Pergamon

Tetrahedron 58 (2002) 2155–2162

TETRAHEDRON

Solvent-free preparation of amides from acids and primary amines under microwave irradiation

Laurence Perreux,[a] André Loupy[a,*] and François Volatron[b]

[a]*Laboratoire des Réactions Sélectives sur Supports, Université Paris-Sud, CNRS, ICMO, UMR 8615, Bâtiment 410, 91405 Orsay Cedex, France*

[b]*Laboratoire de Chimie Physique, Université Paris-Sud, 91405 Orsay Cedex, France*

Received 26 July 2001; revised 19 October 2001; accepted 27 December 2001

Abstract—Synthesis of amides via pyrolysis of the salts obtained by mixing neat primary amines and carboxylic acids were realized under solvent-free conditions within short times and appreciable yields under microwave activation. The evident specific non-thermal microwave effects are attributed to polarity increase during the course of the reaction, due to development of a dipole in the transition state.

1. Introduction

There is considerable interest in the formation of amides by the direct combination of carboxylic acids and amines, as the methods employed may also be utilized in peptide and lactam synthesis. In general, the formation of carboxamides from amines and carboxylic acids implies the activation of the carboxyl group.[1] The most common methods involve either conversion of carboxylic acid to a more reactive functional group such as an acyl chloride, mixed anhydride, acyl azide or active esters, or via an in situ activation of carboxyl group by some coupling reagents such as carbodiimides.[2,3] More recently, new systems were recommended such as titanium or divalent tin reagents of type $Sn(N(TMS)_2)_2$,[4] treatment with equivalent amounts of triphenylphosphine and *N*-halosuccinimides such as NBS.[5] or with trichloroacetonitrile.[6]

With the aim of simplification of the procedures, especially in order to avoid the preliminary and often expensive synthesis of coupling reagents, pyrolitic preparations of amides should be considered as the most interesting method for their syntheses in the absence of any catalyst and solvent.[7] It consists of the pyrolysis of the corresponding salts obtained by mixture of the amine and the carboxylic acid (Eq. (1)).

$$RCO_2H + R'NH_2 \rightleftharpoons RCO_2^-, {}^+NH_3R' \xrightarrow[-H_2O]{\Delta} RCONHR' \quad (1)$$

However, this method usually suffers from rather harsh conditions with respect to temperature and reaction times.

In recent developments, the use of microwave irradiation (MW) to simplify and improve classic organic reactions has become a very popular method,[8–10] because it often leads to higher yields, cleaner reactions and shorter reaction times. In connection with solvent-free conditions, MW methods result in efficient and safe technology, 'Green Chemistry'.[10,11]

Microwave activation has been used with a great deal of success in several cases of amide synthesis by direct irradiation of amine–carboxylic acid mixtures. They involved different kinds of catalysts such as K-10 montmorillonite,[12] imidazole,[13] zeolite-HY,[14] polyphosphoric acid,[15] *p*-toluenesulfonic acid,[16] $TaCl_5$-silica gel,[17] KF–alumina and silica gel.[18] In a few cases, reactions were performed in the absence of catalyst for the synthesis of aromatic amides,[19] 2-oxazolines[20] and imides from dicarboxylic acids.[21]

This set of reactions was carried out using domestic microwave ovens, i.e. without any control of temperature and emitted power. There was no comparison provided with conventional heating (Δ) under identical conditions (medium, temperature, time, pressure) to check for possible specific purely non-thermal microwave effects. To this purpose, we have studied the synthesis of typical amides by pyrolysis of the salts obtained quasi-instantaneously from mixtures of an amine and a carboxylic acid. Reactions were performed under mechanical stirring to avoid macroscopic hot spots,[22] using a monomode reactor with focused waves[10] (Prolabo Synthewave® 402) with accurate control of power and temperature (by infrared detection or with an optical fibre) during the course of the reaction. Experiments

Keywords: amides synthesis; microwave irradiation; solvent-free reaction; polarity; pyrolysis of salts.

* Corresponding author. Tel.: +33-1-69-15-76-50; fax: +33-1-69-15-46-79; e-mail: aloupy@icmo.u-psud.fr

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00085-6

were then repeated, for sake of comparison with microwave activation, under exactly the same conditions including similar profiles of rises in temperature by conventional heating (using a thermostated oil bath).

2. Results

Experiments were carried out without catalyst (in contrast to ester aminolysis which could be realized either under neutral or basic conditions and studied elsewhere under microwave irradiation[23]) with conjugated and non-conjugated carboxylic acids and amines. The reaction temperature selected was 150°C in order to favour shifting of the equilibrium by water removal (Eq. (2)).

$$\underset{1}{RCO_2H} + \underset{2}{R'NH_2} \rightleftharpoons \underset{3}{RCONHR'} + H_2O \quad (2)$$

R=C_6H_5, $C_6H_5CH_2$, *n*-C_9H_{19};
R′=C_6H_5, *p*-$CH_3OC_6H_4$, $C_6H_5CH_2$, *n*-C_8H_{17}.

2.1. Reaction of benzylamine (2, R′=$C_6H_5CH_2$) with several carboxylic acids (Table 1)

Table 1. Reaction of benzylamine with RCO_2H at 150°C (scale: 3 mmol) under microwave activation (MW) or by conventional heating in a thermostated oil bath (△)

R	Reaction time (min)	Relative amount **1/2**	Yields[a] (%**3**)	
			MW	△
C_6H_5	30	1:1	10	10
	30	1:1.5	80	8
	30	1.5:1	75	17
$C_6H_5CH_2$	10	1:1	51	24
	30	1:1	80	63
	30	1:1.5	92	40
	30	1.5:1	93	72
n-C_9H_{19}	10	1:1	80	34
	30	1:1	85	49

[a] In isolated products.

In all cases, good to excellent yields were obtained within 30 min of microwave exposure. The excess of one or the other reagent (**1** or **2**) is highly favourable, especially in the case of benzoic acid, as it allowed for noticeable improvement in yields.

Under these conditions, very important specific purely non-thermal microwave effects were evidenced, especially in the case of benzoic acid amidation under similar conventional heating profiles of temperature increase (Fig. 1).

2.2. Reaction of the *n*-octylamine (2, R′=*n*-C_8H_{17}) (Table 2)

Table 2. Reaction of *n*-octylamine with RCO_2H at 150°C within 30 min (scale: 3 mmol) under microwave activation (MW) or classical heating (△)

R	Relative amount **1/2**	Yields[a] (%**3**)	
		MW	△
C_6H_5	1:1	3	–
	1:1.5	2	–
	1.5:1	10	–
$C_6H_5CH_2$	1:1	54	23
	1:1.5	82	41
	1.5:1	52	35
n-C_9H_{19}	1:1	63	54
	1:1.5	68	68
	1.5:1	52	46

[a] In isolated products.

Under these conditions, benzoic acid failed to react regardless of the relative amount of acid/amine used. Quite excellent yields were obtained in the two next cases but only phenylacetic acid revealed the intervention of specific microwave effects.

When considering the most favourable conditions, one can establish the following sequence for the different acid reactivities:

$$n\text{-}C_9H_{19}CO_2H \geq C_6H_5CH_2CO_2H \gg C_6H_5CO_2H$$

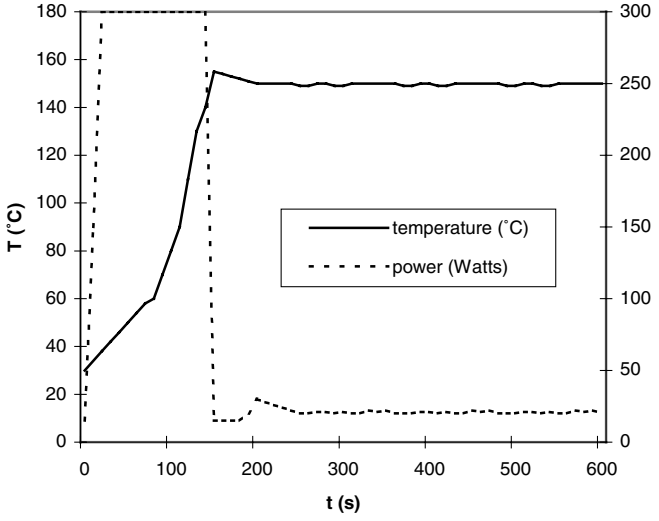


Figure 1. Profile of rise in temperature under microwave irradiation by modulation of emitted power for the reaction of benzoic acid with benzylamine (**1/2**=1:1.5).

2.3. Reaction of aniline (2, R′=C_6H_5) (Table 3)

Table 3. Reaction of aniline with RCO_2H at 150°C (scale: 3 mmol) under microwave activation (MW) or classical heating (△)

R	Reaction time (min)	Relative amount **1/2**	Yields[a] (%**3**)	
			MW	△
C_6H_5	120	1:1.5	12	–
$C_6H_5CH_2$	30	1:1	40	33
	30	1:1.5	40	41
	30	1.5:1	52	45
n-C_9H_{19}	30	1:1.5	14	–
	120	1:1	40	35
	120	1:1.5	34	30

[a] In isolated products.

Poor to moderate yields were obtained in the case of aniline. They were only slightly modified by extending reaction times or changing the amounts of reagents.

2.4. Reaction of *p*-methoxyaniline (2, R′=*p*-$CH_3OC_6H_4$) (Table 4)

Table 4. Reaction of *p*-methoxyaniline with RCO_2H at 150°C (scale: 3 mmol) under microwave activation (MW) or classical heating (△)

R	Reaction time (min)	Relative amount **1/2**	Yields[a] (%**3**)	
			MW	△
C_6H_5	30	1:1	29	18
	30	1:1.5	33	32
	30	1.5:1	28	25
$C_6H_5CH_2$	30	1:1	62	44
	30	1:1.5	68	59
	30	1.5:1	69	59
	120	1:1.5	85	74
n-C_9H_{19}	30	1:1	23	20
	30	1.5:1	34	28
	30	1:1.5	58	30
	60	1:1.5	71	33
	120	1:1.5	86	70

[a] In isolated products.

Yields were significantly enhanced due to the electron-donating effect of the methoxy group. These experiments correlated better with phenylacetic and decanoic acid experiments with evidence for some rather limited specific microwave effects.

3. Discussion

In the examples described in Tables 1–4, one can conclude that good to excellent yields of amides (except in some cases with benzoic acid) can be obtained by simple mixing of reagents under microwave irradiation with reduced reaction times (10–30 min). Significant differences in reactivities were observed according to the structures of the reagents:

Carboxylic acid : n-$C_9H_{19}CO_2H \geq C_6H_5CH_2CO_2H \gg C_6H_5CO_2H$

Amines : $C_6H_5CH_2NH_2 > n$-$C_8H_{17}NH_2 > p$-$CH_3OC_6H_4NH_2 > C_6H_5NH_2$

3.1. Mechanistic considerations

At room temperature, mixing of an amine and a carboxylic acid leads to the rapid formation of the corresponding ammonium salt by an acid–base equilibrium (Eq. (3)).

$$RCO_2H + R'NH_2 \rightleftharpoons RCO_2^-, {}^+NH_3R' \quad (3)$$

Subsequently, the pyrolysis of this salt leads to amide formation by equilibrium retrogradation and subsequent nucleophilic attack of the amine on the carbonyl group. This process needs temperatures higher than 100°C for water elimination (Eq. (4)).

$$RCO_2^-, {}^+NH_3R' \rightleftharpoons RCO_2H$$
$$+ R'NH_2 \rightarrow RCONHR' + H_2O \quad (4)$$

Different factors can be considered to justify the relative reactivities of amines and carboxylic acids:

In a first approach, amide formation could be favoured by displacement to the right of the previous equilibrium (Eq. (3)).

Table 5. pK values[24] for amines and carboxylic acid

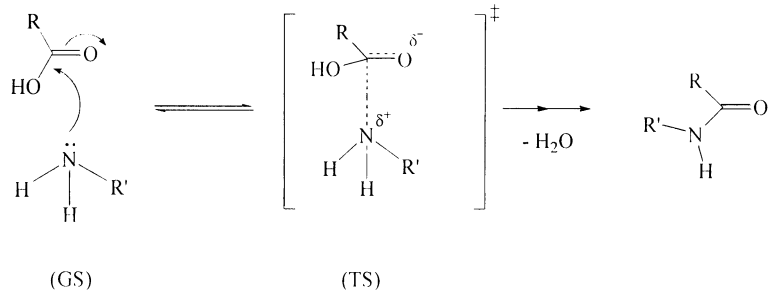
	n-$C_8H_{17}NH_2$	$C_6H_5CH_2NH_2$	p-$CH_3OC_6H_4NH_2$	$C_6H_5NH_2$
pK_b	3.35	4.67	8.66	9.40
	$C_6H_5CO_2H$	$C_6H_5CH_2CO_2H$	n-$C_9H_{19}CO_2H$	
pK_a	4.21	4.31	4.89	

From pK values for amines and carboxylic acids (Table 5), one can expect rather similar behaviours of the different carboxylic acids due to their close pK_a values and a large influence of the amine structure between aliphatic (p$K_b \approx 3$–5) and the less basic aromatic ones (8–10). As the experimental sequences (Tables 1–4) are clearly different from the ones we can expect from these predictions, this possible influence on the position of acid–base equilibrium has to be rejected.

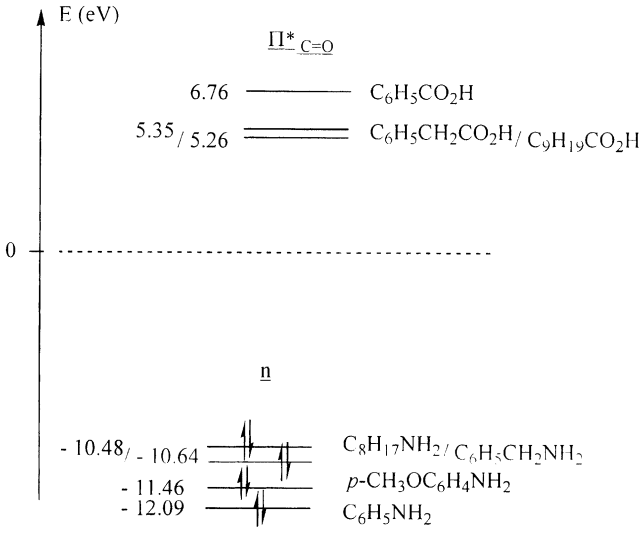
3.2. Nucleophilic attack of amine on carbonyl group (Eq. (4))

It constitutes the rate-determining step and occurs by the attack of nitrogen atom on carbonyl group of the acid (Scheme 1).

Ab initio calculations (geometry, charges and orbital levels) have allowed us the conclusion that this reaction occurs presumably under orbital control[25] as there is no connection with charge densities on N and C atoms of amine and acid, respectively. Conversely, good correlations are obtained with the relative energy levels of the molecular orbitals (MOs) involved in the electronic transfer (Scheme 2).[26] These are the occupied N-non-bonding orbital (n_N) describing the amine lone pair and the empty $\pi^*_{C=O}$ orbital on the carboxyl moiety.[27]



Scheme 1. Mechanism for nucleophilic attack of amine on carboxylic acid.



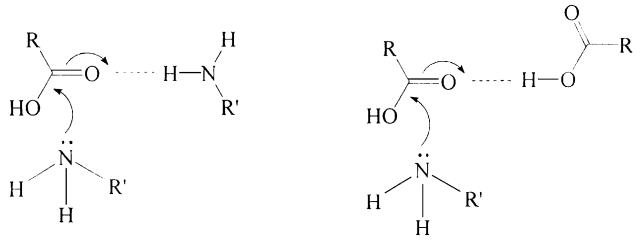
Scheme 2. Energy diagram representing the interactions between the different reactants.

The highest n_N orbitals of the amines are found for non-conjugated compounds that indeed correspond to the most reactive species. Due to conjugation with the orbitals of the phenyl ring, the n_N orbital is lowered in energy in the case of aniline which is the less reactive species. Similar trends are found in the $\pi^*_{C=O}$ series: when conjugation with the phenyl ring MOs occurs, the $\pi^*_{C=O}$ rises in energy. As a consequence, benzoic acid is predicted to be the less reactive species.

3.3. Influence of the excess of one reagent

The most striking case concerns the influence of the ratio of **1/2** for the reaction of benzoic acid with benzylamine (Table 1). Among some other possibilities, the most simple and adapted interpretation for this observation lies in the possibility of complexation by hydrogen bonding of the carbonyl group of RCO_2H with the excess of either amine or acid. This provides some explanation of its electrophilic assistance to nucleophilic attack by N atom (Scheme 3).

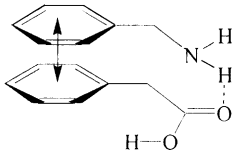
A similar observation was made by Baldwin et al.[13a] with respects to the reaction of benzylamine with benzoic acid under microwave activation. They have shown that the addition of one equivalent of imidazole induced an increase in the yields (from 13 to 61%). This secondary amine did not react with the carboxylic acid but electrophilically assisted the carbonyl group.



Scheme 3. Electrophilic assistance to nucleophilic attack by amine.

3.4. On the possibility of π-stacking

When each reagent (amine and acid) bears an aromatic ring in adequate relative position to give possible π–π interactions at distances 3–4 Å, π-stacking can be involved.[28] They are shown to play an important role especially under solvent-free conditions[29,30] where they can be developed with their optimal magnitude as restrictions imposed by solvent–substrate interactions are minimal (Scheme 4).



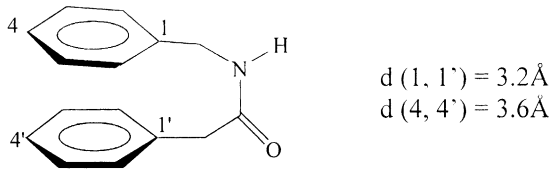
Scheme 4. Approach showing an optimal magnitude of π–π interactions.

This may be the case of two benzylic reagents, i.e. benzylamine and phenylacetic acid (Scheme 4). This phenomenon allows for a stabilization of the transition state (TS) of the reaction thus leading to a decrease in activation energy and therefore enhancement in yields.

To support the possibility of π-stacking, molecular modelling calculations (MP3 type which is the most adapted method to describe hydrogen bonding and the interactions between non-bonding atoms—Hyperchem program) were done on *N*-benzylbenzamide. The most stable form is the one where overlapping between π systems is involved (Scheme 5).

3.5. Interpretation of specific microwave effects

Very important specific non-thermal microwave effects are evidenced in the majority of the reactions concerned. They seem to be increasingly important in the case of sluggish reactions. For instance, they allow for an improvement in



Scheme 5. Optimized geometry for *N*-benzylphenylacetamide.

yields from 8–17% (conventional heating) to 75–80% (microwave activation) in the reaction of benzoic acid and benzylamine.

It is evident that the effect lies in the enhancement by microwave radiation of nucleophilic attack by the nitrogen atom on the carbonyl group (the rate-determining step) as the temperature (150°C) allows for a water removal regardless the mode of activation.

These effects can be easily understood by considering the possible microwave activation affects by dipole–dipole interactions according to mechanistic considerations and to an increase of the polarity of the system during the progress of the reaction[31] (Scheme 1).

It is well established that microwave–materials interactions are increased with the polarity of the materials.[32] As the TS is consequently more polar than the ground state (GS), its stabilization is more affected (by dipole–dipole interactions with the electromagnetic field), thus resulting in a decrease in activation energy (Scheme 6).

It is important here to state that the preliminary formation of ammonium salts be considered of prime interest as it generates polar species prone to interact strongly with microwave radiation which induces a noticeable rise in temperature (Scheme 7).

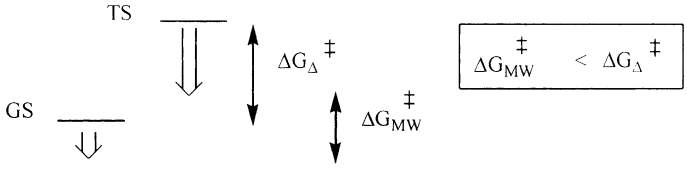
The profiles of the elevation in temperature obtained under microwave irradiation are representative of the polarity of the reactants as they interact strongly with the electromagnetic field. The amine and the carboxylic acid interact weakly with microwave radiation, as the temperatures obtained, after 30 min of microwave exposure, are 125 and 80°C, respectively. On the other hand, there is a significant enhancement in the polarity with the liquid ammonium carboxylate and amide, i.e. when above their melting point (175 and 122°C, respectively).

The increase in the polarity of the system provided by the ammonium carboxylate thus strongly favours to the reaction as well as the formation of polar amide during the course of the reaction.

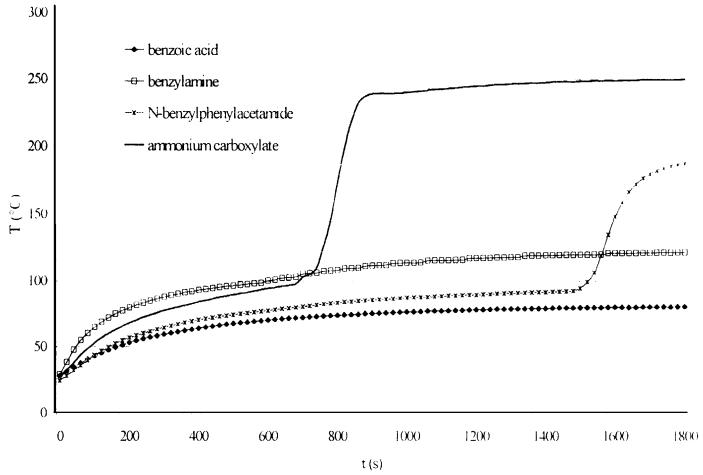
Some measurements of dielectric characteristics (ε' and ε'') are in progress to support these hypotheses.

4. Conclusion

Pyrolysis of salts obtained by mixing neat primary amines and carboxylic acids were, in a great majority of cases, realized under solvent-free conditions within short times and appreciable yields with microwave activation. The evident specific non-thermal microwave effects are attributed to enhancements in microwave–materials interaction due to polarity increase during the progress of the reaction. Further experiments including dielectric character-



Scheme 6. Relative stabilizations of a more polar TS when compared to GS (polar mechanism).



Scheme 7. Profile of rise in temperature of the different reactants for the reaction of benzylamine with benzoic acid when submitted to microwaves (emitted power=300 W).

istics measurements and theoretical approaches are under progress.

5. Experimental

5.1. Theoretical calculations

Ab initio calculations were performed at the RHF level using the Gaussian set of programs.[33] The polarized split-valence basis set 6-31G(d) was used throughout. Geometries of amines and acids were fully optimized. Characterizations of the optimized extrema were performed by frequencies calculations.

5.2. Reactants and equipment

The microwave reactor was a monomode system (Synthewave® 402 from Prolabo) with focused waves operating at 2.45 GHz. The temperature was controlled throughout the reaction and evaluated by an infrared detector which indicated the surface temperature (the IR probe was calibrated by tuning the emissivity factor using a thermo-couple introduced into the reaction mixture). Temperature was maintained constant at a chosen value by modulation of emitted MW power (Fig. 1). Mechanical stirring during the irradiation period provided good homogeneity (power and temperature). Data gathering and treatment was performed by a computer. All reactions were performed in cylindrical Pyrex open vessels.

In order to compare microwave irradiation with conventional heating, the reactions were performed under similar experimental conditions (weight of reactants, time and temperature) using a thermostated oil bath. The temperature was measured by the insertion of a Quick digital thermometer into the reaction mixture and the rate of the temperature rise was adjusted to be the same as to that measured under microwave irradiation.

^{1}H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, and at 250 and 62.5 MHz (Brüker WP 200, WP 250, respectively). Chemical shifts are given in ppm downfield from internal standard tetramethylsilane (δ=0.00 ppm).

5.3. General procedure for the synthesis of amides

Synthesis of amides was performed under microwave irradiation or conventional heating. In a Pyrex cylindrical open reactor adapted to the Synthewave reactor, 3 mmol of amine were mixed with 3 mmol of carboxylic acid. The mixture was then homogenized and subjected to microwave irradiation with mechanical stirring. At the end of irradiation, the reaction mixture was cooled to room temperature and extracted with chloroform. The extracts were washed successively with a solution of 2 M HCl (50 mL) and a solution of 5% $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified by simple washing with pentane.

5.3.1. *N*-Benzylbenzamide. (**3**, R=C_6H_5, R′=$C_6H_5CH_2$): mp=105–107°C (lit.[34] mp=105°C); ^{1}H NMR (250 MHz, $CDCl_3$):[3] δ 4.65 (s, 2H), 6.40 (br s, 1H), 7.40 (m, 8H), 7.80 (d, 2H, J=8.0 Hz).

5.3.2. *N*-Benzylphenylacetamide. (**3**, R=$C_6H_5CH_2$, R′=$C_6H_5CH_2$): mp=118–120°C (lit.[35] mp=118–119°C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.46 (s, 2H), 4.25 (s, 2H), 7.27 (m, 10H), 8.60 (br s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 43.48, 43.64, 127.19, 127.27, 127.39, 128.52, 128.86, 129.29, 134.89, 138.19, 170.62.

5.3.3. *N*-Benzyldecanamide. (**3**, R=C_9H_{19}, R′=$C_6H_5CH_2$): mp=60–62°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H, J=3.4 Hz), 1.24 (m, 12H), 1.65 (m, 2H), 2.20 (t, 2H, J=3.9 Hz), 4.43 (d, 2H, J=2.8 Hz), 5.60 (br s, 1H), 7.30 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.0, 22.59, 25.74, 29.29, 29.38, 31.80, 36.72, 43.52, 127.36, 127.72, 128.60, 173.01. HRMS: calcd 261.41, found 261.21.

5.3.4. *N*-Octylbenzamide.[36] (**3**, R=C_6H_5, R′=C_8H_{17}): mp=39–41°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.9 (t, 3H, J=6.6 Hz), 1.35 (m, 10H), 1.60 (m, 2H), 3.40 (t, 1H, J=6.4 Hz), 3.45 (t, 1H, J=6.6 Hz), 6.05 (br s, 1H), 7.45 (m, 3H), 7.75 (d, 2H, J=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.90, 22.48, 28.91, 29.07, 29.17, 29.55, 31.66, 40.04, 126.92, 128.26, 131.06, 134.81, 167.51.

5.3.5. *N*-Octylphenylacetamide. (**3**, R=$C_6H_5CH_2$, R′=C_8H_{17}): mp=61–64°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.85 (t, 3H, J=6.6 Hz), 1.10–1.50 (m, 10H), 1.45 (m, 2H), 3.10 (t, 1H, J=6.3 Hz), 3.15 (t, 1H, J=6.7 Hz), 3.55 (s, 2H), 5.03 (br s, 1H), 7.30 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 13.79, 22.26, 25.36, 31.37, 36.45, 43.27, 127.15, 127.53, 128.43, 134.56, 173.16; HRMS: calcd 247.38, found 247.19.

5.3.6. *N*-Octyldecanamide. (**3**, R=C_9H_{19}, R′=C_8H_{17}): mp=63–64°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 6H, J=6.6 Hz), 1.25 (m, 22H), 1.45–1.65 (m, 4H), 2.15 (t, 2H, J=7.5 Hz), 3.20 (t, 1H, J=6.3 Hz), 3.25 (t, 1H, J=6.5 Hz), 7.40 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.78, 22.40, 25.77, 26.81, 29.16, 31.60, 36.46, 39.27, 173.28.

5.3.7. *N*-Phenylbenzamide.[3] (**3**, R=C_6H_5, R′=C_6H_5): commercial compound.

5.3.8. *N*-Phenylphenylacetamide. (**3**, R=$C_6H_5CH_2$, R′=C_6H_5): mp=117–119°C (lit.[37] mp=117–118°C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.65 (s, 2H), 7.05–7.35 (m, 10H).

5.3.9. *N*-Phenyldecanamide. (**3**, R=C_9H_{19}, R′=C_6H_5): mp=65–66°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.85 (t, 3H, J=6.4 Hz), 1.25 (m, 12H), 1.72 (m, 2H), 2.35 (t, 2H, J=7.5 Hz), 7.10 (t, 2H, J=7.8 Hz), 7.30 (t, 1H, J=7.8 Hz), 7.50 (t, 2H, J=7.9 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 14.03, 22.56, 25.68, 29.22, 29.35, 31.78, 37.62, 120.00, 124.03, 128.77, 138.06, 172.03; HRMS: calcd 247.38, found 247.19.

5.3.10. *N*-(*p*-Methoxyphenyl)benzamide. (**3**, R=C_6H_5, R′=*p*-$CH_3OC_6H_4$): mp=162–163°C, ^{1}H NMR (200 MHz, DMSO): δ 3.75 (s, 3H), 6.95 (d, 2H, J=8.9 Hz), 7.50 (m,

3H), 7.70 (d, 2H, J=8.9 Hz), 7.95 (d, 2H, J=8.0 Hz), 10.15 (br s, 1H); ^{13}C NMR (50 MHz, DMSO): δ 55.13, 113.71, 122.00, 127.55, 128.32, 131.35, 132.34, 135.07, 155.55, 165.13; Anal. calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16; O, 14.08. Found: C, 73.47; H, 5.78; N, 6.04; O, 14.01.

5.3.11. *N*-(*p*-Methoxyphenyl)phenylacetamide. (**3**, R=$C_6H_5CH_2$, R′=*p*-$CH_3OC_6H_4$): mp=124–125°C, ^{1}H NMR (200 MHz, DMSO): δ 3.70 (s, 5H), 6.90 (d, 2H, J=8.9 Hz), 7.35 (m, 5H), 7.65 (d, 2H, J=8.9 Hz), 10.15 (br s, 1H); ^{13}C NMR (50 MHz, DMSO): δ 43.38, 55.02, 113.81, 120.86, 126.48, 128.27, 129.12, 132.47, 136.23, 155.32, 168.74; HRMS: calcd 241.29, found 241.11.

5.3.12. *N*-(*p*-Methoxyphenyl)decanamide. (**3**, R=C_9H_{19}, R′=*p*-$CH_3OC_6H_4$): mp=102–103°C, ^{1}H NMR (200 MHz, DMSO): δ 0.85 (m, 3H), 1.25 (m, 12H), 1.70 (m, 2H), 2.30 (t, 2H, J=7.5 Hz), 3.80 (s, 3H), 6.75 (d, 2H, J=8.8 Hz), 7.40 (d, 2H, J=8.8 Hz), 8.35 (br s, 1H); ^{13}C NMR (50 MHz, DMSO): δ 13.96, 22.52, 25.73, 29.21, 29.34, 31.73, 37.25, 55.21, 113.74, 121.94, 131.26, 156.04, 171.99; HRMS: calcd 277.41, found 277.20.

5.3.13. *N*-Phenethylbenzamide. (**3**, R=$C_6H_5CH_2$, R′=$C_6H_5CH_2CH_2$): mp=94–96°C, ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.70 (t, 2H, J=6.9 Hz), 3.40 (t, 1H, J=6.8 Hz), 3.45 (t, 1H, J=6.9 Hz), 3.50 (s, 2H), 6.00 (br s, 1H), 7.05 (d, 2H, J=7.7 Hz), 7.25 (m, 8H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 35.17, 40.50, 43.37, 126.10, 126.89, 128.26, 128.43, 128.59, 129.08, 134.73, 138.51, 170.85; HRMS: calcd 239.31, found 239.13.

5.3.14. *N*-Benzylhydrocinnamide. (**3**, R=$C_6H_5CH_2CH_2$, R′=$C_6H_5CH_2$): mp=84–86°C, ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50 (t, 2H, J=7.7 Hz), 2.95 (t, 2H, J=7.6 Hz), 4.30 (d, 2H, J=5.7 Hz), 5.60 (br s, 1H), 7.25 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 31.41, 37.77, 42.50, 125.88, 126.93, 127.23, 128.09, 128.21, 140.55, 172.08; Anal. calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85; O, 6.69. Found: C, 79.81; H, 7.15; N, 5.98; O, 6.89.

5.3.15. *N*-Phenethylhydrocinnamide. (**3**, R=$C_6H_5CH_2CH_2$, R′=$C_6H_5CH_2CH_2$): mp=98–100°C, ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.45 (t, 2H, J=6.6 Hz), 2.70 (t, 2H, J=6.7 Hz), 2.95 (t, 2H, J=6.6 Hz), 3.40 (t, 1H, J=6.6 Hz), 3.45 (t, 1H, J=6.7 Hz), 5.30 (br s, 1H), 7.05 (m, 2H), 7.20 (m, 8H); Anal. calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53; O, 6.32. Found: C, 80.48; H, 7.57; N, 5.59; O, 6.51.

Acknowledgements

We sincerely thank 'Electricité de France' (E.D.F.), Research and Development Division—77818 Moret sur Loing Cedex—(France) and especially Dr Michel MONEUSE and Dr Karine BURLE for their appreciated financial and scientific support.

References

1. Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Winterfeld, E., Ed.; Pergamon: Oxford, 1991; Vol. 6.
2. Sheehan, J. C.; Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067.
3. Lawrence, R. H.; Biller, S. A.; Fryszman, O. M.; Poss, M. A. *Synthesis* **1997**, 553.
4. Burnell-Curty, C.; Roskamp, E. J. *Tetrahedron Lett.* **1993**, *34*, 5193.
5. Froyen, P. *Synth. Commun.* **1995**, *25*, 959.
6. Jang, D. O.; Park, D. J.; Kim, J. *Tetrahedron Lett.* **1999**, *40*, 5323.
7. Jursic, B. S.; Zdravkovski, Z. *Synth. Commun.* **1993**, *23*, 2761.
8. Abramovich, R. *Org. Prep. Proced. Int.* **1991**, *23*, 683.
9. Caddick, S. *Tetrahedron* **1995**, *51*, 10403.
10. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213.
11. Varma, R. S. *Green Chem.* **1999**, *1*, 43.
12. Ruault, P.; Pilard, J. F.; Touaux, B.; Texier-Boullet, F.; Hamelin, J. *Synlett* **1994**, 935.
13. (a) Baldwin, B. W.; Hirose, T.; Wang, Z. H. *J. Chem. Soc., Chem. Commun.* **1996**, 2669. (b) Hirose, T.; Baldwin, B. W.; Wang, Z. H. *Jpn. Kokai Tokkyo Koho* **1998**, 10036294 *Chem. Abstr.*, **1998**, *128*, 180333.
14. Gadhwal, S.; Prakash Dutta, M.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Indian J. Chem.* **1998**, *37B*, 725.
15. El'Tsov, A. V.; Martynova, V. P.; Sokolova, N. B.; Dmitrieva, N. N.; Brykov, A. S. *Russ. J. Gen. Chem.* **1995**, *65*, 454.
16. Hajipour, A. R.; Ghasemi, M. *Indian J. Chem. (B)* **2001**, *40*, 504.
17. Chandrasekhar, S.; Takhi, M.; Uma, G. *Tetrahedron Lett.* **1997**, *38*, 8089.
18. Marquez, H.; Plutin, A.; Rodriguez, Y.; Perez, E.; Loupy, A. *Synth. Commun.* **2000**, *30*, 1067.
19. Vasquez-Tato, M. P. *Synlett* **1993**, 506.
20. Marrero-Terrero, A. L.; Loupy, A. *Synlett* **1996**, 245.
21. Seijas, J. A.; Vasquez-Tato, M. P.; Montserrat Martinez, M.; Nunez-Corredoira, G. *J. Chem. Res. (S)* **1999**, 420.
22. (a) Stuerga, D.; Gaillard, P. *Tetrahedron* **1996**, *52*, 5505. (b) Stuerga, D.; Gaillard, P. *J. Microwave Power Electrom. Energy* **1996**, *31*, 87.
23. Loupy, A.; Perreux, L. Unpublished results.
24. Howard, P. H.; Meylan, W. M. In *Handbook of Physical Properties of Organic Chemicals*; Lewis, E., Ed.; CRC: New York, 1997.
25. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976; pp 5–32.
26. To simplify the calculations, we modelled methylamine and acetic acid for octylamine and decanoic acid, respectively (a long chain does not modify the results).
27. These orbitals may not be the frontier orbitals strictly speaking: for instance, the LUMO in phenylacetic acid is a molecular orbital located on the phenyl ring as the HOMO in the case of the benzylamine.
28. Jones, G. B.; Chapmann, B. J. *Synthesis* **1995**, 475.
29. Loupy, A.; Zaparucha, A. *Tetrahedron Lett.* **1993**, *30*, 333.
30. Diez-Barra, E.; de la Hoz, A.; Merino, S.; Sanchez-Verdu, P. *Tetrahedron Lett.* **1997**, *38*, 2359.
31. Loupy, A.; Perreux, L.; Liagre, M.; Burle, K.; Moneuse, M. *Pure Appl. Chem.* **2001**, *73*, 161.
32. Gedye, R. N.; Smith, F. E.; Westaway, K. C. *Can. J. Chem.* **1998**, *66*, 17.
33. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.;

Ochtersky, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liaschenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S; Pople, J. A. Gaussian 98, Revision A.1, Gaussian, Inc., Pittsburgh, PA, 1998.

34. Trapani, G.; Reho, A.; Latrofa, A. *Synthesis* **1983**, 1013.
35. Cossy, J.; Pale-Grosdemange, C. *Tetrahedron Lett.* **1989**, *30*, 2771.
36. Ishii, Y.; Takeno, M.; Kawasaki, Y.; Muromachi, A.; Nishiyama, Y.; Sakaguchi, S. *J. Org. Chem.* **1996**, *61*, 3088.
37. Mestres, R.; Palomo, C. *Synthesis* **1982**, *4*, 288.