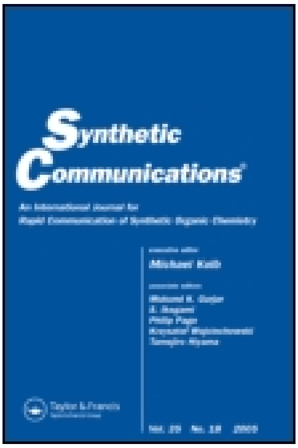

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IMIDAZOLE-PROMOTED SYNTHESIS OF *N*-SUBSTITUTED PHTHALIMIDE FROM *N,N′*-DISUBSTITUTED UREAS IN SOLVENTLESS CONDITIONS

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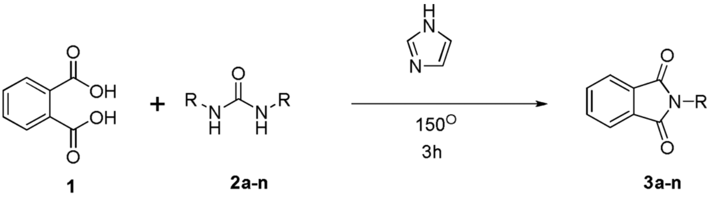
GRAPHICAL ABSTRACT



a) H
b) CH_3
c) C_6H_{11}
d) CH_2Ph
e) Ph
f) 4-CH_3Ph
g) 3-FPh
i) 4-FPh
h) 3-ClPh
j) 4-Cl
k) 4-BrPh
l) 4-CH_3OPh
m) 4-NO_2Ph

Abstract *A series of* N-*substituted phthalimides was synthesized by a thermal reaction between* N,N′-*disubstituted ureas and phthalic acid catalyzed by imidazole in solventless conditions. The products have been obtained in moderate to good yields (53–92%).*

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Keywords Imidazole; phthalimide; solventless; urea

INTRODUCTION

N-Substituted phthalimides are well known for exhibiting a wide range of biological profiles as described in a recent review by Sharma and coworkers.[1] In

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1950, a drug based on the phthalimide scaffold, (Talidomide) was marketed as a sedative, although 11 years later it was withdrawn from the market because of teratogenic effects. It has recently returned for use in the treatment of AIDS, leprosy, and other related diseases.[1] Other promising drugs, such as the in vivo anti-inflammatory LASSBio-468 and anti-androgenic DIMP also possess a phthalimide moiety as the pharmacophoric group.[2] The applications of these compounds are not limited only to therapeutics but also have been mentioned as having an effect in regulation of plant growth. For example, the *N*-substituted phthalimide AC 94,377 can act as an analog of exogenous gibberellins, stimulating germination of dormant seeds in *Avena fatua, Brasica kaber, Rumex crispus, Thlaspi arvense, Phacelia tanacetifolia*, and *Solanum nigrum* (Fig. 1).[3]

Other *N*-substituted phthalimides have displayed various properties such as hypolipidemic,[4] antimicrobial,[5] antifungal,[6] anticonvulsivant,[7] antihistaminic,[8] histone-deacetylase-inhibitory,[9] and HIV-1 transcriptase inhibitory[10] activities. Apart from the biological applications, the usefulness of phthalimide-containing compounds in the fields of liquid crystals,[11] functional materials,[12] and polymer and supramolecular chemistry has also been reported.[13] The multidisciplinary interest in this class of compounds is clearly evident.[14]

The most employed method for synthesizing *N*-substituted phthalimide is the thermal cyclodehydratation between phthalic anhydride and secondary amines.[1] There are several described protocols for performing this reaction, including refluxing in acetic acid,[13] toluene,[15] nitrobenzene,[4b] PEG400,[16] and solvent-free microwave irradiation.[17] Some have reported procedures where urea has been successfully employed as an ammonia equivalent.[18] Although the synthetic method described is often employed for synthesizing *N*-substituted phthalimides, it still suffers certain drawbacks, for example, reactions involving low-molecular-mass or gaseous amines, such as ammonia and methyl amine, are difficult to perform. Further, these reagents, in particular aromatic amines, undergo oxidation during storage and require further purification before use. The same problem is found for phthalic anhydride, which decomposes spontaneously to phthalic acid. Urea and *N*,*N*′-disubstituted ureas are usually stable,[19] solid, and widely available reagents.[20] The thermal decomposition

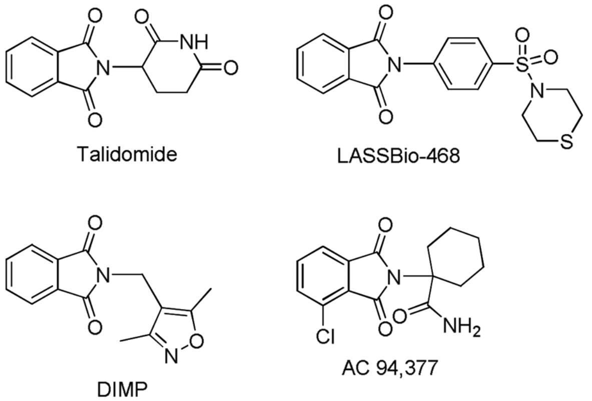
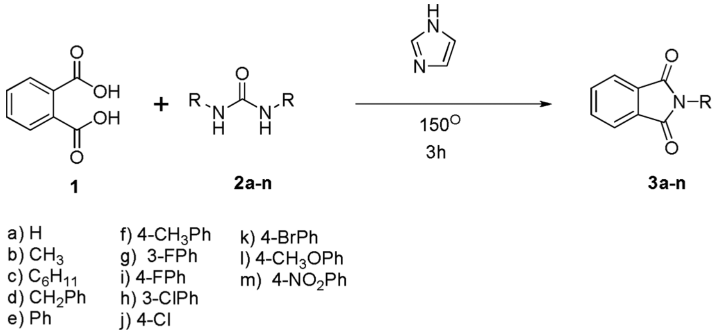


Figure 1.



Scheme 1.

of these reagents releases amines and carbon dioxide. Because of this feature they have been employed in several reactions as a source of amines.[21] The decomposition of urea can be catalyzed by imidazole and it plays a fundamental role in the urea-urease binding in living organisms.[22] Recently, this catalyst has been employed in the direct synthesis of primary amides from carboxylic acids and urea under heating.[23]

It would be very advantageous to develop a method that allows the preparation of *N*-substituted phthalimide directly from phthalic acid and more stable sources of amines. With this in mind we set out to demonstrate that the thermal reaction between phthalic acid and urea or *N*,*N′*-disubstituted ureas catalyzed by imidazole could yield *N*-substituted phthalimides (Scheme 1).

RESULTS AND DISCUSSION

With the aim to determine the proper conditions for the reaction, we performed the thermal reaction between equimolar amounts of phthalic acid **1** and urea **2a** under several conditions, summarized in in Table 1. First, the reaction was carried out at 100 °C during 3 h under solvent-free conditions; this experiment gave the desired phthalimide **3a** in 25% yield (Table 1, entry 1). It is already reported that the addition of small amounts of high-boiling-point polar solvents is beneficial for some solventless reactions. Therefore, to improve the yields, the experiment was repeated along with the addition of few drops of dimethylformamide (DMF) (3 drops/mmol of **1**)

Table 1. Effect of conditions on yields

Entry	Conditions/temperature/time (h)	Yield of **3a** (%)[a]
1	Neat /100 °C/3 h	25
2	3 drops DMF/100 °C/3 h	47
3	3 drops DMF/150 °C/3 h	76
4	3 drops DMF/150 °C/3 h[b]	92

[a] Chemical yield of pure product after recrystallization from ethanol.

[b] Experiment performed employing 2 eq. of urea and 1.5 eq. of imidazole.

Table 2. Imidazole-catalyzed synthesis of *N*-substituted phthalimides

Entry	R	Yield (%)	Mp (°C)	Mp (°C) [Lit.]
1	H	92	225–226	226–228[24]
2	CH_3	75	132–133	130–132[25]
3	C_6H_{11}	68	160–161	159–161[26]
4	CH_2Ph	73	132–133	131–132[26]
5	Ph	75 (68)[a]	208–209	210[4]
6	4-CH_3Ph	74	205–206	207–209[26]
7	3-FPh	72	205–206	206–207[4]
8	4-FPh	69	181–182	180–181[4]
9	3-ClPh	67	168–170	168–169[4]
10	4-ClPh	75	200–201	200–201[4]
11	4-BrPh	68	203–204	205–206[17]
12	4-CH_3OPh	76	145–146	143–145[26]
13	4-NO_2Ph	53	255–256	250–252[26]

[a] Experiment has been done at 25-mmol scale.

and this generated the desired product **3a** in 47% yield (Table 1, entry 2). By increasing the temperature to 150 °C and employing the previously described conditions, the yield was further improved to 76% (Table 1, entry 3). Then, by using excess of urea **2a** (3 equiv.) and imidazole (1.5 equiv), it was possible to improve the yield of **3a** up to 92% (Table 1, entry 4).

After determining the optimal condition, we decided to investigate the application of our method on other substrates (i.e., *N*,*N*′-disubstituted ureas **2b–m**). The reaction is in general quite clean, and some compounds could be purified by recrystallization from ethanol. In some cases column chromatography had been used for purification. The reaction worked quite well with *N*,*N*′-dialkyl **2b–d** (Table 2, entries 2–4) and *N*,*N*′-diaryl ureas **2e–m** (Table 2, entries 5–13), generating the desired compounds **3b–m** in moderate to good yields (53–76%). By employing *N*,*N*′-diaryl ureas containing electron-donating groups attached to the phenyl rings, good yields of the desired compounds could be obtained. Conversely, *N*,*N*′-diaryl ureas containing electron-withdrawing groups appeared to be less reactive. It is noteworthy that the reaction involving *N*,*N*′-2-nitrophenyl urea resulted in a complex mixture of unidentified products. Nevertheless, **2 m** was a reactive substrate and resulted in the formation of product **3 m** in 53% yield (Table 2, entry 13). As *N*-substituted phthalimides are compounds of great interest, it would be quite beneficial to scale up the present method for multigram synthesis. So far, we have tested the reaction using **1**, **2e**, and imidazole at 25-mmol scale and got results comparable to the earlier experiments. The structures of the obtained compounds **3a–m** have been confirmed by comparison of melting points and ^1H NMR spectra with the values previously described in literature (Table 2).[4,17,24–26]

CONCLUSION

In summary, we have develop a new method for synthesizing *N*-substituted phthalimides from phthalic acid and *N*,*N*′-dialkyl- or *N*,*N*′-diaryl-ureas catalyzed by imidazole under solventless conditions in moderate to good yields of 53–92%.

EXPERIMENTAL

A mixture of phithalic acid **1** (0.332 g, 2 mmol), imidazole (0.264 g, 3 mmol), and the suitable urea (4 mmol) were well triturated and placed in a 25-ml flask, followed by the addition of six drops of DMF. The mixture was heated at 150 °C in an oil bath for 3 h. The crude material was cooled down, triturated, and stirred in a 10% v/v aqueous HCl solution for 10 min. The resulting solid residue was filtered off and purified by recrystallization from ethanol or column chromatography with gradient ethyl acetate–*n*-hexane (1:4) to generate the desired pure products.

For complete experimental details, please see the Supplementary Information, available online.

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