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Convenient synthetic routes to bidentate and monodentate 2-, 3- and 4-pyridyl phosphines: potentially useful ligands for water-soluble complex catalysts

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Abstract

The monodentate and bidentate pyridyl phosphines, PR_3 and $R_2P(CH_2)_2PR_2$, where R = 3- or 4-pyridyl can be prepared in high yields by treatment of butyllithium/TMEDA/3- or 4-bromopyridine with PCl_3 or $Cl_2P(CH_2)_2PCl_2$ at low temperature. 1,2-Bis(di-2-pyridylphosphino)ethane is conveniently synthesised by an alternative route involving reaction of 1,2-dibromoethane with lithium di-2-pyridylphosphide.

Keywords: Pyridylphosphines; 3-Pyridyl; 4-Pyridyl

1. Introduction

Water-soluble organometallic chemistry has received significant interest in the past few years, particularly in the area of biphasic catalysis [1]. A severe limitation is the lack of suitable water-soluble ligands, tertiary phosphines in particular. Our interest in water-soluble bidentate phosphines is in the investigation of the antitumour properties of their Au(I), Ag(I) and Cu(I) complexes [2,3]. As part of our studies in this area we required a series of hydrophilic analogues of the hydrophobic bidentate phosphine 1,2-bis(diphenylphosphino)ethane (dppe). The substitution of pyridyl groups for the phenyl groups of this molecule appeared to be an attractive option and one such ligand 1,2-bis(di-2-pyridylphosphino)ethane (**1a**) has been prepared by reaction of 2-pyridyllithium and 1,2-bis(dichlorophosphino)ethane in anhydrous ether [4,5]. However, this procedure fails, or gives very low yields when applied to the synthesis of 3- or 4-pyridyl substituted bidentate phosphines [5,6]. Similar problems have been encountered in the attempted synthesis of monodentate ligands such as tris–3- (**2b**) and tris–4- (**2c**) pyridylphosphines [7] and in a recent review, Newkome [8] noted evidence for only one 3-pyridylphosphine[1], PPh(4-Br-Ph)(3-pyridyl), prepared in 1944 by Davies and Mann [11] in very low yield. It is notable that reports of the preparation, reactions and catalytic properties of pyridylphosphines and their metal complexes have been confined, almost exclusively, to those with 2-pyridyl substituents [8].

We report here that the elusive mono- and bi-dentate 3- and 4-pyridylphosphines can be prepared in good yield by a straightforward modification of the standard butyllithium metal halogen exchange method. We report also an alternative synthesis for the 2-pyridyl

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[1] The application of **2b** and **2c** as surface modifiers for the promotion of direct electrochemistry of cytochrome c has been reported by Hill, but no details were reported about the synthetic routes to these compounds, or the yields obtained [9,10].

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compound **1a** that avoids the use of the expensive precursor $Cl_2P(CH_2)_2PCl_2$.

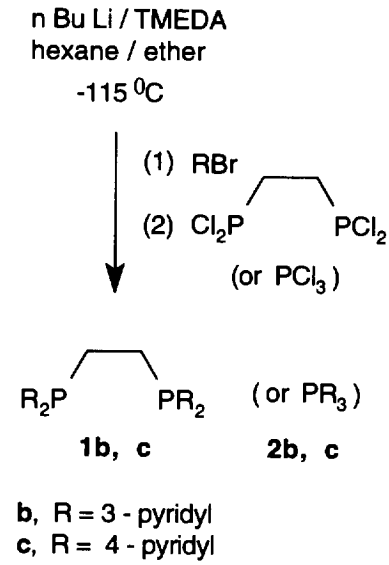
2. Results and discussion

We investigated the syntheses of the bidentate 2-, 3- and 4-pyridyl phosphines (**1a–c**) from the appropriate bromopyridine under standard butlyllithium metal halogen exchange conditions (diethyl ether, −78°C) and subsequent reaction with the commercially available chlorophosphine $Cl_2P(CH_2)_2PCl_2$. As expected, good yields of the bidentate 2-pyridyl compound **1a** were obtained under these conditions, but the 3- and 4-pyridyl systems gave complex reaction mixtures and very low yields of compounds **1b** and **1c**. Gas chromatography/mass spectral (GC/MS) analyses of methanol quenched 3- and 4-pyridyllithium reaction mixtures indicated that, while significant metal halogen exchange had occurred, compounds formed from addition and coupling reactions (butyl substituted pyridines and dipyridines) were major by-products. These reactions compete with nucleophilic attack by pyridyllithium on the chlorophosphine. Furthermore, the low yields of compounds **1b** and **1c** indicated that the pyridyllithium was quite unreactive towards the chlorophosphine.

We have modified the reaction conditions to (a) decrease the likelihood of addition/coupling reactions during the formation of the pyridyllithium and (b) increase the reactivity of the pyridyllithium towards the chlorophosphine. This was achieved by a combination of low temperatures, addition of N,N,N′,N′-tetramethylethylenediamine (TMEDA), and careful timing in the addition of the various reagents.

The novel 3-pyridyl phosphine **1b** was prepared in good yield by slow addition of 3-bromopyridine to an ethereal solution of butyllithium and TMEDA at −115°C, followed by quenching with 1,2-bis(-dichlorophosphino)ethane. The reaction was stirred for 2 h, then allowed to warm to −80°C over an 11 h period, followed by warming to ambient temperature over a 3–4 h period. The bidentate 4-pyridyl analog **1c** and the monodentate tris–3- and tris–4-pyridyl phosphines (**2b, c**) were similarly prepared, in good to excellent yields, by reaction of butyllithium/TMEDA/3- or 4-bromopyridine with either $Cl_2P(CH_2)_2PCl_2$ or PCl_3, as appropriate (Scheme 1).

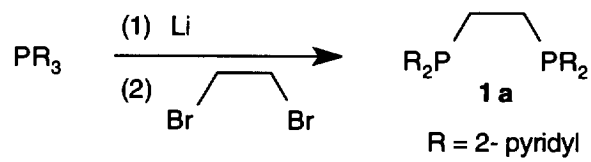
The addition of TMEDA clearly increases the reactivity of the pyridyllithium toward the chlorophosphine and the low temperatures suppress competitive addition/coupling reactions. However, in the 3-pyridyl case, even at −115°C, side reactions occur. By GC analysis we found that addition of 3-bromopyridine to TMEDA·*n*-BuLi in ether at −115°C, followed by immediate quenching with methanol, led to the formation of the corresponding dipyridine (35%), possibly via an $S_{RN}1$ mechanism or a 'benzyne' mechanism [12]. The lithiation of the 4-pyridyl compound was less temperature sensitive and these reactions proceeded cleanly, and generally in higher yield, than the 3-pyridyl analogues. These results reflect the expected higher reactivity of 3-pyridyllithium compared to the 4-pyridyllithium [13].



Scheme 1.

Compound **1a** was also prepared by an alternative method, involving treatment of 1,2-dibromoethane with two equivalents of lithium di-2-pyridyl-phosphide, generated from tris(2-pyridyl)phosphine and lithium metal [14] (Scheme 2). This route is an attractive alternative to the use of $Cl_2P(CH_2)_2PCl_2$ which, while commercially available, is expensive and hazardous to synthesise in the laboratory [15]. However, difficulties in obtaining the corresponding 3- and 4-pyridyl metal phosphides have so far precluded synthesis of compounds **1b** and **1c** by this route. Treatment of either **2b** or **2c** with lithium in tetrahydrofuran, sodium in liquid ammonia, or potassium in dioxane, led to decomposition of the starting material with no evidence of metal phosphide formation.

In summary, the TMEDA/buyllithium procedure should be generally applicable to the synthesis of a wide



Scheme 2.

variety of mono- and bi-dentate 3- and 4-pyridyl tertiary phosphines, which until now have not been readily accessible. This is significant as the 3- and 4-pyridyl compounds (Scheme 1) exhibit considerably greater water solubility than their 2-pyridyl analogues. The availability of these ligands will be particularly useful for investigations of new organometallic reagents for use in biphasic catalysis.

3. Experimental

3.1. General

$Cl_2P(CH_2)_2PCl_2$ was purchased from Strem Chemicals, or prepared according to the literature procedure [15]. All other starting materials were purchased from Aldrich. All operations were performed using flame dried apparatus under an argon atmosphere using common Schlenk techniques. Diethylether and thf were dried over sodium and distilled from benzophenone sodium ketyl before use. ^1H, ^{31}P and ^{13}C-NMR spectra were obtained on a Varian Gemini 200 spectrometer at 200, 80 and 50 MHz, respectively and are referenced to TMS (^1H and ^{13}C) and external 85% H_3PO_4 (^{31}P).

3.2. 1,2-Bis(di-2-pyridylphosphino)ethane, *1a*

2-Bromopyridine (9.05 ml, 95 mmol) in dry ether (50 ml) was added dropwise to a stirred solution of butyllithium (1.6 M solution in hexane, 60 ml, 95 mmol) in dry ether (500 ml) at −72°C. This mixture was stirred (5 h, −72°C) then $Cl_2P(CH_2)_2PCl_2$ (5.2 g, 22.6 mmol) in ether (100 ml) was added dropwise over 30 min. The mixture was allowed to warm to room temperature (r.t.) overnight and extracted with degassed water (4 × 400 ml). The combined aqueous extracts and precipitated solids were extracted with dichloromethane (3 × 400 ml), dried ($MgSO_4$), the solvent removed and the resulting solid recrystallised from acetone/acetonitrile. Yield 5.7 g (81%), colourless crystals, m.p. 135–137°C, (lit. 134–135°C [5]). ^{31}P-NMR ($CDCl_3$): $\delta = -6.0$ (lit. −6.1 [4]).

Alternatively, compound **1a** was synthesised via tris(2-pyridyl)phosphine (**2a**), prepared by a modification of the published procedures [7,16]. The addition of PCl_3 to three equivalents of 2-pyridyllithium (prepared as above) followed by the standard work up described for **1a** gave a brown solid which was recrystallised from methanol/water to give pure **2a** as a white solid (74%), m.p. 113°C, (lit. 113–114°C [16]); ^{31}P-NMR ($CDCl_3$): $\delta = -1.3$ (lit. −1.3 [16]). Compound **2a** (1.5 g, 5.6 mmol) in thf (20 ml) was treated with freshly cut slivers of lithium metal (75 mg, 11.2 mmol), and sonicated (16 h). The deep red mixture of lithium di-2-pyridyl-phosphide (^{31}P-NMR (thf): $\delta = 17.0$ (lit. 13.0 (C_6D_6) [14]) was then treated with freshly distilled dry *t*-butyl chloride (0.52 g, 5.6 mmol) and stirred (1 h, r.t.). This solution was cooled (−72°C) and 1,2-dibromoethane (0.44 g, 2.3 mmol) in diethyl ether (5 ml) was added and the solution stirred (2 h, −72°C) then allowed to warm slowly to r.t. The solvent was removed and the brown solid was extracted with dichloromethane (100 ml), washed with water (20 ml), dried ($MgSO_4$) and the solvent removed to afford a yellow solid which was recrystallised from acetone. Yield 0.42 g (45%). m.p. and ^{31}P-NMR identical to that obtained above.

3.3. 1,2-Bis(di-3-pyridylphosphino)ethane, *1b*

Butyllithium (121 ml, 192 mmol, 1.6 M in hexane) and dry TMEDA (29.2 ml, 192 mmol) were stirred for 15 min at r.t. then cooled to −72°C when cold ether (−72°C, 600 ml) was added. This mixture was then cooled to −115°C and 3-bromopyridine (18.1 ml, 192 mmol) in ether (100 ml) was added dropwise over 15 min, with vigorous stirring. This mixture was stirred (5 min) then $Cl_2P(CH_2)_2PCl_2$ (10.9 g, 47.2 mmol) was added dropwise over 1 min and the yellow mixture stirred for 2 h and then slowly warmed to −80°C over an 11 h period, followed by warming to r.t. over a 3–4 h period. The mixture was extracted with degassed water (4 × 200 ml) and the combined aqueous layers extracted with chloroform (4 × 200 ml) and dried ($MgSO_4$). The solvent and TMEDA were removed under high vacuum (0.2 mm, 5 h) to yield a dark yellow solid which was recrystallised from acetone. Yield 8.4 g (47%), light yellow crystals, m.p. 114–116°C. ^{31}P-NMR ($CDCl_3$): $\delta = -23.7$. ^1H-NMR ($CDCl_3$): $\delta = 2.16$ vt, $[^2J(P,H) + {}^3J(P,H)] = 8.7$ Hz, 4H, bridging CH_2; 7.59, m, 4H, H_4; 7.27, m, 4H, H_5; 8.59, m, 8H, H_2, H_6. $^{13}C\{^1H\}$-NMR ($CDCl_3$): $\delta = 22.91$, s, bridging CH_2; 123.70, s, C_5; 132.40, vt, $J(P,C) = 8.95$ Hz, C_3; 139.82, vt, $J(P,C) = 7.32$ Hz, C_4; 150.30, s, C_6; 153.18, vt, $J(P,C) = 12.61$ Hz, C_2. Anal. Found: C, 65.3; H, 5.1; N, 14.3. $C_{22}H_{20}N_4P_2$. Calc.: C, 65.67; H, 5.01; N, 13.92%.

3.4. 1,2-Bis(di-4-pyridylphosphino)ethane, *1c*

This compound was prepared by a similar procedure to compound **1b**. 4-Bromopyridine (15.3 g, 96.8 mmol) was added to TMEDA·*n*-BuLi (96.8 mmol) in ether at −115°C, followed by the immediate addition of $Cl_2P(CH_2)_2PCl_2$ (3.7 g, 15.8 mmol). After stirring for 15 min at −115°C the mixture was allowed to warm slowly to r.t. overnight, then was quenched with degassed saturated aqueous ammonium chloride solution (30 ml) and extracted with degassed water (7 × 60 ml). The combined aqueous phases were extracted with chloroform (6 × 40 ml) and the chloroform extracts then dried ($MgSO_4$), filtered and concentrated in vacuo. The product was obtained after washing with small

amounts of cold water. Yield 5.8 g (91%). An analytically pure sample was obtained by recrystallisation from ethanol, colourless crystals, m.p. 185–187°C. ^{31}P-NMR ($CDCl_3$): $\delta = -16.4$. ^{1}H-NMR ($CDCl_3$): $\delta =$ 8.58, m, 8H, H_2, H_6; 7.18, m, 8H, H_3, H_5; 2.12, vt, $J[^2J(P,H) + {}^3J(P,H)] = 9.3$ Hz, 4H, bridging CH_2. $^{13}C\{^1H\}$ ($CDCl_3$): $\delta = 149.79$, s, C_2, C_6; 146.30 ,vt, $J(P,C) = 9.86$ Hz, C_4; 126.93, vt, $J(P,C) = 8.14$ Hz, C_3,C_5; 22.33, bs, bridging CH_2. Anal. Found: C, 65.59; H, 5.01; N, 13.77. $C_{22}H_{20}N_4P_2$. Calc.: C, 65.67; H, 5.01; N, 13.92%.

3.5. Tris(3-pyridyl)phosphine, 2b

This was prepared by an analogous procedure to **1b**. 3-Bromopyridine (2.5 ml, 25.3 mmol) was added to TMEDA·*n*-BuLi (24 mmol) in ether at −115°C, followed by the immediate addition of PCl_3 (0.46 ml, 4.9 mmol). After 30 min, more PCl_3 (0.2 ml, 2.1 mmol) was added and the yellow mixture was stirred for 2 h at −100°C, before warming to r.t. overnight. The mixture was extracted with degassed water (3 × 100 ml) and the combined aqueous layers were extracted with chloroform (4 × 200 ml). Chloroform extracts were dried ($MgSO_4$), the solvent removed under high vacuum (0.2 mm, 5 h) to give a yellow oil (1.66 g). Repeated chromatography (basic alumina activity grade 1, chloroform/hexane 1/1) gave **2b**. Yield 1.03 g (47%), colourless oil. ^{31}P ($CDCl_3$): $\delta = -24.7$. ^{1}H ($CDCl_3$): $\delta = 7.32$, m, H_5; 7.62, m, H_4; 8.56, m, H_6; 8.64, m, H_2. $^{13}C\{^1H\}$ ($CDCl_3$): $\delta = 123.1$, d, $^3J(C,P) = 4.9$ Hz, C_5; 130.1, d, $^1J(C,P) = 15$ Hz, C_3; 140.1, d, $^2J(C,P) = 15.4$ Hz, C_4; 149.8, s, C_6; 153.2, d, $^2J(C,P) = 25$ Hz, C_2. Anal. Found: C, 67.5; H, 4.7; N, 15.6. $C_{15}H_{12}N_3P$. Calc.: C, 67.90; H, 4.56; N, 15.85%.

3.6. Tris(4-pyridyl)phosphine, 2c

PCl_3 (0.93 ml, 10.6 mmol) was reacted with a 4-pyridyllithium/TMEDA mixture (48.4 mmol) in ether at −115°C according to the standard method. A crude solid was obtained upon work-up by the procedure described for **1b** and was recrystallised from ethanol/hexane. Yield 1.4 g (49%), colourless crystals, m.p. 147°C. ^{31}P ($CDCl_3$): $\delta = -10.8$. ^{1}H ($CDCl_3$): $\delta = 7.06$, AA′BB′ multiplet, H_2, H_6; 8.50, AA′BB′ multiplet, H_3, H_5. $^{13}C\{^1H\}$ ($CDCl_3$): $\delta = 127.5$, d, $^2J(P,C) = 16.8$ Hz, C_3, C_5; 143.6, d, $^1J(P,C) = 16.9$ Hz, C_4; 149.7, d, $^3J(P,C) = 5.2$ Hz, C_2, C_6. Anal. Found: C, 67.7; H, 4.4; N, 15.7. $C_{15}H_{12}N_3P$. Calc.: C, 67.90; H, 4.56; N, 15.85%.

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