Molecular Catalysis 438 (2017) 30–36

Contents lists available at ScienceDirect

Molecular Catalysis

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

MCAT

Research paper

Inhibitory effect of the nucleophile in Ullmann condensation: Theoretical and experimental investigation

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ARTICLE INFO

Article history:
Received 2 November 2016
Received in revised form 2 May 2017
Accepted 16 May 2017

Keywords:
Ullmann
Aminoacids
Ligands
Copper
Benzylamine
Bromobenzene

ABSTRACT

This article reports a study on amino acid chelated Cu(I) catalyzed coupling of benzylamine and bromobenzene. Experiments were conducted at 80 °C with Cu(I) chelated to methionine, proline, hydroxyproline, tryptophan and tyrosine in dimethylsulfoxide (DMSO). In order to investigate kinetic effects, reaction time was restricted to 90 min. Kinetically controlled product yields over amino acid ligated Cu(I) were in the order proline > hydroxyproline > methionine > tryptophan > tyrosine. Theoretical investigation of the reaction was carried out using density functional theory method, B3LYP/6-31+G(d,p) employing the solvation model SCRF = CPCM. The effective core potential of LANL2DZ was used to model copper and bromine. Geometry optimization of the structures of reactants, intermediates and activated complexes were carried out in the solvent DMSO. It was found that the reaction over amino acid Cu(I) complexes that gave low product yields are associated with high energy barriers for aryl halide bond activation. Further, the theoretical investigation revealed that benzylamine coordinates from nitrogen and phenyl ring and it hinders the pi-cordination of bromobenzene. Therefore, in order for the reaction to progress, formation of amioacid chelated copper bromobenzene complex and subsequent activation of C—Br bond must occur before the coordination of benzylamine. As the stability of the aminoacid ligated copper benzyl amine complex is much higher than the stability of the corresponding bromobenzene complex, the resting state can be taken as the amine complex. Therefore, it is proposed that benzylamine must be replaced by bromobenzene in order for the formation of aminoacid chelated copper bromobenzene complex.

1. Introduction

Ullmann coupling reaction mediated by copper(I) is useful in many synthetic procedures and have been utilized in the synthesis of C—O [1–6], C—N [7–12], C—S [13,14] and C—P [15] coupled products. Mechanistic aspect of Ullmann coupling reaction has been extensively reviewed [16].

However, this reaction remains underutilized due to its characteristic poor yields. It has been reported that the use of chelating ligands improves the yields of Ullmann reaction [17]. However, there is no universal agreement about the mechanism by which copper catalyzes these coupling reactions. In this article we report an experimental and theoretical study on the mechanism of amino acid chelated copper (I) catalyzed coupling reaction between bromobenzene and benzylamine. The coupling reaction has been studied in dimethylsulfoxide (DMSO).

The use of amino acids as catalysts in copper assisted Ullmann coupling between aryl halides and different amines was first shown by Ma and Cai [17,18]. Their results have shown that alpha-amino acids can reduce the high reaction temperatures (normally above 150 °C) to about 60–90 °C and increase the reaction rate. Reports on successful usage of amino acids such as proline and *N*,*N*-dimethylglycine in Ullmann type coupling in the synthesis of cyclopeptides can be found in the literature. It has been shown that amino acids themselves can couple with aryl halides to give *N*-arylated amino acids in the presence of CuI [18].

Mechanisms for Ullmann reaction can be divided into two major categories; mechanisms where the oxidation state of copper changes and mechanisms where the oxidation state of copper remains constant during the catalytic cycle [19]. One can find

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http://dx.doi.org/10.1016/j.mcat.2017.05.013
2468-8231/

experimental as well as theoretical investigations supporting all these mechanisms in the literature. However, the majority of studies are supportive of oxidative addition-reductive elimination mechanism. Following paragraphs highlight some of the recent experimental and theoretical findings supporting these different types of mechanisms.

A detailed theoretical study on cross-coupling between bromobenzene (PhBr) and acetamide (NH_2Ac) catalyzed by ethylene diamine copper (I) complex has been carried out by Zhang et al. [20]. They have investigated a number of possible pathways by which the products could be formed. Pathways involving different intermediates have been theoretically investigated. The minimum energy pathway proposed after theoretical investigation consists of the steps, diamine-Cu-NHAc formation, pi coordination of PhBr, dissociation of Ph—Br bond and the formation of diamine-Cu-NHAc,Ph,Br penta-coordinated complex (oxidative addition) and reorientation of ligands in the penta-coordinated complex and finally the formation Ph-NH-Ac (reductive elimination). The largest contribution to the overall energy barrier is associated with the dissociation of the Ph—Br bond of pi-coordinated PhBr.

A mechanism involving the reaction of haloarene with a diamine ligated copper complex is reported by Strieter et al. [21]. van Allen has investigated the formation of C-P coupled products using CuI as a catalyst [15]. By way of elimination, he has arrived at the conclusion that the coupling of diphenylphosphine and bromobenzene occurs by the mechanism of sigma-bond metathesis.

Tye et al. have investigated a series of Cu(I) complexes containing ancillary N—N donor ligands and reactive amidate and imidate ligands [22]. These complexes, which are believed to be intermediates in the copper catalyzed aryl halide activation, have been isolated and their solid state structures have been determined. It has been observed that these complexes exist predominately in ionic form in dimethyl sulfoxide (DMSO) and in *N*,*N*-dimethyl formamide (DMF). Further, they have reported that the product formation is first order with respect to Cu-complex and iodobenzene.

Ligand directed selectivity of Ullmann coupling reactions has also been investigated by Jones et al. [23]. Coupling of iodobenzene with methanol and methylamine has been theoretically investigated. Calculations have been performed in solvents, acetonitrile and dimethylformamide in the presence of 1,10-phenanthroline-Cu(I) or beta-diketone-Cu(I) as catalysts. It has been proposed that the coordination of the nucleophile to the ligand-Cu(I) occurs prior to the activation of iodobenzene (PhI). Several possible pathways such as oxidative addition-reductive elimination, sigma bond metathesis, iodine atom transfer (IAT) and single electron transfer (SET) have been investigated. They reported that a mechanism involving single electron transfer to iodobenzene is favored when beta-diketone is ligated to Cu(I) and iodine atom transfer mechanism is favored when 1,10-phenthroline is ligated to Cu(I).

An alternative explanation for the ligand directed selectivity of the above reaction was provided by Yu et al. [24]. They reported that the selectivity can be explained by oxidative addition reductive elimination mechanism. Further, they proposed that the aryl halide activation occurs readily in the absence of the nucleophile over a beta-diketone ligated copper catalyst. This is an example where, aryl halide activation occurs prior to the coordination of the nucleophile.

Present study was undertaken to investigate the mechanism by which amino acid chelated copper promotes Ullmann reaction between bromobenzene and benzylamine. Based on the results of experimental and theoretical investigations, aryl halide activation was identified as the rate limiting step. Conductivity, pH and analysis of reaction products by NMR showed that the reaction proceeds even at room temperature (27 °C). In the present investigation, we have shown that the coupling reaction is inhibited, if benzylamine is complexed first with the catalytic center. Theoretical investigation revealed that the coordination of benzylamine to ligated Cu(I) occurs via both, nitrogen and phenyl ring, blocking the access of bromobenzene. Therefore, it is proposed that the pi-complexation of aryl halide should occur before the coordination of benzylamine for the successful product formation.

2. Materials and methods

2.1. Reaction

A typical reaction mixture contained DMSO 1.2 mL, K_2CO_3 1.0 mmol, CuI 1.0 mmol aminoacid 1.0 mmol, bromobenzene 1.0 mmol and benzylamine 1.5 mmol. All the chemicals were from BDH unless mentioned otherwise and used as received. The above mixture was maintained at 80 °C for 90 min in a thermostated water bath. The amino acids methionine, proline, hydroxyproline, tryptophan and tyrosine were used as chelating ligands.

Room temperature experiments were carried out using two benzylamine:bromobenzene ratios (3.0 mmol of benzylamine:1.0 mmol of bromobenzene and 0.5 mmol of benzylamine:1.0 mmol of bromobenzene) using proline as the amino acid in a reaction mixture having the other reagents at the above described composition.

The reaction was further investigated using DMSO as the sovent (volume adjusted to 2.8 mL), 2.0 mmol of K_2CO_3, 0.2 mmol of CuI, 0.2 mmol of proline. In one set of experiments, the amount of bromobenzene was maintained at 2.0 mmol and the amount of benzylamine was varied (3.0, 2.0, 1.4, 1.0, 0.6, mmol). In the other set of experiments, the amount of benzylamine was kept constant at 2.0 mmol and the amount of bromobenzene was varied (3.0, 2.0, 1.4, 1.0, 0.6 mmol). In this manner, the effect of bromobenzene:benzylamine ratio on the reaction rate was studied at 80 °C for 90 min. Inorder to maintain a low conversion of the reactants, a small amount of the catalyst (0.2 mmol of CuI-proline) was used in these experiments.

Separation of products was acheived using column chromatography. A column with the diameter of 1.0 cm and height 6 cm, containing silica gel (2.5 g silica gel 60 having the mesh size of 70–230 (Arihant, India)) as the stationary phase was used. A mixture of hexane and 5% ethylacetate was used as the mobile phase. Fractions from the column were collected, the solution was evaporated and the product was obtained as a yellow oil. The product was then dissolved in $CDCl_3$ and characterized by NMR. ^{1}H NMR spectra of the purified product were obtained using a Varian Mercury Model (300 MHz) spectrometer.

2.2. Conductivity and pH

Conductivity measurements were made using a mixture containing 100.0 mL of DMSO and the other ingredients in the quantities, benzylamine 1.5 mmol, bromobenzene 1.0 mmol, CuI 0.1 mmol, K_2CO_3 1.0 mmol and proline 0.2 mmol at 27 °C. A large amount of DMSO was used in order to facilitate conductivity measurements (to be able to immerse the conductivity probe). Conductivity measurements were carried out at two other benzylamine:bromobenzene ratios (0.5 mmol:1.0 mmol and 3.0 mmol:1.0 mmol). Conductivity variation was also monitored at 50 °C using benzylamine:bromobenzene ratio of 0.5 mmol:1.0 mmol. Two similar experiments using tyrosine were conducted at 27 °C and 50 °C for comparison. A Jenway model 4510 bench top conductivity meter was used to obtain conductivity measurements. Hydrogen ion activity in the medium was measured using an Eutech instruments pH–510 pH meter. The