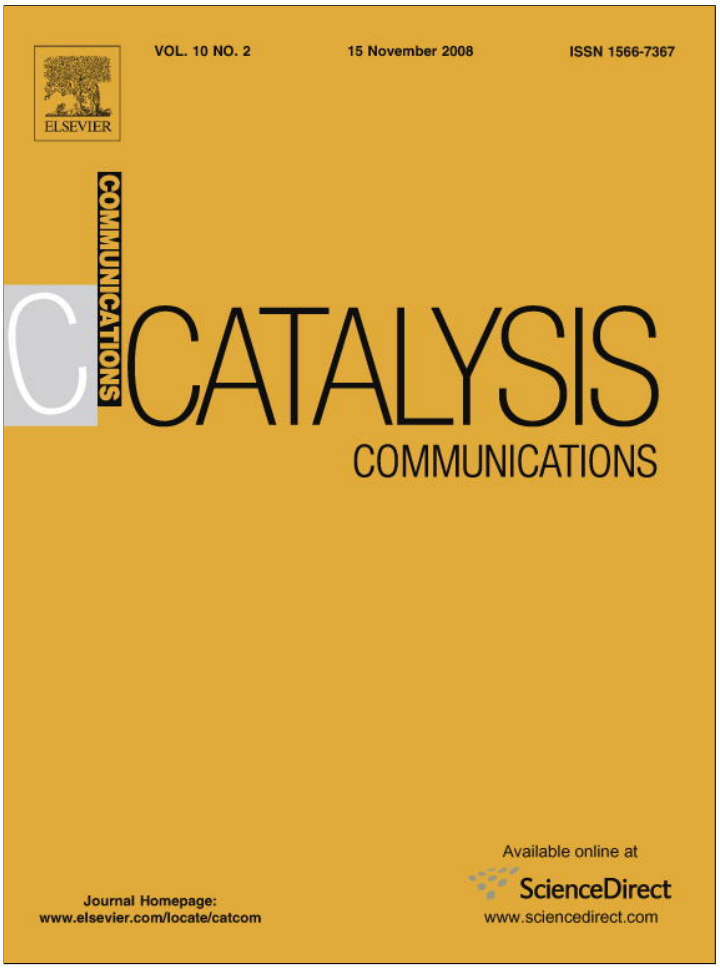

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Organocatalyzed Beckmann rearrangement of cyclohexanone oxime by trifluoroacetic acid in aprotic solvent

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ABSTRACT

The Beckmann rearrangement of cyclohexanone oxime to ε-caprolactam catalyzed by trifluoroacetic acid in aprotic solvents such as toluene, 1,2-dichloroethane, acetonitrile, benzonitrile, nitromethane and their mixtures is described. High yield and selectivity in ε-caprolactam have been observed. Data relative to cyclohexanone oxime protonation equilibrium, interaction of ε-caprolactam with the acid, solvent effect on reaction kinetics and apparent activation energy are given together with some thoughts on the reaction mechanism.

1. Introduction

Nowadays, the production of ε-caprolactam is mainly based on the Beckmann rearrangement of cyclohexanone oxime employing oleum as homogeneous catalyst [1,2]. In the industrial process problems due to product separation, hazardous working conditions, corrosion of the reactor and formation of large amounts of ammonium sulfate as by-product are encountered [1,2].

In order to overcome these problems a large variety of solid acids were employed as catalysts in the Beckmann rearrangement of cyclohexanone oximes both in gas and liquid phase processes [3–5]. However, the fast catalyst deactivation, which is the main problem encountered with the heterogeneous systems, limits their practical application only to complex plants with continuum catalyst regeneration [6].

Recently, progresses on the Beckmann rearrangement are observed by using organic co-catalysts and promoters and these studies directly derive from the early studies of Beckmann and Kuhara [7,8]. In their original works they respectively employed acetic anhydride and acetyl chloride as promoters for oximes rearrangement. In particular, Kuhara recognized the acetyl oxime as the active intermediate able to promote the reaction in the presence of hydrochloric acid [8]. Later, species like acetyl- and picril-oximes or oxime carbonate, tosylate, sulfonate etc. were extensively studied by many authors [8–10]. In general, reagents that allow the Beckmann rearrangement of ketoximes at relatively low temperatures convert the oximes to more reactive ether or ester intermediates [11]. These compounds, respect to the corresponding oximes, have a lower electronic density on the nitrogen atom and consequently a greater tendency to rearrange even without Brønsted acids [9,12–14]. More recently, it has been observed that 2,4,6-trichlorotriazine (TCT) in *N*,*N*-dimethylformamide (DMF) is able to react with oximes giving in high yield the corresponding amides [15]. A catalytic process has been developed by using TCT in the presence of $ZnCl_2$ as Lewis acid at 353–373 K in CH_3CN. In such a system, however, substrates like cycloalkanone oximes do not react [16].

The need of using strong inorganic acids in the Beckmann rearrangement of cyclohexanone oxime is accepted as a common synthetic practice [17]. However, on considering the recent developments regarding the mechanism of the rearrangement, this kind of reaction does not necessarily need high protonation ability [18]. For instance, cyclohexanone oxime in aqueous solvent is fully protonated in the pH range 2–3 [19]. In the acid catalyzed Beckmann rearrangement the key points are the proton transfer from the nitrogen to the oxygen and the concerted extraction of the water molecule with the displacement of the carbon atom. This process is allowed by the formation of electron-poor nitrogen, which is the driving force for the rearrangement together with a strong solvent participation effect which consists in assisting the 1–2 shift by a proton-jump type mechanism, a particular solvent participation mechanism of the acid itself [18,20].

The presence of a strongly electrophilic nitrogen may induce side reactions in the presence of nucleophiles such as water and/or the non protonated oxime [21,22]. As a matter of fact, a strong acid is required to ensure the complete protonation of the oxime, thus avoiding side reactions due to the non protonated oxime

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[21,22]. The solvent may play an important role on aiding the hydrogen transfer as well as the concerted water extraction with the consequent rearrangement [18]. This is the case of the Beckmann rearrangement of oximes in the presence of sulfamic acid [23]. Such a weak inorganic acid (pK_a = 1.18) allows the rearrangement of several oximes in non aqueous solvents: in particular, with cyclohexanone oximes a yield of 40% in ε-caprolactam at 363 K after 6 h has been reported [23].

The rearrangement of the acetyl cyclohexanone oxime gives acetyl caprolactam, which readily reacts in the presence of cyclohexanone oxime to give ε-caprolactam and acetyl cyclohexanone oxime [7]. In a previous paper a catalytic cycle based on the rearrangement of the acetyl cyclohexanone oxime to acetyl caprolactam was attempted, but several side reactions limited its synthetic efficacy [21]. On the progress of these studies, the synthesis of trifluoroacetyl cyclohexanone was carried out by addition of trifluoroacetic anhydride to the oxime, but together with the trifluoracetylated product a clear yield in ε-caprolactam was observed. Starting from this evidence we gave some preliminary results on the rearrangement of cyclohexanone oxime promoted by CF_3COOH in non aqueous solvent, where a practically quantitative conversion was obtained [21].

In the present paper we give new insight on the Beckmann rearrangement of cyclohexanone oxime catalyzed by CF_3COOH in aprotic solvent: data relative to cyclohexanone oxime protonation equilibrium, interaction of ε-caprolactam with the acid, solvent effect on reaction kinetics and apparent activation energy are also given.

2. Experimental

2.1. Materials

Reagents (cyclohexanone oxime, ε-caprolactam, trifluoroacetic acid), were purchased from Aldrich. The purity of the commercially available samples was checked by the usual methods (melting point, TLC, HPLC, GC and GC–MS) and further purifications were carried out when necessary. In particular, cyclohexanone oxime was crystallized from cyclohexane, dried in vacuo and stored under nitrogen at 248 K. Reaction solvents were HPLC grade products used without further purifications. Deuterated acetonitrile was purchased from Euriso-Top.

Table 1
Influence of dielectric constant of the solvent on initial reaction rate and on the selectivity at complete conversion

Entry	Solvent	ε[a]	10^5 r_0 (mol $L^{-1}s^{-1}$)	Selectivity at complete conversion (%)
A	Toluene	2.30	2.0	96
B	1,2-Dichloroethane	10.20	2.8	96
C	0.43 Acetonitrile/0.57 toluene	10.31[b]	3.3	93
D	0.55 acetonitrile/0.45 1,2-dichloroethane	20.76[b]	4.8	92
E	Benzonitrile	25.20	5.0	84
F	Nitromethane	35.87	6.7	94
G	Acetonitrile	37.50	6.7	92

Run conditions: T 363 K, cyclohexanone oxime concentration 0.29 mol L^{-1}, CF_3COOH concentration 1.0 mol L^{-1}, reaction volume 10 mL.
[a] Data from [19].
[b] Dielectric constant calculated following the procedure reported in [25].

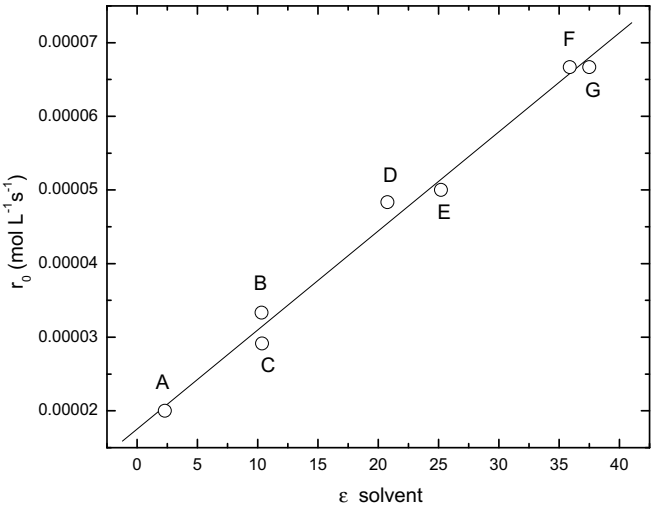


Fig. 2. Effect of the solvent and of the dielectric constant on initial reaction rate: A = toluene, B = 1,2-dichloroethane, C = 0.43 acetonitrile/0.57 toluene, D = 0.55 acetonitrile/0.45 1,2-dichloroethane, E = benzonitrile, F = nitromethane, G = acetonitrile. Run conditions: T 363 K, cyclohexanone oxime 0.29 mol L^{-1}, CF_3COOH 1.0 mol L^{-1}, reaction volume 10 mL.

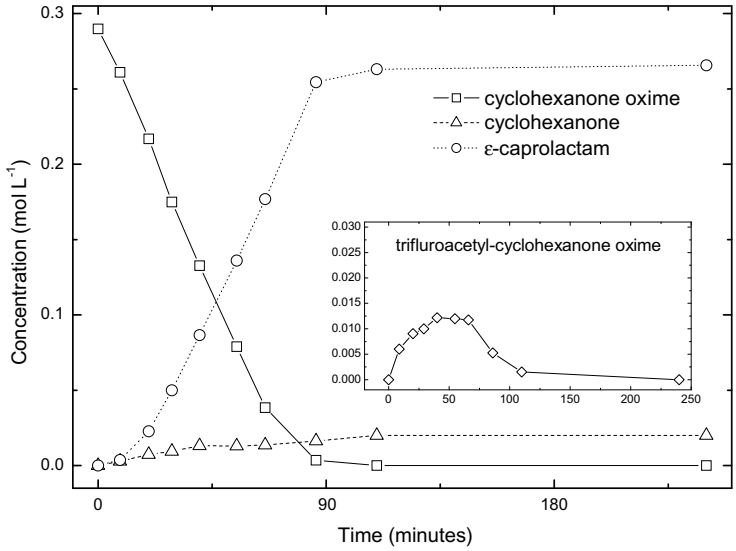


Fig. 1. Typical reaction profile. Run conditions: T 363 K, cyclohexanone oxime concentration 0.29 mol L^{-1}, CF_3COOH concentration 1.0 mol L^{-1}, reaction volume 10 mL, solvent CH_3CN.

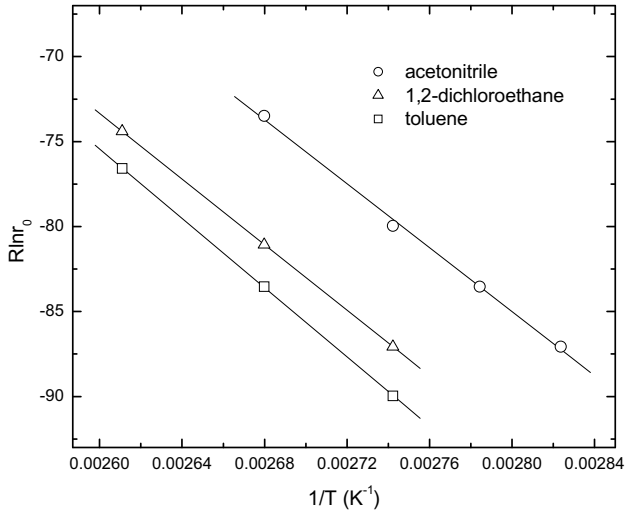


Fig. 3. Apparent activation energy in different solvent: acetonitrile 94 kJ mol^{-1}, 1,2-dichloroethane 96 kJ mol^{-1}, toluene 102 kJ mol^{-1}.

Table 2
Equilibrium constants for the reactions M + HA ↔ MHA in CD_3CN at different temperatures

Temperature (K)	*K* (cyclohexanone oxime) (L mol^{-1})	*K* (ε-caprolactam) (L mol^{-1})
248	25.2	2.0
268	12.4	2.3
288	7.2	2.6
298	5.4	2.8

M = cyclohexanone oxime or ε-caprolactam; HA = trifluoroacetic acid.

2.2. Reactions in batch

The kinetic runs were performed in a well-stirred pressurized glass reactor thermostated by a circulation bath in the range 354–383 K and containing weighed samples of the solvent and of the reagents. Small amounts of the reaction mixtures were drawn at different times and the samples were analyzed by GC and GC–MS, using an HP5 capillary column (300 m i.d. 30 m long, 95% methyl, 5% phenyl silicone phase). The samples were also checked by HPLC using a Perkin Elmer apparatus and a Lichrosphere 100 (RP-18, 5 m) column.

2.3. NMR measurements

All the ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer operating at 200.13 MHz. The sample temperature was varied in the range 248–298 K. The reagent concentrations were chosen in order to simulate the real catalytic conditions. In a typical experiment, a weighted amount of cyclohexanone oxime or ε-caprolactam (0.22 mmol) was dissolved in 0.75 mL of CD_3CN in a screw-cap tube and, after recording the ^{1}H NMR spectrum at the temperatures of interest; known amounts of CF_3COOH were successively added with a microsyringe. The substrate/acid ratio was progressively varied from 1:1 to 1:10. After every addition of acid the NMR spectra at the various temperatures were collected. A dead time of 10 min was waited after every acid addition or temperature change. The followed chemical shifts were that of the most downfield aliphatic signal in the case of cyclohexanone oxime and that of the NH group in the case of ε-caprolactam. All the chemical shifts were referred to internal tetramethylsilane.

3. Results and discussion

3.1. Concentration profile: reagent, intermediates and products

A typical concentration profile of the Beckmann rearrangement in acetonitrile as a solvent is reported in Fig. 1. A qualitative analysis shows that the reaction follows an apparent zero order kinetics until conversion of 70–80%. In the other investigated solvents analogous reaction profiles are obtained, even though a noticeable difference on the initial reaction rate is observed (see Table 1 and Fig. 2). Except in benzonitrile as a solvent, where the reaction has a selectivity of 84% in ε-caprolactam (due to side reactions of benzonitrile, e.g. hydration and condensation), in the other cases the

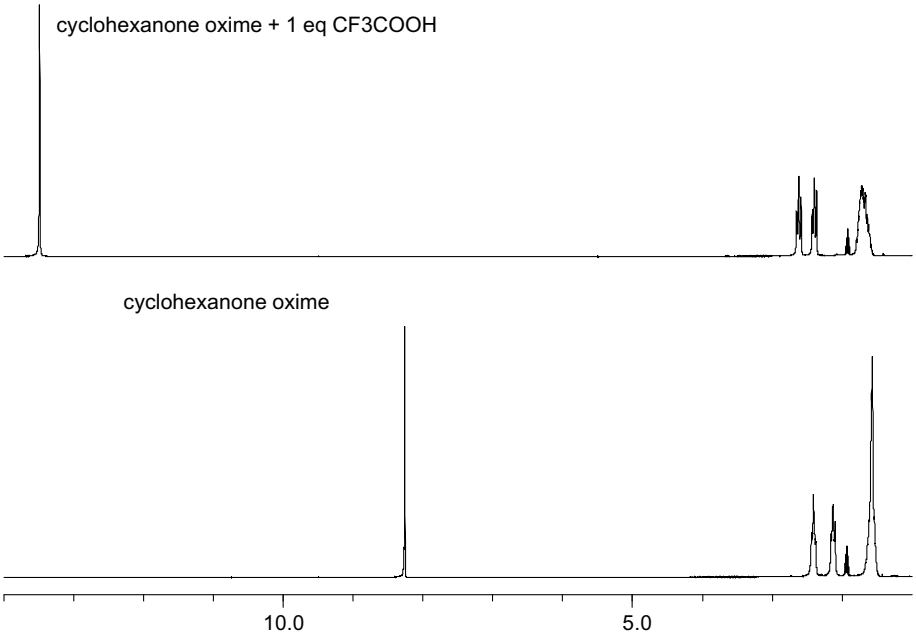


Fig. 4. ^{1}H NMR spectra (CD_3CN, 278 K) of cyclohexanone oxime (bottom) and cyclohexanone oxime + 1 equivalent of CF_3COOH (top).

selectivity is higher than 92%. As expected, in acetonitrile and nitromethane the selectivity at final conversion is slightly lower than in 1,2-dicholoroethane and toluene, probably because of the higher water content of these solvents. The formation of trifluoroacetyl-cyclohexanone oxime and trifluoroacetyl caprolactam as low concentration intermediates, the latter observed only in trace amount, suggests that a multi-stage reaction path is occurring.

In Fig. 3 the Arrhenius plot of the initial reactions rates in different solvents shows that the apparent activation energy of the reaction is poorly influenced by the solvent nature. The measured values are between 94 and 102 kJ mol^{-1}, which are similar to those reported for concentrated mineral acids and for oxime *p*-toluensolfonates in non aqueous solvent [9,19]. An almost negligible solvent effect on the reaction rate is observed (Table 1 and Fig. 2), suggesting that the transition state is poorly stabilized by solvation [24]. Furthermore, the quite linear trend observed between dielectric constant and initial reaction rate can not be simply explained in terms of Kirkwood theory [24], which means that a complex pathway relating charged, neutral and dipolar stages should be involved on a concerted bond-breaking and -making mechanism.

3.2. Interactions of cyclohexanone oxime and ε-caprolactam with CF_3COOH in aprotic solvent

The low-temperature interactions between trifluoroacetic acid (HA) and cyclohexanone oxime or ε-caprolactam (M) in deuterated acetonitrile have been studied by NMR spectroscopy and the equilibrium constants K at different temperatures for the generic reaction between the substrate M and the trifluoroacetic acid HA to form the product MHA have been obtained. The equilibrium constants values, reported in Table 2, have been computed by resolving the following system of equations, where [M], [MHA], [HA], n(M), n(MHA) and n(HA) are the concentrations and the moles of reactant, product and trifluoroacetic acid, $n(M_0)$ and $n(HA_0)$ are the moles of substrate and acid before the reaction, δ is the measured chemical shift, δ_M and δ_{MHA} are the chemical shifts of the pure M and MHA species. Figs. 4 and 5 show the ^{1}H NMR spectra of cyclohexanone oxime and ε-caprolactam in CD_3CN before and after the addition of one equivalent of CF_3COOH.

$$\begin{cases} K = \frac{[MHA]}{[M][HA]} \\ n(MHA) + n(M) = n(M_0) \\ n(HA) + n(MHA) = n(HA_0) \\ \delta = \delta_M \frac{n(M)}{n(M_0)} + \delta_{MHA} \frac{n(MHA)}{n(M_0)} \end{cases} \quad (1)$$

To give insight into the nature of the interactions of trifluoroacetic acid and the considered substrates in the described experimental conditions, the enthalpy variations have been calculated from the plots of $-R \ln K$ versus $1/T$, depicted in Fig. 6.

The reaction of CF_3COOH with cyclohexanone oxime in CD_3CN is esoenthalpic with a ΔH value of about -19 kJ mol^{-1}. The ΔH value for the interaction between ε-caprolactam and trifluoroacetic acid is, instead, about +4 kJ/mol, highlighting the strongly different

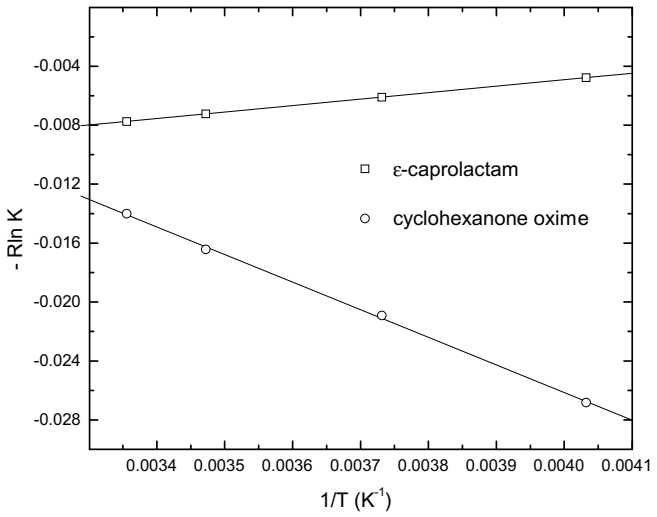


Fig. 6. Plots of $-R \ln K$ versus 1/T for the reactions between CF_3COOH and cyclohexanone oxime ($\Delta H = -19$ kJ mol^{-1}) and between CF_3COOH and ε-caprolactam ($\Delta H = 4$ kJ mol^{-1}).

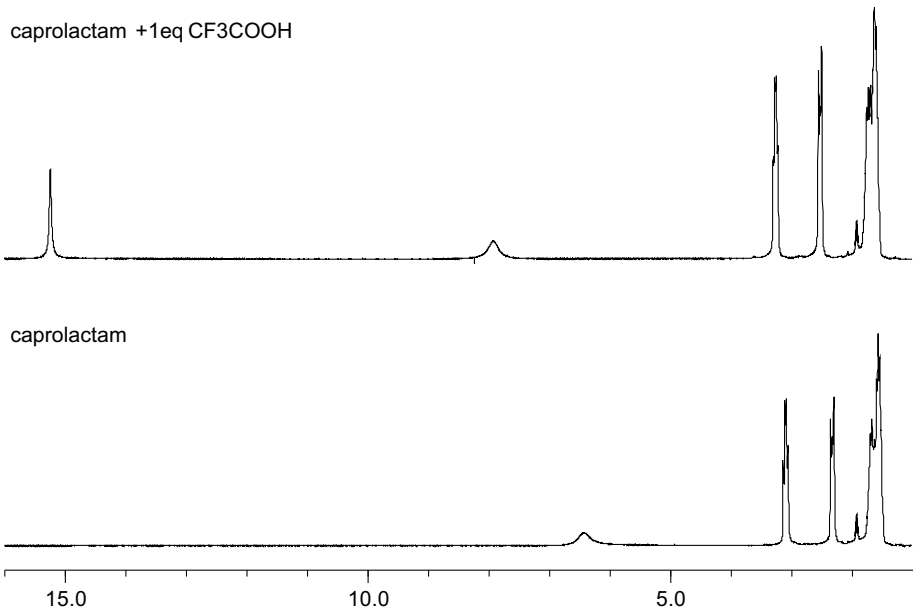
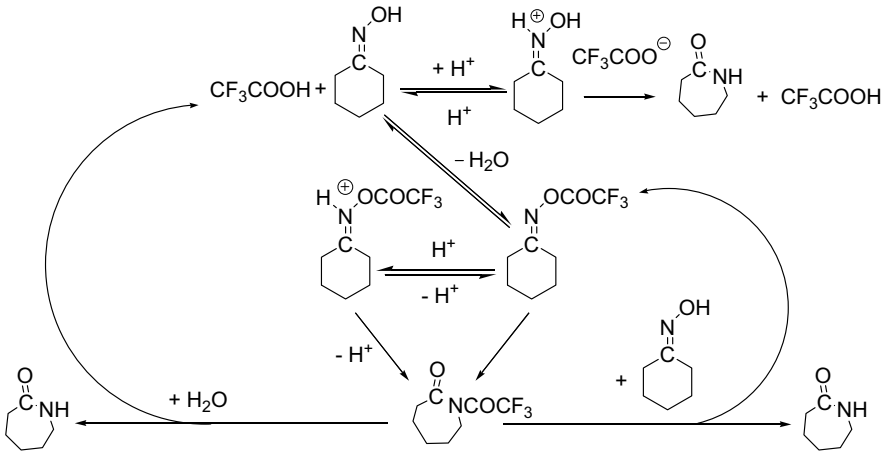


Fig. 5. ^{1}H NMR spectra (CD_3CN, 278 K) of ε-caprolactam (bottom) and ε-caprolactam oxime + one equivalent of CF_3COOH (top).



Scheme 1. Sketches of the possible pathways and equilibria involved in the trifluoroacetic-catalyzed rearrangement of cyclohexanone oxime in aprotic solvent.

kinds of interaction of the catalyst with the reactant and the product. Cyclohexanone oxime is protonated by CF_3COOH, especially at low temperatures, with the probable formation of ion pairs in solution on considering both the relatively high concentrations of reactants and the polarity of the considered solvent. On the basis of the constant values reported in Table 2 this reaction should be, however, strongly unfavored in the temperature range useful for the catalytic conversion of the substrate to ε-caprolactam. On the other hand, the NMR measurements suggest that ε-caprolactam poorly interacts with CF_3COOH.

3.3. Some thoughts on the reaction mechanism

Starting from all these evidences, it is likely that reaction proceeds following a mechanism similar to that proposed for the rearrangement of the cyclohexanone oxime in the presence of acetyl caprolactam as a promoter [21]. However, the key point of the reaction is the equilibrium of cyclohexanone oxime esterification with trifluoroacetic acid, which gives trifluoroacetyl cyclohexanone oxime. As expected, the rearrangement proceeds via trifluoroacetyl caprolactam, but such an intermediate is present only in trace amounts because it is able to readily react with free oxime and/or water giving trifluoroacetic acid and ε-caprolactam. It is likely that the role of the acid is not only related with the formation of the trifluoroacetyl cyclohexanone oxime but also with the protonation of the ester itself. As already reported [21], the presence of acid favors the rearrangement of oxime esters, even though rearrangement of an ester can also occur without protonation since picril and benzensulfonyl oxime rearrange spontaneously on increasing the temperature [7–9]. In addition, direct rearrangement of the protonated oxime, by the well known proton transfer mechanism [20], may occur too, since methanesulfonic acid as a catalyst promotes the rearrangement of cyclohexanone oxime in aprotic solvent [26]. In Scheme 1 possible pathways and equilibria involved in the reaction are sketched. A great difference respect to previously acid or organic catalyzed Beckmann rearrangement is the fact that the trifluoroacetic acid does not form salts or stable adducts with caprolactam. For this reason there are no needs of neutralization or dilution with water and the acid returns into the catalytic cycle at the end. Furthermore, the catalyst can be easily recovered by distillation, due to its low boiling point (345.5 K).

4. Conclusions

The synthetic interest of using CF_3COOH as acid catalyst in the Beckmann rearrangement in aprotic solvent is due to several factors, such as the good activity and selectivity and the ease of the separation stage if compared with the common industrial processes. Respect to other organocatalyzed Beckmann rearrangements this reaction is a step forward because of the facile separation of the catalyst from the reaction mixture [15,16,23]. The reaction is also environmental friendly due to the almost complete reuse of the catalyst and of the solvent, without the inconvenience of undesired byproducts. Finally, a detailed kinetics and thermodynamic study of the reaction will give the parameters for the optimization of the process.

Acknowledgements

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