'Dry' Hydrolysis of Nitriles Effected by Microwave Heating

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The preparation of carboxylic acids from their corresponding nitriles by a 'dry hydrolysis' with dicarboxylic acids, in the absence of solvent, has been investigated. The reaction proceeds very slowly at atmospheric pressure, but high yields can be obtained in much shorter reaction times under pressure. The mechanism of the reaction has been studied and its rate constant and activation energy determined in the case of a model reaction (preparation of phenylacetic acid from benzyl cyanide with phthalic acid) under both microwave and conventional heating. No 'microwave kinetic effect' has been detected, but at high temperatures microwave heating gives better yields and selectivities.

Within the past 15 years, there has been a growing interest in new reaction conditions and activation: 'dry conditions' (reactions without solvent),[1] reactions under extreme or non-classical conditions (high pressure,[2] ultrasound[3] or microwave activation[4]). The effects usually expected are rate enhancements, yield or selectivity improvement, easier work-up or less polluting processes.

In the course of our current interest in organic synthesis under microwave irradiation, we felt that the 'dry hydrolysis' of nitriles to carboxylic acids,[5] could be a good candidate as a model reaction, in order to determine whether microwave heating results in some kind of molecular activation. This reaction (Scheme 1) which consists of heating a mixture of nitrile and phthalic acid (or substituted analogues) without solvent, involves polar compounds and reaction intermediates, and should therefore be very sensitive to microwave heating.

Another possible interest in this reaction lies in the rather mild acidic conditions, compared with the usual conditions for nitrile hydrolysis which require prolonged heating in a strongly acidic (concentrated sulfuric acid) or basic medium.[6–9]

In this paper we describe the reaction mechanism and kinetics using phthalic acid and phenylacetonitrile as a model system, before a study of the microwave version of the process is given.

Results and Discussion

In a standard procedure (see the Experimental section) the nitrile is simply heated with phthalic acid (20% excess) in the absence of solvent ('dry conditions').

Reaction Mechanism.—A kinetic study (*vide infra*), together with a GLC–MS (gas chromatography with a mass spectrometer detector) investigation of the crude reaction mixture at different reaction times, allowed the reaction pathway illustrated in Scheme 1 to be established.

The intermediate compounds **3** and **4**, respectively the amide corresponding to the starting nitrile and phthalic anhydride, as well as the reaction intermediates **I**, **II** and the expected compounds, carboxylic acid **5** and phthalimide **6**, have been identified by the GLC–MS technique.

The first step is probably protonation of the nitrile, as suggested by the influence of the acid pK_a (*vide infra*), followed by a nucleophilic attack giving the identified intermediate **I**.

An internal proton shift and substitution give anhydride **4** and the intermediate amide **3**. Reaction of **3** with **4** by a similar pathway gives **II**, whose hydrolysis with the water generated gives the expected acid **5** and phthalimide.

Furthermore, heating **3** with **4** under the reaction conditions,
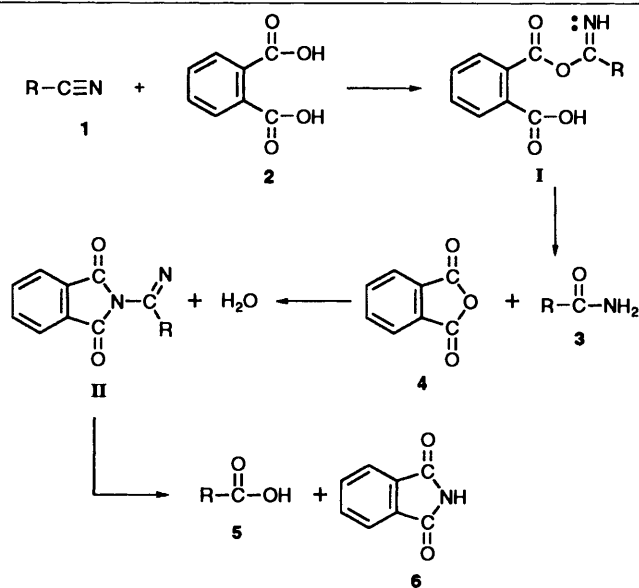
Scheme 1   Reaction mechanism

in the presence of a catalytic amount of phthalic acid, gives **5**. This clearly shows that **3** is the actual reaction intermediate, in contrast with Gribble's suggestion,[5b,c] who considered amide **3** to be a side product.

Influence of Temperature and Pressure.—In previous studies,[5] the reaction was carried out by heating the nitrile–phthalic acid mixture under reflux at atmospheric pressure. But the reaction was desperately slow, and several days were needed to obtain significant conversion yields, most probably due to the vaporisation of the nitrile. We therefore carried out the reaction in a closed vessel, under pressure. In Fig. 1 the yields and selectivity for our model reaction are compared, after a 1 h reaction time, under atmospheric pressure [curves (c),(d)] or under 4 atm [curves (a),(b)]. The temperature was varied in the range 140–320 °C. The selectivity represents the acid:acid + amide (5:5 + 3) ratio.

It appears that optimal yields and selectivity are obtained under pressure at a temperature of around 250 °C. Beyond this temperature product degradation is observed.

Kinetic Study.—In order to gain further insight into this reaction, kinetic studies have been carried out, under carefully monitored reaction conditions, at different temperatures, keep-
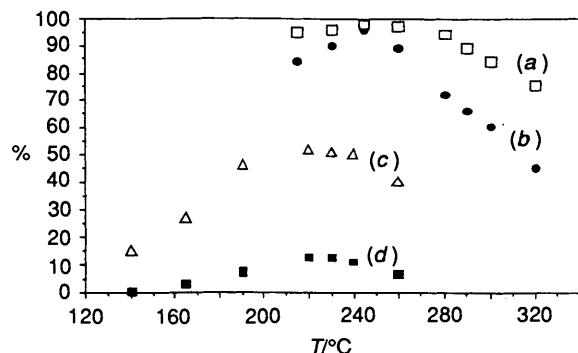
Fig. 1 Temperature and pressure effects on hydrolysis of phenylacetonitrile by phthalic acid: open symbols ($\square$,$\triangle$) = selectivity; filled symbols ($\bullet$,$\blacksquare$) = chemical yield; (a), (b): P 4 atm; (c), (d): P 1 atm
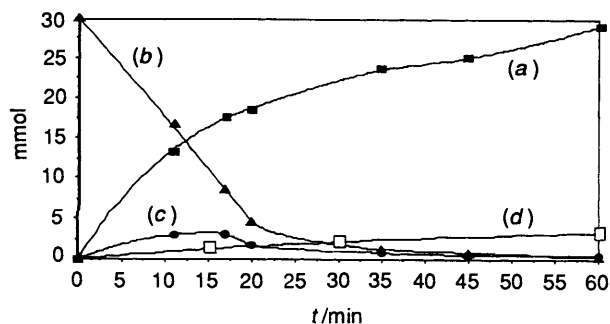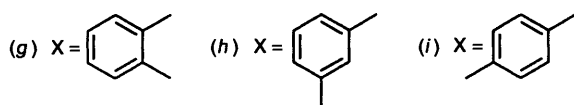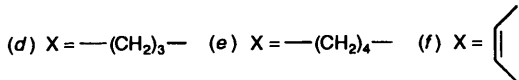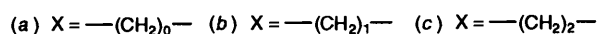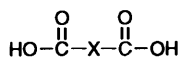

Fig. 2 Kinetics of the reaction of phenylacetonitrile with phthalic acid at 245 °C: (a) phenylacetic acid; P 4 atm; (b) phenylacetonitrile; P 4 atm; (c) phenylacetamide; P 4 atm; (d) phenylacetic acid; P 1 atm. Initial amount of phenylacetonitrile: 30 mmol.
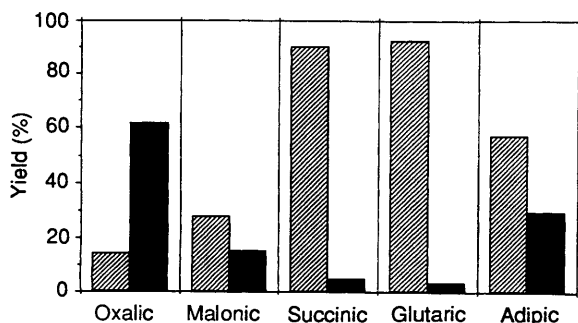

Scheme 2

Fig. 3 Hydrolysis of phenylacetonitrile by aliphatic diacids; ▨ phenylacetic acid; ■ phenylacetamide

ing the pressure constant at 4 atm. An example is illustrated in Fig. 2. In this figure, we also give the carboxylic acid yield under atmospheric pressure [curve (d)].

It can be seen that the amide concentration, always low, passes through a smooth maximum, after ca. 15 min, then decreases. This observation is consistent with a two step path-
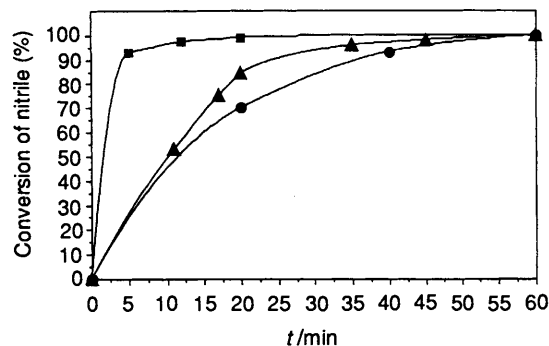

Fig. 4 Hydrolysis of phenylacetonitrile (T 240 °C; P 4 atm) with maleic (■); phthalic (▲) and succinic (●) acids

way, with the amide as an intermediate, similar to conventional nitrile hydrolysis under acidic conditions. Since the amount of amide remains very low, it seems likely that the first step is rate determining.

In fact, within experimental error, our results fit nicely with the second order kinetic eqn. (1).

$$-\text{d}[1]/\text{d}t = k_1[1]^1[2]^1 \qquad (1)$$

By varying the temperature in the 220–245 °C range, the activation energy determined using the Arrhenius equation is $E_a = 8.49 \times 10^3$ J mol^{-1}, and the preexponential constant is $\ln A(4\text{ atm}) = 9.1$.

Influence of the Nature of the Diacid.—In order to increase the reaction rates, Gribble *et al.* used halogenated derivatives of phthalic acid, and showed that the reaction proceeds much faster with the tetrachloro or tetrafluoro analogue.[5b,c] However, these reagents are much more expensive, and useless on an industrial scale.

Although phthalic acid is a very cheap reagent, we tested some other carboxylic diacids: (a) oxalic, (b) malonic, (c) succinic, (d) glutaric, (e) adipic, (f) maleic, (g) phthalic, (h) isophthalic and (i) terephthalic. This is illustrated in Scheme 2, and the results are reported in Table 1.

In the aromatic series, iso- and tere-phthalic acids, which cannot cyclise to the anhydride or imide, give much poorer yields, selectivity, and overall conversion. With aliphatic diacids results are somewhat more complex and are further illustrated in Fig. 3, where amide yields, not given in Table 1 are compared with the carboxylic acid yields.

With oxalic acid, the amide yield (60%) and overall conversion (84%) are good, but selectivity and phenylacetic acid yield are low. Malonic acid is unsatisfactory. Much better results are obtained with succinic and glutaric acids; with adipic acid selectivity decreases dramatically although overall conversion remains very high (90%).

In fact, the reaction rate (or overall conversion) and selectivity are two different problems. Selectivity is high when the diacid can form a cyclic five- or six-membered ring anhydride or amide; this is the case with phthalic, succinic and glutaric acids. Due to entropy (with adipic acid), or bond strain (with oxalic and malonic acids), the formation of the cyclic intermediate II is much less favoured, and the 3:5 (amide:acid) ratio increases. In these cases, formation of II should be rate determining. On the other hand, the reaction rate depends on the first acidity constant: kinetic studies clearly show that the reaction rate increases with K_a (values are given in Table 1), as illustrated in Fig. 4.

Maleic, phthalic and succinic acids give similar results in terms of yields and selectivity, however, it can be seen that the reaction rate is much higher with maleic acid, whose K_a value is

**Table 1** 'Dry' hydrolysis of phenylacetonitrile by carboxylic diacids (T 240 °C, P 4 atm, reaction time 1 h)

Diacid	M.p. (°C)	Acidity ($\times 10^5$)		P = 1 atm		P = 4–5 atm	
		K_1	K_2	Yield	Selectivity	Yield	Selectivity
(a) Oxalic	189	5400	5.2	1.5	15	14	18
(b) Malonic	136	140	0.20	4	42	27	65
(c) Succinic	185	6.4	0.23	10	55	90	95
(d) Glutaric	98	4.5	0.38	12	53	92	96
(e) Adipic	151	3.7	0.39	9.3	42	57	66
(f) Maleic	130.5	1000	0.055	1.7	25	79	80
(g) Phthalic	231	110	0.4	11	50	96	98
(h) Isophthalic	348.5	24	2.5	2	28	16	75
(i) Terephthalic	300 (subl.)	29	3.5	1	23	12	70
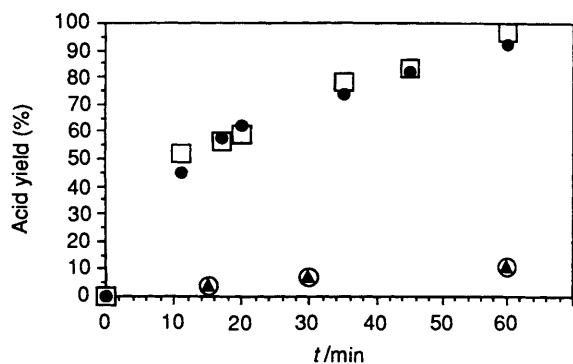
Fig. 5 Kinetics of the 'dry' hydrolysis of phenylacetonitrile at 245 °C; ($\square$) P 4 atm, conventional heating; ($\bullet$) P 4 atm, microwave heating; ($\bigcirc$) P 1 atm, conventional heating; ($\blacktriangle$) 1 atm, microwave heating
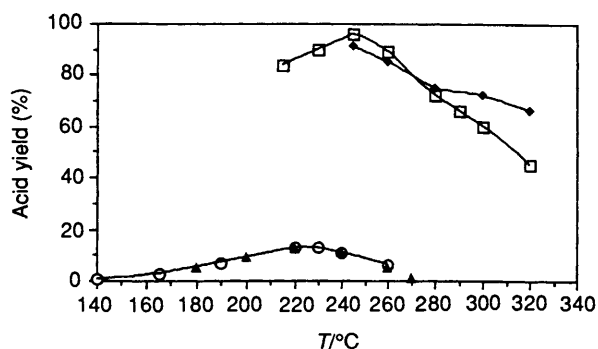
Fig. 6 Influence of the nature of heating on hydrolysis of phenyl-acetonitrile by phthalic acid; ($\square$) P 4 atm, conventional heating; ($\blacklozenge$) P 4 atm, microwave heating; ($\bigcirc$) P 1 atm, conventional heating; ($\blacktriangle$) P 1 atm, microwave heating

Table 2 Second order rate constants for the hydrolysis of phenyl-acetonitrile by phthalic acid under pressure (P 4 atm)

T/°C	Microwave $k_1/10^{-5}$ s^{-1} mol^{-1}	Conventional $k_1/10^{-5}$ s^{-1} mol^{-1}
215	5.9	5.8
230	7.2	7.5
245	10.2	10.4

respectively two and one order of magnitude higher than that of succinic and phthalic acids. Accurate comparisons with oxalic or malonic acids could not be made, due to competitive partial decomposition of these acids.

Application of Microwave Heating to the Process.—The current development of microwave chemistry[4,10-15] lead us to explore this non-conventional heating to the reaction under study. The purpose was not only to try to improve the above
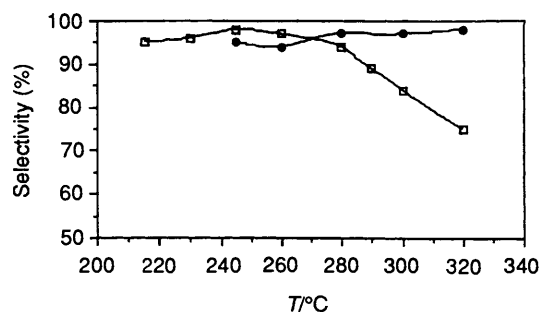
Fig. 7 Selectivity at P 4 atm; ($\square$) conventional heating; ($\bullet$) microwave heating

results, but also to provide some new data on several controversial points, among these the effectiveness of the non-classical effect.[16-18]

There is a fundamental difference between microwave and conventional heating: conventional heating is an inward heat transfer (from the heating device, *e.g.* the walls of the reactor for jacketed tanks, to the medium); in microwave heating, thermal energy is generated *in situ* due to the interaction of polar molecules or ionic species with the electric field.[4,19] It is a mass heating, and heat transfer occurs from the medium to the outside of the reactor, an outward transfer.

'Reversed heat transfer' could result in abnormal effects, through the generation of 'hot spots' in the reaction mixture, which could account for rate enhancements. This could be named 'false microwave activation'. This is probably what has been observed in most cases, especially in heterogeneous reaction mixtures.[20,21] The question of what could be named, in contrast, 'true microwave activation', that is true molecular activation still remains open.

Comparative Kinetic Studies between Conventional and Microwave Heating.—The kinetic study described before was repeated for the microwave reaction, which follows the same second order law. Comparative kinetics are illustrated in Fig. 5, for two different reaction conditions: at atmospheric pressure and under 4 atm. In both cases the reaction temperature was kept at 245 °C.

Rate constants, under 4 atm pressure, determined at three different temperatures, in the range 215–245 °C are given in Table 2. Using the Arrhenius equation, the activation energy was determined for both microwave and conventional heating: E_a(microwave) 8 ± 0.5 kJ mol^{-1}, E_a(conv. heat) 8.5 ± 0.5 kJ mol^{-1}; ln A(microwave) 9 ± 1, ln A(conv. heat) 9 ± 1.

It can be seen that there is no significant kinetic microwave effect: within experimental error, kinetic constants and activation energy are the same under conventional heating. But a careful mass balance of the reaction products shows that microwave heating can be of interest, as is shown below.

Table 3 'Dry' hydrolysis of nitriles 1 with phthalic acid (T 240 °C; P 4 atm; reaction time 1 h)

Entry	R	B.p. (°C)	Yield (%) Conventional	Yield (%) Microwave	Selectivity (%) Conventional	Selectivity (%) Microwave
1	$PhCH_2$	233	96	91	98	95
2	Ph	191	71	73	100	98
3	C_4H_9	141	91	89	95	93
4	$(C_3H_7)_2CH$	183	74	73	96	94
5	p-HOPh	—	70	70	85	84
6	ClC_2H_4	174	72	71	89	88
7	HOC_2H_4	228	65	64	80	78
8	$C_2H_5O(O)CCH_2$	208	7–10	7–10	—	—
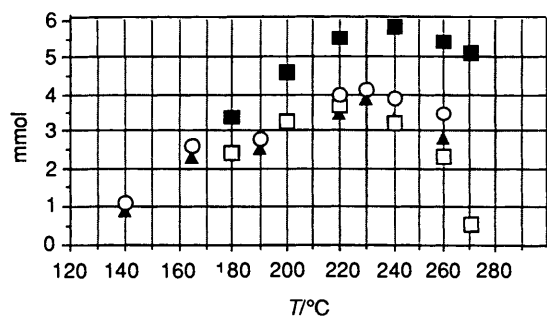
Fig. 8 Aryl amide:phthalic anhydride ratio; (■) anhydride, microwave heating; (○) anhydride, conventional heating; (▲) amide, conventional heating; (□) amide, microwave heating

Influence of the Nature of Heating on Reaction Yield and Selectivity.—For comparison with the results obtained under classical heating, the yields and selectivity were determined for the microwave process under otherwise identical conditions (Figs. 6 and 7). Under atmospheric pressure the reaction is too slow, and no difference could be detected within experimental error.

For a higher pressure, optimum yield and selectivity are observed at about 245 °C. Below this optimum, no significant difference is observed between microwave and conventional heating, within experimental error. But at higher temperatures much better results are clearly obtained with microwave heating: the carboxylic acid yield decreases less rapidly than under conventional heating; the selectivity remains almost constant under microwave irradiation, while it decreases dramatically with conventional heating. At the same time, total product recovery decreases much more rapidly with conventional heating. All these observations are consistent with a faster degradation of the carboxylic acid than the corresponding amide, probably *via* a decarboxylation process.

The nature of the heat transfer probably accounts for these striking differences. With conventional heating, heat transfer occurs from the outside to the reacting mixture, through the walls of the reactor. As a consequence, overheating of the walls is needed in order to maintain a constant bulk temperature, and this probably results in faster decarboxylation. In contrast, due to the mass heating effect of microwaves, no overheating of the walls of the reactor is needed to maintain the reaction mixture at the required temperature.

Scope of the Reaction: Hydrolysis of Substituted Nitriles.—The generally drastic conditions of nitrile hydrolysis lead to severe drawbacks with compounds containing sensitive functional groups. The method described here was tested as a possible alternative. In Table 3 the results obtained with a series of bifunctional compounds are displayed. Fairly good yields and selectivities are obtained simply by using the reaction conditions optimised for phenylacetonitrile. No reaction side

product was detected, except for ethyl cyanoacetate (entry 8). In this case, competitive hydrolysis of the ester group, and some decarboxylation reaction occur; malonic acid and acetonitrile have been identified as reaction side products.

In every case, the yields are identical, within experimental error, under conventional or microwave heating. It might have been expected that the presence of a polar functional group would give some kind of 'antenna group effect'.[13] This is not actually the case. However, these results clearly show that even at a relatively high temperature this method can be used to hydrolyse some nitriles bearing other functional groups.

Conclusions

'Dry hydrolysis' of nitriles with phthalic acid can be an interesting alternative route to carboxylic acids. The reaction requires only a moderate pressure of a few atm to prevent nitrile evaporation, and allows the presence of some functional groups thanks to rather mild acidic conditions. Indeed, in order to reduce reaction times, rather high temperatures are required, and this parameter should be optimised in each particular case.

Phthalic acid is a very cheap industrial reagent, and furthermore the generated phthalimide can easily be separated and recycled.[22] Work-up and purification of the expected acid are very easy, and an industrial process could be designed.

The question of a specific non-thermal activation by microwaves has been addressed during the past decade. In the case of the title reaction, the answer is clearly no. This is consistent with the low energy level of the microwave quantum.[19,23] The microwave quantum energy is given by the usual equation $W = h\nu$. Within the frequency domain of microwaves and hyperfrequencies (300 MHz–300 GHz), the corresponding energies are respectively 1.99×10^{-25} J (1.24×10^{-6} eV) and 1.99×10^{-22} J (1.24×10^{-3} eV). These energies are much lower than the usual ionisation energies of biological compounds, of bond energies, hydrogen bonds, Van der Waals intermolecular interactions and even lower than the energy associated to Brownian motion at 37 °C (0.0027 eV).[19] From this point of view, it is quite clear that direct molecular activation of microwaves should be excluded. Some kind of step by step accumulation of the energy, giving rise to a high activated state should be totally excluded due to fast relaxation.

However, some 'abnormal' effects have been reported,[16-18] and this is also the case in the present study: in the course of our kinetic study, we determined the intermediate aryl amide:phthalic anhydride ratio under 1 and 4 atm. Under pressure, this ratio is about 1, as expected from the established reaction mechanism, whatever the heating system is. However, under atmospheric pressure it is about 2 with microwave heating, and 1 with conventional heating, as illustrated in Fig. 8. At the same time, the amount of unchanged phthalic acid is two times lower under microwave heating.

When phthalic acid is heated above its melting point, internal

Fig. 9
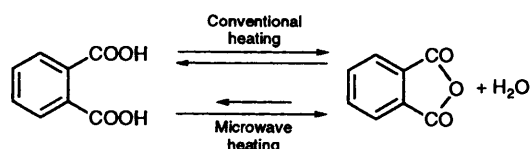
dehydration, leading to the corresponding anhydride takes place. In a closed vessel, under pressure, the reaction is an equilibrium. From our results, it can be concluded that under atmospheric pressure microwave heating favours water evaporation, shifting the equilibrium to the right. Unfortunately, attempts to obtain direct evidence of this phenomenon up to now have failed due to experimental problems, but this quite surprising effect is still under investigation.

Even in the absence of any attractive kinetic or 'specific chemical effect', we have established that microwave heating is of interest in synthesis (see also refs, 24, 25). Under conventional heating the penetration depth is very weak (1 to 10 μm), and heat transfers are based on convective or/and conductive effects. This most often results in a high temperature gradient at the heating system–medium interface. With microwaves, heat is generated *in situ*, and the penetration depth D_p, is given by eqn. (2)[26] (D_p = distance at which the power drops to e^{-1} from its

$$D_p = \lambda_0 \ ^*\varepsilon'/2\pi\varepsilon'' \qquad (2)$$

value at the surface; λ_0 = wavelength in the liquid; ε' = relative permittivity; ε'' = loss factor). It is generally in the range 1 to 10 cm. Indeed, it is well known that even with monomode cavities, the electric field, and as a consequence the dissipated energy, are not totally even in the volume treated. This can result in temperature 'hot spots'. The temperature difference between these hot spots and the bulk mean temperature can be quite high in solids and poorly heat-conductive materials (this is well known for example in defrosting), but is probably much lower in liquids due to heat transfer and convection currents. In this case, especially at high temperatures as illustrated in the present study, due to this 'mass heating' effect, microwave heating can help to avoid degradation of the products. This could be of interest for some industrial applications, the other well known advantage of microwaves being that heating stops immediately when the power is switched off.

Experimental

The nitriles, except for 2-propylpentanenitrile, and their corresponding carboxylic acids were purchased from Janssen or Aldrich (99% purity) and were used without further purification. Dipropylacetonitrile and the corresponding acid were given by Sanofi; phthalimide, phthalic acid and anhydride, and the dicarboxylic acids were purchased from Prolabo.

Phenylacetamide was prepared from phenylacetonitrile by hydrolysis with concentrated aqueous hydrochloride for 1.5 h at 40–50 °C. After cooling at 15 °C and addition of 400 cm³ of cold water (15 °C), phenylacetamide crystallised and was separated by filtration in 80% yield. M.p. 155 °C; m/z 135; δ_H(200 MHz, CDCl$_3$, Me$_4$Si) 9.9 (2 H, s, NH$_2$), 4.2 (2 H, s, COCH$_2$), 8 (5 H, s, C$_6$H$_5$); ν_{max}/cm^{-1} 3166 and 3352 (NH$_2$), 1630 (CO–NH$_2$).

Runs were carried out under the same conditions of temperature and pressure with microwave or conventional heating. The temperature was measured on line with a Luxtron optic fibre thermometer, coupled to a Bravo PC 286 computer in the case of microwave heating, and with a thermocouple in the case of conventional heating. Both temperature measurements were compared under the same conditions with a thermostatted oil bath. The pressure was measured with a manometer (AOIP M2000-VN 4110).
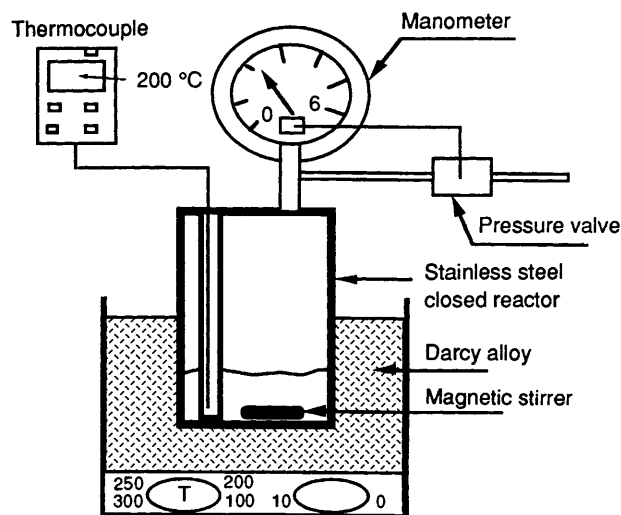
Reactions under atmospheric pressure. The reactor was a round bottomed quartz tube (2 cm diameter, 15 cm length) fitted with a condenser. The temperature probe was dipped through the condenser into the reaction mixture. The reaction mixture was heated in an oil bath (conventional heating) or in the microwave cavity. The equilibrium temperature was reached within less than 3 min, and it was checked that this delay had no influence on the reaction yield.

Reactions under pressure. (i) Conventional heating: the reactor (Fig. 9) (overall volume 63 cm³) was made of stainless steel. It was connected to a pressure gauge, and the temperature probe was inserted in a thick quartz tube (internal diameter 2 mm) tightly fitted to the reactor with a locking ring and a Viton O-ring seal.

(ii) Microwave heating: the reactor was similar to that used for conventional heating, but made of a thick quartz tube (thickness 4 mm; internal diameter 30 mm) with a Teflon cap. The microwave device was a Prolabo Maxidigest MX 350 (monomode cavity; frequency 2.45 GHz; power range 0–300 W).

Standard Procedure.—In a typical run, the nitrile (30 mmol) and phthalic acid (36 mmol) were introduced into the reactor, and heated under stirring. In the kinetic studies, time zero is taken at complete dissolution of the phthalic acid. At the desired reaction time, the reactor was rapidly cooled in a water–ice mixture and then chloroform (30 cm³) was added. The mixture was stirred for 5 min and then the solid filtered off. The chloroform solution contains the unchanged nitrile, the amide and the carboxylic acid. The residual solid contains unchanged phthalic acid, phthalimide, and as the major component, phthalic anhydride. The volume of the chloroform solution was adjusted to 50 cm³ and naphthalene was added as an internal standard. The resulting solution was analysed by GLC (Hewlett Packard 3690; QC BP20 capillary column, 25 m). Helium was used as the carrier gas at a flow rate of 3 cm³ min⁻¹. The oven was maintained at 100 °C for 9 min and then heated at 10 °C min⁻¹ to a final temperature of 220 °C. The final temperature was held for 4 min. The residual solid was analysed by HPLC (Spectraphysics P1500-UV150) with a Spherisorb silica 5 μ column (125 × 4.6 mm), the mobile phase was acetonitrile–water (8:2). The conditions were: flow rate: 1 cm³ min⁻¹, ambient temperature, detection wavelength 254 nm. Retention time (t_r) of phthalic anhydride: 6 min.

The reported values are the average values of at least three identical runs. Reproducibility was within a ± 3% range.

All the carboxylic acids prepared were compared with authentic samples (GLC, HPLC, FTIR and NMR, m.p.). The intermediates **II** (C$_{16}$H$_{13}$O$_4$N; m/z 283) and **I** (C$_{16}$H$_{11}$O$_3$N;

m/z 265) (R = C₆H₅CH₂) were detected by GLC (HP 3690) with a mass spectrometer detector (HP 1090).

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