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Selectivity under microwave irradiation. Benzylation of 2-pyridone: an experimental and theoretical study

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ABSTRACT

The reaction of 2-pyridone with benzyl bromide in the absence of base and under solvent-free conditions has been studied experimentally and by computational methods. This reaction was one of the first reported examples in which modification of selectivity under microwave irradiation was observed. C- and/or N-alkylations were obtained depending on the benzyl halide and the heating system. N-Alkylation through mechanism A (S_N2 mechanism) is kinetically favoured while C-alkylation through an S_N1-type mechanism is thermodynamically favoured and is observed under microwave irradiation. Two S_N1-type mechanisms (mechanisms B and C) have been calculated, mechanism C being a kind of S_Ni. The influence of the pyridone/benzyl bromide ratio was studied. A second molecule of pyridone stabilizes the transition state and assists the leaving of the bromide ion. The occurrence of C-alkylation under microwave irradiation is explained by the predominance of the thermodynamic control in these conditions. Under microwave irradiation N-alkylation through an S_N1-type mechanism (mechanism C) can also occur. The dependence of the outcome of N-alkylation on the benzyl bromide ratio has been explained by a shift in the mechanism from S_N2 to S_N1 under microwave irradiation. Computational calculations have shown to be a useful tool for determination of the origin of the selectivity under microwave irradiation.

1. Introduction

Microwave heating is very attractive for chemical applications and has become a widely accepted non-conventional energy source for performing organic synthesis.

A large number of examples of reactions have been described in organic synthesis.[1] Several reviews have been published on the application of microwaves to cycloaddition reactions,[2] heterocyclic chemistry,[3] carbohydrates and natural products,[4] fullerene and nanotubes chemistry,[5] polymers,[6] the synthesis of radioisotopes,[7] medicinal and combinatorial chemistry,[8] homogeneous[9] and heterogeneous catalysis,[10] solvent-free reactions,[11] green chemistry[12] and, more recently, to proteomics[13] and biological chemistry.[14]

Microwave-assisted organic synthesis is characterized by the spectacular accelerations produced in many reactions as a consequence of the heating rate, which cannot be reproduced by classical heating. Higher yields, milder reaction conditions and shorter reaction times can be used and many processes can be improved. Indeed, even reactions that do not occur by conventional heating can be performed using microwaves.

The results obtained cannot always be explained by the effect of rapid heating alone, and this has led various authors to postulate the existence of a so-called 'microwave effect'. Hence, acceleration or changes in reactivity and selectivity could be explained by a specific radiation effect and not merely by a thermal effect.[15]

Control of the desired selectivity (chemo-, regio-, stereo- and enantioselectivity) is the most important objective in organic synthesis: The efficient use of reaction conditions (temperature, time, solvent, etc.), kinetic versus thermodynamic control, protecting or activating groups (for example, chiral auxiliaries) and catalysts (including chiral catalysts) have all been used to obtain the desired isomer.[16]

A large number of examples have been described where microwave irradiation leads to a different selectivity than conventional heating.[17] These are very attractive results because of the possibility of controlling the selectivity just by changing the mode of heating, i.e., conventional heating versus microwave irradiation.

Alkylation of 2-pyridone under basic conditions is one of the most studied and interesting examples of selectivity in ambident anions where the reactive sites are connected through

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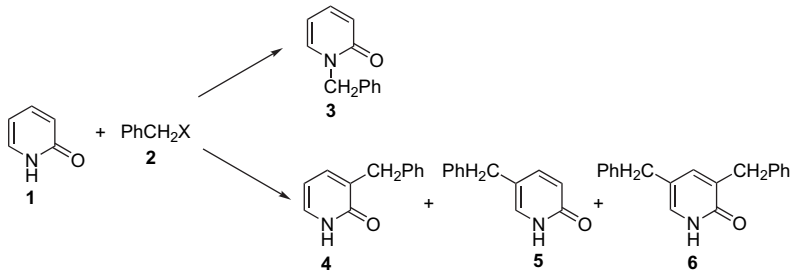


Scheme 1. Benzylation of 2-pyridone under solvent-free conditions and in the absence of base.

mesomerism.[18] Alkylation of 2-pyridone salts is very sensitive to the reaction conditions such as counterion, solvent, alkylation agent, leaving group and temperature.

We have described the benzylation of 2-pyridone in solvent-free conditions in the absence of base under conventional heating and microwave irradiation.[19] This reaction produced interesting modifications in the selectivity and these depended on the leaving group and the mode of heating. Indeed, this was one of the first examples in which the selectivity of a reaction was modified under microwave irradiation.

Our research group has maintained an interest in the theoretical study of reactions carried out under microwave irradiation in order to rationalize the effects of this energy source in chemical synthesis.[20] We think that theoretical calculations can be used to elucidate the reaction mechanisms under conventional heating and microwave irradiation, to determine the origin of the modification in the selectivity and to solve the problems encountered with temperature determination under microwave irradiation.

In the literature there are very few examples of ab initio calculations for full S_N1 processes and these are only applied to small molecules, generally *tert*-butyl chloride. However, calculations concerning some aspects of S_N1 mechanisms have been performed. In these examples two kinds of approaches were used. In the first, explicit water molecules were introduced in order to simulate solvent effects in all calculations. With the semi-empirical PM3 QM/MM method the solute molecule was surrounded by 483 water molecules.[21] The Monte Carlo method is also well adapted to simulate the hydrolysis of *t*-BuCl.[22] In addition, a cluster of *t*-BuCl and four water molecules was chosen to represent the solvent–solute complex evolution, and HF and MP2 ab initio calculations were performed to obtain a full reaction path.[23] In the second approach, solvent effects were treated by a dielectric continuum. In this case, elongation of the C–Cl bond of *t*-BuCl until full dissociation of ions was used to achieve S_N1 energy profiles. Water was also used for AM1 and MNDO semi-empirical calculations[24a] or HF and MP2 ab initio calculations.[24b] Some valence bond calculations were carried out in order to calculate solvent barriers with four organic solvents.[25] With a dielectric continuum model, only C–Cl elongation was used to represent the S_N1 mechanism and so a transition state (TS) was not characterized by Hessian eigenvalues.

Within this context, in this paper we present an experimental and theoretical study on the selectivity in the alkylation of 2-pyridone with benzyl bromide in an attempt to understand the modification in selectivity observed.

2. Results

Reactions were performed by mixing 10 mmol of 2-pyridone and 20 mmol of benzyl halide and heating the mixture under solvent-free conditions in the absence of base. Under solvent-free conditions, the influence of microwave irradiation should be more marked as the radiation is directly absorbed by the reagents and not by the solvent.[11a] Under microwave irradiation, reactions were performed in closed Teflon vessels in a domestic oven and the temperature was measured at the end of the reaction. Reactions involving conventional heating were performed in screw-cap sealed reaction vessels and heated in a closed aluminium block previously heated to the desired temperature.[26]

The selectivity in the benzylation of 2-pyridone under solvent-free conditions and in the absence of base was found to depend strongly on the alkylation agent, i.e., the leaving group and the mode of heating, microwave irradiation or conventional heating, with *N*- and *C*-alkylation products the only observed compounds (Scheme 1 and Table 1). O-Alkylation was not detected under these conditions.

With benzyl chloride, N-alkylation was the exclusive process regardless of the mode of heating. In contrast, with benzyl iodide the selectivity was found to depend on the mode of heating; with conventional heating traces of *N*-alkylation product were detected while under microwave irradiation C-alkylation was observed exclusively. Finally, with benzyl bromide the selectivity depends again on the mode of heating and, under microwaves, on the power applied. Conventional heating again leads to N-alkylation exclusively, while microwave irradiation at 150 W produced N-alkylation and at 450 W only C-alkylation was observed. As microwave reactions were performed in a domestic oven that always works at the maximum power, these results must be a consequence of the different heating rates and reaction temperatures.

In order to gain a deeper insight into the results of these reactions we studied experimentally and theoretically the reaction of 2-pyridone with benzyl bromide under conventional heating and microwave irradiation. In order to rationalize our previous results we carried out some new reactions. In these cases, the reactions were performed in a monomode reactor with 10 mmol of pyridone for 10 min, under solvent-free conditions and in the absence of base. At the end of the reaction, the crude mixture was dissolved in deuterated chloroform and the N/C ratio was determined by ^{1}H NMR spectroscopy by integration of the benzyl CH_2 group (C–CH_2 δ=3.5–4.0; N–CH_2 δ=5.0–5.5). Reactions under conventional heating were performed in an aluminium block previously heated to the desired temperature.[26] Reactions under microwave irradiation were performed in a focused PROLABO MAXIDIGEST MX250

Table 1
Benzylation of 2-pyridone using conventional heating and microwave irradiation, under solvent-free conditions and in the absence of base[19]

X	Conditions	Time (min)	Temperature (°C)	N/C ratio
Cl	MW,[a] 780 W	5	198[c]	100:0
Cl	CH[b]	5	176	100:0
Br	MW,[a] 150 W	5	81[c]	100:0
Br	MW,[a] 450 W	2.5	180[c]	0:100
Br	CH[b]	5	196	100:0
I	MW,[a] 150 W	5	146[c]	0:100
I	CH[b]	5	180	Traces:0

[a] MW, microwave irradiation.
[b] CH, conventional heating.
[c] Determined at the end of the reaction.

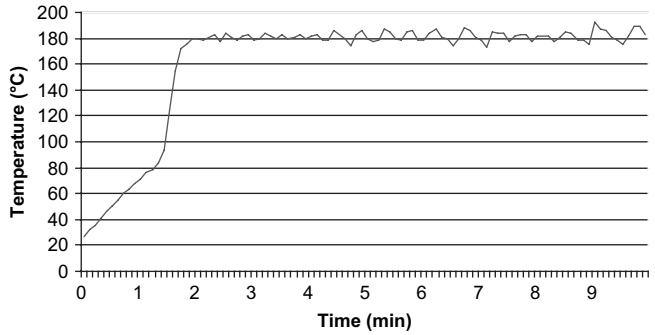


Figure 1. Temperature profile of a typical reaction under microwave irradiation. Reaction time 10 min, temperature 180 °C, power 50 W, pyridone/benzyl bromide ratio 1:2.

Table 2
Reaction of 2-pyridone with benzyl bromide under microwave irradiation (pyridone 10 mmol, benzyl bromide 20 mmol, power 150 W)

Temperature (°C)	N (%)	C (%)	Conversion (%)
80	95.3	4.7	43.1
110	95.4	4.6	51.0
140	79.9	20.1	72.4
170	58.5	41.5	85.9

microwave reactor modified with a stirring system and an IR pyrometer. The IR pyrometer was calibrated with a fibre optic sensor in order to give an accurate temperature measurement. Reaction conditions, temperature, time and power were controlled with specially designed software (Fig. 1).[27]

Firstly, we performed two series of experiments in order to ascertain if the modification of selectivity was a consequence of the heating rate, or a consequence of the applied power.

In the first series, reactions were performed with 20 mmol of benzyl bromide with a fixed irradiation power of 150 W and the temperature was changed from 80 to 170 °C. In each case, the reaction gave a complex mixture but the C-ratio increased with temperature (Table 2 and Fig. 2).

In the second series, reactions were performed with a fixed temperature of 170 °C and the irradiation power was changed from

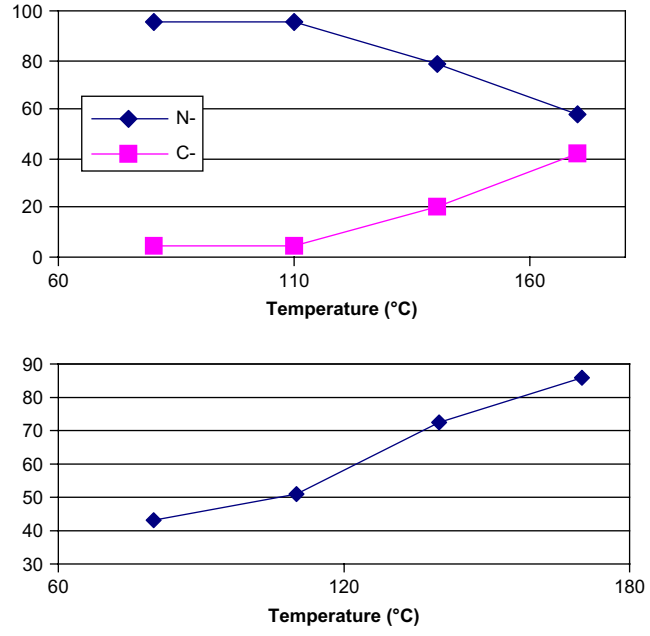


Figure 2. N/C ratio and conversion in the reaction of 2-pyridone with benzyl bromide (Table 2).

Table 3
Reaction of 2-pyridone with benzyl bromide under microwave irradiation (pyridone 10 mmol, temperature 180 °C, power 150 W)

$BrCH_2Ph$ (mmol)	N (%)	C (%)	Conversion (%)
10	28.2	71.8	78.3
15	52.7	47.3	79.1
20	79	20.6	94.3
25	90.1	9.9	100
30	90	10	100

30 to 300 W. In all reactions the same N/C ratio was observed. As a consequence it can be concluded that under microwave irradiation the selectivity depends exclusively on the reaction temperature and not on the irradiation power. On using conventional heating only N-alkylation was observed, regardless of the temperature used in the reaction.

Secondly, we performed a series of experiments in an effort to elucidate the possible mechanism of the benzylation. N- and C-benzylation can occur by S_N1 and S_N2 mechanisms and these may occur by a similar or a different path.

Reactions were performed with 10 mmol of pyridone, at 180 °C, irradiation at 150 W for 10 min and a variable ratio of benzyl bromide from 10 to 30 mmol (Table 3 and Fig. 3).

The dependence observed in the N/C ratio with the initial benzyl bromide/2-pyridone ratio indicates that N- and C-alkylation do not follow the same mechanism and that N-alkylation must proceed through an S_N2 mechanism while C-alkylation must follow an S_N1 mechanism.

Once again, under conventional heating conditions (180 °C, 10 min) N-alkylation was always observed regardless of the initial pyridone/benzyl bromide ratio.

Formation of the *C*-alkylated product must occur by a nucleophilic substitution with the pyridone acting as a nucleophile. Other possibilities were previously ruled out: (i) an *N*-benzyl to *C*-benzyl and an *O*-benzyl to *C*-benzyl rearrangements were excluded because the *N*-alkyl and *O*-alkyl derivatives are stable under the

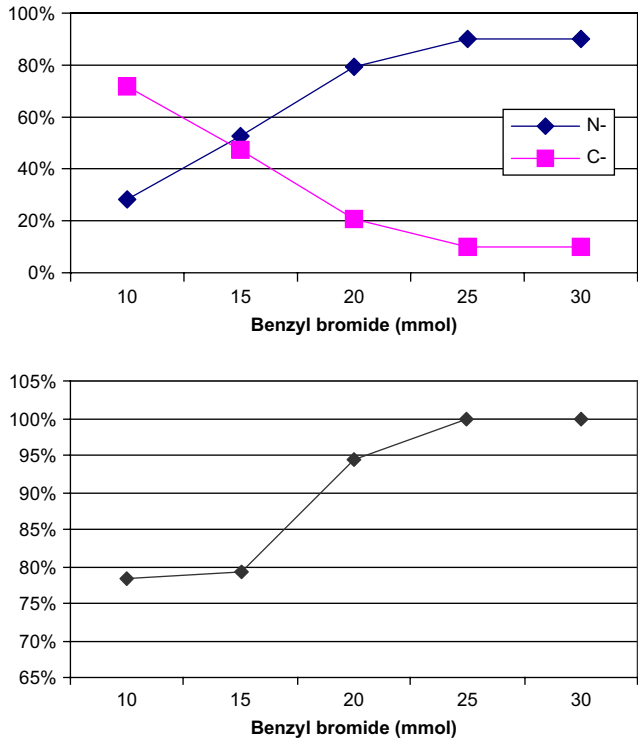


Figure 3. N/C ratio and conversion in the reaction of 2-pyridone with benzyl bromide (Table 3).

reaction conditions, in the presence of benzyl bromide and (ii) a radical substitution was excluded as reaction takes place in the presence of a radical scavenger.[19]

The use of microwave irradiation, solvent-free conditions (heterogeneous conditions), closed vessels and short reaction times prevented the use of kinetic analysis in this reaction. In consequence, in order to explain the experimental results, to justify the exclusive formation of the *C*-alkylation product under microwave irradiation and to clarify the mechanism of the benzylation, computational studies on this reaction were performed.

3. Computational calculations

3.1. Methodology

As Kormos and Cramer[28] pointed out all efforts to find solvated separated ionic transition states with PBE/CPCM were unsuccessful, so we applied AM1/SM5.2 model, which allowed us to obtain both S_N1 and S_N2 full reaction paths. First, we had to verify that AM1/SM5.2 has a qualitative agreement with PBE/CPCM for S_N2 mechanisms.

In this exploratory study, most of the calculations reported were performed with the semi-empirical AM1 method available in the AMPAC software.[29] This method gave reasonable results for organic chemical reactivity studies.[30] Geometries of stationary points were determined by energy minimizations with respect to all geometric parameters. All reaction paths were determined by the fullchn procedure.[29]

All transition structures (TS) of full reaction paths were located by the chain method[31] and characterized by one and only one negative eigenvalue of the Hessian matrix, and the corresponding vibration was found to be associated with nuclear motions along the reaction coordinate.

Stationary point connections from TS to minima were obtained either by a steepest descent if the slope was sufficient, or a polynomial interpolation for nearly flat reaction path regions. This polynomial interpolation is very useful for S_N1 mechanisms. All these successive steps are included in the fullchn process. With this automatic process we obtained a full reaction path in a single run.

Solvent effects were estimated by means of the AMSOL/SM5.2 model.[32,33] This non-rigid cavity solvent model can be applied to chemical reactions involving bond dissociation and full solvent reaction paths were obtained with the fullchn process. However, some calculation instabilities can occur when two cavities are very close, but these difficulties could be overcome by changing some data. Bromobenzene was chosen as the medium for semi-empirical calculations because its dielectric constant (ε) is close to that of benzyl bromide.

In order to check that the AM1/SM5.2 model is adapted for this study, we performed PBE/CPCM calculations for C- and N-alkylation S_N2 mechanisms. Ab initio calculations were carried out using the Gaussian 03[34] series of programs, with the standard 6-31G* basis set.[35] Density Functional Theory (DFT)[36] was used to include electron correlation at a reasonable computational cost. In this study, these calculations were carried out by means of the functional developed by Perdew et al.,[37] which is usually denoted as PBE. All TS structures and minima were fully characterized by harmonic analysis. Solvent effects were estimated by means of the polarizable conductor calculation model CPCM.[38] As we did not have all physical constants for benzyl bromide, chlorobenzene was used as the medium given that the dielectric constants of these two compounds are similar. Indeed, with the CPCM model, PBE functional and 6-31G* basis and solvent cavities are well adapted for optimization convergences, so we obtained optimized TS and minimum structures. C- and N-alkylation TS are shown Figure 4 and their main structural data are collected in Table 4.

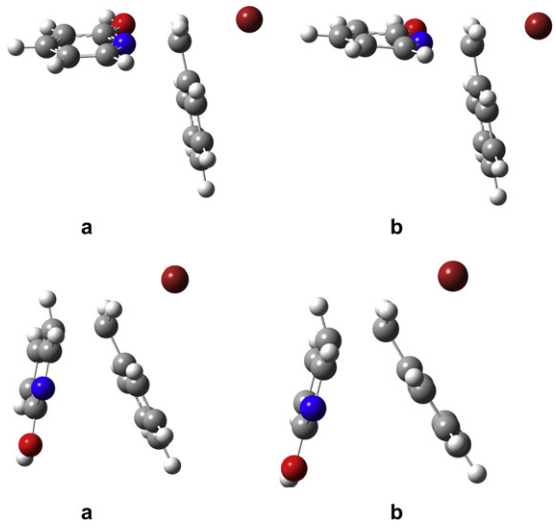


Figure 4. Transition structures of C-alkylation and N-alkylation (S_N2) computed at PBE/6-31G*: a, and AM1: b.

The AM1 with AMSOL/SM5.2 methods allows describing the S_N1 mechanism, in which ionic intermediates exist, to be treated as carbocation and carbanion. In our experiments, the medium was benzyl bromide, which is less polar than water and, consequently, we could not use cluster strategies to stabilize ions. Solvent effects were included in our semi-empirical calculations by means of a dielectric medium. In this way all full reaction paths were obtained in a reasonable computing time.

DFT and AM1 TS structures are similar. However, polarization atomic orbitals are only included in PBE/6-31G* calculations, so it is not surprising that, for non-linked reactive atoms in both S_N2 mechanisms, nitrogen–carbon (N-alkylation) or carbon–carbon (C-alkylation) and carbon–bromide distances are longer for DFT calculations than AM1 calculations (Table 4). With both methods, activation and reaction energies E_a and E_{rxn} are lower for N-alkylation than C-alkylation, even if AM1/SM5.2 activation energies are overestimated. Therefore, there is a qualitative agreement between DFT and AM1 calculations. As a consequence, PBE/CPCM calculations validate AM1/SM5.2 calculations for qualitative studies. Moreover, the same reactants are also present for all N-alkylation and C-alkylation mechanisms. AM1 calculations are therefore sufficient to explain our experimental results because we have only studied different evolutions of the same system.

Experimental results (Table 3) indicate that N-alkylation and C-alkylation reactions could occur through different mechanisms.

AM1 with AMSOL/SM5.2 was used to compute all mechanisms for these reactions (N-alkylation S_N2, N-alkylation S_N1, C-alkylation S_N2, C-alkylation S_N1).

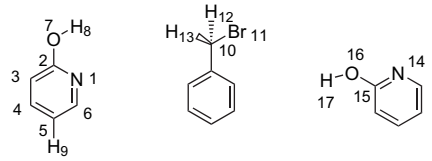
For all calculations, we only used the hydroxypyridine tautomer rather than the pyridone tautomer, because: (i) in our experiments, O-alkylation has never been detected, which means that our reactants are the hydroxypyridine tautomer and benzyl bromide for all alkylation reactions. Intermolecular keto-enolization between

Table 4
Geometrical data, distances (Å), activation energies (ΔE_a, kcal/mol), reaction energies (ΔE_{rxn}, kcal/mol) of transition structure for C- and N-alkylation (S_N2) computed at PBE/6-31G*

Entry			*d* C–C	*d* C–N	*d* C–Br	E_a	E_{rxn}
1	NA[a]	DFT		1.94	2.59	21.29	−17.44
2		AM1		1.78	2.39	55.24	−3.28
3	CA[a]	DFT	1.86		2.91	40.42	−22.98
4		AM1	1.84		2.67	71.80	−19.53

[a] NA denotes N-alkylation and CA denotes C-alkylation.

two pyridone molecules occurs easily. Indeed, with PBE/CPCM the activation energy for the keto-enolization reaction is only 11.08 kcal/mol and 4.25 kcal/mol for the reverse reaction. (ii) For N-alkylation mechanisms the nitrogen lone pair has to be available. (iii) For C-alkylation mechanisms, the benzyl carbocation has to be stabilized and benzyl bromide is not sufficiently polar to achieve this. If a pyridone molecule stabilizes this ion through an oxygen lone pair, 2-benzyloxypyridine should always be obtained through this mechanism. As this compound has never been observed in any of our experiments, pyridone molecules were replaced by hydroxypyridine molecules in our calculations and, in this way, the correct compound was obtained. Moreover, the hydroxypyridine–bromide complex (O···H···Br) is stable enough for the bromide ion to move in the reaction path, but this complex can easily release the bromide ion, which catches a hydrogen atom (H9 or H5) (Scheme 2) to give hydrogen bromide.



Scheme 2. Atom numbering for the two hydroxypyridine and benzyl bromide molecules.

Activation and reaction energies in solution are collected in Table 5. It has been proposed that dipole moments play an important role in reactions induced by microwave irradiation and these values are also collected in Table 5.[15a] In S_N1 mechanisms there are generally at least two TS and these are denoted as 1 and 2. Activation energies are given for higher TS.

In S_N1-type mechanisms the ions that form during the process have to be stabilized. As stabilization by benzyl bromide is weak, a second molecule of hydroxypyridine, which stabilizes the benzyl carbocation and the TS, was introduced. Thus we have included two hydroxypyridine molecules for one benzyl bromide molecule in the calculations. The main results are collected in Table 6.

In all cases, activation energies were lower when two hydroxypyridine molecules were introduced into our calculations. As expected, this decrease in the activation energy is more significant for S_N1-type mechanisms (mechanisms B and C), where a carbocation is formed, than for S_N2 mechanisms (mechanisms A). As a result, only full reaction path drawings with two hydroxypyridine molecules are included in this study.

3.2. Description of the calculated mechanisms

3.2.1. Mechanisms A

Mechanisms A are S_N2 mechanisms. In order to limit the size of figures, C-alkylation energy profile drawings are restricted to the hydroxypyridine derivative, but all reaction energies are given for the pyridone derivative (Tables 4–6). Indeed, the last tautomerism is common for all C-alkylation mechanisms with low activation energy. Energy profiles are similar for N- and C-alkylation, although the activation energy for N-alkylation is lower than that for C-alkylation (Table 6, entry 1 vs 2). Examination of TS structures shows that interatomic distances C5–C10 and C10–Br11 are longer in the TS for C-alkylation than interatomic distances N1–C10 and C10–Br11 in the TS for N-alkylation (Table 7), a situation that explains why the activation energy for C-alkylation is 14 kcal/mol higher than that for N-alkylation (Table 6, entry 1 vs 2). The weak slopes of these energy profiles are associated with the movement of the bromide ion. This motion is facilitated by the formation of a bromide–hydroxypyridine complex—a situation confirmed by the short Br11–H17 distance (Table 7), where H17 belongs to the second hydroxypyridine unit (Figs. 5 and 6)

Two possible reactions paths were found for mechanisms B and C, they are S_N1-type mechanisms as benzyl cation is formed in the first step. In both cases assistance of one hydroxypyridine unit is required for releasing the bromide ion. The fundamental difference between these mechanisms is in the first step and the attacking hydroxypyridine unit.

Table 5
Activation energies (ΔE_a, kcal/mol), reaction energies (ΔE_{rxn}, kcal/mol) and dipole moments (debye)

Entry	Mechanism	μ	ΔE_a	ΔE_{rxn}
1	A (NA)	15.26	55.24	−3.28
2	A (CA)	16.03	71.80	−19.53
3	B (NA)-1[a]	16.89	63.42	−3.28
4	B (NA)-2[a]	28.10	—	
5	C (NA)-1[a]	22.72	—	
6	C (NA)-2[a]	23.65	58.15	−3.28
7	B (CA)-1[a]	19.31	—	
8	B (CA)-2[a]	12.83	71.98	−19.53
9	C (CA)-1[a]	18.51	62.85	−19.53
10	C (CA)-2[a]	9.46	—	

Mechanisms determined with one hydroxypyridine molecule.
[a] NA denotes N-alkylation and CA denotes C-alkylation.

Table 6
Activation energies (ΔE_a, kcal/mol), reaction energies (ΔE_{rxn}, kcal/mol) and dipole moments (debye)

Entry	Mechanism	μ	ΔE_a	ΔE_{rxn}
1	A (NA)	12.62	53.26	−1.57
2	A (CA)	14.07	67.55	−16.14
3	B (NA)-1[a]	16.06	56.68	−1.57
4	B (NA)-2[a]	25.69	—	
5	C (NA)-b-1[a]	24.23	55.66	−1.57
6	C (NA)-b-2[a]	—		
7	B (CA)-1[a]	20.33	—	
8	B (CA)-2[a]	20.78	66.45	−16.14
9	C (CA)-b-1[a]	27.77	—	
10	C (CA)-b-2[a]	24.73	59.15	−16.14

Mechanisms determined with two hydroxypyridine molecules.
[a] NA denotes N-alkylation and CA denotes C-alkylation.

3.2.2. Mechanisms B

In mechanism B, the bromide anion is released from benzyl bromide and stabilized by a hydroxypyridine molecule. A second hydroxypyridine is then linked by the other side of the benzyl carbocation with the N1 atom (N-alkylation) or C5 atom (C-alkylation). Finally, the bromide ion catches a hydrogen atom (H9) to give a molecule of hydrogen bromide (Figs. 7 and 8). All fragments in this mechanism are well separated; as a consequence, interatomic distances cannot explain the difference in the activation energy between these two mechanisms, i.e., N- and C-alkylation (Table 6, entry 3 vs 8). A detailed inspection of all TS structures in these mechanisms indicates that the two first TS of each mechanism are similar, where the carbocation is stabilized by two lone pairs—one from a nitrogen atom and one from an oxygen atom, and the bromide ion is also stabilized by an OH group (Br11–H17 distance: 1.99 Å, Table 7). Consequently, the energies are very close.

Table 7
Geometrical data for transition structures

	Distances (Å)	S_N2	S_N1		S_N1-b	
		TS	TS1	TS2	TS1	TS2
N-Alkylation	N1–C10	1.83	3.92	2.69	3.54	
	C10–Br11	2.40	3.70	6.18	4.01	
	Br11–H17	2.15	1.99	2.07	6.45	
C-Alkylation	C5–C10	1.96	5.02	2.11	5.67	3.11
	C10–Br11	2.88	4.78	6.19	3.74	6.18
	Br11–H17	2.07	1.99	2.01	6.61	7.95

Mechanisms determined with two hydroxypyridine molecules.

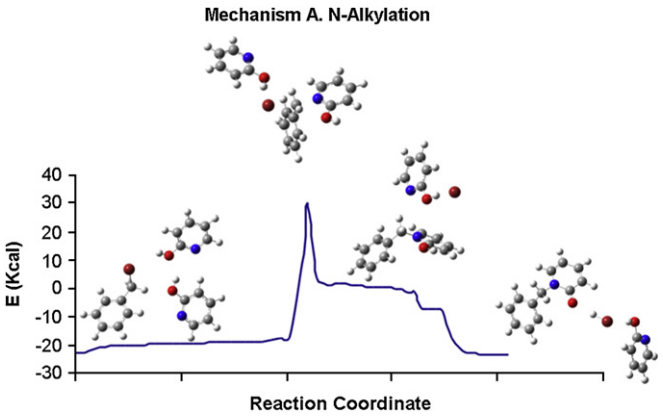


Figure 5. Energy profile for the N-alkylation through mechanism A (S_N2).

In contrast, the second TS structures are different. For N-alkylation, the carbocation is stabilized by the nitrogen lone pair and the bromide ion by two OH groups (Br11–H17 distance: 2.07 Å). For C-alkylation there is no stabilization by the lone pair as the interatomic distance C5–C10 is 2.11 Å (Table 7), which produces only a weak interaction between the carbocation and the π system of the pyridine ring. Moreover, the bromide ion is only stabilized by one OH group (Br11–H17 distance: 2.01 Å). This structural difference could explain why the activation energy for C-alkylation is 10 kcal/mol higher than for N-alkylation (Table 6, entry 3 vs 8).

3.2.3. *Mechanisms C*

In mechanism C, the bromide ion and a proton (H8) from the hydroxy group are released to give hydrogen bromide. The remaining reactive groups, i.e., the benzyl cation and hydroxypyridine anion, are bonded through the two reactive sites N1 (N-alkylation) or C5 (C-alkylation) with C10 in a kind of internal Nucleophilic Substitution (S_Ni). Nucleophilic attack takes place by the same side of the removal of bromide ion. N-Alkylation is completed at this stage (Fig. 9). For C-alkylation, a hydrogen exchange (H8 and H9) from hydrogen bromide occurs with the help of a second hydroxypyridine unit (Fig. 10). The small difference in the activation energy (3 kcal/mol) between these two mechanisms (Table 6, entry 5 vs 10) can be explained in terms of the higher TS structures of these mechanisms. Indeed, for N-alkylation the carbocation is further stabilized in the TS by two nitrogen lone pairs, while for C-alkylation one lone pair can be used for such stabilization. In these mechanisms bromide is always linked and, as such, stabilization of hydroxypyridine is not necessary, meaning that the Br11–H17 distance is greater than 6 Å (Table 7).

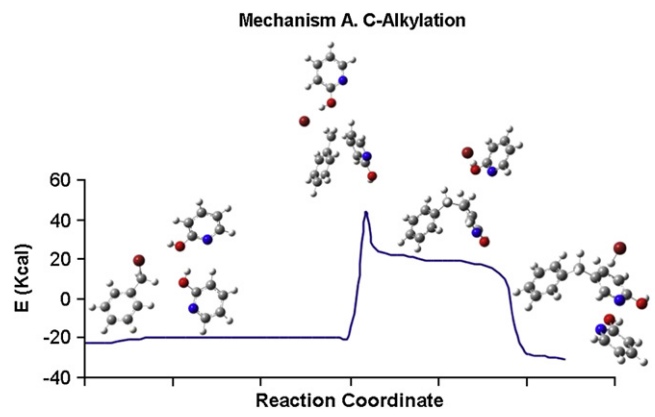


Figure 6. Energy profile for the C-alkylation through mechanism A (S_N2).

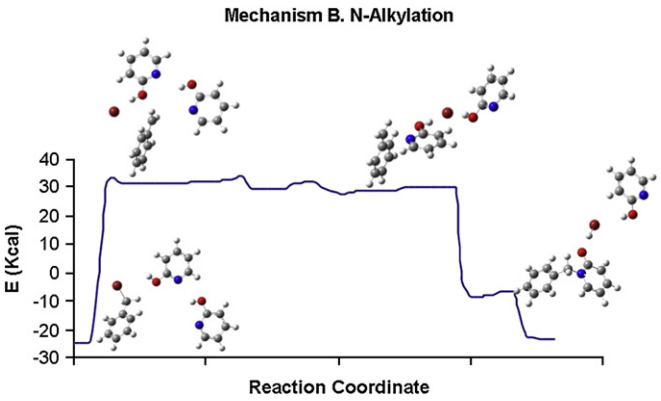


Figure 7. Energy profile for the N-alkylation through mechanism B (S_N1).

4. Discussion

The reaction of pyridone with benzyl bromide in solvent-free conditions and in the absence of base follows a complex path. Experimental results show that under conventional heating N-alkylation is produced regardless of the reaction conditions, temperature, time and molar ratio of reagents. Under microwave irradiation, however, the selectivity N/C-alkylation depends on the temperature and the benzyl bromide/pyridone ratio, but not on the power used at a fixed temperature. These results indicate that in this reaction microwave irradiation favours the thermodynamic control path.

Computational calculations helped to elucidate the reaction paths and to explain the experimental results. All calculations show that assistance of a second molecule of 2-hydroxypyridine leads to a reduction in the free energy of activation of all processes.

Theoretical results indicate that N-alkylation through mechanism A (S_N2) is the kinetically favourable process because it has the lowest activation energy (Table 6, entry 1). This process is observed exclusively under conventional heating conditions.

At high temperatures, the process has enough energy to pass the two energy barriers corresponding to N-alkylation (mechanism A, S_N2) and C-alkylation (mechanism C, S_Ni) (Table 6, entry 1 vs 10). This latter process is favoured thermodynamically and is observed under microwave irradiation.

The acceleration of reactions by microwave exposure may be a result of the interaction of the radiation with matter. Dielectric heating results from dipolar polarization as a consequence of dipole–dipole interactions between polar molecules and the electromagnetic field. These interactions lead to a dissipation of energy

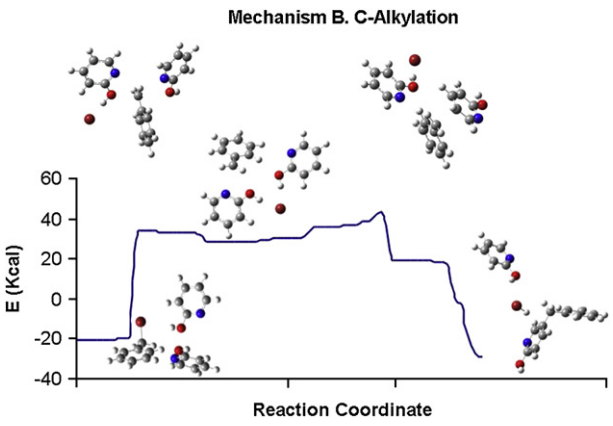


Figure 8. Energy profile for the C-alkylation through mechanism B (S_N1).

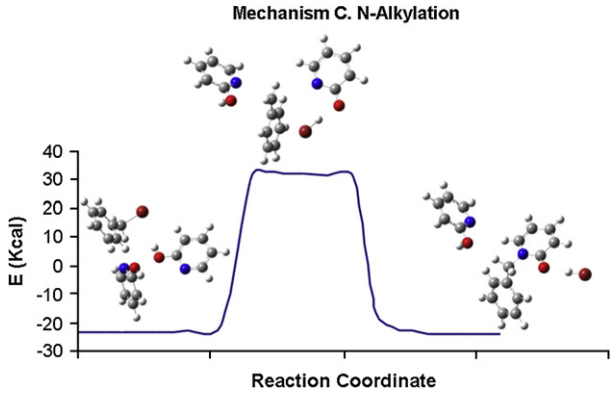


Figure 9. Energy profile for the N-alkylation through mechanism C (S_Ni).

as heat. This energy dissipation in the core of the material allows a much more regular repartition in the temperature when compared to classical heating. In this way thermodynamically controlled processes are favoured under microwave irradiation. In our case, the reaction energy is 14.57 kcal/mol lower for C-alkylation than that for N-alkylation (Table 6, entries 2, 8, 10 vs 1, 3, 5).

In our process, the TS corresponding to C-alkylation are also much more polar (15.15 D) than the TS corresponding to N-alkylation (Table 6, entry 1 vs 9).[39,40]

Therefore, under microwave irradiation C-alkylation occurs because this process is thermodynamically favourable. The reaction rate for C-alkylation is enhanced at high temperatures. C-Alkylation is produced by a kind of S_Ni mechanism (mechanism C). This is not a pure S_N1 mechanism as a molecule of 2-hydroxypyridine facilitates the formation of hydrogen bromide and, in consequence it participates in the rate determining step.

Experimentally, N-alkylation also occurs under microwave irradiation. The small difference in the activation energies between mechanism C (S_Ni, N-alkylation) and mechanism A (S_N2, N-alkylation) and the high dipole moment for mechanism C (S_Ni, N-alkylation) TS 24.23 D (Table 6, entry 5) indicate that N-alkylation under microwaves can occur through mechanism C. This behaviour is similar to that observed for the mechanism C (S_Ni, C-alkylation) (Table 6, entry 9), even though the activation energy is 3 kcal/mol higher than that for mechanism B (S_N1-type, N-alkylation). Consequently, computational results are consistent with the occurrence of N-alkylation and C-alkylation under microwave irradiation.

4.1. Influence of the ratio of benzyl bromide

Experimental results show that under microwave irradiation an increase in the proportion of benzyl bromide produces an inversion in the selectivity to favour N-alkylation (Table 3). To simulate this effect we performed calculations with one molecule of hydroxypyridine, which represents a higher concentration of benzyl bromide.

Our results (Table 5) reveal that N-alkylation through mechanism C (S_Ni) now has not only a lower activation energy (−4.70 kcal/mol) but also a higher dipole moment (+5.14 D) than the C-alkylation through mechanism C (Table 5, entry 6 vs 9). In contrast, with 2 equiv of hydroxypyridine the N-alkylation through mechanism C has still a lower activation energy (−3.49 kcal/mol) but a similar dipole moment (−0.50 D) to the C-alkylation through mechanism C (Table 6, entry 5 vs 10). As a consequence, the increase in the proportion of benzyl bromide produces a modification of the mechanism, from C-alkylation to N-alkylation, under microwave irradiation in good agreement with the experimentally observed inversion of the selectivity.

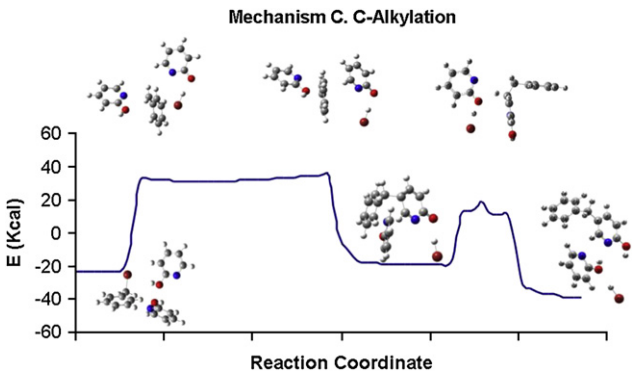


Figure 10. Energy profile for the C-alkylation through mechanism C (S_Ni).

5. Conclusion

The mechanism of the benzylation of 2-pyridone in solvent-free conditions and in the absence of base has been elucidated by computational calculations.

Computational calculations showed that modification on selectivity can be explained through thermal effects that lead to thermodynamic control under microwave irradiation. N-Alkylation occurs through mechanism A (S_N2), and C-Alkylation through mechanism C (S_Ni). Microwave irradiation also induces a shift from C- to N-alkylation (mechanism C) with an excess of benzyl bromide.

It should be noted that mechanisms C (S_Ni) were determined for the first time, thanks to fullchn calculations, which represent a powerful research tool.

Finally, we performed calculations exclusively with benzyl bromide because the most dramatic modifications were observed with this alkylation agent. Results obtained with benzyl chloride and benzyl iodide can be rationalized by considering the modifications expected in the mechanism according to the nature of the leaving group (chloride, S_N2 favourable, exclusive N-alkylation; iodide, S_N1 favourable, exclusive C-alkylation under microwave irradiation).

The effect of microwave irradiation on chemical synthesis results from material–wave interactions that lead to thermal effects that can be proved by temperature measurements. Some authors have also postulated the existence of non-thermal effects. Many of these described non-thermal effects have been a consequence of the use of non-appropriate techniques for temperature measurement. Even using multiple fibre-optic probes, the presence of microscopic hot spots in heterogeneous reactions cannot be discarded.[41] In this paper we have shown that theoretical calculations can be used not only to elucidate the mechanism but to explain the origin of the modification of selectivity under microwave irradiation, avoiding possible errors in temperature measurements.

6. Experimental section

6.1. General

All reactions were performed under the conditions described in Section 2 and Tables 2 and 3. The crude products were dissolved in $CDCl_3$ (1 mL) and isomer ratios were determined by ^1H NMR by integration of the benzyl protons. *C*- and *N*-Alkylation products were isolated by column chromatography on silica gel using hexane/ethyl acetate as the eluent.

*6.1.1. 1-Benzyl-2-pyridone (**3**)*

Bp 230 °C/0.01 mmHg; ^1H NMR (500 MHz, $CDCl_3$): 5.18 (s, 2H, N–CH_2), 6.14 (td, 1H, J=1.4, 6.4 Hz, H-5), 6.62 (ddd, 1H, J=0.8, 1.4, 9.2 Hz, H-3), 7.25 (ddd, J=0.8, 2.1, 6.4 Hz, H-6), 7.2–7.4 (m, 6H, Ph, H-4); ^{13}C

NMR (125 MHz, $CDCl_3$): 51.0 (N–CH_2), 105.45 (C-5), 119.83 (C-3), 127.41 (*p*-C), 127.57 (*o*-C), 128.48 (*m*-C), 137.40 (6-C), 139.09 (*i*-C), 140.01 (4-C), 161.33 (C=O). IR (KBr): ν=3261, 2938, 1641, 1613, 1561, 1490, 1472, 1448, 774, 723, 695 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{11}NO$ (185.23): C 77.88, H 5.99, N 7.57; found: C 77.91, H 5.80, N 7.30.

*6.1.2. 3-Benzyl-2-pyridone (**4**)*

Mp 144–145 °C (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$): 3.89 (s, 2H, 3-CH_2), 6.19 (t, 1H, *J*=9.9 Hz, 5-H), 7.06 (d, 1H, *J*=9.9 Hz, 4-H), 6.9–7.3 (m, 6H, Ph, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): 35.80 (3-CH_2), 106.71 (5-C), 126.26 (*p*-C), 128.48 (*m*-C), 129.29 (*o*-C), 132.08 (3-C), 132.78 (6-C), 138.83 (4-C), 139.20 (*i*-C), 164.57 (C=O). IR (KBr): ν=3261, 2938, 1641, 1613, 1561, 1490, 1472, 1448, 774, 723, 695 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{11}NO$ (185.23): C 77.88, H 5.99, N 7.57; found: C 77.91, H 5.80, N 7.30.

*6.1.3. 5-Benzyl-2-pyridone (**5**)*

Mp 114–115 °C (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$): 3.66 (s, 2H, CH_2-5), 6.48 (d, 1H, *J*=14.4 Hz, H-3), 7.1 (dd, 1H, *J*=14.4 Hz, H-4), 7.2–7.7 (m, 5H, Ph), 7.40 (d, 1H, *J*=2.7 Hz, H-6); ^{13}C NMR (125 MHz, $CDCl_3$): 37.44 (5-CH_2), 120.09 (3-C), 120.85 (5-C), 126.63 (6-C), 128.66 (*p*-C), 128.70 (*m*-C), 132.68 (*o*-C), 139.21 (*i*-C), 143.93 (4-C), 163.08 (C=O); IR (KBr): ν=3057, 1654, 1597, 1543, 1490, 802, 732, 699 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_{11}NO$ (185.23): C 77.88, H 5.99, N 7.57; found: C 78.13, H 5.82, N 7.92.

*6.1.4. 3,5-Dibenzyl-2-pyridone (**6**)*

Mp 93–94 °C (ethyl acetate); ^1H NMR (500 MHz, $CDCl_3$): 3.65 (s, 2H, CH_2-5), 3.84 (s, 2H, CH_2-3), 7.00 (s, 1H, H-4), 7.21 (s, 1H, H-6), 6.9–7.4 (m, 10H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): 35.82 (3-CH_2), 37.65 (5-CH_2), 119.46 (5-C), 126.20 (*p*-C), 126.48 (*p*-C), 128.43 (6-C), 128.62 (*m*-C), 128.69 (*m*-C), 129.16 (*o*-C), 130.27 (*o*-C), 132.34 (3-C), 139.30 (*i*-C), 139.42 (*i*-C), 140.80 (4-C), 163.86 (C=O). IR (KBr): ν=3021, 1653, 1623, 1558, 1490, 1475, 1450, 737, 696 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{17}NO$ (275.35): C 82.88, H 6.22, N 5.09; found: C 82.91, H 6.04, N 5.21.

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References and notes

1. (a) *Microwaves in Organic Synthesis*, 2nd ed.; Loupy, A., Ed.; Wiley: Weinheim, 2006; (b) *Microwave-Assisted Organic Synthesis*; Lidström, P., Tierney, J. P., Eds.; Blackwell Scientific: Oxford, 2004; (c) Kappe, C. O.; Stadler, A. *Microwaves in Organic and Medicinal Chemistry*; Wiley-VCH: Weinheim, 2005.
2. Díaz-Ortiz, A.; Langa, F.; de la Hoz, A.; Moreno, A. *Eur. J. Org. Chem.* **2000**, *4*, 3659–3673.
3. *Microwave-Assisted Synthesis of Heterocycles*; Van der Eycken, E., Kappe, C. O., Eds.; Topics in Heterocyclic Chemistry; Springer: New York, NY, 2006.
4. Corsaro, A.; Chiacchio, U.; Pistara, V.; Romeo, G. *Curr. Org. Chem.* **2004**, *8*, 511–538.
5. Langa, F.; de la Cruz, P.; Espíldora, E.; de la Hoz, A. *Applications of Microwave Irradiation to Fullerene Chemistry*. Fullerenes; The Electrochemical Society: New York, NY, 2000; Vol. 9, pp 168–178.
6. (a) Zong, L.; Zhou, S.; Sgriccia, N.; Hawley, M. C.; Kempel, L. C. *J. Microwav. Power Electromagn. Energ.* **2003**, *38*, 49–74; (b) Zhang, C.; Liao, L.; Gong, S. *Green Chem.* **2007**, *9*, 303–314.
7. (a) Elander, N.; Jones, J. R.; Lu, S. Y.; Stone-Elander, S. *Chem. Soc. Rev.* **2000**, *29*, 239–249; (b) Stone-Elander, S.; Elander, N. *J. Labelled Compd. Radiopharm.* **2002**, *45*, 715–746.
8. (a) Blackwell, H. E. *Org. Biomol. Chem.* **2003**, *1*, 1251–1255; (b) Dallinger, D.; Kappe, C. O. *Nat. Rev. Drug Discov.* **2006**, 51–63.
9. Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717–727.
10. Will, H.; Scholz, P.; Ondruschka, B. *Chem. Ing. Tech.* **2002**, *74*, 1057–1067.
11. (a) Loupy, A. *Solvent-free Reactions in Modern Solvents in Organic Chemistry*; Springer: 1999; Vol. 206, pp 155–207; (b) Varma, R. S. *Tetrahedron* **2002**, *58*, 1235–1255.
12. (a) Bose, A. K.; Manhas, M. S.; Ganguly, S. N.; Sharma, A. H.; Banik, B. K. *Synthesis* **2002**, 1578–1591; (b) Varma, R. S. *Advances in Green Chemistry: Chemical Syntheses Using Microwave Irradiation*; AstraZeneca Research Foundation, Kavitha Printers: Bangalore, India, 2002; (c) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005**, *38*, 653–681.
13. Sandoval, W. N.; Pham, V.; Ingle, E. S.; Liu, P. S.; Lill, J. R. *Comb. Chem. High Throughput Screening* **2007**, *10*, 751–765.
14. Collins, J. M.; Leadbeater, N. E. *Org. Biomol. Chem.* **2007**, *5*, 1141–1150.
15. (a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223; (b) Díaz-Ortiz, A.; de la Hoz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, 157–168.
16. Ward, R. S. *Selectivity in Organic Synthesis*; John Wiley and Sons: New York, NY, 1999.
17. (a) Langa, F.; de la Cruz, P.; de la Hoz, A.; Díaz-Ortiz, A.; Díez-Barra, E. *Contemp. Org. Synth.* **1997**, 373–386; (b) Díaz-Ortiz, A.; de la Hoz, A.; Moreno, A. *Curr. Org. Chem.* **2004**, *8*, 903–918.
18. Reutov, O. A.; Beletskaya, I. P.; Kurts, A. L. *Ambident Anions*; Plenum: New York, NY, 1983.
19. Almena, I.; Díaz-Ortiz, A.; Díez-Barra, E.; de la Hoz, A.; Loupy, A. *Chem. Lett.* **1996**, 333–334.
20. (a) Díaz-Ortiz, A.; Carrillo, J. R.; Cossío, F. P.; Gómez-Escalonilla, M. J.; de la Hoz, A.; Moreno, A.; Prieto, P. *Tetrahedron* **2000**, *56*, 1569–1577; (b) Fraile, J. M.; García, J. I.; Gómez, M. A.; de la Hoz, A.; Mayoral, J. A.; Moreno, A.; Prieto, P.; Salvatella, L.; Vazquez, E. *Eur. J. Org. Chem.* **2001**, 2891–2899; (c) Prieto, P.; Cossío, F. P.; Carrillo, J. R.; de la Hoz, A.; Díaz-Ortiz, A.; Moreno, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1257–1263; (d) Pinto, D. C. G. A.; Silva, A. M. S.; Brito, C. M.; Sandulache, A.; Carrillo, J. R.; Prieto, P.; Díaz-Ortiz, A.; de la Hoz, A.; Calvaleiro, J. A. S. *Eur. J. Org. Chem.* **2005**, 2973–2986; (e) 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. *J. Org. Chem.* **2007**, *72*, 4313–4322; (f) Cossío, F. P.; Díaz, A.; Rivacoba, A.; Lopez, X.; Carrillo, J. R.; de la Hoz, A. *J. Am. Chem. Soc.*, submitted for publication.
21. Hartsough, D. S.; Merz, K. M. *J. Phys. Chem.* **1995**, *99*, 384–390.
22. Jorgensen, W. L.; Buckner, J. K.; Huston, S. E.; Rossky, P. J. *J. Am. Chem. Soc.* **1987**, *109*, 1891–1899.
23. Okuno, Y. *J. Phys. Chem. A* **1999**, *103*, 190–196.
24. (a) Ford, G. P.; Wang, B. *J. Am. Chem. Soc.* **1992**, *114*, 10563–10569; (b) Takahashi, O.; Sawahata, H.; Ogawa, Y.; Kikuchi, O. *J. Mol. Struct. (Theochem)* **1997**, *393*, 141–150.
25. Mathis, J. R.; Hynes, J. T. *J. Phys. Chem.* **1994**, *98*, 5445–5459.
26. Begtrup, M. *J. Chem. Educ.* **1987**, *64*, 974.
27. Pacam, MPX-2 software. Calibration of the IR probe was performed heating a blank experiment with a fibre optic probe, measuring at various temperatures and introducing these data in the software as a calibration line.
28. Kormos, B. L.; Cramer, C. J. *J. Org. Chem.* **2003**, 6375–6386.
29. *AMPAC 8.53*, Semichem, PO Box 1649, Shawnee, KS 66222, USA.
30. Coulombel, L.; Rajzmann, M.; Pons, J.-M.; Olivero, S.; Duñach, E. *Chem.—Eur. J.* **2006**, *12*, 6356–6365.
31. Pons, J.-M.; Oblin, M.; Pommier, A.; Rajzmann, M.; Liotard, D. *J. Am. Chem. Soc.* **1997**, *119*, 3333–3338.
32. Liotard, D. A. *Int. J. Quantum Chem.* **1992**, *44*, 723–741.
33. (a) Tucker, S. C.; Truhlar, D. G. *Chem. Phys. Lett.* **1989**, 157–164; (b) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 8305–8311; (c) Hawkins, G. D.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **1998**, *102*, 3257–3271.
34. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T., Jr.; 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.; 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.; Gui, Q.; Baboul, A. G.; Clifford, S.; Gioslowski, 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.; González, C.; Pople, J. A. *Gaussian 03, Revision A. 1*; Gaussian: Pittsburgh, PA, 2003.
35. Hehre, W. J.; Radom, L.; Schleyer, P. R.; Pople, J. A. *Ab initio Molecular Orbital Theory*; Wiley: New York, NY, 1986; pp 65–88 and references therein.
36. (a) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, NY, 1994; (b) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651–667.
37. Perdew, J. P.; Burke, K.; Ernzerhof, M. *Phys. Rev. Lett.* **1996**, *77*, 3865–3868; Errata correction *Phys. Rev. Lett.* **1997**, *78*, 1396.
38. (a) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995–2001; (b) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669–671.
39. Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* **1998**, *66*, 17–26.
40. Abramovich, R. A. *Org. Prep. Proced. Int.* **1991**, *23*, 683–711.
41. Bogdal, D.; Bednarz, S.; Lukasiewicz, M. *Tetrahedron* **2002**, *62*, 9440–9445.