Ain Shams University
University College of Women
For Arts, Science and Education
Chemistry Department

Enhanced One-Pot Microwave Efficient Synthesis Versus Conventional Thermal Synthesis of Some Nitrogenous Sulfur Compounds and Evaluation of Their Biological Activity

A Thesis Submitted for the Degree of Ph. D.
In
Organic Chemistry

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Approval of Chemistry Department Council / /2009
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بِسْمِ اللهِ الرَّحْمنِ الرَّحِيمِ

سُبْحَنَكَ لاَ عِلْمَ لَنَآ إِلاَّ مَا عَلَّمْتَنَآ إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صَدَقَ اللهُ الْعَظِيمُ

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DEDICATION

To the light of my life
My family
Thank you for supporting
and helping me
in love and gratitude

QUALIFICATION

Student Name: Fatehia Ibrahim Abd El-Monem

Scientific Degree: M. Sc.

Department: Chemistry

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B. Sc. Graduation Year: 1998

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CONTENTS

ABSTRACT

Microwave irradiation and conventional thermal heating techniques for the condensation of 2-[methyl(4-methylphenyl)-methylene]butanedioic anhydride(1), 2-[methyl(4-chlorophenyl)-methylene]butanedioic anhydride (2), or 2-diphenylmethylene-butanedioic anhydride (3) with different N-substituted 4-amino-benzenesulfonamides give the corresponding N-(N'-substituted benzenesulfonamido)-3-carboxy-4-aryl-3-butenamide derivatives, N-(N'-substituted benzenesulfonamido)-3-arylethylidinepyrrolidine-2,5-dione derivatives and N-(N'-substituted benzenesulfonamido)-3-diphenylmethylenepyrrolidine-2,5-dione derivatives (4-49).

The results obtained show that microwave irradiation technique furnishes the formation of the products in excellent yield, in shorter time, and more regiospecific than the conventional thermal heating one.

Some synthesized compounds show antimicrobial biological activity depending on the substituents. The benzenesulfonamido group results in low reactivity toward condensation whereas it shows high biological activity.

The structural formulas of the products were confirmed by their spectral analysis; ^{1}HNMR, MS and IR.

AIM OF THE WORK

The aim of the present work is to synthesize some butenamide and pyrrolidine-2,5-dione derivatives, which are known as bio-active compounds, having widely medical applications and anti-bacterial activities, in appreciable high yields, purity and safety using a rapid convenient and environmental technique knowing as green chemistry. Such a technique should be an alternative to the conventional prolonging heating technique under reflux in solvents with low yields, and less purity.

These compounds were prepared by condensation of α, β-unsaturated carbonyl compounds with different N-substituted 4-aminobenzenesulfonamides and amines using microwave irra-diation technique and comparing the results with that obtained from conventional method.

The study also aimed to assess the factors affecting the synthesis of the butenamides and pyrrolidine-2,5-diones such as:

1- Microwave effects.
2- Polarity of amine and anhydride.
3- Structural effect (electronic and/or steric).
4- Basicity of amines.

The structural formulas of the obtained compounds were confirmed by their spectral data; IR, ^{1}HNMR and MS.

The bacterial activities of some prepared compounds have been estimated using diffusion disk procedure.

SUMMARY

The highly important medical applications of amides, imides, and sulfonamides and also due to their biological activity as bacteriocides, fungicides and insecticides, led us to synthesize some butenamide and pyrrolidine-2,5-dione derivatives from the reaction of α, β-unsaturated carbonyl compounds, 2-[methyl(4-methylphenyl)methylene]butanedioic anhydride (1), 2-[methyl(4-chlorophenyl)methylene]butanedioic anhydride (2), or 2-diphenyl-methylenebutanedioic anhydride (3), with 4-aminobenzenesulfon-amide derivatives and amines using enhancing microwave irradiation heating and compare it with the conventional thermal heating technique. The microwave irradiation technique proves its convenience, utility and advantages rather than conventional thermal heating technique.

Solvent-free Microwave Irradiation Heating Versus Conventional Thermal Heating Technique

The condensation of andydrides (1-3) with N-substituted 4-aminobenzenesulfonamides, furnished the formation of the corresponding butenamides and/or pyrrolidine-2,5-diones (4-49) in high efficiency, yield, within 5 minutes, easier working out, and safety in addition to the fact that the experimental procedure was

much easier and friendly environmental, comparable to the conventional thermal heating technique.

The aim of using solvent-free conditions under microwave irradiation is to avoid the disadvantages of most of them.

I. Solvent-free Microwave Irradiation Technique for the Condensation of Anhydrides (1-3) with N-Substituted 4-Aminobenzenesulfonamides

Comparison between products furnished from the microwave irradiation of anhydrides (1-3) with N-substituted 4-aminobenzene-sulfonamide derivatives show that the reaction is affected by the following factors:

5- Microwave effects.

6- Polarity of amine and anhydride.

7- Structural effect (electronic and/or steric).

8- Basicity of amines.

With N-phenyl-4-aminobenzenesulfonamide and N-(4-methyl-phenyl)-4-aminobenzenesulfonamide:

The formation of the cyclic products (23, 25) can be attributed to the ease of anchimeric assistance of the basic nitrogen of the amido group toward intramolecular nucleophilic attack on the carbonyl carbon due to the coplanarity of the two phenyl rings in anhydride (3).

The formation of butenamides (14, 15) can be ascribed to the presence of the electron withdrawal chlorine atom in anhydride (2), whereas the formation of separable mixtures of butenamides (4, 6) as major products, and pyrrolidine-2,5-diones (5, 7) as minor products, can be attributed to the presence of the electron-releasing two methyl groups in anhydride (1). The results indicate that the coplanarity outweighs the electronic factor in addition to the microwave effects.

With N-(4-methoxyphenyl)-4-aminobenzenesulfonamide:

The formation of pyrrolidine-2,5-dione (27) can also be attributed to the ease of cycilzation due to the coplanarity of the two phenyl rings in anhydride (3), in addition to the microwave effects.

The formation of the separable mixtures of butenamides (8, 16) and pyrrolidine-2,5-diones (9, 17), can be attributed to the presence of the mesomeric effect and polarity of the methoxyl group resulting in an increase of its reactivity towards nucleophilic attack on the carbonyl carbon and also enhances the microwave effects. The formation of separable mixtures of butenamides (8, 16) and pyrrolidine-2,5-diones (9, 17), respectively from anhydrides (1) and (2) although anhydride (1) has electron releasing methyl group and anhydride (2) includes electron withdrawal

chlorine atom ascertained the basicity effect and microwave effects of the methoxyl group in the sulfonamido moiety.

With N-(4-chlorophenyl)-4-aminobenzenesulfonamide and N-(4-nitrophenyl)-4-aminobenzenesulfonamide:

The formation of butenamide derivatives (10, 18) resulted from the condensation of anhydrides (1) and (2), respectively with N-(4-chlorophenyl)-4-aminobenzenesulfonamide and butenamides (11, 19) with N-(4-nitrophenyl)-4-aminobenzenesulfonamide can be attributed to the electronic effect exerted by electron withdrawal chlorine atom and nitro group in the amine, comparable to the electron releasing methoxyl group in the N-(4-methoxyphenyl)-4-aminobenzenesulfonamide. This indicates that the electronic effect outweighs the microwave effects. It can also be attributed to the steric hindrance resulted from the methyl group in the anhydrides (1) and (2).

The formation of separable mixtures from butenamides (28, 30) as minor products and pyrrolidine-2,5-diones (29, 31) as major products with anhydride (3) can be ascribed to the coplanarity of the phenyl rings in addition to the microwave effects, which outweighs the electronic effect.

With N-(1-naphthyl)-4-aminobenzenesulfonamide:

The formation of butenamides (12, 20) resulted from the condensation of anhydrides (1) and (2), respectively with

N-(1-naphthyl)-4-aminobenzenesulfonamide can be attributed to the steric hinderance exerted by the methyl groups in anhydrides (1) and (2). The coplanarity of phenyl groups in anhydride (3) facilitates the nucleophilic attack by the amido group nitrogen on the carbonyl carbon to give the corresponding pyrrolidine-2, 5-dione (33) as a minor product together with the butenamide (32) as a major product.

This indicates that coplanarity of the phenyl groups outweighs the electronic effects produced by the electron withdrawal chlorine atom and electron releasing methyl group.

With N-benzyl-4-aminobenzenesulfonamide:

The results obtained from the microwave irradiation of anhydrides (1-3) with N-benzyl-4-aminobenzenesulfonamide to give butenamides (13, 21, 34), respectively can be ascribed to the steric effect exerted by the tetrahedron carbon in the benzyl group in sulfonamido moiety.

This effect can be ascertained by the comparison of results obtained from condensation of anhydride (3) with N-phenyl-4-aminobenzenesulfonamide to give pyrrolidine-2, 5-dione (23), whereas it gives with N-benzyl-4-aminobenzenesulfonamide the butenamide (34).