

ORIGINAL ARTICLE

Role of Heavy Metal Catalysts in Polyhydroquinolines Synthesis in Ionic Liquids: A DFT Study

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ABSTRACT

Polyhydroquinolines and its derivatives are an important group of organic heterocyclic compounds due to their applications in pharmaceutical and chemical industries. Hantzsch reaction that is generally used for its synthesis involves numerous factors for which the reaction efficiency is low. The most critical component includes heterogeneous and reusable catalyst. In order to increase the efficiency of polyhydroquinolines synthesis using the heterogeneous and reusable catalysts inside ionic liquids, we used the B3LYP/6-31g optimization method with different ionic liquids, such as aromaticaldehyde, dimedone, ethyl acetate and ammonium acetate in the presence of catalyst.

Keywords: Ionic liquids, DFT, heavy metal catalysts, Hantzsch reaction, polyhydroquinolines, B3LYP/6-31g

Received 07.04.2016 Accepted 15.07.2016

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INTRODUCTION

Organic heterocyclic compounds, such as polyhydroquinolines and its derivatives are widely used in pharmaceutical and chemical industries. Preparation of these compounds is often time consuming and tedious. For the first time, Arture Hantzsch in 1882 synthesized, 1,4-symmetrically substituted dihydropyridine by condensation of two molecules of ethyl acetoacetate, aromaticaldehyde and ammonia in one-pot. This technique assimilates the reaction in acetic acid or in an ethanolic solvent under the reflux conditions. Certainly, there are many drawbacks in this technique, like longer reaction time, harsh reaction conditions, using volatile organic solvents and lower efficiency [1]. Numerous alterations to the original reaction components of the Hantzsch reaction has been performed to increase the efficiency. Previous studies have modified the original Hantzsch reaction by using ammonium acetate instead of ammonia in the reaction, which lead to raised reaction efficiency. Another strategy to improve the polyhydroxyquinolines synthesis is usage of cyclic compounds, 1,3- D-ketone in the Hantzsch reaction. [1]. Furthermore, Mobinikhaledi *et al.* [2] and Ko *et al.* [3] applied ionic liquids, microwave irradiation, polymers, heteropolyacid and ceric ammonium nitrate for efficient synthesis of polyhydroxyquinoline derivatives. However, the use of high temperatures, expensive metal precursors and catalysts those are harmful to environment, and longer reaction times limit the use of these methods. Therefore, development of mild and efficient synthesis of polyhydroquinolines in short duration remains a demand. To accomplish this goal various alterations in the four-components of the reaction, reaction medium as well as the catalyst needs to be implemented to achieve higher output precisely.

Heterogeneous and reusable catalyst have shown to affect the rate of synthesis of polyhydroquinoline derivatives. Nagarapu *et al* [4] provided a novel way for synthesizing polyhydroquinoline derivatives with a four-component reaction of aromaticaldehyde, dimedone, ethyl acetoacetate and ammonium acetate in solvent-free conditions adopting MCM-41 as a heterogeneous catalyst. Mobinikhaledi *et al.* [2] illustrated that four-component Hantzsch reaction can synthesize polyhydroquinolines and its derivatives employing silica sulfuric acid as a heterogeneous and reusable catalyst under controlled temperature conditions provided by microwave irradiation. Moreover, Ko *et al.* [3] reported synthesis of -1, 4-dihydropyridine derivatives at room temperature using iodine as catalyst. Moghaddam *et al.* [5] presented another procedure for synthesis of polyhydroquinolines derivatives and 1,4-dihydropyridine through a four-component reaction of aldehydes, ammonium, ethyl acetoacetate, 5,5-dimethyl and 1,3-cyclohexadiene in the presence of zinc oxide (ZnO) as the catalyst. Heravi *et al.* [6] synthesized polyhydroquinolines derivatives via a three-component Hantzsch reaction in the presence of some green

and cheap catalyst Potassium Tungsten Cobalt phosphate ($K_7PW_{11}CoO_4$). However, in the study by Khabazzadeha *et al.* [7] synthesis of polyhydroquinolines using a heterogeneous and reusable catalyst, $Cs_{2.5}H_{0.5}PW_{12}O_{40}$, showed higher efficiency in short time.

Recently, applications of ionic liquids in organic synthesis have attracted considerable attention due to their special properties such as good solvating capability, wide liquid range, non-inflammability, negligible vapour pressure, easy of recycling, high thermal stability and rate enhancers. Also, ionic liquids as environmentally friendly media for catalytic processes and much attention has currently been focused on organic reaction catalyzed by ionic liquids have been reported with high performance [8-11]. Various studies have demonstrated the usage of different ionic liquids as a medium for synthesis of polyhydroquinolines and its derivatives. Prior experiments have exhibited the four-component Hantzsch reaction in the solvent-free conditions using sulfamic acid. Some also indicated that four-component condensation of divergent aromatic aldehydes, cyclic compounds of 1,3-diketone, ***β-keto ester***, ammonium acetate and catalytic amount from an ionic liquid Tetrabutylammonium, -2-acrylamide, -2-methyl-propane sulfonate (TBA-AMPS) yields polyhydroquinolines derivatives [12]. However, few developed a more simplified and effective technique for polyhydroquinolines synthesis through the four-component reaction of aldehydes, dimedone, ethyl acetoacetate and ammonium acetate in the presence of *p*-Toluenesulfonic acid in ethanolic solvent at room temperature. Siddaiah *et al.* (2012) synthesized 1,4-dihydropyridines and polyhydroquinolines derivatives through the Hantzsch reaction by using polyethylene glycol (PEG) reagent in solvent-free conditions. The products were directly crystallized with hot methanol. The reaction efficiency with low molecular weight PEG was as appropriate as high molecular weight PEG [13]. Interestingly, Khabazzadeh *et al.* [7] introduced a process for synthesizing polyhydroquinoline derivatives with Hantzsch four-component condensation reaction using aromatic aldehyde, dimedone, ethyl acetoacetate and ammonium acetate in molten salt media as an alternative to hazardous organic solvents. However, continuous increase in the number of ionic liquids makes it difficult to physically study all of them for increasing the efficiency of polyhydroquinoline synthesis. In such a situation, application of computational method is advantageous as large number of variables can be analyzed in a short duration.

Recently, density functional theory (DFT) calculations have emerged as very powerful theoretical method for assessment of reaction energy. Among different DFT methods, hybrid method, such as B3LYP, are often the method of choice for reaction calculations. The most significant advantage of DFT methods is a significant increase in computational accuracy without the additional increase in computing time. DFT methods such as B3LYP/6-31G (d) are often considered to be a standard model chemistry for many applications. However, determining the most appropriate method for a particular application is a prior requirement to DFT application.

Hence the present study aims to investigate the effect of different ionic liquids as solvent molten media by B3LYP/6-31g method on polyhydroquinolines synthesis using dimedone, cyclohexa 1,3- aldehydearyl, ***β-keto ester and*** ammonium acetate solvent of $Cs_{2.5}H_{0.5}O_{40}W_{12}P$ as the catalyst.

MATERIALS AND METHODS

The polyhydroquinoline synthesis by Hantzsch reaction is illustrated in Figure 1. Using B3LYP/6-31g method through Gaussian 03 software, the synthesis of polyhydroquinolines was optimized for a set of raw materials, additives, reaction conditions and products in presence of divergent ionic liquids as molten solvents. The different ionic liquids evaluated as molten solvents whose effect was studied, includes tetrabutylammonium, tetramethylammonium, tetrapropylammonium, tetrapanthylationium and tetrahexylammonium. The ionic liquids structures were optimized using the B3LYP/6-31g theory method.

In the reaction, functional groups R1 and R2 are methyl group and varying ionic liquids enters at each step in their action mechanism. The relevant energy value is obtained for the reaction in each ionic liquid and the reaction process was compared.

RESULTS AND DISCUSSION

For thermodynamic assessment of a chemical process measurement of process energy is a useful technique. Estimation of the process energy is accomplished by using conventional reaction energy formula i.e.:

$$rE = \sum \vartheta fE - \sum \vartheta fE$$

where, rE is Reaction energy
 ϑ is Balanced number of each compound
 fE is Formation energy

Therefore, initially we calculated the sustainable energies for the raw materials involved in the reaction process using Gaussian 03 software and B3LYP/6-31G method. The optimized sustainable structural energy estimated by B3LYP/6-31G method is presented in Table 1. Subsequently, we computed the reaction energy for each effective ionic liquid in the synthesis process. The optimized structures of different ionic liquids as molten solvents are shown in Table 2. The hydroquinolines synthesis reaction, which occurs on the basis of the Hantzsch reaction, performs in the presence of catalyst. Since the reaction takes place inside ionic liquids due to special features and benefits of ionic liquids including creation of molten instead of solvent condition with higher rate of efficiency, we planned to evaluate the reaction condition in the ionic liquids computationally with different organic functional groups. The sustainable energy of ionic liquids (Table 1) indicates that longer functional group chain causes more stable ionic liquid structure and consequently, the rate of energy is considerably lowered. As a result of increased length of aliphatic chain, the stability may be resulted by varying reasons. In this regard, quantum mechanics computations confirm the stability. The required energy to conduct the above reaction is 4079096.86 joules, which suggests spontaneous process of reaction. The selected ionic liquid is a type of raw material and in case its negative value goes up it can increase positive value of the reaction energy. As a result, the ionic liquid stimulates the reaction towards further spontaneous process leading to such an undesirable result giving more power to metal catalyst in the reaction process. Hence, we conclude that the metal catalyst in the molten ionic liquid acts as the driving force for the spontaneous reaction.

Using hybrid method of DFT i.e. B3LYP/6-31g method we tested five ionic liquid in molten state as a medium for efficient synthesis of polyhydroquinolines. We were able to optimize the reaction condition computationally using tetrabutylammonium as molten ionic liquid medium along with dimedone, cyclohexa 1,3, - aldehydearyl, β -keto ester and, ammonium acetate solvent of Cs2.5H0.5O40W12P as the catalyst. Moreover we also show that metal catalyst present in the molten liquid is responsible for the spontaneity of the reaction.

Table 1 Optimized structural energy estimated by B3LYP/6-31G method

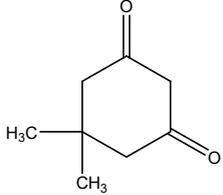
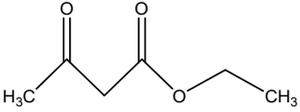
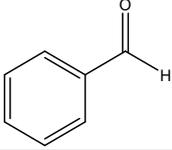
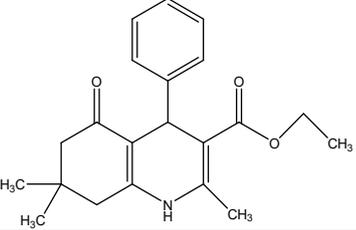
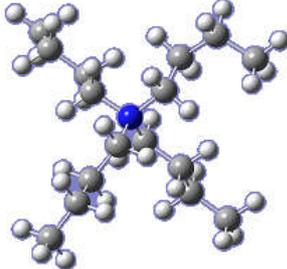
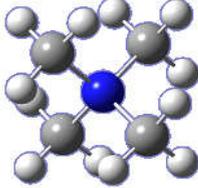
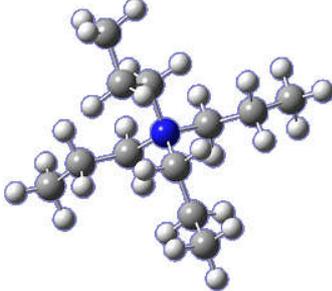
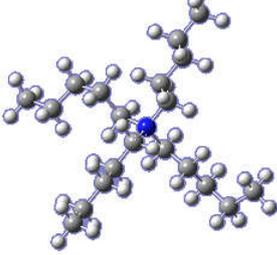
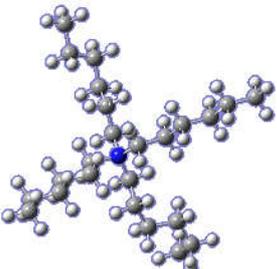
Role	Energy(Joule)	Composition
Raw material (Dimedone)	-1217019.14	
Raw material (Acetate)	-1208248.415	
Raw material (Benzoyl peroxide)	-907070.0897	
Final product (dihexahydroquinolin)		
Ionic liquid	-1835754.929	Tetrabutylammoniumbromide (TBAB)
catalyst		\oplus H
catalyst	749759.2211-	NH ₄ OAC

Table 2 Optimized structures of different ionic liquids as molten solvents

Composition name	Energy (joule)	Optimized structure
Tetrabutylammonium	-1800844.17	
Tetramethylammonium	-562489.52	
Tetrapropylammonium	-1387985.70	
Tetrapanthylammonium	-2213700.51	
Tetrahexylammonium	-2626554.86	

COMPLIANCE WITH ETHICAL STANDARDS**FUNDING**

There is no funding involved in this study.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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CITE THIS ARTICLE

S Ali Ahmadi, R Razavi, M Mehdi Foroghi: Role of Heavy Metal Catalysts in Polyhydroquinolines Synthesis in Ionic Liquids: A DFT Study. *Res. J. Chem. Env. Sci.* Vol 4 [4] August 2016. 35-39