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MICROWAVE-AIDED REACTIONS OF ANILINE DERIVATIVES WITH FORMIC ACID: INQUIRY-BASED LEARNING EXPERIMENTS

Abstract: The synthesis of amides belongs to traditional experimental tasks not only in organic chemistry exercises at universities but also at chemically focused secondary schools or in special practices at general high schools. An example of such a synthesis may be the preparation of acetanilide *via* reaction of aniline with acetic acid or acetic anhydride. However, both of these reactions are associated with a rather long reaction time and certain hazards that limit their straightforward use in pedagogical practice. Conveniently, the reaction of aniline with acetic acid may be significantly optimised if it is performed under solvent-free conditions in the presence of microwaves, which reduces considerably the reaction time and provides very good yield, compared to traditional heating by a heating nest. In this study, the main pedagogical aim of the experimental design is elucidation of the influence of the structure of the amines on the course of the reaction with formic acid through inquiry-based learning. Specifically, the proposed experiments consist in investigation of the chemical yield achieved in microwave assisted reactions of aniline and its derivatives with formic acid in such a way that is adequate for constructive learning of undergraduate chemistry students. The selected series of amines involves aniline, 4-methoxyaniline, 4-chloroaniline, and 4-nitroaniline. In accordance with the chemical reactivity principles, students gradually realise that the influence of the substituent is reflected in the reaction yield, which grows in the following order: N-(4-nitrophenyl)formamide < N-(4-chlorophenyl)formamide < N-phenylformamide < N-(4-methoxyphenyl)formamide. Therefore, the results of the experiments enable students to discover that stronger basicity of the amine increases the yield of the amide. In order to deepen the students' chemical knowledge and skills, the concept of the experiments was transformed to support inquiry-based student learning. The proposed experiments are intended for experimental learning in universities educating future chemistry teachers, but they may be also utilised in the form of workshops for students at secondary schools of a general educational nature.

Keywords: inquiry-based learning, amide synthesis, microwave synthesis, amine structure, amide yield

Introduction

In recent years, a special emphasis has been placed on the preparation of new chemicals with rationally designed structure and properties [1, 2]. One of the most important areas that operate with a large number of such chemicals are pharmaceutical research and biotechnological development [3-5]. In fact, relationships between the structure and physical-chemical properties emerge within many different contexts, including, for instance, rational design of new drugs, optimisation of food additives,

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preparation of selective pesticides, or, unfortunately, development powerful chemical weapons [6-8]. Current demands on general effectivity and competitiveness in all fields also prompt a significant transformation of organic synthesis processes, which is the main tool for the preparation of special substances and materials. The structure-property and structure-reactivity relationships represent, therefore, a crucial factor for further evolution of existing synthetic processes, and as such it should be adequately reflected in modern chemistry education [9, 10].

One of the main principles of organic synthesis is the preparation of substances of the desired structure in the highest possible yield within the shortest time. In this area, the ecological and economic aspects of organic synthesis cannot be overlooked anymore like before. Inevitably, great attention is currently placed on the former aspect, which has been adopted in principles of so-called Green Chemistry [11-13]. One of the ways leading to achievement of a high reaction yield in a relatively short time is the use of microwave support in organic synthesis [14, 15]. Another important principle is the synthesis in a solvent-free phase, which has a number of advantages both in terms of ecological and economic interests [16]. As a result, a new direction in organic as well as inorganic chemistry has recently been established, which is called microwave-assisted synthesis [17, 18]. Although the use of microwaves is not a universal means for refining the quality of all synthetic processes, microwave heating of the reaction mixture leads to a significant improvement of the yield and reaction time for many chemical reactions.

These trends in organic synthesis should be also considered in the field of chemical education as a way to support development of the learners' responsibility towards nature and environment. Fortunately, there is a significant circumstance that enables the implementation of chemical experiments in the presence of microwaves even under the conditions of secondary schools. It is the vast availability of common kitchen microwave ovens that can be employed for such chemical experiments. This fact establishes a starting point for the successful implementation of educational experiments in the field of organic synthesis, which are carried out in the presence of microwave irradiation [19].

In the present study, we decided to use an ordinary kitchen microwave oven for the synthesis of carboxylic acid amides through the reaction of formic acid with a set of primary amines (i.e. aniline, 4-methoxyaniline, 4-chloroaniline and 4-nitroaniline). Such a synthesis was chosen for a number of reasons. The first is the high selectivity of the reaction, and the other is the formation of almost one product. As an important condition for successful microwave heating is the overall molecular polarity, we selected such starting substances for the synthesis of amides and intermediates of the reaction to meet this requirement. The proposed synthetic procedure can also be carried out using traditional heating of the reaction mixture (e.g., by sand or water bath), but the reaction time gets significantly prolonged in this way. Since the traditional synthesis of amides based on the reaction of halides or carboxylic acid anhydrides with ammonia or amines does not meet the ecological requirements of Green Chemistry, the microwave synthesis without a solvent therefore seems to be the optimal approach.

In this work, microwave-assisted amide synthesis has been designed and studied as an inquiry-based learning approach for experimental evaluation of structure-reactivity relationships with the perspective of its application in university mandatory chemistry courses and specialised chemical practices in secondary schools [20]. Inquiry-based learning can be utilised to train students in formulating hypotheses, making observations, conducting experiments, and finally, revealing causal relations [21]. In this context,

reactions of aromatic carboxylic acids with aliphatic amines and reactions of aliphatic carboxylic acids with aromatic amines as problem-solving tasks have been investigated for long time in our team. The present work is essentially based on these studies [22].

Theoretical part

Amides are functional derivatives of carboxylic and other acids besides derivatives like esters, anhydrides or halides [23]. They are classified according to the initial substances from which they can be prepared. The most common cases are N-alkylamides and N,N-dialkylamides. The hydrocarbon residues in amides can be aliphatic and aromatic. Furthermore, undergraduate chemistry courses also frequently introduce cyclic amides, called lactams, which opens the door to a considerable structural diversity of amides (Fig. 1).

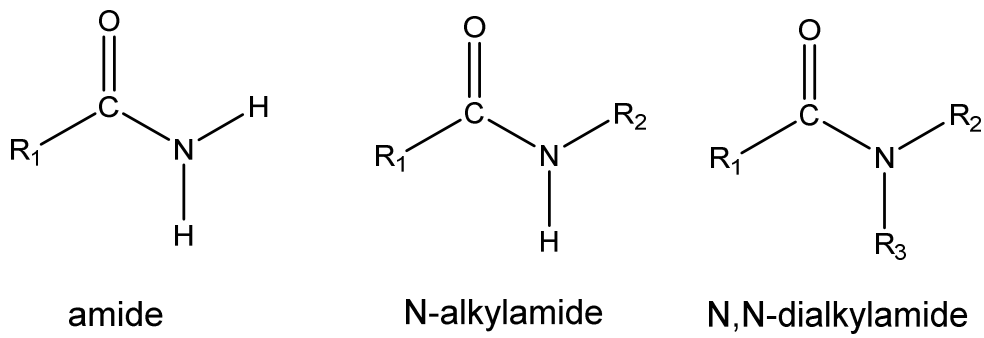


Fig. 1. Basic types of amides

Amides show basically a broad range of reactions, like hydrolysis and dehydration that are the most significant ones. In comparison with other functional derivatives (i.e. halides of carboxylic acids, anhydrides of carboxylic acids, and esters of carboxylic acids) hydrolysis of amides proceeds with considerable difficulties. The cause is significant electron transfer (i.e. back electron donation) in the amide molecule, which is very strong in comparison with esters, anhydrides, and halides, and is related to the electron donating properties of the nitrogen atom of the amide group. In carboxylic acid halides, the opposite is true; the electron-donating capacity of the halogen atom is significantly smaller (Fig. 2). The electron donation of the nitrogen atom, the essence of which is a positive mesomeric effect, causes a decrease in the partial positive charge on the central carbon atom of the amide group. As a result, the carbon atom becomes a weaker reaction centre for nucleophilic attack, for example, by a water molecule. It is understandable that the hydrolysis of carboxylic acid halides occurs spontaneously under normal conditions without the presence of a catalyst. Hydrolysis of amides yielding carboxylic acid is difficult and therefore the presence of an acidic or basic catalyst is necessary. Dehydration of amides is a reaction that takes place in the presence of such reagents as phosphorus pentoxide or phosphorus pentachloride. The organic product of the reaction with PCl_5 is a nitrile compound, and additionally phosphoryl chloride and hydrogen chloride.

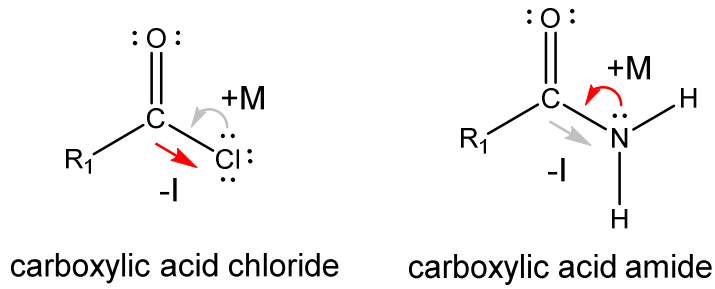


Fig. 2. Mesomeric (+M) and inductive (–I) substituent effects in acyl chlorides and amides. The chlorine atom has weak +M (grey) and strong –I (red) electron effects. The nitrogen atom has strong +M (red) and weak –I (grey) electron effects

A basic procedure that is used for the preparation of amides is the reaction of amines with halides or anhydrides of carboxylic acids [23]. These syntheses are very efficient in terms of the product yield. The synthesis of amides as functional derivatives of carboxylic acids is one of the popular tasks within laboratory exercises in organic chemistry in universities and chemically oriented secondary schools. A well-known example is the synthesis of acetanilide (N-phenylacetamide) from aniline and acetic anhydride as starting substances (Fig. 3).

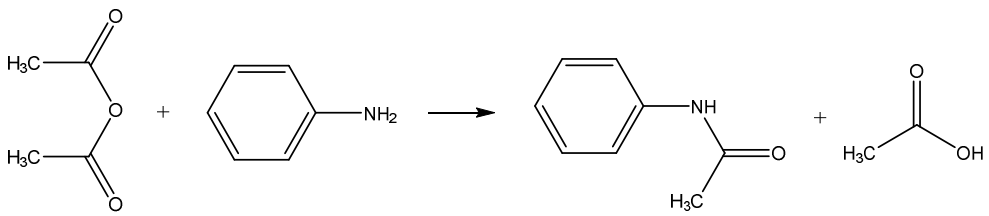


Fig. 3. Reaction scheme for the synthesis of acetanilide (N-phenylacetamide) from aniline and acetic anhydride

Acetanilide (sold as Antifebrin) became the first analgesic-antipyretic drug related with aniline used in medical practice. Subsequently, due to its side effects, it was withdrawn from the clinical use. Further modification of the structure led to N-(4-hydroxyphenyl)acetamide, which is a more effective antipyretic with lower toxicity [24]. It is produced under the name Paralen or Panadol and currently belongs to the most widely used analgesics-antipyretics. This fact may be an important motivating element in connection with the implementation of this experimental task in pedagogical practice.

The acetanilide synthesis consists in heating a mixture of aniline and acetic anhydride in a flask under the reflux condenser by a heating nest, then cooling the reaction mixture and recrystallisation of the raw product from the aqueous solution [25-28]. The older version of acetanilide synthesis is based on heating aniline with concentrated acetic acid [29, 30]. This option is less convenient for the needs of laboratory exercises since it requires heating the reaction mixture for several hours.

However, with respect to the principles of Green Chemistry, a number of problems arise due to the negative effect of the starting substances on the human body since halides

and anhydrides of carboxylic acids are aggressive, lacrimating and irritating substances (Fig. 4) [31]. The replacement of halides and anhydrides with carboxylic acids meets the requirements for a safe ecological impact of the synthesis. Nevertheless, this reaction takes a relatively long time if it is performed in the traditional way. In addition, there are also special synthetic procedures that utilise reactions of carboxylic acid with urea. Amides are also products of Beckmann's rearrangement of oximes.

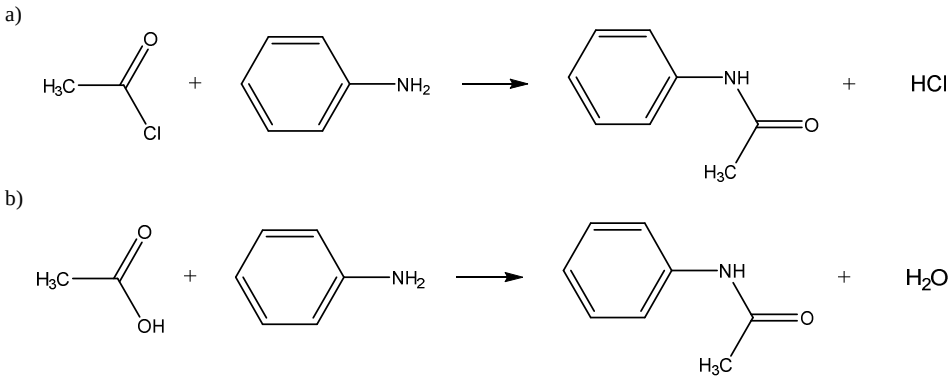


Fig. 4. Reaction schemes of acetanilide (N-phenylacetamide) synthesis: a) from aniline and acetylchloride or b) from aniline and acetic acid

Microwave irradiation appears in various forms in a wide range of human activities. The application of microwaves has also found its place in chemistry, as well as in chemistry education (e.g., Diels-Alder cyclisation, Wittig reaction, Williamson ether synthesis) [32-42]. Microwaves can also be found in other chemical fields, such as pre-treatment of samples in analytical chemistry replacing classical mineralisation [43]. From our point of view, application of microwaves in organic synthesis is particularly interesting. Microwave heating has proven to be very effective from a practical point of view, although it is limited by the properties of chemicals involved in the synthesis. Today, organic synthesis processes involving the use of microwaves represent a wide range of applications: synthesis of dioxolane, cleavage of aldehyde diacetates, deoximation, synthesis of imines, alkylation reaction of phthalimide, oxidation reactions of arenes and alcohols, reduction reactions of carbonyl compounds, reduction amination of carbonyl compounds, synthesis of heterocyclic compounds or transformation of aromatic aldehydes into nitriles [44-48]. These examples are only a fraction of the real number of possible microwave-assisted organic synthesis reactions. Various design improvements may expand the range of microwave applications in different areas of organic synthesis in the future, depending on the development of microwave technologies (e.g., ovens, reactors).

For more than 10 years, publications focused on teaching chemistry with microwave oven applications have appeared in the scientific literature [33, 34, 36, 38-40, 49-51]. In addition to motivational experiments with the microwave oven such as investigation of the effect of microwaves on filter paper, basic tasks implementing microwaves in synthesis of organic compounds have recently been reported [52-55]. These educational laboratory tasks include, for example, the acetylation of salicylic acid with acetic anhydride to form acetylsalicylic acid (i.e. aspirin) [56]. Having known about such educational tasks, we

wondered if it would be possible to propose a similar reaction leading to the formation of a functional derivative of carboxylic acid. The objective stems from the fact that the synthesis of functional derivatives of carboxylic acids is characterised, as already mentioned, by high selectivity and yield with which the product is formed. In this context, we were interested in the reaction of carboxylic acids with amines or ammonia to form amides [22, 57, 58]. This reaction has also several advantages for inquiry-based learning since it enables to propose several physicochemical properties as crucial factors that influence the amines' reactivity and formulate many working hypotheses. The starting substances have different polarity, and the synthesis leads to an intermediate in the form of ammonium salt, which causes a stronger response to microwave heating. Moreover, the final product can be easily isolated from the reaction mixture and can be studied as well. Therefore, the reactions allow to investigate the influence of the structure of reactants on the course of the reaction, the influence of the heating time on the course of the reaction, the influence of microwave power on the course of the reaction, or the influence of the mutual ratio of reactants on the product yield.

The use of microwave irradiation appears to be a promising factor in the synthesis of amides from carboxylic acids and amines as a starting material [59]. These compounds meet the conditions for the absorption of microwave irradiation because they are polar molecules. Another benefit is the fact that the predominant product of the interaction of carboxylic acid with amine is ammonium salt, which is also a polar substance. Evidently, the conditions for effective microwave heating are met in the synthesis of amides in this way. Furthermore, the reaction of carboxylic acid with amine can also be performed as a solvent-free reaction (Fig. 5).

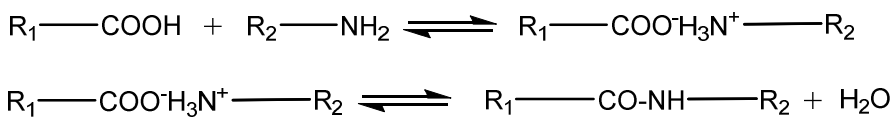


Fig. 5. Formation of amides by decomposition of ammonium-carboxylate salts

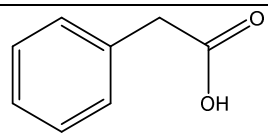
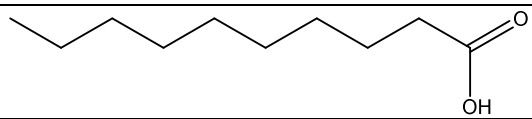
Reactions of this type have been studied in association with an increase in yield and a reduction in reaction time. Research has been carried out on reactions of various types of carboxylic acids and amines [42, 59]. In this context, the effects of the heating time of the reaction mixture, the temperature of the reaction mixture, the ratio of reactants and other factors on the reaction yield have been investigated. An example of such studies is the reaction of n-octylamine with phenylacetic acid and decanoic acid, where the method of heating of the reaction mixture was investigated. The yields of the reaction carried out with traditional and microwave heating of the reaction mixture were compared. For example, reactions carried out at 150 °C for 30 minutes are associated with the following results (Table 1) [59].

The yields of the reaction carried out with microwave heating are higher than the yields of the reaction when the reaction mixture is heated in the traditional way. It is clear from Table 1 that an increase in the amount of acid compared to amine leads to an increase in the yield of the reaction; on the contrary, an increase in the amount of amine in the reaction mixture leads to a decrease in the reaction yield. Similar dependencies indicate the effect of the heating time on the reaction yield or the effect of the microwave power on the

yield. The course of the reaction can also be affected in the presence of a catalyst. It turned out that catalysts of an acidic nature have a positive effect on the course of the reaction and increase in yield. In contrast, inhibit the course of the reaction and are reflected in a decrease in yield. In the microwave synthesis of amides as a solvent-free reaction, microporous materials such as bentonites and montmorillonites were also used [60].

Table 1

Results of reactions of n-octylamine with various carboxylic acids after 30 minutes at 150 °C [59]

Carboxylic acid	Molar amine-acid ratio	Yield [%]
	1:1	54
	1:1.5	82
	1.5:1	52
	1:1	63
	1:1.5	68
	1.5:1	52

In this study, the traditional protocol for amides synthesis has been modified in the following way:

1. Acetic anhydride or acetic acid have been replaced by formic acid [61, 62]. The reason for the elimination of acetic anhydride is its toxicological drawbacks with respect to the principles of Green Chemistry. Replacement of acetic acid, which is a more suitable reactant than acetic anhydride due to safety, with formic acid is also justified by a higher reactivity of this substance compared to acetic acid.
2. The reaction was carried out at a semi-micro scale. Again, this is option follows from a respect for the principles of Green Chemistry (e.g., saving chemicals, reducing the volume of waste, etc.)
3. Microwave heating was used in the reaction. This leads to a relative energy saving, since the reaction time in this case is significantly reduced from hours to minutes compared to the traditional method of heating with a heating nest or bath.
4. Finally, the influence of aniline substituents (e.g., no substituent in aniline, 4-methoxyaniline, 4-chloroaniline, and 4-nitroaniline) on the course of the reaction with formic acid and the yield of the product was also studied. The study of the structure-reactivity relationship in this case forms the basis for the application of the inquiry-based method within laboratory exercises.

The influence of aniline structure on the course of the reaction has become the central theme of the experimental task, which is based on the investigation of the influence of the substituent at the *para* position in aniline on the yield of the respective N-phenylformamide. The use of microwave assisted organic synthesis in teaching seems to be acceptable because a microwave reactor, which is a professional device for this type of synthesis, can be replaced by a commercial microwave oven. For these reasons and given our experience to date, we have designed a model series of aromatic amines (e.g., aniline derivatives) for reaction with formic acid for this purpose. The aim of the work was to show the influence of the structure of the amine on the course of the reaction and the yield of the product.

Based on the performed experiments, a step-by-step protocol was proposed, which is applicable to the needs of teaching. The final intention was the elaboration of an experimental task with the perspective of use in university laboratory exercises from organic chemistry or in the practice of school chemical experiments; the task was also assumed to be used in a selected practice at secondary school. The task allows to show the influence of the structure of reactants on the course of synthesis, but also to investigate the influence of the heating time of the reaction mixture - the influence of microwave power, the influence of the location of the reaction vessel in the microwave oven, etc.

Experimental part

Chemicals

For the experiments with microwave oven, a number of chemical substances was necessary. The list of substances and their properties are given in Table 2.

Table 2

Overview of chemicals used

Compound	Producer	Country of origin
Formic acid, p.	Lach-Ner	Czech Republic
Aniline, p.	Lachema	Czech Republic
4-methoxyaniline, p.	Acros Organics	Belgium
4-chloroaniline, p.	Acros Organics	Belgium
4-nitroaniline, p.	Acros Organics	Belgium
Chloroform, p.	Penta	Czech Republic
Ethyl acetate, p.	Lach-Ner	Czech Republic
Anhydrous sodium sulphate, p.	Lachema	Czech Republic
Hydrochloric acid (conc.), p.	Lach-Ner	Czech Republic
Sodium bicarbonate, p.	Penta	Czech Republic

Tools and instrumentation

The proposed chemical reactions were performed in a porcelain crucible covered with watch glasses, using the following instruments and tools:

1. Chromatographic chamber with cover glass
2. Thin layer for chromatography
   - Name: ALUGRAM SIL G/UV_{254}
   - Manufacturer: Macherey - Nagel
   - Country of origin: Germany
3. UV chamber for chromatogram detection
   - Manufacturer: Camag
   - Country of origin: Switzerland
4. Laboratory scales
   - Manufacturer: Kern & Sohn
   - Country of origin: Germany
5. Kitchen microwave oven
   - Manufacturer: Goddess
   - Country of origin: China

TLC analysis of reaction products

For the purpose of analysing the reaction mixture, chromatography of the starting substances and products on a thin layer (TLC) of silica gel with a luminescent indicator (wavelength λ = 254 nm) was proposed as well. Chloroform and ethyl acetate were used as the elution agents. The chromatograms were evaluated using a UV detection chamber. Individual retardation factors (R_F) are listed in Table 3.

Table 3

R_F values of the starting substances and reaction products (thin layer: silica gel)

Compound	R_F eluent: chloroform	R_F eluent: ethyl acetate
aniline	0.51	0.87
4-methoxyaniline	0.20	0.63
4-chloroaniline	0.40	0.73
4-nitroaniline	0.40	0.75
N-phenylformamide	0.09	0.79
N-(4-methoxyphenyl)formamide	0.04	0.59
N-(4-chlorophenyl)formamide	0.07	0.63
N-(4-nitrophenyl)formamide	0.05	0.65

Synthesis procedure

Based on the study of the literature and our own experience, a microwave-assisted organic synthesis procedure was proposed, which also included the isolation of the product from the reaction mixture [41, 61]. The procedure was used to elaborate an educational experimental task.

- In four porcelain crucibles (V = 10 mL), gradually weigh 0.003 moles of aniline (0.28 g) 4-methoxyaniline (0.37 g), 4-chloroaniline (0.38 g) and 4-nitroaniline (0.41 g). Then add 0.003 moles of formic acid (0.14 g) with a dropper to each crucible.
- Cover the crucibles with watch glasses and place them in the microwave oven 2 cm from the centre of the rotating plate.
- Heat the reaction mixture in crucibles for 10 minutes with medium microwave power (approximately 350 W).
- After heating, remove the crucibles from the microwave oven and, after free cooling, transfer their contents to a beaker, add 25 mL of chloroform and stir until the product is dissolved.
- Carefully shake the solution of the reaction mixture in the separating funnel with 50 mL hydrochloric acid (c = 2 M), then separate the hydrochloric acid layer from the layer containing the reaction mixture.
- Subsequently, shake the solution of the reaction mixture in a separating funnel with 50 mL of 5 % (*w/w*) aqueous sodium bicarbonate, then separate the layer of aqueous sodium bicarbonate solution from the layer containing the reaction mixture.
- From the solution of the reaction mixture in chloroform placed in a beaker, remove water by adding anhydrous sodium sulphate, then separate the sodium sulphate by filtration.
- Put a drop of the reaction mixture before and after the separation operations on a thin layer of silica gel together with the standards of the studied amines. Prepare duplicate

TLC strips with the samples and place them in two chromatographic chambers with chloroform and ethyl acetate as elution agents.

- Pull out the chromatograms from the chambers and detect the samples under the UV lamp. The corresponding amide and amine pairs form dark spots on the thin layer. Calculate the retardation factor (R_F) values for both substances and compare them with data from the literature.
- Evaporate the solution of the reaction product to dryness in a water bath (in a hood), weigh the product and calculate the reaction yield.

Results and discussion

The proposed educational project consists of four parts: 1) amide synthesis, 2) the influence of amine structure on the course of amide synthesis, 3) the influence of microwaves on amide synthesis, and 4) educational applications of microwave amide synthesis. The influence of aniline structure on the course of the reaction and the yield of the product, which is the corresponding N-phenylformamide, was the principal knowledge that was necessary to obtain from the experiments. The reaction was carried out as a solvent-free synthesis in the presence of microwaves using a common kitchen microwave oven (Fig. 6).

Fig. 6. Kitchen microwave oven with four crucibles containing reaction mixtures of formic acid and four different aniline derivatives

After the conditions for the implementation of the experiment were defined and the influence of the aniline structure on the course of the reaction was explored, the preliminary research conclusions were used as material for transforming the experimental task into

an inquiry-based learning method for laboratory exercises in organic chemistry at universities or for selected practical courses in chemistry at secondary schools.

The proposed organic syntheses were performed in a microwave oven, using porcelain crucibles as reaction vessels, which were covered with watch glasses of appropriate size. The starting compounds (e.g., formic acid and aniline derivatives) were placed in porcelain crucibles and heated in a microwave oven for 10 minutes (Figs. 7-10).

Fig. 7. Crucible with the product of the reaction of formic acid with aniline

Fig. 8. Crucible with the product of the reaction of formic acid with 4-methoxyaniline

Fig. 9. Crucible with the product of the reaction of formic acid with 4-chloroaniline

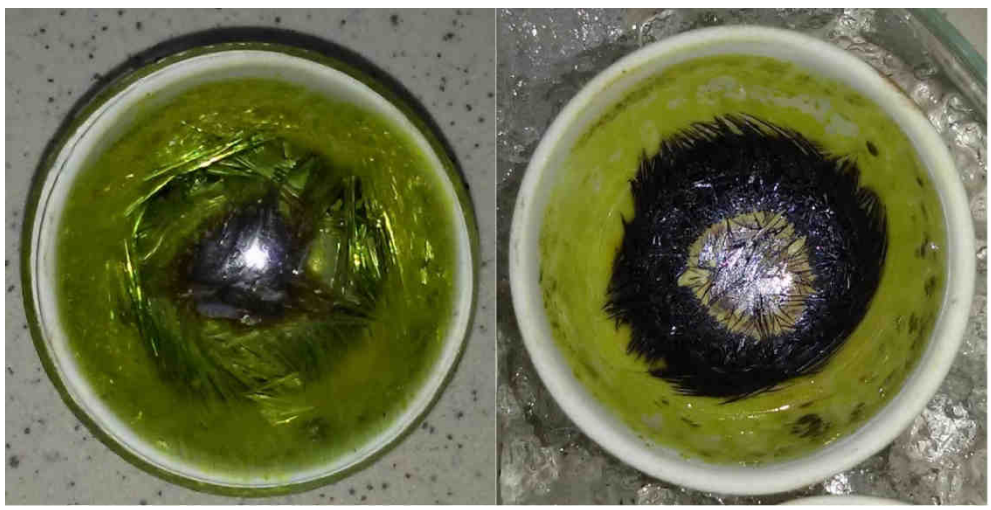


Fig. 10. Crucible with the product of the reaction of formic acid with 4-nitroaniline

After the reaction mixture was cooled down, the reaction mixture was dissolved in chloroform and shaken with dilute hydrochloric acid to remove the unreacted amine. Subsequently, the chloroform solution was separated and shaken with a dilute solution of sodium hydrogen carbonate, which removed the residues of formic and hydrochloric acid. Finally, the chloroform phase was separated, evaporated and the produced amides were weighed, and the yield calculated. Each reaction was repeated twice, and the average results were discussed with respect to the structure of the reactants and the reaction conditions, taking into account the inhomogeneity of the microwave field and the fact that the melt represents an inhomogeneous environment.

The object of this work was to develop a procedure for inquiry-based learning in which the effect of the amine structure on the reaction yield had to be analysed. As already stated at the beginning of the study, the given reaction is supported if the acidity of carboxylic acid and the basicity of the amine are higher. Under these conditions, the nucleophilic attack of the central carbon atom of the carboxyl group is led by the nitrogen atom of the amino group. In this work, one carboxylic acid and four different aromatic amines were used: unsubstituted aniline, 4-methoxyaniline, 4-chloroaniline and 4-nitroaniline. 4-methoxyaniline is a substance more basic than aniline due to the electron-donor action of the methoxy group in *para* position. On the contrary, 4-chloroaniline and 4-nitroaniline are less basic than aniline because they contain substituents of electron acceptor character. According to the theoretical presumptions, it can be expected that aniline substituted by an electron donor function reacts more easily with formic acid than aniline substituted by electron acceptor functions. Accordingly, it was observed in this study that 4-methoxyaniline provided a greater amide yield than 4-chloroaniline and 4-nitroaniline. The latter amine shows the lowest amide yield in this group of reactions. The results of the experiments are perfectly in accordance with the theory of substituent electron effects, even though the reaction was carried out without a solvent in the melt and irradiated in inhomogeneous microwave field (Table 4).

Table 4

Amide yields

Amine	**Amide yield [%]**
4-methoxyaniline	47
aniline	40
4-chloroaniline	33
4-nitroaniline	11

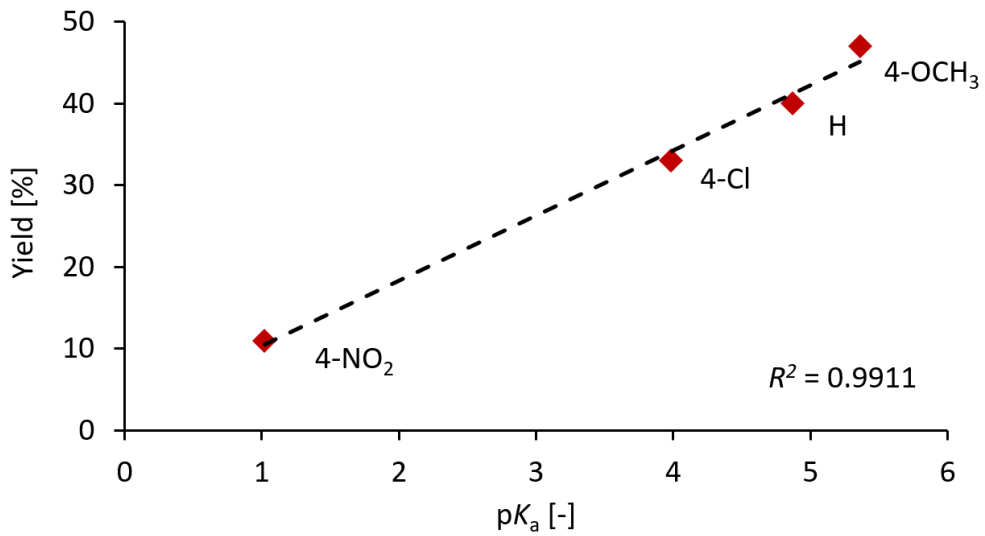


Fig. 11. Relationship between the amide yields and the pK_a values

The concept of structure-reactivity can be even more elucidated if the amide yields are correlated with the negative decimal logarithm of the conjugated acid dissociation constants (i.e. pK_a) that represent the basicity of the studied amines. The pK_a values for the studied amines can easily be obtained from the literature [63, 64]. Although the yield-pK_a correlation analysis is not included in the basic proposal of this learning method, it can be optionally implemented if students achieve sufficient knowledge of the solved problem. The plot representing an excellent correlation (R^2 = 0.9911) between pK_a values and the observed amide yields is given in Figure 11.

Conclusion

The proposed microwave-assisted experiments may be used for designing inquiry-based learning exercises to support understanding of the relationship between the chemical structure of organic substances and their chemical reactivity within education of organic chemistry. According to a current survey by Rusek et al. [65], educational experiments, especially in organic chemistry, deserve more attention since they are rather disregarded in chemistry education reality, although they may considerably help learners grasp the vital essence of the chemistry phenomena. Therefore, four different aromatic amines were selected and examined for their ability to yield amides with formic acid under microwave irradiation in this study. Importantly, these chemical experiments are optimised for utilisation of a common kitchen microwave oven and may be performed within 10 minutes in basic chemistry labs either at universities or secondary schools. Through a simple quantification of the produced amides by weighing, students may easily observe the impact of various substituents on the amine group reactivity, because substituents that donate the amine function with electrons increase the amine basicity and, as a consequence, provide a higher yield of the amide in the reaction with formic acid. If students are skilful enough to statistically analyse the results, they might calculate the coefficient of determination R^2 between the yields and the pK_a values of the amines, which reveals an excellent linear dependence (i.e. R^2 = 0.9911). However, such a strong correlation may be generally lower when the microwave field is not homogenous. The selected type of organic synthesis can be also tested on several other compounds, for example aniline derivatives substituted at positions 2- and 3-. It is also possible to expand the number of aromatic amines with other substituents. Such experimental tasks with microwaves can be therefore easily implemented in inquiry-based learning at universities and, in certain cases, in exercises at secondary schools to help students experience step-by-step crucial principles of organic chemistry.

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