

# Microwave assisted Acetylation of Amines using Imidazole Hydrochloride under solvent-free condition

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## Abstract

A simple and novel microwave irradiation method has been developed for *N*-acetylation of both aliphatic and aromatic amines with *N,N*-dimethylacetamide via *N*-acetyl imidazole by using Imidazole hydrochloride under solvent-free condition. The method proved more eco-friendly and economic.

**Keywords:** *N*-Acetylation, Amine, *N,N*-Dimethylacetamide (DMAc), Imidazole hydrochloride, Microwave irradiation.

## Introduction

Amides<sup>1</sup> are one of the most important organic functional group and occurred in many natural products, pharmaceuticals, polymers and agrochemicals<sup>2</sup>. The acetylation of amino group is commonly used as protecting group to avoid unwanted side reactions. Acetylation is often used in a multistep synthesis to construct a target molecule. Generally, acetylation of amines relies on activation of carboxylic acid derivatives. Most of the methods available at present for the *N*-acetylation of amines require harsh reaction conditions, energetic reagents, inert atmosphere, hazardous chemicals, need of dry solvents and also resulting in tedious workup and isolation.

Conventionally amides have been synthesised by the coupling of amines with carboxylic acid or their derivatives such as lachrymatory acetyl chloride, acetic anhydride and esters. Among them, several catalytic methods have been reported recently for the acetylation of amine by using acetyl chloride and acetic anhydride in the presence of various catalysts such as Fe(NO<sub>3</sub>)<sub>3</sub>·9H<sub>2</sub>O<sup>3</sup>, Ir(III)<sup>4</sup>, sulfonic acid functionalized hyper-cross-linked poly(2-naphthol)<sup>5</sup>, ruthenium metal<sup>6</sup>, mesoporous aluminophosphate solid acids<sup>7</sup>, yttrium triflate<sup>8</sup>, silica, sulfuric acid<sup>9</sup>, silica-supported boric acid<sup>10</sup>, TiO<sub>2</sub> NPs<sup>11</sup>, zirconyl triflate<sup>12</sup>, copper<sup>13</sup>, Fe(III)<sup>14</sup>, Pd(OAc)<sub>2</sub><sup>15</sup>, Zn(II) chloride and other Lewis acids<sup>16</sup>, ZnO<sup>17</sup>, indium<sup>18</sup>, carbon nanotube-gold nanohybrid (Au-CNT)<sup>19</sup>, nanocerium oxide<sup>20</sup>, K<sub>3</sub>PO<sub>4</sub><sup>21</sup>, heteropolyanion-based ionic liquids (HPAILS)<sup>22</sup>, oaryl oxide-*N*-heterocyclic carbene ruthenium(II) ([Ru-NHC] complex)<sup>23</sup>, molybdate sulfuric acid<sup>24</sup> and sulfuric acid on silica<sup>25</sup>.

However, most of these catalytic methods suffer from several drawbacks such as use of expensive solvents and catalysts, formation of byproducts, critical workup procedures, long reaction timing with lower yields. In view of the above catalytic methods, we step forwarded to green methodology for acetylation of various amines. Herein we report the acetylation of various amines with *N,N*-dimethylacetamide

(DMAc) in the presence of Imidazole hydrochloride under microwave assisted solvent-free condition.

## Material and Methods

All reagents were procured from the commercially available sources and used directly without any additional purification. All reactions were performed under inert atmosphere to maintain the dry condition.

## General procedure for the *N*-acylation of amines with DMAc and Imidazole hydrochloride under microwave condition:

Amines (1a-r) (1.0 equiv), Imidazole hydrochloride (1.5 equiv) and *N,N*-Dimethyl acetamide (2.0 equiv) were taken into a quartz tube and then subjected to microwave irradiation at 480 W for 8 min (irradiation continued at 130-135 °C). After 8 min, TLC analysis of the reaction mixture showed the complete conversion of the starting material. The reaction mixture was cooled to 20-25 °C and diluted with water (15 mL), then extracted with ethyl acetate (2 x 10 mL).

Organic layers were combined and washed with brine solution (15 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtered solvent was concentrated under vacuum to provide the corresponding acetylated products (2a-r). All the products are well characterized by NMR spectroscopy and comparison of their physical properties is listed in table 1 with those of authentic samples<sup>35</sup>.

## Results and Discussion

Previously, we have reported a convenient method for *N*-acetylation of amines with DMAc in the presence of carbonyldiimidazole (CDI) which proceeds through formation of 1-acetylimidazole<sup>5</sup>. This observation has led to the use of Imidazole hydrochloride as an efficient acetylation agent. The success of this acetylation relies on the *in situ* generation of 1-acetylimidazole by heating *N,N*-dimethylacetamide with Imidazole hydrochloride at 130-135 °C. Thus initial experiment encouraged us to explore further on this unique acetylation reaction.

To optimize the reaction conditions, we carried out acetylation reaction on aniline with DMAc (Table 1) and clearly observed that this is a temperature dependent reaction. Initially, the reaction was performed in the absence of imidazole hydrochloride at 100-105°C. Reaction temperature over the period of 16 hours gave only 6% of the desired product (Table 1, entry 1). By using 1.5 equivalent of Imidazole hydrochloride at 100-105 °C, the reaction provided the amide in 83% yield (Table 1, entry 2). Gratifyingly, increasing the reaction temperature to 130-135

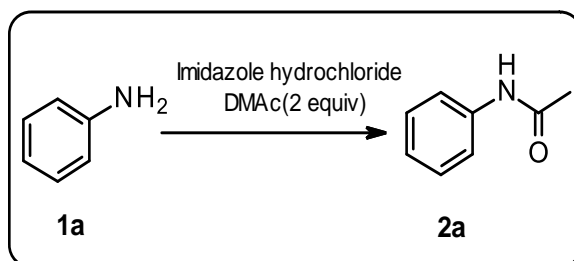
°C improved the yield (91%) (Table 1, entry 3) whereas extending the reaction time to 24 hours provided the desired amide in a quantitative yield (Table 1, entry 4).

Reaction with 1.0 equivalent of imidazole hydrochloride at 130 -135°C resulted in the reduced yield (78%) (Table 1, entry 5). Upon using 2.0 equivalents of Imidazole hydrochloride at 130-135°C (Table 1, entry 6), it was not giving a better conversion. Reaction also proceeded in the presence of imidazole as a catalyst instead of imidazole

hydrochloride, however, there was a significant drop in the yield (Table 1, entry 7).

Finally, the model reaction was carried out under microwave at 480 W using the best condition obtained from the above conventional screening that is 1.5 equivalents of Imidazole hydrochloride and 2.0 equivalents of DMAc. The microwave assisted *N*-acetylation of aniline (1a) proceeded smoothly only in 8 minutes to afford the desired product 2a in a quantitative yield.

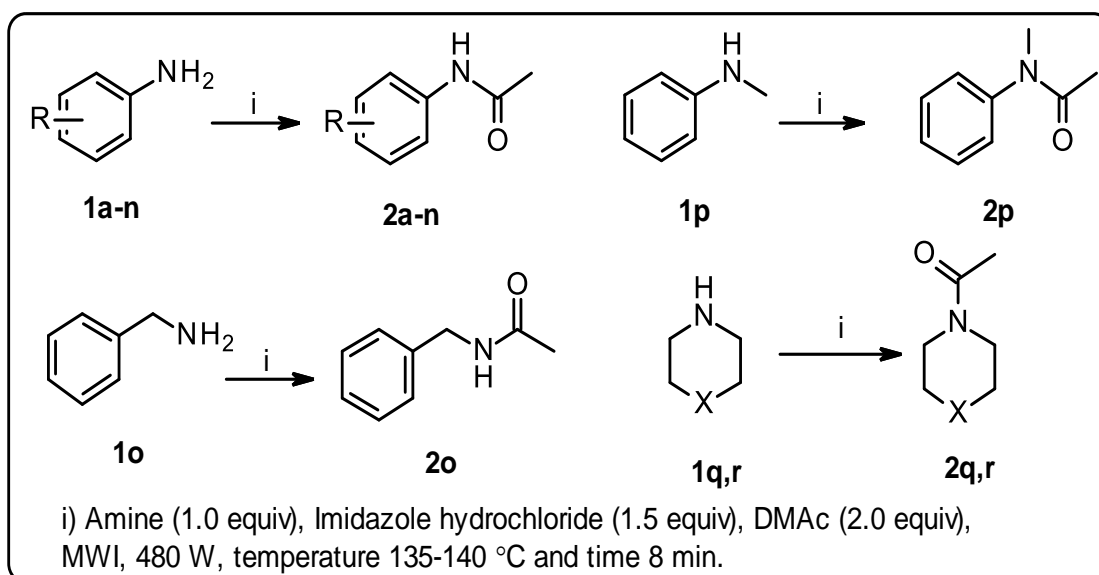
**Table 1**  
**Optimisation *N*-Acetylation reaction of aniline using conventional method**



Entry	Imidazole hydrochloride (mol equiv)	Imidazole (mol equiv)	Temp <sup>a</sup> (°C)	Time (h)	Yield (%) <sup>b</sup>
1	--	--	100-105	24	6
2	1.5	--	100-105	24	83
3	1.5	--	130-135	16	91
4	1.5	--	130-135	24	100
5	1.0	--	130-135	24	78
6	2.0	--	130-135	24	92
7	--	2.0	130-135	24	58

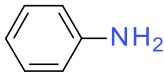
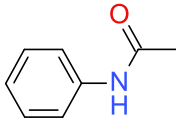
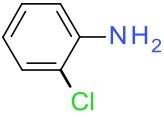
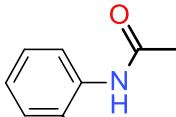
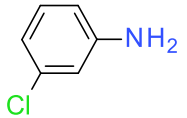
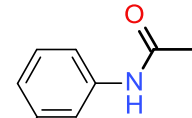
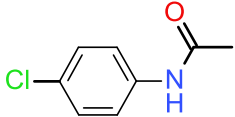
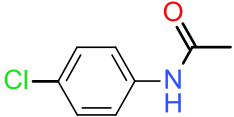
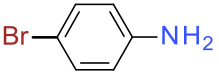
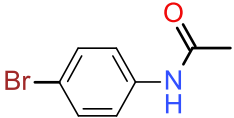
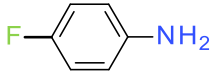
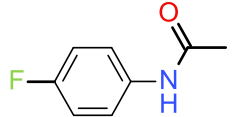
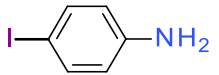
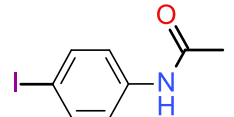
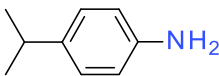
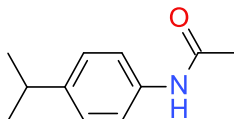
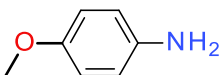
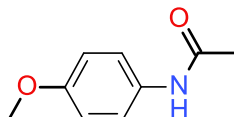
<sup>a</sup>Reaction was carried out by heating a mixture of Aniline (1.0g, 0.01mol), DMAc (2.0 equiv) and Imidazole/Imidazole hydrochloride at respective temperatures with vigorous stirring.

<sup>b</sup>Isolated Yields



**Scheme 1: Synthesis of *N*-acetylation of amine**

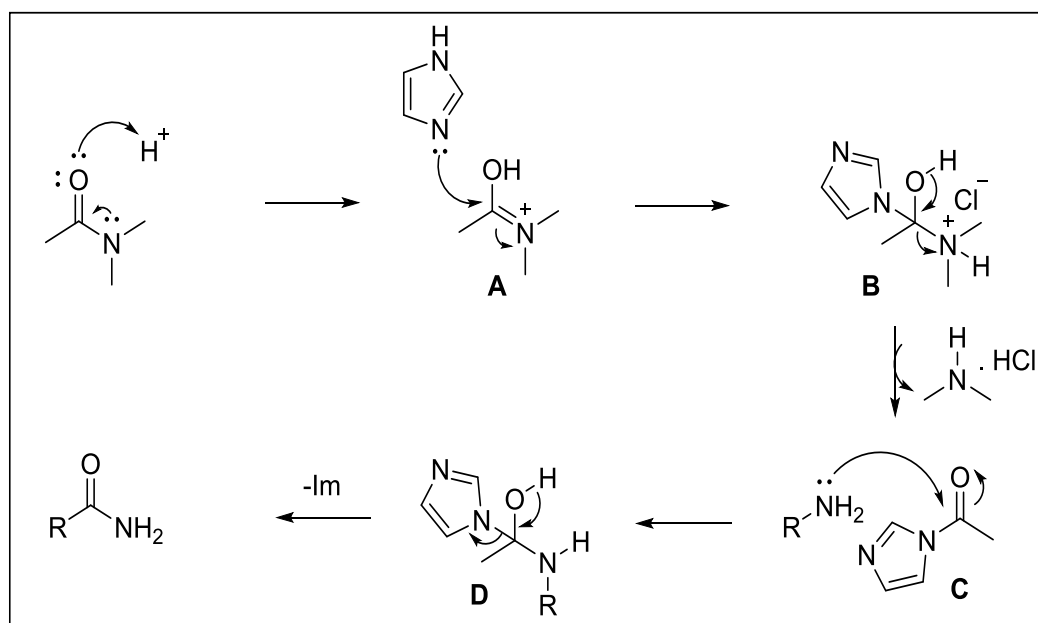
**Table 2**  
**N-Acylation of amines using DMAc and Imidazole hydrochloride<sup>a</sup>**

Entry	Substrate	Product	Yield <sup>b</sup> (%)	Melting Point (%)	
				Found	Report
1			100	112-114	114 <sup>26</sup>
2			93	87-89	88 <sup>26</sup>
3			100	75-77	74-77 <sup>27</sup>
4			100	177-179	179 <sup>26</sup>
5			95	166-168	167 <sup>26</sup>
6			98	152-154	154 <sup>30</sup>
7			95	172-174	172-174 <sup>32</sup>
8			99	104-106	105-106 <sup>31</sup>
9			100	128-130	130 <sup>26</sup>

10			88	159-161	160-162 <sup>32</sup>
11			90	166-168	167 <sup>26</sup>
12			88	127-128	128 <sup>33</sup>
13			88	103-105	103-105 <sup>30</sup>
14			85	145-147	146-147 <sup>34</sup>
15			100	58-60	60 <sup>26</sup>
16			95	102-104	103 <sup>27</sup>
17			75	225-227	226-227 <sup>29</sup>
18			70	Oil	Oil 14 <sup>29</sup>

<sup>a</sup> Experimental conditions: Amine (1.0 equiv), DMAc (2.0 equiv), Imidazole hydrochloride (1.5 equiv), MWI, 480 W, 100 °C and time 8 min.

<sup>b</sup> Isolated yields



**Scheme 2: A proposed mechanism for the imidazole hydrochloride catalyzed *N*-acetylation of amines with *N,N*-dimethylacetamide.**

Having optimized microwave condition in hand, we then applied this condition to range of amines and the results are summarized in table 2. The acetylation reactions of primary/secondary amines proceeded smoothly to afford the corresponding amide products in excellent yields. The ortho substituted primary anilines gave less yields when compared to meta or para substituent anilines (Table 2, entry 2, 10, 12, 14) because of the steric reasons. This methodology was also employed for aliphatic heterocyclic system like piperidine and morpholine yielding corresponding acetylation products in 75% and 70% yields respectively (Table 2, entry 17 and 18). Benzyl amine on acetylation gave 100% yield (Table 2, entry 15) and *N*-methylaniline gave 95% yield (Table 2, entry 16). The method employed cheaper reagents, inert atmosphere, wet solvents and harsh reaction conditions. The method proved as more eco-friendly and economic.

**Plausible mechanism:** A plausible mechanism for the *N*-acetylation of amines is depicted in scheme 2. Imidazole attacks on the iminium intermediate generated by the protonation of DMAC and results in the formation of a aminol intermediate A. Elimination of dimethylamine from intermediate B leads to the formation of the highly reactive acylating reagent *N*-acetylimidazole (intermediate C). Finally, nucleophilic amine attacks on the intermediate C to give the tetrahedral intermediate D, which upon elimination of imidazole affords the *N*-acetylated product.

## Conclusion

In conclusion, we have demonstrated a simple and convenient method for *N*-acetylation of different amines using *N,N*-dimethylacetamide in presence of Imidazole hydrochloride under solvent-free microwave irradiation method. The methodology proved as an easy, simple, inexpensive, high yield with shorter reaction time.

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