Synthesis of Acetaminophen by Liquid Phase Beckmann Rearrangement of 4-Hydroxyacetophenone Oxime over Nano-Ordered Zn-MCM-41

Mohammad G. Dekamin,* Neda Nazary

Pharmaceutical and Biologically-Active Compounds Research Laboratory, Department of chemistry, Iran University of Science and Technology, Tehran, 16846-13114, Iran

E-Mail: *mdekamin@iust.ac.ir*

Abstract: Nano-Ordered Zn-MCM-41 materials were synthesized using different zinc sources and applied for liquid phase Beckman rearrangement of 4-hydroxyacetophenone oxime to acetaminophen. The reaction conditions such as amount of the catalyst and solvent were optimized to afford acetaminophen in high yields. It was found that aprotic solvents with high dielectric constant are preferred for this transformation.

***Keywords*:** Acetaminophen; Beckmann Rearrangement; 4-Hydroxyacetophenone Oxime, Zn-MCM-41; Nano-Ordered Catalyst.

Introduction

The Beckman rearrangement of ketoximes to amides or lactams in the presence of acid catalysts is widely used for the preparation of acetaminophen and caprolactam, the monomer used in the production of nylon-6, in chemical industry. Acetaminophen (*N*-acetyl-*p*-aminophenol or Paracetamol) is a valuable non-steroidal anti-inflammatory drug in widespread use for decreasing of pain and fever in a variety of patients, including children, pregnant women, the elderly; and those with osteoarthritis, simple headaches, and non-inflammatory musculoskeletal diseases [1,2]. Since its first synthesis by Morse in 1878, acetaminophen has been one of the most widely used analgesics and an important commodity. Traditionally, the large-scale preparation of acetaminophen mainly employs the acetylation of 4-aminophenol with acetic anhydride. As the main use for acetaminophen is as a pharmaceutical, the presence of impurities must be kept at very low values.

In the mid of 1980s, Davenport and Hilton reported an innovative method for the preparation of acetaminophen that involves a two-step process. The first step involves reacting of 4-hydroxyacetophenone with hydroxylamine hydrochloride to afford the corresponding ketoxime (4-hydroxyacetophenone oxime) followed by the Beckmann rearrangement in the presence of an acid catalyst, such as fuming sulfuric, hydrochloric, trifluoroacetic, methanesulfonic or *p*-toluenesulfonic acid, amberlyst, nafion, or thionyl chloride in liquid sulfur dioxide. The use of homogeneous acid catalysts requires tedious workup procedures and the necessary neutralization of the strong acidic media produces undesired wastes. For instance, when oleum is used as a catalyst, acetaminophen is recovered from the reaction mixture by neutralization of sulfuric acid with aqueous ammonia. In this case a large amount of ammonium sulfate is formed. Therefore, the use of insoluble acid catalysts will allow an easy separation work up (no neutralization step required) and catalyst recycling, avoiding equipment corrosion and contaminant wastes is in high demand [3,4]. In this context, modified MCM nanoreactors demonstrate high potential to replace the traditional homogeneous catalytic systems. MCM-41 is a novel mesoporous material first described by Mobil researchers in 1992. MCM-41 possesses unidirectional channel-like pores of uniform size, which are arranged in a regular hexagonal pattern. The pore diameters are adjustable in the range 15–100 Å, depending on the synthesis conditions, such as temperature, type, and size of the templating tetraalkylammonium cations. Current research on MCM-41has two major aims. One is to find cheaper raw materials for synthesis. The other aim is to modify the framework of

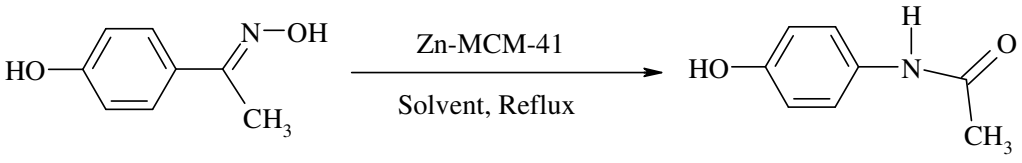
MCM-41, to generate catalytic sites needed for different types of reactions. Isomorphous substitution of Al, B, Ti, Fe, Zn, Ga or V in the MCM-41 framework has been described in the literature [5,6].

In continuation of our interest to develop different environmentally benign protocols for organic transformations using solid acids [7-9], especially atom economic reactions such as Fries [7] and Thia-Fries [8] rearrangement, we herein wish to report efficient Beckman rearrangement of 4-hydroxyacetophenone oxime over nano-ordered Zn-MCM-41to afford acetaminophen in high yield.

Results and Discussion

Zinc-substituted MCM-41 samples (Zn-MCM-41) were synthesized *via* an introduced hydrothermal method with *in-situ* incorporation of zinc. The obtained Zn-MCM-41 samples were characterized by FT-IR spectroscopy [6].

The Beckmann rearrangement of 4-hydroxyacetophenone oxime was investigated in the liquid phase using 0.1 g Zn-MCM-41, pre-activated in air at 400 ^{o}C, suspended in a solution of 0.15 g (1 mmol) of 4-hydroxyacetophenone oxime in 10 mL of different solvents such as EtOH, MeOH and acetone (**Scheme 1**). The reaction mixture was heated under reflux conditions in each case and stirred for 1 h. Then, the reaction mixture was filtered and diluted with methanol and the reaction products were analyzed using GC or after recrystallization of the products from EtOH by measuring their melting points.



Scheme 1. Beckmann rearrangement of 4-hydroxyacetophenone oxime to acetaminophen.

Interestingly, the nature of solvent influences the reaction performance strongly. It is noteworthy that the reaction did not proceed in the polar protic media such as EtOH or

MeOH. However, in the presence of a polar aprotic solvent such as acetone, the reaction progressed to a considerable conversion (**Table 1**).

Table 1. Solvent screening for the Beckmann rearrangement of 4-hydroxyacetophenone catalyzed by Zn-MCM-41

Entry	Solvent	Dielectric constant (D^a)	Conversion (%)
1	Ethanol	25.3	0
2	Methanol	33.0	0
3	Acetone	21.01	87

[a] Debye.

Furthermore, acetaminophen was produced selectively in the reaction mixture (87% isolated yield after 1 h). In the Beckmann rearrangement, it is well known that the migrating group is generally *anti* to the leaving group. Hence, the predominant *anti*-migration of 4-hydroxyphenyl group results in the high selectivity toward acetaminophen. Therefore, there were no other products, such as *N*-methyl-*p*-hydroxybenzamide (MHBA) or *p*-aminophenol, which may be formed as a result of *syn*-migration of the methyl substituent or by hydrolysis of acetaminophen, respectively.

Conclusion

Acetaminophen was synthesized over nano-ordered Zn-MCM-41. Zn-MCM-41 is very active and selective for the preparation of acetaminophen by Beckmann rearrangement, achieving good conversion of the corresponding oxime in relatively short reaction time. Furthermore, the nature of the solvent has a strong effect on the activity of the catalyst.

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Materials

Methanol, ethanol, 4-hydroxyacetophenone, *N*-cetyl-*N*-*N*-*N*-trimethylammonium bromide (CTAB), zinc chlorid and solvents were obtained from Merck with the maximum purity degree, and used as received. In the case of 4-hydroxyacetophenone, the purity of the commercial chemical was >98%. However, after preparing the 4-hydroxyacetophenone oxime, it was purified by crystallization and its purity was over 99.8%. The synthesis of 4-hydroxyacetophenone oxime was carried out by the general method reported in the literature [4].

General Procedure for the Beckman Rearrangement of 4-Hydroxyacetophenone Oxime

The Beckmann rearrangement of 4-hydroxyacetophenone oxime was carried out in the liquid phase in a 50 mL two-necked, round-bottomed flask immersed in a thermo-stated bath and equipped with a reflux condenser and a magnetic stirrer. For the cases when acetone or an alcohol was used, the reaction temperature was maintained at the reflux temperature. A typical reaction run was as follows: 0.1 g catalyst, pre-activated in air at 400 ˚C, was suspended in a solution of 0.15 g (1 mmol) of 4-hydroxyacetophenone oxime in 10 mL of solvent, which was allowed to equilibrate the set temperature. The reaction mixture was heated to reflux conditions and stirred for 1 h. When the reaction was completed, the reaction mixture was filtered and diluted with methanol and the reaction products were analyzed using by GC or comparison of their physical data with authentic samples after recrystallization of the products from EtOH.

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