

Dedicated to Professor Victor-Emanuel Sahini
on the occasion of his 80th anniversary

FORMAMIDE, A NOVEL CHALLENGING REAGENT FOR THE DIRECT SYNTHESIS OF NON-*N*-SUBSTITUTED CYCLIC IMIDES

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Aliphatic and aromatic cyclic imides have been prepared in high to moderate yields from cyclic carboxylic anhydrides or corresponding dicarboxylic acids, using formamide as reagent at 170-180°C for 5-6 hours. In the case of aromatic products with lower solubility in formamide, we used *N*-methyl-2-pyrrolidinone (NMP) as supplementary solvent, which facilitates the reaction.

INTRODUCTION

Cyclic imides and their derivatives have been found to be an important moiety in creation of novel medical,¹ polymeric,² photonic,³ and electronic materials.⁴ Often, these cyclic imides are oxidative stable,⁵ heat retardant, solvent resistant,⁶ and have superior mechanic properties.⁷ The specific reactivity of imides is a result of the relative acidity of the NH group, a direct consequence of the presence of the two carbonyl groups.

The conventional syntheses of substituted cyclic imides are well documented in the literature,^{8,9} however the syntheses of *N*-unsubstituted cyclic imides are often limited due to the severe conditions necessary.^{10,11} There are several conventional synthetic techniques for preparation of *N*-unsubstituted imides commonly used in the literature. These approaches include: the condensation of liquid and/or gas ammonia with generic cyclic anhydrides,¹² the cyclization of an amide - acid with 1,1'-carbonyldiimidazole (CDI) and 4-dimethylaminopyridine (DMAP),¹³ the condensation of diacid chlorides with lithium nitride,¹⁴ the reaction of a primary or a secondary amide with AlCl₃,¹⁵ the reaction of

urea/thiourea,^{13,16,17} sulfamic acid,¹⁸ ammonium carbonate¹⁹ with cyclic anhydrides or their corresponding dicarboxylic acids. In the absence of solvents, the reactions with urea, thiourea and ammonium carbonate evolve in heterogeneous system. These reactions can often cause low yields, by-product formation and long reaction times.¹² When condensing agents are employed in the direct reaction of dicarboxylic acids with some of the above mentioned reagents, the synthesis takes place at lower temperatures and in short intervals.^{8,20}

The development of new general synthetic protocols for the synthesis of various organic compounds by direct condensation is still an active field, in spite of the great variety of well-known and applied methods, and where we do have some recent contributions concerning designed synthesis of different condensates.²¹⁻²³

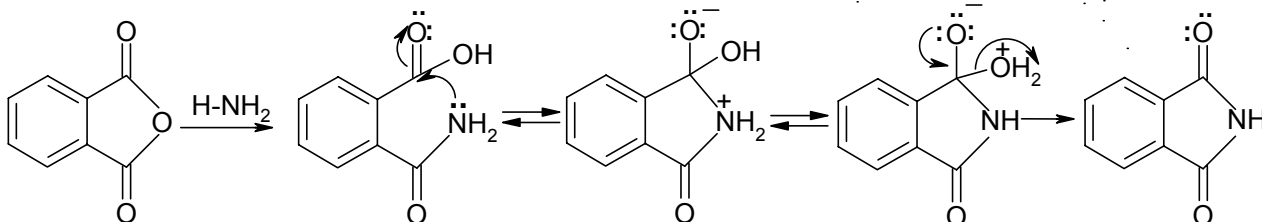
In the present communication, we report on a novel and affordable reagent for obtaining non-*N*-substituted cyclic imides directly from cyclic carboxylic anhydrides or their corresponding acids, namely formamide. This new alternative route is an efficient one-step easy-to-approach synthesis, which evolves in satisfactory yields and with low amounts of by-products.

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RESULTS AND DISCUSSION

Generally, aromatic or aliphatic cyclic imides and their derivatives are obtained by the reaction of dicarboxylic acids or their corresponding

anhydrides with reagents bearing a reactive amino ($-\text{NH}_2$) functional group, through a nucleophilic attack of amino group to anhydride moiety, by a mechanism presented in Scheme 1.



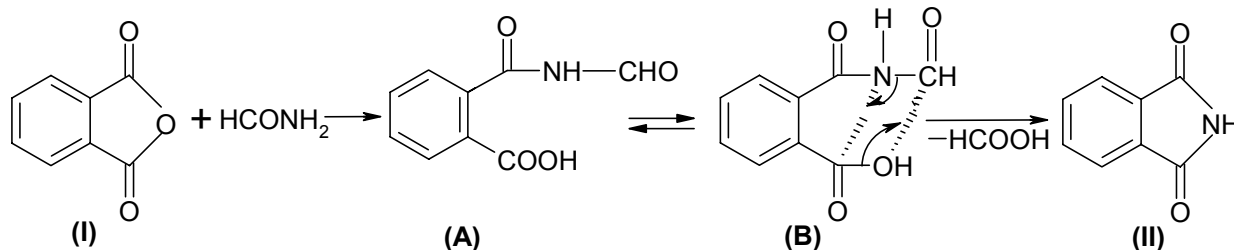
Scheme 1. Mechanism of imide formation by direct condensation.

Cyclic imides synthesis using an amide as reagent is not widely known and used. A brief communication was reported by H. Galons *et al.*⁸ concerning the exclusive synthesis of some biological active glutarimides, through a direct reaction of glutaric acid derivatives and trifluoroacetamide, in the presence of various condensing agents.

In this communication, we introduce a simpler, general and interesting synthetic pathway for the synthesis of imides by direct condensation using cyclic anhydrides or their corresponding dicarboxylic acids and formamide which is a simple affordable reagent. This approach has the advantage that this specific reagent can also serve

as solvent, especially for aliphatic imides. For aromatic cyclic imides with lower solubility in formamide, another appropriate solvent can be supplementary used in order to maintain a homogeneous reaction medium and to allow the main product to be obtained in high yields.

Taking into consideration all these theoretic and experimental aspects, by stepwise investigation, we ascertained that cyclic anhydrides **I** can react with formamide, at 170-180°C for 5-6 hours, resulting in corresponding imides **II** in 59-93% yields and formic acid as by-product, as presented in Scheme 2.



Scheme 2. Synthesis of imides in the presence of formamide as reagent.

An important stage of our research was to establish if this new approach is equally appropriate for aromatic/aliphatic dicarboxylic acids. We assumed that, under the experimental conditions of this reaction, dicarboxylic acids which can afford cyclic anhydrides are suitable reagents for this type of synthesis. The experimental data confirmed our hypothesis, good results being obtained not only for aliphatic dicarboxylic acids, but also for aromatic ones, in spite of their lower reactivity. This proves that in case of dicarboxylic acids, the synthesis evolves

through an intermediate stage when the corresponding cyclic anhydride results and subsequently reacts with formamide, yielding in the corresponding imide. An important fact is that dehydration water does not prevent the imide formation because it is eliminated during the reaction. The final products were obtained in good yields, after purification, and were identified by melting point measurements and IR and $^1\text{H-NMR}$ spectroscopy. All experimental results obtained are summarized in Table 1.

Table 1

Imides obtained using formamide as reagent

Anhydrides/Acids	Imides ^a			
	Solvent (NMP) (mL)	Yield ^b (%)	Melting point ^c (°C)	Reported m.p. (°C)
Phthalic anhydride	7	93.10	227-229	228-229 ¹⁶
3-Nitrophthalic anhydride	10	91.80	211-213	212-213 ¹⁶
4-Nitrophthalic anhydride	10	90.15	198-199	197-198 ¹⁶
Pyromelic anhydride	15	87.65	452-454	450-455 ²⁴ (dec.)
1,8-Naphthalic anhydride	15	86.80	298-300	299-300 ¹⁶
Succinic anhydride	-	63.70	124-126	125-126 ²⁵
Phthalic acid	15	91.90	227-229	228-229 ¹⁶
2,2-Dimethylglutaric acid	-	61.50	141-143	139-144 ²⁶
1,2-Phenylenediacetic acid	5	82.30	191-192	193 ²⁷
Glutaric acid	-	59.80	153-155	154-157 ²⁸
2,2-Dimethylsuccinic acid	-	65.80	101-103	105-107 ²⁸

^a The products were identified by comparison of their m.p. and IR and ¹H-NMR spectra with authentic samples.

^b Yields calculated based on the cyclic carboxylic anhydride employed, before crystallization.

^c After crystallization.

A study on the reaction parameters, in order to establish optimal conditions for this synthesis, was carried out.

With regards to reagent stoichiometry, one mole of formamide is required for one mole of cyclic carboxylic anhydride/acid to yield imides. Experimentally, we used three mole of formamide because the excess acts as solvent for reagents and products and the reaction evolves in homogeneous medium.

In the case of aromatic imides with lower solubility in formamide, we used NMP as supplementary solvent, which facilitates the reaction, as proved by our experimental results. Thus, when 3-nitrophthalimide was prepared in the absence of NMP, the yield was 48.75%, while the addition of 10 mL of NMP to the reaction mixture determined an increased yield, up to 91.80%. In all studied experiments, homogeneous media were obtained when these two aprotic dipolar solvents were employed.

As for the temperature regime, all products were obtained after heating the reaction mixtures at 170-180°C for 5-6 h, when cyclic imides resulted in good yields starting from cyclic carboxylic anhydrides, as well as from the corresponding carboxylic acids, because under these conditions carboxylic acids give the corresponding cyclic anhydrides, products which can easily react with formamide. At lower temperatures, the yields decreased. For example, in the case of phthalimide obtained from phthalic anhydride the yield decreased from 93.10 to 47.70%, when the reaction was conducted at 150°C. The same situation occurred when the synthesis was performed in

smaller intervals; i.e., when the reaction is carried out in 3h, the yield of phthalimide obtained from phthalic anhydride decreased from 93.10 to 52.30%.

Based on theoretical and experimental data,²⁹⁻³¹ we can state that this reaction takes place by a mechanism which involves a nucleophilic attack of amino reactive group from formamide to an anhydride group, followed by the formation of a four-centred transition state, presented in Fig. 1, which generates the final product.

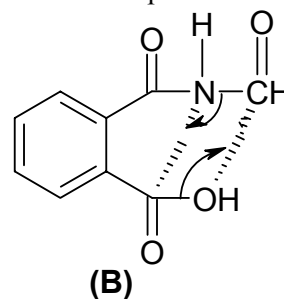


Fig. 1 – The four-centred transition state.

For example, from phthalic anhydride and formamide a formylate monoamide (A) results as an intermediate in the first stage (see Scheme 2); in the second stage, it gives phthalimide and formic acid as byproduct, this last reaction being a thermal cyclization during which the intermediate (A) is merging into a four-centred transition state (B).

CONCLUSION

A novel reagent for the direct synthesis of non-*N*-substituted cyclic imides in satisfactory yields,

starting from cyclic carboxylic anhydrides, has been identified. Formamide was proved to be an effective reagent for cyclic imides synthesis from corresponding dicarboxylic acids as well. In the case of this reaction system, formamide is not only a reagent, but also a solvent, when aliphatic compounds are employed. In order to improve the solubility of aromatic compounds and consequently the yield in main product, NMP was used as supplementary solvent.

EXPERIMENTAL

Reagents and materials

All reagent-grade cyclic anhydrides and dicarboxylic acids were purchased from Sigma Aldrich Co. and used as received. Formamide is commercially available (Fluka) and it was anhydridized prior to use by vacuum distillation over calcium hydride and stored over molecular sieves (4Å).

Measurements

The IR absorption spectra were recorded on a Carl Zeiss Jena SPECORD M80 spectrophotometer on KBr pellets. The ¹H-NMR spectra were run using a Bruker Avance DRX 400 spectrometer with DMSO-*d*₆ as solvent and tetramethylsilane as internal standard. The melting points were measured with a Gallenkamp hot-block melting point apparatus.

Synthesis of imides

Typical procedure for the synthesis of phthalimide from phthalic anhydride and formamide as reagent: to 7.4 g (0.05 mole) phthalic anhydride, 6 mL (0.15 mole) formamide and 7 mL NMP were added under stirring into a flask provided with a thermometer and air cooled ascendent condenser. The obtained mixture is heated up to 170-180°C, for 5-6 h when this solution becomes clear. At the end of the reaction, the still warm solution was poured into a large volume of water (80-100 mL) under stirring when the desired product precipitated. The precipitate was collected by filtration, washed three times with 20-25 mL water and dried, when phthalimide (6.85g, yield 93.1%) was obtained. The product has m.p. 227-229°C after recrystallization from water. Anal. calcd for C₈H₅NO₂: C, 65.11; H, 3.41; N, 9.48%. Found: C, 65.04; H, 3.35; N, 9.36%. Under similar conditions, the other imides presented in Table 1 were obtained using NMP as supplementary solvent.

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