International Journal of Analytical, Experimental and Finite Element Analysis (IJAEFEA), Issue. 3, Vol. 3, Dec 2016.
e-ISSN: 2394-5141, p-ISSN: 2394-5133, pp 46-51

Indium Chloride catalyzed [2+2] Cycloaddition reactions in an environmentally benign solvent system

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ABSTRACT – Chemist have been painstakingly searching for an ideal solvent for organic reactions that possesses the following criteria : good Chemical & thermal stabilities ,low vapor pressure , low toxicity, high fluidity, wide liquid range, good solubility for a wide range of organic and inorganic reagents and ready recyclability. Indium Chloride catalyzes efficiently the cycladdition reactions of aryl imines with vinyl ether under mild reaction conditions to afford corresponding Azetidine in high yields with diastereoselectivity. Cycloaddition reaction is one of the most powerful synthetic routes for constructing nitrogen containing four membered heterocycles. Azetidine derivatives are an important class of compounds in the field of pharmaceuticals and exhibit a wide spectrum of biological activity including psychotropic,antiallergic,anti-inflammatory and estrogenic activity. Generally Lewis Acids [$InCl_3$,$Zn(BF_4)_2$,$LiBF_4$] are known to catalyze the cycloaddition reactions to produce Azetidine derivatives.It has contemplated exploring& utility of $InCl_3$ as Lewis acid catalyst in presence of environmentally benign solvent systemto afford a new motifs whichhave potency as biologically active agents.

Keywords- Lewis Acid catalyst-$InCl_3$,Green solvent ,[2+2] cycloaddition Reactions.

I.INTRODUCTION

Recently Organic cycloadditionfinding a very interesting and important chemical reaction due to its role in organic synthesis as well as from academic considerations.[1]It gives cyclic products without the formation of any side products i.e. without the loss of atoms and requires nothing other than light or heat for initiation. Cycloaddition reactions are stereo specific and regiospecific in nature and are obviously very important for the preparation of specific heterocyclic compounds. The cyclic compounds containing hetero-atoms are called heterocyclic compounds. They are very important for biological and industrial use. In modern organic synthesis, cycloaddition reactions are important tools allowing the generation of at least two new bonds in one cyclic single step.Additionally, these transformations provide the assembly of complex molecular structures in an easy fashion, with high atom economy and consequently minimization of waste production.[2]The [2+2] cycloaddition reaction obtains its significance in organic synthesis from its ability to create two carbon-carbon bonds with concomitant installation of up to four new stereogenic centres.[3] This potentially highly useful synthetic reaction can be promoted photochemically, mediated by Lewis acids, or catalyzed by transition metals.Azetidine derivatives are reported to show a variety of antimicrobial[4-6],antitubercular[7], anticonvulsant[8]and anti-inflammatory activities[9].Four member saturated nitrogen containing hetero-cycles, azetidines , are important agrochemical and pharmacological motifs.[10]Certain azetidine analogues of nucleosides and nucleoside phosphorylase inhibitors, the use of these compounds as pharmaceuticals, pharmaceutical compositions.[11]Generally, Lewis acids are known to catalyze thecycloaddition reactions to produce 4-6 member heterocyclic derivatives.Metal Triflates[12,13]are also found to be effective Lewis acid in promoting cycloaddition Reaction. However there are no reports on the synthesis of Azetidine from imines(generated from Aryl Amines & aryl aldehydes) with ethyl vinyl ether.

Indium metal has drawn significant importance due to its miscellaneous physical properties. Unlike most other metals, indium is non-toxic, stable to air and moisture which helps in the recovery and recycling of the catalyst .[14]The lower first ionization potential of this metal makes it ideal to participate in Single electron transfer (SET) reactions.[15]Itis an ideal catalyst or reagent for the C-C bond formation. Indiumtrichloride has evolved as a mild and water tolerant Lewis acid imparting high regiochemo and diastereos electivity in various organic reactions . They can be easily used in both aqueous and non aqueous medium and can be recovered from aqueous layer on work-up and recycled for use in subsequent reactions. Furthermore, they are highly efficient to activate nitrogen-containing compounds such as imines and hydrazones etc. [16,17] The utilization of Indium salts has been significantly expanded due to their characteristic properties as they easily provide carbon nucleophiles by transmetallation and can be used in water.

Solvents have a characteristic part of the environmental performance of processes in chemical industry and also impact on cost, safety and health issues.

The idea of "green" solvents expresses the target to minimize the environmental impact resulting from the use of solvents in chemical production.[18]Among the challenges for researcher include invention and development of novel and simple environmentally non hazardous chemical processes for selective synthesis by identifying alternative reaction conditions and solvents for much improved selectivity, energy conservation and less or nonpoisonous waste generation and essentially safer chemical products. Therefore, to address depletion of natural resources and preservation of ecosystem it is very significant to adopt "greener technologies'' to make chemical agents for well being of human health.

II. EXPERIMENTAL

Melting points were recorded on Buchi R-535 apparatus and are uncorrected .IR spectra were recorded on a Perkin Elmer FT-IR 240-c spectrophotometer using KBr Optics.1H nad^{13}C NMR spectra were recorded on BrukerAvance II 400 NMR spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Q-TOF Micromass (ESI-MS) mass spectrometer operating at 70 eV. CHN analysis was recorded on a Vario EL analyzer.

A. General Procedure for the preparation of Azetidiene using InCl3 catalyst via [2+2] cycloaddition reactions:

A mixture of aryl amine(2.5 mmol), ethyl vinyl ether (2.5 mmol) and InCl3 (15 mol %) in acetonitrile (5ml) was stirred at room temperature for appropriate time (Table 1). After completion of the reaction as indicated by TLC , the reaction mixture was poured in water where there is a formation of product(1a) in a high yield. Filtered it and recrystallized it using ethanol.Purified by column chromatography on silica gel(Merck, 100-200 mesh, using hexane: ethyl acetate 2:8) to afford pure azetidine in 90 % yield (1.18 g). Filtrate containing water was concentrated under reduced pressure to recover the catalyst.

B. Spectral Data: (5a) 2-ethoxy-4-(4-methoxyphenyl)-1-p-tolylazetidine

Solid,M.Pt.=192^{0}C, IR (KBr) :1158, 1250, 1350, 1489, 1617,2861,2891,2965 cm^{-1} ; ^{1}H NMR(DMSO-d6) :δ1.24(t,3H,CH3), 2.17-2.45(dd,2H, CH2), 2.52(s,3H, CH3), 3.73 (q,2H,CH2), 3.32 (s, 3H, OCH3), 4.66 (t,1H, CH), 5.28 (t,1H,CH), 6.46(d,1H,ph,J=12 Hz), 6.78(d,1H,ph,J=3.6Hz);7.14(d,1H,ph,J=6Hz);7.44(d,1H,ph,J=6.8 Hz); ^{13}CNMR (DMSO- d6):δ15.52, 21.8, 37.17, 54.13,55.09,62.90,79.13,112.38, 113.49, 113.98, 114.29, 128.09, 128.62, 129.08,131.26,131.65,136.00, 143.03, 158.44; MS : m/z 297; C,76.55;H,7.66;N,4.66;O,10.44.

C. (5b) 2-ethoxy-4-(3,4,5trimethoxyphenyl)-1-p-tolylazetidine

Solid , M.Pt.=191^{0}C , IR (KBr): 1248-1252, 1350, 1488,1615,2858,2889,2962 cm^{-1};^{1}H NMR (DMSO-d6):δ1.34(t,3H,CH3), 2.17-2.35(dd,2H,CH2), 2.52(s,3H, CH3), 3.73(q,2H,CH2), 3.30 (s,3H. OCH3),3.32(s.3H, OCH3),3.32 (s,3H,OCH3),4.75(t,1H,CH),5.38(t,1H,CH), 6.06 (s,2H,ph),6.33(d,2H, ph, J=20Hz), 7.08 (d,2H, ph,J=6Hz);^{13}C NMR(DMSO-d6) :δ 15.42, 23.08, 37.10, 55.90, 55.94,56.49, 91.49,107.09,113.98, 114.29, 127.78, 131.26, 131.65, 136.00,136.25,148.03,154.89;MS : m/z 357.19;C,70.51; H, 7.44; N, 3.90; O, 17.88.

D. (5c) 2-(4-chlorophenyl)-4-ethoxy-1-p-tolylazetidine: Solid, M.pt. =195.17 ^{0}C,IR (KBr): 775,1160,1356,1487,1620,2863,2890,2966 cm^1;^{1}H NMR (DMSO-d6) :δ1.30(t,3H,CH3), 2.62(s,3H, CH3),2.07-2.12(dd,2H,CH2),3.54(q,2H,CH2),4.65(t,1H,CH),5.24(t, 1H,CH),6.43(d,1H,ph,J=11.84Hz), 6.78(d,1H, ph, J=3.6 Hz), 7.08(d,1H, ph,J=5.68Hz), 7.45(d,1H,ph,J=14.8Hz); ^{13}C NMR(DMSO-d6) :δ 15.25,25.36,36.94,53.21, 60.96, 79.15,112.38,112.91,128.07,129.07,129.15,129.55, 129.96, 131.07,131.96,137.50,146.10 ;MS : m/z 301.12 ; C, 71.60; H, 6.60; Cl, 11.72;N, 4.60; O, 5.20.

E. (5d) 4-(4-ethoxy-1-p-tolylazetidin-2-yl)-N, N-dimethyl -benzenamine

Solid , M.Pt. =214.5 ^{0}C;IR (KBr) : 1158, 1338, 1359, 1491, 1619, 2866, 2888, 2971cm^{-1}; ^{1}H NMR (DMSO-d6):δ 1.44(t,3H,CH3), 2.52(s,3H,CH3),2.07-2.22 (dd,2H, CH2),3.38 (s,3H,CH3), 3.39 (s,3H, CH3), 3.80(q,2H, CH2), 4.70(t,1H,CH),5.25(t,1H,CH), 6.45 (d,1H,ph, J=12Hz),6.75(d,1H,ph,J=3.6Hz),7.10(d,1H,ph,J=6Hz),7. 55(d,1H,ph,J=14.8Hz); ^{13}C NMR (DMSO-d6) :δ 15.52, 22.18, 39.35, 39.98, 40.19, 52.93, 61.98, 92.49, 113.98, 114.29, 128.09, 128.62, 131.66, 149.13 ; M/S : m/z 310.43; C, 77.36; H,8.34; N, 9.04; O, 5.10.

F. (5e) 2-ethoxy-1,4dip-tolylazetidine

Solid; M.Pt.= 176.6 ^{0}C;IR (KBr) :1168, 1356, 1489, 1616,2861,2965,2981cm^{-1}; ^{1}H NMR (DMSO-d6):δ1.32 (t,3H,CH3), 2.62(s,3H,CH3),2.62(s,3H,CH3),2.01-2.12 (dd,2H,CH2),3.73(q,2H,CH2),4.65(t,1H,CH),5.48(t,1H,CH), 6.46(d,1H,ph,J=12Hz), 7.10(d,1H,ph,J=6.04Hz), 7.73(s,4H,ph); ^{13}C NMR (DMSO-d6):δ 15.12, 23.90, 24.08, 38.94,53.13,62.80,93.49,113.93,114.39,128.24, 128.34,128.62, 131.26, 131.65, 136.10, 136.25, 137.45, 148.03; MS: m/z 281.39; C, 81.09; H, 8.22; N, 4.89; O, 5.89.

G. (5f) 2-(4-Chlorophenyl)-4-ethoxy-1-(4-nitrophenyl) azetidine

Solid , M.Pt.= 188 ^{0}C ,IR (KBr) : 777,1156,1353, 1491,1515,1617,2861,2890,2966 cm^{-1};^{1}H NMR (DMSO-d6): δ 1.13(t,3H,CH3), 1.49(t,1H,CH), 2.43-2.78 (dd,2H, CH2), 3.40(q,2H,CH2), 4.77(t,1H,CH), 7.01-7.19(m,4H, Ar-H),^{13}C NMR (DMSO-d6): δ 15.52, 24.31, 25.45, 39.28, 52.69, 60.22, 92.1, 115.10, 122.5, 128.66, 129.52, 131.44, 137.2,138.44,155.69;MS : m/z 332; C, 61.33 ; H, 5.08 ; Cl, 10.55; N, 8.32; O,14.33.

H. (5g) 4-(4-ethoxy-1-(4-nitrophenyl)azetidin-2yl)-N,N-dimethylbenzenamine

Solid, M.Pt.= 190.7 ^{0}C,IR (KBr) :1340, 1355, 1486, 1533, 1621,2871,2899,2961cm^{-1};^{1}H NMR (DMSO-d6) : δ1.07(t,3H,CH3), 1.44(t,1H,CH), 2.44-2.68(dd,2H,CH2),

2.81 (s,3H,CH3), 2.81 (s,3H, CH3), 3.40(q,2H,CH2), 4.77(t,1H,CH),6.50-6.91(m,4H,Ar-H),6.82-7.99(m,4H, Ar-H);^{13}C NMR (DMSO-d6): δ 15.45, 24.23, 25.45, 39.23,52.57,60.23,92.1,114.08,115.18,121.6,129.01,130. 1,137.89,146.88,155.67 ; M/S:m/z 341; C, 66.81 ; H,6.78; N, 12.23; O,14.02.

I. (5h) 4-(4-ethoxy-1-(4-fluorophenyl)azetidin-2-yl)-N,N-dimethylbenzenamine

Solid,M.Pt.= 204.3 ^{0}C;IR (KBr):1066,1158,1351,1359, 1492,1614,2866,2891,2965cm^{-1};^{1}H NMR (DMSO-d6) : δ1.12(t,3H,CH3), 1.42(t,1H,CH), 2.48-2.72(dd,2H,CH2), 2.85 (s,3H,CH3), 2.87 (s,3H, CH3), 3.39(q,2H,CH2), 4.77(t,1H,CH),6.52-6.92(m,4H,Ar-H),6.56-6.77(m,4H, Ar-H); ^{13}C NMR (DMSO-d6) : δ 15.35, 24.33, 25.45, 39.23,40.23,52.67,60.2,114.2,115.89,116.42,129.11,130. 01,145.22,146.68,152.34; M/S : m/z 314 ;C, 72.56; H, 7.33; F,6.02 ;N, 8.81; O, 5.10 .

J. (5i)2-ethoxy-1-(4-fluorophenyl)-4 (3, 4, 5 trimethoxy-phenyl) azetidine

Solid,M.Pt.= 233.2 ^{0}C ,IR (KBr) :1070, 1158,1253-1256,1350,1492,1617,2855,2890,2965 cm^{-1};^{1}H NMR (DMSO-d6 :δ1.05(t,3H,CH3), 1.46(t,1H,CH),2.46-2.72 (dd,2H,CH2), 3.71 (s,3H,CH3), 3.70(s,3H,CH3), 3.70 (s,3H,CH3), 3.38(q,2H,CH2),4.76(t,1H,CH),6.52-6.78(m, 4H,Ar-H), 6.06(s,2H,Ar-H);^{13}C NMR (DMSO-d6):δ 15.45, 24.28,25.45,39.33,53.28,56.18,56.45,60.28,91.35, 105.45,115.88,116.34,134.78,136.44,145.18,150.56,152. 34; M/S : m/z 361 ; C, 66.44 ; H, 6.61; F, 5.24; N,3.81;O, 17.68 .

K. (5j) 4-(4-ethoxy-1-(4-methoxyphenyl)azetidin-2yl)-N, N-dimethylbenzenamine

Solid, M.Pt.= 228.9 ^{0}C, IR (KBr):1158, 1256, 1350, 1359, 1489,1616,2861,2890, 2965cm^{-1};^{1}H NMR (DMSO-d6): δ1.10(t,3H,CH3), 1.49(t,1H,CH), 2.49-2.75 (dd,2H, CH2), 2.87(s,3H,CH3), 2.88(s,3H,CH3), 3.42 (q,2H, CH2), 3.71 (s,3H,CH3), 4.81(t,1H,CH),6.51-6.90(m,4H, Ar-H);^{13}C NMR (DMSO-d6) : δ 15.51, 24.31, 25.51, 39.23,40.30,52.77,55.89,55.88,114.10,115.22,115.28,129 .18,130.05,141.89,146.78,150.22; M/S: m/z 326 , C, 73.58; H, 8.01 ; N,8.56 ;O,9.78.

III. Results and Discussion

This paper describes a novel & highly efficient method for synthesis of azetidinevia[2+2] cycloaddition reaction using a catalytic amount of Indium trichloride as Lewis acidcatalyst. Thus [2+2] cycloaddition reaction of imines with ethyl vinyl ether in presence of 15mol% InCl3 in acetonitrile was conducted with stirring at room temperature for 4 hrs, afforded corresponding Azetidine(5a) in 90 % yield(Scheme 1).

Similarly, several aryl imines reacted smoothly with ethyl vinyl ether to give corresponding azetidines in 80-90 % yield. The reaction proceeded efficiently in high yields at ambient temperature.

IR spectra of compounds 4(a-j) showed peaks at 1350 cm-1 due to –CN function, strong and sharp absorption bands observed at 2861 to 2965 cm-1 due to –CH starching and bands at 1489 cm-1 for CH2 group suggested formation of four member cyclic ring structure. Bands at 1489-1594 cm-1 suggested the presence of C=C. In addition bands were observed at 1091 cm-1 corresponding to the –O-C2H5 group.

The ^{1}H NMR spectra of compounds 5(a-e) displayed signals at δ 1.34(J=0.8 Hz) as a triplet for CH3 protons, quartet at δ=3.73(J= 2.4Hz) for CH2 protons , downfield triplets shows at δ=4.65(J=2.0Hz) and at δ=5.28 (J=16.8 Hz) observed for –CH protons of azetidine. ^{1}H NMR spectra of compounds revealed double dublet at δ=2.17 having coupling constant J=4.8 Hz for CH2 protons.

In addition, -OCH3 group of compounds5b resonated at singlet at δ=3.32 integrated for three protons, -N-(CH3)2 group of compounds 5d resonated at δ =3.38-3.39. The characteristic proton resonance signal shifted to aromatic region at δ = 6.43-6.78 for azet ring. 1H NMR of 2-ethoxy-4- (diphenyl) -1- p- tolylazetidine displayed signals at δ =7.08-7.73(m,8H,Ph)

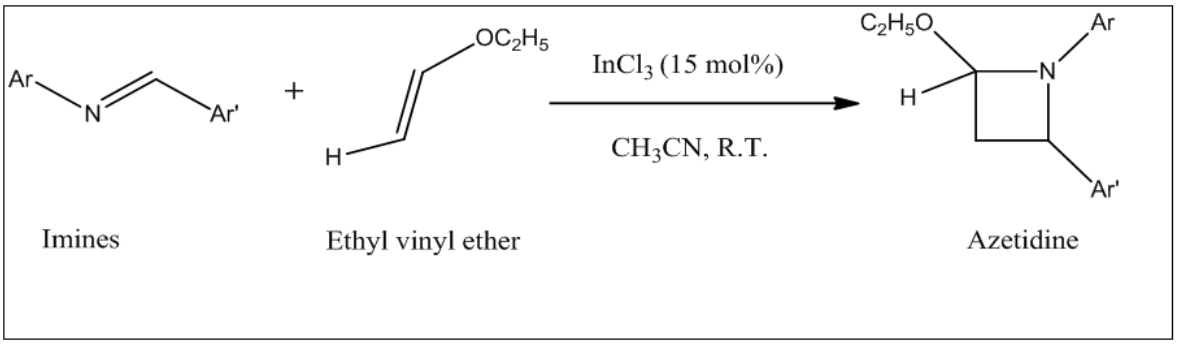
Molecular ion peak appears at 191.42with further fragments at 188.11,145.09,107.41,76.03

The characteristic ^{13}C NMR peaks obtained at 107 to 158.44 for aromatic region, 54.13,79.15 for CH^{+}gp. ,37.17,62.90for CH2^{+} group.and15.52 for CH3^{+} gp.^{13}C NMR peaks at values 79.15 , 54.13 ,37.17 indicate for azetidinegp. In addition, ^{13}C NMR peaks shows at 55.09 - 55.94 for –OCH3 group of compounds 5b and 39.98, 40.19 for –N-(CH3)2 group of compounds 5d.

InCl3 which have several advantages for this transformation which include mild reaction conditions, improved yields, enhanced selectivity, simplicity in operation and work-up conditions. This method does not require anhydrous solvents or stringent reaction conditions whilst no specific precautions need to be taken to entrap moisture from the reaction medium. The solvent acetonitrile appears to be the superior affording best yields. Acetonirile does notrequire any hazardous reaction conditions, It can work at Room temperature by stirring method, here no or less energy required to proceed reactions.

A. Catalyst Optimization

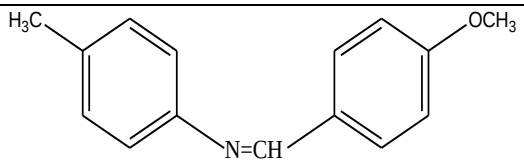
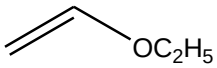
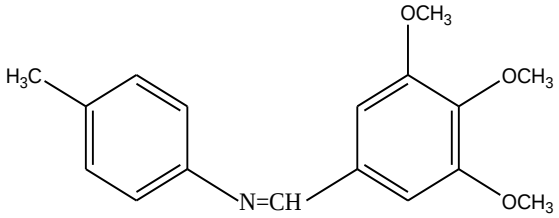
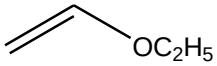
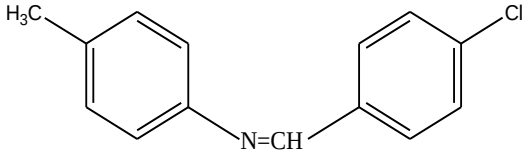
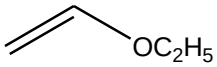
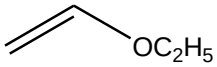
As a part of regular approach of fine tuning the amount of catalyst and reaction conditions optimized the amount of catalyst in the process. Initially 5 mol% (0.05mmol) of catalyst was loaded to the mixture. No color change observed even after 2 hrs. After 2 hrs color changed from orange to Red implying the formation of product. The yield was 60 % obtained after isolation by column Chromatography. Increasing the amount of catalyst up to 15 mol % (0.15mmol) resulted in 90 % yield at 4 hrs. The % conversion with time was co-related with time factor table.



Scheme 1: Indium Chloride Catalyzed [2+2] cycloaddition reaction for the formation of substituted 2- ethoxy-4-(diphenyl)-1-p-tolylazetidine

The scope and generality of this process is illustrated with respect to various substituted imines and ethyl vinyl ether and the results are presented in Table 1.

TABLE I
INCL3 CATALYZED[2+2] CYCLOADDITION REACTION FOR THE SYNTHESIS OF AZETIDINES

Sr. No.	Aryl imines	Ethyl vinyl ether	Product No.	Reaction Time(h)	Yield (%)[a]
1.			5a)	4	90
2.			5b)	4.5	89.5
3.			5c)	4.5	90
4.			5d)	5	89

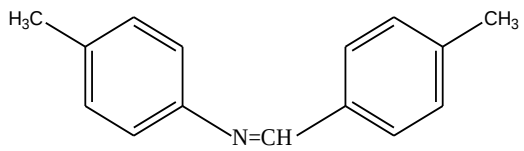
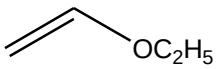
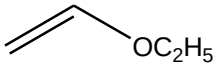
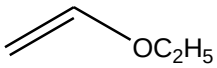
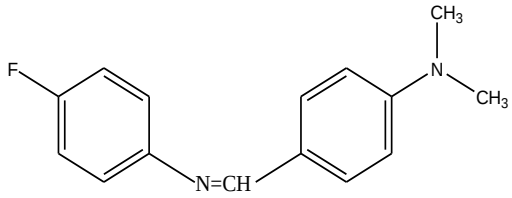
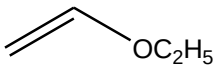
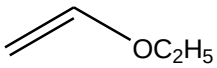
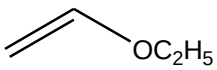
5.			5e)	5	88
6.			5f)	5	89
7.			5g)	5	88
8.			5h)	4	90
9.			5i)	4.5	91
10.			5j)	4.5	92

TABLE II
OPTIMIZED REACTION OF IMINES AND ETHYL VINYL ETHER:

Sr. No.	Catalyst/Solvent system	Temp /^{o}C	Time/ hrs	Yield (%)
1	$ZnBF_4/CH_3CN+H_2O$	R.T.	7	74
2	$ZnBF_4/CH_3CN$	R.T.	6	76
3	$LiBF_4/CH_3CN$	R.T.	8	70
4	$CPMC/H_2O$	R.T.	---	No Reaction
5	$CPMC/CH_3CN+H_2O$	R.T.	---	No reaction
6	$InCl_3/CH_3CN$	R.T.	4	90

TABLE III
PERFORMANCE OF INCL3 CATALYST AT VARIOUS MOLE RATIO

Entry	% Mol of catalyst	Mol Conversion %
1	5	60
2	8	66
3	10	70
4	12	78
5	15	90
6	16	90
7	18	90
8	20	90

IV. CONCLUSION

In summary, the paper describes a novel and highly efficient method for the synthesis of Azetidine derivatives from aryl imines and ethyl vinyl ethers using a highly efficient catalytic amount of indiumtrichloride. The Characteristic features of this procedure are mild reaction conditions, greater selectivity, improved yields, cleaner reaction profiles, enhanced rates and operational simplicity which make it a environmentally prominent and attractive process for the synthesis of four member heterocyclic motif which have a biological importance.

V. ACKNOWLEDGEMENTS

Authors wish to express their deep gratitude toDepartment of Chemistry, Institute of Science, Nagpur , Department of Pharmacy R.T.M. University, Nagpur for FTIR spectral analysis, SAIF Chandigarh for ^{1}H-NMR, ^{13}C ,MASS spectroscopic Analysis.

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