A Facile and Inexpensive Synthesis of 6-Ethynylbipyridine

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Received April 6, 2011; revised May 16, 2011; accepted May 21, 2011

Abstract

An inexpensive synthesis of 6-ethynylbipyridine has been accomplished using Sonogashira coupling of 2-bromo-6-iodopyridine with 2-methyl-3-butyn-2-ol. Subsequent Stille coupling with 2-(trimethylstannanyl)pyridine and hydrolysis provided the target compound in an overall high yield.

Keywords: 6-Ethynylbipyridine, 2-Bromo-6-Iodopyridine, 2-Methyl-3-Butyne-2-ol, Palladium Coupling

1. Introduction

Bipyridines are widely used structures that are found in a large range of functions. These include ligands in coordination chemistry, photocatalysts, functionalized polymers, sensors, supramolecular assemblies and metallo-DNA conjugates. Thus, their importance in inorganic, organic and medicinal chemistry cannot be overstated. The syntheses of functionalized 2,2’-bipyridines for the above areas are therefore needed and although numerous methods exist in the literature inexpensive and facile procedures are desirable. One such bipyridine is 6-ethynylbipyridine (1), which has the ability to undergo Sonogashira coupling to a host of other materials and has therefore been used in the synthesis of metallo-DNA conjugates [1], nucleosides bearing metal complexes for antiviral activity [2-4] and photoactive materials [5-8].

The reported synthesis [1] (Scheme 1) relies on a Stille reaction in the first step for the formation of 6-bromo-2,2’-bipyridine (a Suzuki coupling has also been reported in 54% yield [9]), which, in a second step, undergoes further coupling of the resulting bromobipyridine product with the expensive trimethylacetylene (TMSA). We recently required large amounts of this material and envisioned that both these issues could easily be resolved by the use of alternative reagents.

2. Results

Our strategy for an alternative synthesis involved the use of 2-bromo-6-iodopyridine and 2-methyl-3-butyn-2-ol as replacement reagents (Scheme 2). The synthesis of 2-bromo-6-iodopyridine has been reported in which a bromine-magnesium exchange using iPrMgCl in THF is employed [10], however we found this procedure difficult to reproduce. Therefore, we adapted Peterson’s [11] procedure, in which the formation of 2-bromo-6-lithiopyridine is accomplished using n-butyllithium in dichloromethane. Treatment of this with iodine provided 2 in high yield. Sonogashira coupling of 2 with 2-methyl-3-butyn-2-ol proceeded in excellent yield as expected, and overcomes the use of expensive TMSA as the cost of 2-methyl-3-butyn-2-ol is inconsequential. We did attempt to couple 2-methyl-3-butyn-2-ol with 2,6-dibromo-pyridine, however unacceptable yields and complex mixtures resulted.

Stille coupling of 3 with 2-(trimethylstannanyl)pyridine [12] gave 4 in excellent yield, which was easily hydrolyzed to give target bipyridine 1 in an overall very good yield.

In conclusion, we have developed an inexpensive and facile synthesis of 6-ethynylbipyridine. In particular, a robust synthesis of 2-bromo-6-iodopyridine (2) has been accomplished, which is critical to this chemistry and is a compound used in a variety of other reported couplings.
In saturated NaHCO₃ solution, the layers were separated and at room temperature. The mixture was quenched with cold bath removed, and the mixture stirred for 30 minutes at –78˚C.

To a flame-dried flask containing 2,6-dibromopyridine (4.25 g, 27.0 mmol) was dissolved in dry Et₂O (100 mL) cooled to –78°C and then n-BuLi (38.0 mL, 1.4M hexanes solution) was added dropwise followed by stirring at –78°C for 2 h. Me₃SnCl (5.75 g, 28.8 mmol) dissolved in Et₂O (20 mL) was added dropwise from a syringe, and the reaction mixture stirred 3 h at –78°C followed by slowly warming to room temperature over 12 h. The reaction flask was concentrated in vacuo and dry hexanes (30 mL) were added from a syringe and the slurry was stirred for 10 minutes. Filtration under argon, concentration in vacuo gave the crude product that can be stored in a freezer and is used in the next step without further purification.

In an oven-dried flask, 2-bromo-6-iodopyridine (2) (470 mg, 1.65 mmol), 2-methyl-3-butyln-2-ol (152 µL, 1.57 mmol), Pd(PPh₃)₄ (10 mg, 0.008 mmol) and copper(I) iodide (10 mg, 0.069 mmol) were dissolved in Et₂NH (50 mL) and stirred for 20 h at room temperature. The mixture was concentrated in vacuo, and quenched with water (20 mL), extracted with Et₂O (2 × 20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo.

3.2. 4-(6-Bromopyridin-2-yl)-2-methyl-3-butyln-2-ol (3)

In an oven-dried flask, 2-bromo-6-iodopyridine (2) (470 mg, 1.65 mmol), 2-methyl-3-butyln-2-ol (152 µL, 1.57 mmol), Pd(PPh₃)₄ (10 mg, 0.008 mmol) and copper(I) iodide (10 mg, 0.069 mmol) were dissolved in Et₂NH (50 mL) and stirred for 20 h at room temperature. The mixture was concentrated in vacuo, and quenched with water (20 mL), extracted with Et₂O (2 × 20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography on silica gel, (1:1 cyclohexane/EtOAc) afforded 370 mg (93%) of 3 as a light yellow solid. ¹H NMR and ¹³C NMR spectra were consistent with published data [10].

3.3. 2-(Trimethylstannyl)pyridine [12]

2-Bromopyridine (4.25 g, 27.0 mmol) was dissolved in dry Et₂O (100 mL) cooled to –78°C and then n-BuLi (38.0 mL, 1.4M hexanes solution) was added dropwise followed by stirring at –78°C for 2 h. Me₃SnCl (5.75 g, 28.8 mmol) dissolved in Et₂O (20 mL) was added dropwise from a syringe, and the reaction mixture stirred 3 h at –78°C followed by slowly warming to room temperature over 12 h. The reaction flask was concentrated in vacuo and dry hexanes (30 mL) were added from a syringe and the slurry was stirred for 10 minutes. Filtration under argon, concentration in vacuo gave the crude product that can be stored in a freezer and is used in the next step without further purification.

3.4. 2-Methyl-4-(6-(2,2-bipyridin)3-butyln-2-ol (4)

The 2-(trimethylstannyl)pyridine obtained above (1.20 g, 4.96 mmol) was dissolved in dry toluene (30 mL), cannulated into a flask equipped with condenser and side-arm containing 3 (770 mg, 3.21 mmol) and the mixture degassed with argon for 1 h. Pd(PPh₃)₄ (10 mg, 0.008 mmol) was added and the reaction mixture was heated under reflux while stirring for 12 h. The mixture was cooled and poured into 2M NaOH (20 mL) and extracted with toluene (2 × 30 mL). The combined organic phases were dried (Na₂SO₄), filtered and concentrated. Flash chromatography on silica gel (10:1 cyclohexane/ EtOAc) afforded 710 mg (92%) of 4 as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 1.67 (s, 6H, (CH₃)₂C), 2.97 (s, 1H, OH), 7.31...
(dq, J = 7.5, 1.2 Hz, 1H), 7.41 (dd, J = 7.6, 1.0 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.81 (td, J = 7.7, 1.7 Hz, 1H), 8.34 (d, J = 7.9 Hz, 1H), 8.44 (d, J = 7.9 Hz, 1H), 8.68 (d, J = 5.1 Hz, 1H); 13C NMR (CDCl3): δ 31.2, 65.4, 81.8, 93.5, 120.4, 121.6, 124.0, 127.2, 137.0, 142.3, 149.0, 155.4, 156.3. IR (neat) 3455, 2228, 1685, 1265, 1250, 935, 1204, 1216, 1240, 1272, 1370, 1423, 1490, 1554, 1563. IR (neat) 3455, 2228, 1685, 1265, 1250, 935, 1204, 1216, 1240, 1272, 1370, 1423, 1490, 1554, 1563.

3.5. 2-Ethynyl-6-2,2-bipyridine (1)

NaOH (1.61 g, 40.18 mmol) and 4 (450 mg, 2.0 mmol), were dissolved in toluene (50 mL) and then brought to a boil for 40 minutes. The resulting brown-golden solution was concentrated and the residues were quenched with H2O (20 mL), with CH2Cl2 (30 mL) being added at the same time. The pH of the mixture was adjusted to 7 by adding 2M HCl dropwise then the layers were separated, and the aqueous layer was extracted with CH2Cl2 (2 × 20 mL). The combined organic extractions were dried MgSO4, filtered and concentrated. Flash chromatography on silica gel (5:1 cyclohexane/EtOAc) afforded 301 mg (83%) of 1 as a white solid. 1H NMR and 13C NMR spectra were consistent with published data [11].

4. Acknowledgements

This work was supported by a grant from the School of Energy Research, University of Wyoming, which is gratefully acknowledged.

5. References


