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Perspective
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Microwave-Induced Synthesis of Enantiopure β - Lactams

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Abstract

Synthesis of enantiopure C-3/C-4 disubstituted β-lactams has been achieved through Staudinger cycloaddition reaction of acid chloride and imine under microwave irradiation. Importantly, reactions has been manipulated by proper selection of substrates to obtain both enantiomers in high yield.

Keywords: Cycloaddition; Imines; Optically active; β Lactams

Introduction

We have been engaged in the synthesis and biological evaluation of diverse β-lactams since 1990. Research on β-lactam is a crucial objective since many of them have demonstrated diverse medicinal properties. Since 1945, β-lactams have saved the life of several million people in the world as very useful antibiotics. Apart from antibacterial properties, β-lactams have demonstrated numerous other crucial applications. For this reasons, many promising methods have been developed to prepare these types of molecules. Reaction of Schiff bases (imines) with acid chlorides in the presence of a tertiary base has been used extensively (Staudinger cycloaddition reaction) for the preparation of racemic and optically active β-lactams [1]. Penicillin-related β-lactam antibiotics were synthesized [2] and they were used extensively to fight against infectious and diseases that may not have any cure [3]. Notably, beta-lactams were applied in other crucial studies for the benefits of human. They were used as promising inhibitors of serine protease [4] and acyl coenzyme A cholesterol transferases (ACAT) [5]. These types of molecules were the key substrates for the preparation of various heterocycles of biological and pharmacological significances [6]. Hydroxy beta-lactam derivatives were the crucial fragments in the semi-synthesis of anticancer drug, Taxol and Taxotere [7]. Studies directed to human leukocyte elastase inhibitory mechanisms were also available [8]. As a result of their significant practical applications, the synthesis of new types of beta-lactams was the focus of active research for many years. The interests in this area had not gone down even after six decades of study. A number of effective strategies were discovered for the synthesis of the 2-azetidinone core ring present in all β-lactams. We and others are pursuing research on the synthesis and biological evaluation of a number of novel anticancer and new β-lactams [9,10]. Our laboratory have been actively engaged in the synthesis of racemic and optically active β-lactams following Staudinger cycloaddition reaction under conventional and microwave-induced methods [11,12]. This reaction may produce β-lactams through diasteroselective or enantioselective pathways depending upon the structure of the starting materials. Each component of the reactants is very important in controlling the stereoselectivity of this reaction. Microwave-mediated process has become highly successful in the synthesis of organic compounds of diverse interests. This process has become highly efficient in the synthesis of β-lactams also. Despite significant successes in the synthesis of β-lactams as useful molecules, availability of optically active β-lactams in both enantiomeric forms has remained a challenging area of research [2]. We report here a facile microwave-induced method for the preparation of a few chiral β-lactams in both enantiomeric forms [13].

Results and Discussion

Several years ago, synthesis of an optically active β-lactam 3 was reported by us following conventional method [3]. Reaction of the imine 2 with acetoxyacetyl chloride 1 in the presence of triethylamine in dry dichloromethane at 0°C room temperature produced a single optically active β-lactam 3 in good yield. Based upon the success in microwave-induced reaction, the same β-lactam 3 is prepared within a few minutes. Thus, reaction of acetoxyacetyl chloride 1 with imine 2 obtained through a 5-membered carbohydrate derivative in dichloroethane in the presence of N-methylmorpholine under microwave irradiation produced an identical β-lactam 3 in good yield. In the microwave-induced method higher boiling N-methylmorpholine was used instead of triethylamine. Similarly, dichloroethane was used instead of dichloromethane in the microwave method. It has found that higher boiling polar solvents and reagents are extremely effective in the microwave-induced reactions. The protective group in 3 was removed with methanolic iodine solution and the intermediate was oxidized with ruthenium-mediated sodium metaperiodate-mediated oxidation to carboxylic acid. The carboxylic acid was esterified to methyl ester with diazomethane without any isolation. By these series of reactions compound 3 is converted to compound 4 with 3S, 4R absolute stereochemistry at the ring system (Scheme 1). In order to obtain the antipode of 4, a different starting material was required. Imine 5 from D-glyceraldehyde acetonide was required to prepare the antipode of molecule 4. The optically active glyceraldehyde was synthesized from protected mannitol derivative through careful deprotection and oxidation method. The optically active glyceraldehyde was condensed with benzyl amine to afford 5 in quantitative yield. Reaction of methoxyacetyl chloride 1 with chiral Schiff base 5 was performed using N-methylmorpholine as the base and dichloroethane as the solvent under microwave irradiation method. This reaction produced a single optically active β-lactam 6. The ketal group in 6 was removed by methanolic iodine and the resulting diol was oxidized to carboxylic acid. The acid was then esterified with diazomethane to afford the ester 7. Compound 7 is the enantiomeric form of 4 with 3R, 4S absolute stereochemistry at the ring system (Scheme 2). Thus, optically active β-lactams in both enantiomeric forms were synthesized by chemical manipulation of the starting imines. The optically active β-lactams 4 and 7 have oxygen containing group at the C-3 position of the ring. In order to diversify the synthesis with nitrogen containing group at the C-3 center, a similar reaction was performed with 8 and 9. Chiral imine 9 was synthesized from glyceraldehydes and p-anisidine. The imine 9 on reaction with phthalimidoacetyl chloride 8 in the presence of dichloroethane and N-metyhlmorpholine under microwave irradiation

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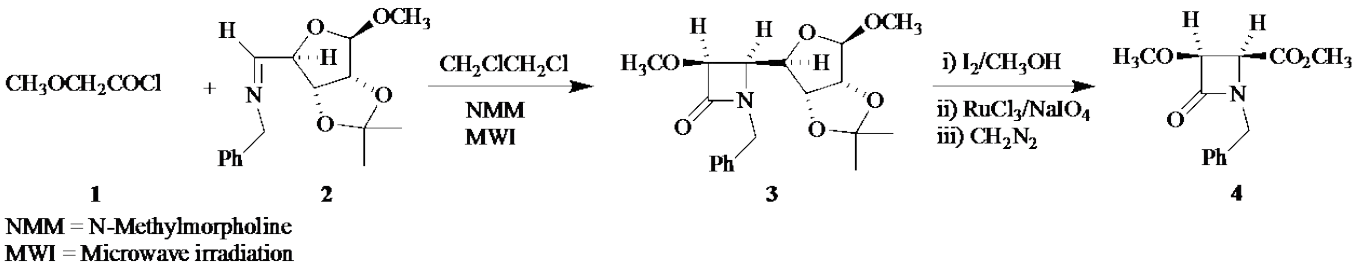
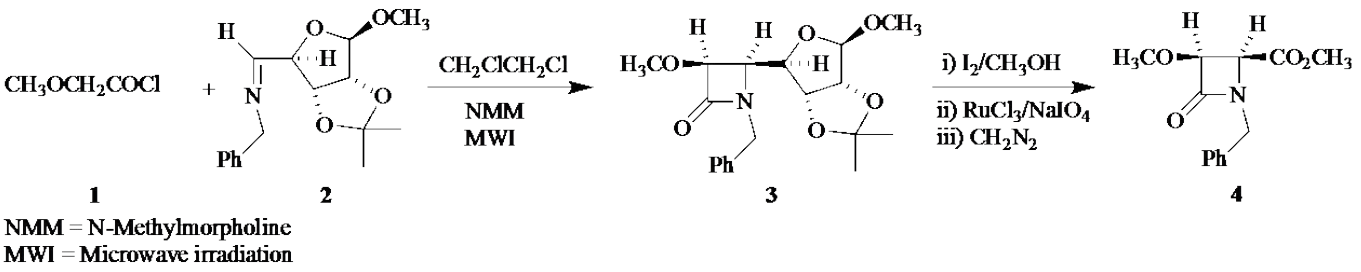
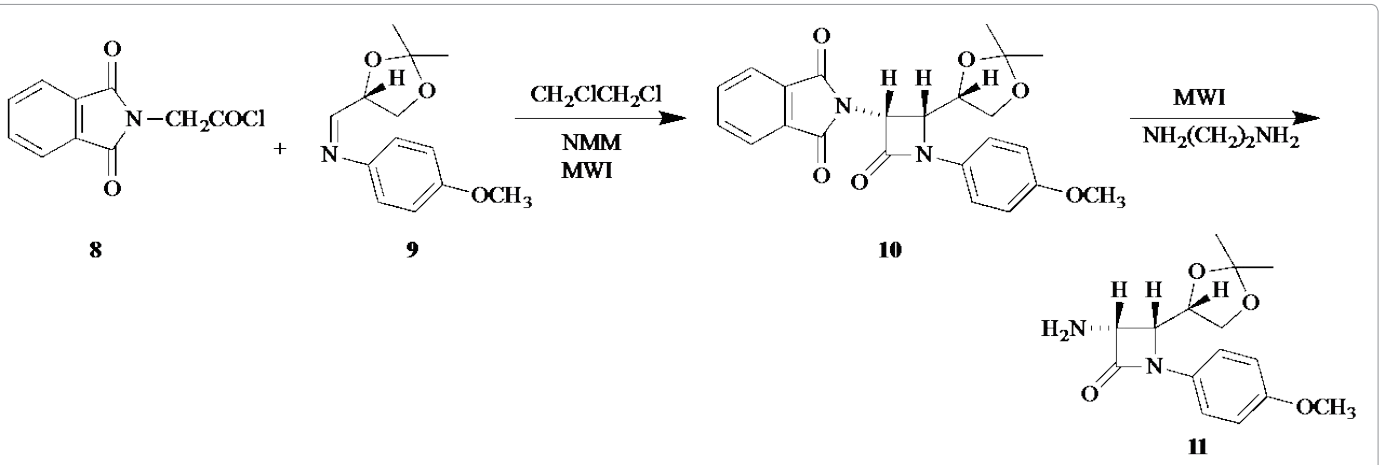


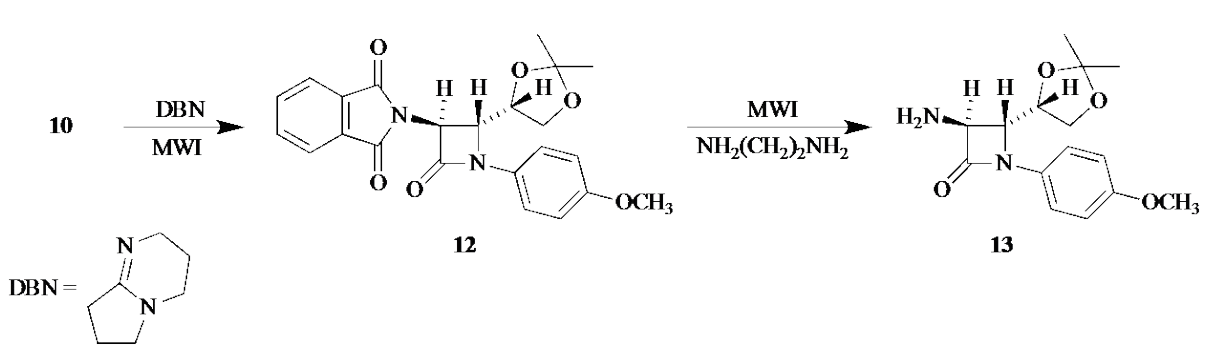
Scheme 1: Highly stereospecific synthesis of optically active β-lactam 4.



Scheme 2: Highly stereospecific synthesis of optically active β-Lactam 7.



Scheme 3: Highly sterospecific synthesis of optically active β-lactam 11.



Scheme 4: Highly enantiospecific synthesis of optically active β-lactam 13.

produced a single optically active β-Lactam 10. The phthalimido group in 10 was then removed by ethylenediamine to produce 11, an amino compound with 3R, 4S absolute stereochemistry at the ring system (Scheme 3). To invert the stereochemistry at the C-3 center, compound 10 was treated with DBN under microwave irradiation method. This process produced 12 which was then transformed to 13 with,

compound 11 and 13 are enantiomeric to each other. Molecule 12 was also made by reacting 8 with 9 in the presence of N-methylmorpholine and DBN under microwave irradiation method. Electron withdrawing phthalimido group facilitates the inversion of configuration at C-3 of 10 in the presence of a strong base DBN. Triethylamine was unable to invert the stereochemistry in 10 (Scheme 4). Compound 13 with 3S, 4S absolute stereochemistry at the ring junction was prepared from compound 12 by the treatment of ethylenediamine under microwave irradiation method.

Conclusion

Preparation of optically active β-lactams by microwave irradiation method using imines derived from carbohydrates is very fast. It is possible to obtain several enantiomeric β-Lactams more effectively than the existing method. The important chiral molecules as described by the short possible route and in a faster way would find several applications considering the enantiomeric and functionalized nature of these β-lactams.

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