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# One-pot Efficient Oximation-Beckmann Rearrangement of Ketones Catalyzed by $Fe_3O_4$ Under Solvent-free Conditions

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$Fe_3O_4$ was employed as an efficient and magnetically separable catalyst for the synthesis of amides *via* one-pot Beckmann rearrangement of ketones under solvent-free conditions. Various secondary amides were synthesized by this method in moderate to good yields. The catalyst showed high thermal stability and was recovered and reused at least five times without any considerable loss of activity. The present process is environmentally benign and economical.

**Keywords:** Magnetic, Beckmann rearrangement, Green catalyst, Ketones, $Fe_3O_4$

## INTRODUCTION

In modern synthetic organic chemistry Lewis acid-catalyzed reactions allow smooth transformation of various functional groups [1]. However, there are many limitations associated with the use of homogeneous Lewis acids. For example, resulting inorganic salts are usually harmful to the environment and the work-up usually results in complete decomposition of the catalyst. In recent years to avoid these problem, heterogeneous catalytic systems have been used extensively in various synthetic transformations [2]. Straightforward experimental procedures, mild reaction conditions, reusability of catalysts and minimal waste disposal, are advantages of heterogeneous systems. In this context, magnetic particles are useful group of heterogeneous catalysts due to their numerous applications in medicine [3] and biotechnology as well as their easy separation from the reaction mixture by using an external magnet [4].

Amides are among the most important functional groups in nature that constitute versatile building blocks in synthetic organic chemistry, and also exhibit a wide range of industrial applications and pharmacological interest [5]. In recent years, diverse elegant methodologies were developed for the synthesis of amides, including reaction of carboxylic acids and derivatives (halides, anhydrides, or esters) with amines [6], oxidative amidation reaction in the presence of various catalyst [7], amino carbonylation of haloarenes [8], Schmidt reaction [9], hydroamination of alkynes [10] transamidation of primary amides [11] and Beckmann rearrangement [12].

The Beckmann rearrangement, is one of the most important and useful transformation in synthetic chemistry. It is generally, effected starting from an oxime that is derived from the corresponding ketone. The classical Beckmann rearrangement requires excess or stoichiometric amounts of strong protic acids such as concentrated sulfuric acid or phosphoric acid [13]. To date, many alternative homogeneous and heterogeneous catalysts, such as silica sulfuric acid [14], zeolites [15], cesium carbonate [16], Ferric chloride [17], $Yb(OTf)_3$ [18], $RuCl_3$ [19], bismuth(III) chloride [20], copper salts [21], chloral [22], 1-chloro-2,3-diphenylcyclo-propenium ion [23], *p*-toluene-sulfonylchloride (TsCl) [24] and zinc oxide [25] have been applied for both aromatic and aliphatic ketones. However, there are several factors in some of these methods which limit their applications. In many of these methods, toxic reagents, harsh conditions, and harmful organic solvents are

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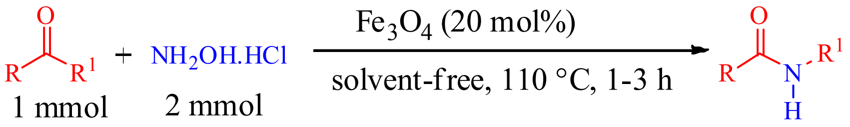


*Scheme 1*. Oximation-Beckmann rearrangement of ketones in the presence of $Fe_3O_4$

**Table 1.** Optimization of Reaction Conditions Using the Model System[a]

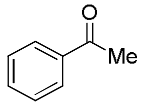
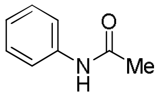
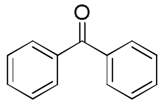
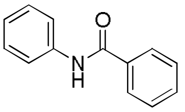
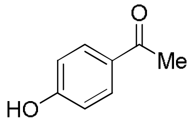
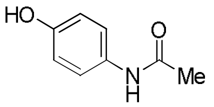
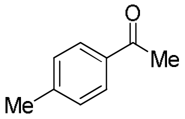
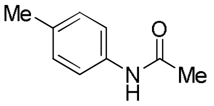
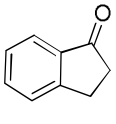
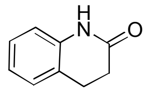
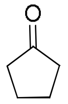
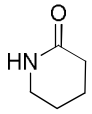
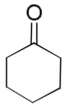
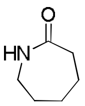
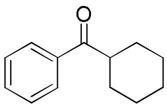
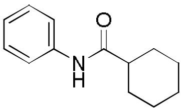
| Entry | Catalyst (mol%) | Solvent | Time (h) | Temp. (°C) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $Fe_3O_4$ (20) | EtOH/$H_2O$ | 3 | 110 | 10 |
| 2 | $Fe_3O_4$ (20) | $H_2O$ | 3 | 110 | 10 |
| 3 | $Fe_3O_4$ (20) | EtOH | 3 | 110 | 0 |
| 4 | $Fe_3O_4$ (20) | $CH_3CN$ | 3 | 110 | 0 |
| 5 | $Fe_3O_4$ (20) | DMSO | 3 | 110 | 0 |
| **6** | **$Fe_3O_4$ (20)** | - | **1** | **110** | **90** |
| 7 | $Fe_3O_4$ (10) | - | 1 | 110 | 50 |
| 8 | $Fe_3O_4$ (5) | - | 1 | 110 | 30 |
| 9 | - | - | 1 | 110 | 0 |
| 10 | $Fe_3O_4$ (20) | - | 1 | 70 | 60 |
| 11 | $Fe_3O_4$ (20) | - | 1 | 130 | 92 |
| 12 | $FeCl_2$ (20) | - | 1 | 110 | 70 |
| 13 | $FeCl_3$ (20) | - | 1 | 110 | 75 |
| 14 | $FeSO_4$ (20) | - | 1 | 110 | 60 |

[a]Reaction conditions: ketone (1 mmol), hydroxylamine hydrochloride (2 mmol), solvent (2 ml). [b]Isolated yield.

used. Moreover, the tedious work-up procedures are expensive or not-accessible. Also, long reaction times and by-products formation are other drawbacks of these protocols. To the best of our knowledge, despite their widespread use in organic synthesis, there is no report in which magnetic $Fe_3O_4$ has been used as catalyst for the synthesis of amides via one-pot Beckmann rearrangement. We now wish to report a simple and efficient process for one-pot Beckmann rearrangement of ketones to amides using $Fe_3O_4$ under solvent-free conditions (Scheme 1). Magnetic properties of this catalyst led to its easy separation as well as reusability.

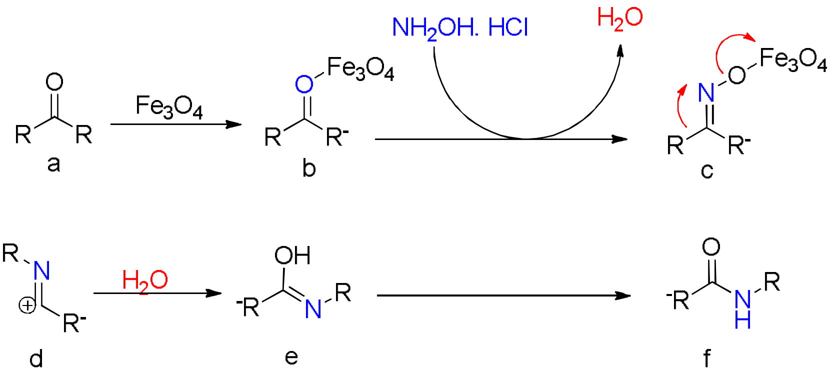
Optimization of the reaction conditions was initiated using acetophenone and hydroxylamine hydrochloride salt as model substrates. The results are summarized in Table 1. The first reaction was performed under the following conditions: acetophenone (1 mmol), hydroxylamine hydrochloride salt (2 mmol), $Fe_3O_4$ as the catalyst (20

**Table 2.** One-pot Oximation-Beckmann Rearrangement of Ketones Catalyzed by $Fe_3O_4$[a]

| Entry | Substrate | Product | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | 1 | 90 |
| 2 |  |  | 1 | 95 |
| 3 |  |  | 3 | 70 |
| 4 |  |  | 1 | 85 |
| 5 |  |  | 1 | Trace |
| 6 |  |  | 3 | 85 |
| 7 |  |  | 3 | 80 |
| 8 |  |  | 1 | 70 |

[a]Reaction conditions: catalyst (20 mg), ketone (1 mmol), hydroxylamine hydrochloride (2 mmol), 110 °C, solvent-free, 1 h. [b]Isolated yield.

mol%), a mixture of EtOH/$H_2O$ (1:1, 2 ml) as the solvent at 110 ºC. After 3 h of reaction time, the desired amide product was isolated in only 10% yield (Table 1, entry 1). Owing to the improved yield, first the effect of solvent on the efficiency of the reaction was considered. To this end, some organic solvents as well as $H_2O$ were examined, however, none of them was encouraging (Table 1, entries 2-5). Surprisingly, when the reaction was conducted under solvent-free conditions, the yield was dramatically increased (Table 1, entry 6). Efficiency decreases according to the reduction of catalyst loading and under catalyst-free conditions the yield diminished to 0% (Table 1, entries 7-9).



*Scheme 2*. The probable mechanistic pathway of one-pot oximation-Beckmann rearrangement of ketones in the presence of $Fe_3O_4$.

**Table 3.** Reusability of $Fe_3O_4$ in the One-pot Beckmann Rearrangement of Ketones[a]

| Run | Reusability (%) | Yield (%)[b] |
|---|---|---|
| 1 | 95 | 90 |
| 2 | 90 | 80 |
| 3 | 88 | 80 |
| 4 | 85 | 75 |
| 5 | 80 | 70 |

[a]Reaction conditions: catalyst (20 mg), ketone (1 mmol), hydroxylamine hydrochloride (2 mmol), 110 °C, solvent-free, 1 h. [b]Isolated yield.

Finally, the role of temperature was probed. It was observed that reducing the temperature to 70 °C led to a significant reduction in the efficiency, whereas increasing the temperature to 130 °C enhanced the yield by a small amount (Table 1, entries 10 and 11). For comparison, the catalytic effect of some iron salts such as $FeCl_2$, $FeCl_3$, and $FeSO_4$ was investigated for this transformation but all of them lacked the competence as that of $Fe_3O_4$ (Table 1, entries 12-14).

With the optimal conditions in hand, we next studied the substrates scope of this reaction by screening the ketone. To this end, a variety of symmetrical and unsymmetrical ketones were subjected under optimal conditions and the result are depicted in Table 2. With the exception of indenone (entry 5), other ketones were converted to the corresponding amide in high yields. In all cases of alkylarylketones (entries 1, 3, 4 and 8), just one of the two possible amides were recovered where the migration of an aryl group predominated over the alkyl group owing to preferred migratory aptitude. All products were known and characterized by IR, $^1H$ and $^{13}C$ NMR data as well as by comparison of their physical data with the literature [14, 26].

The probable mechanistic pathway that can explain the formation of one-pot oximation-Beckmann rearrangement of ketones is depicted in Scheme 2.

**Table 4.** $Fe_3O_4$ Catalyzed One-pot Oximation-Beckmann Rearrangement of Acetophenone with Hydroxylamine Hydrochloride in Comparison with some Previously Reported Catalysts

| Catalyst | Temp. (°C) | Solvent | Time (h) | Yield (%) | Ref. |
|---|---|---|---|---|---|
| $Fe_3O_4$ | 110 | - | 1 | 90 | Present work |
| oxalic acid | 110 | - | 8 | 69 | Chandrasekhar *et al.* [12] |
| Trifluoro acetic acid | 70 | Trifluoroacetic acid | 16 | 80 | Arico *et al.* [27] |
| Silica Sulfuric Acid | MW | - | 8 min | 92 | Eshghi *et al.* [14] |
| Zinc oxide | 140 | - | 1 | 90 | Sharghi *et al.* [25] |
| Ferric chloride | 130 | - | 1 | 90 | Mahajan *et al.* [17] |

Easy separation by external magnet and reusability up to five times are prominent features of our catalyst. Reusability of the catalyst was tested in the model reaction. After completion of the reaction in the first run, the catalyst was easily separated from the reaction mixture by using an external magnet; it was washed twice with ethyl acetate, dried at ambient temperature and immediately used in the next step. The reaction was repeated for up to five consecutive runs without significant change in the efficiency of the reaction (Table 3).

The efficacy of $Fe_3O_4$ in comparison with some previously reported catalysts of acetophenone with hydroxylamine hydrochloride is shown in Table 4. The advantages of our catalyst is evident regarding the time, conditions of the reactions, ease of separation and reusability.

In conclusion, we have presented a simple and effective method for the direct conversion of ketones to secondary amides. High yields, being an inexpensive and easy recoverable catalyst ($Fe_3O_4$), and the absence of solvent are advantages of the present protocol.

### General Procedure for One-pot Oximation-Beckmann Rearrangement of Ketones in the Presence of $Fe_3O_4$

To a mixture of ketone (1 mmol) and hydroxylamine hydrochloride (2 mmol) was added 20 mg of $Fe_3O_4$. The mixture was heated and stirred at 110 °C for 25 min. The progress of the reaction was monitored by TLC. After 1 h, $Fe_3O_4$ was separated with an external magnet from the reaction mixture and washed with deionized water and diethyl ether repeatedly. Water (50 ml) was then added to the reaction mixture and extracted with $CH_2Cl_2$ (2 × 25 ml) and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to give the crude product. The residue was subjected to column chromatography using n-hexane/ethyl acetate (4:1) as an eluent to afford pure product.

## ACKNOWLEDGEMENTS

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