Formation of *N*-Boc pyrrole 2-ethyl ester, a key intermediate in the Donohoe synthesis of omuralide.

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Method Article

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Abstract

Introduction

Heterocyclic rings, such as pyrrolidines, tetrahydrofurans and piperidines, are found in the vast majority of natural product molecules including many of those exhibiting a wide variety of potent biological activities. These heterocyclic rings are often highly substituted and constitute part of complex structures and, therefore, represent a significant challenge to synthetic chemists. The use of aromatic compounds as precursors to these structural motifs is an attractive option because, by controlling the degree of reduction achieved, dihydro or tetrahydro compounds can be formed selectively. These can then be reacted further, increasing substitution and complexity, via use of a wide variety of standard synthetic chemistry found within the literature. The Birch \(Li/NH_3) and ammonia-free \(Li/di- _tert_-butyl biphenyl \[DBB])[1] partial reductions, using the conditions developed by Donohoe, are applicable to a wide range of heteroaromatic compounds with a variety of substitution patterns, resulting in formation of the respective dihydro compounds in typically good to excellent yields.[2-8] The reduction of the N-Boc pyrrole whose formation is described herein,[9] \(Figure 1) has recently been published by Donohoe et al. as a key step in the route to the biologically active natural product omuralide.[9, 10] **Figure 1** See figure in Figures section.

Reagents

• Ethyl pyrrole-2-carboxylate \(Alfa Aesar, cat. no. L16382) • Di-tert-butyl dicarbonate \(Sigma-Aldrich, cat. no. 205249) • Triethylamine \(Rathburn, cat. no. RPH3018) CRITICAL The triethylamine should be purified prior to the reaction by distillation from calcium hydride. It can be stored for several months if kept in dark conditions over calcium hydride under an inert atmosphere. • 4-Di\(methylamino)pyridine \(Alfa Aesar, cat. no. A13016) • Acetonitrile, HPLC grade \(Rathburn, cat. no. RH1015) CRITICAL The acetonitrile should be distilled from 4Å molecular sieves prior to use. It can be stored over 4Å molecular sieves for several months. • Diethyl ether, glass distilled grade \(Rathburn, cat. no. RG2013) • Acetone, HPLC grade \(Fisher Scientific, cat. no. A/0606/17) • 40-60° Petroleum spirit, glass distilled grade \(Rathburn, cat. no. RG2031) • Sodium sulfate, anhydrous \(Acros Organics) • Silica gel for flash column chromatography \(BDH, cat. no. 153325P) • Sand, general purpose grade \(Fisher Scientific) • Thin-layer chromatography plates on aluminium backing, silica gel 60 F254 \(Merck) • Deuterated chloroform \(Sigma-Aldrich, cat. no. 151823)

Equipment

• Magnetic hotplate stirrer \(eg. IKA® RCT Basic) • Digital temperature probe • Oil bath • 50 mL round-bottom flask • Water condenser \(to fit neck of flask) • Rubber septa \(to fit neck of flask) • Glass syringes, luer lock \(10 mL) • Teflon-coated magnetic stirrer bar • Balloon fitted to disposable 2.5 mL syringe barrel • Disposable 21 gauge needles • Heat gun • Filter paper \(150 mm diameter) • Rotary evaporator \(Büchi) • Pyrex chromatographic column \(approx. diameter 4 cm) • NMR tubes CRITICAL All glassware used

during the reaction stages should be either oven-dried prior to use or, alternatively flame-dried under vacuum using a Bunsen burner. Glassware should be allowed to cool to room temperature by either storage in a dessicator containing self-indicating silica gel or by attaching to a high-vacuum line.

Procedure

1] Weigh out 1.4 g \(10 mmol) of ethyl pyrrole-2-carboxylate into a 50 mL round-bottomed flask containing a Teflon-coated magnetic stirrer bar. Fit the flask with a water condenser in the main neck and also a rubber septum in the second neck. Place a rubber septum into the of top of the condenser. Flush the flask with argon and maintain under a positive pressure of argon by use of an argon balloon. Place the flask into an oil bath on the hotplate stirrer and fit a digital temperature probe to the hotplate stirrer. 2] Transfer 10 mL of distilled acetonitrile into the flask using a glass syringe and reusable 21 gauge needle. Turn the magnetic stirrer on. 3] Transfer 4.2 mL \(30 mmol) of distilled triethylamine into the flask using a second glass syringe and reusable 21 gauge needle. 4] Weigh out 61 mg \(0.5 mmol) of 4-di\(methylamino)pyridine into a weighing boat and transfer to the reaction vessel by rapid removal of the rubber septum and subsequent replacement following addition. 5] Weigh out 3.1 g \(14 mmol) of di-_tert_-butyl dicarbonate into a weighing boat and transfer to the reaction vessel by rapid removal of the rubber septum and subsequent replacement following addition. 6] Heat the reaction vessel to 50 °C and stir at this temperature for 48 hours. 7] Cool the reaction to room temperature by lifting the vessel out of the oil bath. 8] Transfer the reaction mixture into a 100 mL separating funnel containing water \(30 mL) and diethyl ether \(30 mL). Separate the layers and extract the aqueous layer with two 30 mL portions of diethyl ether. Dry the combined organic layers with sodium sulfate \(approx. 1 g). 9] Filter the mixture through filter paper into a round-bottomed flask and evaporate the solvent to dryness using a rotary evaporator. PAUSE POINT: The reaction mixture can be left overnight at room temperature. 10] Purify the desired product by flash column chromatography on silica gel eluting with 1:9 acetone to petroleum spirit to yield the desired product as a pale yellow oil.

Timing

50 hours including purification

Troubleshooting

Low yield: Repeat reaction with fresh reagents and dry glassware, ensuring that all are anhydrous and that the reaction is maintained under an inert atmosphere.

Anticipated Results

Typical isolated yield of pyrrole should be 2.2 g, 91%. Analytical data: **^{1}H NMR** \(500 MHz, $CDCl_3$) δ_H 7.31 \(1 H, dd, ^{3} _J_\(H,H)=3.6, ^{3} _J_\(H,H)=2.0 Hz, ArH), 6.83 \(1 H, dd, ^{3} _J_\(H,H)=3.6, ^{3} _J_\(H,H)=1.6 Hz, ArH), 6.17 \(1 H, t, ^{3} _J_\(H,H)=3.6 Hz, ArH), 4.31 \(2 H, q, ^{3} _J_\(H,H)=7.2 Hz, OC _H_$_2$Me), 1.59 \(9 H,

s, CMe_3), 1.36 \(3 H, t, ^{3} _J_\(H,H)=7.2 Hz, OCH_2 _Me_); **^{13}C NMR** \(125 MHz, $CDCl_3$) δ_C 160.9, 148.4, 126.5, 125.6, 120.6, 110.0, 84.7, 60.8, 27.6, 14.3; **IR \(neat)** 2982-2875 \(CH), 1752 \(C=O), 1725 \(C=O); **HRMS \(ESI)** _m/z_ calcd for $C_{14}H_{20}N_2O_4Na$: 303.1320; found 303.1320 \[_M_$^+$ + CH_3CN + Na].

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Figures

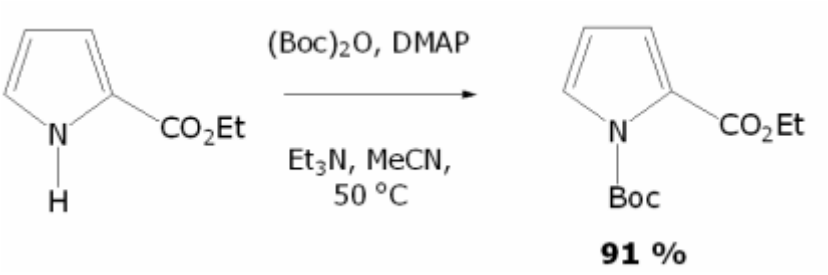

Figure 1