

Synthesis of *N*-arylphthalimides catalyzed by 1,4-diazabicyclo[2,2,2]octane [DABCO] in solventless system

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Abstract

Solvent-free reactions between phthalic anhydride and aryl amines, catalyzed by DABCO (1,4-diaza-bicyclo[2,2,2]octane) in short reaction times and high yields is described.

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1. Introduction

Phthalimides and *N*-substituted phthalimides are an important class of compounds because they show interesting biological activities [1]. In spite of their wide applicability, available procedures for their synthesis are limited. Many catalysts including Lewis acids and hexamethyldisilazane [2] have been proposed for the synthesis of *N*-alkyl and *N*-aryl imide derivatives.

Microwave-enhanced chemical reactions [3], especially on mineral solid supports and those are conducted under solventless conditions [4], have recently attracted much attention. Microwave assisted addition of amines to phthalic anhydride has been also reported [5]. However, Westaway and Gedye [6a], did not see any differences when the reaction was carried out by microwave or conventional heating in DMF. Preparation of imides under microwave irradiation in solventless system using tantalum chloride–silica gel have also been reported [7]. Loupy and coworkers claimed that solvent-free microwave reaction, between phthalic anhydride and amines, need at least one liquid phase [8]. However in 2002, Li et al. claimed a rapid synthesis of *N*-arylphthalimide under microwave irradiation in the absence of solvent [9].

DABCO has been widely used as a catalyst for the Baylis–Hillman reactions [10]. It has also been reported as a catalyst for acceleration of benzylation reactions [11]. DABCO has been applied for the synthesis of zeolite as a structure directing agent [12] and can catalyze the self and cross-condensation of α -acetylenic ketones [13]. It has also been used to catalyze the coupling of α -keto-esters with acrylonitrile [14] and for the dimerization of α,β -unsaturated ketones and nitriles [15]. DABCO/Pd(0) has been used for the highly efficient deprotection of peptides [16].

In view of the emerging importance of phthalimides and our general interest in solventless chemical process [17], we envisioned expediting the synthesis of phthalimides from the reaction of phthalic anhydride and anilines under classical DABCO catalyzed conditions.

2. Experimental

Phthalic anhydride was crystallized prior to use.

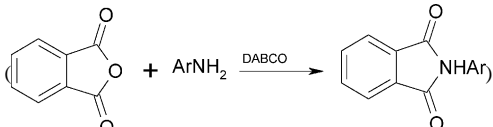
2.1. Synthesis of *N*-arylphthalimides: general procedure

An appropriate amine (1 mmol), phthalic anhydride (1.1 mmol) and DABCO (10 mol%) were crushed for 2 min using pestle and mortar. The reaction takes place almost immediately. The mixture was taken to water (5 mL) and filtered

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Table 1

Reaction of phthalic anhydride with aryl amines catalyzed by DABCO



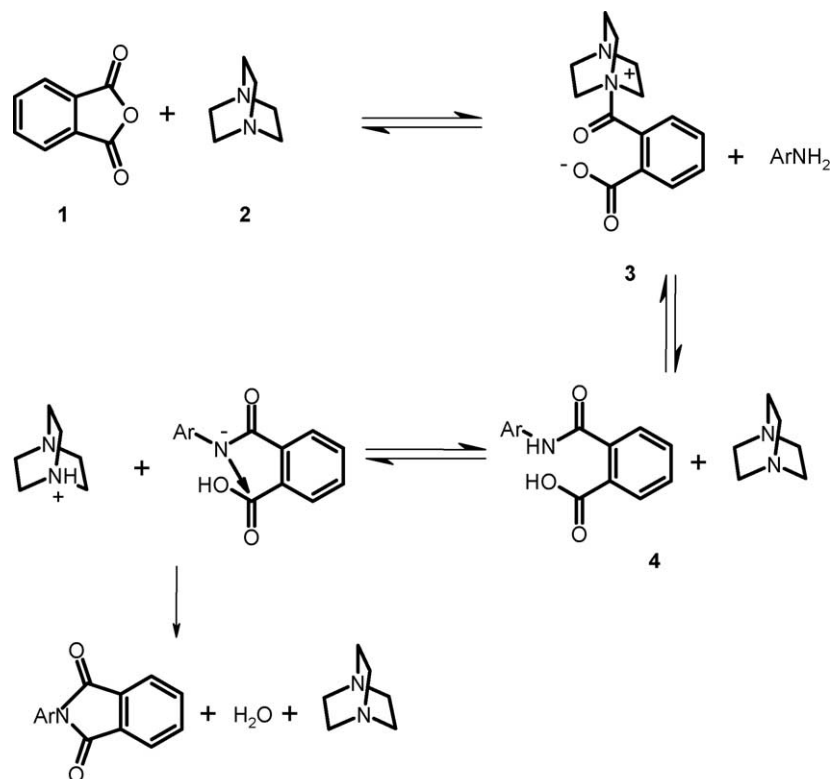
Entry	Amine used Ar	Phthalimide Ar	Yield	mp (found)	mp (reported)
1	Phenyl	Phenyl	79	202 (ethanol)	204 [9]
2	4-Chlorophenyl	4-Chlorophenyl	78	204 (ethanol)	206 [9]
3	4-Bromophenyl	4-Bromophenyl	81	198–199 (ethanol)	203–204 [9]
4	2-Chlorophenyl	2-Chlorophenyl	76	178 (ethanol)	180 [18]
5	4-Methylphenyl	4-Methylphenyl	82	202–204 (ethanol)	204 [9]
6	2-Nitrophenyl	2-Nitrophenyl	77	202–208 (ethanol)	202–203 [19]
7	3-Nitrophenyl	3-Nitrophenyl	86	242 (ethanol)	242–243 [20]
8	4-Nitrophenyl	4-Nitrophenyl	90	264 (ethanol)	266 [9]
9	2-Hydroxyphenyl	2-Hydroxyphenyl	75	216 (acetic acid)	220 [21]
10	3-Hydroxyphenyl	3-Hydroxyphenyl	72	218 (acetic acid)	220 [25]
11	3-Methoxyphenyl	3-Methoxyphenyl	77	156 (acetic acid)	Not reported
12	4-Aminophenyl	Bisimide	85	345 (ethanol)	350 [24]
13	4-Aminoacetyl	4-Aminoacetyl	80	245 (ethanol)	287–288 [26]

off. The solid was crystallized from an appropriate solvent. All products were known and their physical data were compared with those of the authentic samples.

3. Results and discussion

We report herein, an efficient and fast method for the preparation of phthalimides that involves grinding of phthalic anhydride, an appropriate aniline derivative and catalytic

amount of DABCO using pestle and mortar. This solvent-free approach requires only a few minutes of reaction time, in contrast to conventional methods that requires long reaction time and a large excess of organic solvent and expensive Lewis acid, which is difficult to handle. Without DABCO reaction does not proceed even under prolonged reflux in solvents. To establish the generality of method, aniline and its various derivatives were reacted with phthalic anhydride in the presence of DABCO to yield the corresponding phthalimide (Table 1).



Scheme 1. Plausible mechanism for the synthesis of *N*-arylphthalimide catalyzed by DABCO.

We believe that the DABCO catalyzed formation of *N*-arylpthalimide proceeds the pathways illustrated in Scheme 1. DABCO could function as nucleophilic catalyst and react with phthalic anhydride to generate a zwitter ion **3**. This zwitter ion is attacked by arylamine to afford the corresponding amide **4** and DABCO via nucleophilic aryl substitution. Deprotonation of **4** by DABCO would lead to an ion pair **5**. This ion pair **5** can undergo intramolecular nucleophilic substitution to afford the corresponding *N*-arylpthalimide, DABCO and H₂O. This mechanism is in accordance with the true catalytic nature and used amount of DABCO.

In summary, we have developed a proving green method for the facile and rapid formation of phthalimides in solvent-free conditions. These reactions catalyzed by DABCO, do not require any solvent or solid support, and eliminate the need of stoichiometric amount of base.

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Further reading

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