

Rapid Communication

Synthesis of *N*-sugar-substituted phthalimides and their derivatives from sugar azides and phthalic anhydride

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Abstract—*N*-Sugar-substituted phthalimides and tetrachlorophthalimide derivatives can be prepared in good yields under essentially neutral conditions. Mixing a sugar azide, NaI, Me₃SiCl, phthalic or substituted phthalic anhydride and tetrabutylammonium iodide as catalyst in acetonitrile at rt or 60 °C, afforded 12 imides in 83–95% yields.

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The phthaloyl and tetrachlorophthaloyl groups are common protecting groups for amines in organic synthesis¹ and are also important pharmacophores.² Common methods for imide synthesis include dehydrative condensation of an anhydride and amine at high temperature,³ the acid-catalyzed cyclization of *N*-substituted amic acids⁴ and direct *N*-alkylation under Mitsunobu conditions.⁵ The condensation of iminophosphoranes with phthaloyl dichloride, followed by alkaline hydrolysis also affords phthalimides.⁶ Garcia et al.⁷ have reported on condensation of iminophosphoranes with phthalic anhydride to give *N*-substituted phthalimides. However, most of these routes have problems when applied to a range of derivatives, especially when utilized to synthesize sugar imide derivatives, where strongly basic or acidic conditions are often unacceptable. An efficient and mild general synthetic approach of sugar imides is thus desirable.

Kamal and co-workers^{8,9} recently reported that the reaction of an anhydride with an azide, with ‘in situ’ reduction through condensation with Me₃SiCl–NaI, gives the corresponding imide derivatives. Here, we report a similar method, involving reaction of an

anhydride with a sugar azide and chlorotrimethylsilane–sodium iodide in acetonitrile at room temperature or at 60 °C to provide the corresponding sugar phthalimide or tetrachlorophthalimide derivatives in high yields (Fig. 1).

Typical procedure. To a solution of the sugar azide (10 mmol) and anhydride (15 mmol) in dry MeCN (150 mL), NaI (30 mmol) and Bu₄N⁺I[−] (1 mmol) are added and this solution is stirred at room temperature. A solution of Me₃SiCl (15 mmol) in dry MeCN (40 mL) is then added dropwise under N₂. The reaction is monitored by TLC [petroleum (60–90 °C)–acetone], and on completion of the reaction the mixture is taken up in ether (100 mL), the solution washed with Na₂S₂O₃, dried (Na₂SO₄) and evaporated. The crude product is purified by column chromatography [petroleum (60–90 °C)–acetone] to afford a pure white solid product. The results are summarized in Table 1.

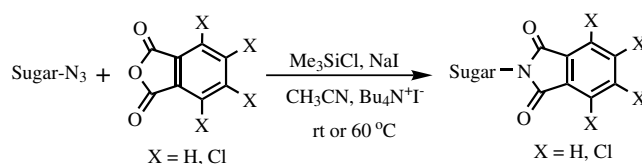


Figure 1. Synthesis of *N*-sugar-substituted phthalimides from a sugar azide and phthalic anhydride.

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Table 1. Data of reaction and products

Entry	Substrate A	Substrate B	Time (h)	Product	Yield (%)
1		B ₁	1.5		83
		B ₂	1.5		89
2		B ₁	2		78
		B ₂	2.5		80
3		B ₁	2		89
		B ₂	2		90
4		B ₁	3		80
		B ₂	3		89
5		B ₁	3		90
		B ₂	1.5		80
6		B ₁	1		92
		B ₂	1		95

B₁ = Phthalic anhydride; B₂ = Tetrachlorophthalic anhydride; R = Phthalimide or tetrachlorophthalimide.

The Me₃SiCl–NaI reagent system is advantageous because it is near neutral and very reactive^{10,11} at least for the 2- and 6-deoxy imides products evaluated. It allows the formation of sugar imides, in very good yields under one-pot conditions and should be useful in natural product synthesis, especially in carbohydrate chemistry.^{12,13}

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