

## 1 Microwave-Induced Montmorillonite-Mediated Facile Synthesis of Enamines

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9 Montmorillonite clay-mediated simple and high yielding protocol for the synthesis of various enamines with secondary amines and  
10 ketones is developed under microwave condition. This protocol is very convenient to access the enamines from cyclic amines with  
11 various carbonyl compounds in high yield under mild reaction conditions with short reaction time.

12 **Keywords:** Microwave, Montmorillonite, Enamine.

### INTRODUCTION

13 Enamines are synthetic equivalents of enol and enolates  
14 and synthesized by the condensation of aldehydes or ketones  
15 with 2° amines under acidic or basic condition [1]. These are  
16 important precursors in organic synthesis because they can under-  
17 goes alkylation and acylation reaction with diverse reagents with  
18 high degree of regioselectivity [2]. Enamines have also serve  
19 important synthetic building block to execute 1,4-conjugate  
20 addition and annulation reaction in the synthesis of diverse  
21 heterocyclic and bioactive natural products including anti-  
22 convulsant, anti-inflammatory and antitumor agents [3]. Enamines  
23 are used to produce 1,4-dihydropyridines, pyrroles, pyrazoles,  
24 pyridones, quinolines, dibenzodiazepines, tetrahydrobenzo-  
25 xazines, tetronic acids, azasteroids with potential biological  
26 activities [4-7]. There are a number of methods available in the  
27 literature for the synthesis of enamines. For example, conden-  
28 sation of 1,3-dicarbonyl compounds with amines, silica gel-  
29 mediated synthesis [8], ionic liquid-induced reactions [9],  
30 bismuth(III) trifluoroacetate-catalyzed conditions [10], ultra-  
31 sonication method [11], palladium-catalyzed coupling reaction  
32 [12] and iodine catalyzed reactions [13].

33 Different types of clay-mediated reactions are easy to per-  
34 form because they are not soluble in organic solvents. Most of

the clays or solid surfaces are acidic or neutral in nature. Clays 35  
have the capability to absorb water and organic compounds 36  
inside the cavity in their structures. It is reported that clays are 37  
catalyze a diverse organic reaction including substitution, addition, 38  
elimination, hydrogenation, hydrogenolysis, dehydration, 39  
aromatization, annulation, Diels-Alder and isomerization. 40  
These methods are efficient in the synthesis of a wide range 41  
of diverse molecules of biological and medicinal interests. 42  
Montmorillonite K-10 has been proven its versatile catalytic 43  
efficiency in organic synthesis [14]. 44

In this article, microwave-induced montmorillonite K-10 45  
clay-mediated facile synthesis of enamines in good yield 46  
is performed. This reaction proceeds at a much faster rate 47  
than the conventional heating method. Clays work well in 48  
microwave induced processes in the absence of any solvent 49  
[15,16]. Microwave assisted reactions are extremely powerful 50  
in accelerating the rate of many chemical reactions [17]. 51  
It is not possible to know the exact temperature of the 52  
montmorillonite K-10-mediated reactions in a microwave 53  
oven. In this paper, a facile synthesis of enamines by reacting 54  
diverse ketones with secondary cyclic amines in the presence 55  
of montmorillonite K-10 under microwave irradiation is 56  
described. 57

## EXPERIMENTAL

58 **General procedure for the synthesis of enamines using**  
 59 **Montmorillonite clay:** To montmorillonite (1 g) was added  
 60 ketone (**1**) (1 mmol) and amine (5-6 mmol) and the mixture was  
 61 mixed. The solid mass was then irradiated in a domestic or  
 62 automated microwave oven for 4-5 min at 50-60 °C. The time  
 63 of reaction was specified in Table-1. For domestic microwave  
 64 reactions, it was necessary to control the temperature of the  
 65 reaction by keeping a beaker of 200 mL of water. After the  
 66 reaction, the solid mass was washed with dichloromethane (20  
 67 mL) and it was then evaporated to obtain enamines. These  
 68 enamines are used as such for next alkylation and acylation  
 69 reactions.

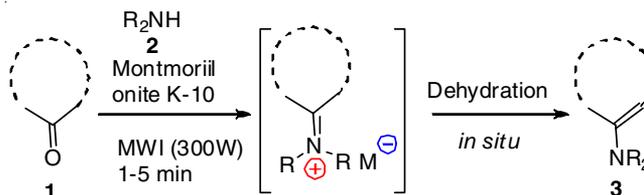
## RESULTS AND DISCUSSION

70 Solid surface-mediated reactions or surface-bound reagents  
 71 are used to study several organic reactions. There are a number  
 72 of factors that need to address when such a reaction is performed.  
 73 The pH of the solid surface is very crucial. Solid surfaces can  
 74 act as Lewis acids or bases during the reactions. The most common  
 75 solid used in laboratory experiment are different forms of clay  
 76 of which montmorillonite is our choice. For examples, syn-  
 77 thesis of  $\beta$ -lactams, nitration of aromatic hydrocarbons and  
 78 functionalized aromatic compounds, nitration of hormones and  
 79  $\beta$ -lactams, de-protection of oximes, oxidation of allylic and  
 80 benzylic alcohols glycosylations of alcohols and synthesis of  
 81 pyrroles were performed by montmorillonite-induced reactions  
 82 [18]. Different forms of silica gel, florisil, molecular sieves  
 83 and alumina were also used. Some of the reactions were per-  
 84 formed in a domestic and automated microwave oven.

85 The cause of rate acceleration by montmorillonite in the  
 86 presence of microwave was not investigated. The inner cavity  
 87 of clay is responsible for binding the reactants and accommo-  
 88 dates water. The synthesis of enamines was usually carried  
 89 out by the condensation of carbonyl compounds with secondary  
 90 amine in presence of dehydrating agents like acid or base at  
 91 high temperature. Under this condition, ketones were transformed  
 92 into corresponding enamines. In this study, we describe the  
 93 montmorillonite K-10-catalyzed synthesis of enamines.

94 Ketone **1** (1 mmol) and 2° amines **2** (5-6 mmol) were taken  
 95 in to microwave vial and 1 g of montmorillonite K-10 clay  
 96 was added to it. The vial was placed in automatic microwave  
 97 reactor and allowed to irradiate for 2-7 min. This reaction produced  
 98 enamine **3** (Scheme-I). The cyclodehydration takes place to  
 99 afford the enamine **3** in good to excellent yield. The driving  
 100 force of this reaction is microwave heating and the acidic nature  
 101 of the montmorillonite K-10 clay. It was observed that crude  
 102 ketone and secondary amine give the reaction with very low  
 103 yield under the stated condition. In present investigations, no  
 104 solvents and neat pyrrolidine were used in excess to execute  
 105 the reaction.

106 The reaction course greatly depends on the structure, substi-  
 107 tuent and the ring size of cyclic ketone. The reaction rate and  
 108 the reactivity of pyrrolidine with ketone eventually depends  
 109 on the basicity of cyclic amine, which measured and quantify  
 110 from the pKa value of its conjugate acid, which revealed that  
 111 higher the value of pKa of conjugate acid, stronger the base.



Scheme-I: Montmorillonite K-10 catalyzed microwave induced synthesis of enamine

112 It is observed that pyrrolidine was much more reactive  
 113 with cyclic ketone in comparison to piperidine and morpholine  
 114 (Tables 1-3. Piperidine have comparable reactivity like pyrro-  
 115 lidine while morpholine was found less reactive towards the  
 116 cyclic ketone and took slightly longer time to complete the  
 117 reaction (Table-3).

118 The ring size and substitution pattern of cyclic ketone  
 119 was also found that have an influence on the reactivity of the  
 120 ketone towards base. Cyclopentanone was found more reactive  
 121 in endocyclic enamine formation (entry 1b, Table-1). It is also  
 122 noticed that the formation of endocyclic enamine and their  
 123 diastereomeric ratio in case of  $\beta$ -tetralone (**1g-i**) is greatly influ-  
 124 nced by the substituents in benzene nucleus. The title endocyclic  
 125 enamine (**3g-i**) is formed exclusively under our stated protocols.  
 126 Any  $\beta$ -unsaturated endocyclic enamine is obtained during the  
 127 course of reaction. The probable reason might be the electronic  
 128 effect of benzene nucleus and the substituents in the ring. Insta-  
 129 lling the endocyclic double bond with respect to benzylic posi-  
 130 tion could be the driving force for this reaction. This probably  
 131 due the conjugation effect, which stabilized the products greatly.

132 The methoxy group in aromatic nucleus make the reaction  
 133 slower because the weak electron donating effects slightly reduce  
 134 the electrophilic character through neutralizing the positive  
 135 charge on carbon atom in carbonyl group, which resulted in  
 136 the retardation of reactivity of carbonyl groups.

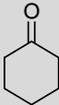
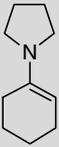
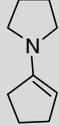
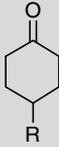
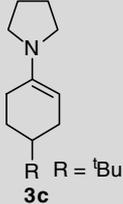
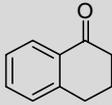
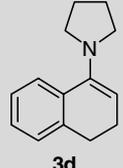
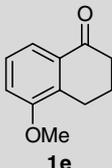
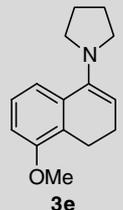
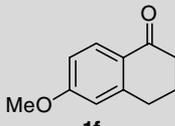
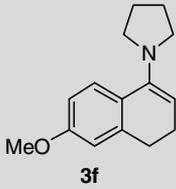
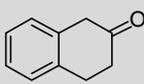
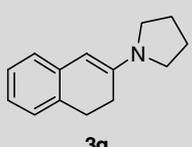
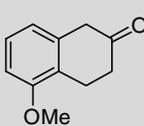
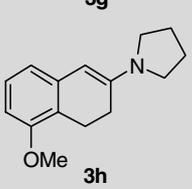
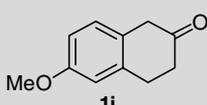
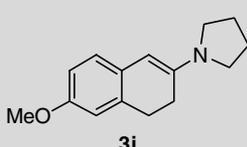
137 In both  $\alpha$ - and  $\beta$ -unsubstituted tetralones (**1d** and **1g**) was  
 138 found more reactive and under goes facile reaction with pyrro-  
 139 lidine to offer the excellent yield of title endocyclic enamine  
 140 (**3d** and **3g**) within shorter reaction time. While methoxy  
 141 substituent in  $\alpha$  and  $\beta$ -tetralone (**1d-f** and **1h-i**) took longer to  
 142 complete with comparatively lower yield. After the successful  
 143 synthesis of various cyclic enamines, next attention was focussed  
 144 to perform the synthetic reaction of another useful class of  
 145 enamine with piperidine as nucleophilic counter having the  
 146 same electrophilic carbonyl compounds.

147 Various enamines with piperidine was successfully synth-  
 148 esized with montmorillonite K-10 catalyzed reaction under  
 149 microwave irradiation yielding excellent yields (Table-2).  
 150 Similarly, using morpholine base, enamies were also  
 151 synthesized successfully in very good yields (Table-3).

## Conclusion

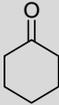
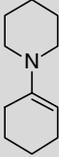
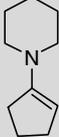
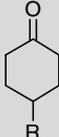
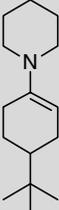
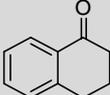
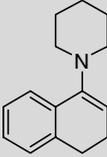
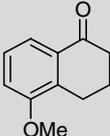
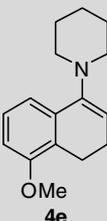
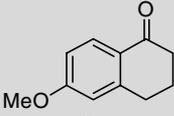
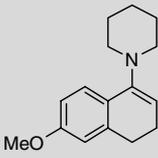
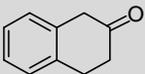
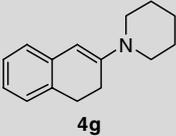
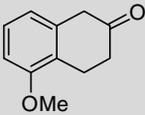
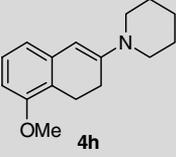
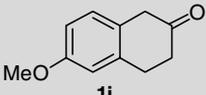
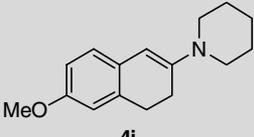
152 A montmorillonite-supported reactions for the synthesis  
 153 of enamines using ketones and 2° amines (pyrrolidines, piperi-  
 154 dine and morpholine) are successfully demonstrated. This  
 155 reaction produces excellent yields of enamines and this method  
 156 allows the isolation of the products very easily. This method  
 157 may find application in the synthesis of products that can be  
 158 formed through dehydration as one of the major pathways.  
 159

TABLE-1  
OPTIMUM REACTION CONDITIONS FOR PYRROLIDINE ENAMINE SYNTHESIS USING MONTMORILLONITE K-10 (1 g)

Ketone	Temp. (°C)	Pyrrolidine (eq.)	Enamine	Yield <sup>a</sup> (%)	Reaction time (min)
 <b>1a</b>	50	5.0	 <b>3a</b>	80	3
 <b>1b</b>	50	4.0	 <b>3b</b>	90	2
 <b>1c</b> (R = <sup>t</sup> Bu)	60	6.0	 <b>3c</b>	75	6
 <b>1d</b>	60	6.0	 <b>3d</b>	80	8
 <b>1e</b>	55	6.0	 <b>3e</b>	75	7
 <b>1f</b>	50	5.0	 <b>3f</b>	70	8
 <b>1g</b>	60	6.0	 <b>3g</b>	80	4
 <b>1h</b>	55	6.0	 <b>3h</b>	75	6
 <b>1i</b>	60	4.0	 <b>3i</b>	70	6

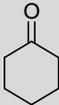
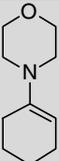
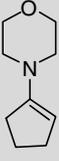
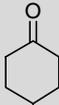
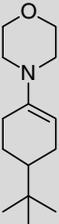
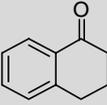
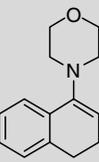
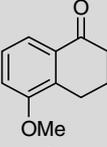
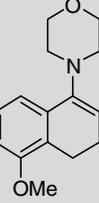
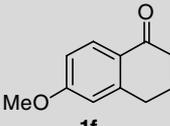
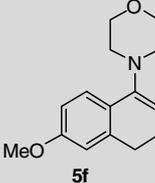
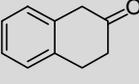
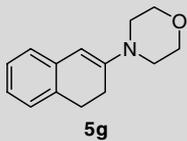
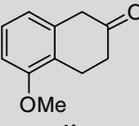
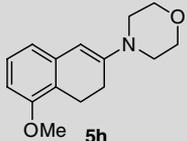
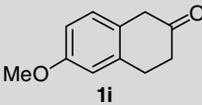
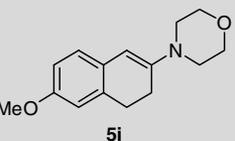
<sup>a</sup>Isolated yield over neutral silica gel filtration

TABLE-2  
OPTIMUM REACTION CONDITIONS FOR PIPERIDINE ENAMINE SYNTHESIS USING MONTMORILLONITE K-10 (1 g)

Ketone	Temp. (°C)	Piperidine (eq.)	Enamine	Yield <sup>a</sup> (%)	Reaction time (min)
 <b>1a</b>	50	3.0	 <b>4a</b>	80	2
 <b>1b</b>	50	4.0	 <b>4b</b>	80	2
 <b>1c</b> (R = <sup>t</sup> Bu)	60	5.0	 <b>4c</b>	75	4
 <b>1d</b>	60	5.0	 <b>4d</b>	70	5
 <b>1e</b>	55	5.0	 <b>4e</b>	75	6
 <b>1f</b>	50	5.0	 <b>4f</b>	70	7
 <b>1g</b>	60	5.0	 <b>4g</b>	70	5
 <b>1h</b>	55	5.0	 <b>4h</b>	75	6
 <b>1i</b>	60	4.0	 <b>4i</b>	70	6

<sup>a</sup>Isolated yield over neutral silica gel filtration

TABLE-3  
OPTIMUM REACTION CONDITIONS FOR MORPHOLINE ENAMINE SYNTHESIS USING MONTMORILLONITE K-10 (1 g)

Ketone	Temp. (°C)	Morpholine (eq.)	Enamine	Yield <sup>a</sup> (%)	Reaction time (min)
 <b>1a</b>	50	3.0	 <b>5a</b>	80	6
 <b>1b</b>	50	4.0	 <b>5b</b>	80	3
 <b>1c</b> (R = <sup>t</sup> Bu)	60	5.0	 <b>5c</b>	75	7
 <b>1d</b>	60	4.0	 <b>5d</b>	70	8
 <b>1e</b>	55	5.0	 <b>5e</b>	75	9
 <b>1f</b>	50	5.0	 <b>5f</b>	70	7
 <b>1g</b>	60	5.0	 <b>5g</b>	70	5
 <b>1h</b>	55	3.0	 <b>5h</b>	75	8
 <b>1i</b>	60	4.0	 <b>5i</b>	70	7

<sup>a</sup>Isolated yield over neutral silica gel filtration

**CONFLICT OF INTEREST**

160 The authors declare that there is no conflict of interests  
161 regarding the publication of this article.

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