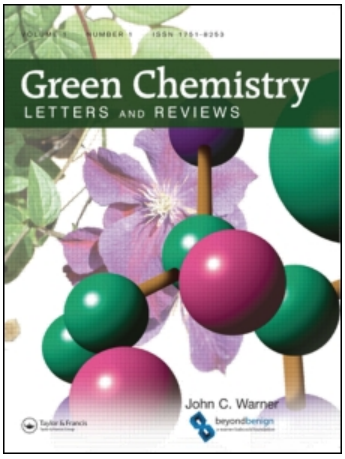


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# Dual role of ammonium acetate for solvent-free synthesis of 1,3-disubstituted-2,3-dihydro-1*H*-naphth-[1,2e] [1,3]-oxazine

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ORIGINAL ARTICLE

# Dual role of ammonium acetate for solvent-free synthesis of 1,3-disubstituted-2,3-dihydro-1*H*-naphth-[1,2e] [1,3]-oxazine

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Ammonium acetate plays a dual role for the solvent-free synthesis of 1,3-oxazine under neat heating at 60°C and under microwave irradiation with excellent yields. The synthetic strategy involved the formation of a Betti base which upon condensation with aromatic aldehydes gives the preferred oxazine ring. The present protocol contributes remarkable advantages, such as solvent- and catalyst-free reaction conditions, simple work-up procedures, shorter reaction times, and environmentally benign methodology.

**Keywords:** microwave; ammonium acetate; solvent-free; oxazine; Betti base



## Introduction

Multi-component condensation reactions constitute an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step and the diversity can be achieved simply by varying the reacting compounds (*1*). In view of the emerging importance of reactions under solvent- and catalyst-free conditions; organic chemists have attracted much attention (*2*). This is because solvent-free reactions are smoothly converted into products within shorter reaction time along with easy product isolation procedures. Therefore, solvent-free conditions have been of increasing interest to chemists for a variety of organic transformation related to green chemistry (*3*).

Heterocycles bearing the 1,3-oxazine nucleus possess a broad spectrum of biological activities, such as analgesic, anticonvulsant, antitubercular, antibacterial, and anticancer activity (*4*). Attention has been paid to the compounds in particular the non-nucleoside reverse transcriptase inhibitor, trifluoromethyl-1, 3-oxazine-2-one, because of high activity against a variety of HIV-1 mutant strains (*5*). Additionally, naphthoxazine derivatives have exhibited therapeutic potential for the treatment of Parkinson's disease (*6*). Furthermore, they can be used as intermediates in the synthesis of *N*-substituted aminoalcohols (Betti base) or in enantioselective syntheses of chiral amines (*7*). A great number of synthetic possibilities are offered to 1,3-*O*,*N*-heterocycles due to the tautomeric character associated with them (*8*). According to our literature survey, naphth-1,3-oxazine derivatives have traditionally been prepared using 2-naphthol and various substituted aryl and heteroaryl aldehydes in the presence of dry methanolic ammonia (*9*). All these reported methods possess several drawbacks, such as low yields, prolonged reaction times, tedious work-up procedures, and exotic reaction conditions.

Aminophenol derivatives have also provided convenient access to many useful synthetic building blocks *via* the amino and phenolic hydroxy functional group (*10*). Moreover, condensation of Betti base derivatives with aromatic aldehydes leads to the formation of the corresponding 1,3-oxazine with varied biological properties (*11*). Our present aim was to extend the synthetic utility of aminobenzyl naphthol (Betti base) by examining its application in the synthesis of heterocyclic 1,3-oxazine compounds. Therefore, we would like to report an uncatalyzed, solvent-free, three-component protocol for the synthesis of 1,3 oxazines in excellent yields.

## Results and discussion

As part of our ongoing investigations on the development of new and efficient methods for synthesis of various heterocyclic compounds (*12*), herein, we would like to report a novel synthetic method for 1,3-disubstituted-2,3-dihydro-1*H*-naphth-[1,2e][1,3] oxazine. The promising advantages of these protocols include the avoidance of organic solvents and catalysts, easy product isolation and short reaction times. A literature survey reveals that ammonium acetate has

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not been previously used for the synthesis of oxazine and Betti base. As the model reaction, we initially examined the one-pot reaction of 3,4-dimethyl benzaldehyde, 2-naphthol, and ammonium acetate at 60°C neat heating in absence of catalyst. It has been observed that the formation of the product takes place within 30 min with 95% yield. On the other hand, the same reaction was carried out under microwave irradiation the product formation takes place in 7 min with 94% yield (Table 1, Scheme 1). In this reaction, ammonium acetate plays dual role as a reactant as well as catalyst. Therefore, we have examined the other derivatives under neat heating as well as under microwave irradiation in absence of any catalyst and solvent.

The one-pot, three-component reaction of 2-naphthol **1**, aromatic aldehydes **2**, and ammonium acetate at 60°C under neat heating and microwave irradiation for the appropriate time (Table 1) afforded oxazine **3** in excellent yields (Scheme 1). Compound **3** on subsequent treatment with dilute HCl and KOH under microwave irradiation, resulted aminobenzyl naphthol **4** and the results are shown in (Table 2). Finally, the reaction of the aminobenzyl naphthol **4** with an equivalent amount of aromatic aldehyde afforded the corresponding 1,3-disubstituted-2,3-dihydro-1*H*-naphth-[1,2e][1,3] oxazine **5(a–e)** (Table 3).

During the reaction course for the synthesis of compounds **3(a–i)** and compounds **5(a–e)**, we have examined the reaction time by both Method A (microwave irradiation) and Method B (neat heating). It is clear that, for the synthesis of compounds **3(a–i)** using Method A, the time required is comparatively less than for the synthesis of compounds **5(a–e)**. However, there is no remarkable difference in the yield of the products. On the other hand, using Method B for the synthesis of compounds **3(a–i)** and compounds **5(a–e)**, there is no significant difference in reaction time and yield of the products. In addition, for the synthesis of aminobenzyl naphthol under microwave irradiation the required time and isolated product yield is also remarkable. We have also observed that aromatic aldehydes containing different functional groups at different positions worked well and did not show significant difference in the yield of products.

## Experimental section

All the reagents and aldehydes were obtained from commercial suppliers and were used without purification. Melting points were determined in an open capillary apparatus and are uncorrected. The progress of the reaction was monitored by thin layer chromatography (TLC). IR spectra were recorded on a Perkins–Elmer FT spectrophotometer in KBr disc. $^1$H NMR spectra were recorded on a Varian 300 MHz spectrophotometer in $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. All the derivatives were carried out by Method A in a microwave oven (BPL, 800 T, 2450 MHz) with power output of 800 W.

### *General experimental procedures*

*Method A: for compounds **3(a–i)***

A mixture of aromatic/heteroaromatic aldehydes (2 mmol), 2-naphthol (1 mmol), and ammonium acetate (1.5 mmol) were taken in a beaker. The reaction mixture was homogenized with the help of glass rod and irradiated in microwave oven (360 W) by interval of 10 second. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and was poured over crushed ice. The obtained solid was filtered, dried, and recrystallized from ethanol.

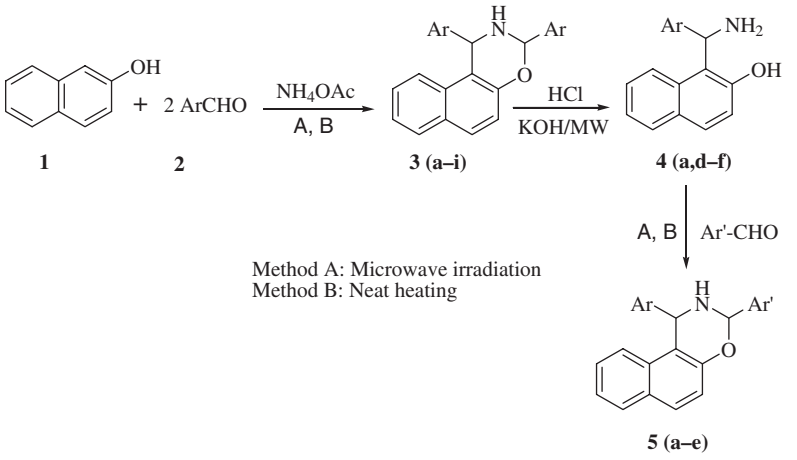
*Method B: for compounds **3(a–i)***

A mixture of aromatic/heteroaromatic aldehydes (2 mmol), 2-naphthol (1 mmol), and ammonium acetate

Table 1. Synthesis of 1,3 oxazine derivatives **3(a–i)**.

| Compounds[a] | Ar | Method A Time (min)/ Yield (%)[b] | Method B Time (min)/ Yield (%)[b] | M.P. (°C) |
|---|---|---|---|---|
| **3a** | $C_6H_5$ | 5/98 | 25/95 | 147–149 (*7a*) |
| **3b** | 3-$OHC_6H_4$ | 7/92 | 30/92 | 102–104 (*9d*) |
| **3c** | 3,4-$MeC_6H_3$ | 7/94 | 30/95 | 112–114 (*9d*) |
| **3d** | 3,4-$OMeC_6H_3$ | 9/94 | 40/92 | 124–126 (*9d*) |
| **3e** | 3,4,5-$OMeC_6H_2$ | 15/95 | 35/96 | 140–142 (*9d*) |
| **3f** | 3-$OPhC_6H_4$ | 10/94 | 30/94 | 109–111 (*9d*) |
| **3g** | 2-OH,5-$BrC_6H_3$ | 10/93 | 35/96 | 200–202 (*9d*) |
| **3h** | 2-Pyridyl | 7/96 | 25/98 | 158–160 (*9d*) |
| **3i** | 2-Thienyl | 7/95 | 25/93 | 168–171 (*9d*) |

[a]All products are known and their physical and spectroscopic data are in good agreement with those of authentic samples.
[b]Yields refer to isolated products.




Scheme 1. Synthesis of 1,3-oxyzine derivatives.

Table 2. Synthesis of aminobenzyl naphthol (Betti base) **4(a, d–f)**.

| Compounds | Ar | MW Time (min) | Yield (%)[a] | M.P. (°C) |
|---|---|---|---|---|
| **4a** | $C_6H_5$ | 15 | 95 | 173–175 |
| **4d** | 3,4-$OMeC_6H_3$ | 20 | 89 | 128–130 (*9d*) |
| **4e** | 3,4,5-$OMeC_6H_3$ | 20 | 90 | 117–119 (*9d*) |
| **4f** | 3-$OPhC_6H_4$ | 20 | 92 | 112–114 (*9d*) |

[a]Yields refer to isolated products.



(1.5 mmol) were taken in round bottom flask. The reaction mass was then heated at 60°C in an oil bath for the appropriate period of time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature and was poured over crushed ice. The obtained solid was filtered, dried, and recrystallized from ethanol.

*General experimental procedures for compounds **4(a, d–f)***

Compounds **3(a, d–f)** (1 mmol) were taken in 2 ml dil HCl in a beaker and followed by irradiation in a microwave (360 W) for about 5 min. KOH (0.2 mmol) was added and was then irradiated for the appropriate time until the completion of the reaction. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature and was poured on crushed ice. The obtained solid was filtered, dried, and recrystallized from ethanol.

*Method A: for compounds **5(a–e)***

A mixture of aminobenzyl naphthol **4** (1 mmol) and aromatic/heteroaromatic aldehydes (1 mmol) was introduced in the microwave oven and irradiated for 10–15 min (360 W). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and was poured over crushed ice. The obtained solid was filtered, dried, and recrystallized from ethanol.

Table 3. Synthesis of 1,3 oxazine derivatives **5(a–e)**.

| Compounds[a] | Ar | Ar′ | Method A Time (min)/Yield (%)[b] | Method B Time (min)/Yield (%)[b] | M.P. (°C) |
|---|---|---|---|---|---|
| **5a** | 3,4-$MeC_6H_3$ | 3,4,5-$OMeC_6H_2$ | 20/95 | 40/96 | 135–137 (*9d*) |
| **5b** | 3,4-$MeC_6H_3$ | 3-$OPhC_6H_4$ | 15/93 | 35/93 | 126–128 (*9d*) |
| **5c** | 3,4-$MeC_6H_3$ | 2-Pyridyl | 10/90 | 30/94 | 144–146 (*9d*) |
| **5d** | $C_6H_5$ | 4-$NO_2C_6H_4$ | 15/89 | 25/85 | 172–174 (*7a*) |
| **5e** | $C_6H_5$ | 4-$ClC_6H_4$ | 10/92 | 30/90 | 167–169 (*7a*) |

[a]All products are known and their physical and spectroscopic data are in good agreement with those of authentic samples.
[b]Yields refer to isolated products.

*Method B: for compounds* ***5(a–e)***

A mixture of aminobenzyl naphthol **4** (1 mmol) and aromatic/heteroaromatic aldehydes (1 mmol) were taken in a round bottom flask. The reaction mass was then heated at 60°C for the appropriate period of time. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and was poured over crushed ice. The obtained solid was filtered, dried, and recrystallized from ethanol.

## Conclusions

In summary, we have successfully developed a simple and efficient method for the synthesis of 1,3-oxazines employing green methodology in excellent yields. The simplicity of the reaction conditions, their efficiency, and the excellent results in shorter reaction times using both Method A and Method B under solvent and catalyst-free conditions, constitute an attractive contribution among the existing methodologies.

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