3.60 (*ddt*, *J* = 11.4, 4.0 and 1.5, 1H, H_{eq}–C(2)); 3.88 (*br. s*, 1H, NH); 4.70 (*d*, *J* = 2.3, 1H, H–C(5)); 5.34 (*d*, *J* = 5.6, 1H, H–C(10b)); 6.61 (*dd*, *J* = 7.7 and 1.2, 1H, H–C(7)); 6.80 (*ddd*, *J* = 7.4, 7.4 and 1.2, 1H, H–C(9)); 7.10 (*dddd*, *J* = 8.0, 7.4, 1.6 and 0.8, 1H, H–C(8)); 7.31 (*br. t*, *J* = 7.2, 1H, H–C(4')); 7.39 (*br. t*, *J* = 7.8, 2H, H–C(3') and H–C(5')); 7.42 (*br. d*, *J* = 7.2, 2H, H–C(2') and H–C(6')); 7.44 (*ddd*, *J* = 7.5, 1.6 and 0.8, 1H, H–C(10)). ¹³C-NMR (125 MHz): 18.01 (C(4)); 25.41 (C(3)); 38.93 (C(4a)); 59.33 (C(5)); 60.64 (C(2)); 72.76 (C(10b)); 114.37 (C(7)); 118.28 (C(9)); 119.89 (C(10a)); 126.80 (C(2') and C(6')); 127.50 (C(4')); 127.63 (C(10)); 128.07 (C(8)); 128.36 (C(3') and C(5')); 141.11 (C(1')); 145.16 (C(6a)). HR-EI-MS: 265.1481 (M^+ , C₁₈H₁₉NO⁺; calc. 265.1461).

Three component reaction between aniline (1), cyclopentadiene (7) and benzaldehyde (3): A mixture of 1.2 equiv. of **1** (1.2 mmol), 2 equiv. of **7** (2 mmol), 1 equiv. of **3** (1 mmol) and 4 equiv. anhydrous calcium sulfate (4 mmol) in 5.4 equiv. [bmim]BF₄ (5.4 mmol) was stirred under argon at r.t. for 4.5 h. After completion of the reaction (TLC), the mixture was extracted with TBME (7×7 mL). The combined organic phases were washed with NaCl solution, dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. Firstly, *endo*-isomer **10a** was separated by recrystallization of the reaction mixture from methanol. *N*-benzylaniline (**11**) and the *exo*-isomer **10b** were volatile enough to be separated via Kugelrohr distillation. The *exo*-isomer **10b** was obtained in pure form by flash chromatography (silica gel; petroleum ether/AcOEt 19:1) of the distillate.

(3aSR,4RS,9bRS)-4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (**10a**): R_f (petroleum ether/AcOEt 8:2) 0.60. M.p. 123-125°. UV (CH₃CN): 209 (4.57), 251 (3.85), 298 (3.38). IR (ATR): 3355, 3025, 1605, 1587, 1498, 1474, 1449, 1361, 1286, 1260, 1137, 1110, 1026, 1005, 929, 844, 778, 745, 700. ¹H-NMR (500 MHz): 1.83 (dddd, $J = 16.3, 8.7, 2.6$ and 1.5 , 1H, H-C(3)); 2.66 (dddd, $J = 16.4, 9.2, 2.4$ and 2.4 , 1H, H-C(3)); 3.03 (dddd, $J = 9.0, 9.0, 9.0$ and 3.3 , 1H, H-C(3a)); 3.76 (s, 1H, NH); 4.13 (br. d , $J = 8.6$, 1H, H-C(9b)); 4.66 (d , $J = 3.1$, 1H, H-C(4)); 5.64 – 5.68 (m , 1H, H-C(2)); 5.84 – 5.88 (m , 1H, H-C(1)); 6.64 (d , $J = 7.4$, 1H, H-C(6)); 6.77 (ddd , $J = 7.3, 7.3$ and 1.4 , 1H, H-C(8)); 7.00 (ddd , $J = 7.7, 7.7$ and 1.8 , 1H, H-C(7)); 7.08 (ddd , $J = 7.6, 1.6$ and 1.0 , 1H, H-C(9)); 7.29 (t , $J = 7.4$, 1H, H-C(4')); 7.39 (t , $J = 7.4$, 2H, H-C(3') and H-C(5')); 7.45 (d , $J = 7.4$, 2H, H-C(2') and H-C(6')). ¹³C-NMR (125 MHz): 31.47 (C(3)); 46.02 (C(3a)); 46.40 (C(9b)); 58.08 (C(4)); 115.90 (C(6)); 119.16 (C(8)); 126.10 (C(9a)); 126.32 (C(7)); 126.48 (C(2') and C(6')); 127.22 (C(4')); 128.48 (C(3') and C(5')); 128.99 (C(9)); 130.36 (C(2)); 133.98 (C(1)); 142.83 (C(1')); 145.62 (C(5a)). EI-MS: 247 (100, M^+), 218 (10), 206 (15), 193 (7), 170 (21), 156 (36), 129 (10), 115 (7), 91 (4), 77 (5), 44 (8), 28 (26).

(3aSR,4SR,9bRS)-4-phenyl-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline (**10b**): R_f (petroleum ether/AcOEt 8:2) 0.60. UV (CH₃CN): 209 (4.50), 251 (3.92), 299 (3.41). IR (ATR): 3368, 3052, 2929, 2847, 1608, 1588, 1495, 1474, 1454, 1421, 1346, 1315, 1296, 1264, 1252, 1173, 1109, 1064, 1029, 923, 871, 807, 747, 717, 701, 669. ¹H-NMR (500 MHz): 2.11 (br. d , $J = 16.8$, 1H, H-C(3)); 2.46 (dm , $J = 16.8$, 1H, H-C(3)); 2.75 (br. ddd , $J = 10.5, 7.2$ and 7.2 , 1H, H-C(3a)); 3.73 (d , $J = 10.5$, 1H, H-C(4)); 3.90 (br. s , 1H, NH); 4.02 (br. d , $J = 7.5$, 1H, H-C(9b)); 5.68 – 5.72 (m , 1H, H-C(2)); 5.93 – 5.96 (m , 1H, H-C(1)); 6.58 (dd , $J = 8.0$ and 1.2 , 1H, H-C(6)); 6.79 (ddd , $J = 7.4, 7.4$ and 1.2 , 1H, H-C(8)); 7.02 (dddd, $J = 8.1, 7.3, 1.6$ and 0.8 , 1H, H-C(7)); 7.26 (br. d , $J = 7.5$, 1H, H-C(9)); 7.31 – 7.35 (m , 1H, H-C(4')); 7.36 – 7.40 (m , 2H, H-C(3') and H-C(5')); 7.41 – 7.44 (m , 2H, H-C(2') and H-C(6')). ¹³C-NMR (125 MHz): 35.75 (C(3)); 43.14 (C(3a)); 46.82 (C(9b)); 58.35 (C(4)); 114.78 (C(6)); 118.37 (C(8)); 124.13 (C(9a)); 126.47 (C(7)); 127.83 (C(4')); 128.07 (C(1)); 128.48 (C(2') and C(6'), C(3') and C(5')); 129.42 (C(9)); 136.09 (C(2)); 142.86 (C(1')); 145.71 (C(5a)).

N-Benzylaniline (**11**): R_f (petroleum ether/AcOEt 8:2) 0.60. M.p. 36–38°. UV (CH₃CN): 202 (4.48), 248 (4.12), 297 (3.29). IR (ATR): 3417, 3027, 1600, 1508, 1492, 1449, 1429, 1328, 1276, 1180, 1118, 1065, 1027, 984, 858, 735, 688. ¹H-NMR (500 MHz): 4.04 (br. s, 1H, NH); 4.34 (s, 2H, H–C(7')); 6.64 (d, J = 8.6, 2H, H–C(2) and H–C(6)); 6.70 – 6.74 (m, 1H, H–C(4)); 7.18 (dd, J = 8.5 and 7.4, 2H, H–C(3) and H–C(5)); 7.28 (t, J = 7.3, 1H, H–C(4')); 7.35 (t, J = 7.4, 2H, H–C(3') and H–C(5')); 7.38 (br. d, J = 7.5, 2H, H–C(2') and H–C(6')). ¹³C-NMR (125 MHz): 48.33 (C(7')); 112.84 (C(2) and C(6)); 117.56 (C(4)); 127.22 (C(4')); 127.50 (C(2') and C(6')); 128.62 (C(3') and C(5')); 129.25 (C(3) and C(5)); 139.42 (C(1')); 148.14 (C(1)).

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14. Abbreviations

Ac	acetyl
Ar	aromatic
br	broad (NMR)
brs	broad singlet (NMR)
brd	broad doublet (NMR)
Bn	benzyl
calcd	calculated
Cy	cyclohexyl
DA	Diels-Alder
d	doublet (NMR)
dd	doublet of doublet (NMR)
δ	chemical shift
DCCl	dicyclohexylcarbodiimide
DMAP	dimethylaminopyridine
dt	doublet of triplet (NMR)
EDG	electron-donating group
EI	electron impact mass spectroscopy
equiv	equivalent
Et	ethyl
eV	electron Volt (MS)

HFIP	hexafluoroisopropanol
h	hour(s)
Hz	Hertz
IR	infrared spectroscopy
<i>J</i>	coupling constant
λ	wavelength (nm)
M^+	molecular ion
m	multiplet (NMR)
mg	milligramm
Me	methyl
min	minute
mL	milliliter
mol	mole (s)
mp	melting point
MS	mass spectrometry
MW	microwave
<i>m/z</i>	mass/charge ratio
Nap	naphthalene
NMR	nuclear magnetic resonance
$\tilde{\nu}$	wave number
Pyr	pyridine
Ph	phenyl

<i>n</i> -Pr	<i>n</i> -propyl
q	quartet (NMR)
RAM	Rink amide resin
rt	room temperature
s	singlet (NMR)
t	triplet (NMR)
<i>t</i> -Bu	<i>tert</i> -butyl
TFA	trifluoroacetic acid
TLC	thin layer chromatography
TfOH	Trifluoromethanesulfonic acid
TFE	trifluorethanol
TsOH	<i>p</i> -toluenesulfonic acid
UV	ultraviolet spectroscopy
W	Watt

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16. Curriculum Vitae

Fadime Mert-Balci

Date of Birth	05 / 01 / 1982
Place of Birth	Akcakale, Turkey
Marital Status	Married
Email	fmertbalci@google.com

Institute of Chemistry
University of Hohenheim
Garbenstr. 30
D -70599 Stuttgart
Germany

Education

2006-2013	PhD in Organic Chemistry
2002-2006	Diploma in Chemistry (Dipl.-Chem.), University of Paderborn, Paderborn, Germany
1999-2002	B.Sc in Chemistry, University of Mersin, Mersin, Turkey

Teaching Experience

06/2006-12/2008 Teaching Assistant in the laboratory of Prof. Dr. Beifuss,
Institute of Chemistry, University of Hohenheim,
Stuttgart, Germany

Research Activities

06/2006-12/2008 Doctoral work in synthetic organic chemistry at the
University of Hohenheim, Stuttgart, Germany under the
supervision of Prof. Dr. Uwe Beifuss

Thesis Title:

*Influence of microwave irradiation and ionic liquids on
multi component reactions*

07/2005-02/2006 Diploma (Dipl.-Chem.) thesis at the University of
Paderborn, Paderborn, Germany under the supervision of
Prof. Dr. Nikolaus Risch

Thesis Title:

*Herstellung von Bausteinen zur Synthese chiraler
verbrückter Terpyridine*

Fellowships

10/2005-12/2005 Scholarship from University of Paderborn

07/2004-12/2004 DAAD (Deutscher Akademischer Austauschdienst)

08/2003-12/2003 DAAD (Deutscher Akademischer Austauschdienst)

17. List of Publications

1. **Fadime Mert-Balci**, Jürgen Conrad, Kathrin Meindl, Thomas Schulz, Dietmar Stalke, and Uwe Beifuss “Microwave-Assisted Three-Component Reaction for the Synthesis of Pyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-ones”, *Synthesis* **2008**, 3649-3656
2. Kathrin Meindl, Daniel Stern, **Fadime Mert-Balci**, and Uwe Beifuss “6-Benzyl-3,4-dimethoxy-10-methylpyrido[2',1':2,3]imidazo[4,5-c]isoquinolin-5(6*H*)-one”, *Acta Cryst. E* **2009**, 65, o2464-o2465
3. Jürgen Conrad, Bernhard Förster-Fromme, Mihaela-Anca Constantin, Vladimir Ondrus, Sabine Mika, **Fadime Mert-Balci**, Iris Klaiber, Jens Pfannstiel, Wolfgang Möller, Harald Rösner, Karin Förster-Fromme, and Uwe Beifuss “Flavonoid Glucuronides and a Chromone from the Aquatic Macrophyte *Stratiotes aloides*”, *J. Nat. Prod.* **2009**, 72, 835-840
4. **Fadime Mert-Balci**, Jürgen Conrad, and Uwe Beifuss “Microwave-assisted three-component reaction in conventional solvents and ionic liquids for the synthesis of amino-substituted imidazo[1,2-*a*]pyridines”, *ARKIVOC* **2012** (iii), 243-256
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