Influence of Polarity on the Scalability and Reproducibility of Solvent-Free Microwave-Assisted Reactions

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Abstract: Organic reactions performed in the absence of solvent in domestic ovens without appropriate temperature control are generally considered as not reproducible, particularly when different instruments are used. For this reason, reproducibility has historically been one of the major issues associated with Microwave-Assisted Organic Synthesis (MAOS) especially when domestic ovens are involved. The lack of reproducibility limits the general applicability and the scale up of these reactions. In this work several solvent-free reactions previously carried out in domestic ovens have been translated into a single-mode microwave reactor and then scaled up in a multimode oven. The results show that most of these reactions, although not considered as reproducible, can be easily updated and applied in microwave reactors using temperature-controlled conditions. Furthermore, computational calculations can assist to explain and/or predict whether a reaction will be reproducible or not.

Keywords: Scalability, reproducibility, solvent-free reactions, microwave-assisted reactions.

INTRODUCTION

The avoidance of solvents in organic synthesis leads to clean, efficient and economical technologies (green chemistry); safety is greatly increased, work-up is considerably simplified, cost is reduced, increased amounts of reactants can be used with the same equipment, and the reactivity and sometimes the selectivity is enhanced without dilution [1-4]. Thus, the absence of solvents coupled with the high yields and short reaction times often associated with reactions of this type make these procedures very attractive in synthesis. It has been shown that solvent-free conditions are especially applicable to microwave activation as reactions can be carried out safely at atmospheric pressure in the presence of significant amounts of products and avoiding the use and recovery of considerable volumes of solvent [1-4]. Furthermore, the use of microwave irradiation as a source of heat has proven to be more energy efficient than the use of traditional heating [5]. For this reason the combination of solvent-free conditions and microwave irradiation has attracted the interest of a large number of green chemists.

Since 2000 the number of publications related to Microwave-Assisted Organic Synthesis (MAOS) has increased dramatically [6-11]. One of the reasons for the increased interest in the use of microwave heating was the introduction, at the dawn of the 21st Century, of dedicated monomode and multimode instruments with appropriate temperature and pressure controls, a development that allows reproducibility of results. However, when the microwave methodology was introduced twenty years ago, most reactions were performed in domestic ovens without appropriate temperature control. Most of these reactions were performed in the absence of solvent for safety reasons.

As a consequence, there is a plethora of interesting green procedures that were originally carried out in domestic ovens without appropriate temperature and pressure controls. These reactions are generally considered as not reproducible, particularly when a different scale or instrument was used, and this has limited the application of such reactions [12, 13]. As a consequence, at present several journals do not accept reports concerning reactions performed in domestic ovens.

In recent years a number of reports have disclosed the reproducibility of results between monomode and multimode microwave instruments for solution chemistry [14-18]. Other authors, such are Hamelin [19] and Loupy [20] have showed how solvent-free reactions can be scale-up in monomode apparatus (Synthewave 402 to Synthewave 1000), and very recently Moseley [21] and Leadbeater [22] reported a comparison of commercial microwave reactors and show how different processing techniques can be used for scale-up microwave-promoted reactions, respectively. However, to the best of our knowledge, studies regarding reproducibility of solvent-free reactions previously performed in domestic ovens have not been described, although since 1986 to 1998 most of the microwave-assisted reactions -involving a lot of interesting synthesis- was performed in these apparatus and in these conditions.

The polarity of the solvent is the most important parameter to consider when microwave reactions are performed in solution. Polar solvents directly absorb the microwave radiation and the polarity of the substrate is

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relatively unimportant. With non-polar solvents the microwave radiation is absorbed by the substrates, but the differences in absorption of the substrates are moderated by the solvent, especially in dilute solution. In both cases, the reaction temperature is limited by the solvent boiling point and microwave-assisted reactions in solution are easily controlled.

In neat reactions, microwave radiation is again absorbed by the substrates but there is no solvent to stabilize the temperature. In this situation the nature of the substituents and the polarity of the substrates influence the absorption of microwave energy [23] and, as a consequence, the yield. Moreover, in the absence of solvent the temperature is not limited by the boiling point of the solvent. A process involving highly polar reagents, intermediates or Transition States can hardly be controlled under microwave irradiation. Hence, it does not follow that a solvent-free reaction previously performed in a domestic oven will be controllable and reproducible in focused microwave reactors in a similar way to reactions in solution, as the field density is very different from one instrument to another [12, 13].

The development of methodologies that allow a successful translation of useful synthetic processes from domestic ovens to microwave reactors is of great importance in order to update information and allow the application of a considerable number of interesting reactions reported in the early years that are, at this moment, overlooked as they are considered as not reproducible. If this approach were applied to solvent-free reactions these investigations would constitute an interesting contribution to green chemistry instrumentation and environmentally friendly processes.

Recently, we have shown for the first time that solvent-free 1,3-dipolar cycloadditions of nitrile *N*-oxides with nitriles, when carried out in a domestic oven [24], can be reproduced, scaled up and parallelized in monomode and multimode microwave reactors [25].

The objective of the work described here is to extend our preliminary results to show whether solvent-free reactions previously performed in a domestic oven, without appropriate temperature and pressure controls, can be reproduced and scaled up in controlled microwave monomode and multimode reactors, and what parameters may have an effect on reproducibility.

In order to achieve our aim, we studied four solvent-free reactions that were previously carried out in domestic ovens. These examples cover a wide range of chemical transformations and, in contrast to the aforementioned cycloaddition reaction, the polarity in the course of the process increases and, as a consequence, it could be more difficult to control. The reactions selected are: *N*-alkylation of (1*H*)-benzotriazoles [26], condensation of anilines with urea (or thiourea) [27], Beckmann rearrangement of ketoximes [28] and oxidation of benzylic bromides to aromatic aldehydes [29]. These microwave-assisted processes were selected on the basis of their synthetic importance and/or environmentally friendly characteristics. Alkylation of benzotriazoles is performed in the absence of any base or phase transfer catalyst simply by mixing the reagents. Substituted ureas and thioureas have important applications in agriculture, medicinal chemistry and chemical transformations. Irradiation of ketoximes on Montmorillonite K10 provides a dry and recyclable medium to carry out a Beckmann rearrangement and avoids the use of highly polluting strong acids. Oxidation of benzylic bromides with pyridine *N*-oxide under microwaves in the absence of solvent and base represents a useful and clean synthetic process. These reactions can also be considered to provide representative examples of a variety of conditions reported in the literature.

In each example we proceeded to compare the results obtained in a monomode reactor Discover™ CEM with those observed in the multimode microwave reactor MultiSYNTH™ Milestone on increasing the amounts of reagents. In each case, we have used reaction conditions described in the original report, none optimization has been performed in these reactions. In order to validate our results, as well as to improve the synthetic utility of the reactions, we chose substrates with different substituents and electron-donating or electron-withdrawing groups, most of which were not described in the original work. These compounds cover a wide range of polarities and, as a consequence, of microwave absorption.

RESULTS

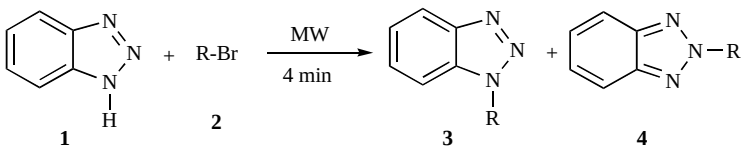
Alkylation of (1*H*)-Benzotriazoles

Following the procedure described by de la Hoz *et al.* [26], irradiation of a mixture of (1*H*)-benzotriazole (**1**) (1 equiv.) and an alkyl bromide (**2**) (2 equiv.) in the absence of any solvent for 4 min gave the alkylated benzotriazoles **3** and **4** (Scheme **1**).

The results obtained with five different alkyl bromides, including 2 new functionalities not represented in the previous report, in monomode and multimode microwave reactors using 3 mmol and 21 mmol scales, respectively, were compared. These reactions were performed at 185ºC for 4 min (see Table **1**) - the same conditions employed in the domestic oven in the original work. Reactions in the multimode oven were performed in separate experiments due to the different heating profiles of each mixture.

Condensation of Anilines with Urea or Thiourea

The anilines **5** were condensed with urea (**6**) (or thiourea, **7**) in a domestic oven in 4 min to afford the diarylureas **8** (or



1 **2** **3** **4**

Scheme 1. Alkylation of (1*H*)-benzotriazole (**1**) with alkyl bromides (**2**).

diarylthioureas) (Scheme **2**) [27]. Purification of the products was achieved simply by washing the crude reaction mixture with water.

Table 1. Alkylation of (1*H*)-Benzotriazole (1) with Alkyl Bromides 2a-e in a Monomode and a Multimode Microwave Reactor at 185ºC for 4 min

Alkyl Bromide	Yield (%) Monomode[a,b]	Yield (%) Multimode[a,c]
n-$C_8H_{17}Br$	81	78
n-$C_{16}H_{33}Br$	63	60
$Ph(CH_2)_3Br$	83	81
$EtO_2C(CH_2)_5Br$	10	10
$PhO(CH_2)_4Br$	25	27

[a]Yields were determined by HPLC by integration of peak areas using the pure product as a standard.
[b]Reactions performed on a 3 mmol scale.
[c]Reactions performed on a 21 mmol scale.

In order to study the translation and scalability of the reaction, five reactions were performed at 180ºC, including anilines with different substituents and thiourea, in both monomode and multimode microwave ovens (Table **2**). The scale used in the latter instrument was 7 times larger than that used in the monomode apparatus. As in the previous example, reactions in the multimode oven were performed in separate experiments. Only the last example in Table **2**, involving aniline + thiourea, had been described in the original work, thus increasing the general applicability of this reaction.

Table 2. Condensation of Anilines 5a-d with Urea (6) or Thiourea (7) in a Monomode and a Multimode Microwave Reactor at 180ºC for 4 min

Reaction	Yield (%) Monomode[a,b]	Yield (%) Multimode[a,c]
o-toluidine + urea	70	72
Aniline + urea	49	48
p-MeS-aniline + urea	60	61
m-Br-aniline + urea	49	46
Aniline + thiourea	56	58

[a]Isolated yields.
[b]Reactions performed on a 3 mmol scale.
[c]Reactions performed on a 21 mmol scale.

Beckmann Rearrangement of Ketoximes

Microwave irradiation in a domestic oven of ketoximes with K-10 montmorillonite in dry media provides an efficient method for the Beckmann rearrangement (Scheme **3**) [28].

In previous examples the scale up was performed in separate experiments due to the different heating profiles of the mixtures. However, in this reaction the main absorption and, hence, temperature is determined by the clay (Montmorillonite K10). As a consequence, we carried out five reactions in the multimode microwave oven at the same time (see Table **3**), which represents one of the first examples of a combination of microwave parallel scale up with green procedures.

Table 3. Beckmann Rearrangement of Ketoximes 9 in a Monomode and Multimode Reactor at 150ºC

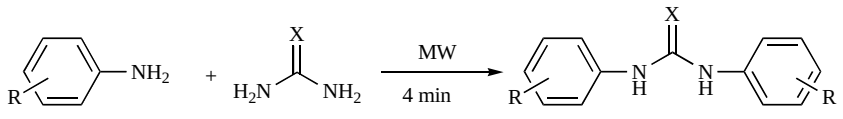
R_1	R_2	Yield (%) Monomode[a,c]	Yield (%) Multimode[b,c]
CH_3	C_6H_5	58	57
C_6H_5	C_6H_5	80	77[d]
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4$	70	67
p-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	77	74
o,*p*-$CH_3OC_6H_4$	*o*,*p*-$CH_3OC_6H_4$	78	77

[a]Reactions performed with 0.3 g of ketoxime.
[b]Reactions performed with 0.75 g of ketoxime.
[c]Ratio ketoxime/K10 1:9 (w/w).
[d]Temperature-controlled reaction in the multimode apparatus.

Oxidation of Benzylic Bromides with Pyridine *N*-Oxide

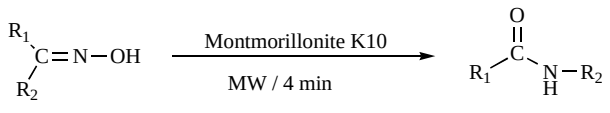
In 1996, Barbry *et al.* [29] described the oxidation of benzylic bromides in the presence of pyridine *N*-oxide without any solvent or base. These reactions took place in a domestic oven to afford high yields of aromatic aldehydes (Scheme **4**).

However, all of our attempts to reproduce and control this reaction using benzyl or *p*-nitrobenzyl bromide in monomode or multimode microwave reactors failed. We assessed a range of times, temperatures and powers (including ramped conditions) but, unfortunately, we were unable to control the process: the reaction temperature did



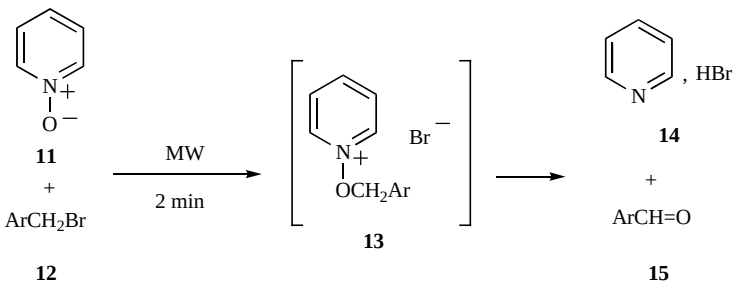
5 **6**, X = O; **7**, X = S **8**

Scheme 2. Condensation of anilines **5** with urea (**6**) or thiourea (**7**).



9 **10**

Scheme 3. Beckmann rearrangement of ketoximes **9**.



Scheme 4. Oxidation of benzylic bromides **12**.

not become stable but rose rapidly to give decomposition of the products.

DISCUSSION

As mentioned above, the reproducibility of microwave-assisted reactions in solution has been unequivocally proved, allowing the efficiency of microwave chemistry to be combined with the productivity of the parallel approach [14-18]. Other studies, involving scale-up of microwave-promoted reactions -including solvent-free reactions- have been also reported [19-22]. In the same way, we reported for the first time that a solvent-free 1,3-dipolar cycloaddition performed in a domestic oven can be reproduced in monomode and multimode reactors [25]. We have now studied four new solvent-free processes previously carried out in a domestic oven, including substitution, condensation, rearrangement and oxidation reactions. Since all of these reactions have polar intermediate species, they show good absorption of microwave radiation. Hence, the results obtained in these five reactions can support a general conclusion, since reproducibility of solvent-free reactions previously reported in a domestic oven has not even been published.

In an effort to prove the reproducibility of solvent-free reactions carried out in a domestic oven, five substrates with different substitution patterns were reacted in both monomode (Discover™ CEM) and multimode (MultiSYNTH™ Milestone) microwave reactors. All of the reactions were performed at the reaction temperatures described in the original references for 4 min (except the oxidation of benzylic bromides, for which the reaction time was 2 min). Likewise, in order to demonstrate the scalability of these reactions, the scale used in the multimode instrument was seven times larger than that used in the monomode apparatus. In the case of the Beckmann rearrangement the scale was 2.5 times higher, but all of the reactions were performed in parallel in a single experiment. Moreover, if the reaction is performed using a solid support, as exemplified in the Beckmann rearrangement, reactions can be performed in parallel in the multimode oven; clearly showing that it is possible to scale up in parallel solvent-free reactions when heating profiles of individual reaction mixtures are similar.

In addition to the environmentally friendly conditions associated with solvent-free microwave irradiation, we wish to emphasize that these reaction products were purified following *green* procedures: (i) alkylation of benzotriazole was analyzed by HPLC; (ii) diarylureas prepared by condensation were isolated from the crude reaction mixture by washing with water; and (iii) amides obtained by Beckmann rearrangement were purified by recrystallization from ethanol.

As can be seen from the results in Tables **1-3**, in the first three reactions studied (where the reaction temperature is easily controlled) the maximum difference in yield between the two instruments in all the examples presented is 3%, with the average difference being 2%. Similar behaviour was observed in the 1,3-dipolar cycloaddition described previously [25]. These results allow us to conclude that solvent-free temperature-controlled reactions are absolutely reproducible across monomode and multimode reactors.

With the aim of explaining why the oxidations of benzylic bromides are not temperature-controlled processes under microwaves, we carried out a computational study of this reaction and the aforementioned 1,3-dipolar cycloaddition [25], which is easily controlled.

Computational Calculations

In this exploratory study, most of the calculations were performed using the semi-empirical AM1 method available in the AMPAC software [30]. This method gives reasonable results for organic chemical reactivity studies [31]. Geometries of stationary points were determined by energy minimizations with respect to all geometric parameters. All reaction paths were determined by the fullchn process [30]. All Transition Structures (TS) of full reaction paths were located by the chain method [32] and characterized by one and only one negative eigenvalue of the Hessian matrix. Furthermore, the corresponding vibration was found to be associated with nuclear motions along the reaction coordinate.

Solvent effects were estimated by means of the AMSOL/SM5.2 model [33-35]. This model can be applied to chemical reactions involving bond dissociation, thus full solvent reaction paths were obtained with the fullchn process. For semi-empirical calculations acetonitrile and bromobenzene were chosen as the media.

Ab initio calculations were carried out using the GAUSSIAN 03 [36] series of programs, with the standard 6-31-G* basis set [37]. In order to include electron correlation at a reasonable computational cost, Density Functional Theory (DFT) [38, 39] was used. In this study, these calculations were carried out by means of the three-parameter functional developed by Becke [40-42], which is usually denoted as B3LYP. All TS structures and minima

were fully characterized by harmonic analysis. Solvent effects were estimated by means of polarization continuum models (PCM) [43] using acetonitirle as the medium.

Loupy and Perreux [44] proposed that microwave effects are due to the dipolar polarization phenomenon; the higher the polarity of a molecule (such as the solvent) the more pronounced the microwave effect when the rise in temperature [45] is considered. In terms of reactivity and kinetics, this effect depends of the mechanism, particularly with regard to how the polarity of the system is altered during the progress of the reaction. For this reason, in our computational study the polarities of all species were calculated.

In the first case studied, the reaction takes place through a 1,3-dipolar cycloaddition between a nitrile *N*-oxide and a nitrile (Scheme **5**).

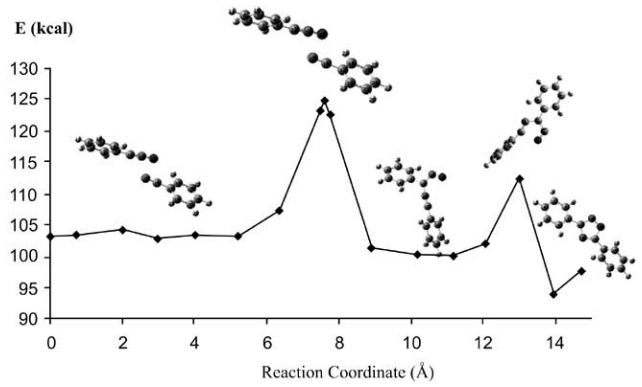
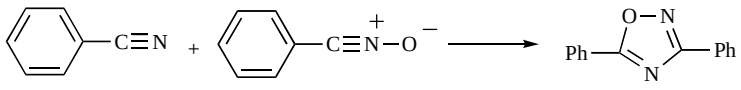


Fig. (1). Reaction profile for 3+2 cycloaddition in solution in acetonitrile.



16 **17** **18**

Scheme 5. 3+2 Cycloaddition of benzonitrile and benzonitrile *N*-oxide.

In principle, two possible reaction paths are conceivable: the concerted and the stepwise mechanisms. The first pathway proceeds in a suprafacial manner for both reactants according to the thermally allowed [$\pi 2_s + \pi 4_s$] mechanism [46, 47]. The second pathway consists of a second-order nucleophilic addition of the 1,3-dipole over the dipolarophile to yield a zwitterionic intermediate, whose ring closure leads to the corresponding five-membered cycloadduct. Several previous cases have shown that this process can involve stepwise mechanisms [48-50]. In our case benzonitrile and the benzonitrile oxide react through a stepwise mechanism. The reaction profile is depicted in Fig. (**1**). Activation and reaction energies in the gas phase and in solution are collected in Table **4** and dipolar moments of all the stationary points are given in Table **5**.

Table 4. Activation Energies (ΔEa, Kcal/mol) and Reaction Energies (ΔE_{rxn}, Kcal/mol)

	ΔEa_1	ΔEa_2	ΔE_{rxn}
Gas phase	25.96	11.45	-10.26
Solution (acetonitrile)	21.74	12.17	-17.37

Table 5. Dipole Moments (Debyes) of all Stationary Points

	Reactants	TS1	Int	TS2	Products
Gas phase	0.97	3.46	6.22	4.32	1.93
Solution (acetonitrile)	5.51	7.91	11.27	6.18	2.48

For this reaction the theoretical values of the dipolar moments during the process show a maximum increase of 5.25 Debyes in the gas phase and 5.76 D in solution. The intermediates have the highest polarity (Table **5**).

With the aim of validating our method, we calculated the reaction profile for this reaction with B3LYP/6-31G* and the PCM solvent model. The energy values and dipolar moments are collected in Tables **6** and **7**.

Table 6. Activation Energies (ΔEa, Kcal/mol) and Reaction Energies (ΔE_{rxn}, Kcal/mol)

	ΔEa_1	ΔEa_2	ΔE_{rxn}
Gas phase	19.30	7.51	-45.29
Solution (acetonitrile)	19.95	8.43	-44.27

Table 7. Dipole Moments (Debyes) of All Stationary Points

	Reactants	TS1	Int	TS2	Products
Gas phase	0.93	1.39	7.04	3.17	2.06
Solution (acetonitrile)	5.19	2.13	12.66	4.44	2.79

DFT and AM1 structures, reaction paths and dipolar moments are similar. Therefore, B3LYP calculations validate AM1 calculations for qualitative studies and AM1 calculations are sufficient to explain our experimental results.

The second reaction studied corresponds to an oxidation of alkyl halides to carbonyl compounds [29, 51]. The mechanism involves the formation of an *N*-benzyloxy pyridinium bromide (**13**) and subsequent proton abstraction to give the benzaldehyde (Scheme **4**).

This reaction could occur through S_N1 or S_N2 mechanisms. The reaction profiles for both processes are depicted in Figs. (**2**, **3**). Activation and reaction energies in the gas phase and in solution are collected in Table **8** and

dipolar moments of all the stationary points are shown in Table **9**.

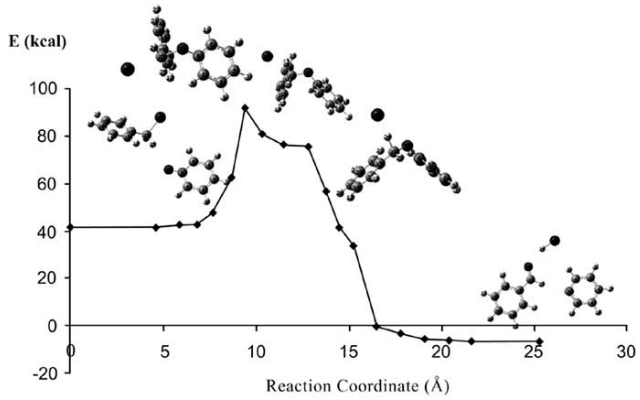


Fig. (2). S_N2 reaction profile for the reaction between benzylic bromide and pyridine *N*-oxide in solution in bromobenzene.

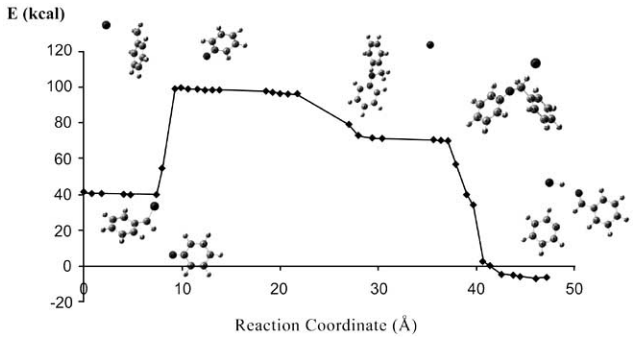


Fig. (3). S_N1 reaction profile for the reaction between benzylic bromide and pyridine *N*-oxide in solution in bromobenzene.

Table 8. Activation Energies (ΔEa, Kcal/mol) and Reaction Energies (ΔE_{rxn}, Kcal/mol)

	ΔEa	**ΔE_{rxn}**
S_N2 Gas phase	67.25	-50.48
S_N2 Solution (bromobenzene)	50.53	-49.47
S_N1 Solution (bromobenzene)	57.59	-47.24

Table 9. Dipole Moments (Debyes) of All Stationary Points

	Reactants	**TS1**	**Int**	**TS2**	**Products**
S_N2 Gas phase	3.60	15.6	--	9.02	3.92
S_N2 Solution (bromobenzene)	5.05	19.98	25.02	23.81	5.00
S_N1 Solution (bromobenzene)	5.55	22.74	52.04	24.88	5.43

It is remarkable that in this process only the S_N2 mechanism could be performed in the gas phase. In this case, the intermediate was not computationally isolated because the bromide ion is not solvated and is highly reactive. For this reason, in the gas phase TS1 leads directly to TS2. We ruled out the S_N1 mechanism because this process possessed higher activation energy than the S_N2 pathway (Table **8**). In the S_N2 mechanism the polarity of the system increased markedly during the reaction (12.0 Debyes in the gas phase and 19.97 Debyes in solution), in contrast to the 1,3-dipolar cycloaddition. This fact can explain why the oxidation of benzylic bromides with pyridine *N*-oxide is not a temperature-controlled process under microwave irradiation. Moreover, if an S_N1 mechanism is considered, the polarity increase is even still higher (46.49 Debyes).

Reactions involving a moderate or medium increase in polarity in the pathway from reactants to products are relatively easy temperature-controlled processes under microwave irradiation. In contrast, large increases in polarity during the reaction path give rise to extreme absorptions of microwave energy and make these processes more difficult to control.

These results show that not all the reactions previously performed in domestic ovens in the absence of solvent are reproducible in single-mode or multimode microwave reactors and could provide a criterion that assist to predict the reproducibility.

CONCLUSIONS

In summary, the results of this work show that most solvent-free reactions previously performed in a domestic oven, without appropriate temperature control, can be reproduced in both monomode and multimode microwave instruments using temperature-controlled conditions. These reactions can also be scaled up either singly or in parallel in multimode instruments depending on the reaction procedure. The range of transformations studied in this work shows that scale up and reproducibility can be extended to other solvent-free reactions when temperature is the parameter to be controlled. We have also shown that, in solvent-free conditions, temperature-controlled reactions can be reproduced and scaled up regardless of the polarity.

In addition, some solvent-free reactions in which polarity undergoes a dramatic increase during the course of the process may not be reproducible in dedicated microwave reactors since the reaction temperature cannot be controlled. These conclusions are in complete agreement with our initial approach: in the absence of solvent there is no element to limit the reaction temperature under microwave irradiation - in contrast to solution reactions - and the process can be controlled by the polarity of the reaction mixture.

These conclusions represent a useful contribution to microwave synthesis and green process research, as they enable the advantages that modern microwave instrumentation offers to be applied to synthetic transformations that have previously been carried out in domestic ovens. Furthermore, these results can provide a tool to predict the reproducibility of such reactions. Nevertheless, the dependence of reproducibility with polarity does not imply any non-thermal effect of the radiation and it is independent of the classical heating results.

EXPERIMENTAL

Monomode microwave irradiations were conducted using a Discover® (CEM) focused microwave reactor. Multimode

microwave irradiations were conducted in a MicroSYNTH labstation multimode microwave oven (MILESTONE). Mps were determined on a Gallenkamp apparatus and are uncorrected. NMR data were obtained at 500 MHz for ^{1}H and 125 MHz for ^{13}C on a Varian Innova spectrometer using $CDCl_3$ as the solvent and TMS as an internal standard. High-resolution mass spectra were recorded on an Agilent-Micromass LCT Time of Flight mass spectrometer with electrospray ionisation and a Lockmass device for mass calibration. Column chromatography was performed using 230-400 mesh Merck type 60 silica gel. Yields were determined using Hitachi L-7420 HPLC equipment fitted with a Lichrospher® 100RP-18 (5 μm) column. Reagents were purchased from commercial suppliers or prepared according to literature procedures.

Alkylation of Benzotriazoles. General Procedure

A mixture of benzotriazole (**1**) (1 equiv.) and the corresponding alkyl bromide (**2**) (2 equiv.) was irradiated at 185ºC for 4 min to obtain a mixture of the alkylated products **3** and **4**. Yields were determined by HPLC using the pure product as standard.

Condensation of Anilines with Urea (or Thiourea). General Procedure

A mixture of the aniline (**5**) (2 equiv.) and urea (**6**) or thiourea (**7**) (1 equiv.) was irradiated at 180ºC for 4 min. The crude reaction mixture was washed with water (2 × 25 mL) and the solid was filtered off and dried under reduced pressure to obtain the diarylurea (or thiourea) **8**.

Beckmann Rearrangement of Ketoximes. General Procedure

A mixture of the ketoxime **9** and Montmorillonite K10 (ratio 1:9 w/w) was irradiated at 150ºC for 4 min. The resulting amide **10** was purified by recrystallization from ethanol.

Characterization of New Compounds

1-(3-Phenylpropyl)-1,2,3-benzotriazole (**3c**). Colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 2.38 (q, 2 H, J = 7.3 Hz), 2.69 (t, 2 H, J = 7.3 Hz), 4.74 (t, 2 H, J = 7.3 Hz), 7.19 (m, 3 H), 7.28 (m, 2 H), 7.37 (m, 1 H), 7.46 (m, 2 H), 8.07 (m, 1 H). ^{13}C NMR ($CDCl_3$) δ (ppm) 30.9, 32.6, 47.3, 109.2, 120.0, 123.8, 126.3, 127.2, 128.4, 128.5, 132.9, 140.2, 145.9. ESI-HRMS $C_{15}H_{15}N_3$ $(M + H)^+$: Calculated: 237.1266. Found: 237.1263.

2-(3-Phenylpropyl)-1,2,3-benzotriazole (**4c**). Colourless oil. ^{1}H NMR ($CDCl_3$) δ (ppm) 2.46 (q, 2 H, J = 7.2 Hz), 2.68 (t, 2 H, J = 7.2 Hz), 4.74 (t, 2 H, J = 7.2 Hz), 7.19 (m, 3 H), 7.27 (m, 2H), 7.37 (m, 2 H), 7.86 (m, 2 H). ^{13}C NMR ($CDCl_3$) δ (ppm) 31.5, 32.6, 55.7, 117.9, 126.2, 140.4, 144.3. ESI-HRMS $C_{15}H_{15}N_3$ $(M + H)^+$: Calculated: 237.1266. Found: 237.1272.

2-(4-Phenoxybutyl)-1,2,3-benzotriazole (**4e**). M.p.: 81-82 ºC. ^{1}H NMR ($CDCl_3$) δ (ppm) 2.05 (q, 2 H, J = 7.3 Hz), 2.18 (q, 2 H, J = 7.3 Hz), 4.68 (t, 2 H, J = 7.3 Hz), 4.78 (t, 2 H, J = 7.3 Hz), 7.38 (m, 3 H), 7.47 (m, 2 H), 7.84 (m, 2 H), 8.05 (d, 2 H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$) δ (ppm) 26.4, 26.9, 47.2, 55.4, 109.1, 117.9, 120.1, 123.9, 126.4, 127.3, 132.8, 144.3, 145.9. ESI-HRMS $C_{16}H_{17}N_3O$ $(M + H)^+$: Calculated: 267.1372. Found: 267.1380.

1,3-Bis(4-methylthiophenyl)urea (**8c**). M.p.: 232-233ºC. ^{1}H NMR (DMSO-d_6) δ (ppm) 2.32 (s, 6 H), 7.21 (d, 2 H, J = 8.7 Hz), 7.41 (d, 2 H, J = 8.7 Hz), 8.65 (s, 2 H). ^{13}C NMR (DMSO-d_6) δ (ppm) 15.9, 118.8, 127.7, 130.8, 137.4, 152.4. ESI-HRMS $C_{15}H_{16}N_2OS_2$ $(M + H)^+$: Calculated: 304.0704. Found: 304.0706.

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REFERENCES

[1] Loupy, A. In: Modern Solvents in Organic Chemistry; Springer-Verlag; Berlin, **1999**, Vol. *206*, pp. 153-207.

[2] Loupy, A.; Bram, G.; Sansoulet, J. Anion activation in solvent-free heterogeneous medium - Use of microwave ovens. *New J. Chem.*, **1992**, *16*, 233-242.

[3] Varma, R.S. Solvent-free organic syntheses - using supported reagents and microwave irradiation. *Green Chem.*, **1999**, *1*, 43-55.

[4] Varma, R.S. Clay and clay-supported reagents in organic synthesis. *Tetrahedron*, **2002**, *58*, 1235-1255.

[5] Gronnow, M.J.; White, R.J.; Clark, J. H.; Macquarrie, D.J. Energy efficiency in chemical reactions: A comparative study of different reaction techniques. *Org. Process Res. Develop.*, **2005**, *9*, 516-518.

[6] Adam, D. Microwave chemistry: Out of the kitchen. *Nature*, **2003**, *421*, 571-572.

[7] Kappe, C.O. Controlled microwave heating in modern organic synthesis. *Angew. Chem. Int. Ed.*, **2004**, *43*, 6250-6284.

[8] Díaz-Ortiz, A.; de la Hoz, A.; Moreno, A. Microwaves in organic synthesis. Thermal and non-thermal microwave effects. *Chem. Soc. Rev.*, **2005**, *34*, 164-178.

[9] Microwaves in Organic Synthesis 2nd Ed.; Loupy, A., Ed.; Wiley-VCH: Weinheim (FRG), **2006**.

[10] Kappe, C.O. Microwave dielectric heating in synthetic organic chemistry. *Chem. Soc. Rev.*, **2008**, *37*, 1127-1139.

[11] Polshettiwar, V.; Varma R.S. Aqueous microwave chemistry: A clean and green synthetic tool for rapid drug discovery. *Chem. Soc. Rev.*, **2008**, *37*, 1546-1557.

[12] Nüchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. Microwave assisted synthesis - A critical technology overview. *Green Chem.*, **2004**, *6*, 128-141.

[13] Nüchter, M.; Müller, U.; Ondruschka, B.; Tied, A.; Lautenschläger, W. Microwave-assisted chemical reactions. *Chem. Eng. Technol.*, **2003**, *26*, 1207-1216.

[14] Stadler, A.; Yousefi, B.H.; Dallinger, D.; Walla, P.; Van der Eycken, E.; Kaval, N.; Kappe, C.O. Scalability of microwave-assisted organic synthesis. From single-mode to multimode parallel batch reactors. *Org. Process Res. Develop.*, **2003**, *7*, 707-716.

[15] Alcázar, J.; Diels, G.; Schoentjes, B. Reproducibility across microwave instruments: First example of genuine parallel scale up of compounds under microwave irradiation. *QSAR Comb. Sci.*, **2004**, *23*, 906-910.

[16] Alcázar, J. Reproducibility across microwave instruments: Preparation of a set of 24 compounds on a multiwell plate under temperature-controlled conditions. *J. Comb. Chem.*, **2005**, *7*, 353-355.

[17] Loones, K.T.J.; Maes, B.U.W.; Rombouts, G.; Hostyna, S.; Diels, G. Microwave-assisted organic synthesis: Scale-up of palladium-catalyzed aminations using single-mode and multi-mode microwave equipment. *Tetrahedron*, **2005**, *61*, 10338-10348.

[18] Murray, J.K.; Gellman, S.H. Microwave-assisted parallel synthesis of a 14-helical beta-peptide library. *J. Comb. Chem.*, **2006**, *8*, 58-65.

[19] Perio, B.; Dozias, M.-J.; Hamelin, J. Ecofriendly fast batch synthesis of dioxolanes, dithiolanes, and oxathiolanes without solvent under microwave irradiation. *Org. Proc. Res. Develop*., **1998**, *2*, 428-430.

[20] Cléophax, J.; Liagre, M.; Loupy, A.; Petit, A. Application of focused microwaves to the scale-up of solvent-free organic reactions. *Org. Proc. Res. Develop*., **2000**, *4*, 498-504.

[21] Moseley, J.D.; Lenden, P.; Lockwood, M.; Ruda, K.; Sherlock, J.P.; Thomson, A.D., Gilday, J.P. A comparison of commercial microwave reactors for scale-up within process chemistry. *Org. Proc. Res. Develop.*, **2008**, *12*, 30-40.

[22] Bowman, M.D.; Holcomb, J.L.; Kormos, C.M.; Leadbeater, N.E.; Williams, V.A. Approaches for scale-up of microwave-promoted reactions. *Org. Proc. Res. Develop*., **2008**, *12*, 41-57.

[23] Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P., Mathé, D. New solvent free organic synthesis using focused microwaves. *Synthesis*, **1998**, 1213-1234.

[24] Díaz-Ortiz, Á.; Díez-Barra, E.; de la Hoz, A.; Moreno, A.; Gómez-Escalonilla, M.J.; Loupy, A. 1,3-Dipolar cycloaddition of nitriles under microwave irradiation in solvent-free conditions. *Heterocycles*, **1996**, *43*, 1021-1030.

[25] Díaz-Ortiz, Á.; de la Hoz, A.; Alcázar, J.; Carrillo, J.R.; Herrero, M.A.; Fontana, A., Muñoz, J. de M. Reproducibility and scalability of solvent-free microwave-assisted reactions: From domestic ovens to controllable parallel applications. *Comb. Chem. High Throughput Screen*., **2007**, *10*, 163-169.

[26] Abenhaïm, D.; Díez-Barra, E.; de la Hoz, A.; Loupy, A.; Sánchez-Migallón, A. Selective alkylations of 1,2,4-triazole and benzotriazole in the absence of solvent. *Heterocycles*, **1994**, *38*, 793-802.

[27] Mojtahedi, M. M.; Saidi, M. R.; Bolourtchian, M. A novel method for the synthesis of disubstituted ureas and thioureas under microwave irradiation. *J. Chem. Res. (S)*, **1999**, 710-711.

[28] Bosch, A. I.; de la Cruz, P.; Díez-Barra, E.; Loupy, A.; Langa, F. Microwave-assisted Beckmann rearrangement of ketoximes in dry media. *Synlett*, **1995**, 1259-1259.

[29] Barbry, D.; Champagne, P. Fast synthesis of aromatic aldehydes from benzylic bromides without solvent under microwave irradiation. *Tetrahedron Lett.*, **1996**, *37*, 7725-7726.

[30] AMPAC 8.53, Semichem, Inc., PO Box 1649, Shawnee, KS 66222, USA.

[31] Coulombel, L.; Rajzmann, M.; Pons, J.M.; Olivero, S.; Duñach, E. Aluminium (III) trifluoromethanesulfonate as an efficient catalyst for the intramolecular hydroalkoxylation of unactivated olefins: Experimental and theoretical approaches. *Chem. Eur. J*., **2006**, *12*, 6356-6365.

[32] Pons, J.-M.; Oblin, M.; Pommier, A.; Rajzmann, M.; Liotard, D. Formation of beta-lactones through Lewis acid-promoted [2+2]cycloaddition reaction. A theoretical study. *J. Am. Chem. Soc*., **1997**, *119*, 3333-3338.

[33] Tucker, S.C.; Truhlar, D.G. Generalized Born fragment charge model for solvation effects as a function of reaction coordinate. *Chem. Phys. Lett*., **1989**, *157*, 164-170.

[34] Cramer, C.J.; Truhlar, D.G. General parameterized SCF model for free-energies of solvation in aqueous-solution. *J. Am. Chem. Soc.*, **1991**, *113*, 8305-8311.

[35] Hawkins, G.D.; Cramer, C.J.; Truhlar, D.G. Universal quantum mechanical model for solvation free energies based on gas-phase geometries. *J. Phys. Chem. B*, **1998**, *102*, 3257-3271.

[36] Gaussian 03, Revision C.02, Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, Jr., J.A.; Vreven, T.; Kudin, K.N.; Burant, J.C.; Millam, J.M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J.E.; Hratchian, H.P.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Ayala, P.Y.; Morokuma, K.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Zakrzewski, V.G.; Dapprich, S.; Daniels, A.D.; Strain, M.C.; Farkas, O.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Ortiz, J.V.; Cui, Q.; Baboul, A.G.; Clifford, S.; Cioslowski, J.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Gonzalez, C.; and Pople, J.A.; Gaussian, Inc., Wallingford CT, **2004**.

[37] Hehre, W.J.; Radom, L.; Schleyer, P.R.; Pople, J.A. In: Ab Initio Molecular Orbital Theory; Wiley: New York, 1986; pp 65-88 and the references therein.

[38] Parr, R. G.; Yang W. Density-Functional Theory of Atoms and Molecules; Oxford University Press, New York, **1994**.

[39] Ziegler, T. Approximate density functional theory as a practical tool in molecular energetics and dynamics. *Chem. Rev*., **1991**, *91*, 651-667.

[40] Kohn, W.; Becke, A.D.; Parr, R.G. Density functional theory of electronic structure. *J. Phys. Chem.*, **1996**, *100*, 12974-12980.

[41] Becke, A.D. Density-functional thermochemistry. 3. The role of exact exchange. *J. Chem. Phys.*, **1993**, *98*, 5648-5652.

[42] Becke, A.D. Density-functional exchange-energy approximation with correct asymptotic-behavior. *Phys. Rev. A*, **1988**, *38*, 3098-3100.

[43] Barone, V.; Cossi, M.; Tomassi, J. A new definition of cavities for the computation of solvation free energies by the polarizable continuum model. *J. Chem. Phys.*, **1997**, *107*, 3210-3221.

[44] Perreux, L.; Loupy, A. A tentative rationalization of microwave effects in organic synthesis according to the reaction medium, and mechanistic considerations. *Tetrahedron*, **2001**, *57*, 9199-9223.

[45] Gedye, R.N.; Smith, F.E.; Westaway, K.C. The rapid synthesis of organic-compounds in microwave-ovens. *Can. J. Chem.*, **1988**, *66*, 17-26.

[46] Houk, K.N.; Gonzalez, J.; Li, Y. Pericyclic reaction transition-states - Passions and punctilios, 1935-1995. *Acc. Chem. Res.*, **1995**, *28*, 81-90.

[47] Arrieta, A.; Otaegui, D.; Zubia, A.; Cossío, F.P.; Díaz-Ortiz, A.; de la Hoz, A.; Herrero, M.A.; Prieto, P.; Foces-Foces, C.; Pizarro, J.L.; Arriortua, M.I. Solvent-free thermal and microwave-assisted [3+2] cycloadditions between stabilized azomethine ylides and nitrostyrenes. An experimental and theoretical study. *J. Org. Chem*., **2007**, *72*, 4313-4322.

[48] Langa, F.; de la Cruz, P.; de la Hoz, A.; Espíldora, E.; Cossío, F.P.; Lecea, B. Modification of regioselectivity in cycloadditions to C-70 under microwave irradiation. *J. Org. Chem.*, **2000**, *65*, 2499-2507.

[49] Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossio, F.P. Origins of the loss of concertedness in pericyclic reactions: Theoretical prediction and direct observation of stepwise mechanisms in [3+2] thermal cycloadditions. *J. Am. Chem Soc.*, **2000**, *122*, 6078-6092.

[50] Rigolet, S.; Goncalo, P.; Melot, J.M.; Lebrel, J. The 1,3-dipolar cycloaddition of 3-methylene-N-substituted isoindolones and nitrones by classical and microwave techniques: Reactivity and stereochemical studies. *J. Chem. Res. (S)*, **1998**, 686-687A.

[51] Feely, W.; Lehn, W.; Boekelheide, V. Alkaline decomposition of quaternary salts of amine oxides. *J. Org. Chem.*, **1957**, *22*, 1135-1135.

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