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# Microwave Assisted Solvent-free Synthesis of 1-Phenyl-1, 2-dihydro-3*H*-naphtho[1, 2-e][1, 3]oxazin-3-one Catalyzed by $FeCl_3$

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**ABSTRACT**

Three-component coupling of 2-naphthol, aldehydes, and urea has been accomplished in the presence of $FeCl_3$ under microwave irradiation and solvent-free conditions to afford the corresponding synthesis of 1-phenyl-1, 2-dihydro-3*H*-naphtho[1,2-e][1,3]oxazin-3-onederivatives in excellent yields. It is a promising catalyst for the microwave-assisted reaction providing high product yield in a short period.

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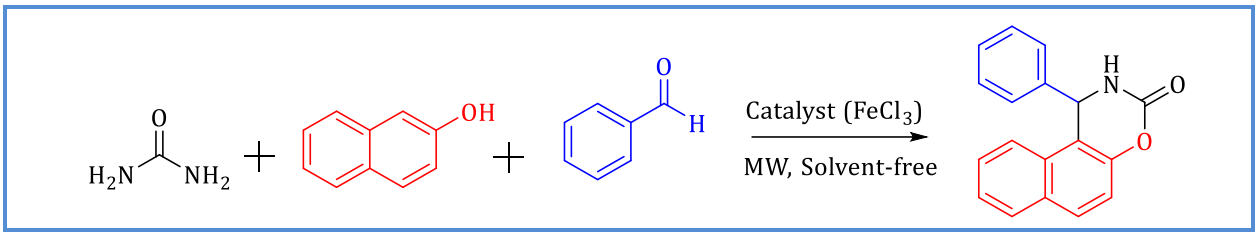
## Graphical Abstract

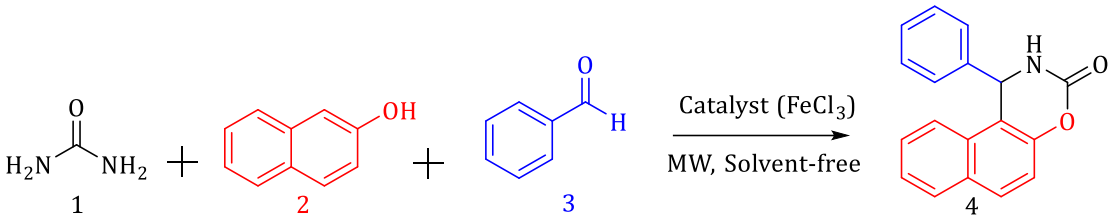



## Introduction

Microwave (MW) irradiation as a novel, efficient and harmless method for reagent activation in the synthesis of organic compounds, and in special heterocyclic compounds, has been applied to achieve milder reaction conditions [1-4].

Multicomponent reactions (MCRs) constitute a particularly attractive synthetic strategy due to the fact that the products are made in a single step while diversity can be promoted only by varying the reacting components [5-11]. Furthermore, multicomponent reactions (MCRs) by the virtue of their convergence, productivity, ease of implementation and generally higher yields of products have attracted considerable attention in the area of combinatorial chemistry [12-16]. The first MCR was described by Strecker in 1850 for the synthesis of amino acids [17]. Yet, in the past decade, there have occurred tremendous developments in the three and four component reactions and, yet, great attempts are continually being appeared to develop new MCRs [18-22].

Over the past few decades, chemistry has become a major field of study for chemists [23-26]. Hence, chemical reactions have greatly caused the environmental problems [27-31]. To overcome these problems and facilitate chemical reactions, alternative energy sources such as UV or microwave are used. Iron is one of the most abundant metals on Earth and $FeCl_3$ (Iron (III) chloride) is an efficient catalyst in modern organic synthesis, environmentally friendly and atom-economical organic transformations that can increase the yield and speed of the reaction [32-35]. $FeCl_3$ has been explored as a powerful catalyst for various organic transformations such as synthesis of tetrasubstituted imidazoles [36], $\alpha$-amino phosphonates [37], quinoline derivatives [17, 38], 3,4-dihyropyrimidinone derivatives [19] and synthesis of dihydropyrimidinones [18]. The reported route is an efficient, convenient and novel method for the condensation of the aldehyde with $\beta$-naphthol and urea in the presence of $FeCl_3$ to afford condensed naphthoxazine-3-one derivatives in good yields (Scheme 1).




**Scheme 1.** Synthesis of 1-phenyl-1, 2-dihydro-3*H*-naphtho [1, 2-e] [1, 3] oxazin-3-one

## Material and Methods

### General

Starting materials were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Melting points were measured on an electrothermal 9100 apparatus and are uncorrected. The microwave-assisted procedures were carried out in a milestone microwave oven operating at 1600 W. All the obtained products are known compounds and were identified by comparing their melting points with those reported in the literature. The progress of reactions was monitored by thin layer chromatography (TLC). $^{1}H$ (DMSO-$d_6$) and $^{13}C$ NMR (DMSO-$d_6$) spectra were recorded on a Bruker DRX-250 avance spectrometer at 250.13 and 62.90 MHz, respectively.

### General procedure for the synthesis of naphthoxazine-3-one derivatives

A mixture of urea **1** (1 mmol), 2-naphthol **2** (1 mmol), benzaldehyde **3** (1 mmol), and 12 mol% of $FeCl_3$ anhydrous (0.02 g) under solvent-free condition was placed for 15 min with the power of 500 W in the microwave. The progress of the reaction was checked by TLC (petroleum ether: EtOAc, 10:2). After completion of the reaction followed by TLC, hot ethanol was added and the catalyst was filtrated off. Then, the residue was poured into crushed ice and stirred for several minutes. The solid product was filtered and the pure product was obtained by recrystallization from hot ethanol.

### The selected spectral data

1,2-dihydro-1-phenylnaphtho[1,2-e][1,3]oxazin-3-one (Table 3, Entry 1): white solid, yield, 90%, $^{1}H$ NMR (250 MHz, DMSO-$d_6$): $\delta$ 8.85 (s, 1H, NH), 7.29-7.99 (m, 10H, Ar-H), 6.16 (s, 1H). $^{13}C$ NMR (62.90 MHz, DMSO, $d_6$): $\delta$ 149.7, 147.8, 143.8, 130.8, 130.6, 129.4, 129, 128.4, 127.8, 127.4, 125.5, 123.5, 117.3, 114.4, 54.2.

## Results and Discussion

Today, the use of catalysts in multi-component reactions is significant. Although the use of $Fecl_3$ having a catalytic role has been proven, the catalytic role of $FeCl_3$ in multi-particulate reactions in free-solvent

reactions was investigated in this study and was confirmed according to the NMR and melting point. We optimized the reaction conditions such as catalyst dosage, microwave power, and reaction times. First, the efficiency and amount of the $FeCl_3$ catalyst were investigated in a model reaction of urea **1** (1 mmol), *β*-naphtol **2** (1 mmol) and benzaldehyde **3a** (1 mmol) for the synthesis of compound **4a** (Table 3, entry 1). As shown in Table 1, the optimum yield of the product was obtained when 12 mol% of $FeCl_3$ was used (Table 1, entry 2).

**Table 1.** Effect of the catalyst dosage on the synthesis of naphthoxazine-3-one derivatives

| Entry | Catalyst (mol%) | Microwave power (W) | Time (min) | Yield (%)a |
|---|---|---|---|---|
| 1 | 9 | 500 | 15 | 83 |
| 2 | 12 | 500 | 15 | 90 |
| 3 | 15.5 | 500 | 15 | 90 |

Reaction conditions: urea **1** (1 mmol), *β*-naphtol**2** (1 mmol) and benzaldehyde **3a** (1 mmol) under microwave irradiation (500 W)
an Isolated yields

The effect of microwave power inputs from 300 to 600 W on the synthesis of compound 4a (Table 3, entry 1) as a model reaction was evaluated (Table 2). The reaction yield increased with the microwave power at 400 W in comparison to 500 W.

**Table 2.** Effect of microwave power on the synthesis of naphthoxazine-3-one derivatives

| Entry | Catalyst (mol%) | Microwave power (W) | Time (min) | Yield (%)a |
|---|---|---|---|---|
| 1 | 12 | 300 | 15 | 71 |
| 2 | 12 | 400 | 15 | 82 |
| 3 | 12 | 500 | 15 | 90 |
| 4 | 12 | 600 | 15 | 90 |

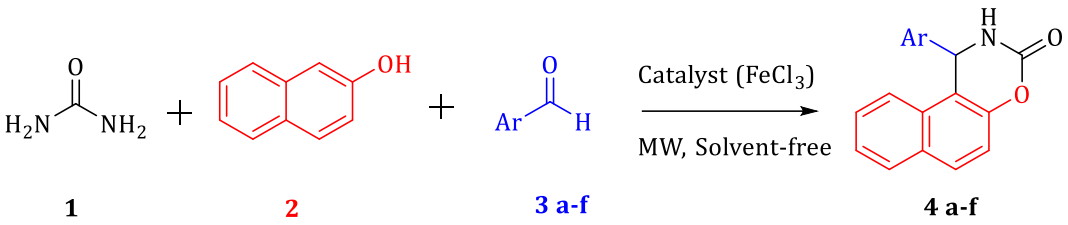
Reaction conditions: urea **1** (1 mmol), *β*-naphtol **2** (1mmol) and benzaldehyde **3a** (1 mmol) and 12 mol% (20 mg) of catalyst.
an Isolated yields

Using this optimized condition, a wide range of aldehydes, urea, and *β*-naphtol (Scheme 2) were subjected to undergo three-component condensation in the presence of $FeCl_3$ under solvent-free conditions (Table 3). Then, various aromatic aldehydes carrying electron-donating and electron-withdrawing groups on the aromatic ring in the ortho, meta, and para positions and heterocyclic aldehydes were evaluated. Yields of all reactions were good to excellent.

**Table 3.** $FeCl_3$ catalyzed the synthesis of naphthoxazine-3-one derivatives

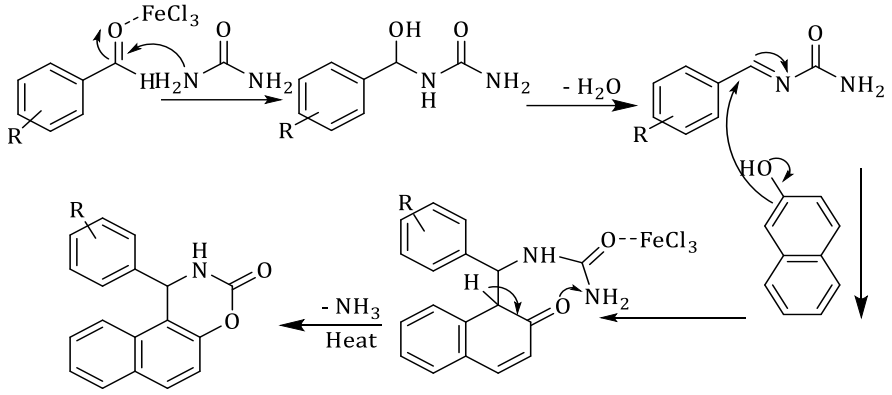
| Entry | Ar | Product | Time (min) | Yield (%)[a] | M.P. (°C) | M.P. (°C) [Ref.] |
|---|---|---|---|---|---|---|
| 1 | Ph | **4a** | 15 | 90 | 223-225 | 220-222 [39] |
| 2 | 3-Cl–$C_6H_4$ | **4b** | 15 | 88 | 193-195 | 194-196 [40] |
| 3 | 4-Cl–$C_6H_4$ | **4c** | 15 | 90 | 208-210 | 210-212 [40] |
| 4 | 2-$NO_2$–$C_6H_4$ | **4d** | 15 | 84 | 197-199 | 195-197 [39] |
| 5 | 4-$NO_2$–$C_6H_4$ | **4e** | 15 | 89 | 189-192 | 188-190 [39] |

Reaction conditions: urea **1** (1 mmol), *β*-naphtol**2** (1 mmol) and benzaldehyde **3a-f** (1 mmol) and 12 mol% of the catalyst under microwave irradiation (500 W) in solvent-free conditions
Isolated yields




**Scheme 2.** $FeCl_3$ catalyzed the synthesis of naphthoxazine-3-one derivatives

Mechanistically, the initial condensation of an aromatic aldehyde with urea in the presence of $FeCl_3$ following by dehydration leads to the formation of benzylidene urea. The nucleophilic addition of the 2-naphthol to benzylidene urea followed by intramolecular cyclization of the resulting species produce the 1,2-dihydro-1-arylnaphtho[1,2-e][1,3]oxazine-3-one (Scheme 3).




**Scheme 3**.The proposed mechanism for the synthesis of naphthoxazine-3-one derivatives

## Conclusions

In summary, we have described a highly efficient solvent-free synthesis for the preparation of naphthoxazine-3-one derivativesin the three-component cyclo-condensation reaction of 2-naphtol, aromatic aldehydes, and urea under microwave irradiation. According to the results of $FeCl_3$, the catalyst can be used for other multicomponent reactions. It can also be said that the method used in this synthesis is optimal, inexpensive and in line with green chemistry.

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