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ARTICLE

Microwave-Induced Catalytic Transfer Hydrogenation in Different Solvents Toward Optically Active Hydroxy β-Lactams: Effects of Penetration Depth

Aparna Das[1,✉], Ram Naresh Yadav[2] and Bimal Krishna Banik[1,✉]

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ABSTRACT

In present work, the stereospecific synthesis of optically active *cis* hydroxy β-lactams by catalytic transfer hydrogenation under diverse microwave-induced conditions is invstigated. The effects of the penetration depth of the solvents are found to be more crucial than solvents with high dipole moments and dielectric constants. Despite significant progress of microwave-induced reactions, no reports have examined the penetration depth of the solvents used in these processes.

KEYWORDS

β-Lactams, Microwave, Penetration depth, Hydrogenation, Catalyst.

Author affiliations:

[1]Department of Mathematics and Natural Sciences-Core Curriculum, Prince Mohammad Bin Fahd University, Al Khobar 31952, Kingdom of Saudi Arabia
[2]Department of Chemistry, Faculty of Engineering & Technology, Veer Bahadur Singh Purvanchal University, Jaunpur-222003, India

✉To whom correspondence to be addressed:

E-mail: bbanik@pmu.edu.sa

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INTRODUCTION

β-Lactams are medicinally significant compounds. These types of compounds have shown several biological activities such as antibacterial [1], anticancer [2], anti-inflammatory [3], antifungal [4], cholesterol absorption inhibitors [5], anti-hepatitis [6], analgesic activities [7] and antihyperglycemic [8] activities. Owing to the wide spectrum of medicinal activities of β-lactams, the synthesis of these types of biologically active molecules is crucial. Scientists have reported several methods for the preparation of β-lactams. Besides, our group also has presented extensively the synthesis of β-lactams and related compounds by diverse methods [9,10] and computational studies on the physico-chemical and structural properties of the compounds [11-16].

Methods assisted by microwave irradiation has several important advantages compared to conventional methods. It is a contactless method; minimizes wall effect as the wall of the reaction chamber is not heated directly; volumetric heating of the feedstock; precise and instantaneous electronic control; rapid energy transfer [17], uniform heating [18], shorter reaction time [19], fewer side reactions [20], products with good select-ivity and purity [21], can operate under solvent-free conditions [22], very high power densities developed in the processing zone [23], superior moisture leveling [23], high level of energy saving [24], higher efficiency of production [23], compact equipment [23], shorter start-up time of apparatus; an important part of green chemistry approach [25]. However, not all the reactions work with microwave irradiation. The reactants must have certain dielectric properties to get efficient heating during microwave irradiation. Besides, it is evidenced that solvents have played a critical role depending on the reactants and reaction conditions. Thus, it is important to analyze the effects of diverse solvents under microwave irradiation. Considering all these facts, in this study the synthesis of hydroxy-β-lactam derivatives by the hydrogenolysis of benzylether group with ammonium formate and Pd/C under microwave irradiation with diverse solvents is considered. Most importantly, this study has revealed the effects of penetration depth of the solvents used in these processes.

EXPERIMENTAL

The Pd/C is flammable, thus, the hydrogenolysis method can generate free hydrogen and can cause a fire. It is advisable to perform hydrogenolysis with a small amount of substrate. For a typical reaction, catalyst (20 mg) was taken in the reaction vessel with ethylene glycol (1 mL) and then β-lactam (100 mg) and ammonium formate (100 mg) were added. Irradiation of the reaction mixture in a microwave oven for 2 min at a medium power level was conducted. To the reaction mixture, water (3 mL) and ethyl acetate (5 mL) were added, the contents were mixed carefully and filtered with filter paper. The filtrate was transferred to a separatory funnel and the organic layer was collected. On removal of the solvent, the crude product was obtained in essentially pure form. The pure product was easily obtained by crystallization from ethyl acetate-hexane to afford approximately 90% yield.

RESULTS AND DISCUSSION

The synthesis of optically active hydroxy-β-lactam derivatives by the hydrogenolysis under microwave irradiation is shown in **Scheme-I**. The reaction of benzyloxyacetyl chloride **1** and imine **2** in the presence of N-methylmorpholine in various solvents produced a single optically active β-lactam **3** following the Staudinger cycloaddition reaction. The benzyloxy group in **3** was removed by catalytic transfer hydrogenation with ammonium formate and Pd/C using the microwave to afford **4**. Several solvents were investigated to identify the best choice and the reasons behind it. Table-1 shows the yield of the products with different solvents.

To optimize the reaction conditions for the synthesis of optically active hydroxy-β-lactam derivatives **4** we considered several solvents such as ethanol, methanol, ethylene glycol, water, acetone, ethyl acetate and xylene. The results indicated

TABLE-1
PRODUCTS OBTAINED AND THEIR YIELD (%)

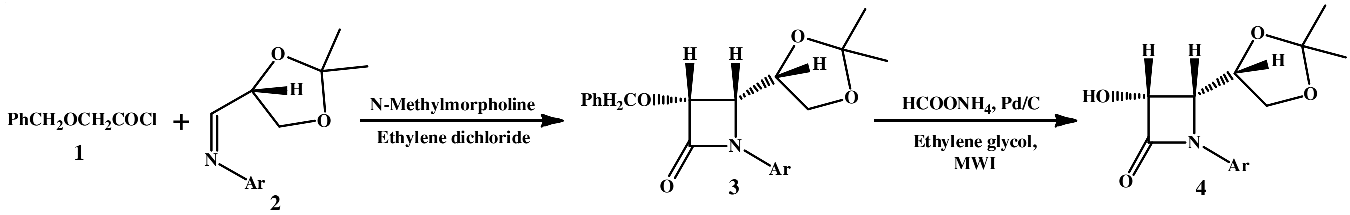
Compound	**4a**
Ar	*p*-Anisyl
Yield (ethylene glycol)	90
Yield (ethanol)	70
Yield (methanol)	70
Yield (propanol)	60
Yield (ethyl acetate)	60
Yield (acetone)	20
Yield (water)	No reaction
Yield (aqueous salt solution)	No reaction
Yield (xylene)	No reaction

that ethylene glycol is the solvent of choice since the highest yields are obtained with it. Compound **4a** was obtained in 90% yield, **4b** in 90%, **4c** in 88% and **4d** in 90% yield, respectively. The on-going work in microwave-induced processes and several experiments have helped us to explain the superiority of ethylene glycol in the catalytic transfer hydrogenation experiment. Since methanol, ethanol, propanol, ethyl acetate, water and xylene were not effective, only a single substrate **4a** was used to study the hydrogenolysis in these solvents. The products derived from this study were compared with known authentic compounds with respect to their melting points [26]. We believe the penetration depth of the solvents in the microwave oven is an important factor, although this physical parameter is completely ignored by scientists.

Microwave radiation does not always heat the full sample volume (entire materials). When electromagnetic radiation enters the surface of a material, a portion of the radiation reflects from the surface and the remaining portion penetrates the material. The radiation which penetrated the material interacts with the molecules and ions. The radiation penetrates the material at various depths depending on the material's properties. In microwave heating, the penetration depth is an important parameter. The penetration depth of a field can be defined as the distance from the surface of the material to a certain internal point where the magnitude of field strength reduces to 1/e (= 36.8%) of the original magnitude at the surface of the material [27]. The penetration depth can be expressed mathematically as [28,29]:

$$d_p = \frac{\lambda_0}{2\pi}\left(\frac{1}{2\pi\varepsilon_0\varepsilon'}\right)^{1/2}\left[(1+(\tan\delta)^2)^{1/2}-1\right]^{-1/2}$$

where d_p is the penetration depth; λ_0 is the wavelength at vacuum conditions; μ_0 is the magnetic permeability of free space; μ' is the magnetic relative permeability; ε^0 is the permittivity in free space; ε' is the relative permeability; tan δ is the loss angle.



4a: Ar = *p*-anisyl; **4b**: Ar = phenyl; **4c**: Ar = tolyl; **4d**: Ar = benzyl

Scheme-I: Synthesis of hydroxy β-lactams

Penetration depths of 2.45 GHz microwaves for selected solvents are shown in Table-2. It is found that the lower penetration depth of solvents is helpful for the hydrogenation experiment. On this basis, alcohols (ethylene glycol, ethanol and methanol) act as a better solvent for the hydrogenolysis experiments for the removal of the benzyloxy group. Considering the alcohols, ethylene glycol has a low penetration depth (0.46 cm) compared to methanol (0.68 cm) and ethanol (0.93 cm). Because of the small penetration depth, electromagnetic radiation penetrates only a very small distance. Thus, controlled and effective heating occurs in the case of ethylene glycol. Controlled and effective heating generates the products in a better way compared to bulk heating of the whole substances together. In the same manner, water, acetone, ethyl acetate and xylene are not effective for this purpose, due to their high penetration depth. Although the penetration depth of these solvents is measured nearly at room temperature, we are aware that this value may increase at higher temperature proportionally for all solvents. Despite the low penetration depth of water and the aqueous salt solution at room temperature, hydrogenolysis does not proceed in water and salt solution. These results are fascinating considering the dielectric constant of water is extremely high and this parameter indeed should assist hydrogenolysis. All other solvents with higher penetration depth are not effective.

TABLE-2
PENETRATION DEPTHS OF THE 2.45 GHz MICROWAVES FOR SELECTED SOLVENTS [Ref. 30]

Material	Penetration depth (cm)	Temp. (°C)
Water (ice)	1100	-12
Water (distilled)	80	100
Water (distilled)	1.60	20
Water (distilled)	2.88	25
0.125 M NaCl solution of saltwater	0.88	25
0.5 M NaCl solution of saltwater	0.45	25
2 M NaCl solution of saltwater	0.14	25
Ethylene glycol	0.46	25
Methanol	0.68	25
Ethanol	0.93	25
1-Propanol	1.39	25
Acetone	7.07	25
Ethyl acetate	11.05	25
Xylene	28.32	25

Ammonium formate is freely soluble in water and this process generates formic acid and ammonium hydroxide. Formic acid is a weak hydrogen donor in the presence of Pd/C and ammonium hydroxide has no hydrogen donor ability. In fact, ammonium hydroxide can retard the hydrogen donor ability of formic acid further. The penetration depth of water is lowered by adding different proportions of sodium chloride. But, the addition of NaCl solution in ammonium formate and Pd/C cannot inhibit the hydrolysis to formic acid and aqueous NH_3. Sodium chloride can increase the ionic strength of aqueous formic acid, but it fails to improve hydrogen donor ability.

Fig. 1 shows the graphical representation of penetration depth *versus* dielectric constant of the selected solvents.

On the basis of data as presented herein, it seems catalytic transfer hydrogenation in non-homogeneous conditions proceeds well in ethylene glycol because of its lower penetration depth

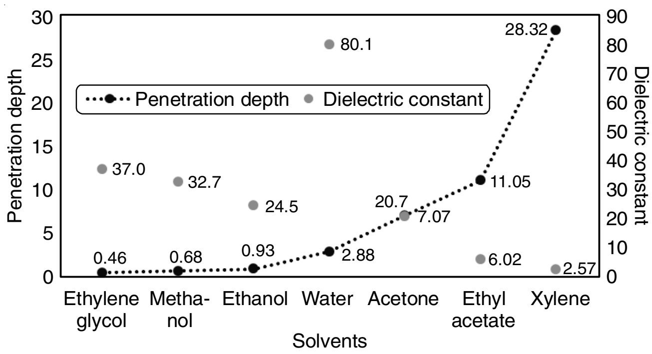


Fig. 1. Penetration depth *vs.* dielectric constant of the selected solvents

value. The solid ammonium formate and palladium-carbon capture more heat from ethylene glycol compared to many other polar solvents. But, significantly lower penetration depth values of ethylene glycol are helpful to have better hydrogenolysis at a fixed temperature (60 ºC). So, it is believed that the penetration depth of solvent is more crucial in microwave-induced hydrogenolysis rather than widely accepted high dielectric constant values. Nevertheless, it is not clear if the high penetration depth factors will be equally applicable to other reactions.

Conclusion

Stereospecific synthesis of optically active *cis* hydroxyl β-lactams under diverse microwave-induced conditions is reported. The effects of the penetration depth of the solvents are found to be more important than solvents with high dipole moments and dielectric constants. Despite significant progress of microwave-induced reactions, no reports have examined the penetration depth of the solvents. The lower penetration depth of polar solvents was helpful for the hydrogenolysis experiment. Because of the small penetration depth, electromagnetic radiation penetrates only a very small distance and, in that way, controlled and effective heating occurs in the case of ethylene glycol.

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