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An Improved Preparation of 4-Ethynylpyridine and its Application to the Synthesis of Linear Bipyridyl Ligands

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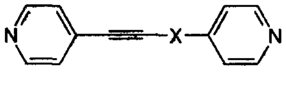
Abstract: A convenient synthesis of 4-ethynylpyridine, **5**, starting from 4-vinylpyridine has been developed. Compound **5** reacts readily with pyridyl- and aryl-iodides to give the linear bidentate ligands **7**, **9**, and **11** in excellent yields.

The application of bidentate ligands derived from 4,4'-bipyridine as rod-like spacers for the construction of molecular frameworks and network polymers is of significant interest [1]. In particular, ligands with alkynyl spacers such as **1**, have attracted much attention due to their conjugated, rigid nature [2]. During the course of our collaborative studies on the synthesis and structure of a range of metal-co-ordination polymers [3], we have become interested in developing new methods of preparation of such ligands.



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A good precursor for the preparation of new heterocyclic ligands is 4-ethynylpyridine, **5**, but the literature syntheses of this material are mostly cumbersome and low-yielding [4]. In 1984, Ciana and Haim reported the two-step synthesis of **5** in an overall yield of 70% [5]. However, this method and its later version [6] are prohibitive because the starting material, 4-bromopyridine hydrochloride, is both expensive and not readily accessible. Furthermore, in reproducing this synthesis [5], we also encountered some problems in work-up and isolation of pure products. We report herein an alternative three-step synthesis affording **5** in good overall yield (65%) starting from cheap, readily available 4-vinylpyridine, making subsequent ligand preparation more accessible.

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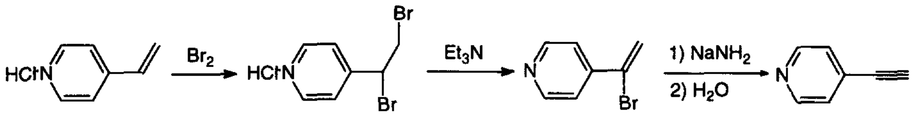

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The literature method for the preparation of 4-(1'-bromoethenyl)pyridine [4c] was used as a guide. Using the conditions reported in the original paper [4c], elimination of the first molecule of HBr from **3** using NEt_3 as base was incomplete in our hands giving only crude samples of **4**. Modification of the reaction conditions yielded pure samples of **4**. This material is rather unstable at room temperature in the absence of solvent, and, therefore, should be used within a few hours of preparation, or alternatively stored at –20°C. The utilisation of a strong base, sodium amide, for elimination of the second equivalent of HBr allowed us to conduct this reaction at low temperatures (-78°C) leading to facile separation of 4-ethynylpyridine, **5**. Interestingly, use of sodium hydride as a base at 20°C afforded the desired product **5** in significantly lower yields (10%), while reducing the temperature of this latter reaction to below 0°C led to even lower overall yields.

This convenient method for the preparation **5** has allowed us to develop the syntheses of new linear bidentate ligands based on a modified Heck reaction:

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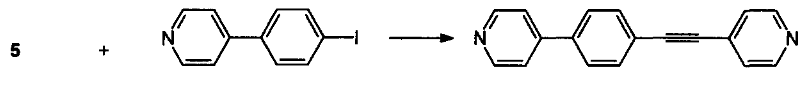

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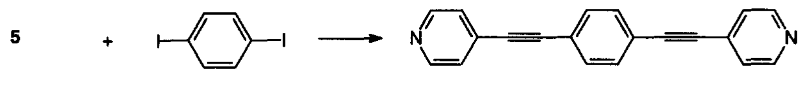

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Compound **5** reacts readily with 4-iodopyridine, **6**, to give 4,4'-bipyridylacetylene, **7**, in 87% yield. This is a higher yielding synthesis than the previously reported routes starting from 4-bromopyridine and acetylene (10% yield) [7a], 4-bromopyridine and 4-ethynylpyridine (5% yield) [7b], or the alternative multi-step route starting from isonicotinic aldehyde (20% yield) [7c]. Under similar conditions, 4-(4'-iodophenyl)pyridine, **8**, couples with **5** to give the new compound **9** which is a promising asymmetrical linear ligand for new co-ordination network chemistry. Other ligands containing long spacers can also be obtained. For example, cross-coupling of 1,4-diodobenzene, **10**, with **5** affords **11** in nearly quantitative yield. This compares with a yield of 15% reported for the synthesis of **11** from the reaction of 1,4-dibromobenzene with **5** under similar conditions [8].

In summary, an optimised method has been developed for the synthesis of 4-ethynylpyridine, **5**, which can be obtained from accessible starting materials in good yield. Coupling reactions of **5** with aryliodides afford bidentate ligands of different length and design.

Experimental:

IR spectra were recorded on a Perkin-Elmer 1600 spectrometer. NMR spectra were recorded at 300 MHz on a Bruker DPX300 spectrometer. Chemical shifts are quoted in δ units using TMS as internal standard reference, and coupling constants, J, are quoted in Hz. Mass spectra were recorded on a VG 70E spectrometer. 4-Vinylpyridine and 1,4-diiodobenzene were purchased from *Aldrich* and 4-vinylpyridine was distilled shortly before use. Triethylamine (*Aldrich*) was dried over CaH_2 and distilled before use. 4-Iodopyridine and 4-(4'-iodophenyl)pyridine were synthesised according to the literature method [9] from the corresponding amines. Bis(triphenylphosphine)palladium(II) dichloride [10] and 4-(1',2'-dibromoethyl)pyridine hydrochloride, **3**, [4c] were prepared according to the literature procedures [4c].

4-(1'-Bromoethenyl)pyridine (**4**). Thoroughly dried 4-(1',2'-dibromoethyl)pyridine hydrochloride (**3**) (40g, 0.132mol) was added in portions to dry triethylamine ($250cm^3$) at room temperature. The suspension was stirred vigorously over 2 days at room temperature and then for 4.5h at 90°C. The reaction mixture was cooled and the grey precipitate filtered off and washed with diethyl ether ($200cm^3$). The solutions of **4** in triethylamine and diethyl ether were combined and the solvent removed under reduced pressure. The residual oil was dried *in vacuo* to remove traces of solvent, and the product **4** was isolated as an amber oil (23.3g, yield 83%). δ_H ($CDCl_3$): 5.98 (1H, d, J = 2.4, C=CH), 6.38 (1H, d, J = 2.4, C=CH), 7.48 (2H, d, J = 6.2), 8.63 (2H, d, J = 6.2).

4-Ethynylpyridine (**5**). A suspension of $NaNH_2$ in liquid NH_3 was prepared from Na (7.53g, 0.327mol) according to the literature procedure [11]. 4-(1'-Bromoethenyl)pyridine, **4**, (20g, 0,109mol) in dry Et_2O ($20cm^3$) was added dropwise into the suspension of $NaNH_2$ at –78°C over 4h. The temperature was increased to –30°C and the reaction mixture stirred under reflux for 2h. The NH_3 was removed under a positive nitrogen pressure. Et_2O ($250cm^3$) was added to the reaction flask fitted with a condenser and the mixture cooled to 0°C using an ice bath. Water ($20cm^3$) was added carefully in small portions through the condenser and the solution of **5** in Et_2O was collected and dried over Na_2SO_4. The solvent was removed and the residue sublimed at 100°C at atmospheric pressure to afford 9.9g of **2** as colourless plates (yield 88%). Mp 64-65°C (lit. 63-65°C, [4]); ν_{max} (KBr)/cm^{-1}: 2100 (C≡C); δ_H ($CDCl_3$): 3.41 (1H, s, C≡CH), 7.36 (2H, d, J = 6.8), 8.62 (2H, d, J = 6.8); m/z^+ = 103 (M^+, 100%).

Coupling of 4-ethynylpyridine with aryliodides (general procedure). Triethylamine ($4cm^3$) was added to a mixture of 4-ethynylpyridine, **5**, (0.32g, 3.1mmol), aryliodide (3.0mmol of **6** or **8**; 1.5mmol of **10**), bis(triphenylphosphine)palladium(II) dichloride (19mg, 0.027mmol) and copper(I) bromide (6mg, 0.042mmol) in a round-bottom flask under N_2 at room temperature. The reaction mixture was stirred at 60°C (external temperature of oil bath) for 1h and the temperature was slowly increased to 90°C and the reaction mixture stirred for 2 days. Triethylamine was removed by evaporation, and the solid residue dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with aqueous K_2CO_3, filtered and dried over Na_2SO_4.

The solvent was removed under vacuum and the residue recrystallised from toluene. The product was isolated as a yellow solid (yields: 87% for **7**; 98% for **9**, 99% for **11**).

4,4'-Bipyridylacetylene (**7**): mp 163-164°C; ν_{max}(KBr)/cm^{-1}: C≡C stretch not observed. δ_H ($CDCl_3$): 7.41 (2H, d, J = 6.0), 8.65 (2H, d, J = 6.0); δ_C ($CDCl_3$): 90.7 (C≡C), 125.6, 130.3, 150.0 (pyridine ring); m/z^+ = 180 (M^+, 100%).

1-Pyridyl-4-(4'-pyridylethynyl)benzene (**9**): mp 167-168°C; ν_{max}(KBr)/cm^{-1}: 2221 (C≡C); δ_H ($CDCl_3$): 7.41 (2H, d, J = 6.0), 7.53 (2H, d, J = 6.0), 7.68 (4H, s), 8.64 (2H, d, J = 6.0), 8.70 (2H, d, J = 6.0); δ_C ($CDCl_3$): 88.2, 93.2 (C≡C), 121.5, 123.0, 125.6, 127.1, 131.2, 132.7, 138.8, 147.3, 149.9, 150.5 (pyridine and benzene rings); m/z^+ = 256 (M^+, 100%). Elemental analysis: calc. for $C_{18}H_{12}N_2$ (%): C 84.38 H 4.69 N 10.94; found (%): C 84.14 H 4.60 N 10.63.

1,4-bis(4'-Pyridylethynyl)benzene (**11**): mp 185-186°C; ν_{max}(KBr)/cm^{-1}: 2220 (C≡C); δ_H ($CDCl_3$): 7.41 (4H, d, J = 6.0), 7.58 (4H, s), 8.64 (4H, d, J = 6.0); δ_C ($CDCl_3$): 88.6, 93.2 (C≡C), 123.0, 125.5, 131.2, 132.0, 149.9 (pyridine and benzene rings); m/z^+ = 280 (M^+, 100%).

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