Short Communication

One-pot oximation–Beckmann rearrangement of ketones and aldehydes to amides of industrial interest: Acetanilide, caprolactam and acetaminophen

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ABSTRACT

High yielding one-pot oximation–Beckmann rearrangement of ketones to amides in ktrifluoroacetic acid has been conducted on several ketones and aldehydes. The substrate reactivity showed to depend on both oximation and Beckmann rearrangement reaction rate. In this synthetic procedure, trifluoroacetic acid acts as solvent, acid catalyst and organocatalyst and can be easily recycled.

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1. Introduction

Amides are important building blocks in organic and material chemistry as they are widely employed not only in plastic, rubber, paper and color industry (crayons, pencils and inks), but also in water and sewage treatment[1–3]. Furthermore, numerous pharmaceutical molecules incorporate amides as core unit; N-acetyl-4-aminophenol and local anesthetic lidocaine and dibucaine are just few examples [1–4]. Thus, considering their importance as intermediate in the industry and as precursor in drug formulation, the development of simpler and more economical process for amide synthesis has been of great interest over the last twenty years [5].

Among the most commonly used synthetic approaches for these compounds many involve the reaction of amine with anhydrides, acyl chlorides or, in some cases, with the acid itself [1]. This latter approach results in the complete conversion of the substrate only when the water, formed during the reaction, is continuously removed [1].

Amides can also be synthesized by a two step reaction: oximation of ketones, a quite facile reaction generally carried out with hydroxylamine hydrochloride or sulfate in an aqueous or water–ethanol solution, followed by Beckmann rearrangement in mineral acids [4–10]. The first step proceeds in the presence of a base to allow the formation of the free hydroxylamine that then attacks the carbonyl group of the ketone.

On the other hand, Beckmann rearrangement is generally carried out in mineral acid i.e. H_2SO_4 or oleum [5–11], for which safety and/or disposal problems must be taken into account especially in the industrial practice [12–17]. Furthermore, the resulting amides are protonated, thus, dilution with water or neutralization of the acid (typically with aqueous ammonia) is required to recover the pure product [12–17]. A commodity produced according to this synthetic approach is caprolactam, the monomer of nylon [12–17]. Nowadays the oximation–rearrangement sequence in oleum is superseded by the Enichem–Sumitomo processes consisting of liquid phase ammoximation [13] followed by a gas phase Beckmann rearrangement [14–17].

Another interesting approach to amide synthesis uses ionic liquids in combination with Lewis acids. This procedure results in a high yielding Beckmann rearrangement for some activated oximes [18,19]. The process, however, requires a preliminary oximation stage and a tedious work-up for both oximation and Beckmann rearrangement.

Recently, examples of direct oximation–Beckmann rearrangement of cyclohexanone to ε-caprolactam has also been reported in liquid phase reaction starting from cyclohexanone, ammonia and air in the presence of bifunctional catalysts [20,21]. Similar results have been claimed by Uhde/Inventa-Fischer in the heterogeneously catalyzed liquid phase ammoximation–Beckmann rearrangement of cyclohexanone to caprolactam [22]. These processes are complex one-pot three-step reactions: ammonia oxidation to hydroxylamine, oximation of cyclohexanone and Beckmann rearrangement of the cyclohexanone oxime.

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However, the final product can be isolated only in moderate yield (20–50%) and the procedure has not been investigated on different ketones.

Several metal-catalyzed one-pot syntheses of amides from aldehyde have also been reported although these processes require either long reaction time, high temperature or toxic solvents [23,24]. In additions, these reactions do not occur with ketones which limit their synthetic interest.
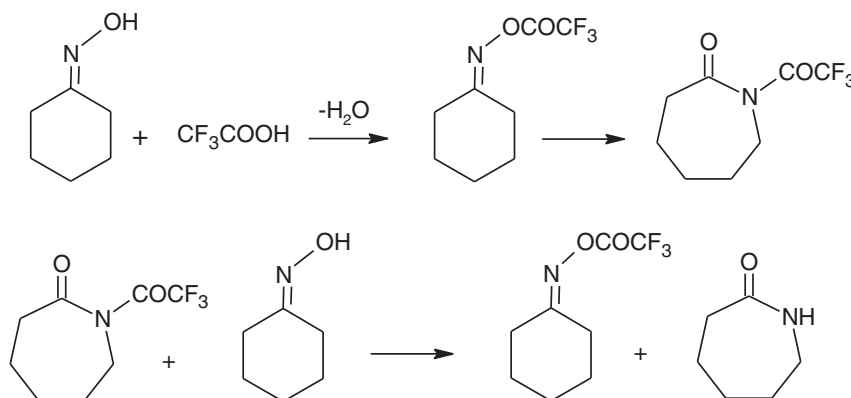
The use of trifluoroacetic acid (TFA) as catalyst in the presence of CH₂Cl₂ as solvent was firstly reported by Cossy and co-workers in the Beckmann rearrangement of oxime carbonate [25]. In this synthetic approach the key step is the formation of the oxime carbonate being more activated than the naked oxime in the Beckmann rearrangement due to the electron withdrawing effect of the carbonate group.

TFA has been also employed as catalyst for the Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam [26–28]. In particular, a TFA/CH₃CN mixture was used for a practical and high yielding synthesis of amides [26–28]. The proposed reaction mechanism envisages the formation of the oxime ester of the trifluoroacetic acid, which, after rearrangement, forms a trifluoroacetyl amide. This compound is the key intermediate of the trifluoroacetylation process of the oxime as it continuously reforms sustaining the catalytic cycle (Scheme 1).

In our previous work we outlined that the mechanism of the Beckmann rearrangement in TFA occurs via esterification of the oxime also for the acetophenone oxime and for the 4-hydroxyacetophenone oxime [29].

Recently, Luo and co-workers reported the Beckmann rearrangement of cyclohexanone oxime to caprolactam in TFA/CH₃CN optimizing the caprolactam yield by using conditions similar to those employed in our previous papers [26–30]. The same authors reported an oximation–Beckmann rearrangement of cyclohexanone to caprolactam using a TFA/CH₃CN system [31]. This synthetic procedure, although interesting, focuses only on one substrate i.e. caprolactam without discussing the general applicability of the system.

In this work, following our previous investigation on the Beckmann rearrangement of ketoximes, we account on a general approach for the synthesis of amides starting from ketones or aldehydes via a one-pot oximation–Beckmann rearrangement. Hydroxylamine is used in industrial processes as oximating agent after neutralization of its sulfate salt being hydroxylamine itself an unstable reagent [1–4]. Here we used hydroxylamine hydrochloride, which is a stable and soluble salt, as oximation agent and TFA as catalyst and solvent. The reaction is of general application and results in the high yielding preparation of amides. The use of TFA as catalyst and solvent renders the processes both sustainable and highly efficient. In fact, the reaction does not require any work-up operations as TFA can be removed by low temperature vacuum distillation and recycled. Furthermore, due to the TFA low protonation ability, the resulting amides can be easily recovered as pure compounds.

2. Experimental

2.1. Materials

All the solvent and products were employed as received without further purification. Acetophenone ≥ 98%, acetone ≥ 99.9%, 2-hydroxy-acetophenone ≥ 98%, 4-methylacetophenone ≥ 95%, 2-methylaceto-phenone ≥ 98%, 2,4,6 trimethylacetophenone ≥ 98%, 4-bromo acetophenone 98%, 2-bromo acetophenone 98%, propiophenone 99%, butyrophenone ≥ 99%, 2,2-dimethylpropiophenone 98%, isobutyro-phenone 97%, benzophenone ≥ 99%, 4-phenyl-2-butanone 98%, ethyl benzoylacetate 97%, 4-nitrobenzaldehyde 98%, 4-isopropyl-benzaldehyde 98%, 2-hydroxy benzaldehyde ≥ 98%, hexanal 98%, trifluoroacetic acid 99%, and hydroxylamine hydrochloride 99% were all Aldrich products; 4-hydroxiacethophenone ≥ 98% (HPLC) was a HPLC grade Fluka product. Cycloexanone 99.8% was an ACROS reagent. Benzaldehyde 99% was a Carlo Erba reagent. Deuterated chloroform and deuterated DMSO-d6 were EurisoTop products.

2.2. Instruments and analysis

Reaction products were analyzed by Gas Chromatography (GC) and Gas Chromatography coupled to Mass Spectroscopy (GC–MS), using an Agilent model 5975C interfaced with a GC Agilent model 7890 a HP5 capillary column (300 μm i.d. 30 m long, 95% methyl, 5% phenyl silicone phase).

The samples were also checked by a high performance liquid chromatography (HPLC). The instrument employed was a Perkin Elmer binary LC pump 250 with phenomenex Luna, 5 μm C18 100 Å, LC column 30 mm × 4.6 mm (detector: Perkin Elmer LC 235 C Diode Array), wavelengths: 255 nm and 220 nm; eluent: water–acetonitrile with a concentration gradient 60% water (9 min), 50% water (5 min) and 30% water (1 min).

The ¹H Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker AC 200 spectrometer operating at 200.13 MHz, and the sample temperature was maintained at 298 K. All the chemical shifts were referred to internal tetramethylsilane.

2.3. Ketones reactivity

All the reactions were carried out in a well stirred pressurized glass reactor thermostated at 70 °C temperature and containing weighed samples of the solvent and reagents.

In a typical experiment a glass reactor equipped with magnetic bar was charge with 1.5 mmol of the selected ketone or aldehyde, 4.4 mmol of hydroxylamine hydrochloride and 22 mmol of trifluoroacetic acid under inert atmosphere of nitrogen. The reaction time was computed after the heating fluid starts to circulate in the

Scheme 1. Reaction mechanism of TFA catalyzed Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam [26–28].