Pergamon

Tetrahedron Letters 40 (1999) 5413–5416

TETRAHEDRON
LETTERS

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

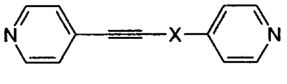
Neil R. Champness[a], Andrei N. Khlobystov[a,b], Alexander G. Majuga[b], Martin Schröder*[a] and Nikolai V. Zyk*[b]

[a] School of Chemistry, University of Nottingham, University Park, Nottingham, UK, NG7 2RD.
[b] Department of Chemistry, Moscow State University, Vorob'ovy Gory, Moscow, Russia 119 899.

Received 21 April 1999; accepted 19 May 1999

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.

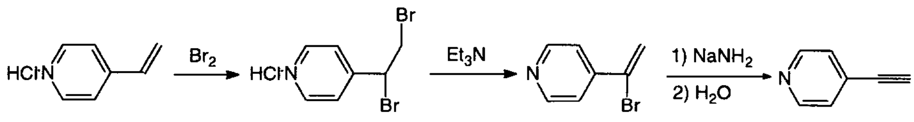
The application of bidentate ligands derived from 4,4'-bipyridine as rod-like spacers for the construction of molecular frameworks and network polymers is of significant interest [1]. In particular, ligands with alkynyl spacers such as **1**, have attracted much attention due to their conjugated, rigid 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.



1

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.

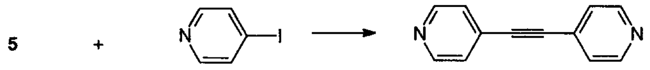
PII: S0040-4039(99)01019-9



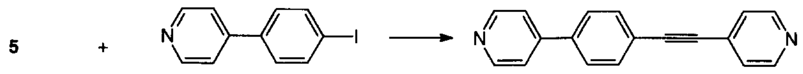
2 3 4 5

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.

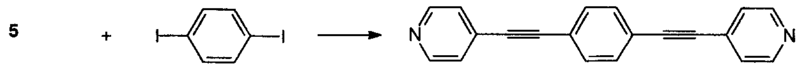
This convenient method for the preparation **5** has allowed us to develop the syntheses of new linear bidentate ligands based on a modified Heck reaction:



6 7



8 9



10 11

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%).

Acknowledgements: We thank the EPSRC for support, and the EPSRC National Service at the University of Swansea for mass spectrometry.

References:

1. (a) A.J. Blake, N.R. Champness, W-S. Li, M.A. Withersby and M. Schröder, *Coord. Chem. Rev.*, 1999, **183**, 117; (b) N.R. Champness and M. Schröder, *Curr. Opinions Solid State and Mat. Chem.*, 1998, **3**, 419; (c) S.R. Batten and R. Robson, *Angew. Chem. Int. Ed.*, 1998, **37**, 1451; (d) O.M. Yaghi, H. Li, C. Davis, D. Richardson and T.L. Troy, *Acc. Chem. Res.*, 1998, **31**, 474.
2. (a) B.F. Abrahams, M.J. Hardie, B.F. Hoskins, R. Robson and E.E. Sutherland, *J. Chem. Soc., Chem. Commun*, 1994, 1049; (b) J.A. Whiteford, C.V. Lu, and P.J. Stang, *J. Am. Chem. Soc.*, 1997, **119**, 2524; (c) L. Carlucci, G. Ciani and D.M. Proserpio, *J. Chem. Soc., Chem. Commun.*, 1999, 449; (d) J.P. Sauvage, J.P. Collin, J.C. Chambron, S. Guillerez, C. Coudret, V. Balzani, F. Barrigelletti, L. DeCola and L. Flamigni, *Chem. Rev*, 1994, **94**, 993.
3. (a) A.J. Blake, N.R. Champness, A.N. Khlobystov, D.A. Lemenovskii, W-S. Li and M. Schröder, *J. Chem. Soc., Chem. Commun.*, 1997, 2027; (b) A.J. Blake, N.R. Champness, A.N. Khlobystov, D.A. Lemenovskii, W-S. Li and M. Schröder, *J. Chem. Soc., Chem. Commun.*, 1997, 1339.
4. (a) U. Haung and H. Furst, *Chem. Ber.*, 1960, **93**, 593 (reported a yield of 3.9% for **5**); (b) M.S. Shvartsberg, A.W. Khozhevnikova and I.L. Kotlyarevskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1971, **8**, 1833 (reported a yield of 5% for **5**); (c) A.P. Gray, H. Krau, D.E. Heitmeier, and R.H. Shiley, *J. Org. Chem.*, 1968, **33**, 3007 (reported a yield of 29% for **5**).
5. L.D. Ciana and A. Haim, *J.Heterocyclic Chem.*, 1984, **21**, 607.
6. J. Suffert and R. Ziessel, *Tet. Letts.*, 1991, **32**, 757.
7. (a) J.E. Sutton and H. Taube, *Inorg. Chem.*, 1981, **20**, 3125; (b) A. Vidal-Ferran, R.A. Hay, P.A. Lowden and J.K.M. Sanders, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2275; (c) K. Kondo, N. Ohnishi and K. Takemoto, *J. Org. Chem.*, 1992, **57**, 1622.
8. A.J. Amoroso, A.M.W. Cargill Thompson, J.P. Maher, J.A. McCleverty and M.D. Ward, *Inorg. Chem.*, 1995, **34**, 4828.
9. C. Coudret, *Synth. Commun.*, 1996, **26**, 3543.
10. J. Chatt and F.G. Mann, *J. Chem. Soc.*, 1939, 1622.
11. J.E. Baldwin and T.C. Barden, *J. Am. Chem. Soc.*, 1984, **106**, 5212.