

ORIGINAL PAPER

Formation of a vanillic Mannich base – theoretical study

Vladimir P. Petrović*, Dušica Simijonović, Zorica D. Petrović, Svetlana Marković

Faculty of Science, University of Kragujevac, Radoja Domanovića 12, 34000 Kragujevac, Serbia

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One-pot *anti*-Mannich reaction of vanillin, aniline and cyclohexanone was successfully catalyzed by ionic liquid triethanolammonium chloroacetate, at room temperature. Yield of the obtained Mannich base was very good and excellent diastereoselectivity was achieved. Mechanism of the reaction was investigated using the density functional theory. The reaction started with a nucleophilic attack of aniline nitrogen at the carbonyl group of vanillin. The intermediate α -amino alcohol formed in this way was further subjected to protonation by the triethanolammonium ion yielding the iminium ion. Theoretically, the obtained iminium ion and the enol form of cyclohexanone can build the protonated Mannich base via the *anti* and *syn* pathways. The chloroacetic anion spontaneously abstracts the proton yielding the final product of the reaction *anti* 2-[1-(*N*-phenylamino)-1-(4-hydroxy-3-methoxyphenyl)]methylcyclohexanone (MB-H). The *syn* pathway requires lower activation energy but the *anti* pathway yields a thermodynamically more stable product, which implies that the examined Mannich reaction is thermodynamically controlled.

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Introduction

Mannich-type reactions represent a very important strategy in the preparation of chiral compounds. Owing to these reactions, organic synthetists can build various magnificent nitrogen-containing molecules which are “architectural” blocks for the construction of many biologically active compounds and pharmaceutical products, such as nucleotides, peptides, alkaloids, steroid hormones, antibiotics, and vitamins (Arend et al., 1998; Touré & Hall, 2009).

Traditional catalysts for direct Mannich reactions of aldehydes, ketones and amines involve mainly Lewis or Brønsted acids (Loh et al., 2000; Akiyama et al., 2001; Manabe et al., 2001; Loh & Chen, 2002; Phukan et al., 2006; Yang et al., 2006). However, the use of these catalysts is followed by a number of serious disadvantages. Involvement of toxic organic solvents and difficult separation of products limit their use, especially in the synthesis of complex molecules. In the past decade, it has been noted that this reaction can be promoted by a wide range of catalysts such as

organocatalysts (Ibrahim et al., 2006; Janey et al., 2006; Kantam et al., 2006; Liu et al., 2007; Yang et al., 2007) and rare metal salts (Wang et al., 2005; Yi & Cai, 2006). In addition, ionic liquids (ILs) are considered as a promising alternative to conventional catalysts (Cole et al., 2002; Zhao et al., 2004; Sahoo et al., 2006; Dong et al., 2007). They have been proved to be highly active and selective, easily recyclable, and environmental friendly. Physico-chemical properties of ILs can be fine-adjusted by changing the structure of the cations and anions, depending on the purpose of the IL (Huddleston et al., 2001; Chiappe & Pieraccini, 2005; Shariati & Peters, 2005; Shariati et al., 2005; Zhao et al., 2005; Keskin et al., 2007). Besides the Mannich reaction (Cole et al., 2002; Zhao et al., 2004; Sahoo et al., 2006; Dong et al., 2007; Gong et al., 2007; Fang et al., 2009; Yue et al., 2009), ILs have found application in a wide range of other organic reactions (Abbott et al., 2002; Aggarwal et al., 2002; Kumar & Pawar, 2004; Xiao & Malhotra, 2005; Yin et al., 2006; Cota et al., 2007; Iglesias et al., 2010; Zhou et al., 2011). In transition metal catalyzed cross coupling reactions,

*Corresponding author, e-mail: vladachem@kg.ac.rs

