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Reactions of Heteroaryllithium Compounds with Phosphorus Trichloride, Phosphorus Oxychloride, and Thionyl Chloride. Formation of Heterocyclic Biaryls

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ABSTRACT

The reactions of four equivalents of heterocyclic aryllithium compounds with phosphorus trichloride or phosphorus oxychloride gave symmetrical heterocyclic biaryls in good yields. A similar coupling was found in the reactions of three equivalents of the lithium compounds with thionyl chloride.

INTRODUCTION

The reactions of organometallic reagents with phosphorus trichloride have been widely used to prepare tertiary alkyl or aryl phosphines. However, we have reported that the reaction of 2-benzothiazyllithium with phosphorus trichloride in diethyl ether gave a ligand coupling product, 2,2′-bibenzothiazyl, as the major product instead of the corresponding tertiary phosphine [1]. In our recent studies, we have found that many tertiary heteroaryl phosphines gave ligand coupling products by treatment with organolithium reagents [2]. Thus, tris(2-benzothiazyl)phosphine or tris(2-pyridyl)phosphine gave 2,2′-bibenzothiazyl or 2,2′-bipyridyl in the reaction with 2-benzothiazyllithium or 2-pyridyllithium, respectively [1,3]. A similar coupling was also found in the reactions of phosphine oxides bearing two or three pyridyl groups with organometallic reagents [3,4]. Also, many 2-pyridyl sulfoxides have been found to undergo ligand coupling by treatment with a Grignard reagent [5,6] or an organolithium reagent [6,7]. This coupling reaction has been applied further for the syntheses of oligopyridines [8]. Recently, 2-thienyllithium was found to react with thionyl chloride, forming 2,2′-bithienyl in good yield [7]. These findings suggest that reactions of heterocyclic aryllithium reagents with phosphorus trichloride, phosphorus oxychloride, or thionyl chloride can be utilized as good routes for the synthesis of heterocyclic biaryls. Thus, we have examined reactions of an excess of heterocyclic aryllithiums with phosphorus trichloride and phosphorus oxychloride, as well as with thionyl chloride, and we have found a new synthetic method to prepare heterocyclic biaryls by ligand coupling.

RESULTS AND DISCUSSION

2-Pyridyllithium compounds were prepared by reactions of the corresponding 2-bromopyridines (**1a–e**) with butyllithium in diethyl ether. 2-Benzothiazyllithium and 2-quinolyllithium were prepared by treating 2-benzothiazole (**1f**) and 2-bromoquinoline, respectively, with butyllithium.

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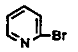
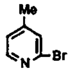
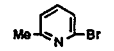
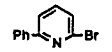
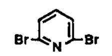
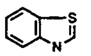
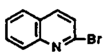
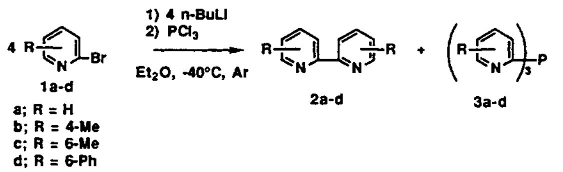
TABLE 1 Reactions of Heterocyclic Aryllithium Compounds with PCl_3, $POCl_3$, and $SOCl_2$

Starting Material		Ligand Coupling Product Yield (%)[a]					
		PCl_3		$POCl_3$		$SOCl_2$	
1a		**2a** **3a**	50 18	**2a**	51	**2a**	55
1b		**2b** **3b**	45 29	**2b**	58	**2b**	47
1c		**2c** **3c**	16 72	**2c**	62	**2c**	63
1d		**2d** **3d**	53 35	**2d**	58	**2d**	75
1e		**2e** **3e**	16 9 36	**2e**	70	**2e**	77
1f				**2f**	55	**2f**	40
1g				**2g**	44	**2g**	43

[a] Isolated yields were calculated based on PCl_3, $POCl_3$, and $SOCl_2$.

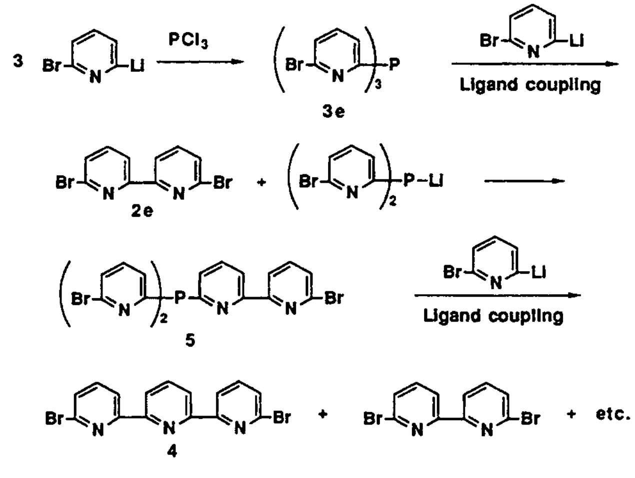
When phosphorus trichloride was added slowly to a solution of four equivalents of 2-pyridyllithium in diethyl ether at −40°C, 2,2′-bipyridyl (**2a**) and tris(2-pyridyl)phosphine (**3a**) were obtained in 50 and 18% yields, respectively. The reactions of some substituted 2-pyridyllithiums with phosphorus trichloride also gave both the coupling products (**2b–e**) and the corresponding tertiary phosphines (**3b–e**) (Equation 1), as shown in Table 1.



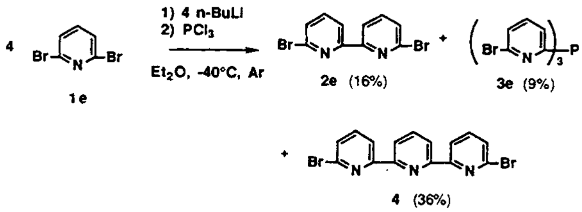
(1)

As expected, substituents present on the pyridine ring affected the yields of the coupling products and the tertiary phosphines. For example, when 2-bromo-6-methylpyridine (**1c**) was used as the starting material, only 16% of the coupling product (**2c**) and 72% of tris[2-(6-methylpyridyl)]phosphine (**3c**) were obtained.

The reaction of phosphorus trichloride with three equivalents of 6-bromopyrid-2-yllithium had been investigated previously by Perks *et al.*, and tris[2-(6-bromopyridyl)]phosphine (**3e**) had been obtained in 75% yield [9]. However, we have now found that when phosphorus trichloride was added to a solution of four equivalents of 6-bromopyrid-2-yllithium, **3e** was obtained in only 9% yield. In this reaction, 6,6′-dibromo-2,2′-bipyridyl (**2e**) and 6,6″-dibromo-2,2′:6′,2″-terpyridine (**4**) were obtained as the coupling products in 16 and 36% yields, respectively (Equation 2).



SCHEME 1



(2)

A possible mechanism for the formation of the 6,6″-dibromo-2,2′:6′,2″-terpyridine involves ligand coupling of **3e** with 6′-bromo-6-lithio-2,2′-pyridine, the 6′-bromo-6-lithio-2,2′-pyridine having been formed by ligand coupling of **3e** with 2,6-dilithiopyridine or by an equilibrium being established between **2e** and 6-bromopyrid-2-yllithium. The latter possibility, however, was ruled out because no 6,6″-dibromo-2,2′:6′,2″-terpyridine was formed in the similar coupling reactions of 6-bromopyrid-2-yllithium with phosphorus oxychloride and thionyl chloride, as will be mentioned subsequently.

The most plausible mechanism for the formation of the 6,6″-dibromo-2,2′:6′,2″-terpyridine is shown in Scheme 1. The mechanism involves the initial formation of bis[2-(6-bromopyridyl)]2-[6-(6′-bromopyrid-2′-yl)]pyridylphosphine (**5**) with a subsequent ligand coupling process involving the resulting phosphine (**5**) by the action of 6-bromopyrid-2-yllithium. The reaction between lithium diphenylphosphide and 6,6′-dibromo-2,2-dipyridyl has been reported by Ziessel [10] to take place under mild conditions to afford the expected tertiary phosphine. The ligand coupling reaction of the phosphine (**5**) with 6-bromopyrid-2-yllithium, however, would give two coupling products, i.e., **2** and **4** as observed. Further studies on the mechanism for the formation of 6,6″-dibromo-2,2′:6′,2″-terpyridine are under way.

The results are rather interesting because the reaction can be used as a one-pot synthesis of 6,6″-dibromo-2,2′:6′,2″-terpyridine from 2,6-dibromopyridine. 6,6″-Dibromo-2,2′:6′,2″-terpyridine has been prepared previously by vapor-phase bromination of 2,2′:6′,2″-terpyridine [11], by treating 1,5-bis(6-bromo-2-pyridyl)-1,5-dioxopentane with ammonium acetate [12], or by the reaction [2′-(6″-bromo-2″-pyridyl)-2′-oxoethyl]pyridinium iodide with 2-bromo-6-(3′-dimethylammonio-1′-oxopropyl)pyridine chloride in the presence of ammonium acetate [12,13].

When the reactions were carried out with phosphorus oxychloride, under the conditions mentioned above, the corresponding 2,2′-bipyridyls were similarly obtained in good to moderate yields. These results are also shown in Table 1. In the reaction of 6-bromopyrid-2-yllithium, **2e** was obtained in a 70% yield, but no 6,6″-dibromo-2,2′:6′,2″-terpyridine was found among the products.

The use of other heterocyclic aryllithium reagents, such as 2-benzothiazyllithium and 2-quinolyllithium, gave similar results to those reported for the reactions of the 2-pyridyllithium reagents, as shown in Table 1 (Scheme 2).

We have also examined the reaction of thionyl chloride with three equivalents of the lithiated heterocycles. As shown in Table 1, the coupling products were obtained in similar yields to those obtained by the reactions with phosphorus oxychloride.

Although some tertiary phosphines were obtained in the reactions of the lithium compounds with phosphorus trichloride, the yields of tertiary phosphine oxides and bis(heteroaryl) sulfoxides were found to be negligible in the reactions with phosphorus oxychloride and thionyl chloride, respectively. These results reveal that the symmetrical heterocyclic biaryls are formed by ligand coupling of the resulting phosphine oxides or sulfoxides with the lithium reagents, and that the ligand coupling reactions of the phosphine oxides and sulfoxides are faster than those of the corresponding tertiary phosphines.

EXPERIMENTAL

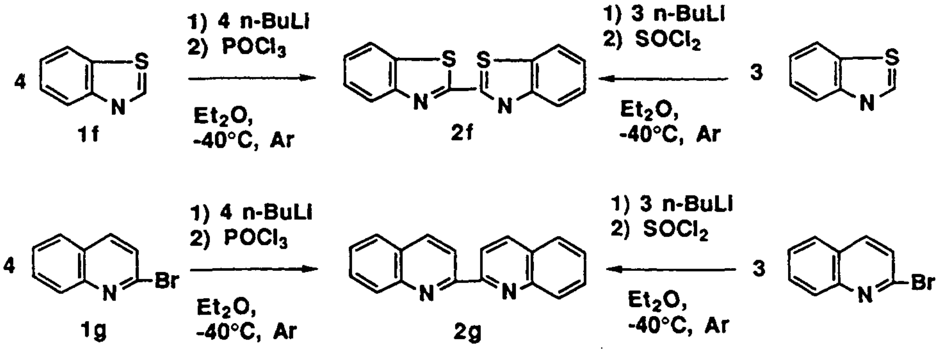
All of the melting points are uncorrected. Mass spectra were measured with a JEOL JMS-AX505W instrument at an ionization voltage of 70 eV.

A Typical Procedure for the Reaction of Heteroaryllithium Compounds with Phosphorus Trichloride or Phosphorus Oxychloride

A solution of butyllithium (30 mmol) in hexane (19 mL) was added to a solution of 2-bromopyridine (4.76 g, 30 mmol) in diethyl ether (20 mL) with stirring at −60°C under an argon atmosphere. After the reaction mixture had been stirred for 2 hours at −40°C, a solution of phosphorus trichloride (1.03 g, 7.5 mmol) in diethyl ether (20 mL) was slowly added at −40°C. The reaction mixture was stirred for 2 hours, warmed to room temperature, and then mixed with water (30 mL). The ether layer was washed with water and dried over Na_2SO_4. After the removal of solvent, the crude product was separated by column chromatography on silica gel using a mixture of benzene and ethyl acetate (1:1) as eluent to afford 2,2′-bipyridyl (**2a**) and tris(2-pyridyl)phosphine (**3a**) in 50 and 18% yields, respectively. The yields of the isolated products listed in Table 1 are based on phosphorus trichloride or phosphorus oxychloride.

Reaction of 6-Bromopyrid-2-yllithium with Phosphorus Trichloride

A solution of butyllithium (50 mmol) in hexane (31 mL) was added to a solution of 2,6-dibromopyridine (11.85 g, 50 mmol) in diethyl ether (50 mL) with stirring at −60°C under an argon atmosphere. After the reaction mixture had been stirred for 2 hours at −40°C, a solution of phosphorus trichloride (1.72 g, 12.5 mmol) in diethyl ether (50 mL) was slowly added at −40°C. The reaction mixture was stirred for 2 hours, warmed to room temper-



SCHEME 2

ature, and then mixed with water (100 mL). The solid product was separated from the solution by filtration, washed with water, and dried. The ether layer was washed with water and dried with Na_2SO_4, and then the solvent was evaporated. The combined crude mixture was subjected to column chromatography (silica gel, toluene). Sublimation of the first fraction gave **2e** and **4** in 16 and 36% yields, respectively, based on phosphorus trichloride used. These products were purified by recrystallization from toluene. The second fraction gave **3e** in a 9% yield.

A Typical Procedure for Reactions of Heteroaryllithiums with Thionyl Chloride

A solution of butyllithium (20 mmol) in hexane (13 mL) was added to a solution of 2-bromoquinoline (4.15 g, 20 mmol) in diethyl ether (20 mL) with stirring at −60°C under an argon atmosphere. After the reaction mixture had been stirred for 2 hours at −40°C, a solution of thionyl chloride (0.78 g, 6.7 mmol) in diethyl ether (20 mL) was added slowly at −40°C. The reaction mixture was stirred for 2 hours, warmed to room temperature, and then treated with water (30 mL). The ethereal layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the crude product was separated by column chromatography on silica gel using dichloromethane as eluent to afford 2,2′-biquinolyl (**2g**) in 43% yield based on thionyl chloride.

2,2′-Bipyridyl (**2a**)

Mp 70.5–71.5°C, lit., mp 70.5–71.5°C [14]; MS *m/z* (rel intensity) 157 (12), 156 (M^+, 100), 155 (39), 129 (19), 128 (23), 78 (16).

4,4′-Dimethyl-2,2′-bipyridyl (**2b**)

Mp 170.0–171.0°C, lit., mp 171–172°C [15]; MS *m/z* (rel intensity) 185 (14), 184 (M^+, 100), 183 (56).

6,6′-Dimethyl-2,2′-bipyridyl (**2c**)

Mp 88.5–89.5°C, lit., mp 88–89°C [16]; MS *m/z* (rel intensity) 185 (14), 184 (M^+, 100), 183 (36), 169(17).

6,6′-Diphenyl-2,2′-bipyridyl (**2d**)

Mp 177–178°C, lit., mp 176–178°C [17]; MS *m/z* (rel intensity) 309 (26), 308 (M^+, 100), 307 (28), 154 (13).

6,6′-Dibromo-2,2′-bipyridyl (**2e**)

Mp 219.5–220.5°C, lit., mp 220–221°C [18]; MS *m/z* (rel intensity) 316 (M^+ +4, 6), 315 (47), 314 (M^+ +2, 13), 313 (100), 312 (M^+, 6), 311 (53), 235 (53), 233 (50), 154 (17), 153 (25), 126 (11), 77 (19), 78 (13).

2,2′-Bibenzothiazyl (**2f**)

Mp 314–316°C, lit., mp 310°C [19]; MS *m/z* (rel intensity) 270 (13), 269 (21), 268 (M^+, 100), 134 (12), 108 (20), 91 (10), 69 (17).

2,2′-Biquinolyl (**2g**)

Mp 192–193°C, lit., mp 192–193°C [20]; MS *m/z* (rel intensity) 257 (19), 256 (M^+, 100), 255 (57), 128 (16).

Tris(2-pyridyl)phosphine (**3a**)

Mp 113–114°C, lit., mp 113–114°C [2]; MS *m/z* (rel intensity) 265 (M^+, 15), 188 (12), 187 (100), 186 (21).

Tris[2-(4-methylpyridyl)]phosphine (**3b**)

Mp 96–97°C, lit., mp 96–97°C [3]; Ms *m/z* (rel intensity) 307 (M^+, 19), 216 (23), 215 (100), 214 (14), 200 (14).

Tris[2-(6-methylpyridyl)]phosphine (**3c**)

Mp 113.5–114.5°C, lit., mp 113.5–114.5°C [3]; Ms *m/z* (rel intensity) 307 (M^+, 26), 216 (15), 215 (100), 214 (13), 200 (15), 93 (11).

Tris[2-(6-phenylpyridyl)]phosphine (**3d**)

Mp 185.5–186.5°C, Ms *m/z* (rel intensity) 493 (M^+, 21), 340 (24), 339 (100), 338 (12), 154 (23), 153 (10), 127 (12), 78 (14). Anal. calcd for $C_{33}H_{24}N_3P$:C, 80.31: H, 4.90; N, 8.51. Found: C, 80.35; H, 4.73; N, 8.42.

Tris[2-(6-bromopyridyl)]phosphine (**3e**)

Mp 225–226°C, lit., mp 226–227°C [9]; Ms *m/z* (rel intensity) 502 (M^+ +3, 13), 500 (M^+ +1, 13), 424 (19), 422 (37), 420 (19), 347 (51), 346 (14), 345 (100), 344 (11), 343 (54), 266 (22), 264 (19), 185 (20), 184 (16), 158 (20), 156 (16), 108 (19), 76 (24).

6,6″-Dibromo-2,2′:6′2″-terpyridine (**4**)

Mp 263–264°C, lit, mp 262–263°C [12,16]; MS *m/z* (rel intensity) 392 (M^+ +3, 52), 390 (M^+ +1, 100), 388 (M^+ −1, 53), 312 (14), 311 (77), 309 (80), 230 (30), 203 (13), 153 (21), 126 (14), 115 (16), 102 (14), 76 (16).

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