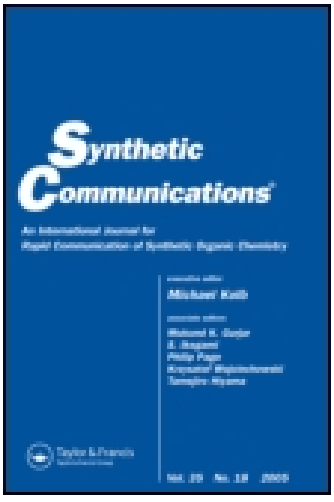

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Efficient Method for Silylation of p-Nitrobenzyl-2-diazoacetoacetate

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Abstract: An efficient new method for the silylation of p-nitrobenzyl-2-diazoacetoacetate using hexamethyl disilane and iodine is presented.

Keywords: Carbapenem, iodotrimethyl silane, silylation

INTRODUCTION

p-Nitrobenzyl-2-diazo-3-trimethylsilyloxy-3-butenoate **(1)** is a useful synthon for the synthesis of thienamycin, imipenem, and other carbapenem antibiotic compounds.[1–3] Different methods are reported in the literature for its synthesis.[1–4] The common method used in the preparation involves silylating p-nitrobenzyl-2-diazoacetoacetate (PNBDAA) **(2)** with trimethyl silyl chloride (TMCS) in presence of triethylamine and sodium iodide in a mixture of acetonitrile and toluene[3] (Scheme 1). This method generates insoluble salts of alkali metal halides during silylation, which interfere with the subsequent reaction. In this article we disclose a new method for the silylation of intermediate **2** using iodotrimethylsilane prepared from hexamethyldisilane (HMD) and iodine.[5]

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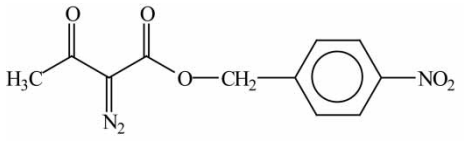
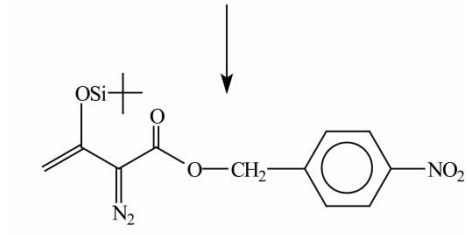


PNBDAA

2



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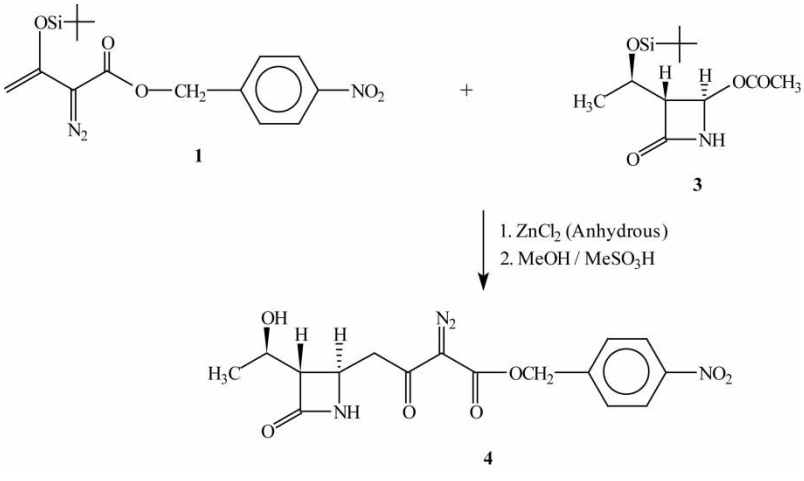
Scheme 1.

This paper describes a new method for silylation of the intermediate **2** using iodotrimethylsilane in the presence of triethylamine. Iodotrimethyl silane is prepared by the reaction of hexamethyldisilane with iodine in dichloromethane.[5] In a typical experiment, iodotrimethylsilane is prepared by refluxing HMD with iodine in dichloromethane, which without isolation was treated with **2** in the presence of triethylamine. The resulting silylated intermediate was immediately treated with **3** in the presence of $ZnCl_2$ to



1

3

4

Scheme 2.

give intermediate **4** in an overall yield of 85–88% with a purity of ≥98% (see Scheme 2).

EXPERIMENTAL

All reagents and solvents were used without further purification. ^{1}H NMR spectra were recorded using a Bruker 300-MHz instrument. The chemical shift data is reported as δ (ppm) downfield from tetramethylsilane. HPLC analysis was performed with a Waters instrument using a Kromasil C-18 (150 mm × 4.6 mm, 5 μ) column, UV detection at 260 nm.

Preparation of p-Nitrobenzyl-3-trimethyl Silyloxy-3-butenoate (1)

Iodine (63.7 g, 0.25 mol) was suspended in dichloromethane (200 mL) and stirred for 15 min HMD (39.0 g, 0.267 mol) was added over 40 min at room temperature. After 30 min, the mixture was heated under reflux for 2 h. In a separate flask, p-nitrobenzyl-2-diazoacetoacetate (**2**, 120 g, 0.446 mol) was suspended in dichloromethane (50 mL) and toluene (100 mL) at 20°C. Triethylamine (54.3 g, 0.536 mol) was added and stirred for 5 min. Iodotrimethyl silane reagent from the previous step was then added over the course of 35 min. The reaction mixture was stirred for 3 h and diluted with toluene (700 mL). The solvent was removed, and the slurry was filtered and washed with toluene (2 × 300 mL). The filtrate was used in the next transformation.

Preparation of (3S,4R)-3-[(1R-)-Hydroxyethyl]-4-[3-(4-nitrobenzyloxy)carbonyl-2-oxo-3-diazo-propyl]-azetidin-2-one (4)

(3R,4R)-4-Acetoxy-3-[(1R)-tert-butyldimethylsilyloxy)ethyl]-acetidin-2-one (**3**) (100 g, 0.348 mol) and anhydrous zinc chloride (16 g, 0.117 mol) were added to the filtrate at 25°C and stirred for 15 h. Methanol (250 mL) and methane sulfonic acid (14.2 g, 0.147 mol) were added to the reaction mixture and stirred for 15 h. It was cooled to 0°C and stirred for 1 h. The solid was filtered, washed with methanol (100 mL), and dried to give 112 g (85.5%) of **4**. Chromatographic purity (by HPLC) ≥98%. ^{1}H NMR ($CDCl_3$): δ 1.29 (d, 3H), 2.85 (dd, 1H), 3.2 (m, 2H), 3.93 (m, 1H), 4.10 (m, 2H), 5.37 (s, 2H), 7.56 (d, 2H), 8.24 (d, 2H).

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