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COMPARISON OF YIELD PERCENTAGE BY 2nd ORDER REACTION KINETICS IN SYNTHESIS OF PIPERAZINE MOIETIES BY GREEN SOLVENTS AND IONIC LIQUID

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ABSTRACT

N-ethyl piperazine has been conjugated with substituted aromatic acid chlorides in J-1 to J-3 series and in J-4 with higher homologous unsubstituted acid chloride and then converted in to Schiff's base by substituted aromatic amines by conventional method (methanol) and green solvents (1-butanol and ionic liquid: triethyl methyl ammonium methyl sulphate). Rate of reaction was tested for all compounds by kinetic study and all compounds were characterized by spectral studies. Final compounds % yield in methanol was found around 88%, in 1-butanol around 66% and in ionic liquid above 99%. Overall rate of reaction was found 2 nd order in kinetic study. Rate of reaction k in methanol was found = 0.0004 $\mu g^{-1}sec^{-1}$and in 1-butanol it was = 0.0001 $\mu g^{-1}sec^{-1}$, half life of reaction was 250 seconds in methanol and 1000 seconds in 1-butanol while overall reaction time in ionic liquid was only 20 seconds. % yield and rate of reaction is highest in ionic liquid compared to other two solvents, so reaction is more ecofriendly and more acceptable in this environmental benign solvent.

Keywords: *N*-ethyl piperazine, Schiff's base, Green solvents, Ionic liquids, Reaction kinetics, Half-life.

INTRODUCTION

Solvents typically make up more than 80% of the material usage for Active Pharmaceutical Ingredient (API) manufacture. Solvent use also consumes about 60% of the overall energy

and accounts for 50% of the post treatment green-house gas emissions; hence solvent selection is a major consideration in the design of chemical synthesis. So, it is very necessary to refer solvent guideline to select alternate solvent to move from undesirable to preferred solvent.

Pfizer solvent guideline: The Pfizer approach is to do a similar, detailed multi-category assessment but then report a much simpler summary of those assessments to the end user and this is shown in Figure-1. Of course there are Pros and Cons to both approaches but Pfizer reports that its simple selection guide is particularly effective when used in the medicinal chemistry environment and has resulted in reduced chloroform usage of 98.5% and di-isopropyl ether usage by 100% over the past few years.[1]

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	TBME	Dichloromethane
Ethyl Acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-MeTHF	NMP
MEK	THF	DMF
1-Butanol	Xylenes	Pyridine
t-Butanol	DMSO	DMAc
	Acetic Acid	Dioxane
	Ethylene Glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

Figure-1: Pfizer solvent guideline[1]

Table-1: The Pfizer solvent replacement table[1]

Undesirable solvents	Alternative
Pentane	Heptane
Hexane(s)	Heptane
Di-isopropyl ether or diethyl ether	2-MeTHF or *tert*-butyl methyl ether
Dioxane or dimethoxyethane	2-MeTHF or *tert*-butyl methyl ether
Chloroform, dichloroethane, carbontetrachloride	Dichloromethane
Dimethyl formamide, dimethyl acetamide, N-methylpyrrolidinone	Acetonitrile
Pyridine	Et_3N (if pyridine used as base)
Dicholomethane (extractions)	EtOAc, *tert*-butyl methyl ether, toluene, 2-MeTHF
Dichloromethane (chromatography)	EtOAc/heptane
Benzene	Toluene

GSK's solvent selection guide: GSK recently made solvent guideline for 110 solvents by considering more parameters than previous guideline. It includes:

- Revising the assessments of factors that impact process safety, separating reactivity from fire and explosion rankings.
- More than doubling the number of solvents in the guide, to a total of 110 from the initial 47.
- Adding a customised solvent selection guide appropriate for medicinal chemistry and analytical laboratories.

The new GSK solvent selection guide enables scientists to objectively assess solvents and determine whether existing or new solvents brought to market as 'greener' alternatives truly represent a more sustainable choice or whether they are just addressing a single issue associated with sustainability.[2]

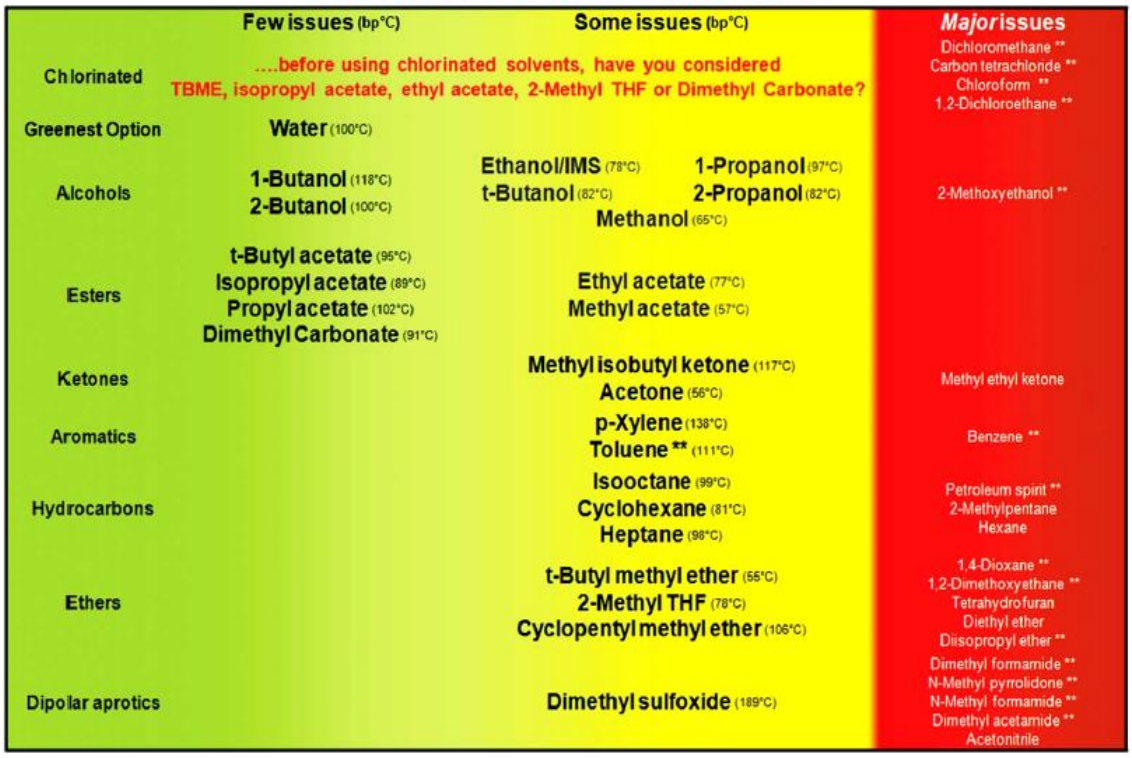


Figure-2: GSK's Solvent guideline[2]

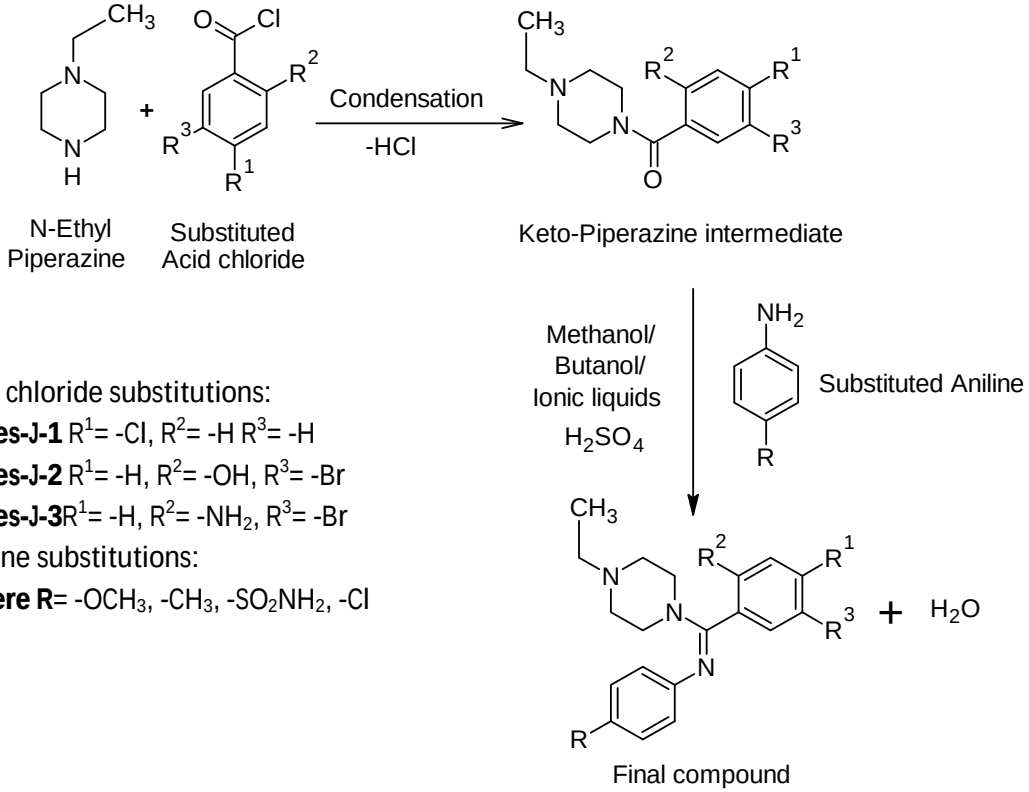
Review for using ionic liquid in synthesis procedure

1. Lorna Crowhurst *et al.* reported the effect of ionic liquids on a class of charge-neutral nucleophiles. They have studied the reactions of *n*-butylamine, di-*n*-butylamine and tri-*n*-butylamine with methyl *p*-nitrobenzenesulfonate in [bmpy][N(Tf)2], [bmpy][OTf] and [bmim][OTf] (bmpy) 1-butyl-1-methylpyrrolidinium; bmim) 1-butyl-3-methylimidazolium)

and compared their reactivities, k_2, to those for the same reactions in the molecular solvents dichloromethane and acetonitrile. It was shown that all of the amines are more nucleophilic in the ionic liquids than in the molecular solvents studied in this work. Comparison is also made with the effect of ionic liquids on the reactivity of chloride ions, which are deactivated in ionic liquids. The Eyring activation parameters revealed that changes in the activation entropies are largely responsible for the effects seen. This can be explained in part by the differing hydrogen-bonding properties, as shown by the Kamlet-Taft solvent parameters, of each of these solvents and the formation of hydrogen bonds between the solvents and the nucleophiles.[3]

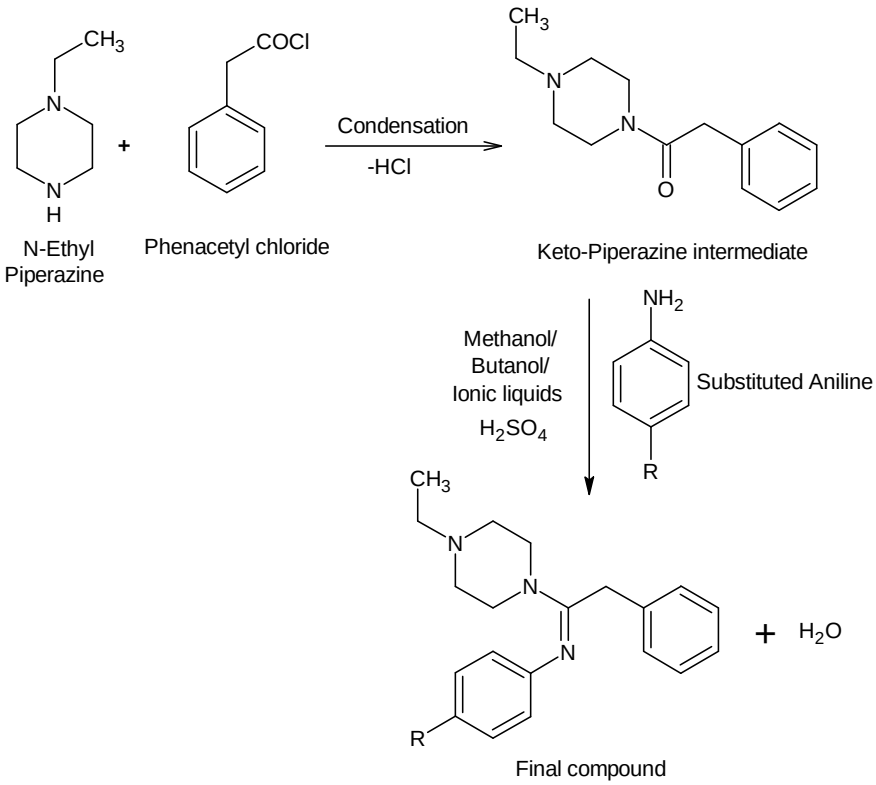
2. Skrzypczak and Neta showed a recent quantitative study by very clearly that the rate of reaction of 1,2-dimethylimidazolewith benzyl bromide (also an SN_2 reaction) increased dramatically in ionic liquids compared to a range of polar protic and aprotic molecular solvents. That the use of an ionic liquid enhances the nucleophilicity of water has also recently been proposed.[4]

Synthetic scheme of series 1-3[5-7]



Acid chloride substitutions:
Series-J-1 R^1= -Cl, R^2= -H R^3= -H
Series-J-2 R^1= -H, R^2= -OH, R^3= -Br
Series-J-3 R^1= -H, R^2= $-NH_2$, R^3= -Br
Aniline substitutions:
Where R= $-OCH_3$, $-CH_3$, $-SO_2NH_2$, -Cl

Synthetic scheme of series 4[5-7]

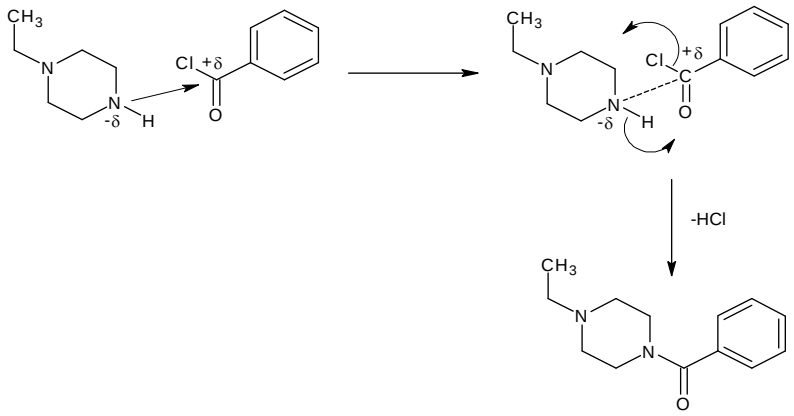


Mechanisms of reaction steps[5-7]

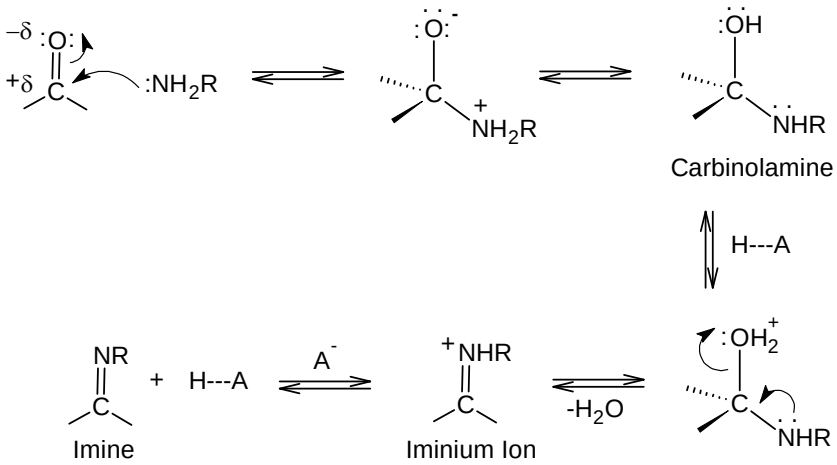
After preparation of acid chloride the synthetic part takes only two steps to prepare final compounds. First step involves the reaction of *N*-ethyl piperazine with different substituted acid chlorides to prepare keto-piperazine intermediate. The mechanism involves in this step is simple condensation reaction. The reaction completes with liberation of hydrochloric acid.

Second step involves reaction of keto-piperazine intermediates with different substituted anilines to yield final products of all four series. It requires a proper solvent for completion. The mechanism involves in this is Neucleophilic addition followed by dehydration. Nitrogen of the $–NH_2$ group of the different substituted anilines do attack on the carbonyl carbon of the keto-piperazine intermediate which is partially positive charged and give carbinolamine intermediate. Further use of dehydrating agent gives iminium intermediate and neutralization gives final imine.

Reaction mechanisms of both steps are given below with their respective intermediates.



Mechanism of step-1: Condensation reaction



Mechanism of step-2: Neucleophilic addition followed by dehydration

Involvement of green guidelines in synthetic part

First step of synthetic work doesn't involve any solvent for reaction completion because it is simple condensation reaction and it requires only direct mixing of *N*-ethyl piperazine and different substituted acid chlorides while second step involves a proper solvent. As per the reviews of synthetic step methanol is proper solvent for this reaction but after reviewing the solvent selection guidelines of GSK and Pfizer we came to know that due to low boiling point methanol has some environmental issue.[7] So alternate of methanol with lower issues will protect the environment from different hazardous issues. 1–butanol is selected after examine the guidelines because it has high boiling compare to methanol so has very less environmental impact.[1,2]

Involvement of ionic liquids in synthetic part[3]

After review of literature which shows involvement of ionic liquids in the synthetic procedures as a solvent, ionic liquids in the synthetic part has been implemented. Some

remarkable characteristics of these are highly inspirable which are:

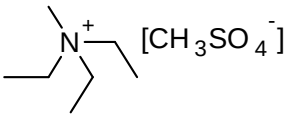
- The first arises from the claim that ionic liquids are environmentally benign solvents, particularly because they have very low vapour pressures under ambient conditions.
- Second, that they might provide improved reactivity in a number of chemical processes.
- Third, the fact that a wide range of cations and anions can be employed give chemists the potential to design the solvent to have specific properties.

Planning has been made to compare % yield, reaction time, reaction rate and half-life of the reaction with conventional solvents and green solvents. Though ionic liquids may or may not increase the rate of reaction of the proposed scheme, plan has been designed to make only one ionic liquid for the experimental purpose. Preparation of ionic liquid has been given below.

Preparation of ionic liquid[8-11]

Preparation of room temperature ionic liquid is simple acid-base neutralization reaction. It can be purified by their solubility profile. Here the reaction between triethylamine and dimethyl sulfate was carried out to make ionic liquid named triethyl methyl ammonium methyl sulphate. The name was given according to nomenclature rule given by Welton T. *et al.*[12]

Procedure: Triethylamine and dimethyl sulphate in 1:1 ratio has been dissolved in ether separately and mixed drop wise in ice bath. The formed ionic liquid doesn't soluble in ether because it is hydrophilic in nature so it can be easily separated from ether and also purified by ether wash. Prepared ionic liquid can be used in pure form as well as after dilution with water as per requirement. Structure of prepared ionic liquid is given below:



Triethyl methyl ammonium methyl sulphate

Kinetic Research[13-15]

Rate, order and half-life

The underlying principle on which all of the science of kinetics is built is the law of mass action. This states that the rate of a chemical reaction (i.e. the speed of the reaction or, simply, how fast it is) is proportional to the active masses of the reacting substances. Active mass is a complicated term to measure, but, fortunately, if the solutions in question are dilute,

the active mass may be replaced by concentration, which is much easier to handle.

The rate of a chemical reaction is, in a dilute solution, proportional to the concentrations of the various reactants each raised to the power of the number of moles of the reactant in the balanced chemical equation. This sounds too easy, and in fact it is. In practice, the rate of a chemical reaction depends only on a small number of concentration terms, and the sum of the powers to which these concentrations are raised is termed the order of the reaction. This is because chemical reactions occur in a number of steps, or stages (called a mechanism) and the rate of the overall reaction is often governed by the rate of the slowest step (called, not surprisingly, the rate determining step). Even if every other stage of a chemical reaction occurs essentially instantaneously, the rate of the reaction as a whole cannot exceed that of the slowest stage.

To further complicate matters, the order of a chemical reaction cannot be predicted from the chemical equation, even if it has been balanced. The order of a reaction is determined experimentally from accurate measurements of the rate under different conditions. It is possible for reactions to be third order, zero order (often found in solid-state reactions such as the release of drug from pharmaceutical suspensions) or even of a fractional order.

Order can be measure simply form the graph as below,
Zero order: [concentration] versus time will be a straight line
First order: ln [concentration] versus time will be a straight line
Second order: 1/[concentration] versus time will be a straight line
The half-life is defined as the time taken for the concentration of reactant to fall to half its original value.

Procedure

- *p*-anisidine and (4-chlorophenyl) (4-ethylpiperazine-1-yl)methanone were taken as per calculated weight separately in methanol/1-butanol/ionic liquid (triethyl methyl ammonium methyl sulphate) and mixed in a manner that final mixture contained 10µg/ml *p*-anisidine and 20µg/ml (4-chlorophenyl) (4- ethylpiperazine-1-yl)methanone.
- Final mixture was made in different volumetric flasks to maintain consistency in study reaction was heated on water-bath at 60º.
- Meanwhile absorbance of *p*-anisidine was measured at λmax 297 in UV-Visible

spectrophotometer at time interval of every five minute until absorbance remains near to steady.

- Same procedure was followed for all solvents.
- After measuring absorbance concentration of *p*-anisidine, order of reaction, rate of reaction and half-life of reaction was measured as below.

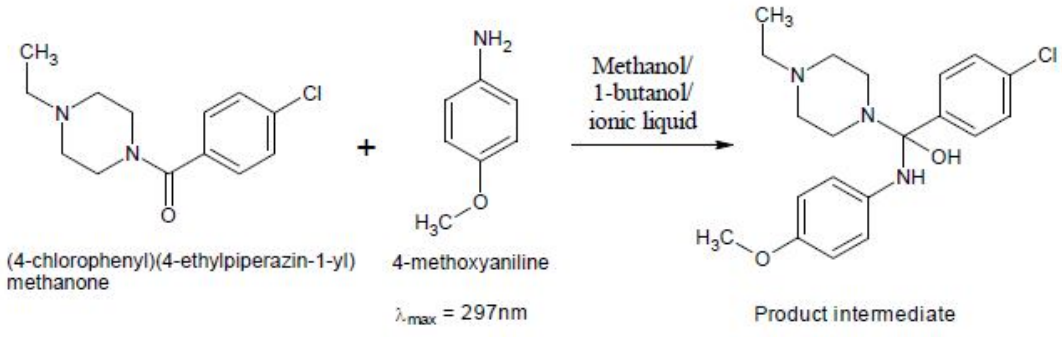


Figure-3: Reaction to be examined in kinetic study

Calculation

Kinetic study of above reaction was performed in triplicate in all three solvents named methanol, 1-butanol and ionic liquid and data were collected. Order of reaction, rate of reaction and half-life of the reaction were calculated after examine all the calculation and graph as stated below.

For methanol as a solvent

Absorbance of amine (*p*-anisidine) was measured in three set and average was taken. All data has been given in table below:

Table-2: Absorbance of amine during reaction in methanol

Time (sec)	Absorbance at 297 nm			Average
	Set-1	Set-2	Set-3	
0	0.5	0.5	0.5	0.5
300	0.3	0.31	0.306	0.305333
600	0.183	0.18	0.185	0.182667
900	0.105	0.107	0.106	0.106
1200	0.079	0.08	0.079	0.079333
1500	0.071	0.073	0.074	0.072667
1800	0.063	0.061	0.06	0.061333

After taking average of absorbance of all three sets calculation of concentration of amine was done as stated below and after it ln concentration and 1/concentration was calculated and graph of time vs. concentration and time vs. 1/concentration was plotted.

Calculation: A = abc

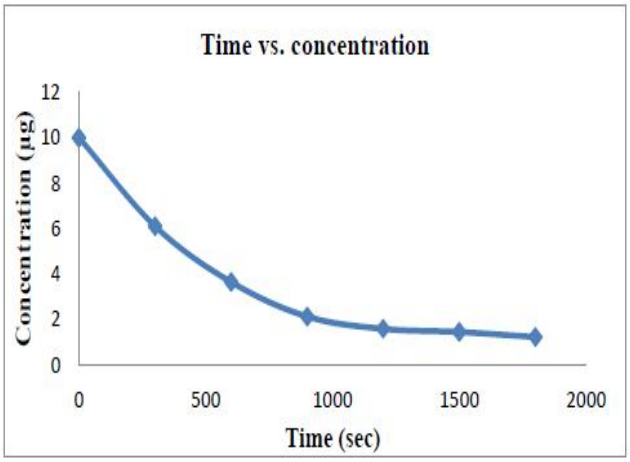
Where, A = absorbance

a = absorptivity 500 gm/100ml; b = cuvette width 1 cm; c = concentration of amine (*p*-anisidine)

$$\text{So,} \quad c = \frac{A}{ab} = \frac{0.305}{500 \times 1} = 6.1 \mu g/ml$$

Table-3: Kinetic research data of amine during reaction in methanol

Time (sec)	Average absorbance	Concentration (µg)	ln concentration	1/concentration
0	0.5	10	2.302585	0.1
300	0.305	6.1	1.808289	0.163934
600	0.182	3.64	1.291984	0.274725
900	0.106	2.12	0.751416	0.471698
1200	0.079	1.58	0.457425	0.632911
1500	0.072	1.44	0.364643	0.694444
1800	0.061	1.22	0.198851	0.819672



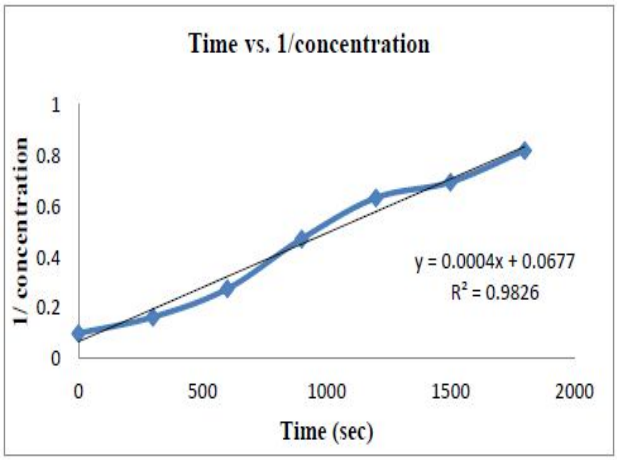


Figure-4 **Figure-5**

Figure-4: Graph of time vs. concentration of amine in methanol

Figure-5: Graph of time vs. 1/concentration of amine in methanol

Graph of time vs. 1/concentration is liner so reaction follows **second order kinetics.**

Rate of reaction is derived from slop that is **k=0.0004 $\mu g^{-1}sec^{-1}$**

Calculation of $t_{1/2}$

$$t_{1/2} = \frac{1}{k[c]initial} = \frac{1}{0.0004 \times 10} = 250 \text{ seconds}$$

For 1-butanol as a solvent

Absorbance of amine (*p*-anisidine) was measured in three set and average was taken. All data have been given in table below:

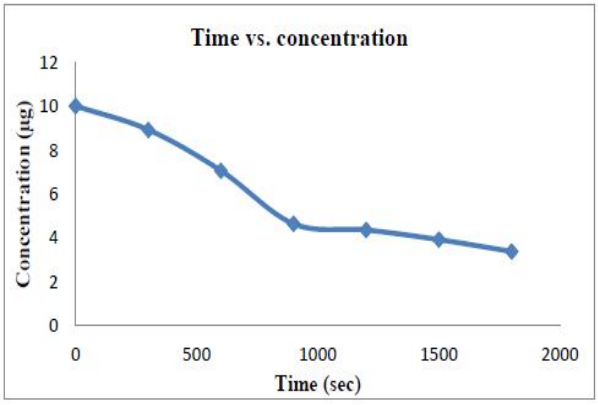
Table-4: Absorbance of amine during reaction in 1-butanol

Time (sec)	Absorbance at 297nm			Average
	Set-1	Set-2	Set-3	
0	0.5	0.5	0.5	0.5
300	0.445	0.444	0.45	0.446333
600	0.36	0.35	0.35	0.353333
900	0.231	0.235	0.231	0.232333
1200	0.22	0.215	0.22	0.218333
1500	0.195	0.198	0.196	0.196333
1800	0.17	0.168	0.17	0.169333

After taking average of absorbance of all three sets calculation of concentration of amine was done by equation A= abc as described above and after it ln concentration and 1/concentration was calculated and graph of time vs. concentration and time vs. 1/concentration was plotted.

Table-5: Kinetic research data of amine during reaction in 1-butanol

Time (sec)	Average absorbance	Concentration (µg)	ln concentration	1/concentration
0	0.5	10	2.302585	0.1
300	0.446	8.92	2.188296	0.112108
600	0.353	7.06	1.954445	0.141643
900	0.232	4.64	1.534714	0.215517
1200	0.218	4.36	1.472472	0.229358
1500	0.196	3.92	1.366092	0.255102
1800	0.169	3.38	1.217876	0.295858



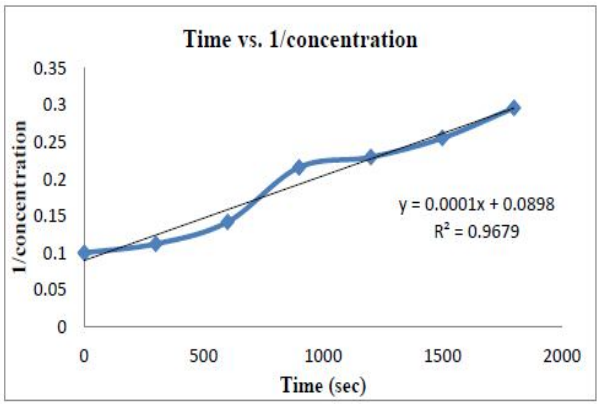


Figure-6 **Figure-7**

Figure-6: Graph of time vs. concentration of amine in 1-butanol

Figure-7: Graph of time vs. 1/concentration of amine in 1-butanol

Graph of time vs. 1/concentration is liner so reaction follows **second order kinetics.**

Rate of reaction is derived from slop that is **k=0.0001 $\mu g^{-1}sec^{-1}$**

Calculation of $t_{1/2}$

$$t_{1/2} = \frac{1}{k[c]initial} = \frac{1}{0.0001 \times 10} = 1000 \text{ seconds}$$

For ionic liquid as a solvent

Reaction in ionic liquid was so fast so it was performed in cuvette and after **20 seconds** the absorbance of amine was observed 0.018 in 100µg/ml concentration. So, remaining concentration of amine was observed 0.3µg/ml.

Calculation: A = abc

Where, A = absorbance

a = absorptivity 500 gm/100ml; b = cuvette width 1 cm; c = concentration of amine (*p*-anisidine)

$$\text{So,} \quad c = \frac{A}{ab} = \frac{0.018}{500 \times 1} = 0.3 \mu g/ml$$

Result of comparison of percentage yield in different solvents

Table-6: Comparison of percentage yield in different solvents

Compound Code	% yield (%w/w)		
	Methanol	1-Butanol	Ionic liquid*
J-11	87.4	66.0	99.7
J-12	86.2	62.6	99.6
J-13	88.2	66.2	99.7
J-14	87.8	65.4	99.7
J-21	88.2	65.6	99.7

J-22	87.2	64.6	99.6
J-23	88.4	66.0	99.6
J-24	88.0	65.6	99.7
J-31	88.0	66.0	99.7
J-32	86.6	65.0	99.6
J-33	88.4	66.4	99.7
J-34	87.8	66.4	99.7
J-41	86.8	64.0	99.6
J-42	85.8	63.0	99.6
J-43	87.2	64.4	99.6
J-44	87.2	64.0	99.5

*Triethyl methyl ammonium methyl sulphate

Calculation of % yield of all the compounds was done by examined the absorbance of remaining concentration of different amines at their respective λ_{max}, for *p*-anisidine it is: 297 nm, for *p*-toluidine it is: 239.50 nm, for sulphanilamide it is: 264 nm and for p-chloroaniline it is: 245 nm.

Result of kinetic study

- Order of reaction overall: **Second order**
- Rate of reaction in Methanol **k = 0.0004 $\mu g^{-1}sec^{-1}$** and **$t_{1/2}$ = 250 seconds**
- Rate of reaction in 1-butanol **k = 0.0001 $\mu g^{-1}sec^{-1}$** and **$t_{1/2}$ = 1000 seconds**
- Overall reaction time in ionic liquid is **20 seconds**

Discussion for % yield and kinetic study

Synthesis of novel *N*-substituted piperazine was carried out in three different solvents named methanol, 1-butanol and ionic liquid to compare % yield, rate of reaction and half-life of reaction. % yield of synthesised compounds in Methanol was found between 86.2 to 88.4%, in 1-butanol it was found between 62.6 to 66.4% and in ionic liquid it was found between 99.5 to 99.7%. So, % yield in ionic liquid was found higher compare to methanol and very higher compare to 1-butanol.

Kinetic study was also performed to find exact impact of solvents on the reaction rate. Methanol is common solvent for above reaction and it has some environmental issues due to low boiling point so against it 1-butanol was selected as per guideline of Pfizer and GSK's solvent guideline and ionic liquid was also selected as an environmentally benign solvent.

Kinetic study was performed in triplicate and results were noted down. In that graph of time vs. 1/concentration was found liner, so reaction follows second order kinetic. Rate of

reaction was found 0.0004 $\mu g^{-1}sec^{-1}$ in methanol and half-life of reaction was found 250 seconds in methanol. In 1-butanol rate of reaction was found 0.0001 $\mu g^{-1}sec^{-1}$ and half-life was found 1000 seconds while in ionic liquid overall reaction time was found 20 seconds. So, reaction seems too fast in ionic liquid. Solvent effect can easily expressed by Hughes Ingold rules for solvent effects.[16] The Hughes-Ingold rules, which describe the effect of solvents on reaction rates, are essentially qualitative and rely on a rather vague, generalized idea of solvent polarity. The rule states that increasing magnitude of charge increase solvation and an increase in solvent polarity accelerates the rates of reactions where a charge is developed in the activated complex from neutral or slightly charged reactant. As the intermediate of synthesised compound has intermediate with charge, polarity can help to increase reaction rate. Methanol is more polar than 1-butanol so rate of reaction and half-life of reaction is more than 1-butanol. Ionic liquid is much polar than methanol and 1-butanol so reaction was finished in only 20 seconds. Mechanism behind it is explained below:

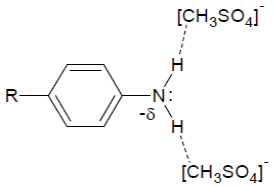


Figure-8: *H*-bond formation between anion of ionic liquid and protons of amines

Anion of ionic liquid forms *H*-bonding with protons of different amines and helps to increase partial negative charge on nitrogen. So, it can be more neucleophilic than in other solvents. Here used ionic liquid is triethyl methyl ammonium methyl sulphate. So, anion is methyl sulphate that made *H*-bond with protons. So reaction rate in ionic liquid was noticed so fast than other used solvents. Another reason that favours above results is the stability of ammonium ion of reaction intermediate. Graphical description is given below:

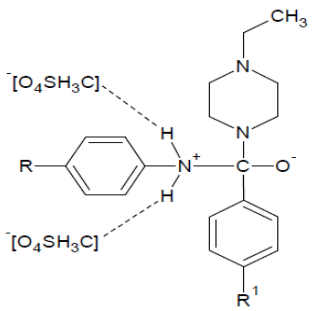


Figure-9: Reaction intermediate of final compound

Ammonium ion is stable so reaction moves towards reaction intermediate and thus % yield is higher in ionic liquid than Methanol and 1-butanol.

CONCLUSION

After performing all relevant experiments it has been concluded that the reaction in ionic liquid is so fast than conventional solvents and % yield is also very high. So it can be said that reaction is more eco-friendly and more acceptable in this environmental benign solvent.

ACKNOWLEDGEMENT

All India GPAT scholar Mr. Viraj P. Jatakiya did his M.Pharm. project (2011-2013) on *Synthesis of N-substituted piperazine derivatives by higher greener solvents and it's antimalarial activity* under the guidance of Prof. Dr. Dhrubo Jyoti Sen and part of his project is *Comparison of yield percentage by 2nd order reaction kinetics in synthesis of piperazine moieties by green solvents and ionic liquid*. This work has been co-assisted by another all India GPAT scholar Mr. Nadim M. R. Chhipa who is currently doing M.Pharm. project (2012-2014) on *Synthesis and anti-HIV activity of chicoric acid analogues* under the same guide in the department of Pharmaceutical Chemistry of Shri Sarvajanik Pharmacy College, Mehsana. Both of these two M.Pharm. projects have been fully funded by RSC Research Grant of United Kingdom. The Royal Society of Chemistry, Great Britain has awarded £2000 to Prof. Sen as RSC Fund in 2009.

REFERENCES

1. 1. A study by Pfizer Global Research and Development: Alfonsi K, Colberg J, Dunn PJ, Fevig T, Jennings S, Johnson TA, Kleine HP, Knight C, Nagy MA, Perry DA and Stefaniak M, "Green chemistry tools to influence a medicinalchemistry and research chemistry based organisation." *Green Chem.***2008**, *10*, 31-36.

2. Henderson RK, Curzones AD, "Expanding GSK's solvent selection guide- embedding sustainability into solvent selection at starting at medicinal chemistry."*Green chem.***2011**, *13*, 854.

3. Crowhurst L, "Manipulating Solute Nucleophilicity with Room TemperatureIonic Liquids."*J. Am. Chem. Soc.***2004**, *126*, 11549-11555.

4. Skrzypczak and Neta A, "Ionic liquid and its industrial application."*P. Int. J. Chem. Kinet.***2004**, *36*, 253-258.

5. Arthur I. Vogel, Practical Organic Chemistry, 3rd Edn. Longman's publication, London, 1964, pp.797-799.

6. Arthur I. Vogel, Practical Organic Chemistry, 3rd Edn. Longman's publication, London, 1964, pp.653-657.

7. Taggi AE, Hafez AM andWack H, "Compare of three ways of synthesis of simple Schiff base."*J. Am. Chem. Soc.***2002**, *124*, 6626.

8. CaiboYue, "Synthesis and application of task-specific ionic liquids used as catalysts and/or solvents in organic unit reactions."*Journal of Molecular Liquids*, **2011**, *163*, 99–121.

9. Varma RS and Namboodiri VV, "Solvent-free preparation of ionic liquids using a household microwave oven."*Pure Appl. Chem.***2001**, *73(8)*, 1309–1313.

10. Aslanov LA, "Ionic liquids: Liquid structure."*Journal of Molecular Liquids*, **2011**, *162*, 101-104.

11. Krossing I, "General Synthesis of Ionic Liquids."*J. Am. Chem. Soc.***2006**, *128*, 13427.

12. Welton T, "Mixtures of ionic liquids."*Chem. Soc. Rev.***2012**, *41*, 7780–7802.

13. Pardue HL, "Kinetic Aspects of Analytical Chemistry."*Anal. Chim. Acta.***1989**, *216*, 69–107.

14. Modern Chemical Techniques, "Ultraviolet/visible spectroscopy," The Royal Society of Chemistry, Unilever production, 2008,pp 92-115.

15. Clyde RM, Physical Chemistry, 1st Edn. McGraw Hill Publishing Company, New York, 1990, pp 345-378.

16. Hughes ED and Ingold CK, "solvent effect on reactions." J. Chem. Soc. **1935**, 244-255.