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## Rapid Synthesis of Amides from Ketoximes using Citric Acid Monohydrate over TBAB under Green Chemistry Conditions

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## ABSTRACT

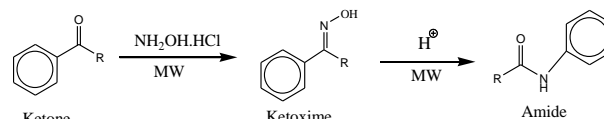
Rapid synthesis of amides from variously substituted ketones through rearrangement reaction of their oximes have been done under solvent-free conditions using new catalytic system, citric acid monohydrate over phase transfer catalyst tetrabutylammonium bromide (TBAB). Amides of different ketoximes were obtained in 72–85% yields. Structural confirmations of all products were done on the basis of spectroscopic analyses- <sup>1</sup>H NMR, <sup>13</sup>C NMR and FT-IR and by comparisons of their melting points with those of authentic samples.

## 1. Introduction

In these environmentally conscious days, the highest priorities for chemical industries and research laboratories are eco-friendly chemical processes, product safety and reducing the adverse consequences of the substances that we use and generate. It requires the development of novel and cost-effective approaches to pollution prevention. Hence, the problem associated with the disposal of waste solvents and the use of excess chemicals should be avoided. This protocol is now termed as Green Chemistry [1-10]. Microwave heating, an alternative to conventional conductive heating, makes it possible to shorten the length of reactions significantly, to increase their selectivity, and to increase the product yields, which is particularly important in the case of high-temperature processes that take a long time as microwave irradiations show specific microwave effects [11, 12]. One of the key areas of Green Chemistry is the elimination of solvents in chemical processes or the replacement of hazardous solvents with environmentally benign solvents. The application of alternative solvents such as water, fluoruous and ionic liquids, supercritical media, and their various combinations is rapidly increasing. The utilization of inorganic solid supported reagents has attracted attention because of enhanced selectivity, milder reaction conditions and associated ease of manipulation [13, 14]. The solvent free technique has been claimed to be particularly environmentally friendly, since it avoid the use of solvents and offers a simple method of workup, improved safety by avoiding low boiling solvents. Organic reactions under solvent-free conditions offer enhanced selectivity and efficiency, ease of manipulation, and often avoid toxic and volatile solvents.

Conversion of ketoxime in to their more stable amide isomer is one of the important organic reactions. Most popular application of this rearrangement is the conversion of cyclohexanone oxime into ε-caprolactam, the latter turns out to be an important industrial chemical which yields Nylon-6 polymer [15]. Sulphuric acid is most commonly used acid for the production of lactam [16, 17]. A wealth of other useful reagents, including have been developed to affect this rearrangement reaction [18-25]. Since, this reaction requires strongly acidic conditions, which suffer from usual limitations such as harsh reaction conditions, hard to handle strong acids, formation of by-products harmful to environment;

the present work aimed to investigate mild, eco-friendly and easy to handle catalytic systems, which would work efficiently under microwave irradiations and solvent free conditions. The citric acid monohydrate has layered over phase transfer catalysts tetrabutylammonium bromide (TBAB), to synthesize amides from ketoximes, under green chemistry conditions (Scheme 1).



Scheme 1 Synthesis of amide from ketone

For this purpose, various substituted ketones like benzophenone, 4-hydroxyacetophenone, acetophenone, cyclohexanone, 4-nitroacetophenone, 4-chloroacetophenone, 4-methoxyacetophenone would be investigated.

## 2. Experimental Methods

## 2.1 General Methods

All ketones were purchased from Sigma-Aldrich and Fluka. Citric acid monohydrate was purchased from LobaChemie, and other reagents were purchased from different commercial sources. The reactions were carried out in a Synthwave 402 Prolabo microwave reactor with an open system of reaction vessel (freq. 2450 MHz) and were monitored by analytical thin layer chromatography (TLC) performed on glass plates precoated with silica gel G as supplied by Sisco Research Laboratories (SRL). Visualization of the resulting chromatograms was done by looking under iodine chamber followed by dipping in a solution of carbon-tetrachloride (CCl<sub>4</sub>) and ethylacetate (CH<sub>3</sub>COOC<sub>2</sub>H<sub>5</sub>). <sup>1</sup>H-NMR was recorded on a 400MHz spectrometer (Bruker Avance II 400). The chemical shifts were determined using tetramethylsilane (TMS) as internal standard at δ 0.0 or to the signal of residual CDCl<sub>3</sub> δ 7.26. <sup>13</sup>C NMR (100MHz) was recorded using CDCl<sub>3</sub> as solvent. FT-IR was recorded using KBr pallets. All commercially accessible chemicals were used without further refinements. Oximes of all ketones were prepared according to reported procedure [26].

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## 2.2 General Procedure for the Synthesis of Amides from Ketoximes

Citric acid monohydrate ( $C_6H_8O_7 \cdot H_2O$ ) (200 mg), TBAB (100 mg) and the oxime of benzophenone (197 mg, 1 mmol) were stirred thoroughly in a 10 mL pyrex beaker in the presence of 3 drops  $H_2O$  for few minutes at room temperature and then subjected to microwave irradiations at 40 °C. The progress of reaction was monitored by TLC ( $CCl_4$ : ethyl acetate/38 : 2) after intervals of 10 sec. when the reaction was found to be completed in 50 sec. The product was extracted with ether, filtered and the solvent evaporated off under reduced pressure to yield the *N*- phenylbenzamide in 85 % yield. Same procedure was followed for the preparation of amides of other ketoximes under the identical reaction conditions. The products were identified on the basis of comparison of their melting points and spectroscopic data with those of the authentic samples and found in good agreement with literature [27-31].

## 2.3 Data Analysis

*N*- Phenylbenzamide: M.P. 163 °C.  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  8.10 (br 1H, NH), 7.85 (d,  $J$  = 7.2 Hz, 2H), 7.64 (d,  $J$  = 7.6 Hz, 2H), 7.25-7.53 (m, 5H), 7.14 (t,  $J$  = 7.2 Hz, 1H).  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$  166.1 (C=O), 139.2 (C-N), 134.0, 131.0, 129.3, 128.5, 128.1, 125.3, 120.5. FT-IR: 1670  $cm^{-1}$ .

*N*- Phenylacetamide: M.P. 115 °C.  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  8.09 (br 1H, NH), 7.51 (d,  $J$  = 7.10 Hz, 2H), 7.28 (d,  $J$  = 7.8 Hz, 2H), 7.08 (t,  $J$  = 7.6 Hz, 1H), 2.13 (s, 3H).  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$  169.4 (C=O), 138.1 (C-N), 128.0, 124.5, 120.5, 24.9. FT-IR: 1663  $cm^{-1}$ .

*N*-(4-hydroxyphenyl)acetamide: M.P. 170 °C.  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  9.97 (br 1H, NH), 9.25 (1H, OH), 7.35 (d,  $J$  = 8.9 Hz, 2H), 6.69 (d,  $J$  = 8.7 Hz, 2H), 2.05 (s, 3H).  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$  167.6 (C=O), 131.4 (C-N), 154.1, 120.8, 115.5, 23.5. FT-IR: 1656  $cm^{-1}$ .

1-aza-2-cycloheptanone: M.P. 68 °C.  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  7.79 (br 1H, NH), 3.13-3.22 (m, 2H), 2.46-2.43 (m, 2H), 1.78-1.61 (m, 6H).  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$  180.2 (C=O), 41.9 (C-N), 37.2, 30.6, 29.7, 24.1. FT-IR: 1647  $cm^{-1}$ .

*N*-(4-nitrophenyl)acetamide: M.P. 213 °C.  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  10.2 (br 1H, NH), 8.25 (d,  $J$  = 9.3 Hz, 2H), 7.82 (d,  $J$  = 9.2 Hz, 2H), 2.09 (s, 3H).  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$  169.7 (C=O), 147.8 (C-N), 143.1, 125.9, 119.5, 22.7. FT-IR: 1670  $cm^{-1}$ .

*N*-(4-chlorophenyl)acetamide: M.P. 177 °C.  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  10.4 (br 1H, NH), 7.65 (d,  $J$  = 7.9 Hz, 2H), 7.35 (d,  $J$  = 7.9 Hz, 2H), 2.06 (s, 3H).  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$  168.7 (C=O), 139.8 (C-N), 128.9, 127.1, 120.5, 23.7. FT-IR: 1673  $cm^{-1}$ .

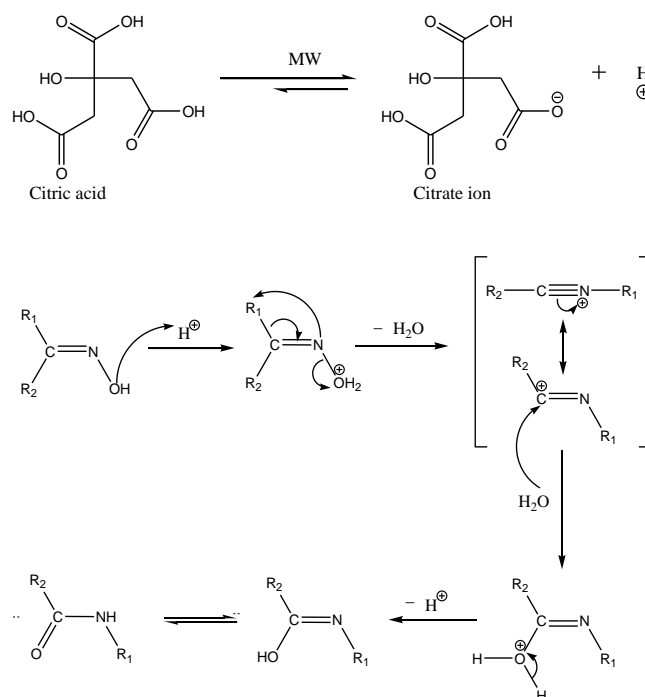
*N*-(4-methoxyphenyl)acetamide: M.P. 125 °C.  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  7.90 (br 1H, NH), 7.39 (d,  $J$  = 8.9 Hz, 2H), 6.69 (d,  $J$  = 8.7 Hz, 2H), 3.90 (s, 3H), 2.10 (s, 3H).  $^{13}C$ -NMR ( $CDCl_3$ ):  $\delta$  169.2 (C=O), 159.2 (C-N), 135.1, 122.2, 114.9, 59.0, 21.9. FT-IR: 1650  $cm^{-1}$ .

## 3. Results and Discussion

The amides of variously substituted ketones, through rearrangement reaction of their oximes using environmentally benign catalysts have been synthesised under green chemistry conditions (Fig. 1). As described earlier, synthesis of amides from ketoximes is an acid catalyzed reaction. Therefore, this reaction tried with different reagents, which are acidic in nature and easily available in laboratories. The synthesis succeeded in finding  $C_6H_8O_7 \cdot H_2O$  over TBAB, catalytic system, which work well under microwave irradiations and solvent free conditions. To begin with benzophenoxime, taken as model compound for investigation, its reaction with  $C_6H_8O_7 \cdot H_2O$  in the presence of TBAB was carried out under MW irradiations. Initially,  $C_6H_8O_7 \cdot H_2O$  was taken in small amounts (40 mg) and TBAB was taken in very small catalytic amount (50 mg) for the reaction with 1 mmol oxime in an open vessel at a moderate temperature of 30 °C, the desired product was formed, but it was attained in low yield which is in line with the results reported in the literature. Evidently, the yield of the product was required to be elevated. Hence, when the reaction was carried out in the presence of 200 mg  $C_6H_8O_7 \cdot H_2O$  and 100 mg TBAB and by elevating the temperature up to 40 °C, the product was attained in about 72-85% yield. Use of phase transfer catalysts TBAB made the reaction mixture homogeneous.

The method was then extended to other aromatic ketoximes substituted with electron donating and electron withdrawing substituents such as 4-hydroxyacetophenoxime, acetophenoxime, 4-nitroacetophenoxime, 4-chloroacetophenoxime, and 4-methoxyacetophenoxime. Synthesis of  $\epsilon$ -caprolactam from

cyclohexanoxime was also carried out and the product was obtained in good yield. The yields of the products formed are summarized in Table 1.



**Fig. 1** Expected Reaction Mechanism for the synthesis of amides from variously substituted ketones through rearrangement reaction of their oximes under solvent-free conditions.

**Table 1** Synthesis of amides from ketoximes (1 mmol) using  $C_6H_8O_7 \cdot H_2O$  (200 mg) over TBAB (100 mg) at 40 °C.

S. No.	Reactants	Products	Yield (%)	Time (sec)
1	benzophenoxime	N- Phenylbenzamide	85	50
2	4-hydroxyacetophenoxime	N-(4-hydroxyphenyl)acetamide	82	60
3	acetophenoxime	N- Phenylacetamide	80	50
4	cyclohexanoxime	1-aza-2-cycloheptanone	72	80
5	4-nitroacetophenoxime	N-(4-nitrophenyl)acetamide	85	90
6	4-chloroacetophenoxime	N-(4-chlorophenyl)acetamide	86	90
7	4-methoxyacetophenoxime	N-(4-methoxyphenyl)acetamide	84	75

#### 4. Conclusion

The rearrangement of ketoximes into their more stable amide isomers have been investigated and worked on mild, eco-friendly and easy to handle, acid catalytic system, which efficiently yield amides from ketoximes under solvent-free conditions upon microwave irradiations.

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