Applied Catalysis A: General 516 (2016) 58–69

Contents lists available at ScienceDirect

Applied Catalysis A: General

journal homepage: www.elsevier.com/locate/apcata

Kinetics and mechanistic study of the Bamberger rearrangement of *N*-phenylhydroxylamine to 4-aminophenol in acetonitrile-trifluoroacetic acid: A substrate acid complex as *para* selectivity driver

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ARTICLE INFO

Article history:
Received 12 November 2015
Received in revised form 15 February 2016
Accepted 16 February 2016
Available online 21 February 2016

Keywords:
Bamberger rearrangement
Trifluoroacetic acid
4-aminophenol
Kinetics and mechanism

ABSTRACT

The paper deals with the kinetics of Bamberger rearrangement of *N*-phenylhydroxylamine to 4-aminophenol in acetonitrile as a solvent catalyzed by TFA. The influence of the water is also investigated being the rearranging moiety in the mechanism. It is evident that the presence of water depresses the rate of the rearrangement suggesting the rate-determining step does not involve water as the key reagent. In acetonitrile, at lower temperature than that of reaction, we evidence the formation of a PHA-TFA complex, and its equilibrium has been measured between 288 K and 298 K. We observe also the addition of water destroys this complex but the ternary equilibrium PHA, water and TFA cannot easily measured because of the complex solvent effect on the Uv–vis and NMR signals. Starting from this evidence, we have proposed a kinetic model, which takes into account all the equilibria, and the results of the fitting gives reliable thermodynamic and kinetic parameters of the entire process. Finally, we have suggested that the PHA-TFA complex is the key intermediate, which determines the regioselectivity of the rearrangement. In fact, preliminary quantum chemistry calculation have shown that the TFA interaction with the —NHOH group causes the hindering of the *ortho* position, thus favoring the attack of water to the *para* one.

1. Introduction

Aminophenols are important raw materials for several products in the field of dyes, polymer and pharmaceutics [1–3]. For instance, acetaminophen (*N*-acetyl-4-aminophenol, also known as paracetamol), benzoxazoles and substitutes compounds are drugs a widely employed as analgesic, antipyretic and intermediates whose production is in continuous growth [4–8]. More recently, a similar reaction path has been employed in the synthesis of heterocycles of industrial importance starting from nitrobenzene and glycerol via modified Skraup reaction [9].

Industrial synthesis of paracetamol is based on 4-aminophenol, which is obtained by different routes, however, the selective hydrogenation of nitrobenzene is likely the most convenient from both economic and environmental point of view [1,2,4–8]. The major concern of this process is, however, the presence of H_2SO_4, which is origin of corrosion, safety, environmental and separation problems. The reaction (see Scheme 1) is industrially carried out in Continuous Stirred Tank Reactor in which the biphasic reaction medium is used to accomplish simultaneously the Pt catalyzed hydrogenation of nitrobenzene and the acid catalyzed Bamberger rearrangement of the intermediate *N*-phenylhydroxylamine (PHA) [4,5,8]. The presence of the aqueous solution of H_2SO_4 is the key for obtaining high selectivity to the 4-aminophenol. The reason of such a behavior is due to the easy protonation of the phenyl hydroxylamine ($pK_a = 1.96$ [10]), which is extracted from the organic phase. In the acid solution (H_2SO_4 concentration 0.6–1 mol L^{-1}), the *N*-phenylhydroxylamonium salt is readily formed and it undergoes fast Bamberger rearrangement to the corresponding 4-hydroxyanilinium cation [11].

From environmental point of view, the major drawback of the process is the neutralization of the acidic phase, with the consequent by-production of sulfate salts, which are undesired low values products and/or wastes. In addition, diluted sulphuric acid causes huge corrosion concern, with the consequent increased costs of the hydrogenation plant [1,2,4,5,8].

Therefore, removal of H_2SO_4 from the reaction is likely the most important target for the improvement of the process. In this sense, several researchers have recently proposed the use of biphasic liquid system or gas phase reactions (water-nitrobenzene) employing

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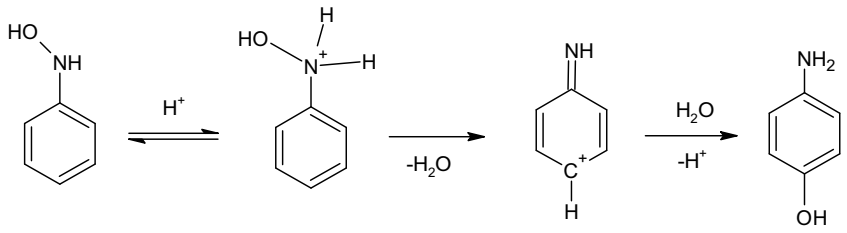
http://dx.doi.org/10.1016/j.apcata.2016.02.020
0926-860X/



Scheme 1. Commonly accepted mechanism for Bamberger rearrangement.

bifunctional Pt supported on solid acid but quite unsatisfactorily results have been obtained for practical purposes [12–15]. Starting from these considerations, a single liquid phase process could be a catwalk to a more sustainable process by using solvent and catalyst easily reusable [16–19]. In fact, very recently we propose the selective hydrogenation of nitrobenzene in a single liquid phase reactions achieving 45% of aminophenol yield in one-step [16]. Bases of these researches have been the recent results in the Beckmann rearrangement of ketoximes in $CH_3C\,N{-}CF_3COOH$ solvent catalytic system [17–19]. The analogy between Beckmann and Bamberger rearrangement originates from the idea that both oximes and PHA are nitrogen-containing compounds, whose interactions with TFA play the key roles in these reactions. Above all, the mechanism of the Bamberger rearrangement is well known from long time and it can be depicted as in Scheme 1, *via* a nitrenium ion intermediate followed by nucleophilic attack of a water molecule [11,20,21].

This mechanism does not explain, however, many features of the reaction, such as the regioselectivity of the hydroxylation in 4-position of the phenyl ring [11,20,21]. This evidence is confirmed also by using solid acid catalyst for which almost complete selectivity in 4-position has been observed [22]. Besides, the Bamberger rearrangement of PHA carried out in aqueous solution of carbon dioxide shows a complete selectivity to *para* position [23]. In fact, reactions whose selectivity toward the 4-position is not respected are those carried out in the presence of metal catalyst, in which the presence of a metal-organic intermediate determine a different reaction product [24].

To say the truth, nobody detects a free nitrenium ion in solution, thus suggesting that this ion is not an existent intermediate, but more likely, a hypothetical stage in concerted mechanisms [20,21,25]. Recently, DFT calculations suggest the absence of the nitrenium intermediate in the Bamberger rearrangement [26]. In this study, the stabilization of a dication intermediate occurs *via* the formation of a complex formed of four hydrogen-bonded molecule of water surrounding the anilinium intermediate, which favors the attack of the water in *para* position, for steric reasons. Actually, in the heterogeneous Pd catalyzed hydrogenation of nitrobenzenes, nitrenium ion is a likely intermediate, since its coordination with Pd may stabilize a surface nitrenium complex [16,27].

Starting from these bases, the study of the Bamberger rearrangement of PHA in non-aqueous solvent, in the presence of TFA, is interesting, not only for synthetic purposes, but also for mechanistic ones. In addition, new insight on the mechanism of the rearrangement may help to develop a more selective and sustainable one pot hydrogenation of nitrobenzene to 4-aminophenol.

Here we present a study on the kinetics of Bamberger rearrangements of PHA in acetonitrile catalyzed by TFA as a reusable homogeneous acid catalyst.

2. Experimental

2.1. Materials

Nitrobenzene, aniline, 4-aminophenol, 2-aminophenol, trifluoroacetic acid, trifluoroacetic anhydride, were all Aldrich products, their purity were checked by the usual methods (melting point, TLC, HPLC, GC and GC–MS) and employed without any purification, acetonitrile HPLC gradient grade was supplied by BDH, methanol, nitromethane, dimethylformamide and dimethyl sulfoxide are ACS reagent supplied by Aldrich. Phenylhydroxylamine was prepared by following the classic procedure proposed by Kamm, scaled down for gram amount synthesis [28].

2.2. Equipment

Products were identified by gas chromatography (GC), gas chromatography coupled mass spectrometry (GC–MS) and high performance liquid chromatography (HPLC). GC and GC–MS analyses were carried out with an Agilent 7890A, equipped with FID or MS detector Agilent 5975C. Separation was achieved by a HP 5 column (I.D. 320 μm 30 m long), using helium as the carrier under the following analysis conditions: injector 523 K, detector 543 K, flow 1 mL min^{-1}, oven 333 K for 3 min 523 K 15 K min^{-1} and 523 K for 15 min.

Due to the thermal instability of the products, routine analysis were carried out by HPLC (Perkin Elmer 250 pump, LC 235 diode array detector and a C 8, 5 μm, 4 mm i.d. 25 cm long column) analysis were carried out with $CH_3C\,N{-}H_2O$ as mobile phase in isocratic 70% of CH_3CN at 1 mL min^{-1}. The response factors obtained by standard solutions of the pure products give conversion, yield and selectivity.

A Perkin Elmer lambda 3 Spectrophotometer were employed for the spectrophotometer measurements of the equilibria and of the kinetics.

A Bruker Avance 300 spectrometer operating at 300.13 MHz allows the recording of the ^1H Nuclear Magnetic Resonance (NMR) spectra of reagents and products.

Conductivity measurements were carried by using a Solartron 1260 gain phase analyzer at 2000 Hz with a standard platinized electrodes cell with 1 cm^{-1} of cell constant.

2.3. Equilibria of N-phenylhydroxylamine TFA in acetonitrile

The standard procedure to measure the interaction of PHA with TFA in acetonitrile has been carried out by using a conventional spectrophotometer in a 3 mL cuvette of 1 cm of optical length. The additions of a concentrated solution of TFA in acetonitrile by a micrometric micro-syringe in the cuvette gives the desired acid concentration.