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Short Communication

Self-catalyzed direct amidation of ketones: A sustainable procedure for acetaminophen synthesis

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ABSTRACT

High yielding amination of ketones and benzaldehyde in acid-less conditions has been conducted on several ketones to achieve amides and nitriles. The reactivity of the selected substrates showed to depend on both oxiamation and Beckmann rearrangement reaction rates. Oxiamation allows the in-situ production of hydrochloric acid that enables Beckmann rearrangement of the oxime to form the corresponding amide or nitrile. It is noteworthy that, using this one-pot synthetic approach, *N*-acetyl-4-aminophenol (acetaminophen drug), can be easily synthesized starting from 4-hydroxy-acetophenone in high yield. Acetanilide and ε-caprolactam can be also efficiently synthesized employing this synthetic procedure.

1. Introduction

Amides are building blocks and/or final product in a wide range of commodities, i.e., rubber, paper, varnish, in water treatment and in the synthesis of several pharmaceutical molecules [1–4]. A poignant example is acetaminophen (*N*-acetyl-4-aminophenol), the amide commercially known as acetaminophen, whose production is in continuous growth [4–6].

In the past, the aspects related to the sustainability (economical and environmental) inherent to the industrial production of amide have been poorly considered, on the contrary recently, the development of new processes to fulfill this requirement has become of great interest [5].

In many industrial processes amides are synthesized by a two-step reaction: oxiamation of the ketone, followed by Beckmann rearrangement [5–9]. The first step proceeds in the presence of a base, thus obtaining hydroxylamine as nucleophile, while the rearrangement is generally carried out in mineral acid [10–12]. Furthermore, neutralization typically with aqueous ammonia is required to recover the pure product [5,6]. A commodity already produced according to this synthetic approach is caprolactam the monomer of nylon [6] even though nowadays, the new plant is mainly based on the new sulfuric acid free processes (Scheme 1, Enichem–Sumitomo process) [7–9].

The commercial drug acetaminophen is nowadays produced in large scale via Hoechst-Celanese process based on the Beckmann rearrangement of 4-hydroxyacetophenone oxime catalyzed by thionyl chloride [5].

Other synthetic approach employs ionic liquids in combination with Lewis acids in two stages but work-up steps are required, similarly [13,14].

The use of organic compounds to promote the Beckmann rearrangement has long been known, [15,16], however trifluoroacetic acid (TFA) has been employed in the Beckmann rearrangement only for activated oxime carbonate [17].

Recently, we have reported the use of TFA as organo-catalyst for the Beckmann rearrangement of keto-oxime to amides [18–21]. The proposed reaction mechanism envisages the formation of the oxime ester of the TFA, which, after rearrangement, forms a trifluoroacetyl amide. The latter is the catalytic active species, see Scheme 2 [18–21].

An efficient one-pot synthesis of caprolactam from cyclohexanone in TFA/CH_3CN in the presence of a moderate excess of hydroxylamine hydrochloride (HOA) has been reported by Luo and coworkers [22,23]. Recently, we have reported an improved synthetic procedure that employed solventless reaction condition and we successfully tested its general application on several ketones and aldehyde [24].

Direct oxiamation-Beckmann rearrangement of cyclohexanone to ε-caprolactam has also been achieved in liquid phase reaction starting from cyclohexanone, ammonia and air in the presence of bifunctional

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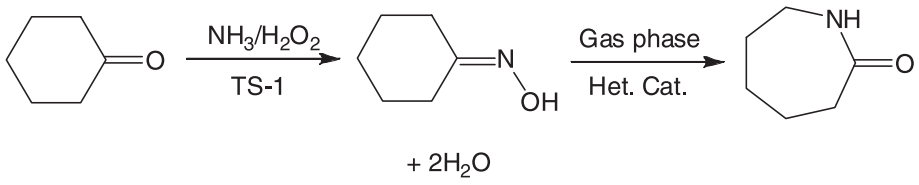


Scheme 1. Enichem–Sumitomo process for the production of ε -caprolactam.

catalysts [25,26]. This complex three-step reaction (ammonia oxidation to hydroxylamine, oximation of cyclohexanone and Beckmann rearrangement of the cyclohexanone oxime) gives caprolactam in moderate yield (40–50%) and the procedure has not been investigated on different ketones.

One-pot synthesis of amides from ketones by microwave irradiation was also observed with selected ketones by Feng and coworkers in moderate yield [27]. Several metal-catalyzed one-pot syntheses of amides from aldehyde have been also reported although these processes require either long reaction time, high temperature or toxic solvents [28,29]. Sharghi and Sarvari reported that TiO_2 catalyzes the one step oximation Beckmann rearrangement in solventless condition in good yield [30].

In this work we account for the first time on the self-catalyzed amination of ketones to amides by using hydroxylamine hydrochloride as the amination agent in the absence of any additional acids or bases. Employing this new reaction condition 4-hydroxyacetanilide (AcP), (acetaminophen drug), was synthesized via 4-hydroxyacetophenone (4-HAP). Furthermore, the procedure was applied for the preparation of industrially relevant intermediates acetanilide (AcA) via acetophenone (AP) and caprolactam (CPL) via cyclohexanone (CyC) [5].

2. Experimental

For materials and more experimental details see supplementary materials.

All the reactions were carried out in a well stirred pressurized glass reactor thermostatted at temperatures comprised between 70 °C and 110 °C containing weighed samples of the solvent and reagents typically 1.5 mmol of the selected ketone, 4.4 mmol of HOA and in some cases 22 mmol CH_3CN.

Reaction products were analyzed by Gas Cromatograph (GC), Gas Cromatograph coupled mass spectroscopy (GC–MS) and by high performance liquid chromatography (HPLC). The ^1H nuclear magnetic resonance (NMR) spectra were recorded at 298 K, referred to tetramethylsilane.

3. Results and discussion

Table 1 shows the reactivity of selected aldehydes and ketones with HOA without the use of any additional acid and in acetonitrile as solvent. Aldehydes resulted generally more reactive than ketones, likely because of the easiest attack of HOA, and they are mainly converted into nitriles [31]. On the other hand, ketones gave as main product amides. Thus, in these reaction conditions, benzaldehyde was easily converted into benzonitrile in high yield (entry 1, Table 1); benzamide was detected only in traces, meanwhile the main by-product was benzoic acid [31]. A similar reactivity was observed for 4-nitrobenzaldehyde (entry 2, Table 1), which formed mainly 4-nitrobenzonitrile.

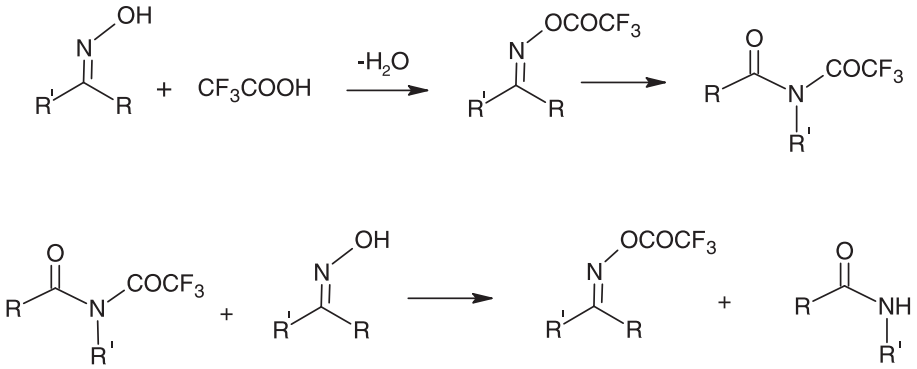
4-Isopropyl benzaldehyde and 2-hydroxy benzaldehyde (entries 3 and 4 Table 1) gave almost quantitative conversion and high selectivity toward the corresponding benzonitrile. The negligible substituent effect is likely due to the high activity of the aldehyde compared to ketones.

When heptanal was employed as starting material the reaction resulted in the complete conversion of the substrate, however, the selectivity toward the amidation products was only moderate (*ca* 50% entry 5, Table 1), this due probably to the even higher reactivity of aliphatic aldehyde compared to the aromatic ones.

As the above mentioned ketones showed only a moderate conversion to oximes, amides were the only rearrangement product. For instance, in the studied reaction conditions, the conversion of AP after 15 h resulted as high as 95%, while without solvent is quite modest (33%, entry 6, Table 1). In addition, the selectivity toward AcA was 85% and acetophenone oxime is present in trace amounts. On the contrary, without solvent the starting ketone was mainly converted into the corresponding oxime (80%). Most probably the beneficial effect of CH_3CN could be ascribed to reagent solubility, especially that of HCl (the acid catalyst of the Beckmann rearrangement) resulting from HOA nucleophilic attack of the ketone.

4-Methylacetophenone and 2-methylacetophenone both resulted quite reactive giving the corresponding amide in 70% of selectivity (entries 7 and 8, Table 1). The main difference between the two molecules is that 4-methylacetophenone gave also 20% of the corresponding oxime as by-product, while 2-methylacetophenone was partially converted into the corresponding amine and some oxidation products. This different behavior might be ascribed to the reactivity of the two ketoxime (the intermediate) in the Beckmann rearrangement. In fact 2-methylacetophenone rearranges more easily compared to 4-methylacetophenone [16,32].

The reactivity of CyC in the presence and in the absence of CH_3CN was also investigated (entry 9, Table 1). In this case the presence of the solvent does not influence the reaction outcome. In both



Scheme 2. Reaction mechanism of TFA catalyzed Beckmann rearrangement of ketoximes to amides.