

Dedicated to Professor Alexandru T. Balaban
on the occasion of his 85th anniversary

NEW INSIGHTS CONCERNING MICROWAVE MECHANISM IN CYCLOADDITION REACTIONS: THERMAL HEATING VERSUS SPECIFIC EFFECTS OF MICROWAVE

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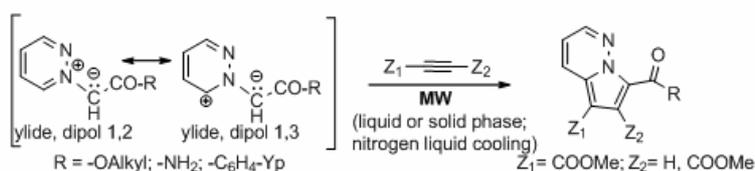
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On our knowledge, we present herein the first study concerning microwave mechanism (thermal *versus* specific microwave effects) in the Huisgen [3+2] dipolar cycloaddition reactions. We also describe a facile, straightforward and efficient method for studying thermal *versus* specific microwave effects for [3+2] dipolar cycloaddition reactions. In order to probe/discharge the existence of specific MW

effects, we chose to overcome the thermal effects of MW and to increase the contribution of specifically MW effects, the reactions being performed using high microwave-absorbing solvents as well as in solvent-free conditions. In both cases, no relevant conclusions concerning the contribution of specific MW were observed. In order to overcome the thermal effects of MW, we “froze” the reaction mixture in liquid nitrogen, thermal agitation being avoided. No matter the conditions we employed, the obtained results were the same, no reactions took place. As a result, we may conclude that no specific MW effects could be described in the Huisgen [3+2] dipolar cycloaddition reactions, the observed effects being purely thermal.



INTRODUCTION

Microwave assisted organic synthesis (MAOS) became a powerful tool in organic synthesis in recent years, offering a versatile and facile pathway in a large variety of syntheses.¹⁻³ Nowadays, it is unanimously accepted that MAOS have some undeniable advantages, such as faster reactions and substantial decreases of reaction time, rapid transfer and less energy consumer, less byproducts, improved yields and high purity of the

compounds, lower costs and simplicity in handling and processing.¹⁻¹²

The mechanism of MW action is very complex and involves thermal and specific (or nonthermal) microwave effects. While the existence of thermal MW effects it is almost unanimously accepted, the existence of specific MW effects is still a controversial matter in the scientific community. Several theories have been proposed to explain specific MW effects admitting that they essentially result from a direct interaction of the electromagnetic

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field with specific molecules, intermediates, or even transition states in the reaction medium.¹⁻⁶ Recent studies by Kappe *et al.*¹² have shown that the MW effect is due to thermal effects only and, “the nonthermal MW effects simply do not exist”. However, there are many examples of chemical transformations that cannot be explained solely by a thermal effect, and it seems that more in-depth study is required to obtain a definite answer.^{3,5,6,13}

In continuing our efforts of using MW irradiation in organic chemistry,¹³⁻¹⁷ we describe herein a detailed study concerning thermal *versus* specific microwave effects in dipolar cycloaddition reactions. All the experiments have been conducted in a single-mode MW reactor (with two individual cells), using the open vessel procedures. In order to probe/discharge the existence of specific MW effects, the Huisgen [3+2] dipolar cycloaddition reactions of cycloimmonium ylides to activate alkynes previously described by us¹⁴⁻¹⁷ were reevaluated.

RESULTS AND DISCUSSION

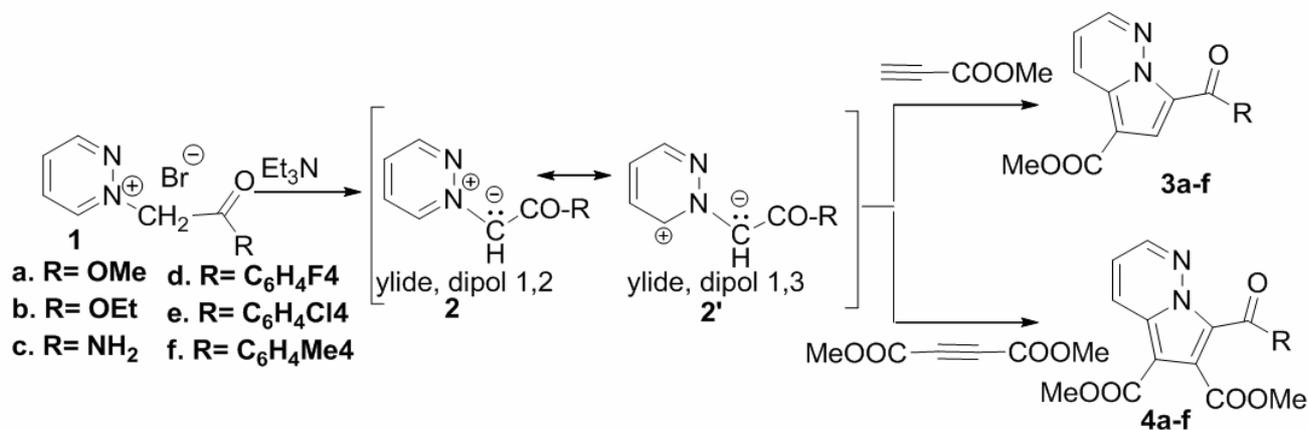
According with the literature data,¹⁻⁶ specific MW effects are most likely to be observed for reactions that follow polar reaction pathways via polar transition states and, another important factor is the proper choice of the solvent, the use of nonpolar (low microwave-absorbing solvents) or even solvent-free conditions being suggested.

Having in mind the above considerations and the fact that we found no literature data concerning the mechanism of MW action in the field of [3+2] dipolar cycloaddition reactions, we decide to

reevaluate some Huisgen [3+2] dipolar cycloaddition reactions previously described by us¹⁴⁻¹⁷. In this respect we chose as case study the Huisgen [3+2] dipolar cycloaddition reactions of pyridazinium ylides **2a-f** (generated *in situ* from the corresponding salts **1a-f**) to activated Z-alkynes, when the corresponding fused azaheterocycles (**3a-f** and **4a-f**) are obtained, Scheme 1. Full details concerning the synthesis and characterization of compounds were presented elsewhere.¹⁴⁻¹⁷

As we previously showed,¹³⁻¹⁷ pyridazinium ylides have a dipolar structure, admitting two canonical structures: a 1,2-dipolar (the ‘octet’ form, structure **2**) and a 1,3-dipolar (the ‘sextet’ form, structure **2'**), the last one being responsible for their function as dipole in cycloaddition reactions (Scheme 1). Because of the dipolar structure, the ylides are excellent microwave-absorbing molecules. As far for the solvents choice, in order to increase the contribution of specific MW effects, the reactions were conducted in a high microwave-absorbing solvent (acetonitrile, loss tangent is 0.659) as well as in a low microwave-absorbing solvent (benzene, loss tangent is zero). Table 1 lists the optimized reaction conditions we employed under MW irradiation.

A comparative analysis for the obtained data in Table 1 indicates that, in liquid phase, there are not significant differences in terms of yields when it is used a high microwave-absorbing solvent (acetonitrile) or a low microwave-absorbing solvent (benzene). Therefore, no relevant conclusions concerning the contribution of specific MW effects could be enlightened in this case.



Scheme 1 – The Huisgen [3+2] dipolar cycloaddition reactions of pyridazinium ylides to activated Z-alkynes under MW irradiation.

Table 1

The synthesis of fused azaheterocycles (**3a-f** and **4a-f**) under MW irradiation

Comp.	Microwaves						
	Reaction time (min)	Liquid phase			Reaction time (min)	Solid phase	
		Acetonitrile	Benzene	Nitrogen liquid cooling		Yield %	Yield %
3a	5	61	59	0	15	58	0
3b	5	60	62	0	15	63	0
3c	5	55	54	0	15	56	0
3d	5	15	14	0	15	15	0
3e	5	72	74	0	15	71	0
3f	5	14	12	0	15	15	0
4a	5	55	56	0	15	59	0
4b	5	62	60	0	15	62	0
4c	5	55	57	0	15	55	0
4d	5	17	20	0	15	18	0
4e	5	85	87	0	15	85	0
4f	5	32	29	0	15	31	0

In the next step, we perform the reactions in solvent-free conditions, the other alternative to increase the contribution of specifically MW effects. We used a mixture of KF-Al₂O₃ with double goal: as solid support (Al₂O₃) and as catalyst (KF, in order to generate the ylides). The obtained results are listed in Table 1 and, again, we found that there are no significant differences in terms of yields in solvent-free conditions comparative with liquid phase.

In order to overcome the thermal effects of MW, we decide to “freeze” the reaction mixture in liquid nitrogen, when thermal agitation is prevented and basically no thermal MW effect could appear. The device we used in this respect is described in experimental part.

No matter the conditions we employed (liquid phase or solvent-free conditions, different solvents, different reactions time), when the reactions were performed using liquid nitrogen as cooling agent, the obtained results were the same, no reaction took place, only starting materials left being obtained. As a result, it appears clear for us that no specific MW effects could be described in the Huisgen [3+2] dipolar cycloaddition reactions, the observed effects being purely thermal.

EXPERIMENTAL

Materials and Methods

For the microwave irradiation we used a 800 W STAR SYSTEM-2 monomode reactor (CEM Corporation). The system is comprised of two individual cells that operate independently of each other, allowing different methods to run

simultaneously or with staggered start times. Each cell has its own proprietary microwave aperture control. Each vessel has its own cell with temperature feedback control. The temperature feedback system (infrared) monitors and controls the energy supplied to each cavity based on the requirements of each method, initiating the opening and closing of the apertures automatically as needed.

General procedure for Huisgen [3+2] dipolar cycloaddition under MW irradiation in liquid phase with or without liquid nitrogen cooling

The experimental setup procedure without liquid nitrogen cooling was previously described.^{15, 17} In a standard Pyrex reaction vessel there was placed a mixture of pyridinium salt **1** (5 mMol), dipolarophile (5.5 mMol) and 10 mL anhydrous benzene (loss tangent zero) or acetonitrile (loss tangent 0.659). Then, triethylamine (5.5 mmol) was added. The solution was exposed to microwave for 5 min. Using MW irradiation, the best results were obtained using a constant irradiation power (20% from the full power of the magnetron, 800 W) and varying the temperature (the so-called “power control” method). Once the heating cycle was completed, the mixture was cooled at room temperature. When benzene was used as solvent, the resulting mixture was filtered hot to remove triethylamine hydrobromide and the clear solution was evaporated by vacuum distillation to give the crude product. When acetonitrile was used as solvent, water was added in the reaction mixture and then the compounds were extracted with chloroform (3 x 50 mL), dried and evaporated to afford a precipitate. The crude product was purified by flash chromatography on silica gel (dichloromethane / methanol 99:1).

When the reaction was performed using nitrogen liquid as cooling agent, the above experimental procedure was modified as follows: the reaction mixture was placed in a Pyrex reaction vessel (with a diameter of 2 cm). On the top of reaction vessel an air condenser was placed and the reaction vessel was placed in a second concentric Pyrex vessel (with a diameter of 4 cm). Nitrogen liquid was then added in the second vessel. The cooled reaction vessels were exposed to MW irradiation for different times (5, 10, 20, 30 min) and, during the reaction time, liquid nitrogen was slowly and

continuously added to the top of the second vessel (in order to complete the evaporated liquid nitrogen). The rest of the experimental setup remains the same as described above.

General procedure for Huisgen [3+2] dipolar cycloaddition under MW irradiation in solid phase with or without liquid nitrogen cooling

Pyridazinium salt (2 mMol), dipolarophile (2.1 mMol) and 10 g of mineral support (KF-Al₂O₃) were ground in an agate mortar until a fine homogeneous mixture was obtained. The mixture was placed in a standard Pyrex reaction vessel and exposed to MW irradiation for 15 min. Using MW irradiation, the best results were obtained using a constant irradiation power (50% from the full power of the magnetron, 800 W) and varying the temperature. Once the heating cycle was completed, the mixture was cooled to room temperature. The activated solid was washed four times: three times with 10 mL of dichloromethane and once with 10 mL of acetone. The acetone and dichloromethane solutions were combined, evaporated by vacuum distillation and, the crude product was purified by flash chromatography on silica gel (dichloromethane / methanol 99:1).

When the reaction was performed using nitrogen liquid as cooling agent, the same experimental procedure as in liquid phase was used.

CONCLUSIONS

In summary, we report herein a detailed study concerning thermal *versus* specifically microwave effects in the Huisgen [3+2] dipolar cycloaddition reactions. To our knowledge this is the first study concerning mechanism of MW action in the field of [3+2] dipolar cycloaddition reactions. We also describe a facile, straightforward and efficient method for studying thermal *versus* specific microwave effects for [3+2] dipolar cycloaddition reactions which we believe that could be applied to all (or at least to majority) microwave assisted organic reactions. In first instance, in order to increase the contribution of specific MW effects, the reactions were conducted in high microwave-absorbing solvents as well as in solvent-free conditions. In liquid phase, we found there are not significant differences in terms of yields when it is used a high microwave-absorbing solvent or a low microwave-absorbing solvent. In solvent-free conditions, using a mixture of KF-Al₂O₃, we found also that there are no significant differences in terms of yields comparative with liquid phase. Therefore, no relevant conclusions concerning the contribution of specifically MW effects could be enlightened for these situations. In order to

overcome the thermal effects of MW, we “froze” the reaction mixture in liquid nitrogen, thermal agitation being avoided. No matter the conditions we employed (liquid phase or solvent-free conditions, different solvents, different reactions time), the obtained results were the same, no reactions tacking place.

As a result, we may conclude that no specific MW effects could be described in the Huisgen [3+2] dipolar cycloaddition reactions, the observed effects being purely thermal.

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