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# Comparison of conventional and green approaches to the synthesis of aromatic Schiff bases

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The chemical industry is one of the key elements in improving the quality of human life. At the same time, it generates pollution influencing the ecosystem and our health. To limit or remove some of the reasons of pollution for two decades less harmful approaches to the synthesis of various organic compounds were developed. Among organic compounds, azomethines, also known as Schiff bases, are of particular interest in biochemistry, medicine, and pharmacy. For over twenty years many novel approaches to the synthesis of these compounds have been investigated. Toxic solvents (benzene, toluene) have been replaced with water, fruit juice, or white egg, and in many cases, temperature and time of process were significantly reduced.

In the review, conventional and green approaches to the synthesis of Schiff bases are presented with a focus on the effectiveness of these methods, including advantages and disadvantages.

**Keywords:** sustainable development, Schiff bases, green chemistry, green synthesis.

## INTRODUCTION

The chemical industry is one of the key elements in improving the quality of our lives. However, it also has dark face, environmental pollution, caused by chemical industry production and chemical disasters. The inglorious face of the mentioned field of human activity forces us to change our approach to the problem of environmental contamination and to look for tools that can reduce the negative impact on the environment that we live in[1–2]. Since Anastas and Warnier presented twelve principles of green chemistry (1990s)[3], a lot of eco-friendly solutions for the chemical industry appeared. Reviewing the literature one can notice that scientists do not stop searching for novel, less harmful methods of chemical compounds' syntheses[2, 4]. One of many groups of compounds for which scientists are looking for eco-friendly solutions are azomethines (imines) known as Schiff bases[4].

Schiff bases constitute a very wide group of organic compounds that differ in structure. However, there is one element that units them - the presence of imine group CH=N in each molecule (Fig. 1)[5–6].

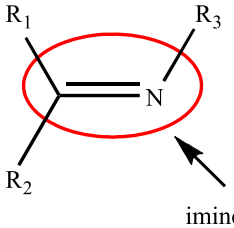



**Figure 1.** General formula of Schiff bases: $R_1$ – H, alkyl, or aryl, $R_2$, $R_3$ – alkyl or aryl

A wide distribution of Schiff bases in nature makes them remarkably interesting compounds for biochemistry, medicine, and pharmacy[6–8]. They are formed in living organisms as intermediate products in many natural processes. For example, one can find Schiff base in rods of the retina, where it is formed between 11-cis-retinal and opsin as the first step of chain of transformations leading to seeing shapes even at dusk[9–10].

Some of Schiff bases successfully bind to DNA[11]. In the situation where it is not possible to restore DNA polymerase, Schiff bases can be an attractive alternative in rebuilding damaged DNA. It may prevent the development of diseases like cancer, neurological disorders or diabetes[12]. However, not only DNA repair can be carried out by some imine systems. Their second indisputable advantage is that, similarly to cis-platin, they can bind to DNA of tumor cells, preventing their multiplication[13]. Hydrazone-, thiosemicarbazone-, or benzazepine-based Schiff bases are under clinical investigations for treatment of different kinds of cancer[14]. For example, aldoxorubicin, hydrazone derivative of doxorubicin (DOX), has undergone three stages of clinical trials for the treatment of soft tissues sarcoma[15–16]. Aldoxorubicin appears to be an excellent replacement for the currently used DOX, because of its less cardiotoxicity and 3–5 times increasing in maximum tolerated dose (MTDs)[16].

Besides anti-cancer properties, imines show a wide spectrum of other biological activity[17]. Some of Schiff bases are antimicrobial (bactericidal, fungicidal, antiviral, anti-helminthic, antiprotozoal, anti-tuberculous), anticonvulsant, antidepressant, analgesic or antihypertensive (Fig. 2)[18–24].

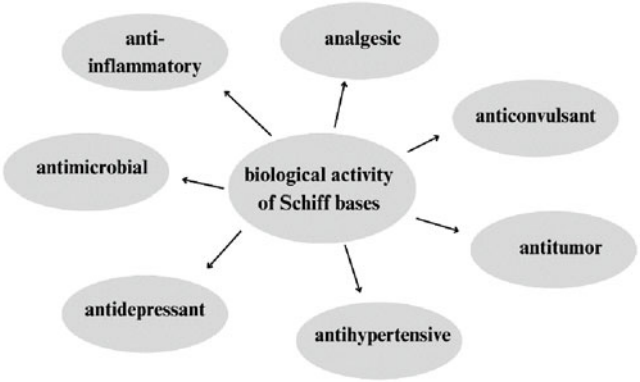



**Figure 2.** Some biological activities of Schiff bases

Some of azomethines found applications as antibacterial active substances in drugs[25]. For example, Furazidine is an active substance in Furaginum used for bacterial urinary tract infections[26] and Clofazimine is used in multidrug therapy against Hansen's disease caused by bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis* (Fig. 3)[27].

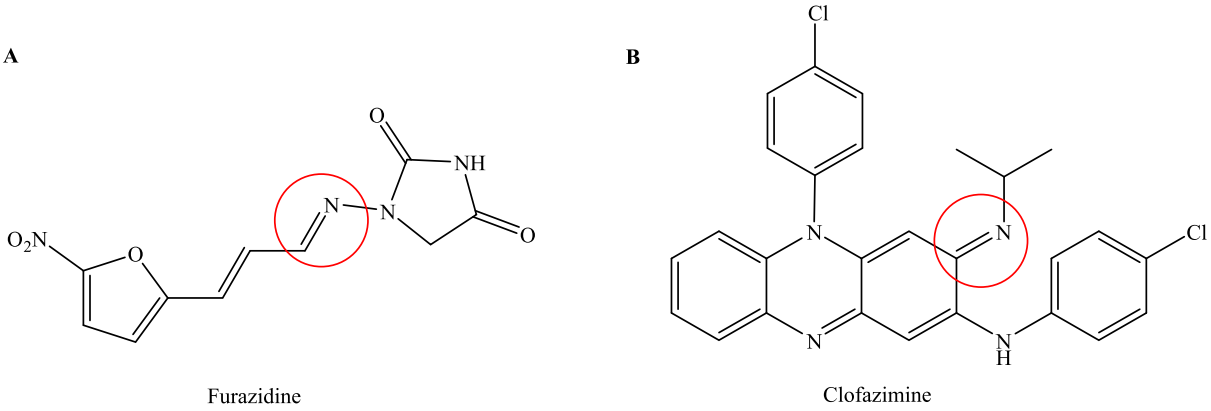



**Figure 3.** Antibacterial Schiff bases: (A) Furazidine, (B) Clofazimine

The antiviral drug, Methisazone, was used to treat smallpox before the vaccine was widely used to protect against the disease. Nowadays it is considered as one of the drugs against COVID-19[14]. The interest in Schiff bases also concerns their ability to form complexes with various metal ions[17, 28]. It is particularly important detail for pharmacy because imine complexes have usually much stronger biological activity than their azomethine analogues[29–30]. Their antimicrobial, antioxidant, and anti-diabetes activity has been widely studied for several decades. Sakthivel et al. studied biological activity of imine complexes based on salicylaldehyde and 4-nitro-1,2-diaminobenzene with transition metal ions: Ni(II), Cu(II), and Co(II). They found a very good antioxidant activity of Ni(II) and Cu(II) complexes. All of synthesized complexes show anti-inflammatory activity comparable to diclofenac sodium drug[31]. Furan-based diamine complexes with some transition metal ions (Cu(II), Co(II), Ni(II), Mn(II), Cd(II), Zn(II), and Fe(III)) were studied as potential anti-bacterial compounds. All of the synthesized complexes have significantly better activity against E. coli, P. vulgaris, B. subtilis, and S. pyogenic than standard antibiotic drug, amikacin[32].

In medicine, the technetium Tc-99m Schiff base complex of exametazime (trade name: *Ceretec*) is used as imaging agent for scintigraphy in the detection of altered regional cerebral perfusion in stroke[14, 33].

The ability of imines to form complexes with metal ions is also used in chemical synthesis. A large group of Schiff base complexes function as catalysts in various organic syntheses[34–35]. For example, the octahedral phenoxy imine cobalt (II) complex (Fig. 4) prepared by Matsubara et al. exhibits high catalytic activity in the reduction of carbonyls to alcohols in a hydrosilylation reaction[36].

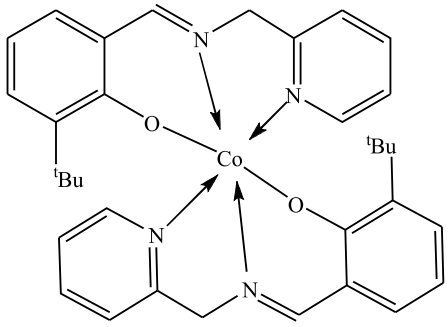


**Figure 4.** Octahedral phenoxyimine cobalt(II) complex exhibiting high catalytic activity in the reduction of carbonyls to alcohols in the hydrosilylation reaction

Schiff bases are one of the oldest groups of liquid-crystalline compounds used in liquid crystal displays (LCD)[37]. In 1970 Schadt and Helfrich presented results of liquid-crystalline properties of 4-octylobenzylidene-4'-cyanoaniline (Fig. 5) that was the first compound used in twisted nematic effect (TN-effect) LCD[38].

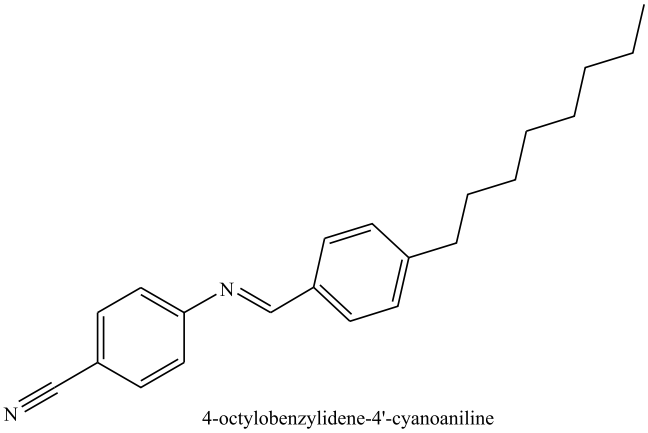



**Figure 5.** One of the first liquid-crystalline compounds Schiff base used in TN-effect LCD

The ever-increasing importance of Schiff bases in various fields, especially in the field of medicine and pharmacy, is reflected in the search for more environmentally friendly ways of synthesizing them. Researchers use eco-friendly synthetic approaches to reduce post-reaction wastes or to enhance the efficiencies of the reactions that influence the economics of technological processes[39–40]. In chemical synthesis, the ideal situation is to achieve degree of substrate conversion close to 100%, combined with the lack of need to use the excess of one of substrates. Additionally, it is important to use inexpensive and available raw materials, and, if it is possible, to engage harmful wastes into the process of removing them from the environment. This review outlines various Schiff base synthesis approaches, conventional and green, with particular attention to the effectiveness of these methods. The advantages and disadvantages of these methods are presented here.

## Methods of Schiff base syntheses

### *The beginning of Schiff bases and the development of their synthesis*

The history of Schiff bases began in 1864 when Hugo Schiff carried out the reaction between aniline and dif-

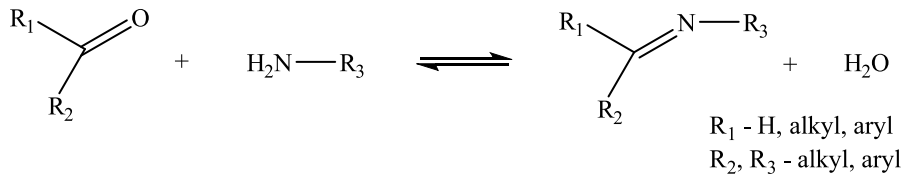



**Figure 6.** General scheme of reaction between carbonyl compound and primary amine

ferent carbonyl compounds[41]. Nowadays we define Schiff bases as compounds having CH=N group in structures of their molecules, and we usually obtain them in the reaction between primary amine and carbonyl compound (Fig. 6) in the reversible process[42].

Since imines have been discovered, their structures, applications and methods of synthesis have developed significantly[6]. The changes over time in connection with the approach to Schiff base synthesis are closely related to changes in the type of solvent employed to synthesize these compounds. However, not only the kind of solvent has changed over the decades. The apparatus used, the time and the temperature of the process have also been altered.

Generally, it is considered that the synthesis of Schiff bases is simple, relatively inexpensive, and desired products are often obtained in satisfactory yields[43]. Nevertheless, green approach decreases cost of synthesis by shortening the reaction time from hours or days to minutes and seconds, standardly carrying out the reaction in room temperature (RT), eliminating toxic solvents or introducing eco-friendly ones etc.[34].

However, using green methods is not always an easy task to obtain azomethines. Aliphatic Schiff bases show low stability in an aqueous environment and in this case, it is much convenient to use organic solvent, preferably anhydrous one. In event of aromatic Schiff bases, the green approach is much easier to apply, because their sensitivity to the water present in the reaction medium is significantly less than in the case of aliphatic imines[44].

## Conventional approach

In the field of conventional methods of obtaining Schiff bases one can distinguish three types of methods.

*Classical synthesis with azeotropic distillation*

This synthetic approach involves the reaction of substrates in the Dean-Stark apparatus, which enables simultaneous azeotropic distillation of the reaction mixture and removal of water generated during the process (Fig. 7.I)[45]. The undoubted advantage of this method is the ability to remove water efficiently from the reaction environment during the Schiff base synthesis. The problem of this process is the type of solvent used (benzene or toluene) that is very toxic for environment and the health of workers[1–2].

*Synthesis in organic solvent*

The disadvantage of the classical method of obtaining Schiff bases causes the need to change the approach to imine synthesis. The first step in decreasing pollution caused by extremely toxic solvents involves replacing them with less toxic solvents (alcohols, especially ethanol and methanol)[46–47]. Generally, the reaction is carried out in a round-bottom flask, where mixture with the excess of one of the substrates is solved in alcohol (usually) and refluxed for hours[48].

Applying the less toxic solvent and simplifying the apparatus can be considered to meet some of the postulates of the principles of green chemistry[1–2]. Nevertheless, the synthesis in organic solvent is not classified as a green chemistry synthesis method.

The advantage of mentioned method includes obtaining imines with moderate to high efficiency without complicated process (Fig. 7.II)[49].

The disadvantage here is using organic solvents that, despite being less toxic than benzene or toluene, still show toxicity. In some cases, anhydrous solvents are necessary

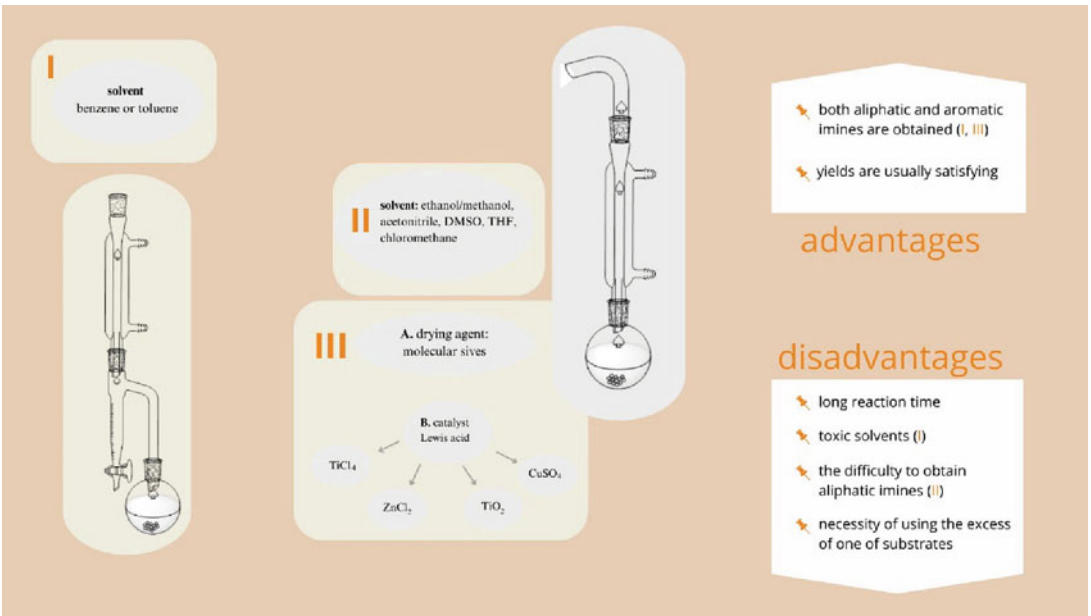



**Figure 7.** Advantages and disadvantages of conventional methods: classical method with azeotropic distillation (I), synthesis in organic solvent (II) and it's modification with addition dehydrating agent (II–III)

significantly increasing the reaction cost[50]. Elevated or hot temperature and long reaction time increases cost and energy consumption[51].

*Synthesis with the addition of dehydrating agent*

The problem of formed water has been solved in the third type of conventional approach to Schiff base synthesis, where dehydrating agent was introduced[7].

In general, the reaction proceeds in organic solvent (most often ethanol, dichloromethane, and tetrahydrofuran) with the addition of molecular sieves or Lewis's acids (Fig. 7.II–III)[52]. The most common Lewis's acids used here are $TiCl_4$ or $ZnCl_2$[53]. Lewis's acid added to the reaction plays two roles: dehydrating agent and catalyst forming a transient complex with the carbonyl compound. It thus promotes the nucleophilic attack of the lone pair of the amino group on the carbonyl carbon atom[7].

The great advantage of this method is the continuous removing the water from the reaction environment. Then it is exceptionally good approach to obtain aliphatic and aromatic azomethines. In the cases of various aromatic Schiff bases there is no need to remove water from the reaction environment to obtain them in satisfying yield.

The crucial factor influencing the yield of aromatic imines is the structure of substrates used in the reaction:

If any aromatic amine with electron-donating substituents in the ring and any aromatic carbonyl compound with electron-withdrawing substituent in the ring are used for the reaction, the yields are generally high (Fig. 8.I).

If any electron-donating substituent is attached to the aromatic carbonyl compound ring, the efficiency may significantly decrease (Fig. 8.II). Sawicz et al. presented yields of two aromatic Schiff bases obtained from o--toluidine and two benzaldehydes: 4-nitrobenzaldehyde (1) and 4-bromobenzaldehyde (2). Using synthesis in methanol compound 1 was obtained with a yield of 75% while compound 2 with a yield of 39%[54].

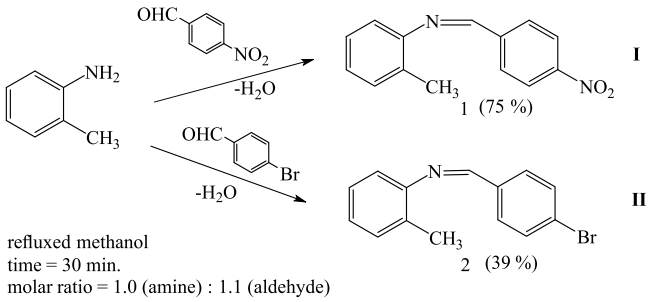



**Figure 8.** Effectiveness of synthesis (in methanol) of obtaining aromatic Schiff bases based on o-toluidine and two aldehydes: 4-nitrobenzaldehyde (I) and 4-bromobenzaldehyde (II)

## Green methods

Comparing conventional and green methods a lot of benefits one can see in the latter, such as shorter time of reaction, better selectivity, simpler separation and purification of products, no need to use an excess of one of the substrates, using eco-friendly environment, most often using room temperature (RT) during the process, usually simpler and less expensive apparatus (Fig. 9)[1, 34, 55].

There are several, known from the literature, approaches to eco-friendly Schiff base synthesis: solvent free synthesis and synthesis with organic solvent. In the first

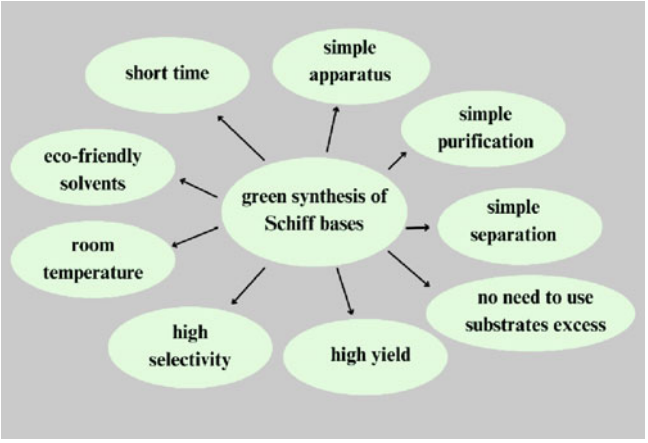



**Figure 9.** Advantages of green methods used for synthesis of aromatic Schiff bases

group one can find grinding in the mortar and synthesis in synthesis in natural environment (water, aqueous solution of organic acids, or fruit juice). Other methods: microwave-, ultrasound-, ultraviolet- and infrared-assisted synthesis are carried out in two ways: synthesis with or without organic solvent (Fig. 10)[56].

*Solvent-free synthesis*

Since most of solvents are toxic, solvent-free approach to aromatic Schiff base synthesis is one of the most attractive[10, 57]. There is no need to use solvent or elevated temperature in this method. Tanaka et al. pointed out that in organic synthesis, in most cases, there is no reason to use solvents. According to the authors a lot of reactions leading to the preparation of organic compounds occur in high yields when solvent-free methods are applied[58].

The most common approach to solvent-free synthesis is grinding method using a mortar and pestle. In this method the mechanical energy coming from grinding a mixture causes molecules to react[59]. Generally, the reaction process proceeds in the following manner: substrates (primary amine and carbonyl compound) are placed in a mortar and grinded for the proper time. In the second step product is recrystallized from ethanol or heated in a vacuum at a temperature of approximately 70 °C[60–61]. Although, some of imines are obtained with a particularly good yield without the second step[54].

Bendale et al. used the grinding approach to carry out the synthesis between p-toluidine and o-vanillin grinding equimolar amounts of substrates in mortar for 10–12 minutes. The raw product was recrystallized from ethanol by shock cooling method giving the final imine with yield ~96%[61].

The example of Schiff base obtained using solvent--free method is N-4-bromo-(3-etoxysalicylidene) aniline (3) (Fig. 11) (yield = 99%)[62]. For the comparison, the efficiency of the reaction for obtaining the mentioned compound using conventional method in ethanol was 82%[63].

Typically, the synthesis is carried out without the addition of catalyst. Although variations for this method can be found in the literature. Boussaid et al. obtained N-benzylideneaniline grinding the substrates with small amount of iron (II) sulfate in mortar for 2 minutes obtaining the product with 57% yield[64].

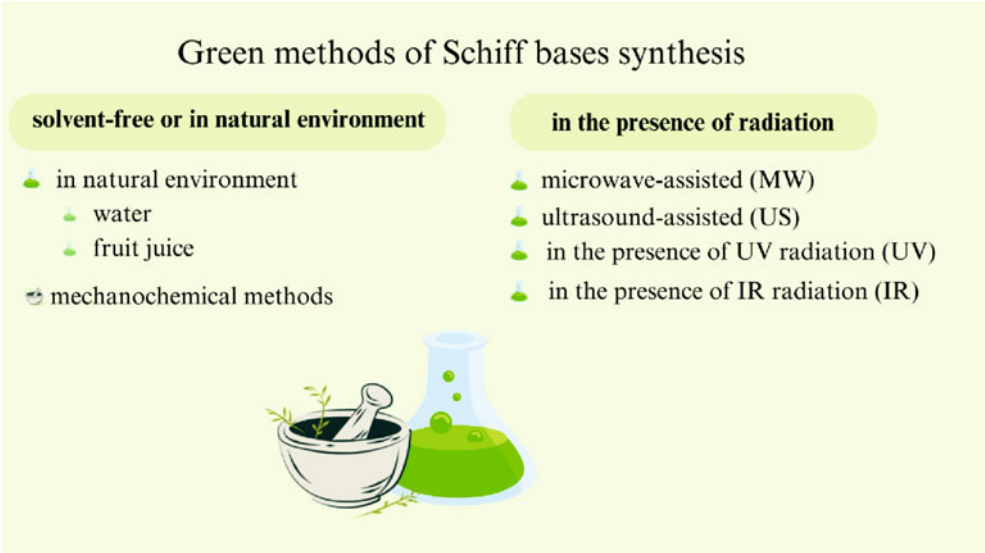



**Figure 10.** Green methods of Schiff base synthesis

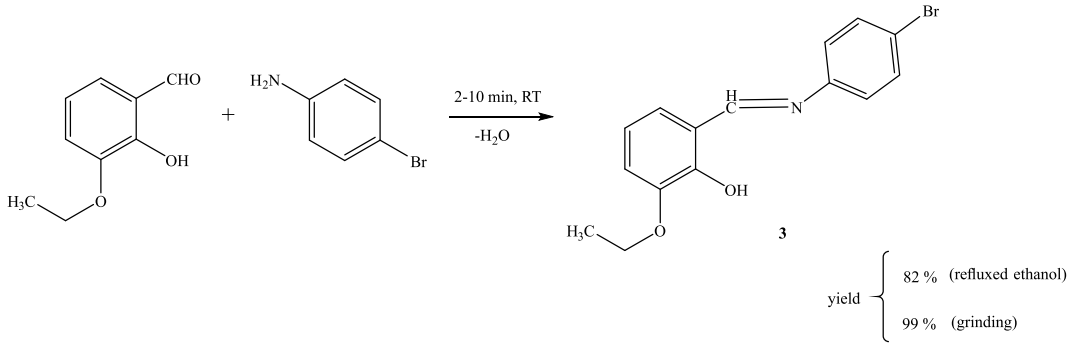


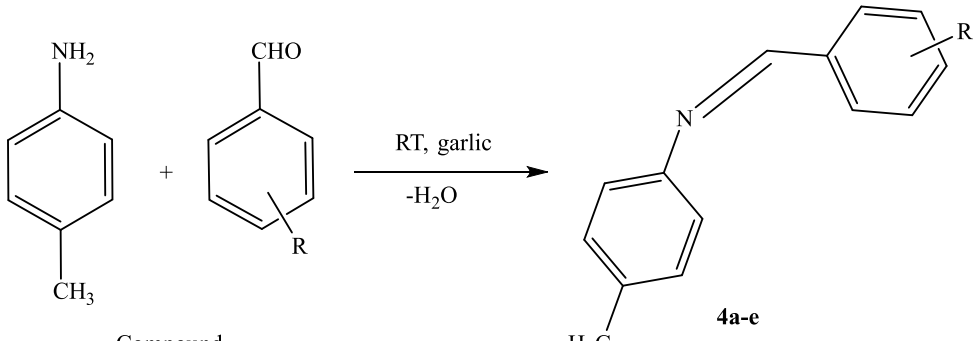

**Figure 11.** Scheme of the reaction of obtaining N-4-bromo(3-ethoxysalicylidene)aniline using solvent-free method

Verma et al. presented interesting variety of solvent--free method used to obtain N-benzylideneaniline. The authors used Kinnow peel wastes as a catalyst in the reaction and obtained the azomethine in 85% yield. The reaction was carried out in test tube in room temperature for 3 minutes in the presence of small amount of dry Kinnow peel powder. Authors compared this method with conventional methods: in dichloromethane (72%), dimethyl sulfoxide (70%), diethyl ether (65%), and acetonitrile (75%)[65].

Veni et al. added a few drops of citric acid to mixture grinded in the mortar to obtain N-4-chlorobenzylidene--2-hydroxyaniline. Although they did not inform about the efficiency of the reaction[66].

Bedi et al. used garlic as a catalyst in the grinding method. The authors mixed p-toluidine, substituted benzaldehydes, and piece of garlic (pH of garlic juice = 5.61) together in mortar for a few minutes. After the reaction solid crude products were recrystallized from absolute ethanol giving the final products (4a–e) with yields from 53 to 81 % depending on the type and placement of substituent in the benzaldehyde ring (Fig. 12)[67].

Particularly interesting approach that one can classified as solvent-free method with the addition of catalyst




| Compound number | R | Yield [%] |
|---|---|---|
| 4a | 4-Cl | 74 |
| 4b | 4-Br | 63 |
| 4c | 2-$NO_2$ | 63 |
| 4d | 3-$NO_2$ | 53 |
| 4e | 4-$NO_2$ | 81 |

**Figure 12.** Scheme of garlic-catalyzed synthesis of N-substituted benzylidene-p-toluidines

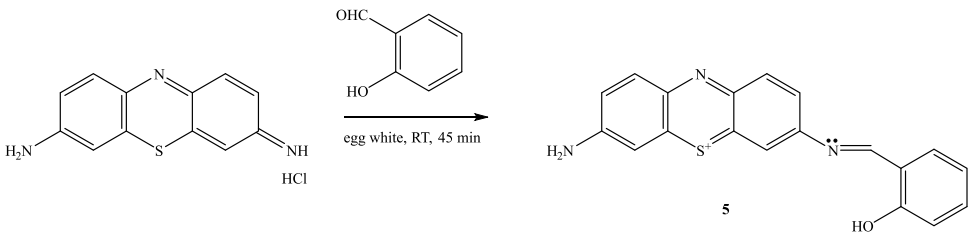



**Figure 13.** Scheme of egg white-catalyzed synthesis of phenothiazinium Schiff base

was applied by Kannaiyan et al. The authors used **egg white** (pH = 6.5) for the synthesis between thionine and salicylaldehyde (Fig. 13). The reaction was carried out for 45 minutes at room temperature and after the reaction product (5) was filtered off and recovered crystallization with water. The authors do not provide the reaction efficiency[68].

In the case of solvent-free synthesis it can be safely said that this approach has much more benefits than disadvantages: short time of reaction (usually 2–10 minutes), small amounts of organic solvent used for product recrystallization or removing this step, stoichiometric quantities of substrates, high degree of substrate conversion that gives high yields of desired product, no addition of catalyst (usually), generally room temperature and simple apparatus[69–71]. These advantages make the solvent-free approach one of the most desired in synthesis of aromatic imines.

A major disadvantage of the manual grinding method is labor-intensive process that can depend on force used for grinding the reaction mixture and speed of grinding. Usually fast and steady grinding decreases time of reaction[69].

Since the difficulty of controlling mechanical force and speed of manual grinding some of researchers applied it is variety, ball-milling, in the Schiff base complexes syntheses[56, 72–73]. Thus, it is a promising approach to synthesize Schiff base ligands using this method.

Benefits of ball-milling route are similar to benefits of grinding method. Although, using mixer or planetary mill, one can control grinding force and speed automatically. From the other side, the apparatus used in this variety of mechanochemical method is much more expensive than mortar used in grinding method.

*Synthesis in eco-friendly environment*

For two decades the topic of changing harmful, toxic organic solvents into eco-friendly environment has been intensively studied by scientists involved in organic synthesis[74]. Among them, there is quite a number of works in which the authors describe green syntheses of Schiff bases using an aqueous environment with or without the addition of organic acids of natural origin, but also using fruit juices as an environment.

The synthesis in water and in fruit juice are being used increasingly with satisfactory results. The general method of carrying out the synthesis in eco-friendly environment is as follows: in the round-bottom flask or in the flat-bottom glass vial the mixture of stoichiometric quantities of substrates is intensively stirred for a short time. After the reaction two routes are applied: air-drying or recrystallization from small amount of organic solvent.

*Synthesis in water environment (water suspension method)*

Synthesis in water environment is more suitable for obtaining aromatic Schiff bases that are less sensitive to water then their aliphatic counterparts[75].

The Schiff base synthesis in water suspension medium was carried out by Jarrahpour and Khalili in 2006. The imines 6 and 7 (Fig. 14) based on the reaction between isatin and 3,3'-diaminophenylmethane or 4,4'-diamniophenylmethane were obtained in the room temperature. The stirring was carried out for 30 hours (compound 6) and 22 hours (compound 7). The raw products were separated, washed with water, and air-dried. The final products were obtained with good yields: 73% (6) and 98% (7)[76].

Zarei and Jarrahpour proceeded the reaction between p-amino azobenzene and 4-nitrobenzaldehyde using two

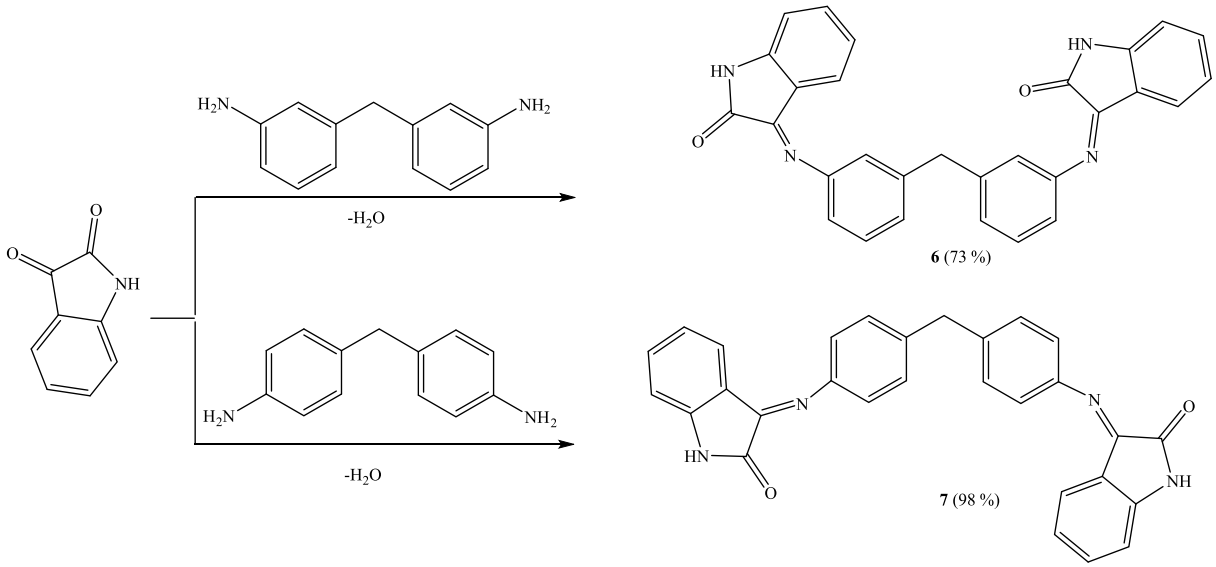
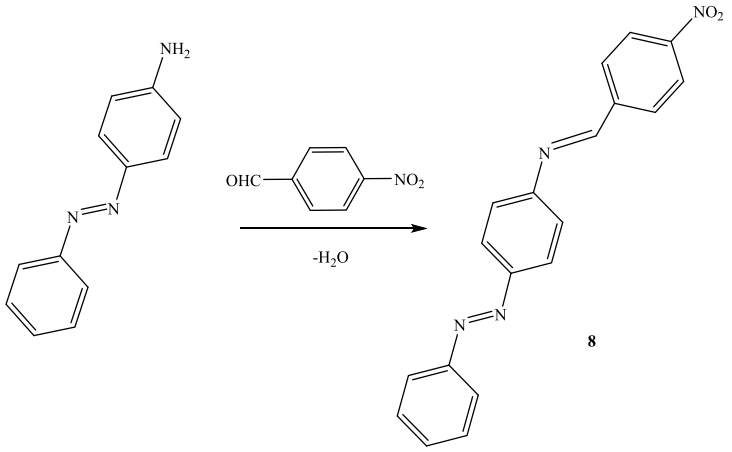



**Figure 14.** Synthesis of di-Schiff bases in water suspension medium




| | Conventional method (refluxed ethanol) | Green method (water) |
|---|---|---|
| molar ratio $n_{amine} : n_{aldehyde}$ | 1.0 : 1.1 | 1.0 : 1.0 |
| temperature [$^0$C] | >78 | room temperature |
| time [min] | 300 | 30 |
| yield [%] | 96 | 98 |

**Figure 15.** Comparison of effectiveness of two synthetic approaches (conventional (refluxed ethanol) and green in water medium) to obtain azomethine based on p-aminoazobenzene and 4-nitrobenzaldehyde

approaches: conventional (refluxed ethanol) and green, where the water was a medium of reaction. The second approach was based on mixing the equimolar amounts of substrates in small amount of water for 30 minutes at room temperature (Fig. 15). The obtained product (8) was filtrated, washed with water, and dried in the desiccator. Comparing two methods of obtaining the mentioned compound, one can see similar yields: 96% (conventional way) and 98% (green approach), considerable time reduction using green method (from 300 to 30 minutes) and reducing the temperature from the boiling point of the reaction mixture to room temperature[77].

Rao et al. compared efficiency of two different approaches used for Schiff bases syntheses: conventional method (refluxed ethanol) and green method in water (Fig. 16). Authors carried out reactions between 1,2-diamniobenzene and salicylaldehyde in molar ratio 1:1 and 1:2, respectively. Conventional method required 2 hours of heating the mixture under reflux and recrystallization crude product. Synthesis in water took much less time (10 minutes) and it did not need recrystallization. Authors noticed that yield of final product obtained using conventional approach was 65% for compound 9 and 53% for 10, while changing the method into synthesis in water increased the yield to 95% and 97%, respectively[78].

The green method in water suspension medium has some advantages such as elimination of hazardous toxic organic solvents, decreasing temperature of process and significantly increasing selectivity and yield of final products. However, time of the reaction is not always competitive with conventional methods.

*Synthesis in acidic environment*

It is well known that the optimal environment for obtaining Schiff bases is acidic in nature[79]. Therefore, modification of the synthesis in water environment, when the acidic catalyst is added to water, is promising solution for obtaining aromatic Schiff bases with higher yields

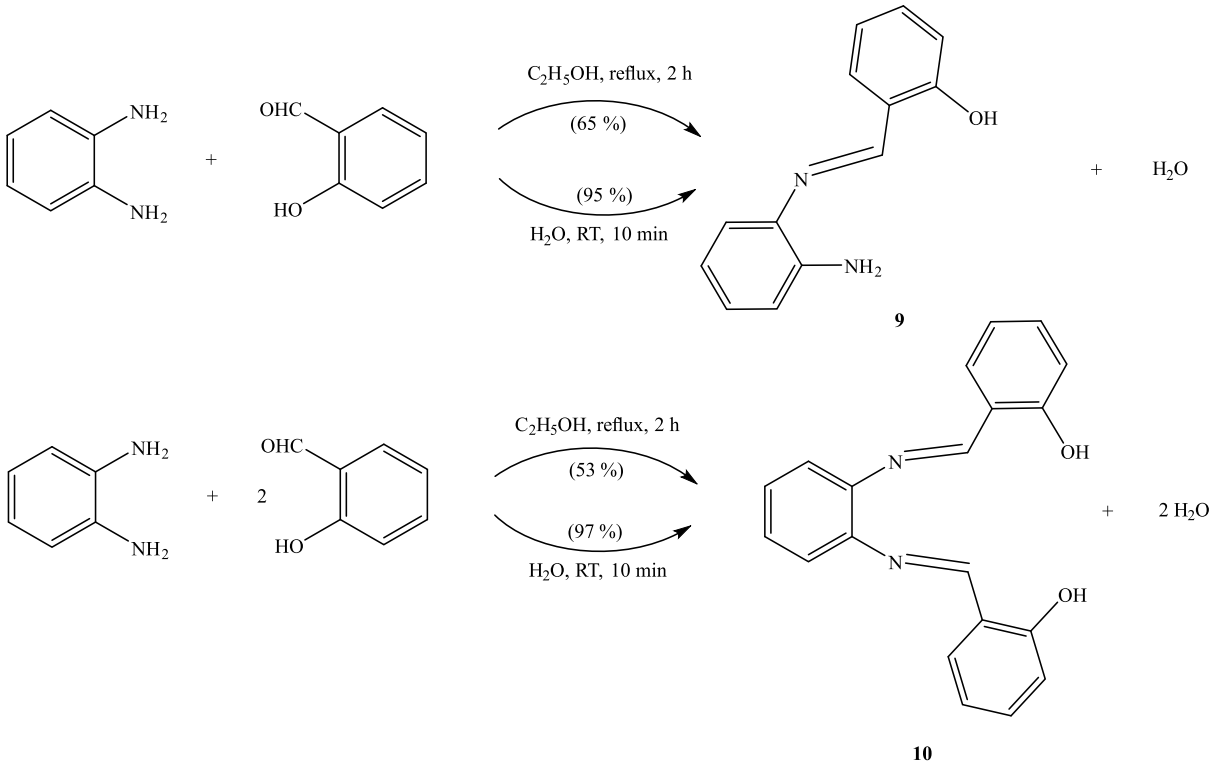



**Figure 16.** Mono- (9) and di-Schiff (10) bases obtained by two different methods: conventional (refluxed ethanol) and green in water suspension medium

and milder conditions. However, till these days there are not many literature reports relating to this method[54].

*The second approach using acidic environment is synthesis in fruit juice.*

A review of literature data shows that the synthesis of Schiff bases using fruit juices has been the subject of numerous studies[1, 4, 80]. Scientists show the high efficiency of obtained imines when they use juice as an environment[54].

The catalytic properties of fruit juices result from the presence of natural organic acids in them, such as: citric, tartaric, malic, or oxalic acid. Fruit juices are readily available, inexpensive, nontoxic (they are green alternative to hazardous solvents)[81], and they play role of catalyst[1–2]. Among the juices, lemon juice is the most used in the preparation of Schiff bases[82–83]. Some of researchers use gooseberry, grape, mango, or apple juice as an eco-friendly environment[54, 56, 84–85].

Regardless of the kind of juice used for the reaction, all steps of process are the same. The first step of the procedure for the synthesis of Schiff bases using this method is the preparation and purification of fruit juice (Fig. 17) usually by filtering the raw juice through a filter pad[7] or cotton wool[83]. It allows for accurate separation of solid particles and obtaining a clear filtrate that is used in the next step of the mentioned procedure: fruit juice is added to the mixture of stoichiometric amounts of substrates and then it is intensively mixed. Synthesis of Schiff bases is usually carried out at room temperature[7, 54] or the mixture is heated to 55 °C[83]. The final product is, the most often, purified by crystallization from small amount of ethanol[7, 80]. Time of the reaction is usually shorter that in conventional approach[1, 54].

Patil et al. carried out the reaction between p-toluidine and salicylaldehyde in the lemon juice environment. In the first step they prepared the juice of lemon manually using domestic presser to extract juice. To remove solid material from the juice, filtration was applied using a cotton cloth and filter paper. The reaction between amine and aldehyde in the presence of small amount of lemon juice was carried out for 30 minutes at room temperature. The product was recovered by recrystallization with ethanol. Yield of the final product was 94%[1].

Sravanthi et al. used four different methods of obtaining 2-(1-((furan-2-ylmethyl)imino)ethyl)phenol (compound 11) from furfuryl amine and 2-hydroxy acetophenone (Fig. 18). In the group of fruit juice methods lemon juice with the lowest pH was the best choice for obtaining this compound.

Sunil et al. have prepared imines based on aniline and three aromatic aldehydes: benzaldehyde, 3-methoxybenzaldehyde, and salicylaldehyde using blackberry fruit juice as a catalyst. To produce blackberry fruit juice authors used freeze-dried powder and the preparation of the juice was time-consuming. The yields of final products were about 92%[44].

Yadav and Mani carried out the reaction between aniline and benzaldehyde using three different juices: lemon, grape and aqueous extract of mango. The yields of product were similar. Although, the best yields one can see, when grape juice is used in the reaction[84].

Sawicz et al. used various solvent-free methods to obtain two aromatic Schiff bases based on o-toluidine and 4-bromo- and 4-nitrobenzaldehydes. Grinding method involved placing equimolar quantities of substrates in mortar, grinding the mixture for 5 minutes, and leaving the mixture for drying in the air (1–2 days). In both cases they obtained pure imines (substrate conversion degree = 100%). Authors also used natural environment (aqueous solution of malic acid and lemon or apple juice) as other approach to carry out reaction between mentioned substrates and they compared applied methods in terms of their efficiency in obtaining two aromatic Schiff bases (Table 1)[54].

Comparing these results with those obtained on the base of conventional approach (Fig. 8), the application of green methods significantly improves the degree of substrate conversion and the efficiency of the process when eliminating toxic organic solvents. Economic costs are also less when applying green approach. Room temperature, brief time of reaction (usually 5–10 minutes), and high substrate conversion contribute to reducing costs of process. Furthermore, the authors come from Poland,

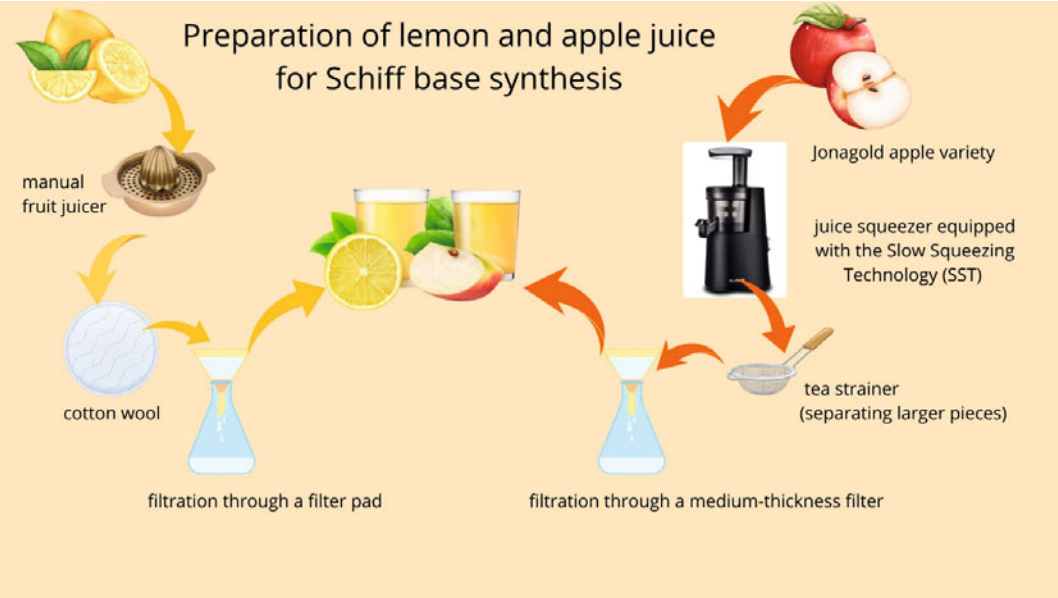
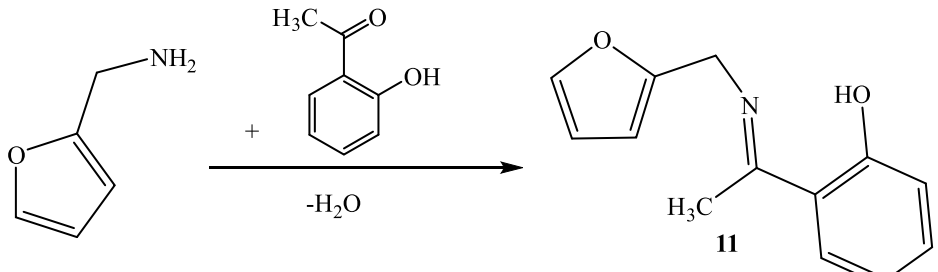



**Figure 17.** Preparation of fruit juices for Schiff base synthesis described by Sawicz et al.[44]




| method | catalyst | amount of catalyst | time [min] | yield [%] |
|---|---|---|---|---|
| refluxed ethanol | glacial acetic acid | 3–4 drops | 360–480 | 80 |
| grinding | —— | —— | 60 | a |
| MW | glacial acetic acid | 2 drops | 14–15 | 80–85 |
| fruit juice + MW | lemon juice (pH = 2.0–2.8) | 0.5 mL | 7 | 88 |
| | orange juice (pH = 3.3–4.1) | 0.5 mL | 10 | 76 |
| | aq. extract of amla (pH = 2.8–3.1) | 0.5 mL | 11 | 76 |

**Figure 18.** Heteroaromatic Schiff base obtained by four different approaches: conventional (refluxed ethanol), mechanochemical (grinding), microwave-assisted, and mixed technique: in fruit juice with microwave radiation

**Table 1.** Comparison of conversion degree of aldehyde in the different green approaches to obtain N-(4-substituted benzylidene )-2-methylanilines (compounds 1 and 2, Fig. 8)

| Compound | Conversion degree of aldehyde depending on green method [%] | | | | |
|---|---|---|---|---|---|
| | Grinding | Aqueous solution with addition of malic acid | | Fruit juice | |
| | | 0.1 M (pH = 2.29) | 0.0005 M (pH = 3.43) | Lemon juice (pH = 2.42) | Apple juice (pH = 3.56) |
| 1 | 100 | 93 | 86 | 97 | 100 |
| 2 | 100 | 100 | 89 | 100 | 95 |

where apple is the most common fruit and Poland is one of the biggest exporters of apples in the world. Thus, introducing the apple juice into the synthesis additionally decreases costs of the reaction in this country.

Authors noticed that in the case of using fruit juice as an environment and catalyst in the reaction of obtaining 4-bromo derivative, a better solution is to use lemon juice with a lower pH, while exceptionally good results were obtained by using apple juice in the reaction of obtaining N-(4-nitrobenzylidene)-2-methylaniline (Fig. 19)[54].

Despite the number of advantages of Schiff base synthesis in fruit juices, it also has some disadvantages. Among them is labor-intensive process of preparing fruit juice and usually necessity of crystallization of the final product using organic solvents, the most often ethanol or methanol[83]. Another problem is the difficulty of obtaining fruit juice with the same composition every time. Fruits have the different composition depend on, among others, cultivar, growing site, environmental conditions, harvest time, ripeness, handling, and storage

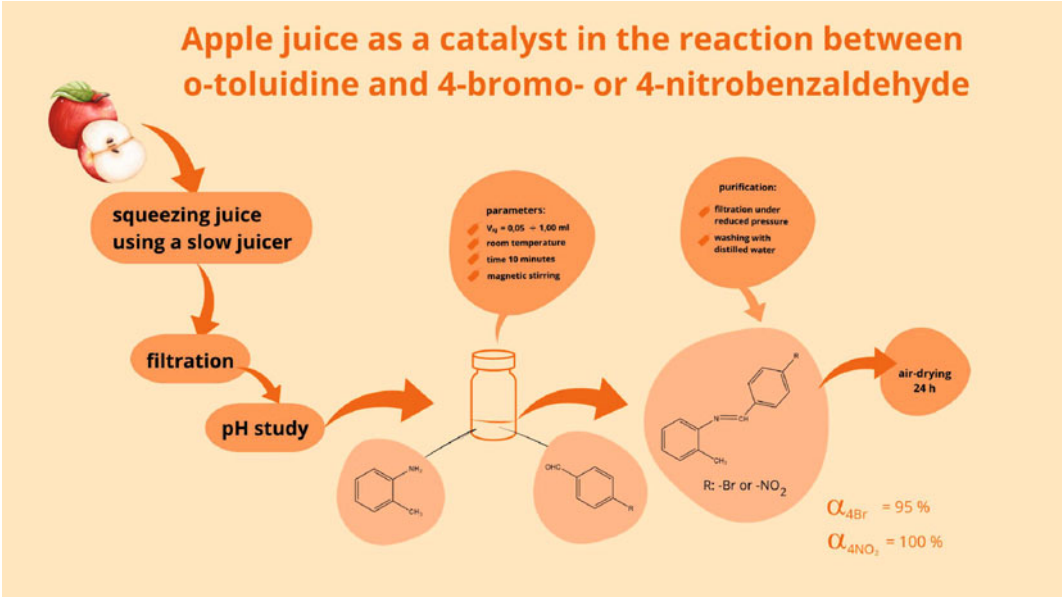



**Figure 19.** The use of apple juice in the green synthesis of N-(4-bromobenzylidene)-o-toluidine and N-(4-nitrobenzylidene)-o-toluidine

conditions after harvest[86–87]. When chemists use fruit juices in the Schiff base syntheses, they do not check the composition of them. Some of researchers examine the pH of juices considering these values as one of the main factors having the strong impact on the reaction efficiency. Another element that is difficult to control is the rapidly changing composition of freshly squeezed juice. Another inconvenience of using fruit juices in the reaction of obtaining Schiff bases is the problem of purifying the juice after the reaction. This issue have not yet been solved. Although, it is certainly very important in a situation, when Schiff bases are not obtained with 100% yield.

Summarizing the topic of solvent-free methods and synthesis in natural environment, they have a few advantages comparing conventional approaches (Fig. 20). Their mild reaction conditions and brief time of reaction, stoichiometric quantities of reagents, no need to use organic solvents, and in the most cases inexpensive apparatus are attractive to pharmaceutical industry.

Some difficulties provide an area for chemists to work on to find solutions to reduce or completely remove disadvantages.

*Synthesis in the presence of irradiation*

*Microwave-assisted synthesis (MW-assisted synthesis)*

Microwave-assisted Schiff base synthesis is used to speed up the process of obtaining product[43]. This approach usually involves mixing substrates of stoichiometric quantities without solvent or in ethanol with the addition of acetic acid[88]. The exposure time to microwaves depends on the progress of the reaction monitored by TLC. The power of the radiation used is vary. The final product is purified by washing it with cold water and then crystallizing from ethanol[89–90].

Significant benefits of this technique involve higher yields and faster time of reaction comparing conventional methods[18, 43, 91]. Synthesis that requires days to be completed can be conducted for hours, minutes, or seconds when microwave irradiation is used[16]. Shntaif and Rashid show the following benefits of using microwave-assisted approach: simplicity, sensitivity, reducing time of reaction, reducing, or eliminating organic solvents, increasing the yields[92].

Apart from the unquestionable benefits of the microwave-assisted method, it also has disadvantage. It is difficult to control the process in terms to temperature inside vessel. The reaction conditions must be carefully controlled to avoid overheating and unwanted side reactions. Comparing to reaction in mortar or in eco-friendly environment the equipment used for microwave heating is relatively expensive[43].

Mersellem et al. compared the effectiveness of conventional and microwave-assisted methods of obtaining imines (12 a–c) based on p-substituted benzaldehyde and p-hydroxy aniline (Fig. 21)[93]. Authors pointed out that green approach significantly reduced time of process from 3–6 hours to 4–8 minutes while efficiency was increased from 64–76% to 89–96%.

Manjare et al. reported a microwave-assisted synthesis of aniline-based Schiff bases using cashew nutshell extract that is a source of anarcadic acid displaying the role of catalyst. They proceeded the reaction between aniline and different aromatic carbonyls. An undoubted advantage of the introducing cashew nutshell extract to the reaction is the inglorious influence of it on environment. Urushiol contained in these shells is very hazardous for environment, but during the preparing cashew shell extract it transforms into anarcadic acid that is main compound responsible for enhancement of Schiff base synthesis. Using cashew nutshell extract in the microwave-assisted synthesis of azomethines enhances reaction rate and yields and decreases time of reaction comparing conventional methods[89]. Using this method for obtaining N-(4-nitrobenzylidene) aniline (13) toxicity of the entire process is significantly reduced comparing with the classical method described by Silverberg et al. (Fig. 22)[90]. Additionally, when catalyst in microwave-assisted method is changed into fly-ash $H_2SO_4$, yield of mentioned imine distinctly decreases[94].

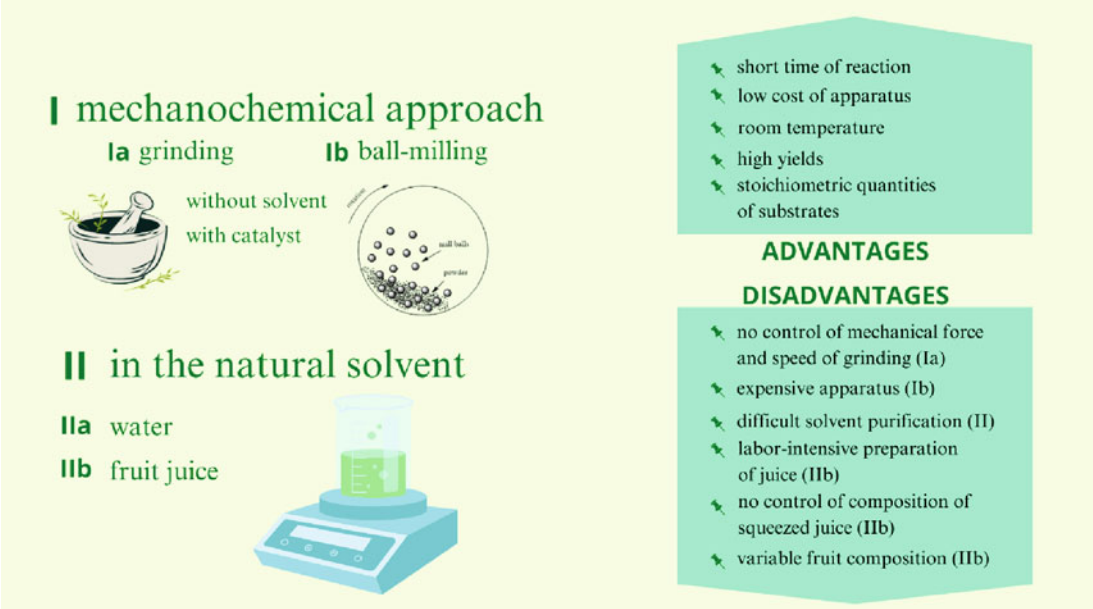
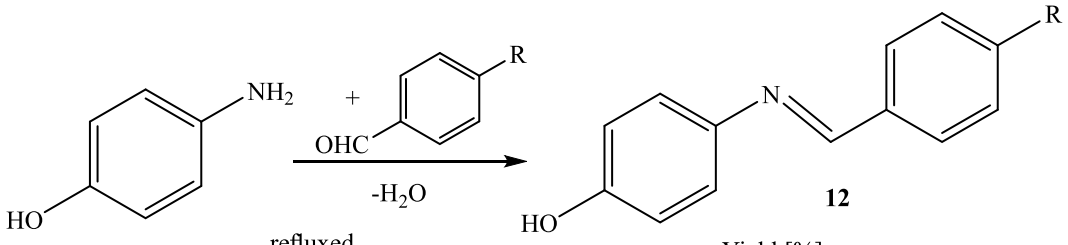



**Figure 20.** Advantages and disadvantages of mechanochemical method and synthesis in natural environment

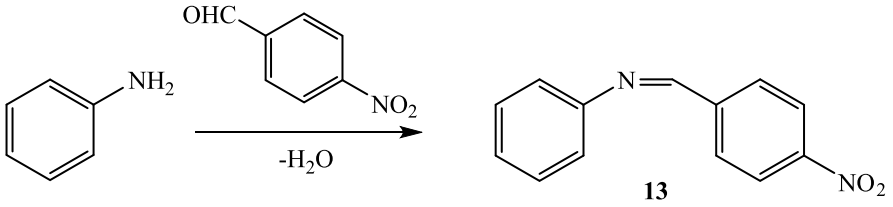



| | refluxed ethanol | MW |
|---|---|---|
| molar ratio $n_{amine}:n_{carbonyl}$ | 1 : 1 | 1 : 1 |
| $V_{ethanol}$ | 10 | 1 |
| time [min] | 180–300 | 4–8 |
| microwave energy [W] | | 100 |

Yield [%]

| -R | refluxed ethanol | MW |
|---|---|---|
| -H | 72 | 92 |
| $-CH_3$ | 76 | 96 |
| $-NO_2$ | 64 | 89 |

**Figure 21.** Comparison of the effectiveness of conventional and microwave-assisted methods used for obtaining imines based on p-substituted benzaldehyde and p-hydroxy aniline




| | classical method with azeotropic distillation | microwave-assisted method in the presence of catalyst | |
|---|---|---|---|
| catalyst | — | fly-ash sulfuric acid | cashew nut shell extract |
| solvent | toluene | — | — |
| temperature [$^0$C] | 70 | | |
| time [s] | 1800 | 360–720 | 80 |
| microwave energy [W] | — | 460 | 600 |
| yield [%] | 73 | 56 | 85 |

**Figure 22.** Comparison of results of conventional and green approaches to obtain 4-nitrobenzylideneaniline: classical method with azeotropic distillation[80] and microwave-assisted (MW) method with the addition of catalyst: fly-ash $H_2SO_4$[84] or cashew nut shell extract[79]

*Ultrasound-assisted synthesis*

Recently ultrasound-assisted synthesis (US) is considered as a powerful technique because of benefits it serves in the field of Schiff base synthesis. Comparing to conventional methods it offers shorter time of reaction, purer products, higher yields, milder reaction conditions[19].

In this method the mixture of amine and carbonyl compound is dissolved in alcohol (usually methanol or ethanol), and then it is subjected to ultrasonication in ultrasonic cleaner machine[59]. The process is continued in room temperature (RT)[95] or in a little bit higher temperature (45–50 °C)[59, 61]. The reaction time varies and depends on the speed at which Schiff base formation reaction occurs[95]. The obtained precipitate is usually washed with water and ethanol, and air-dried or additionally purified by recrystallization from ethanol[61, 95].

Arafa and Shaker carried out a series of syntheses using the conventional approach and two green methods (microwave-assisted and ultrasonication) to obtain di--Schiff bases based on three diamines: trans-1,4-diaminocyclohexane, p-xylene diamine, and ethylenediamine dihydrochloride with various 2-hydroxy aromatic aldehydes. The authors set up that among the synthetic methods used, the most effective and the most economical method for obtaining Schiff bases based on mentioned substrates was ultrasonication (US). Compared to the microwave-assisted synthesis (MW) the time was reduced 2–5 times and the yield of the obtained imines was significantly increased from 70–87% to 97–99%[19]. The results of different approaches to obtain the product (14) based on p-xylene diamine and 4-nitrosalicyladehyde are presented in the Fig. 23.

Kargar et al. obtained six imines based on 3-ethoxysalicylaldehyde and 2-aminopyridine derivatives solving the substrates in ethanol and placing the mixture in ultrasonic bath for 5 minutes at room temperature. The yield of obtained Schiff bases was between 92 and 97%[96].

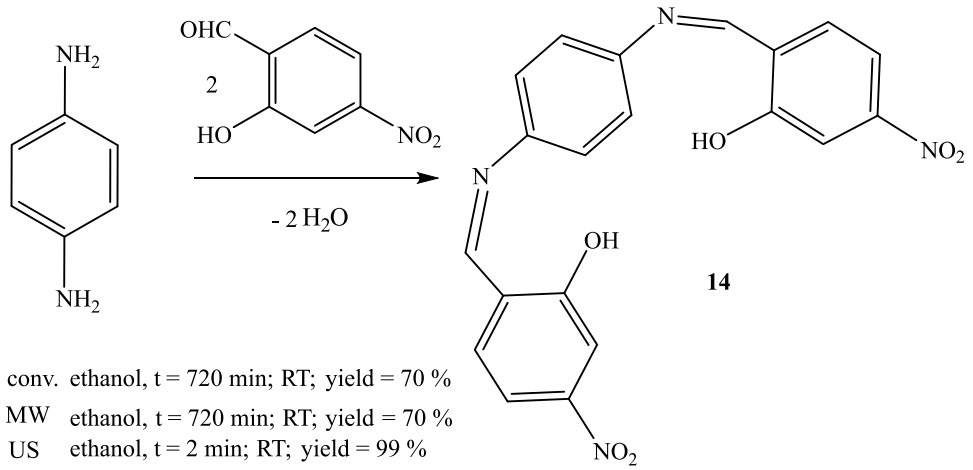



**Figure 23.** Results of three methods of reaction between p-xylene diamine and 4-nitrosalicylaldehyde: conventional in ethanol (conv.), microwave-assisted (MW), and ultrasound-assisted (US)

*Synthesis in the presence of UV-radiation*

This method is used to obtain Schiff bases very rarely and there are only few reports about this method.

Yaseen et al. describe the synthesis in the presence of UV rays applied for the reaction between p-toluidine and o-vanillin[80]. The authors compare the yields obtained in two different approaches: conventional (78%) and green in the presence of UV radiation (97%).

Bendale et al. compared effectiveness of obtaining N-(3-methoxysalicylidene)-p-toluidine (15) using four methods: conventional (refluxed ethanol), ultrasound-assisted, synthesis in the presence of UV-radiation, and solvent-free method in mortar (Fig. 24). Using conventional method authors carried out the reaction for 60–90 minutes and obtain final product with 72–78% yield, whereas green approaches allowed for reducing time of reaction to 10–17 minutes while increasing the reaction efficiency to 96–98%. Synthesis in the presence of UV-radiation appeared as comparable in its efficiency to other green methods used in this publication[61].

*Synthesis in the presence of IR*

Similarly to synthesis in the presence of UV radiation, literature data about synthesis in the presence of IR radiation are exceedingly rare.

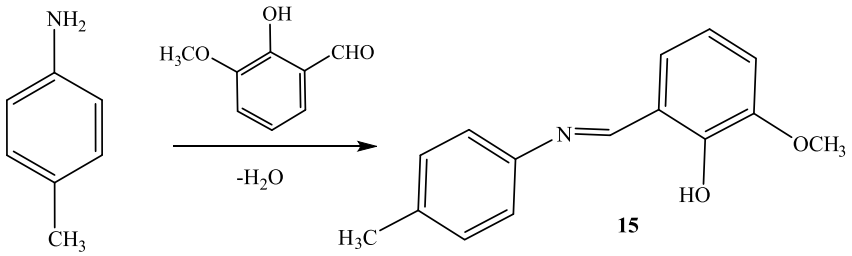
Vázquez et al. (2004) applied IR radiation in solvent-free method as one of three different approaches (I. heating at 45 °C, II. in room temperature, III. with IR radiation). The authors placed substrates in round-bottom flask and carried out the reaction between various benzaldehydes and the set of three anilines without solvent and without stirring. The time of reaction was between 10 and 40 minutes to improve the process. The best results were achieved for the reaction in the presence of IR radiation. The best time of the reaction was determined for each compound separately[42].

An example of the product, N-benzylideneaniline (16), together with reaction conditions and conversion degrees, is shown in Fig. 25.

One can notice that the reaction in the presence of IR radiation depends significantly on time of process. The best result authors achieved when they provide the reaction for 20 minutes.

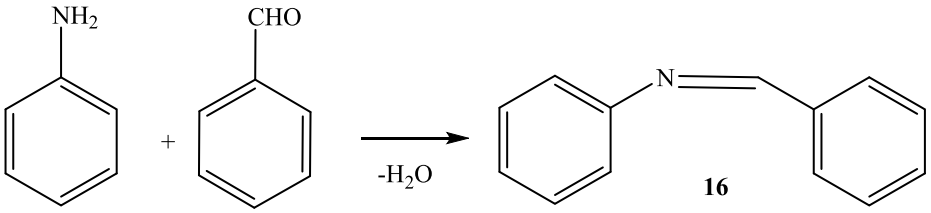
It is difficult to compare the results obtained by Vazquez[42] with the results achieved by Verma et al.[66] (see *Solvent-free synthesis*), because Vazquez did not specify yield of studied compound. Although, one can notice that the reaction carried out in the presence of IR radiation ($\alpha_{10}$ = 93% and $\alpha_{20}$ = 98%) and reaction with using Kinnow peel (yield = 85%) are the best of what has been done to obtain compound 16.

Summarizing the topic of radiation methods, they show significant advantages over conventional ones. It is difficult to choose the best radiation for obtaining Schiff bases. Two of reasons for this situation are the




| | refluxed ethanol | UV | US | | mortar |
|---|---|---|---|---|---|
| catalyst | — | — | — | $CH_3COOH$ | — |
| time [min] | 60–90 | 15 | 15 | 10 | 17 |
| yield [%] | 72–78 | 97 | 97 | 98 | 96 |

**Figure 24.** Comparison of the effectiveness of four different methods used to obtain N-(3-methoxysalicylidene)-p-toluidine: conventional (refluxed ethanol), UV-assisted, US-assisted with or without catalyst, and solvent-free method using mortar




| | I | II | III | |
|---|---|---|---|---|
| time [min] | 40 | 40 | 10 | 20 |
| temperature [$^0$C] | 45 | RT | RT | |
| IR radiation | - | - | 250W 125V | |
| conversion degree (α) [%] | complex mixture of by-products | 57 | 93 | 98 |

**Figure 25.** Degree of substrate conversion (α) dependently on obtaining of N-benzylidene aniline by three methods: I. heating at 45 °C, II. in room temperature, III. with IR radiation

enormous diversity of azomethines and scarcity of sufficient literature reports on the different methods used to obtain the same imine systems.

What constitutes the advantages of all the syntheses in the presence of radiation is, first, a significant reduction in reaction time and temperature of the process and simultaneous increase in yield compared to conventional approaches (Fig. 26). A valuable variation of these methods is that in which no solvent is used during the synthesis, thus reducing the environmental pollution.

The disadvantage of these methods is the price of the apparatus that far exceeds the cost of that used in conventional syntheses.

## CONCLUSION

Schiff bases, organic compounds of great interest in medicine and pharmacy, are diverse in structure and application. During the XX century they were obtained mainly with conventional approaches. Because of toxic solvents (benzene, toluene) used in some conventional Schiff base syntheses, there is a need to find alternative approaches to synthesize these compounds. Besides, at the end of the 1990s, the scientific world began the search for "green" alternatives to the well-known syntheses of a variety of chemical compounds with important, interesting applications. As a result of these explorations, science has been enriched by a group of green methods increasingly used to obtain organic compounds, including Schiff bases.

There are various green ways of synthesizing imines including grinding and ball-milling methods, the water suspension method, synthesis in fruit juices, microwave-assisted synthesis, ultrasound radiation and synthesis in the presence of UV or IR radiation that are used to replace the conventional methods. They offer advantages such as elimination or reducing amounts of organic solvents, economic costs (room temperature of process, brief time of reaction, high yields), or using hazardous wastes.

In the article discussion about conventional and green methods of Schiff bases synthesis was carried out. The advantages and disadvantages of these approaches were presented.

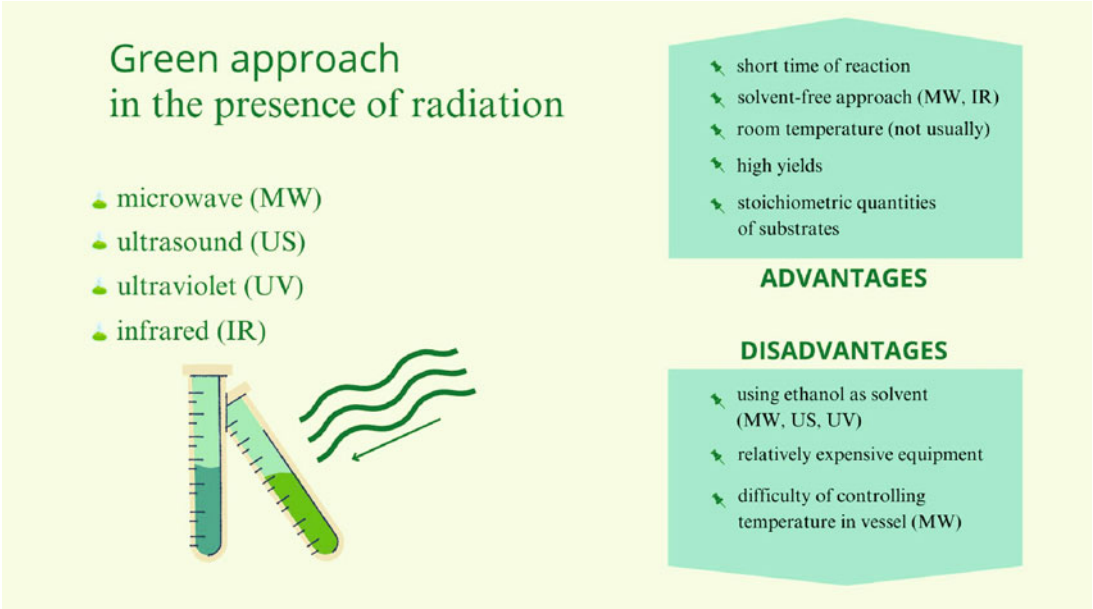



**Figure 26.** Advantages and disadvantages of radiation-assisted green syntheses of Schiff bases

Currently, one of the best green methods of imines synthesis is the solvent-free approach. Their unquestionable advantage is the elimination of organic solvent during the process and high reaction yields.

The youngest of the green approaches used to synthesize aromatic imines is synthesis in fruit juice. In the literature, there is quite a lot of information about obtaining Schiff bases using lemon juice. In 2020 the results of the Schiff bases synthesis in lemon or apple juice obtained from Jonagold apple variety were presented for the first time. Authors have shown the relationship between pH of fruit juice and the structure of the aldehyde used to obtain Schiff base.

Even though green methods used for obtaining Schiff bases have a brief history, it can already be said that they have pretty much to offer the chemical industry. Although each of the methods has disadvantages that we should not forget about, green methods appear as really good alternative to conventional approaches.

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