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LETTERS

## A mild and convenient 'dry' hydrolysis of amides to carboxylic acids

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### Abstract

A one-pot preparation of carboxylic acids is described that proceeds from their corresponding amides by a 'dry' hydrolysis with phthalic anhydride in the absence of water and solvent. The method affords carboxylic acids in good yields and is applicable to a variety of substrates. © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* hydrolysis; amides; carboxylic acids and derivatives.

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Hydrolysis is a fundamental process in organic chemistry. The introduction of new reagents and the modification of existing ones are a continuous challenge.<sup>1,2</sup> 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, drastic conditions, lack of sensitivity, toxicity, instability, etc.<sup>3,4</sup>

The hydrolysis of amides by phthalic anhydride is roughly one century old<sup>5</sup> and during this period, there have been very few studies.<sup>6,7</sup> The need for high reaction temperature, expensive co-reagents (tetrachloro and tetrafluoro phthalic anhydrides) and long reaction periods (6 days to obtain often only low to moderate yields) has overshadowed its potential advantages and applications in organic chemistry.<sup>7</sup>

We have now found that using a moderate pressure of 4 to 10 atm in a closed reactor<sup>2</sup> under solvent and water-free conditions, the hydrolysis of amides with phthalic anhydride takes place in excellent yield and short reaction times. The reaction allows for the presence of some functional groups thanks to the rather mild acidic conditions.

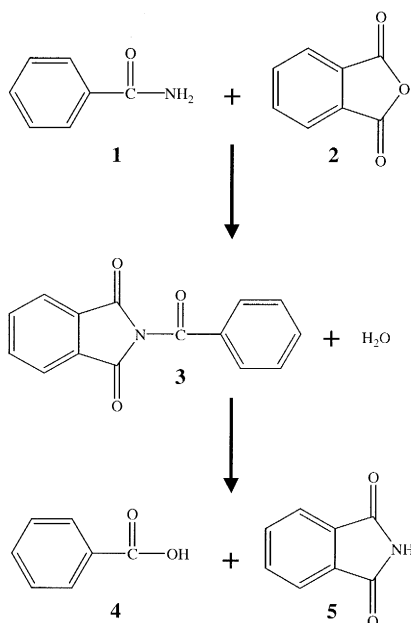
Identification with GLC–MS (gas chromatography with a mass spectrometer detector) of the components of the reaction mixtures, initially containing equimolar quantities of benzamide and phthalic anhydride, allowed the reaction pathway illustrated in Scheme 1 to be established. The expected compounds **4** and **5**, respectively the carboxylic acid and phthalimide corresponding to the starting amide **1** and phthalic anhydride **2**, as well as the reaction intermediate **3**, have been identified.<sup>8</sup>

The water equivalent needed for complete hydrolysis of the amide is provided by phthalic anhydride, which is converted to phthalimide. Because this hydrolysis reaction is run without the addition of water, we call it 'dry' hydrolysis.

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Scheme 1.

The generally drastic conditions of amide hydrolysis lead to severe drawbacks with compounds containing sensitive functional groups. The method described here was tested as a possible alternative.<sup>9</sup> The results obtained with a series of bifunctional compounds are displayed (see Table 1).<sup>10</sup> Fairly good yields were obtained simply by using the mild reaction conditions even for pivalamide with its steric hindrance. No side product was detected, except for ethylamidoacetate. In this case, decarboxylation also occurs: malonic acid, acetic acid and acetamide have been identified as side products.

Table 1  
‘Dry’ hydrolysis of amides **1** to carboxylic acids **4** ( $T=240\text{--}250^\circ\text{C}$ ;  $P=4$  atm)

Amide		Time (min.)	Yield (%)
Benzamide	$\text{PhCONH}_2$	30	99
Phenylacetamide	$\text{PhCH}_2\text{CONH}_2$	45	95
Phenoxyacetamide	$\text{PhOCH}_2\text{CONH}_2$	90	75
Ethylamidoacetate	$\text{C}_2\text{H}_5\text{OOCCH}_2\text{CONH}_2$	60	53
p-Hydroxyphenylacetamide	$\text{HOPhCH}_2\text{CONH}_2$	60	86
Valeramide	$(\text{C}_3\text{H}_7)_2\text{CHCONH}_2$	45	92
Pivalamide	$(\text{CH}_3)_3\text{CCONH}_2$	35	91

In summary, an extremely simple method for the preparation of carboxylic acids and phthalimides has been developed that uses cheap co-reagents and a reactor with moderate pressure of a few atms, available in every organic laboratory. This method generally affords good yields of carboxylic acids in short reaction times (less than 1 h) using phthalic anhydride as a means of generating water in situ.

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8. The intermediate **3** (C<sub>15</sub>H<sub>9</sub>O<sub>3</sub>N; *m/z* 251) was detected by GLC (HP 3690) with a mass spectrometer detector (HP 1090). All the carboxylic acids prepared were compared with authentic samples (GLC, HPLC, FTIR, NMR, mp).
9. In a typical run, the amide (30 mmol) and phthalic anhydride (30 mmol) were introduced into the reactor, and heated under stirring. The reactor was made of stainless steel. It was connected to a pressure gauge, and fitted with a thermocouple for temperature control. At the desired reaction time, the reactor was rapidly cooled down in a water–ice mixture, and chloroform (30 mL) is added. The mixture was stirred for 5 min, and the solid filtered off. The chloroform solution contained the unreacted amide and the carboxylic acid. The residual solid contained unchanged phthalic anhydride and phthalimide. The volume of the chloroform solution was adjusted to 50 mL and naphthalene was added as internal standard. The resulting solution was analysed by GLC (Hewlett–Packard 3690; QC BP20 capillary column, 25 m).
10. The amides and their corresponding carboxylic acids were purchased from Janssen and Aldrich (99% purity) except for valeramide, which was given by Sanofi.