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A Facile and Inexpensive Synthesis of 6-Ethynylbipyridine

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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

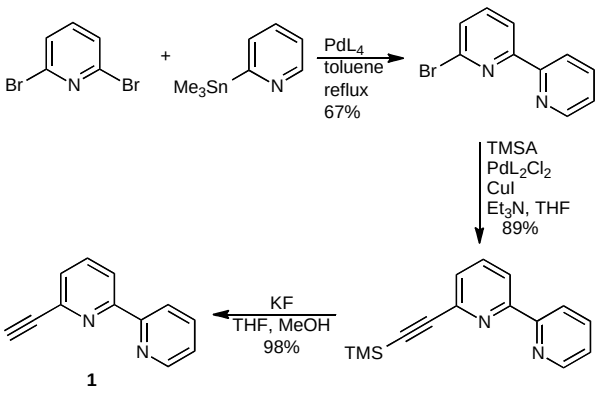
Bipyridines are widely used structures that are found in a large range of functions. These include ligands in coordination chemistry, photocatalysts, functionalized polymers, sensors, supramolecular assemblies and metallo-DNA conjugates. Thus, their importance in inorganic, organic and medicinal chemistry 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

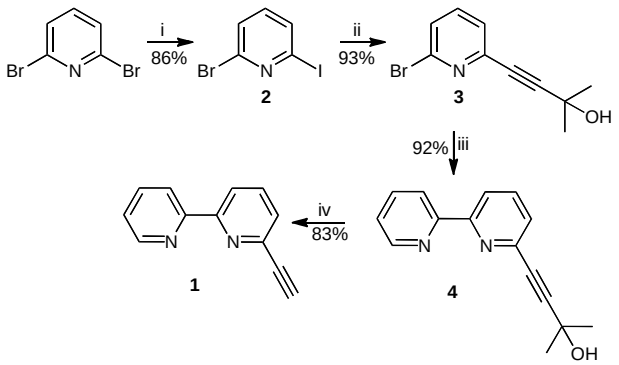
Our strategy for an alternative synthesis involved the use of 2-bromo-6-iodopyridine and 2-methyl-3-butyn-2-ol as replacement reagents (Scheme 2). The synthesis of 2-bromo-6-iodopyridine has been reported in which a bromine-magnesium exchange using iPrMgCl in THF is employed [10], however we found this 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-dibromopyridine, however unacceptable yields and complex mixtures resulted.

Stille coupling of **3** with 2-(trimethylstannyl)pyridine [12] gave **4** in excellent yield, which was easily hydrolized 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



Scheme 1



Scheme 2. Reagents and conditions: (i) *n*-BuLi then I_2, CH_2Cl_2, −78˚C, 3 h; (ii) 2-methyl-3-butyn-2-ol, $Pd(PPh_3)_4$, CuI, Et_2NH, r.t., 20 h; (iii) 2-(trimethylstannyl)pyridine, $Pd(PPh_3)_4$, toluene, 110˚C, 12 h; (iv) NaOH, toluene, 90˚C - 100˚C, then H^+40 min.

[13-17]. Furthermore, the use 2-methyl-3-butyn-2-ol in replacement of TMSA has been shown to be successful in bipyridine chemistry.

3. Experimental

^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively in the indicated solvent. Chemical shifts are reported in δ units, *J* in Hz relative to $CDCl_3$ (7.24 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR). Infrared spectra were determined on a Perkin Elmer Paragon 500 FT-IR spectrophotometer. Et_2O was distilled from NaK; toluene and CH_2Cl_2 were distilled from calcium hydride. Flash chromatography was performed using Silicycle ultra pure silica gel 60 Å (230 - 400 Mesh). Standard syringe techniques were employed for handling air-sensitive reagents and all reactions were carried out under argon.

3.1. 2-Bromo-6-iodopyridine (2)

To a flame-dried flask containing 2,6-dibromopyridine (1.00 g, 4.22 mmol), dry CH_2Cl_2 (100 mL) and cooled to –78˚C was slowly added n-BuLi (3.3 mL, 4.6 mmol of a 1.4 M hexanes solution). The reaction was stirred for 20 minutes at –78˚C then a solution of I_2 (1.06 g, 4.2 mmol, dissolved in 20 mL of CH_2Cl_2) was added via cannula. The resulting mixture was stirred at –78˚C for 3 h, the cold bath removed, and the mixture stirred for 30 minutes at room temperature. The mixture was quenched with saturated $NaHCO_3$ solution, the layers were separated and the aqueous layer extracted twice with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuo. Gradient flash chromatography on silica gel (cyclohexane then 15:1 cyclohexane/EtOAc) afforded 1.13 g (3.63 mmol, 86%) **2** as a light yellow solid. ^1H NMR and ^{13}C NMR spectra were consistent with published data [10].

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

In an oven-dried flask, 2-bromo-6-iodopyridine (**2**) (470 mg, 1.65 mmol), 2-methyl-3-butyn-2-ol (152 μL, 1.57 mmol), $Pd(PPh_3)_4$ (10 mg, 0.008 mmol) and copper(I) iodide (10 mg, 0.069 mmol) were dissolved in Et_2NH (50 mL) and stirred for 20 h at room temperature. The mixture was concentrated in vacuo, and quenched with water (20 mL), extracted with Et_2O (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography on silica gel, (1:1 cyclohexane/EtOAc) afforded 370 mg (93%) of **3** as a yellow oil. ^1H NMR ($CDCl_3$): δ1.62 (*s*, 6H, $(CH_3)_2C$), 2.70 (*s*, 1H, OH), 7.34 (*d*, *J* = 7.5 Hz, 1H), 7.41 (*d*, *J* = 7.8 Hz, 1H), 7.52 (*t*, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 30.9, 65.2, 80.2, 95.5, 125.9, 127.4, 138.3, 141.4, 143.3. IR (neat): 3450, 2910, 2231, 1550, 1420, 1300 cm^{-1}.

3.3. 2-(Trimethylstannyl)pyridine [12]

2-Bromopyridine (4.25 g, 27.0 mmol) was dissolved in dry Et_2O (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. Me_3SnCl (5.75 g, 28.8 mmol) dissolved in Et_2O (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-butyn-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 equiped with condensor and side-arm containing **3** (770 mg, 3.21 mmol) and the mixture degassed with argon for 1 h. $Pd(PPh_3)_4$ (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 (Na_2SO_4), 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, $CDCl_3$): δ 1.67 (*s*, 6H, $(CH_3)_2C$), 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); ^{13}C NMR ($CDCl_3$): 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, 1150, 1125 cm^{-1}.

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 golden-brown solution was concentrated and the residues were quenched with H_2O (20 mL), with CH_2Cl_2 (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 CH_2Cl_2 (2 × 20 mL). The combined organic extractions were dried $MgSO_4$, filtered and concentrated. Flash chromatography on silica gel (5:1 cyclohexane/EtOAc) afforded 301 mg (83%) of **1** as a white solid. ^{1}H NMR and ^{13}C NMR spectra were consistent with published data [11].

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