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Original Article

OPTIMIZATION OF MICROWAVE ASSISTED SOLVENT-FREE SYNTHESIS OF SOME SCHIFF BASES

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ABSTRACT

Objective: To optimize microwave assisted solvent free synthesis of Schiff bases of aromatic aldehydes and aromatic amines (ethyl 4-aminobenzoate) by using wetting reagent β-ethoxyethanol. The goal of this study was to investigate the % yields and time required for the completion of reaction for Schiff bases by microwave and conventional conditions.

Methods: Schiff bases have been synthesized by condensation of substituted various aromatic aldehyde (.001 mol) with Ethyl 4-aminobenzoate (.001 mol) by two different methods as by conventional method (Heating) & Microwave accelerated synthesis by using wetting reagent -ethoxyethanol. The reaction time for conventional method and microwave method is in the range of 60-240 min and 10-180s respectively. All the synthesized compounds recrystallized & characterized by IR, NMR, and Mass and element analysis.

Results: The simple microwave assisted solvent-free method for the synthesis of Schiff bases using a wetting reagent (β-ethoxyethanol) led to improvement in the yield of all the target compounds with reduction in their reaction byproducts & substantially reduced the overall process time as expected as compare to traditional method. Excellent isolated yields (up to 96%) were attained within short reaction times (typically, 60s) when the reaction was performed under microwaves irradiation.

Conclusion: The advantages of this environmentally benign and safe protocol include a simple reaction set-up, high product yields, short reaction times as well as the elimination of side products.

Keywords: Schiff bases, β-ethoxyethanol, Solvent-free, Microwave heating, Environmentally friendly.

INTRODUCTION

Compounds containing the–C=N–(azomethine group) structure are known as Schiff bases, usually synthesized from the condensation of primary amines and active carbonyl groups [1]. The reaction is acid-catalyzed and is generally carried out by refluxing the carbonyl compound and amine, with an azeotroping agent if necessary, and separating the water as formed [2]. Schiff bases are well known for their biological applications as antibacterial, antifungal, anticancer, and antiviral agents; furthermore, they have been used as intermediates inmedical substrates and as ligands in complex formation with some metal ions [1, 3]. The synthesis of imine was firstly reported by Hugo Schiff in 1864 and they have been known since then [4]. The imine compounds have been prepared using molecular sieves [5, 6], infrared irradiation [7], Mg(ClO4)2 [8], P2O5/SiO2 [9], ZnCl2 [10], CaO under microwave power [11], ethyl lactate as a tunable solvent [12], K10 clay [13], TiCl4 [14], alumina [15], CeCl3·7H2O [16], ultrasound irradiation [17], polymer-supported [18], nanotube TiO2 (in sunlight) [19], and Ti(OEt)4 [20, 21].

In the recent years, microwave assisted organic reactions have emerged as a new tool in organic synthesis. Important advantages of this technique include highly accelerated rate of the reaction, reduction in reaction time with an improvement in the yield and quality of the product. Moreover the technique is considered as an important approach towards "Green Chemistry" because of its eco-friendly nature. Conventional methods of organic synthesis usually need longer heating time, elaborate and tedious apparatus set up, which result in higher cost of process and the excessive use of solvent/reagents leads to environmental pollution. [22] Microwave assisted reactions in solvent or solvent free conditions have gained popularity because of rapid reaction rate, cleaner reactions and ease of manipulation [23].

Drug companies are exploiting microwaves in the area of organic/pharmaceutical synthesis for drug screening and discovery [24-26]. Scientists have demonstrated the potential of microwave-assisted organic synthesis using ionic liquids as solvent, co solvent, additives and/or catalyst [27]. Among the wide variety of drug molecules that have been explored for developing microwave assisted synthetic process include pharmaceutical drugs in various biological activities like analgesic, antihypertensive, central nervous system depressant, antiviral, bactericidal and fungicidal activities. [28-30].

2-Ethoxyethanol is a solvent used widely in commercial and industrial applications. It is a clear, colorless, nearly odorless liquid that is miscible with water, ethanol, diethyl ether, acetone, and ethyl acetate. A polar solvent that is capable of acting as a hydron (proton) donor having property of being able to dissolve chemically diverse compounds [31].

The present work reveals the comparative aspects of condensation of some aromatic amines with aldehyde derivatives using microwave and conventional methods. The amine and aldehyde compounds as starting materials, β-ethoxyethanol as a wetting reagent and microwave power as an effective source of heating are used. The corresponding imine compounds were prepared in high yields and short reaction times using this effective and environment friendly method. The new microwave procedures were developed by considering two important parameters: minimum reaction time and minimum by-product formation leading to maximum yield of the pure product with desired quality.

Experimental methods

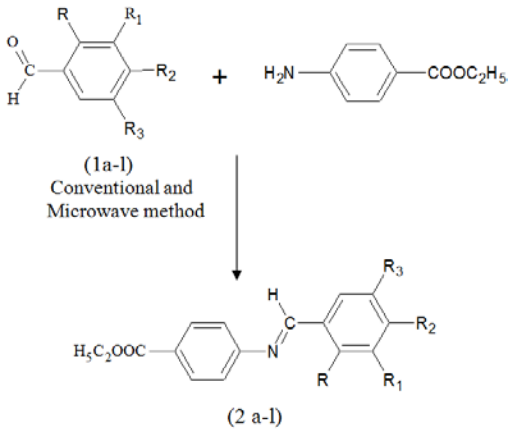
All the chemicals used were obtained from S. D. Fine Chem. Ltd. and E Merck Ltd., Mumbai while the reagents and solvents were of analytical grade & few were prepared according to standard methods. Melting points were determined with an Electrothermal 9100 apparatus. The infrared absorption spectrum of the compounds has been recorded in the region at 4000 and 400 cm^{-1}ranges using a Bruker Vertex 80/80 v spectrophotometer using

KBr pressed pellet technique at room temperature. The ^{1}H NMR and [13]C NMR spectra were recorded using a Bruker AC 200NMR 200MHz spectrometer in CDCl3-*d*1 and DMSO-*d*6 using TMS as the internal standard. Elemental analyses were conducted at the METU Central Laboratory using a LECO, CHNS-932. All syntheses were carried out in A MC767W (Electrolux) modified microwave oven.

Schiff bases have been synthesized by condensation of substituted various aromatic aldehyde with Ethyl 4-aminobenzoate by two different methods,

a) By conventional method (Heating).

b) Microwave accelerated synthesis.



Scheme 1: Synthesis of schiff bases from Ethyl 4-aminobenzoate

Compound No.	R	R_1	R_2	R_3
2a	OH	H	H	H
2b	OH	Br	H	Br
2c	OH	I	H	I
2d	OH	H	H	CI
2e	H	OCH_3	OCH_3	H
2f	OCH_3	H	H	OCH_3
2g	H	OCH_3	OCH_3	OCH_3
2h	H	NO_2	H	H
2i	H	H	NO_2	H
2j	H	Br	OH	OCH_3
2k	H	I	OH	OCH_3
2l	H	H	$N(CH_3)_2$	H

Method I: Conventional method for synthesis of schiff bases compound (2d)

Ethyl 4-aminobenzoate (0.165 g, 0.001 mol) and 5-Chloro salicyladehyde (0.157 g, 0.001 mol) was dissolved in 20 ml of methanol, in this solution mixture two drops of *β*-ethoxyethanol as awetting reagent were mixed. The solution was refluxed for 1 h, then cools to room temperature and poured it into ice cold water. The solid product was collected through filtration and then dried using drying oven at 80º C and recrystallized from: Water (9:1) to gave ethyl 4-[(5-chloro-2-hydroxybenzylidene) amino] benzoate. The reaction was monitored by TLC. The structure of Schiff bases were assigned on the basis of element analysis and spectral data. The physico-chemical data for synthesized Schiff base are given in table 3.

Method II: Microwave-accelerated synthesis of Schiff bases (2d)

Ethyl 4-aminobenzoate (0.165 g, 0.001 mol), 5-Chloro salicyladehyde (0.157, 0.001 mol) and two drops of *β*-ethoxyethanol as awetting reagent were mixed in a beaker. Then the beaker was placed in the microwave oven and was exposed to microwave irradiation for 10s. The product obtained by reaction was washed with cold ethanol.

Then, it was recrystallized from DMF: Water. By following the same procedure, all other compounds were prepared within 10-180s. The characterization data and the impact of microwave irradiation and conventional heating for the synthesis of Schiff bases compounds have been compared. Moreover, the % yield and time on the reaction were also studied and the results summarized in tables 3.

The spectra data of the some compounds such as 1b. 1c, 1d, 1e, 1i & 1l are as follows.

2d: Ethyl 4-[(5-chloro-2-hydroxybenzylidene) amino] benzoate

Yield: 86% (Light brownish crystals), M. P.:178 °C. Found IR (KBr) cm^{-1}: 2980, 1892, 1716 (C=O), 1701, 1618 (N=CH), 1599, 1481 (Ar C=C stretch), 1356, 1286, 825 (Ar-Cl); ^{1}H NMR ($CDCl_3$ δ ppm): 12.91 (s, 1H, OH), 8.56 (s, 1H, N=CH), 6.97-8.13 (m, 7H, Ar-H), 4.36 (q, 2H, CH_2), 1.41 (t, 3H, CH_3), MS (m/z): 304 (M^+, 100), 303, 269, 258, 230, 213,196, 167, 139, 120, 97, 76, 65, 51; Halogen Analysis: $C_{16}H_{14}Cl NO_3$ Required Cl: 11.67 % Found Cl: 11.87 % Element Analysis: Calculated (Found): C, 63.27 (63.53); H, 4.65 (4.54); N, 4.61 (4.53); Similarly the rest of the other compounds from series 2a-l were prepared by same methods by following same procedure only change in completion of reaction time interval. The melting points, % yields of conventional and microwave methods and R_f value of different Schiff bases are listed in table 3.

2b: Ethyl 4-[(3, 5-dibromo-2-hydroxybenzylidene) amino] benzoate

^{1}H NMR ($CDCl_3$ δ ppm): 14.04 (s., 1H, OH), 8.56 (s., 1H, N =CH), 6.93-8.14 (m., 6H, Ar-H), 4.36 (q., 2H, CH_2), 1.41 (t., 3H, CH_3); MS (m/z): 427 (M^+), 399, 382, 347(100), 320, 240, 194, 167, 139, 120, 103, 91, 76.

2c: Ethyl 4-[(2-hydroxy-3, 5-diiodobenzylidene) amino] benzoate

IR (KBr) cm^{-1}: 3049, 2978, 1806, 1701(C=O), 1622 (-N=CH-), 1541, 1438 (Ar C=C stretch), 1361, 1284, 1201, 1014, 1020, 854, 773 (Ar-I), 532, ^{1}H NMR ($CDCl_3$ δ ppm): 14.28 (s, 1H, OH), 8.56 (s, 1H, N=CH),

6.97-8.13 (m., 6H, Ar-H), 4.38 (q., 2H, CH_2), 1.41 (t., 3H, CH_3). MS (m/z): 521(M^+, 100), 505, 493, 476, 448, 321, 238, 166, 139, 120, 97, 76, 69, 41.

2e: Ethyl 4-[(3, 4-dimethoxybenzylidene) amino] benzoate

IR (KBr) cm^{-1}: 2841, 1842, 1708(C=O), 1618(s, 1H,-N=CH), 1577, 1512 (Ar C=C Stretch), 1365, 1155(Ar-OCH_3), 1018, 868, 810, 771; ^1H NMR ($CDCl_3$ δ ppm): 8.34 (s., 1H, CH=N), 6.93-8.08 (m., 7H, Ar-H), 4.34 (q., 2H, CH_2), 3.96 (d., 3H, Ar-OCH_3), 1.39 (t, 3H, CH_3); MS (m/z): 313 (M^+, 100), 298, 284, 268, 254, 240, 224, 166, 148, 134, 120, 103, 95, 77, 65, 51;

2i: Ethyl 4-[(3-nitrobenzylidene) amino] benzoate

^1H NMR ($CDCl_3$ δ ppm): 8.76 (s., 1H, N=CH), 7.23-8.53 (m, 8H, Ar-H), 4.36 (q, 2H, CH2), 1.39 (t, 3H, CH3); MS (m/z): 298(M^+), 270, 253(100), 237, 223, 207, 178, 167, 151, 139, 121, 103, 89, 76, 65, 50, 41;

2l: Ethyl 4-{[4-(dimethylamino) benzylidene] amino} benzoate

^1H NMR ($CDCl_3$ δ ppm): 8.30 (s., 1H, CH=N), 6.62-8.06 (m., 8H, Ar-H), 4.04-4.41 (m, 2H, CH_2), 3.06 [s., (-$N(CH_3)_2$], 1.33 (t., 3H, CH_3); MS (m/z): 296 (M^+), 281, 267, 251, 223, 165, 137, 120(100), 111, 92, 77, 65;

Table 1: The optimization of microwave conditions for compound 1a

S. No.	Watt	Microwave method		Yields %
		Time (s)	Reaction conditions	
1	180	10	Wetting agent β-ethoxyethanol	89
2	180	30	Wetting agent β-ethoxyethanol	86
3	180	60	Wetting agent β-ethoxyethanol	84
4	180	90	Wetting agent β-ethoxyethanol	80
5	180	120	Wetting agent β-ethoxyethanol	80
6	200	120	Wetting agent β-ethoxyethanol	85
7	200	90	Wetting agent β-ethoxyethanol	85
8	200	60	Wetting agent β-ethoxyethanol	87
9	200	30	Wetting agent β-ethoxyethanol	93
10	200	10	Wetting agent β-ethoxyethanol	95
11	360	120	Neat	85
12	360	60	Neat	82
13	360	10	Neat	80
14	180	120	Neat	80

Table 2: The optimization of classical conditions for compound 1a

S. No.	Time (Min)	Reaction conditions	Yields %
1	10	Reflux	00
2	30	Reflux	78
3	60	Reflux	85
4	90	Reflux	84
5	120	Reflux	82
6	150	Reflux	82
7	180	Reflux	80

Table 3: Characterization data and comparison of % yield and reaction time required to complete the reaction by conventional and microwave methods for synthesis of Schiff bases compound (2a-l)

Compd. No.	M. P. (°C)	Mol. Wt.	Molecular formula	Elemental analysis (%) calculated (Found)		R_f value
				N	Cl/Br/I	
2a	163	269.29	$C_{16}H_{15}NO_3$	5.20 (5.43)	-	0.56
2b	169	427.08	$C_{16}H_{13}Br_2NO_3$	3.28(3.39)	37.42 (37.34)	0.72
2c	190	521.08	$C_{16}H_{13}I_2NO_3$	2.69 (2.78)	48.71 (48.86)	0.66
2d	179	303.74	$C_{16}H_{14}ClNO_3$	4.61 (4.58)	11.67 (11.76)	0.64
2e	121	313.34	$C_{18}H_{19}NO_4$	4.47 (4.56)	-	0.65
2f	165	313.34	$C_{18}H_{19}NO_4$	4.47 (4.36)	-	0.63
2g	148	343.37	$C_{19}H_{21}NO_5$	4.08 (4.23)	-	0.72
2h	208	298.29	$C_{16}H_{14}N_2O_4$	9.39 (9.57)	-	0.73
2i	211	298.29	$C_{16}H_{14}N_2O_4$	9.39 (9.57)	-	0.59
2j	241	378.21	$C_{17}H_{16}BrNO_4$	3.70 (3.80)	21.13 (21.37)	0.53
2k	259	425.21	$C_{17}H_{16}INO_4$	3.29 (3.47)	29.84 (29.95)	0.64
2l	195	296.36	$C_{18}H_{20}N_2O_2$	9.45 (9.68)	-	0.70

RESULTS AND DISCUSSION

In this present work, we synthesized quickly and efficiently a series of imine derivatives (2a–l) (Scheme-I) by condensation of aromatic amines i.e. Ethyl 4-aminobenzoate and aldehyde derivatives such as salicylaldehyde (1a), 3,5-dibromosalicylaldehyde (1b), 3,5-diiodo salicylaldehyde (1c), 5-chlorosalicylaldehyde(1d), 3,4-dimethoxy benzaldehyde (1e), 5-methoxybenzaldehyde(1f), 3,4,5-Trimethoxy benzaldehyde (1g) 3-nitrobenzaldehyde (1h), 4-nitrobenzaldehyde (1j)„ 3-bromo-4-hydroxy-5-methoxybenzaldehyde (1j), 3-iodo-4-hydroxy-5-methoxy benzaldehyde (1k), 4-N,N-dimethyl benzaldehyde (1l) under microwave-assisted solvent free conditions using β-EE as wetting reagent. β-EE that is a polar molecule quickly absorbs microwaves and therefore heats up and heats around effectively. As a result, β-EE, which increases the polarity of the reaction medium, has an active role in the heating of the reaction medium by microwaves.

The general reaction was summarized in Scheme 1. In addition, we tested the effect of different microwave power such as 180, 200,

360, 600, 900W and detected the microwave power of 180W and 360W are more appropriate choices for the reaction. Hence, the optimum microwave reaction conditions were determined using 180 and 360W microwave power and neat and wetting with β-EE for compound 1a. The highest reaction yield (95%) and shorter reaction time (10s.). Yunus Bekdemir *et al.*[32] developed a simple microwave assisted solvent-free method for the synthesis of imines using a wetting reagent (β-ethoxyethanol). In addition, they tested the effect of different microwave power such as 180, 360, 600, 900W and detected the microwave power of 180W and 360W are more appropriate choices for the reaction. Hence, the optimum microwave reaction conditions were determined using 180 and 360W microwave power and neat and wetting with β-ethoxyethanol. In the absence of wetting reagent, the reaction yields are 81% for 1.5 min and 88% for 5 min. It is understood that the reaction yield was increased by wetting reagent that increases the polarity of the reaction medium. The method works well for the reaction type amines & aldehydes and imine compounds were prepared in high yields and short reaction times so this method found more effective and environment friendly.

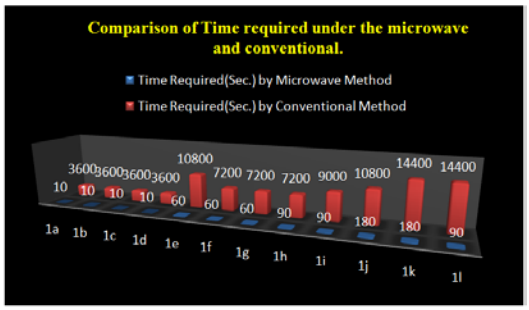


Fig. 1: Comparison of time required to complete reaction under the microwave and conventional

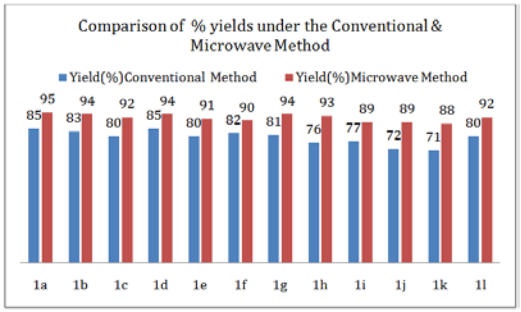


Fig. 2: Comparison of % yields under the conventional & microwave Method

This research work reveals that, the optimum microwave reaction conditions for synthesis of novel Schiff bases by using a wetting reagent (β-ethoxyethanol) were in between 180 and 360W microwave power. Our findings are also parallel to previous work down by Yunus Bekdemir *et al.* for synthesis of imines using a wetting reagent (β-ethoxyethanol). The method works well for the reaction type amines & aldehydes and Schiff bases compounds were prepared in high yields and short reaction times so this method is more easy, effective, economical, fast and environment friendly.

All the results such as reactions time, yields, Rf factor, elemental analysis and melting points of the compounds were presented in table 3. In addition, the comparison of % yields and time required for the completion of reaction for imines by microwave and conventional conditions were expressed graphically in fig. 1 & fig. 2.

CONCLUSION

In conclusion, we have developed a simple microwave assisted solvent-free method for the synthesis of Schiff bases using a wetting reagent (β-ethoxyethanol). The method works well for the reaction of amine and various substituted aldehydes. Because, we have synthesized imine compounds for good yields and fast reaction times in our method. Our method has some advances such as higher reaction yields, shorter reaction times, and green reaction conditions than classical requirements used of a solvent and conventional heat source (like hot plate) and other some microwave methods used of catalyst and solid supports. In addition, some Schiff bases were synthesized for the first time by us with this study.

The developed simple microwave assisted solvent-free method for the synthesis of Schiff bases using a wetting reagent (β-ethoxyethanol) were found more efficient on overall performance compare to conventional method as desired. The microwave irradiation technique led to improvement in the yield of all the target compounds with reduction in their reaction byproducts. The microwave process also substantially reduced the overall process time as expected, by reduction in reaction time against the described conventional method.

The chemistry for the synthesis of target compounds using microwave irradiation is established in the lab by carrying out three successive experiments post initial optimization of key parameters; to ensure process robustness. The results of these validation experiments were found to be promising, indicating its wide use for researchers. Using more advance instruments and infrastructure in Microwave assisted organic reaction enhancement (MORE); the process can be further evaluated for its scale up potential.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests regarding the publication of this paper

Abbreviation

%: Percentage, Mol: Mole, min: Minute, s: Second, IR: Infrared, NMR: Nuclear Magnetic Resonance

cm^{-1}: Per Centimeter, KBr: Potassium bromide, ^{1}HNMR: Proton Nuclear Magnetic Resonance

CDCl3-*d*1: Chloroform-d1, DMSO-*d*6: Dimethyl sulfoxide-d6, TMS: Tetramethylsilane, g: Gram, TLC: Thin Layer Chromatography, ^{0}C: Degree Celsius, DMF: Dimethylformamide, W: Watt, □-EE: □-ethoxyethanol, s: Singlet, m: Multiple Peak, q: Quadrate Peak, t: Triplet Peak, MS: Mass Spectroscopy, M^+: Molecular Ion Peak, m/z: Mass to Charge ratio, R_f: Retention Factor, $CDCl_3$: Chloroform, ppm: Part Per Million, hr: Hour, W: Watt, β-EE: β-ethoxyethanol, Fig.: Figure, MORE: Microwave assisted organic reaction enhancement.

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