

# An Atom Economic Acid Catalyzed Synthetic Method for Aromatic Imines

Shyamal Baruah<sup>1</sup>, Alexander Fisyuk<sup>2</sup>, Ivan V. Kulakov<sup>2</sup> and Amrit Puzari<sup>1\*</sup>

<sup>1</sup>Department of Chemistry, National Institute of Technology Nagaland, Chumukedima, Dimapur - 797103, Nagaland, India; amrit09us@yahoo.com

<sup>2</sup>Department of Chemistry, OMSK State University, OMSK, Russia

## Abstract

A new one-pot acid catalyzed synthetic methodology has been described for synthesis of aromatic imines. The reaction is carried out under microwave irradiation using minimum amount of methanol as solvent. Aqueous solution of the acid catalyst act as solvent for amine dissolution. The reaction yields substantial yield of product imine. The simplicity and environmentally benign nature of the process are the most notable features. The process can also be extended to include wide number of substrates. Product of the reaction can be isolated by simple procedure. The reaction can be carried out under mild conditions without heating to a higher temperature which eventually prevents the formation of nitrile byproducts in the reaction. Byproduct formation was significantly less during the reaction.

**Keywords:** Aromatic Imine, Environmentally benign, High yield, Microwave, Tolerant

## 1. Introduction

Imines, which are commonly referred to as Schiff bases or azomethines<sup>1</sup> are important for many important organic synthesis<sup>2</sup>. Therefore imine synthesis processes have lots of significance in organic and pharmaceutical Chemistry<sup>3</sup>. Some of the important organic synthesis where imines are used as a component are asymmetric synthesis of  $\alpha$ -aminonitriles<sup>4</sup>, Cycloaddition reactions<sup>5</sup> etc. Imines are also known as biologically significant compound because of their anti-inflammatory nature as well their applicability as anticancer agent<sup>6</sup>. Imines also possess antibacterial and antifungal behavior<sup>7</sup>. Imine synthesis was first reported by Hugo Schiff and since then lots of articles have been published on Imine synthesis. Newer techniques reported for imine synthesis include the use of ionic liquid<sup>8</sup>, microwave<sup>9</sup>, ultrasound irradiation<sup>10</sup> and so on. Usually the established equilibrium between the reactant and the product influences the yield of the reaction. Additional interference also appears from water that is produced as byproduct. These kind of complications were addressed by the use of dehydrating agents like  $P_2O_5/SiO_2$ <sup>11</sup>,  $MgSO_4 \cdot Mg(ClO_4)_2$ <sup>12</sup>, fuming  $TiCl_4$ <sup>13</sup> and

so on. These procedures often involve large quantities of toxic aromatic solvents, longer reaction time, costly reagents and high temperature. Apart from these some of these procedure is limited to synthesis of particular type of imines only.

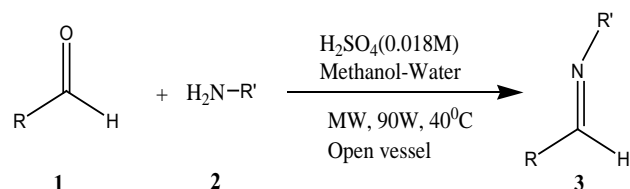
Therefore, development of new efficient mild procedure for synthesis of imines is always of high demand. Several publications are available for such kind of transformations. Reaction of aromatic aldehyde with alkyl bromide in presence of aqueous ammonia produces imine in excellent yield<sup>14</sup>. This reaction responded to range of functional groups. Similarly, nonvolatile amines react with various aromatic aldehyde under microwave irradiation at 100°C to produce imine in good yield. This reaction does not require the presence of any catalyst or solvent<sup>15</sup>. In another report  $Tris(2,2,2\text{-trifluoroethyl})borate [B(OCH_2CF_3)_3]$  has been used as a mild reagent for condensation of amides or amines with carbonyl compound. This was employed for synthesis of varieties of aldimines like N-Sulfinyl, N-toluenesulfonyl, N-(4methoxyphenyl) aldimines at room temperature<sup>16</sup>. Pyrrolidine found to act as an organocatalyst for synthesis of aldimines from aldehyde and compound containing an

\* Author for correspondence

amino group<sup>17</sup>. This has been considered as an efficient biomimetic method. For conversion of alcohols to imines Manganese dioxide is employed as an oxidant<sup>18</sup>. There are reported microwave promoted neat condensation of carbonyl compounds with (*R*)-2-methylpropane-2-sulfinamide using  $\text{Ti}(\text{OEt})_4$  as catalyst which was employed for the synthesis of optically pure aldimines in excellent yield<sup>19</sup>. Despite the availability of numerous procedure for synthesis of Imines, development of new mild, atom economic and efficient processes for synthesis of imine is still of high demand keeping in view its industrial and biological significance.

## 2. Result and Discussion

Herein we are presenting one simple, mild and efficient procedure for synthesis of Aromatic imines under microwave irradiation and in presence of less hazardous solvent system (scheme 1). This high yielding ecofriendly method makes use of inexpensive catalyst and also have the advantage of operational simplicity.



R, R' = Alkyl, Aryl

**Figure 1.** Synthesis of Imines.

The methodology reported in the article was optimized through a series of experiments carried out with varying concentration of the acid catalyst and also by changing other parameters, especially solvent. For optimization of the methodology we have started with 2,4-dichlorobenzaldehyde (Table 1) and n-propylamine in equimolar quantities and varying the amount of acid catalyst. Aqueous sulfuric acid solution was employed as catalyst which also helped in dissolution of the amine. The reactions were carried out under microwave irradiation at 40°C and were monitored through preliminary observations with TLC. Finally it has been observed that significant amount of product formation was indicated when we used 0.018M  $\text{H}_2\text{SO}_4$  acid as the catalyst. Product of the reaction was further characterized by using FT-IR, NMR, Mass spectroscopy and through elemental

analysis. The same reaction was also investigated at 40°C under ambient condition for 12 hours in which case we observed less amount of products compared to microwave irradiated condition. Microwave irradiations are usually being employed for synthesis of imine at constant temperature<sup>20</sup>. Some of such microwave assisted imine synthesis has also been carried out under solvent free conditions<sup>21</sup>. Keeping these facts in mind we have employed this methodology to carry out similar reactions with different aromatic aldehydes having different kind of substituent in the ring. The methodology was also tested for aromatic amines.

In almost all the cases yield of the products were found to be more than 80%. It can be asserted that the methodology is tolerant to various types of aromatic aldehydes like electron rich and electron poor aromatic aldehydes. The method developed can be employed to synthesize imine from aliphatic as well as aromatic amines. Thus a series of aromatic aldehydes **1a-i** (Table 1, entries 2-9) were selected for the study along with n-Propyl amine, n-Butylamine and Aniline as the amine substrate. The results of the reactions are summarized in Table 1.

**Table 1.** Synthesis of imines 3a-i<sup>a</sup>

Entry	1	R	2	R'	3	Yield (%) <sup>b</sup>
1	1a	2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2a	n-C <sub>3</sub> H <sub>7</sub>	3a	82
2	1b	Ph	2b	n-C <sub>3</sub> H <sub>7</sub>	3b	79
3	1c	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2c	n-C <sub>3</sub> H <sub>7</sub>	3c	83
4	1d	3,4-(HO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2d	n-C <sub>3</sub> H <sub>7</sub>	3d	81
5	1e	3,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2e	n-C <sub>3</sub> H <sub>7</sub>	3e	80
6	1f	2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2f	n-C <sub>4</sub> H <sub>9</sub>	3f	83
7	1g	3,4-(HO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2g	n-C <sub>4</sub> H <sub>9</sub>	3g	82
8	1h	3,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	2h	n-C <sub>4</sub> H <sub>9</sub>	3h	80
9	1i	Ph	2i	C <sub>6</sub> H <sub>5</sub>	3i	80

<sup>a</sup> Compounds 1 and 2 were taken in equimolar ratio.

<sup>b</sup> Yield corresponds to isolated materials. Product characterization was done by using <sup>1</sup>H, <sup>13</sup>C NMR, IR, MS and Elemental analysis<sup>c</sup>.

Apart from the atom economic nature of the reaction, another important feature of the reaction is that the reaction can be carried out at relatively lower temperature under microwave irradiation. Since higher temperature can lead to formation of nitrile compound of the corresponding aldehyde in appreciable amounts<sup>22</sup> therefore this methodology can significantly resist the formation of such byproducts. In our case the reactions proceeded without significant formation of any byproduct.

### 3. Experimental

All the chemicals used for the synthesis were procured from Sigma-Aldrich or TCI Chemicals and were used as received. The reaction progress was monitored by using thin layer chromatography (GF254). IR (KBr) spectra were recorded on a Perkin-Elmer FTIR spectrophotometer and the values are expressed as  $\nu_{\max}$   $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR and  $^{13}\text{C}\{^1\text{H}\}$  NMR spectra were recorded on Bruker AvIII HD-300 MHz FTNMR and VARIAN Mercury Plus 300 MHz NMR Spectrometer using TMS as internal standard. Mass spectral data were recorded on Waters UPLC- TQD(ESI-MS) and Triple Quadrupole (L C-MS/MS) mass spectrometer. Elemental analysis was performed Thermo finnigan FLASH EA 1112 CHN/CHNS/O analyzer and Perkin Elmer PR 2400 series II elemental analyzer.

#### 3.1 General Procedure for Synthesis of Imine

Aromatic aldehyde (2.0 mmol) was dissolved in 1.0 ml methanol in a test tube. Equimolar amount of amine was dissolved separately in another test tube containing 1.0 ml of 0.018M  $\text{H}_2\text{SO}_4$  solution. The solutions were then mixed properly in a 25.0 ml round bottom flask. The reaction mixture was then transferred into a microwave oven maintained at  $40^\circ\text{C}$ . The reaction was allowed to continue for 15 minutes under microwave irradiation. Product of the reaction was extracted with dichloromethane (2 x 10.0 ml). Solvent was removed under reduced pressure to obtain the product. Products were further purified by passing through a small column using 10% Ethyl acetate solution in hexane as the eluent.

### 4. Conclusion

We have demonstrated a facile environmentally benign synthetic method for synthesis of aromatic imines. The method developed produces the corresponding imines at substantial yield under mild reaction conditions. The reaction does not require heating to a higher temperature and therefore formation of nitrile byproduct was significantly less. Apart from environmental aspect, methodology developed has high atom economy.

### 5. Acknowledgement

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