http://dx.doi.org/10.434/jpb.v13i2.16
Vol. 13 no. 2, pp. 194-200 (September 2016)
http://ajol.info/index.php/jpb

Journal of
PHARMACY AND BIORESOURCES

Quantitative assessment of the effect of anhydrous zinc chloride catalysis on the synthesis of some imine derivatives in toluene

John O. Uwaya and Lucky O. Okunrobo*

Department Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, Benin city. Nigeria

Received 13th April 2016; Accepted 29th August 2016

Abstract

Imines are formed when any primary amines react with an aldehyde or a ketone under specific conditions. The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation. In the 1990s an in-situ method for water elimination was developed using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate another way to remove the water by-product is to use substances that function as Bronsted-Lowry or Lewis acids like $ZnCl_2$, $TiCl_4$, $MgSO_4$, H_3COOH, $Mg(ClO_4)_2$ to activate the carbonyl group of benzaldehyde, catalyse the nucleophilic attack by amines, and dehydrate the system, and eliminate water as the final steps. Anhydrous zinc chloride has been extensively used in literature for its affordability and reliability, however there is limited information if any, of its quantitative effects in synthesis, this has prompted this present study. The reaction involved the condensation between 4-Methoxybenzaldehyde and *para*- substituted aniline derivatives (4-chloroaniline, 4-nitroaniline and 4-methylaniline) in toluene. The reaction process was evaluated to determine the effect of temperature, concentration of anhydrous zinc chloride and effect of microwave assisted synthesis on the yield of the products. Results show that increasing the concentration anhydrous zinc chloride at elevated temperature increases the yield of the imine derivatives studied.

Keywords: Imines, anhydrous zinc chloride, toluene, microwave assisted synthesis

---

INTRODUCTION

Schiff bases (or imines), named after Hugo Schiff (Schiff, 1864), are formed when any primary amines react with an aldehyde or a ketone under specific conditions. Structurally a Schiff base is a nitrogen analogue of an aldehyde or ketone in which the carbon (C=O) has been replaced by an imine or azomethine group (C=N). Schiff bases are one of the most widely used organic compounds. They are used as pigments and dyes, catalysts, intermediates in organic synthesis and as polymer stabilizers (De suza *et al.*, 2007).

The first preparation of Schiff base was reported in the 19th century by Schiff (1864); since then a variety of methods for the synthesis of imines have been described (Zheng *et al.*, 2009*).* Imines are the product of condensation reaction between carbonyls and amines (De suza *et al.*, 2007). The classical synthesis reported by Schiff involves the condensation of a carbonyl compound with an amine under azeotropic distillation (Moffett, 1963). Molecular sieves are then used to

---

[*] Corresponding author. *E-mail*: okunrobo@uniben.edu *Tel*: +234 (0) 8034725416

ISSN 0189-8442 © 2016 Faculty of Pharmaceutical Sciences, University of Jos, Jos. Nigeria.

completely remove the water formed in the system (Taguchi and Westheimer, 1971).

In the 1990s an *in situ* method for water elimination was developed using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate (Love and Ren, 1993). In 2004, Chakbaborh and coworker (Chakbaborh *et al.,* 2004*)* demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compound and strongly nucleophilic amines. They proposed as an alternative the use of substances that function as Bronsted-Lowry or Lewis acids to activate the carbonyl group of benzaldehyde, catalyse the nucleophilic attack by amines, and dehydrate the system, and eliminate water as the final steps (Chakbaborh *et al.,* 2004). Examples of Bronsted-Lowry or Lewis acid used in the synthesis of Schiff bases include $ZnCl_2$, $TiCl_4$, $MgSO_4$, H_3COOH and $Mg(ClO_4)_2$. If the solution is too acidic, however, protonation of the amine is blocked, therefore, there is some optimal pH, usually about 3- 5, at which the reaction rate is maximum (Dave and Bansal, 2013). In the past two decades, a number of innovations and new techniques have been reported, including solvent-free/clay/microwave irradiation, solid state synthesis, water suspension medium, infrared irradiation/ no solvent, silica/ ultrasound irradiation (Varma *et al*., 1997 and Schmeyers *et al*., 1998). Among these innovations, microwave irradiation has been extensively used due to its operational simplicity, enhanced reaction rates and great selectivity (Gopalakrishnan *et al*., 2007). Anhydrous zinc chloride has been extensively used in literature for its affordability and reliability, however there limited information if any, of its quantitative effects in synthesis; this has prompted this present study.

EXPERIMENTAL

All reagents were purchased from commercial sources and used without any further purification. ^1H NMR Spectra were recorded on a Bruker ARX 500 spectrometer (500MHz). Chemical shifts are reported in ppm relative to tetramethylsilane as reference standard. The multiplicities are represented as follows: s = singlet, d = doublet, J = coupling constant, Hz = hertz.^{13}C NMR spectra were recorded on a Bruker ARX 500 spectrometer (125MHz). Chemical shifts are reported in ppm relative to tetramethylsilane as reference standard. Analytical HPLC was run on Agilent 1100 series with photodiode ray detector. Mass spectra were acquired on a Finnigan LCQ-DECA mass spectrometer (Thermo Finnigan San Jose, California, USA) at 70eV.Elemental analysis was determined using the Perkin-Elmer 2400 CHN Elemental Analyzer, Waltham, Massachusetts, USA. Melting points were determined on a KoflerElectrothermal^R melting point apparatus CAT No 1A6304, England. Haier Thermocool HSB2070E domestic microwave oven, operating at 2450MHz, 700 watt MW power and maximum operating temperature of 100°C was used in the microwave assisted synthesis.

Synthetic plan. See Scheme 1.
During this synthetic procedure the effects of temperature, zinc chloride as a catalyst and the effect of microwaves where evaluated. All reactions were monitored by analytical TLC using appropriate solvent systems and viewed under UV wave lengths of 254nm and 366nm respectively. The following methods were employed:

Method I. Equimolar amount of the anilines (0.018mol) was added to 30 ml toluene in a 150 ml round bottom flask. The mixture was stirred with the aid of a magnetic stirrer for 15 minutes to aid dissolution at room temperature. 0.018 mol (2.2 ml) of 4-methoxybenzaldehyde was added in two portions. The reaction mixture was then allowed to stir for 48hours.

Method II. Equimolar amount of the anilines (0.018 mol) was added to 30 ml toluene in a 150 ml round bottom flask under reflux at 130^{O}C. 15 minutes later 0.018 mol (2.2ml) of 4-methoxybenzaldehyde was added in two portions. The reaction mixture was then allowed to reflux for 12 – 18 hours.

Method III. Into 30 ml of toluene in a 150 ml flat bottom flask was added 0.018 mol of aniline, 0.018 mol (2.2ml) of 4-methoxybenzaldehyde. The mixture was properly mixed by shaking and placed in the microwave oven operating at 700 watts for 5minutes.

Method IV. To 200 mg of anhydrous zinc chloride was added 30 ml of toluene in a 150 ml around bottom flask and stirred for 5 minutes at room temperature. Equimolar amounts of the anilines (0.018mol) were added and the mixture was stirred with the aid of a magnetic stirrer for 15 minutes at room temperature. 0.018 mol (2.2ml) of 4-methoxybenzaldehyde was added in two portions. The mixture was further stirred for another 48 hours.

Method V. To 200 mg of anhydrous zinc chloride was added 30 ml of toluene in a 150 ml round bottom flask and heated under reflux at 130^{O}C. Equimolar amounts of the anilines (0.018 mol) was added, 15 minutes later 0.018 mol (2.2ml) of 4-methoxybenzaldehyde was added in two portions. The reaction was allowed to proceed under reflux and monitored.

Method VI. To 200 mg of anhydrous zinc chloride was added 50 ml of toluene in a 150ml flat bottom flask, the mixture was pre-heated in the microwave for 2 minutes. Equimolar amounts of aniline (0.018mol), 4-methoxybenzaldehyde (0.018mol; 2.2ml). The mixture was mixed properly and placed in the microwave to react for 5 minutes.

Method VII. To determine the effect of the concentration of anhydrous zinc chloride on the product yield method V above was carried out using 0.5g, 1.0g and 2.0g of anhydrous $ZnCl_2$.

Experimental work-up. At the end of each reaction processes (indicated by no reaction or no further reaction on analytical TLC). The reactions where there was no reaction were not worked-up. At the end of the reaction the reaction vessel was removed, 50 ml of absolute ethanol was added and the mixture properly shaken, 30 ml of ice water was later added with shaking and the whole mixture transferred into a 500 ml separating funnel. The crude mixture was exhaustively partitioned with dichloromethane. The dichloromethane fraction was washed severally with water, and allowed to evaporate. The compounds were purified by column chromatography and recrystallized with dichloromethane/absolute Ethanol. Results are mean values of two synthetic procedures.

RESULTS AND DISCUSSION

Synthetic procedure. No reaction was observed in methods I, II, III and IV. Three identical compounds were obtained (JX1, JX3 and JX6) from the reactions of method V, VI and VII.

4-Methoxy-N-(4-chlorobenzylidene)aniline (1)

Ultra-violet spectrum: λ = 230nm (benzene); λ max =382.0nm

^{1}H NMR (DMSO d_6, 250MHz, δ in ppm): 3.82 (s, 3H, OCH_3); 7.04 – 7.07 (d, 2H, J=7.50Hz, Ar-H); 7.23-7.27 (d, 2H, J=10.00Hz, Ar-H); 7.41-7.44 (d, 2H, J=7.50Hz, Ar-H); 7.85-7.89 (d, 2H, J=10.00Hz, Ar-H); 8.52 (s, 1H, =CH)

^{13}C NMR (DMSO d_6, 60MHz, δ in ppm): 55.85 (OCH_3), 114.73, 123.19, 129.15, 129.50, 130.20, 131.07, 150.97, 161.05 (Ar-C), 162.53(=CH).

Mass spectra: 268.6[M + Na^{+}]* 15%, 266.0 15%, 260.9 20%, 259.5 30%, 258.7 90%, 257.2 20%, 255.1 15%, 250.7 50%, 249.0 100%, 247.2 40%, 244.9 30%, 241.0 15%.

Elemental analysis: Molecular formula $C_{14}H_{12}ClNO$ (245.70). Calculated: C 68.37, H 4.89, Cl 14.44, N 5.69, O 6.51

Found: C 67.92, H 4.54, Cl 14.29, N 5.62, O 6.37

4-Methoxy-N-(4-nitrobenzylidine)aniline (2)

Ultra-violet spectrum: λ = 228.0nm (benzene); λ max = 384.0nm

^{1}HNMR (DMSO d_6, 500MHz, δ in ppm): 3.83 (s,3H, OCH_3); 7.06-7.08 (d, 2H, J= 10.00Hz, Ar-H); 7.24-7.26 (d, 2H, J= i0.00Hz, Ar-H); 6.09-6.11 (d, 2H, J=10.00Hz, Ar-H); 7.42-7.44 (d, 2H, J=10.00Hz, Ar-H), 7.87-7.89 (d, 2H, Ar-H); 8.53 (s, 1H, =CH)

^{13}C NMR (DMSO d_6, 125MHz, δ in ppm): 55.40 (OCH_3); 114.27, 122.74, 128.71, 129.05, 129.73, 130.61, 150.54, 162.06 (Ar-C); 160.61(=CH)

Mass spectra: 255.3 [M - 1]* 2%, 245.0 5%, 240.1 10%, 238.9 20%, 235.0 100%, 233.7 5%, 227.0 30%, 224.7 2%, 219.0 5%, 213.8 10%

Elemental analysis: Molecular formula $C_{14}H_{12}N_2O_3$ (256.26). Calculated: C. 65.63 H. 4.72 N. 10.93 O. 18.75 Found: C. 65.47 H. 4.29 N. 10.89 O. 18.62

4-Methoxy-N-(4-methylbenzylidene)aniline (3)

Ultra-violet spectrum: λ= 230.0nm (benzene), 258.0nm, 286.0nm, λ max=302.0nm.

^{1}H NMR (DMSO d_6, 500MHz, δ in ppm): 2.31 (s, 3H, CH_3); 3.33 (s, 3H, OCH_3); 7.05-7.07 (d, 2H, J=10.00Hz, Ar-H); 7.13-7.15 (d, 2H, J=10.00Hz, Ar-H); 7.19-7.21 (d, 2H, J=10.00Hz, Ar-H); 7.86-7.88 (d, 2H, J=10.00Hz, Ar-H); 8.5 (s, 1H, =CH)

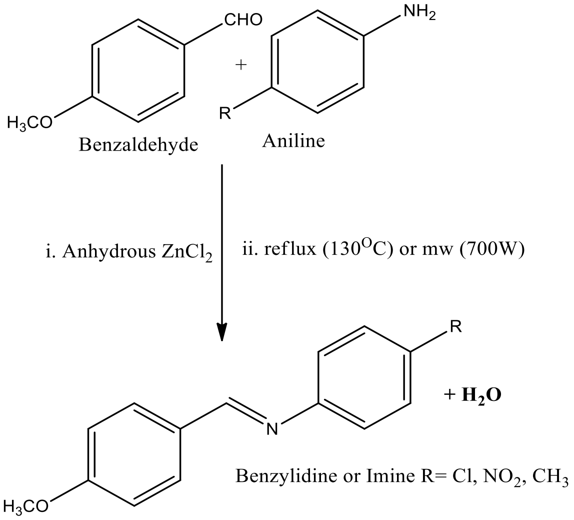
^{13}C NMR (DMSO d_6, 125MHz, δ in ppm): 20.55 (CH_3); 55.38 (OCH_3); 114.23, 120.85, 128.4, 129.64, 130.31, 134.82, 149.79, 158.95 (Ar-C); 162.25 (=CH).

Mass spectra: 243.0 [M + H_2O]* 5%, 217.9 2%, 190.9 5%, 181.0 7.5%, 158.9 100%, 145.1 2%, 136.7 15%

Elemental analysis: Molecular formula $C_{15}H_{15}NO$ (225.29). Calculated: C. 79.90 H. 4.42 N. 12.38 O. 7.10 Found: C. 79.23 H. 4.22 N. 12.02 O. 6.98

Effect of concentration of anhydrous zinc chloride on yield of synthesized compounds

The effect of concentration anhydrous zinc chloride on the yield of the synthesized compounds are summarized in Table 2. The graphical representation of the effect of change in zinc chloride concentration is presented in Fig. 1 a, b and c.



Scheme 1: Synthetic scheme for the imine derivatives.
i=toluene/reflux/anhydrous $ZnCl_2$; ii= toluene/MW (700 watt)/200mg anhydrous $ZnCl_2$

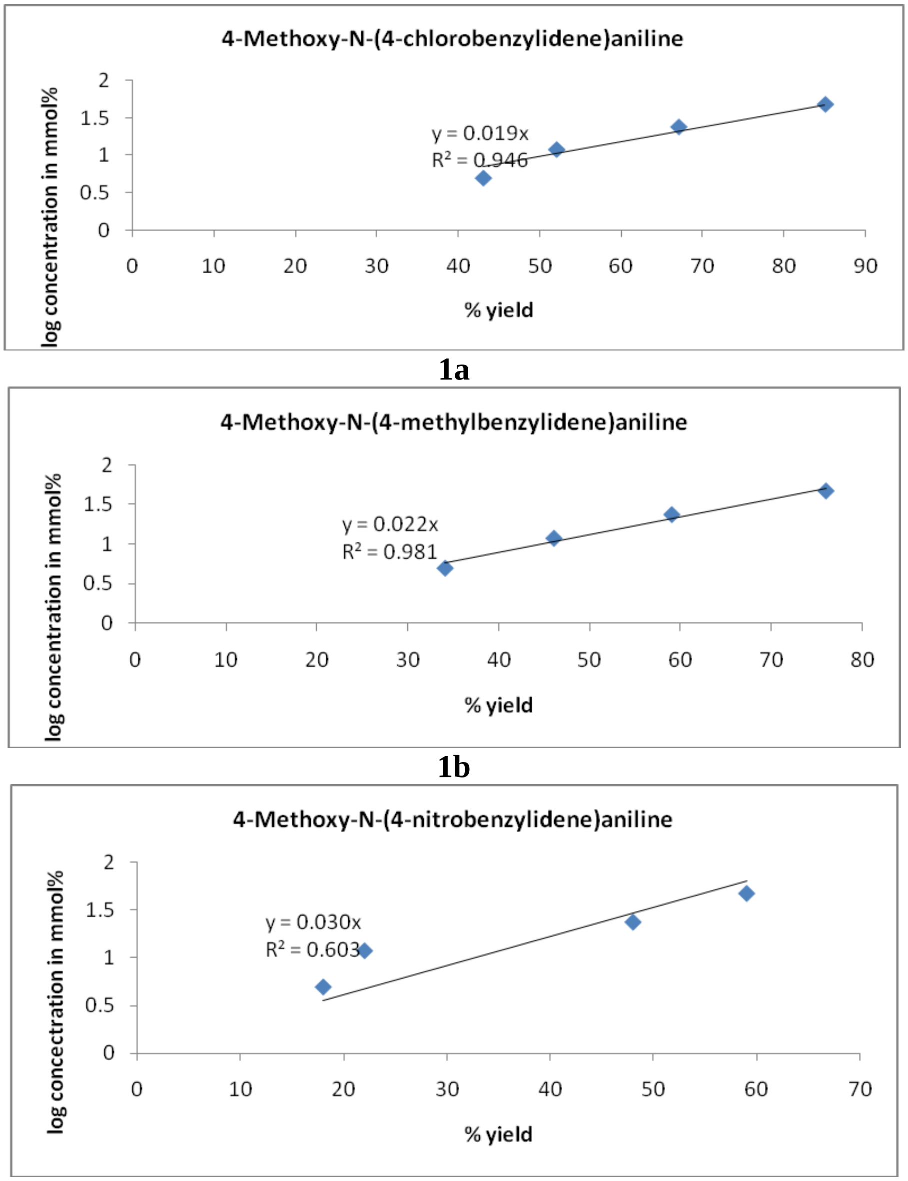
Table 1: Some physicochemical characteristics of the synthesized compound

Compound	% Yield	Recrystallization solvent	Melting point	Solvent system	R_f value	Mol. Wt.
1	43^{a} 72^{b}	Dichloromethane/ Ethanol	82-84°C	CH_3OH:Ethyl acetate:Hexane (1:1:1)	0.92	245.70
2	18^{a} 57^{b}	Dichloromethane/ Ethanol	138-140°C	CH_3OH:Ethyl acetate:Hexane (1:1:1)	0.85	226.23
3	34^{a} 68^{b}	Dichloromethane/ Ethanol	78-80°C	CH_3OH:Ethyl acetate:Hexane (1:1:1)	0.67	225.28

a=toluene/reflux/200mg anhydrous $ZnCl_2$; b= toluene/MW (700 watt)/200mg anhydrous $ZnCl_2$

Table 2: Effect of concentration of anhydrous $ZnCl_2$ on the yield of synthesized compounds.

Compound	Conc of anhydrous $ZnCl_2$	Yield	Reaction time (h)
1	0.5g (12mmol%)	52	2.0
	1.0g (24mmol%)	67	1.5
	2.0g (48mmol%)	85	0.5
2	0.5g (12mmol%)	22	5
	1.0g (24mmol%)	48	3.5
	2.0g (48mmol%)	59	1
3	0.5g (12mmol%)	46	2.5
	1.0g (24mmol%)	59	1.75
	2.0g (48mmol%)	76	0.5



1a

1b

1c

Fig 1: Effect of change in concentration anhydrous $ZnCl_2$ on yield of the imine derivatives

DISCUSSION

The compounds were obtained in yields of 18% - 43% for the reaction under reflux with the lowest yield obtained for 4-Methoxy-N-(4-nitrobenzylidene)aniline (18%), followed by 4-Methoxy–N-(4-methylbenzylidene) aniline (34%) and 4-Methoxy-N-(4-chloro-benzylidene)aniline (43%) respectively. The yields of the compounds were greatly improved in the microwave assisted synthetic procedure with yields of 57% - 72% obtained for the respective compounds, this result is in consonance with the advantages of microwave assisted synthesis which include Shorter reaction times and Improved yield (Lidstrom, 2001).

An increase in the concentration of anhydrous zinc chloride was found to increase the percentage yield of the imine derivatives obtained in the reaction, for example the yield of 4-Methoxy-N-(4-chlorobenzylidene) aniline increased from 52% to 67% and then to 85% as the concentration of anhydrous zinc chloride in the reaction medium was increased from 0.50g to 1.00g and then to 2.00g. This same trend was observed for the other two compounds obtained. The yield of 4-Methoxy-N-(4-nitrobenzylidene) aniline is less with all the methods employed due to the deactivation of the amino group by the electron withdrawing effect of nitro group at position 4. The yields of the chloro- and methyl- derivatives were higher because of electron cloud and inductive effect respectively leading to the activation of the amino group which facilitated the reaction process.

From the plots on figure 1, it is possible to estimate the yield of the imine derivatives at any given concentration of anhydrous zinc chloride working at the stated reaction conditions of this study. However, it is obvious that these conclusions can and should not be drawn for all synthetic approaches for imine derivatives because reactants differ in their intrinsic reactivities and are continually affected by varying reaction conditions. We will therefore conclude at this point that increasing the concentration of anhydrous zinc chloride at elevated temperature in the synthesis of these imines derivatives studied in toluene will lead to a favourable increase in yield and a reduction in the reaction duration, possibly due an increase in dehydration by the presence of more anhydrous zinc chloride in the reaction medium.

REFERENCES

Chakbaborh A. K., Bhagat S., Rudrowar S. (2004): Magnetic perchlorate as an efficient catalyst for the synthesis of imines and phenylhydrazones. *Tetrahedron let*; 45(41): 7641-7644.

Dave S. and Bansal N. (*2013*): Analgesic and anti-inflammatory activities of Schiff base metal complexes – a review *Inter. J. Basic Appl Chem.l Sci.* 3 (1) :31-40

De Suza A.O, Galetti F.C.S, Silva C.L., Bicalho B., Parma M.M, Fonseca S.F. (2007), Antimycobacteria and Cytotoxicity activity of Synthetic and natural compounds. *Quin Nova* 32 (7): 1363-1366.

Devi KS, Ramaiah M, Roopa DL, Vaidya VP. (2010): Synthesis and Investigation of Antimicrobial and Antioxidant Activity of 3-Nitro-*N*-(3-chloro-2-oxosubstituted- phenylazetidin-1-yl) naphtha[2,1-*b*]furan-2-carboxamides. *E. J Chem*.;7(S1): S358-S362.

Gopalakrishnan M., Sureshkumar P., Konagangen N., Thanusu J. (2007): new environmentally friendly solvent-free synthesis of imines using calcium oxide under microwave irradiation, *Res Chem Intermed*, 33(6) 541-548.

Lidstrom R., Tierney J., Wathey B., westman J., (2001): microwave assisted organic synthesis-a review *tetrahedron Lett*: 57, 9225-9283.

Love B. E., Ren J., (1993): synthesis of sterically hindered imines; *J Org Chem*, 58(20): 5556-5557.

Moffett R.B (1963): Organic Synthesis vol. 4; John Wiley and Sons Inc. New York., pp 605-608.

Schmeyers J., Toda F., Boy J., Kaupp G. (1998): Quantitative Solid- solid synthesis of Azamethines. *J Chem Soc Perkin Trans* 2: 989-993.

Taguchi K., Westheimer F.H., (1971) catalysis by molecular sieves in the preparation of ketimines and enamines. *J. Org Chem*: 36 (11); 1570-1572.

Verma R.S., Dahya R., Kumar S. (1997): Clay catalyzed synthesis of imines and enamines under solvent-free conditions using microwave production. *Tetrahedron Lett*., 38(12) 2039-2049.

Zheng Y., Mak L.H., He J., Sun X. (2009): One pot synthesis of imines from aromatic nitro compounds with a novel Ni/SiO$_2$ magnetic catalyst. *Catal. Lett*: 128 (3,4), 465-474.