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

Environmental Friendly Microwave One-Pot Synthesis of Some Nitrogenous Sulfur Organic Compounds

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

Presented
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بِسْمِ اللهِ الرَّحْمنِ الرَّحِيم

وَمَا أُوتِيتُمْ مِنْ العِلمِ إلا قلِيلا

صدق الله العظيم

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DEDICATION

To

my distinguished parents

I do appreciate my God

for giving me such wonderfully parents

who are enlighting and always supporting me

in all my life.

I also thank my husband and my family

For continous encouragement and help.

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QUALIFICATION

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B. Sc. Graduation Year: ٢٠٠٤

M. Sc. Graduation Year: ٢٠٠٩

Ph. D. Graduation Year: ٢٠١٢

CONTENTS

Abstract

Synthesis of compounds ٣-٥٨ that are expected to have medicinal and biological activities was carried out by reaction of (E)-٣-(٣،٤-dimethoxybenzylidene)dihydrofuran-٢،٥-dione ١ and (E)-٣-(benzo[d][١،٣]dioxol-٥-ylmethylene)dihydrofuran-٢،٥-dione ٢ with aniline, ٢-substituted aniline, ٢-aminopyridine, and ٢-aminothiazole (a-h), and with N-substituted-٤-aminobenzenesulfonamides (i-o) using microwave and conventional thermal heating techniques to study the structural effect of reactants and techniques used, on the reaction mechanism and yields.

Microwave irradiation of anhydrides ١ and ٢, with amines (a-h) gave either derivatives of the butanoic acid, pyrrolidine-٢،٥-dione, or mixtures of both of them (٣-٣٢). Also, microwave irradiation of anhydrides ١ and ٢ with N-substituted-٤-aminobenzenesulfonamides (i-o) gave either derivatives of butanoic acid, bezenesulfonamide, or mixtures of both of them (٣٣-٥٨).

Conventional thermal heating technique yielded only the corresponding butanoic acids.

The results obtained showed that microwave irradiation technique, enhances the yield, regioselectivity, and purity of products. It accomplished the reactions in shorter times, and eco-friendly environmental safety, i.e., (green chemistry) with easier working up. Such requirements are important for the synthesis of compounds having medicinal applications (cytotoxic) and biological activities. Some synthesized compounds showed antimicrobial and/or cytotoxic activity from moderate to low values against human liver carcinoma cell line using Doxorubicin as a reference drug and human breast carcinoma cell line using Flouraciele as a reference drug.

Keywords: Microwave irradiation, butanoic acids, pyrrolidine-٢،٥-diones, arylbenzenesulfonamides, antimicrobial, and cytotoxic activities**.**

AIM OF THE WORK

This work aimed to synthesize some nitrogenous and nitrogenous sulfur organic compounds; that are expected to have medicinal applications (cytotoxic) and antibacterial activities, such as arylaminobutanoic acid, pyrrolidine-٢،٥-dione, and benzenesulfonamide derivatives in one-pot reaction, environmentally-safe technique (green chemistry), appreciable high yields, and purity.

Such requirements are essential for medicinal and bioactive compounds. We also aimed to assess the factors that affecting the synthesis of targeted compounds such as; structural effect of reactants, basicity of amines or amine sulfur, medium of reaction, and techniques used.

Abstract

Synthesis of compounds ٣-٥٨ of expected medicinal and biological activities have been carried out by reaction of (E)-٣-(٣،٤-dimethoxybenzylidene)dihydrofuran-٢،٥-dione ١ and (E)-٣-(benzo[d][١،٣]dioxol-٥-ylmethylene)dihydrofuran-٢،٥-dione ٢ with aniline, ٢-aminoaniline, ٢-mercaptoaniline, ٢-hydroxyaniline, ٢-methoxyaniline, ٢-methylaniline, ٢-aminopyridine, ٢-aminothiazole (a-h), and N-substituted ٤-aminobenzenesulfonamide (i-o) using microwave and conventional thermal heating techniques to study the structural effect of reactants, basicity of amines, and technique used.

Microwave irradiation of anhydrides ١ and ٢, with amines (a-h) gave either derivatives of butanoic acid, pyrrolidine-٢،٥-dione, or mixture of both of them (٣-٣٢). Also, microwave irradiation of anhydrides ١ and ٢ with amines (i-o) gave either derivatives of butanoic acid, benzenesulfonamide, or mixture of both of them (٣٣-٥٨). Conventional thermal heating technique yielded only the corresponding butanoic acids. The results obtained showed that microwave irradiation technique, enhances the yield, speed of reaction, regioselectivity, and purity. It accomplished the reactions in shorter time, simplest working up, and safe environment (green chemistry). Such requirements are important for the synthesis of compounds having medicinal applications (cytotoxic) and biological activities. Some synthesized compounds showed antimicrobial and/or cytotoxic activity from moderate to low values against human liver carcinoma cell line and human breast carcinoma cell line.

Keywords: Microwave irradiation, butanoic acids, pyrrolidine-٢،٥-diones, arylbenzenesulfonamides, antimicrobial and cytotoxic activities

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INTRODUCTION

Gedye R. N. et al., (١٩٨٦) published the first pioneering reports on the use of microwave heating to carry out synthetic organic transformations. It was realized that performing organic synthesis under microwave irradiation has some significant advantages as compared to classical heating techniques, to generate rapid intense heating of polar substances with consequent significant reduction in reaction times, cleaner reactions that are easier in working up and in many cases offers higher yields. In fact, many reactions that do not occur by classical heating or that occur in very low yields can be performed in high yields under microwave irradiation.

The main advantage of microwave heating is the almost instantaneous "in core" heating of materials in homogeneous and selective manner (in contrast to conventional heating). Not surprisingly, microwave-assisted organic synthesis has become popular, useful technology in organic chemistry and interest in it has increased in the recent years from academic, governmental, and industrial laboratories. This is due to its characteristic accelerations for a wide range of organic reactions specially when carried out under solvent-free conditions.

The combination of solvent-free reactions and microwave irradiation leads to large reduction in reaction time, enhancement in conversions, and sometimes, in selectivity with several advantages of the eco-friendly approach, termed green chemistry as described by ***Loupy A. et al., (١٩٩٨)*** and ***Varma R. S., (١٩٩٩)***.

Some Properties and Effects of Microwave Irradiation

The microwave region of the electromagnetic spectrum lies between infrared radiation and radio frequencies and corresponds to wavelengths between ١cm and ١m (frequencies of ٣٠ GHz to ٣٠٠ MHz). In order to avoid interference with RADAR and telecommunication applications, domestic and industrial microwave reactors for chemical use operate at ٢٫٤٥ GHz were used.

١. Microwave Effects

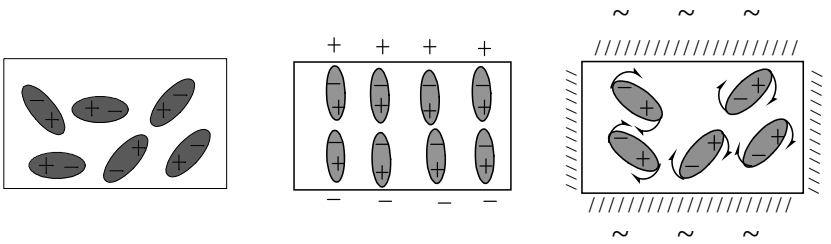
In case of microwaves, the energy transfer does not occur by conduction or convection, as in conventional heating, but by dielectric loss. Materials dissipate microwave energy by two main mechanisms; dipole rotation and ionic conduction. When molecules with permanent (or inducible) dipoles are exposed to an electric field, they become aligned. If this field oscillates, the orientation changes with each alternation. The strong agitation provided by the reorientation of molecules which are in phase with the electrical field excitation, causes an intense internal heating.

The acceleration of reactions by microwave exposure results from material-wave interactions leading to thermal effects (which may be easily estimated by temperature measurements) and specific (non-purely thermal) effects. Clearly, a combination of these two contributions can be responsible for the observed effects.

Thermal effects

Thermal effects (dielectric heating) can result from dipolar polarization as a consequence of dipole-dipole interactions between

polar molecules and the electromagnetic field. They originate in dissipation of energy into heat as an outcome of agitation and intermolecular friction of molecules when dipoles change their mutual orientation at each alternation of electric field at a very high frequency (υ = ٢٤٥٠ MHz) as shown below, ***Perreux L.and Loupy A., (٢٠٠١)***.



Without any effect | Submitted to electric field | Alternating high frequency electric field

This energy dissipation in the core of materials allows much more regular partition in temperature when compared to classical heating.

Specific microwave effects

Specific microwave effects can be expected for the polar mechanisms, when the polarity is increased during the reaction from the ground state towards the transition state. The outcome is essentially dependent on the medium and the reaction mechanism. If stabilization of the transition state is more effective than that of the ground state, this results in an enhancement of reactivity due to the decrease in the activation energy.

٢. Solvent Effect

Langa F. et al., (٢٠٠٠) showed that microwave effects should additionally be considered according to the reaction medium. Solvent effects are of a particular importance. Clearly, solvent influence seems