Conventional vs Microwave assisted SiO_2/P_2O_5 catalyzed synthesis of Schiff bases

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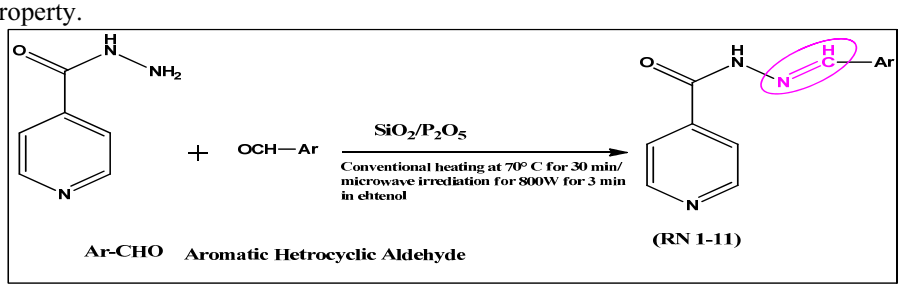
Abstract: Here in this work we have carried out synthesis of isoniazid and their benzaldehyde derivative in the presence of SiO_2/P_2O_5 catalyzed utilizing conventional and microwave assisted protocols. Both these protocols examined comparatively and we found that microwave assisted synthesis is more efficient, eco-friendly and economical method as compared to conventional method. Yield of product is also higher than conventional method. Use of heterogeneous catalyst is also promoting the yield of product and it is very easy to separate from the product by simple filtration and centrifugation. These synthesized compounds are characterized by physical and spectral studies (IR, UV-VIS, NMR spectroscopy) Isoniazid having excellent anti-tubercular activity and due to presence of Isoniazid they may have good antibiotic property.



Keyword: Schiff bases, microwave assisted synthesis, isoniazid, SiO_2/P_2O_5 catalyst, heterogeneous catalyst.

1. Introduction:

Several methods for the synthesis of azomethine group have been described in last few years. There are number of new developed techniques and innovations that has been reported like solvent-free reaction, K-10 clay, microwave irradiation, solid-state synthesis in presence of ionic-liquid and presence of some phase transfer catalyst.[1]In these following techniques, microwave irradiation method with presence of catalyst, mostly used because of its operational simplicity, promote the reaction rates, and reaction route selectivity.[2]Schiff bases are used for the synthesis of wide range synthetic organic products as pigments and dyes, catalysts, and as polymer stabilisers.[3]The tremendous advances in the bio-inorganic chemistry has attracted interest of chemists in complexes of Schiff base, it well

established recognition that many of the complexes based on Schiff base act as models for species that are biologically relevent.[3] Schiff bases exhibits a plethora of activities which are hugely relevant in biological field which prominently includes antifungal, antibacterial, antimalarial, anti-proliferative, anti-inflammatory, antiviral, and antipyretic.[3]Azomethine group of Schiff base is present in wide variety of naturally derived as well as in synthetic compounds.

Its activity against tuberculosis was firstly reported in the late 1940s[4]and as a drug into clinical market in 1952.[4-6] Various Nano emulsion compositions derived from carvone Schiff base based on isoniazid.[7] Isoniazid (CSB-INH) designed and developed utilizing the method of aqueous phase titration in order to explore its anticancer potential for chemoprevention against colon cancer**.** Azetidinone scaffold developed by simple conventional synthesis, that exhibits potent antimicrobial and anti-mycobacterial activity.[8]Schiff bases of isonicotinic hydrazide those have potent tuberculostatic and radical scavenging activities against INH-induced oxidative hepatic damage.[9]Isoniazid derivatives have been synthesized and evaluated for anticonvulsant and anti-mycobacterial activity of standard strain H37Rv.[10]

Microwave irradiation use in organic synthesis has become popular in pharmaceutical and academic areas.[11]Because it is used as a powerful technique to promote a variety of chemical reactions and as a new enabling technology for the development of drugdiscovery.[12-13]Reactions applied in microwave in solvent-free condition are hugely beneficial due to reduced pollution and economical due to its simple handling.[14] Catalysis which employ a catalyst having phase different from its reactant partners and interact with them is termed heterogeneous catalysis. The catalysis action is carried forward when catalyst adsorb reactants on its surface thereby increasing the rate of reaction.[15]Heterogeneous and homogeneous catalysis may offer advantages depending on specific cases. Heterogeneous catalyst specifically are more advantageous easy separation and recoverable can be employed for liquid and gas phase based processes. Heterogeneous catalysis was appreciated firstly in the sector of refining of the petroleum products and in industries producing chemicals at large scale.[16]

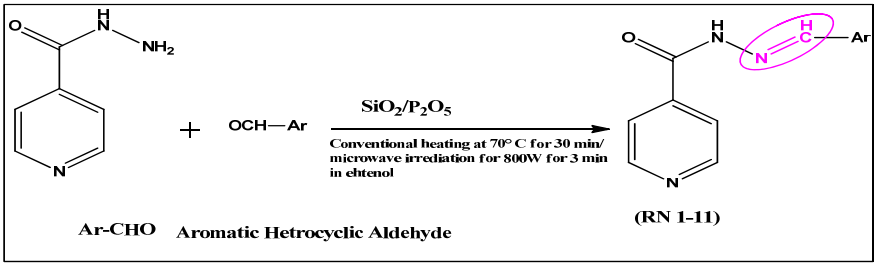
2. Materials and instrumentation

All reagent grade chemicals were purchased from commercially sources. Chromatographic grade silica gel 60 Merck and Isoniazid were purchased from Merck and Sigma-Aldrich. All other analytical grade reagents and solvents by purchased from S.D. chemicals, and Thomas baker Company. Melting points all reported are uncorrected, recorded using in electro thermal melting point apparatus. Thin layer chromatography (TLC) performed by using E-Merck pre coated 60 G254 plates and the spots were rendered visible by observing in UV light. IR spectra recorded utilizing shimadzu FT-IR 8300 Spectrophotometer. 1H NMR and 13C NMR spectra were recorded on Jeol resonance spectrometer in DMSO-*d6* at 300 MHz.

2.1Conventional method: Equimolar mixture of Isoniazid (0.02 mol) and 2,4-dichloro benzaldehyde (0.02 mol) and 0.050g of SiO_2/P_2O_5catalyst thoroughly mixed then reaction mixture transferred to an open Pyrex 100 mL round bottom flask with 25 mL ethanol and refluxed at 70°C .Reaction monitored by using chloroform and methanol (8:2 v/v as eluent) for TLC. After 30 minutes when completion of reaction mixture cooled to room temperature. The reaction mixture was filtered to remove the catalyst and concentrated to furnish product. The resulting mass purified by column chromatography using (chloroform /methanol) as eluant to get product. The obtained purified product was recrystallized from ethanol as white crystal of compound.**RN-1 Yield 70%;m.p. 240-**

242°C. Other compounds RN-18 to RN-27 was prepared similarly by treating **1** with various aromatic aldehydes Characterization data (**RN-1 to RN–11)** are presented.

2.2 Microwave method: Equimolar mixture of reactants with 0.050g of SiO_2/P_2O_5catalyst is prepared in similar manner as described above. This mixture transferred in 5 mL ethanol to an open glass vessel and reaction was performed at 800W power, on microwave irradiation and reaction monitored with the help of TLC in chloroform and methanol (8:2 v/v as eluent). After 2-3minutes when completion of reaction, mixture was cooled to room temperature. The resulting mass purified by column chromatography with (chloroform/methanol) as eluent to get product. This product was recrystallized from ethanol to obtained white crystal of compound **RN-1. Yield 95%, m.p. 240-242°C.**Other compounds RN-2 to RN-11 were prepared similarly by treating **1** with various aromatic aldehydes. Characterization data of the compounds (**RN-1to RN–11)** were found to similar as reported for conventional method and are given.



Scheme-1. Synthesis of RN-1 to RN-11

3. Characterization of Schiff bases products (RN-1 to RN-11)

***N′*-(2,4-Dichlorobenzylidene)-isonicotinohydrazide (RN-1):** The product was obtained as a white crystal, Molecular formula; $C_{13}H_9C_{l2}N_3O$, mp. 240-242° C; **IR υmax (cm^{-1})** : 3195 (NH), 3026 (C-H), 1665 (C=O), 3048,1598 (C=N), 1612 (C=N str., Schiff base), 1087 (C-Cl). **^{1}H NMR** δppm: 8.65 (d, 2H), 11.8 (s, 1H, N-H), 7.80 (d, 2H,), 8.90 (s, 1H of N=CH), 7.51 (d, 1H of aromatic ring), 7.95 (d, 1H, aromatic).**13C NMR**(CDCl3, 100 MHz): 127.3- 132.4 (C of aromatic ring), 139.2 (N=CH, azomethine),162.5 (C of amide C=O), 121.3-147.8 (C of pyridine ring) in the δppm ranges.

***N′*-(3-Bromobenzylidene)-isonicotinohydrazide (RN-12):** The product was obtained as white-brownish crystals, Molecular Formula $C_{13}H_{10}BrN_3O$.mp 248-250°C. IR, υmax (cm^{-1}): 3188 (N-H), 3009 (C-H), 1668 (C=O), 3046, 1618 (C=N str.), 1596 (C=N). ^{1}H NMR (300 MHz) δppm: 8.80 (d, H), 10.66 (s, H, N-H), 7.80 (d, H), 8.40 (s, 1H of N=CH), 7.55-7.54 (d, 1H, aromatic), 7.70-7.71 (d, 1H, aromatic), 7.32-7.31 (d, 1H). 13C NMR ($CDCl_3$, 100 MHz): 123.2- 135.7 (C), 145.2(N=CH, azomethine), 161. 5 (C of amide C=O), 121.6 -148.8 (C of pyridine ring) in theδppm ranges.

***N′*-(4-Bromobenzylidene) isonicotinohydrazide (RN-3):**The product was obtained as pinkish white crystals, Molecular Formula $C_{13}H_{10}BrN_3O$.mp 246-252°C; IR υmax (cm^{-1}) : 3187 (N-H), 3017 (C-H), 1662 (C=O),3043, 1615 (C=N str.), 1594 (C=N). ^{1}H NMR (300 MHz) δppm: 8.81-8.77 (m, H, of pyridine), 7.85-7.83 (m for H of pyridine), 10.82 (s, H,NH), 7.24 (s, 1H of N=CH), 7.64 (m for H of aromatic), 7.66 (m for 2H ofaromatic). ($CDCl_3$, 100 MHz): 125.2- 132.7 (C of aromatic ring),

147.8(N=CH, azomethine), 161. 2 (C of amide C=O), 121.7 -149.8 (C of pyridine ring) in theδppm ranges.

***N′*-(3-Methylbenzylidene)-isonicotinohydrazide (RN-4):** The product was obtained as brown-white crystals, Molecular Formula $C_{14}H_{13}N_3O$. m.p. 210°C; IR υmax (cm^{-1}) : 3192 (N-H), 3029 (C-H), 1667 (amide C=O), 3044,1612 (C=N str.), 1598 (imine C=N). ^{1}H NMR (300 MHz) δppm: 8.77-8.76 (m, 2H, of pyridine), 7.82-7.80 (m, H), 11.82 (s, 1H,N-H), 8.41 (s, 1H of N=CH), 7.74 (d for 1H of aromatic), 7.66 (m for 2H of aromatic),2.40 (s for 3H of CH3), 7.42-7.25 (d for 2H of aromatic).**13C NMR** (CDCl3, 100 MHz):127.2- 138.7 (C of aromatic ring), 146.8 (N=CH, azomethine), 163. 21(C of amideC=O), 22.3 (C of methyl carbon), 121.7 -149.8 (C of pyridine ring) in the δppm ranges.

***N′*-(4-Methylbenzylidene)-isonicotinohydrazide (RN-5):** The product was obtained as light orange shiny crystals, Molecular Formula $C_{14}H_{13}N_3O$.m.p. 212-214°C; IR υmax (cm^{-1}) : 3194 (N-H), 3028 (C-H), 1667 (amide C=O), 1608(C=N str., Schiff base), 3044, 1592 (imine C=N). ^{1}H NMR (300 MHz) δppm: 8.77-8.76 (m, 2H, of pyridine), 7.82-7.80 (m for 2H of pyridine), 11.62 (s, 1H,NH), 7.55 (s, 1H of N=CH), 7.74 (d for 1H of aromatic), 7.76 (d for 1H of aromatic),2.41 (s for 3H of CH3), 7.23-7.25 (m for 2H of aromatic).^{13}C NMR (CDCl3, 100 MHz):128.2- 126.6(C of aromatic ring), 146.8 (N=CH, azomethine), 163. 0 (C of amide C=O),21.6 (C of methyl carbon), 121.7 -149.8 (C of pyridine ring) in the δppm ranges.

***N′*-(2-Methoxybenzylidene)-isonicotinohydrazide (RN-6):** The product was obtained as light pink crystals, Molecular Formula $C_{14}H_{13}N_3O_2$.m.p.192°-194°C; IR υmax (cm^{-1}) : 3214 (N-H), 3055 (C-H), 1602 (C=N str.), 1662 (C=O), 1612 (C=N). ^{1}H NMR (300 MHz) δppm:8.78-8.76 (m, H), 7.83-7.81 (m, H), 11.65 (s, 1H, NH), 8.65(s, H of N=CH), 7.84 (d for 1H of aromatic), 7.46 (d for 1H ofaromatic), 3.78 (s for3H of OCH3), 7.26 (d for 1H of aromatic), 7.15-7.14 (m for 2H of aromatic).^{13}CNMR (CDCl3, 100 MHz): 111.6- 133.7 (C of aromatic ring), 146.2 (N=CH, azomethine), 163. 5 (C of amide C=O), 54.6 (C of methoxy carbon), 121.5 -149.6 (C ofpyridine ring) in the δppm ranges.

***N′*-(4-Methoxybenzylidene)- isonicotinohydrazide (RN-7):**The product was obtained as light yellow crystals, Molecular Formula $C_{14}H_{13}N_3O_2$.m.p.196-198°C. IR υmax (cm^{-1}) : 3216 (N-H), 3051 (C-H), 1610 (C=N str.), 1664 (C=O), 1608 (C=N). ^{1}H NMR (300 MHz) δppm:8.78-8.76 (m, 2H, of pyridine), 7.82-7.81 (m, H), 11.62 (s, H), 7.65(s, H), 7.83 (d, H), 7.06 (m for 1H of aromatic), 3.82 (s for3H of OCH3).^{13}C NMR ($CDCl_3$, 100 MHz): 114.6- 130.3 (C of aromatic ring), 146.6(N=CH, azomethine), 163. 2 (C of amide C=O), 55.6 (C of methoxy carbon), 121.4 -149.7 (C of pyridine ring) in the δppm ranges.

***N′*-(3-Methoxybenzylidene)-isonicotinohydrazide (RN-8):**The product was obtained as light red crystals, Molecular Formula $C_{14}H_{13}N_3O_2$. m.p. 198°C. IR υmax (cm^{-1}): 3218 (N-H), 3052(C-H), 1615 (C=N str.),1662 (C=O), 1604 (C=N). ^{1}H NMR (300 MHz) δppm: 8.78 (d,1H, of pyridine), 7.81 (d, H), 11.67 (s, H), 8.45 (s, 1H of N=CH),7.43-7.42 (m for 1H of aromatic), 7.04 (m for 1H of aromatic), 3.76 (s for 3H ofOCH3).^{13}C NMR ($CDCl_3$, 100 MHz): 111.6- 160.5 (C of aromatic ring), 146.7 (N=CH,azomethine), 163.1 (C of amide C=O), 55.4 (C of methoxy carbon), 121.6 -149.5 (C of pyridine ring) in the δppm ranges.

***N′*-(3,4,5-Trimethoxybenzylidene)-isonicotinohydrazide (RN-9):**The product was obtained as light orange crystals, Molecular Formula $C_{16}H_{17}N_3O_4$. m.p. 218°C. IR υmax (cm^{-1}): 3220 (N-H), 3055(C-H), 1668 (C=O), 1598(C=N str.), 1608 (C=N). ^{1}H NMR (300 MHz) δppm:8.78 (d, H), 7.81 (d, H), 11.65 (s, 1H, N-H), 8.42 (s, 1H),7.20 (s, 2H) 3.81(s, H), 3.70 (s, H).^{13}CNMR (CDCl3, 100 MHz): 111.6- 160.5 (C of aromatic ring), 146.7 (N=CH,azomethine), 163.1 (C of amide C=O), 55.4 (C of methoxy carbon), 121.6 -149.5 (C ofpyridine ring) in the δppm ranges.

***N′*-(Furan-2-yl-methylene)-isonicotinohydrazide] (RN-10):** The product was obtained as brown crystals, Molecular Formula $C_{11}H_9N_3O_2$. m.p. 95-97°C. IR υmax (cm^{-1}): 3272 (N-H), 3051(C-H), 1658 (C=O), 1592 (C=N str.), 1620 (C=N). ^{1}H NMR (300 MHz) δppm: 8.78 (d, H), 7.81 (d, H), 10.75 (s, 1H, NH), 8.32 (s, 1H of N=CH),7.82(m , 1H), 6.61 (m, H), 5.92 (d for 1H of furfuralring).**13C NMR** (CDCl3, 100 MHz): 112.6- 148.1 (C of furfural ring), 136.7 (N=CH,azomethine), 163.1 (C of amide C=O), 121.5 -149.7 (C of pyridine ring) in the δppmranges.

***N*'-(2-Nitrobenzylidene)-isonicotinohydrazide (RN-11):**The product was obtained as light creamy shiny powder, Molecular Formula $C_{13}H_{10}N_4O_3$.m.p. 205°C . IR υmax (cm^{-1}): 3182 (N-H), 3001(C-H), 1608 (C=N str., Schiffbase), 1685 (C=O), 1590 (C=N), 1512 (NO2). ^{1}H NMR (300 MHz)(DMSO-*d6*) δppm: 8.78 (d, 1H, of pyridine), 7.81 (d for 2H of pyridine), 10.72 (s, 1H,N-H), 8.32 (s, 1H) 8.02 (m , 1H of aromatic ring), 7.91(m, 1H), 7.72 (m, H).^{13}C NMR (CDCl3, 100 MHz): 122.6- 145.8 (C ofaromatic ring), 142.7 (N=CH, azomethine), 163.5 (C of amide C=O), 121.1 -149.7 (C ofpyridine ring) in the δppm ranges

4. Proposed mechanism for Schiff Base synthesis

Reaction mechanism that involved in Schiff Base generation is the nucleophilic attack carried out by amino group of isoniazid on the aldehyde which posses electrophilic carbonyl carbon to form an imine. This step being reversible in nature so formation of Schiff base mainly depend on the rate of removal of water. The imines that were reported by Schiff involves carbonyl compound and amine condensation involving azeotropic distillation to remove water. Removal of water was becomes more efficient with the help of molecular sieves. Dehydrating solvents used as an *in situ* dehydration strategy has been able to generate product in moderate yields. Taking all these in consideration, in the present protocol, we make their utilization.

5. Comparative study of yield vs time for conventional vs microwave assisted synthesis. Schiff bases (RN-1 to RN-11) using from heterogeneous Catalyst (SiO_2/P_2O_5): It is interesting to mention that all the reactions under microwave irradiation in case of synthesis of Schiff bases **(RN-1 to RN-11)** presence of heterogeneous **(SiO_2/P_2O_5)** catalyst were completed within approximately 2-3 minutes with excellent yields on the other hand same reaction in conventional heating at reflux takes about 30 minutes approx. gave lower yields as compare to microwave method. The comparative implications of microwave irradiation vs conventional heating for the synthesis of Schiff bases **(RN-1 to RN-11)** have been summed up in Table1.

Table 1. Yield of product via conventionaland microwave irradiation method

Compounds	**Conventional**		**Microwave**	
Code	*Time (min)*	*Yield (%)*	*Time (min)*	*Yield (%)*
RN-1	70	30	2.5	95
RN-2	71	30	3	92
RN-3	76	25	3	94
RN-4	80	30	2	92
RN-5	72	30	2.5	90
RN-6	81	30	2	90
RN-7	70	22	3	95
RN-8	70	20	3	92
RN-9	70	25	3	91
RN-10	79	22	3	95
RN-11	82	30	2.5	92

6.Catalyst recyclability

The reusability of the (SiO_2/P_2O_5) catalyst was examined for Schiff base condensation inethanol solvent. This reaction was performing in between Equimolar Isoniazid andfurfural aldehyde in presence of catalytic amount of catalyst for 3 minutes by microwaveassisted synthesis at 800W or 30 minutes and 70°c from conventional synthesis. After appropriate reaction time product collect as a liquid forms for analysis, and the solid catalyst separated by filtration. The separated SiO_2/P_2O_5 catalyst was investigated for its further usability. For this purpose we performed the condensation of Schiff base using 2 mole of the substrate with optimized reaction conditions. When first cycle of reaction gets completed catalyst filtered out and washed with acetone then after with and then allowed to dry in an oven(100°C) for 12 to 15 hours and used as it is for further reaction for synthesis of Azomethine. The catalyst showed proper efficiency in catalyzing the reaction and delivered excellent yields up to the 4th time use.

7.Chemistry

The formation of imine via heterogeneous catalyst through Schiff base condensation. It was confirmed by 1H NMR, 13C NMR and IRspectra that the Schiff base condensation reaction possibly done using SiO2/P2O5 heterogeneous catalyst in green conditions. After that the cyclization reaction takes placeat azomethine position (N=CH) in high yield. In IR- band at1598 (C=N), 1658 (C=O-NH), 1592-1618 (C=N str., Schiff base). In ^{1}H NMR spectra signals that appear: a singlet at δ 8.40-8.90 correspondsto Schiff base (azomethine), 7.32-7.71 (doublets for Ar-H of benzylidene), 10.66 (s forCONH). A doublet at δ ppm 7.80 corresponds to pyridine ring proton. The structures of compounds (RN-1 to RN-11) were supported by IR spectra are observed in (RN-1 to RN–11) with absence of 1602-1620 cm^{-1} for -N=C- band with presence of 1652-1692 cm^{-1} for ketone group of azetidinone.

8.Conclusions

In case of synthesis assisted by SiO_2/P_2O_5 Lewis acid heterogeneous catalyst due to its high surface area and acid-site it makes reaction more efficient and easily utilized for synthesis under solid state reaction method. This material shows excellent catalytic activity for the formation of Schiff base, in EtOH solvent to give maximum yields of 92-90% (Microwave), 70-80%(conventional) respectively, under microwave-assisted /conventional heating at 800W/70°C . The EtOH used as a green solvent in the reaction, gave highly efficient Schiffbase yield from Isoniazid. Under comparable reaction

conditions, the silica supported phosphorous-pentaoxide (SiO_2/P_2O_5) catalyst with highly acidic site and surface area produced 20% more Schiff base, than the corresponding catalyst with a smaller surface area and lower acidity, which suggests that the surface area and acidity of the catalyst play important roles in the Schiff base synthesis. According to all the above outcomes in conclusion, we report in this experiment a mild and efficient catalyst for the preparation of azomethine via Schiff base condensation from Isoniazid with corresponding aromatic aldehydes in presence of green solvent with excellent reusability of catalyst. That was further converted into substituted 3-chloro-2-oxo-azitidine in good yields with short reaction times. Substituted group positions also affect the synthesis of isoniazid derivatives.

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