Pergamon

Tetrahedron Letters 39 (1998) 8733–8734

TETRAHEDRON
LETTERS

Efficient One-Pot Synthesis of N-Substituted Phthalimides/Naphthalimides from Azides and Anhydrides by Iodotrimethylsilane

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Received 30 June 1998; accepted 14 September 1998

Abstract: N-Substituted phthalimides and naphthalimides have been obtained in good to excellent yields, employing chlorotrimethylsilane and sodium iodide (*in situ* generation of iodotrimethylsilane) from corresponding azides and anhydrides under mild conditions.

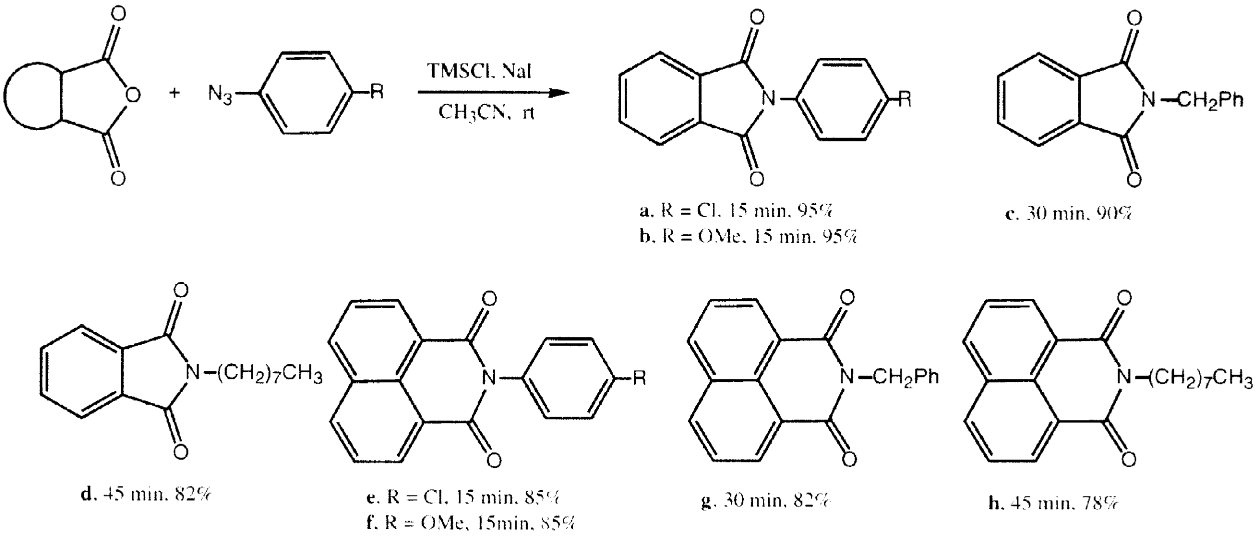
Imide derivatives have numerous applications in biology,[1] synthetic[2] and polymer[3] chemistry. Despite their wide applicability, available routes for these compounds are limited.[4] Well known methods are: dehydrative condensation of an anhydride and amine at high temperatures[1a] and the cyclization of the N-substituted amic acid in the presence of acidic reagents.[4d] Direct N-alkylation under Mitsunobu conditions is also a method for the synthesis of imide derivatives.[4a] The condensation of iminophosphoranes with phthaloyl dichloride followed by alkaline hydrolysis also affords phthalimides.[5] However, most of these routes have their own synthetic problems when applied to a range of derivatives. Therefore, preparation of functionalized imide derivatives is a major challenge in organic synthesis. We describe herein, an efficient and mild approach for the synthesis of phthalimide and naphthalimide derivatives.

The lead has been taken from the work on iminophosphorane condensation with phthalic anhydride,[6] and our recent finding on the reduction of azide functionality to amine by chlorotrimethylsilane-sodium iodide.[7] Based on this, we envisioned that the reaction of an anhydride with an azide, with *in situ* reduction by condensation with chlorotrimethylsilane-sodium iodide, would give the corresponding imide derivative. In order to substantiate this concept, various azides have been reacted with phthalic/naphthalic anhydrides.

In a typical procedure; to a solution of phthalic anhydride (1 mmol) in acetonitrile (15 ml), sodium iodide (1.5 mmol) and *p*-chlorophenyl azide (1 mmol) was added and stirred for 5 min at room temperature. To this stirred suspension, a solution of chlorotrimethylsilane (1.5 mmol) in acetonitrile (2 ml) was added dropwise and the stirring continued for another 15 min. On completion of the reaction as indicated by TLC (ethyl acetate), the reaction mixture was quenched with 10% sodium thiosulphate solution and it was extracted with ethyl acetate (25 ml). The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the crude product. This was purified by column chromotography (ethyl acetate-hexane, 4:1) to afford pure N-(*p*-chlorophenyl)phthalimide as white solid (yield 95%).

PII: S0040-4039(98)01937-6

The results are summarised as follows, which also depict the generality of this procedure:



Iodotrimethylsilane, with remarkable reactivity as a hard-soft reagent, has a wide spectrum of synthetic applications.[8] The use of the chlorotrimethylsilane-sodium iodide reagent system is desirable because it is near neutral, more reactive and more commercially viable in comparison to the use of iodotrimethylsilane directly.[9] Although mechanistic aspects of this reductive condensation cannot be defined clearly, it may be assumed, on the basis of earlier iminophosphorane studies,[6] that the reaction may proceed *via* an iminosilane intermediate which on subsequent condensation with an anhydride could give the imide.

In summary, we have demonstrated an economical and useful method for the synthesis of phthalimide as well as naphthalimide derivatives by employing inexpensive and readily available reagents under mild conditions. Further, from its practical simplicity, spontaneity and high efficiency, this method is expected to have wide utility, particularly in the preparation of functionalized imide derivatives of biological and chemical importance.

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IICT Commun. No. 4084