'Dry' hydrolysis of nitriles by sodium perborate and copper salts in heterogeneous media

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Nitriles react with sodium perborate or copper salts to yield carboxylic acids under mild acidic conditions. The multiphase reaction can be carried out in the absence of solvent, water, added acid or base. The yields are good, and the nitrile group can be hydrolysed in the presence of other functional groups. A comparative study between microwave and conventional heating shows that there is no specific activation from the electromagnetic field. However, careful attention to temperature and pressure measurements in the experimental apparatus is clearly needed.

Introduction

Hydrolysis is a fundamental process in organic chemistry. The introduction of new reagents and the modification of existing ones are a continuous challenge. Reagents are now available for almost every conceivable type of hydrolysis, but in very many instances there are disadvantages associated with their use: high cost, difficulty in handling, lack of sensitivity, toxicity, instability, *etc.* Sodium perborate or copper salts are very cheap, large scale industrial chemicals (over 500 000 tons per annum for $NaBO_3{\cdot}4H_2O$). Surprisingly, few studies have been performed on possible applications of these stable, crystalline and long shelf-life reagents in the hydrolysis of organic substrates.[1–3]

In the last paper,[4] we described a 'dry' hydrolysis of nitriles by dicarboxylic acids in homogeneous media. The reaction is an interesting alternative way to carboxylic acids. The 'dry' hydrolysis requires only a moderate pressure of a few atm to prevent nitrile evaporation, and allows the presence of some functional groups thanks to the rather mild acidic conditions used. A comparative study between microwave and conventional heating shows that there is no specific activation from the electromagnetic field.

In the present complementary paper, we report the hydrolysis of nitriles by mineral salts ($NaBO_3{\cdot}4H_2O$) or metals ($CuCl_2{\cdot}2H_2O$) in heterogeneous media. This 'dry' hydrolysis of nitriles is an interesting reaction for industrial development as a 'clean process' because there is no toxic waste water. On the other hand, interest in this reaction also lies in carrying out a comparative study between microwave and conventional heating in a multiphase reaction.

Results and discussion

In a standard procedure (see Experimental section) the nitrile (liquid phase) is simply heated with a mineral or a metal salt (solid phase) in the absence of solvent: 'dry' reaction conditions in heterogeneous media.

Reaction mechanism and kinetic study

Identification by GLC-MS (gas chromatography with a mass spectrometer detector) of the components of the reaction mixtures, initially containing equimolar quantities of phenyl acetonitrile and copper chloride ($CuCl_2{\cdot}2H_2O$), reveals the presence of the nitrile, the corresponding carboxylic acid and intermediates such as amide. Moreover, the kinetic study presented in Fig. 1 indicates that this hydrolysis is a successive reaction. At the end of the reaction, a red–yellow deposit appears corresponding to the copper metal. The electrochemical analysis of the reaction mixture by amperometry shows the presence of different forms of copper (Cu, Cu^+ and Cu^{2+}) in the corresponding proportions 69%, 27% and 4%, respectively. This result shows that this 'dry' hydrolysis of nitriles by metal salts could be a succession of oxido–reduction reactions. The mechanism of this reaction is presented in Scheme 1.

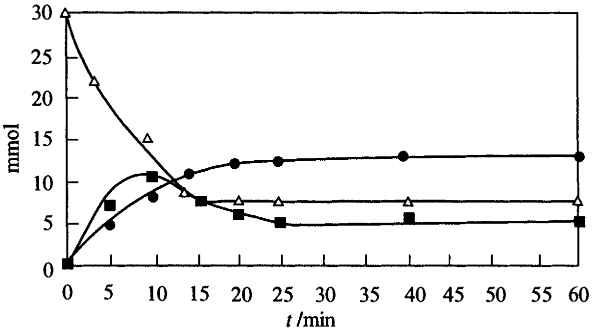


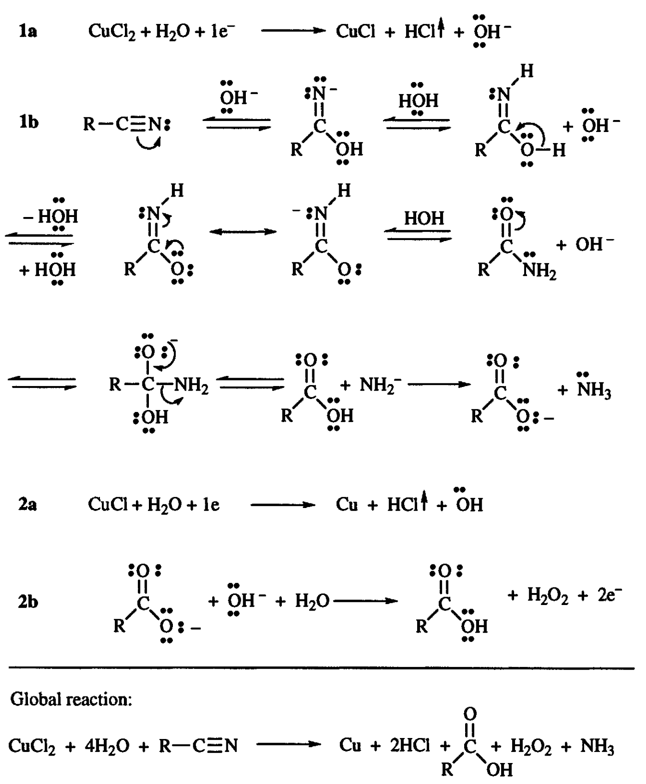
Fig. 1 Kinetic study of the 'dry' hydrolysis of phenylacetonitrile by copper chloride in equimolar quantities at a temperature of 245 °C. ● Acid, △ nitrile, ■ amide, initial quantity of nitrile = 30 mmol

The first step is the reduction of copper salt from $CuCl_2$ to CuCl with the formation of hydrochloric acid and hydroxide ion OH^-. Hydrochloric acid is a dissolved gas which evaporates at high temperature. The reaction is followed by a nucleophilate attack of the OH^- on the nitrile function to form the carboxylate ion. The second step is the reduction of the copper salt CuCl to copper metal Cu with the formation, like the first step of the mechanism, of hydrochloric acid and hydroxide ion OH^-. Hydroxide ion OH^- then oxidizes the carboxylate ion into carboxylic acid and hydrogen peroxide H_2O_2. The two electrons consumed by the copper salt result from oxidation of the carboxylic acid.

The side product 'hydrogen peroxide' can also oxidize the nitrile into carboxylic acid by another competitive mechanism.

The hydrolysis of the nitrile by copper salt $CuCl_2$ requires four water molecules. Then, for $CuCl_2{\cdot}2H_2O$ and $PhCH_2CN$ reactants in an equimolar ratio, the yields do not exceed 50%. On the other hand, for an excess of the hydrated copper salt, the ratio H_2O/nitrile is higher and the total nitrile will be converted into carboxylic acid. The results summarized in Table 1 confirm these propositions and the proposed mechanism.

The mechanism of the 'dry' hydrolysis of nitriles can be compared with those of Gupton *et al.*[5] and Green *et al.*[6] concerning the oxidation of nitriles with sodium perborate or copper chloride to carboxylic amides and acids. According to



Scheme 1 Mechanism of the oxido-reduction reaction of phenylacetonitrile (R = $PhCH_2$) with copper chloride ($CuCl_2{\cdot}2H_2O$)

Table 1 Effect of mineral and metal salts on the 'dry' hydrolysis of phenylacetonitrile, *T* = 240 °C, reaction time = 1 h

	Salt	H_2O:nitrile	Pressure (bar)	Yield (%)	Selectivity (%)
1	$CuCl_2{\cdot}2H_2O$	1	1 (reflux)	0.3	—
2	$CuCl_2{\cdot}2H_2O$	1	3	30	50
3	$CuCl_2{\cdot}2H_2O$	excess > 4	>6	94.3	98.6
4	$CuSO_4{\cdot}H_2O$	excess > 4	>6	93	95
5	$CuCl{\cdot}H_2O$	excess > 4	>6	40	50
6	$CoCl{\cdot}H_2O$	excess > 4	>6	86	95
7	$NaBO_3{\cdot}4H_2O$	1	1 (reflux)	0.3	—
8	$NaBO_3{\cdot}4H_2O$	1	3	25	40
9	$NaBO_3{\cdot}4H_2O$	excess > 4	>6	95	98
10	$MgSO_4{\cdot}4H_2O$	excess > 4	>6	1.1	—
11	$Na_2SO_4{\cdot}10H_2O$	excess > 4	>6	1.6	—

these authors, the hydrolysis of nitriles is an oxidation reaction using strong oxidative forms like peroxide H_2O_2 derived from the mineral and the metal salts. The mechanism is an electron transfer by a series of oxido–reduction reactions.

Effect of mineral salts

Several mineral salts and transition metals were tested as co-reagents in the 'dry' hydrolysis of phenyl acetonitrile and the results are reported in Table 1.

This study allows us to propose that:

(i) Copper salts, cobalt chloride and sodium perborate efficiently hydrolyse phenylacetonitrile. On the other hand, salts like $Na_2SO_4{\cdot}10H_2O$ or $MgSO_4{\cdot}4H_2O$ cannot do this in spite of the presence of excess water.

(ii) Optimal yields and selectivity are obtained in a closed vessel under 3 to 10 atm pressure. Under reflux at atmospheric pressure, the reaction is extremely slow, probably due to vaporization of nitrile.

(iii) The rate of hydrolysis is slowed down by using the first oxidative form of copper chloride (Cu^+) instead of the copper dichloride form (Cu^{2+}). On the other hand, the reaction is not affected by a change of the counter-ion such as chloride or sulfate.

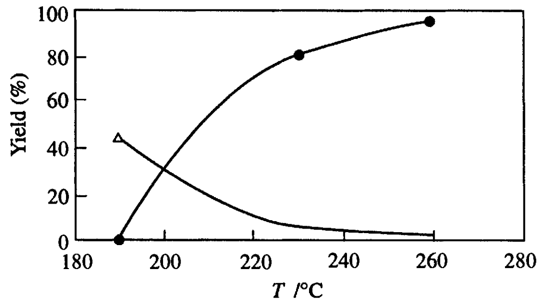


Fig. 2 Influence of temperature on the 'dry' hydrolysis of phenylacetonitrile in closed vessel (*T* = 240 °C; reaction time = 1 h; H_2O/nitrile = in excess > 4), ● phenylacetic acid, △ phenylacetamide

In Fig. 2, the yields of phenylacetic acid and phenylacetamide are compared, after 1 h reaction time, under 10 atm. The temperature was varied in the range 190–260 °C. It appears that an optimal yield of phenylacetic acid is obtained at higher temperatures. On the other hand, the production of phenylacetamide is favoured when the reaction is carried out at low temperature and pressure.

Scope of the reaction: hydrolysis of substituted nitriles

Hydrolysis of nitriles is an important method for the preparation of carboxylic acids on an industrial scale. It is generally achieved by heating the nitrile in aqueous, strongly acidic (H_2SO_4 60–80%) or basic reagents, for several hours at a temperature of 60 to 130 °C.[7] These rather drastic conditions have a severe drawback, however nitriles with sensitive functional groups can be degraded.

'Dry hydrolysis' with mineral or metal salts under moderate pressures give a high yield, good selectivity and can offer an alternative to the usual processes by using mild acidic conditions. It was therefore of interest to investigate this reaction in the case of nitriles with functional substrates. This investigation is reported in Table 2, entries 1–6 respectively, for phenylacetonitrile, benzonitrile, valeronitrile, dipropyl acetonitrile, 3-chloropropionitrile and ethyl cyanoacetate.

Fairly good yields and selectivity are obtained, although the reaction conditions were optimized only in the case of phenylacetonitrile. No side reaction product was detected, except for ethyl cyanoacetate (entry 6). In this case, some decarboxylation reaction occurs; malonic acid and acetonitrile were identified as by-products.

Influence of the nature of heating

A comparative study between microwave and conventional heating was carried out using phenylacetonitrile as a model substrate. The yields were determined under otherwise identical conditions. Comparative studies are illustrated in Table 3 for two different reaction conditions: under atmospheric pressure and in a closed vessel (6–10 atm). In both cases the reaction temperature was kept at 240 °C.

It can be seen that there is no significant microwave activation effect: within experimental error, yields and selectivity are the same under conventional heating.

Since this is a 'dry' hydrolysis of nitriles by dicarboxylic acids, the reaction requires only a moderate pressure to prevent nitrile evaporation, and is not affected by the mode of heating under the same reaction conditions.

Conclusions

The above results clearly demonstrate that 'dry' hydrolysis of nitriles by mineral or metal salts can be an interesting

Table 2 'Dry' hydrolysis of nitriles by mineral and metal salts in closed vessel, T = 240 °C, reaction time = 1 h

	Nitrile, R	Bp (°C)	Salt	H_2O:nitrile	Yield (%)	Selectivity (%)
1	$PhCH_2$	233	$CuCl_2 \cdot 2H_2O$	excess > 4	94.3	98.6
2	Ph	191	$NaBO_3 \cdot 4H_2O$	excess > 4	75.3	80
3	Bu^n	141	$CuCl_2 \cdot 2H_2O$	excess > 4	70	78.6
4	$(Pr^n)_2CH$	183	$NaBO_3 \cdot 4H_2O$	excess > 4	82.5	90
5	$ClCH_2(CH_2)_2$	141	$CuSO_4 \cdot H_2O$	excess > 4	65	75
6	$C_2H_5OOCCH_2$	208	$CuSO_4 \cdot H_2O$	excess > 4	9	—

Table 3 'Dry' hydrolysis of phenylacetonitrile by mineral or metal salts under microwave or conventional heating in heterogeneous media, T = 240 °C, reaction time = 1 h

	Salts	H_2O:nitrile	Pressure (atm.)	Yield (%), conventional	Yield (%) microwave
1	$CuCl_2 \cdot 2H_2O$	1	1 (reflux)	0.3	0
2	$CuCl_2 \cdot 2H_2O$	1	3	30	20
3	$CuCl_2 \cdot 2H_2O$	excess > 4	>6	94.3	89.3
4	$CuSO_4 \cdot H_2O$	excess > 4	>6	93	92
5	$CuCl \cdot H_2O$	excess > 4	>6	40	30
6	$NaBO_3 \cdot 4H_2O$	1	1 (reflux)	0.3	0
7	$NaBO_3 \cdot 4H_2O$	1	3	25	23
8	$NaBO_3 \cdot 4H_2O$	excess > 4	>6	95	94

alternative route to carboxylic acids. The reaction can be carried out in the absence of solvent, water, added acid or base. The yields are good, and the nitrile group can be hydrolysed in the presence of other functional groups. An additional, but by no means unimportant, aspect of the use of sodium perborate and copper salts is that the by-products are completely innocuous—thousands of tons are discharged into drainage systems every day—and hence there is no effluent problem in large scale applications.

The potential of sodium perborate or metal salts as hydrolysing agents for organic compounds continues to expand. Their application in the hydrolysis of nitriles to carboxylic acids and amides could be a satisfactory replacement of alkaline hydroperoxide processes.

No special microwave heating effects on the 'dry' hydrolysis of nitriles by mineral or metal salts were observed. In every case, the yields were identical under conventional and microwave heating.

This study underscores the importance of accurate temperature and pressure control. Researchers interested in examining the difference between microwave and other methods of heating need to pay careful attention to temperature and pressure measurements in their experimental design.

Experimental

The nitriles (Janssen or Aldrich, 99% purity), sodium perborate (Merck, 99% purity) and copper or cobalt salts (Prolabo, 99% purity) were used without further purification.

The standard procedure has already been described.[4] 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 fibre optic 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 is a round bottom quartz tube (2 cm diameter, 15 cm length) fitted with a condenser. The temperature probe is dipped through the condenser into the reaction mixture. The reaction mixture is heated in an oil bath (conventional heating) or in the microwave cavity. Equilibrium temperature is reached in less than 3 min, and it has been verified that this delay has no influence on the reaction yield.

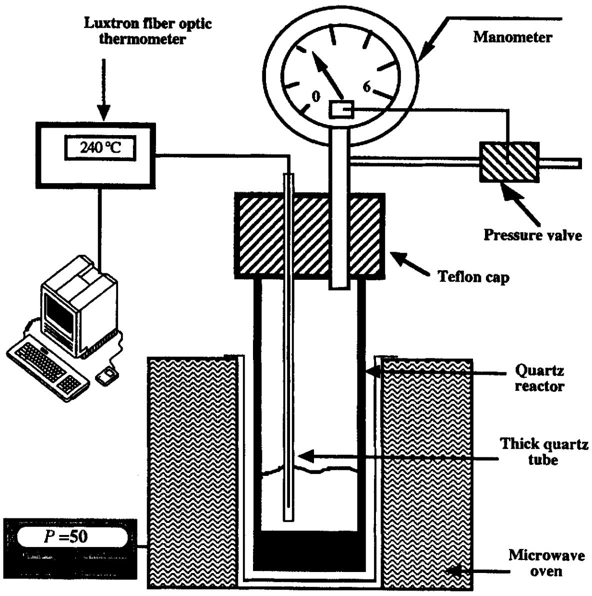


Fig. 3 Reactor device schematic

Reactions under pressure:

(i) Conventional heating: the stainless steel reactor (overall volume 63 cm^3) is described in the preceding paper.

(ii) Microwave heating: the reactor (Fig. 3) is similar to that used for conventional heating, but made in a thick quartz tube (thickness 4 mm; internal diameter 30 mm) with a Teflon cap. The microwave device is a Prolabo Maxidigest MX 350 (monomode cavity; frequency 2.45 GHz; power range 0–300 W).

In a typical run, the nitrile (30 mmol) and copper chloride $CuCl_2 \cdot H_2O$ (H_2O:nitrile = 2) are introduced in the reactor, and heated with stirring. 'H_2O:nitrile' refers to the ratio between the number of mmol of water hydrated by the salt and the number of mmol of nitrile introduced into the reactor. After the desired reaction time, the reactor is rapidly cooled down in a water–ice mixture, and chloroform (30 cm^3) is added. The mixture is stirred for 5 min, and the solid filtered off. The chloroform solution contains the unreacted nitrile, the amide and the carboxylic acid. The residual solid contains unreacted copper(II) chloride, copper(I) chloride, and the major part is copper(0). The volume of the chloroform solution is adjusted to 50 cm^3 and naphthalene is added as internal standard. The resulting solution is analysed by GLC (Hewlett-Packard 3690; QC BP20 capillary column, 25 m) with a mass spectrometer detector (HP 1090). Helium was used as a carrier gas at a flow rate of 3 cm^3 min^{-1}. The oven was maintained at 100 °C for 9 min, 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 linear voltammetry (ELECROMAT-ISMP Toulouse). The standard potential of detected ions are, respectively: E° Cu^{2+}/Cu = 0.34 V and E° Cu^{+}/Cu = 0.52 V.

Yield = carboxylic acid (mmol)/initial nitrile (mmol)

Selectivity = carboxylic acid (mmol)/[carboxylic acid (mmol) + carboxylic amide (mmol)]

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

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