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MICROWAVE-INDUCED CONVERSION OF ELECTROMAGNETIC ENERGY INTO HEAT ENERGY IN DIFFERENT SOLVENTS: SYNTHESIS OF *β*-LACTAMS

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Abstract. This article describes the effect of loss tangent (tan*δ*) values of the solvents in the stereospecific synthesis of optically active cis *β*-lactams under diverse microwave-induced conditions. The effects of low tan*δ* values of the solvents are found to be more crucial than solvents with high dipole moments and dielectric constants. Although, a significant progress of microwave-induced reactions has been registered lately, no reports have examined the tan*δ* values of the solvents in reactions conducted in a microwave. In this study, the synthesis of hydroxy-*β*-lactams under microwave irradiation with diverse solvents was considered by focusing on their tan*δ* values. The results indicated that for the synthesis of *β*-lactams solvents with low tan*δ* and high dipole moment and high dielectric constant are necessary. Compared to DMSO (tan*δ*= 0.82) and DMF (tan*δ*= 0.16), dichloroethane (tanδ= 0.12), dichloromethane (tan*δ*= 0.04) and tetrahydrofuran (tan*δ*= 0.04) are observed to be more effective.

Keywords: *β*-lactam, loss tangent, microwave, stereospecific, optically active.

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Introduction

Beta-lactams (*β*-lactams) are medicinally important compounds due to their wide range of applications. The medicinal activity of the *β*-lactams includes the anticancer [1], antifungal [2], antiviral [3], anti-inflammatory [4], cholesterol absorption inhibitors [5], analgesic [6], anti-hepatitis [7], and antihyperglycemic [8] activities. Thus, synthesis of the *β*-lactams based compounds is very crucial. Diverse methods are available for the synthesis of *β*-lactams. These include the Staudinger cycloaddition reaction, ester enolate-imine condensation, hydroxamate approach, alkene-isocyanate method, catalytic asymmetric synthesis, the alkyne-nitrone reaction (Kinugasa reaction), and polymer-supported synthesis [9-14]. The synthesis of *β*-lactams and related compounds by various methods [9] and computational analysis of the physicochemical and structural properties of the compounds [10-14] were studied extensively, as well.

Microwave-assisted methods have several advantages compared to conventional methods, such as: contactless method; minimized 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 [15]; uniform heating, thus products with good quality will be obtained [16]; shorter reaction time (shorter duration of processes) [17]; fewer side reactions [18]; products with good selectivity and purity [19]; operate under solvent-free conditions [20]; very high power densities developed in the processing zone [21]; superior moisture leveling [21]; high level of energy saving [22]; higher efficiency of production [21]; compact equipment [21]; shorter start-up time of apparatus; an important part of green chemistry approach [23]. However, not all the reactions work with microwave irradiation (MWI), the material must have certain dielectric properties to get efficient heating during microwave irradiation. Besides, during our synthetic study, it has come to our attention that solvents have played a critical role depending on the reactants and reaction conditions. Thus, it is crucial to study the effects of various solvents under microwave irradiation and to reveal the reason for it. Considering all these facts, in this study, the synthesis of hydroxy-*β*-lactams under MWI with diverse solvents was considered by focusing on their tan*δ* values.

The goal of the study was to analyze the effect of tanδ values of the solvents in the stereospecific synthesis of optically active *cis*-β-lactams. In a microwave method, a material's heating characteristics are related to the ability of that material to change electromagnetic energy into heat energy. The ability of the material to convert the energy is expressed as tanδ, the loss tangent.

Experimental

Materials

Benzyloxy acetyl chloride, all aromatic amines and aldehyde, ethylene dichloride, and *N*-methyl-morpholine were purchased from Sigma-Aldrich Chemical Company, U.S.A.

The following solvents were used: Ethylene dichloride, dichloromethane, ethyl acetate, hexane, butanol, chloroform, ethylene glycol, dichlorobenzene, acetonitrile, dimethylsulfoxide (DMSO), propyl alcohol, methanol, nitrobenzene, *t*-butanol, acetic acid, dimethylformamide (DMF), water, chlorobenzene, acetone, tetrahydrofuran (THF), toluene, hexane and xylene.

Methods

*Synthetic procedure for the preparation of compound **3a**:* To a solution of imine **2a** (1 mmol) in ethylene dichloride (2 mL) and *N*-methylmorpholine (3 mmol) was added benzyloxyacetyl chloride **1** (1.5 mmol) in a microwave sample vial (Scheme 1). The reaction mixture was then irradiated in a CEM automated microwave (U.S.A.) with a frequency of 2.45 GHz and power 300 W at 40°C for 5 min. Afterwards, the reaction mixture was cooled at room temperature, water (5 mL) was added to it and the contents were transferred to a separating funnel. After mixing the reaction mixture, the lower layer (organic layer) was collected, washed with dilute aqueous hydrochloric acid solution (5%, 2x5 mL), aqueous sodium bicarbonate solution (5%, 2x5 mL), and then with brine (2x5 mL). The reaction contents were then dried with anhydrous sodium sulphate (2 g), the solvent was evaporated and the crude product was obtained. This crude material was crystallized using ethylacetate-hexane as the solvents to afford the pure beta-lactam **3a** in 90% yield.

By following an identical procedure as described here, compounds **3b-d** was prepared from **2b-d**. The structure of compounds was confirmed by using FTIR (Bruker IFS 55 Equinox FTIR spectrophotometer, U.S.A.) and NMR spectroscopy (with a Bruker superconducting UltrashieldTM Plus 600 MHz NMR spectrometer U.S.A.). The Fisher Scientific electrochemical Mel-Temp* manual melting point apparatus (Model 1001, U.S.A) equipped with a 300°C thermometer was used to determine the melting point values. The melting points values of the four obtained compounds **3a-3d** were compared with known authentic compounds and found to be identical with the compounds synthesized earlier, thus **3a** (120ºC), **3b** (63ºC), **3c** (110ºC), and **3d** (118ºC) [24].

Evaluation of the loss tangent of the solvents used for the synthesis: The loss tangent (tanδ) of the compounds can be determined by using the Eq.(1) [25-27].

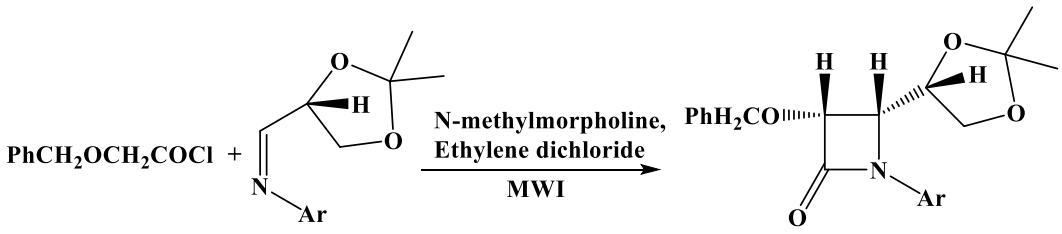
$$tan\delta = \frac{\varepsilon''}{\varepsilon'} \quad (1)$$

where, ε''- dielectric loss (efficiency with which electromagnetic radiation is converted into heat);

ε'- dielectric constant (polarizability of molecules in the electric field).

Results and discussion

The synthesis of optically active β-lactams under MWI is shown in Scheme 1. 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. Several solvents were considered to optimize the reaction conditions, as presented in Tables 1,2.



1 **2a-d** **3a-d**

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

Scheme 1. Synthesis of optically active *cis* β-lactams.

Table 1

Tanδ values of selected organic solvents in the microwave field at 2.45 GHz and 20ºC [30-32].

Solvent	*tanδ*
Ethylene glycol	1.35
Ethanol	0.94
DMSO	0.82
2-Propanol	0.79
Formic acid	0.72
Methanol	0.65
Nitrobenzene	0.58
1-Butanol	0.57
2-Butanol	0.44
Dichlorobenzene	0.28
NMP	0.27
Acetic acid	0.17
DMF	0.16
Dichloroethane	0.12
Water	0.12
Chlorobenzene	0.10
Chloroform	0.09
Acetonitrile	0.06
Ethyl acetate	0.05
Acetone	0.05
THF	0.04
Dichloromethane	0.04
Toluene	0.04
Xylene	0.04
Hexane	0.02

The same reaction was performed in a microwave oven with ethylene dichloride in an open vessel for 5 min and identical β-lactams were produced. To maintain an identical or better yield of the product, other physical parameters of solvents were examined.

In order to be efficiently heated in the microwave, the material must possess certain dielectric properties. Under microwave treatment, the heating characteristics of a material depend on the ability of that material to convert electromagnetic energy into heat energy. The ability can be expressed as tanδ, the loss tangent. The tanδ values of some selected organic solvents are summarized in Table 1.

For fast heating, a solvent with a high tanδ is required. At the same time, solvents with low tanδ values can be also useful for microwave synthesis. In that case, either substrates or reagents/catalysts must be polar and the overall dielectric properties of a reaction mixture allow sufficient heating by microwaves. Thus, microwave heating is also possible even with a non-polar solvent. Besides, if the reaction mixture is non-polar, passive heating elements can be added to the mixture to assist the heating process.

After a search of the scientific literature, tanδ parameters of a few comparable solvents were found. The function of tanδ was analyzed more carefully in order to identify their effects in the β-lactam synthesis. Indeed, dichloromethane with tanδ 0.042 was capable of producing the same lactam after 5 min of microwave exposure at 40ºC. On the other hand, the reaction was not completed in toluene with tanδ 0.04 at 80ºC even after 10 min of microwave irradiation. The obtained data are shown in Table 2 (for **3a**). Solvents that have lower tanδ values are very effective. Table 3 compares the dipole moment, and dielectric constant of the used organic solvents.

The failure of some solvents to produce reasonable β-lactams is due to the occurrence of other reactions. In principle, the acid chloride, the intermediate ketene, the imines, and the products can react with alcoholic solvents (methanol, ethanol, 1-butanol, 2-butanol, and isopropanol), water, acetone, and acetonitrile.

Table 2

Dependence of product yield and reaction time on each solvent.

Solvent	*Reaction time*	*Product yield*
Ethylene glycol	5 min	10%
Ethanol	5 min	10%
Methanol	5 min	10%
Water	5 min	No reaction
1,2-Dichloroethane	5 min	90%
Dichloromethane	5 min	90%
THF	5 min	80%
Toluene	5 min	25%
Acetonitrile	5 min	80%
DMSO	5 min	60%
DMF	5 min	80%
Xylene	5 min	25%

Table 3

Dipole moment, and dielectric constant values of selected organic solvents.

Solvent	*Dipole moment*	*Dielectric constant*
Ethylene glycol	2	37.00
Ethanol	1.69	24.5
Methanol	1.7	32.7
Water	1.85	80.1
Ethyl acetate	1.78	6.02
Acetone	2.88	20.7
1,2-Dichloroethane	1.86	10.36
Dichloromethane	1.55	8.93
THF	1.63	7.52
Toluene	0.43	2.38
Acetonitrile	3.92	36.6
DMSO	3.96	47.2
DMF	3.82	38.3
Xylene	0.62	2.57

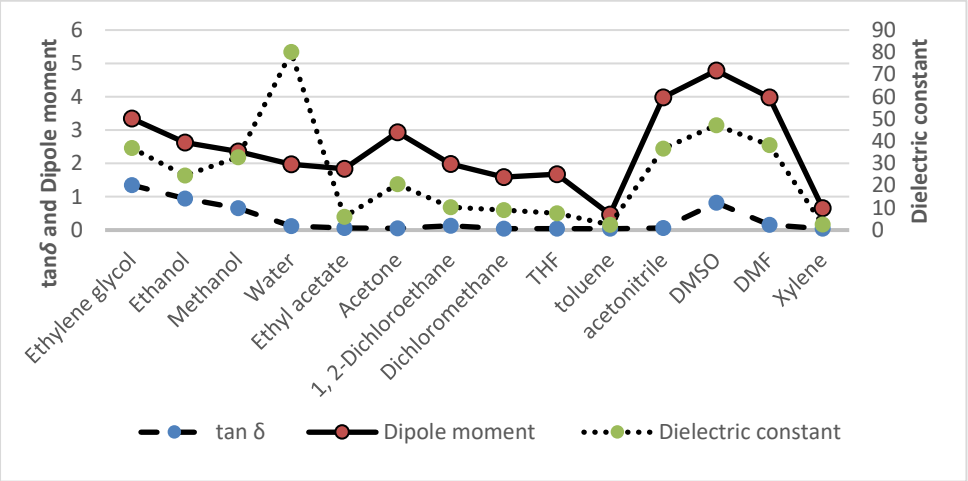


Figure 2. Comparison of the tanδ values, dipole moment, and dielectric constant of the used organic solvents.

The failure of some solvents to produce reasonable β-lactams is due to the occurrence of other reactions. In principle, the acid chloride, the intermediate ketene, the imines, and the products can react with alcoholic solvents (methanol, ethanol, 1-butanol, 2-butanol, and isopropanol), water, acetone, and acetonitrile. However, the reactivity of the intermediates is slow in acetonitrile. Since the formation of the β-lactams is a rapid process, it seems acetonitrile gives good yields of the products. These side reactions limit their use in the synthesis of β-lactams. Hydrocarbon solvents, like toluene (tanδ= 0.04) and xylene (tanδ= 0.04) do not produce products in good yield despite their low tanδ values. The dipole moment and dielectric constant of toluene and xylene are also low. DMF is effective because of low tanδ (tanδ= 0.16) and high dipole moments, and dielectric constant. This study indicates for the synthesis of β-lactams solvents with low tanδ and high dipole moment and high dielectric constant are necessary. Being an amide, DMF cannot react with any of the reagents, intermediates, and products. Lower tanδ values of solvents control the product formation even more than the solvent high dielectric constant values. For example, dichloroethane (tanδ= 0.12), dichloromethane (tanδ= 0.04) and tetrahydrofuran (tanδ= 0.04) are more effective than DMSO (tanδ= 0.82) and DMF (tanδ= 0.16). The polar DMSO and DMF have higher tanδ, but comparable dipole moment. Figure 2 compares the tanδ values, dipole moment, and dielectric constant of the used organic solvents.

Conclusions

In this work, the stereospecific synthesis of optically active *cis*-β-lactams under diverse microwave-induced conditions using diverse solvents was reported. The effects of low tanδ values of the solvents are found to be more crucial than solvents with high dipole moments and dielectric constants.

The results of this study indicated that for the synthesis of β-lactams solvents with low tanδ and high dipole moment and high dielectric constant are necessary. Dichloroethane (tanδ= 0.12), dichloromethane (tanδ= 0.04) and tetrahydrofuran (tanδ= 0.04) were found to be more effective than DMSO (tanδ= 0.82) and DMF (tanδ= 0.16). Best of the knowledge this is the first report that examined the importance of tanδ values of the solvents in β-lactams synthesis.

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