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SYNTHESES EMPLOYING PYRIDYLLITHIUM REAGENTS: NEW ROUTES TO 2,6-DISUBSTITUTED PYRIDINES AND 6,6′-DISUBSTITUTED 2,2′-BIPYRIDYLS

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SUMMARY

New 2,6-disubstituted pyridine derivatives have been synthesized employing 6-bromo-2-lithiopyridine as an intermediate. Subsequent replacement of the 6-bromine can be effected by metal–halogen exchange or other reactions in some cases. Reactions of the previously unreported 6-lithio-2,2′-bipyridyl and 6,6′-dilithio-2,2′-bipyridyl are described. Cupric chloride was found to be an effective coupling agents for lithiopyridine reagents, allowing facile and high yield syntheses of substituted 2,2′-bipyridyls.

INTRODUCTION

While organolithium compounds are among the most versatile reagents in synthetic chemistry, those in which lithium is bound to a carbon atom in a pyridine ring have received considerably less attention. Although the three isomeric pyridyllithiums and several of their variously substituted congeners have been employed in the synthesis of substituted pyridines[1], the introduction of two substituents into the pyridine ring via pyridyllithium intermediates has not been described. In addition, organolithium derivatives of a polypyridyl have not been reported**.

In the course of a program to synthesize six-coordinate transition metal complexes of non-octahedral geometry[3,4], the previously unknown compound tris(2-aldoximo-6-pyridyl)phosphine was desired. The successful route to this substance took advantage of Gilman's observation[5] that 2,6-dibromopyridine is only monolithiated on metal–halogen exchange with n-butyllithium. Treatment of 2-lithio-6-bromopyridine with DMF afforded the 2-aldehyde, whose 6-lithio-2-dioxolanyl derivative yielded the corresponding tripyridylphosphine upon treatment with phosphorous trichloride. Liberation of the aldehyde and oximation gave the desired compound[3]. We have investigated the reactions of 6-bromo-2-pyridyllithium with a

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** Polypyridyllithium derivatives referred to in this article are those containing carbon–lithium bonds, in distinction to the "ionic" species formed in the reaction between lithium metal and 2,2′-bipyridyl in ethereal solvents[2].

(*continued on p.* 56)

TABLE 1

SYNTHESES EMPLOYING 6-BROMO-2-PYRIDYLLITHIUM (I)

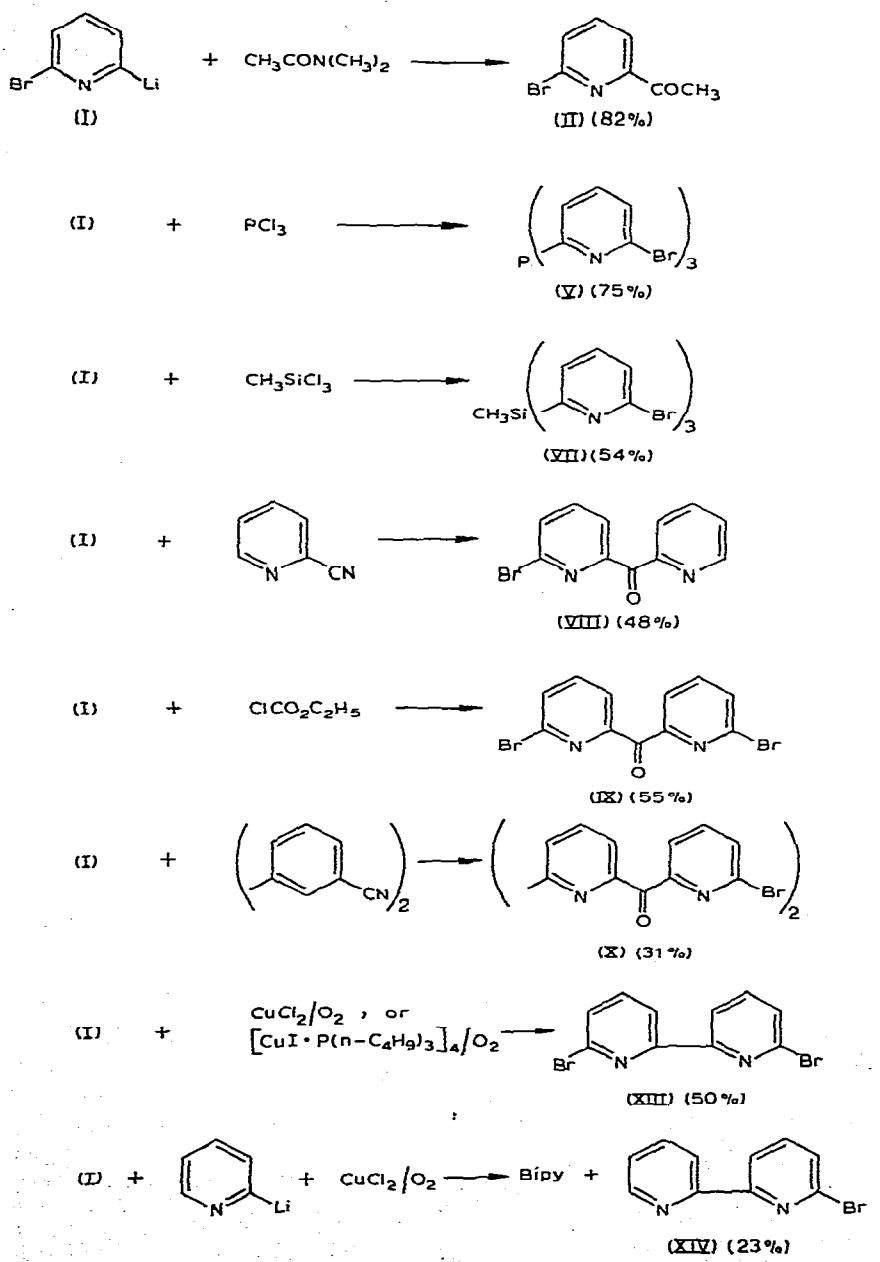
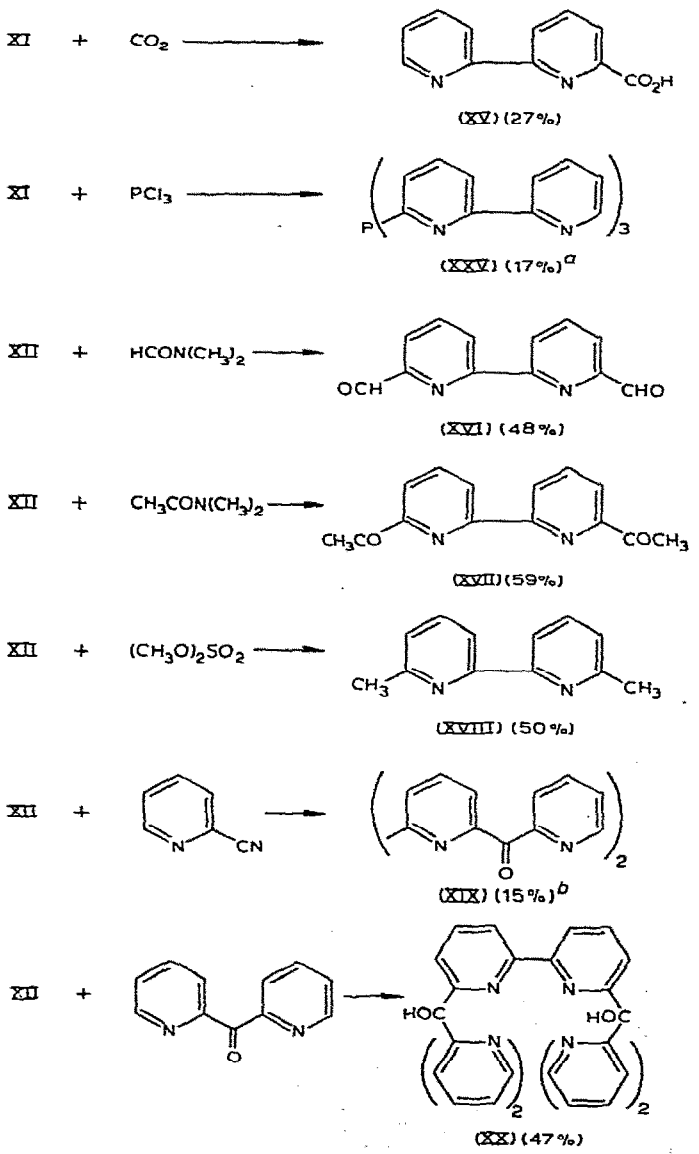


TABLE 2

SYNTHESES EMPLOYING 6-LITHIO-2,2'-BIPYRIDYL (XI) AND 6,6'-DILITHIO-2,2-BIPYRIDYL (XII)



[a] *Cf.* ref. 4. [b] This compound was also prepared by an Ullman coupling reaction employing 6-bromo-2-picolinoylpyridine (VIII) and copper powder in hot DMF (yield 6.6% after purification).

wide variety of substrates, leading to the synthesis of 6-bromo-2-substituted pyridines (Table 1). The 6-bromo substituent in certain of these compounds can be utilized to introduce additional functional groups via metal–halogen exchange. Alternatively, addition of appropriate coupling reagents to the 6-lithio intermediates allows the formation of substituted polypyridyls. Bromobipyridyls prepared in this manner can serve as starting materials for further lithiation reactions, thus extending the range of synthetic possibilities (Table 2).

EXPERIMENTAL

Materials. Substituted pyridines were purchased from Aldrich Chemical Company. Hexane solutions of n-butyllithium (Foote Mineral Co.) were analyzed by the double titration method[6,7], using a 1,2-dibromoethane quench; typical concentrations were 1.62–1.66 *N*. Diethyl ether and tetrahydrofuran (THF) were distilled under nitrogen from lithium aluminum hydride before use. All reactions involving organolithium reagents were run under nitrogen.

Physical measurements. PMR spectra were obtained on Varian T-60 or HA-100 spectrometers and chemical shifts are referred to internal TMS. Infrared spectra were measured in Kel-F mulls with a Perkin–Elmer Model 337 grating spectrophotometer. Mass spectra were recorded at 70 eV using a Hitachi–Perkin–Elmer Model RMU-6 instrument with a direct inlet attachment. Melting points are corrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. or by the Microchemical Laboratory at MIT.

Reaction set-up. All reactions were carried out in a 3-necked flask equipped with a pressure-equalizing addition funnel, a mechanical stirrer, and a thermometer (low temp.) and nitrogen inlet. Temperatures were controlled by means of a pentane–liquid nitrogen slush bath that could be raised and lowered below the reaction vessel so as to allow various degrees of immersion.

6-Bromo-2-lithiopyridine (I). To a slurry of 2,6-dibromopyridine (190 g, 0.80 mol) recrystallized from benzene–heptane (m.p. 118–119°) in ether (1500 ml) cooled below −60°, n-butyllithium (500 ml, 1.6 *N* in hexane) was added at such a rate that the temperature of the reaction mixture did not exceed −60°. After addition was complete, the reaction mixture was allowed to warm to −40° for 15 min; a clear yellow solution resulted. (Warming above −40° resulted in green solutions and lower yields.) Solutions prepared in this manner were cooled to the required temperature and used in the subsequent reactions.

Compounds obtained from 6-bromo-2-lithiopyridine

6-Bromo-2-acetylpyridine (II). *N,N'*-Dimethylacetamide (16.3 ml, 0.13 mol) was added at −80° to 6-bromo-2-lithiopyridine (from 29.7 g of 2,6-dibromopyridine and 78.3 ml of 1.6 *N* n-butyllithium solution) in ether solution (300 ml). The solution was allowed to warm to −40° while stirring for 2 h, and was then hydrolyzed with saturated aqueous NH_4Cl (50 ml). The aqueous layer was separated, washed twice with ether and the united ether extracts were dried (Na_2SO_4) and evaporated to a solid residue. Two recrystallizations from ether–pentane gave white crystals of 6-bromo-2-acetylpyridine (20.5 g, 82%), m.p. 54–55°. (Found: C, 42.39; H, 3.00; N, 7.41. C_7H_6BrNO calcd.: C, 42.02; H, 3.00; N, 7.00%). IR (Kel-F mull) 1700 cm^{-1} (C=O).

PMR ($CDCl_3$): multiplet, 7.6 to 8.0 ppm, (3, ring protons); singlet, 2.60 ppm (3, methyl); mol. wt. 199, 201 (mass spectr.).

6-Bromo -2-(2-methyl-1,3-dioxolan-2-yl)pyridine (III). A mixture of 6-bromo-2-acetylpyridine (16.5 g, 0.081 mol), ethylene glycol (10 ml, 0.17 mol), *p*-toluenesulfonic acid monohydrate (4.5 g), 2,2'-dimethoxypropane (6.9 g, 0.11 mol) and benzene (300 ml) was slowly distilled (Vigreux column) over a 4 h period until the boiling point exceeded 61°. The undistilled residue was added to an aqueous sodium carbonate solution (250 ml, saturated), the aqueous and organic layers separated, washed with water (2 × 50 ml), dried (Na_2SO_4), and evaporated to a greenish oil which distilled at 100–110° (0.2 mm) and solidified to a white solid. Recrystallization from ether–hexane afforded pure III (13.6 g, 68%), m.p. 44–46°. (Found: C, 44.31; H, 4.06; N, 5.68. $C_9H_{10}BrNO_2$ calcd.: C, 44.26; H, 4.13; N, 5.74%.) PMR ($CDCl_3$), multiplet 7.3–7.6 ppm, (3, ring protons); singlet 1.70 ppm, (3, methyl); 3.8–4.2 ppm, (4, dioxolanyl ring).

2-(2-Methyl-1,3-dioxolan-2-yl)pyridine (IV). n-Butyllithium (6.25 ml of 1.6 *N* in hexane, 0.01 mol) was treated at −50° with III (2.44 g, 0.01 mol) in ether solution (50 ml). A yellow precipitate formed immediately. The suspension was hydrolyzed with water (15 ml) after stirring for 30 min at −50°. The aqueous fraction was washed with ether (2 × 50 ml), the combined ether fractions were dried and evaporated, and the residue recrystallized from ether at −40° to give white crystals of IV (1.35 g, 83%). The compound was identified by comparison with an authentic sample[8].

Tris(6-bromo-2-pyridyl)phosphine (V). Phosphorus trichloride (3.7 g, 0.27 mol) in 50 ml ether was slowly added during the course of 30 min to an ether solution (500 ml) of 6-bromo-2-lithiopyridine (from 194 g of 2,6-dibromopyridine and 505 ml of 1.6 *N* n-butyllithium) at −90°. After an initial blood red color developed, the reaction mixture turned pale yellow and deposited a white solid. After warming to −10° during 4 h, the reaction mixture was quenched with HCl (2 *N*, 200 ml) and filtered. Washing of the precipitate with acetone and recrystallization from boiling xylene (3000 ml) gave white needles of V (100 g, 75%), m.p. 226–227°. (Found: C, 35.54; H, 1.93; N, 8.18. $C_{15}H_9Br_3N_3P$ calcd.: C, 35.86; H, 1.79; N, 8.36%.)

Tris(6-cyano-2-pyridyl)phosphine (VI). Finely powdered V (25 g, 0.050 mol) was added to a well-stirred solution of cuprous cyanide (25 g, 0.280 mol) in dry pyridine (150 ml) and refluxed for 12 h. After cooling (ice-bath), saturated aqueous sodium cyanide (200 ml) was added, the mixture stirred for 8 h and then filtered. The crude solid product was washed with small portions of water (5 × 50 ml) and then with methanol until the washings were colorless. Sublimation (240°, 0.001 mm) and recrystallization from DMF/1-butanol yielded white crystals of VI (9.0–10.5 g, 53–62%), m.p. 257–259°. (Found: C, 63.57; H, 2.88; N, 24.78; P, 9.15. $C_{18}H_9N_6P$ calcd.; C, 63.52; H, 2.65; N, 24.70; P, 9.13%.) IR (Kel-F mull) 2230 cm^{-1} ($C\equiv N$).

Methyltris(6-bromo-2-pyridyl)silane (VII). Freshly distilled methyltrichlorosilane (1.50 g, 0.010 mol) in 100 ml ether was added slowly over 30 min to 150 ml of an ether solution of 6-bromo-2-lithiopyridine (from 7.1 g of 2,6-bromopyridine and 14.7 ml of 1.6 *N* n-butyllithium) at −90°. The red-brown solution was stirred for 2h, allowed to warm to −40°, and quenched with methanol (40 ml). The solvent was removed and the residue recrystallized under nitrogen from THF to give colorless crystals of VII (2.8 g, 54%), m.p. 147–149°. (Found: C, 37.59; H, 2.31; N, 8.54. $C_{16}H_{12}Br_3N_3Si$ calcd.: C, 37.38; H, 2.35; N, 8.17%.) The compound is quickly

hydrolyzed by water. PMR($CDCl_3$): multiplet, 7.4–7.8 ppm (3, ring protons); singlet, 1.0 ppm, (1, $SiCH_3$).

6-Bromo-2-picolinoylpyridine (VIII). A solution of 2-cyanopyridine (10.9 g, 0.10 mol) in 125 ml of ether was added to an ether solution (750 ml) of 6-bromo-2-lithiopyridine (from 23.7 g of 2,6-dibromopyridine and 62.5 ml of 1.6 *N* n-butyllithium) at −80° at an addition rate maintaining the temperature below −70°. The purple suspension was stirred at −70° for 30 min, and allowed to warm to room temperature. The mixture was poured over ice (500 g), extracted with dilute HCl (1 *N*, 3 × 150 ml), and the acidic aqueous fraction was warmed on the steam bath for 1 h. Neutralization with sodium carbonate precipitated the product, which was dried, triturated with cold ether (100 ml), sublimed twice (120°, 0.01 mm) and recrystallized from ether–pentane to give white prisms of VIII (12.5 g, 48%), m.p. 84.5–86.5°. (Found: C, 50.50; H, 2.61; N, 10.68. $C_{11}H_7BrN_2O$ calcd.: C, 50.21; H, 2.68; N, 10.65%.) IR (Kel-F mull) 1690 cm^{-1} (C=O); mol. wt. 262, 264 (mass spectr.).

Bis(6-bromo-2-pyridyl)ketone (IX). A solution of ethyl chloroformate (7.2 g, 0.067 mol) in 500 ml of ether was added during 15 min to an ether solution (250 ml) of 6-bromo-2-lithiopyridine (from 23.7 g of 2,6-dibromopyridine and 62.5 ml of 1.6 *N* n-butyllithium) cooled to −90°. The deep blue solution was stirred for 1 h, warmed to −40° for 30 min, and quenched successively with methanol (50 ml), conc. HCl (10 ml), and water (50 ml). Ether was removed on a rotary evaporator, the resulting slurry was extracted with chloroform (50 ml), the organic extract was washed with water (50 ml), dried (Na_2SO_4), and the solvent was removed to yield a buff solid. The product was triturated with boiling ether (2 × 50 ml), and the residue was recrystallized twice from 95% ethanol to give off-white needles of IX (7.9 g, 55%), m.p. 155–156.5°. (Found: C, 38.62; H, 1.84; N, 7.75. $C_{11}H_6Br_2N_2O$ calcd.: C, 38.63; H, 1.77; N, 8.19%.) IR (Kel-F mull) 1690 cm^{-1} (C=O); PMR($CDCl_3$): multiplet, 7.69 ppm (2); multiplet, 8.05 ppm (1).

6,6′-Bis(6-bromo-2-picolinoyl)-2,2′-bipyridyl (X). A solution of 6,6′-dicyano-2,2′-bipyridyl[9] (4.6 g, 0.044 mol) was added to an ether solution of 6-bromo-2-lithiopyridine (from 9.48 g of 2,6-dibromopyridine and 25 ml of 1.6 *N* n-butyllithium) at −80° at an addition rate maintaining the temperature between −70° to −65°. The deep purple solution was stirred for 90 min, warmed to −30°, and quenched with HCl (2 *N*, 100 ml). The solvent was stripped off, the residue boiled for 1 h with HCl (6 *N*, 200 ml), and the product was filtered. Three recrystallizations from benzene gave pale yellow X (3.3 g, 31%), m.p. 221–222°. (Found: C, 50.45; H, 2.17; N, 10.50. $C_{22}H_{12}Br_2N_4O_2$ calcd.: C, 50.41; H, 2.31; N, 10.69%.) IR (Kel-F mull) 1680 cm^{-1} (C=O).

Compounds obtained from 6-lithio-2,2′-bipyridyl (XI) and 6,6′-dilithio-2,2′-bipyridyl (XII)

The precursors to the desired lithium reagents, 6-bromo-2,2′-bipyridyl and 6,6′-dibromo-2,2′-bipyridyl, have previously been prepared by the inconvenient procedure of gas phase bromination of 2,2′-bipyridyl[9]. 6-Bromo-2,2′-bipyridyl has also been obtained via a three-step synthesis from 2,2′-bipyridyl[10]. The following methods are simpler and give comparable or better yields.

6,6′-Dibromo-2,2′-bipyridyl (XIII). A solution of 6-bromo-2-lithiopyridine (from 119 g of 2,6-dibromopyridine and 313 ml of 1.6 *N* n-butyllithium) in ether

(1000 ml) was cooled to −90°, and powdered anhydrous cupric chloride (33.6 g, 0.250 mol) was added. The strongly stirred yellow suspension was allowed to warm to the reaction temperature of −70°, where a strongly exothermic reaction lasting about one minute began. The suspension was stirred and cooled well enough to keep the temperature below −50°, with stirring being continued for an additional 30 min after the reaction had subsided. Oxidation with dry compressed air at −60 to −50° for 20 min or until the brown suspension turned green led to precipitation of the product. The suspension was hydrolyzed with HCl (6 *N*, 500 ml), and filtered at room temperature. The ether fraction may be concentrated to give an additional few grams of product. The yellow solid was washed with dilute HCl to extract traces of copper, dried (Na_2SO_4), and recrystallized from benzene to give white needles of XIII (39.3 g, 50%), m.p. 221–223° (lit[9]., 218°). Alternatively, $[CuI \cdot P(n\text{-}C_4H_9)_3]_4^7$ (4.91 g, 0.0125 mol) in ether (25 ml) was added to 6-bromo-2-lithiopyridine (from 5.88 g of 2,6-dibromopyridine and 15.6 ml of 1.6 *N* n-butyllithium) at −78°. In contrast to the preceding reaction, there was no noticeable liberation of heat; the solution turned red-orange. Dry oxygen was then bubbled through, with the color changing first to green and then to black. The mixture was hydrolyzed with conc. HBr (10 ml), and worked up as above. Sublimation of the crude product (220°, 20 mm) and recrystallization gave white needles of XIII (1.90 g, 49%), m.p. 226–227°. Oxidation of the dipyridylcuprate intermediate with nitrobenzene or bis(acetylacetonato)copper (II) gave inferior yields (23 and 30%, respectively). Substitution of THF for ether as solvent failed to improve any of the above yields.

6-Bromo-2,2'-bipyridyl (*XIV*). A mixture of 2,6-dibromopyridine (23.5 g, 0.10 mol) and 2-bromopyridine (31.6 g, 0.20 mol) in THF (300 ml) was treated with n-butyllithium (188 ml of 1.6 *N*, 0.30 mol) using the conditions described for 6-bromo-2-lithiopyridine. The mixture was treated with anhydrous cupric chloride (21.6 g, 0.16 mol) at −90°, and allowed to react as previously described for XIII. The brown suspension obtained after oxygenation was hydrolyzed with water (250 ml) at −40°, the THF evaporated and sufficient KCN added to complex all copper (loss of green color). (Use of H_2S to destroy the copper complexes leads to slightly lower yields.) The mixture was extracted with chloroform (3 × 150 ml), the extracts washed with water, and the chloroform removed. The bipyridyl and monobromobipyridyl were extracted into several portions of warm dilute HCl (2 *N*, 50 ml each). After recovery of the bipyridyls from the neutralized extract, they were separated by fractional distillation at 2.2 mm, 2,2'-bipyridyl being collected at 96–100°, and 6-bromo-2,2'-bipyridyl at 130–133°. Recrystallization from hexane gave white flakes of XIV (5.3 g, 23%), m.p. 69–70° (lit. 74°[9], 70–71°[10]).

2,2'-Bipyridyl-6-carboxylic acid (*XV*). An ether solution (25 ml) of 6-bromo-2,2'-bipyridyl (1.41 g, 6.0 mmol) was added to 3.75 ml of 1.6 *N* n-butyllithium in 25 ml of ether at −70°. The brick-red solution was stirred at −40° for 25 min and carbonated (Dry-Ice/ether slush). The ether suspension was extracted with several portions of dilute NaOH; the basic solution was chilled, acidified to pH 1 with HCl, and extracted with ether to remove valeric acid (11%). The acidic solution was buffered with sodium acetate, and addition of cupric acetate (0.6 g) precipitated a copper complex of XV (0.80 g). This complex was suspended in water (250 ml) and decomposed with H_2S; concentration of the solution after filtering through celite gave white crystals of XV (0.32 g, 27%), m.p. 205° (sint. 155°) (lit.[9], 210–220° (dec.)).

6,6'-Dilithio-2,2'-bipyridyl (XII). n-Butyllithium (12.5 ml of 1.6 *N*, 0.020 mol) was transferred via syringe into dry THF (100 ml) at −80°. A warm solution of 6,6'-dibromo-2,2'-bipyridyl (3.14 g, 0.010 mol) in THF (150 ml) was then dropped into the cooled solution at a rate fast enough to avoid extensive precipitation at the spout of the addition funnel, yet slow enough to maintain the temperature below −70°. The reaction mixture became dark red after 45 min stirring at −75° (higher temperatures resulted in greenish solutions and lower yield). *Assay*: The above solution was quenched at −70° with methanol (50 ml), warmed to room temperature, evaporated to dryness and the solid residue extracted with boiling benzene (3 × 50 ml). TLC (alumina, benzene) revealed three components identified as 6,6'-dibromo-, 6-bromo-, and unsubstituted 2,2'-bipyridyl by comparing R_f values with those of authentic samples. The benzene solution was concentrated and chromatographed on a 1" × 6" alumina column. The first fraction eluted (1.4 g) was shown to be 93% 2,2'-bipyridyl and 7% 6-bromo-2,2'-bipyridyl (PMR spectrum). The yield of 6,6'-dilithio-2,2'-bipyridyl was therefore 80%.

6,6'-Diformyl-2,2'-bipyridyl (XVI). *N,N*-Dimethylformamide (3.9 ml, 50 mmol) in 50 ml of ether was added during 20 min to a solution of 6,6'-dilithio-2,2'-bipyridyl (from 4.72 g of 6,6'-dibromo-2,2'-bipyridyl and 19.4 ml of 1.6 *N* n-butyllithium) in 350 ml of THF at −80°. The deep purple solution was stirred for 1 h at −80°, allowed to warm to −30°, and hydrolyzed with HCl (4 *N*, 50 ml) to precipitate a white powder. The solid was filtered off at room temperature, and the remaining solution evaporated to dryness. The solid fractions were combined, washed with methanol (50 ml), and recrystallized from boiling xylene (250 ml) to afford white crystals of XVI (1.50 g, 48%), m.p. 235°. (Found: C, 67.66; H, 3.66; N, 13.09. $C_{12}H_8N_2O_2$ calcd.: C, 67.92; H, 3.80; N, 13.09%.) IR (Kel-F mull) 2865, 1700 cm^{-1} (CHO); mol. wt. 212 (mass spectr.).

6,6'-Diacetyl-2,2'-bipyridyl (XVII). *N,N*-Dimethylacetamide (1.92 g, 0.022 mol) in 50 ml of ether was added during 20 min to 6,6'-dilithio-2,2'-bipyridyl (from 3.14 g of 6,6'-dibromo-2,2'-bipyridyl and 12.5 ml of 1.6 *N* n-butyllithium) in 250 ml of THF at −80°. The resulting deep purple solution was stirred for 2 h, allowed to warm to −10°, and hydrolyzed with HCl (6 *N*, 20 ml). The solvent was removed on the rotary evaporator, the wet residue made basic with NaOH and extracted with chloroform (3 × 30 ml) and the extracts washed with water (20 ml) and dried (Na_2SO_4). The chloroform was evaporated and the residue recrystallized twice from ethanol to give white needles of XVII (1.41 g, 59%), m.p. 178.5–179.5°. (Found: C, 69.80, 70.66; H, 5.15, 4.89; N, 11.67. $C_{14}H_{12}N_2O_2$ calcd.: C, 69.98; H, 5.04; N, 11.66%.) IR (Kel-F mull) 1700 cm^{-1} (C=O). PMR ($CDCl_3$): singlet, 3.17 ppm (3, CH_3); multiplet, 8.06 (2); multiplet, 8.77 ppm (1); mol. wt. 242 (mass spectr.). The dioxime derivative was prepared by heating XVII for 15 min with excess hydroxylamine hydrochloride and sodium hydroxide (to neutrality) in ethanol, filtering, and recrystallizing from DMF/ethanol. Drying for 24 h *in vacuo* (100°) gave white crystals, m.p. 300.5°. (Found: C, 62.03; H, 5.17; N, 20.67. $C_{14}H_{14}N_4O_2$ calcd.: C, 62.21; H, 5.22; N, 20.73%).

6,6'-Dimethyl-2,2'-bipyridyl (XVIII). Freshly distilled dimethyl sulfate (8 ml, 0.085 mol) was added to 6,6'-dilithio-2,2'-bipyridyl (from 3.14 g of 6,6'-dibromo-2,2'-bipyridyl and 12.5 ml of 1.6 *N* n-butyllithium) in 250 ml of THF solution at −90°. On warming to −30° during 4 h, the dark red color of the reaction mixture changed to brown. After hydrolysis with HCl (2*N*, 100 ml), THF was removed on the rotary

evaporator, the acidic solution was neutralized, the yellow precipitate was filtered off, dried, and recrystallized from n-pentane to afford colorless crystals of XVIII (0.92 g, 50%), m.p. 89–90° (lit.[11], 89.5–90.5°). Rapid addition of excess dimethyl sulfate to the dipyridyllithium solution below the reaction temperature of −40° proved to be necessary in order to prevent metallation of the acidic methyl groups by the unreacted lithium reagent.

6,6′-Dipicolinoyl-2,2′-bipyridyl (*XIX*). A solution of 2-cyanopyridine (2.29 g, 0.022 mol) in 50 ml of THF was added during 30 min to a solution of 6,6′-dilithio-2,2′-bipyridyl (from 3.14 g of 6,6′-dibromo-2,2′-bipyridyl and 12.5 ml of 1.6 *N* n-butyllithium) in 250 ml of THF at −80°. The resulting red solution was stirred for 1 h at −70° and hydrolyzed with HCl (2 *N*, 100 ml). Ether and THF were stripped off and the aqueous solution was boiled for 1 h, cooled, made basic, and extracted with benzene. Concentration and cooling of the dried (Na_2SO_4) benzene solution gave white XIX (0.55 g, 15%), m.p. 218–219°. (Found: C, 72.39; H, 3.66; N, 15.35. $C_{22}H_{14}N_4O_2$ calcd.: C, 72.13; H, 3.82; N, 15.30%.) IR (Kel-F mull) 1680 cm^{-1} (C=O).

6,6′-Bis(di-2-pyridylhydroxymethyl)-2,2′-bipyridyl (*XX*). Di-2-pyridyl ketone (4.05 g, 0.022 mol) in 150 ml of ether was added during 30 min to 6,6′-dilithio-2,2′-bipyridyl (from 3.14 g of 6,6′-dibromo-2,2-bipyridyl and 12.5 ml of 1.6 *N* n-butyllithium) in 250 ml of THF at −80°. The resulting deep purple solution was stirred at −80° for 2 h, allowed to warm to −20°, and hydrolyzed with HCl (6 *N*, 40 ml). The THF was removed on the rotary evaporator, and the aqueous residue made basic and filtered. The yellow solid was washed with water and with methanol, and recrystallized from boiling xylene to give XX as a white powder (2.60 g, 47%), m.p. 271–272°. (Found: C, 73.50; H, 4.70; N, 15,62. $C_{32}H_{24}N_6O_2$ calcd.: C, 73.27; H, 4.61; N, 16.03%.) IR (Kel-F mull) 3270 cm^{-1} (OH); mol. wt. 524 (mass spectr.).

Other syntheses involving lithiopyridines.

6-Picolinoyl-2,2′-bipyridyl (*XXI*). After washing with dilute NaOH to remove HBr, 2-bromopyridine was washed with water, dried (Na_2SO_4), and distilled (b.p. 190–193°). A solution of 2-bromopyridine (1.58 g, 0.01 mol) in ether (25 ml) was added to an ether solution (25 ml) of n-butyllithium (6.15 ml of 1.6 *N*, 0.01 mol) at −20°. After seven min of stirring, the red solution was cooled to −65° and 6-cyano-2,2′-bipyridyl[9,10] (1.81 g, 0.01 mol) was added. The mixture was warmed to −45° and stirred for 30 min before hydrolysis with water (10 ml). The ether solution was extracted until colorless with portions of dilute HCl, which were then combined and heated on the steam bath for 30 min. The cooled solution was neutralized, extracted with chloroform (4 × 50 ml), the extracts treated with a little activated charcoal, dried, filtered and evaporated to give a brown oil. This oil was then dissolved in boiling hexane (250 ml) as much as possible, the solution decanted and the oily residue discarded. Careful evaporation of the hexane solution produced a mixture of crystals and oil; the crystals were separated and recrystallized from hexane, giving white needles of XXI (0.56 g, 22%), m.p. 78–80°. (Found: C, 73.74; H, 3.87; N, 16.08. $C_{16}H_{11}N_3O$ calcd.: C, 73.55; H, 4.24; N, 16.08%.) IR (Kel-F mull) 1690 cm^{-1} (C=O); mol. wt. 261 (mass spectr.).

6,6′-Dipicolinoyl-2,2′-bipyridyl (*XIX*). This compound was prepared in 18% yield from 6,6′-dicyano-2,2′-bipyridyl[9] and 2-pyridyllithium by the method described above for 6,6′-bis(6-bromo-2-picolinoyl)-2,2′-bipyridyl (X). The yield is comparable with that obtained from the reaction of 2-cyanopyridine and 6,6′-dilithio-2,2′-bipyridyl (*vide supra*).

6,6′-Bis(1,3-dioxolan-2-yl)-2,2′-*bipyridyl* (*XXII*). Anhydrous cupric chloride (1.35 g, 0.010 mol) was added to an ether solution (100 ml) of 6-(1,3-dioxolan-2-yl)-2-lithiopyridine[3] (0.020 mol) cooled to −90°. On warming to −70°, an exothermic reaction took place and a brown suspension was formed. Stirring was continued for 30 min at −70°, and dry oxygen was bubbled through the suspension until the last traces of brown had faded (~20 min). The green suspension was hydrolyzed with water (100 ml), the ether was removed, and excess KCN was dissolved in the well-stirred aqueous solution to remove all copper. The precipitated solid was filtered off and recrystallized twice from ethanol to give white needles of XXII (1.40 g, 46%); m.p. 120–121.5°. (Found: C, 63.78; H, 5.31; N, 9.14. $C_{16}H_{16}N_2O_4$ calcd.: C, 63.99; H, 5.37; N, 9.33%.) PMR ($CDCl_3$): 8.68 ppm (3-H); 8.00 ppm (4-H); 7.70 ppm (5-H); J_{34} 8.1 Hz, J_{35} 1.3 Hz, J_{45} 7.6 Hz; singlet, 6.02 ppm (CHO_2); multiplet, 4.20 ppm (C_2H_4). The compound was further identified by its quantitative hydrolysis to 6,6′-diformyl-2,2′-bipyridyl (XVI) upon refluxing with HCl (4 *N*, 50 ml) under nitrogen for 4 h.

RESULTS AND DISCUSSION

2-Bromopyridine and 2,6-dibromopyridine each react with one equiv. of n-butyllithium–hexane in ether at −20° to −40° to give solutions of 2-lithiopyridine and 6-bromo-2-lithiopyridine (I), respectively, in good yield after 15 min stirring. When 6-bromo-2,2′-bipyridyl (in ether) and 6,6′-dibromo-2,2′-bipyridyl (in THF, 2 equivalents of n-butyllithium) were similarly treated, only tarry mixtures and low yields of the desired products were obtained. The use of lower temperatures (−70° to −100°) and longer reaction times (45 min) in these metalation reactions, as well as those of 6-(1,3-dioxolan-2-yl)-2-bromopyridine[3] and its 3-methyl-1,3-dioxolan-2-yl analog was found to afford the lithium reagents 6-lithio-2,2′-bipyridyl (XI), 6,6′-dilithio-2,2′-bipyridyl (XII), 6-(1,3-dioxolan-2-yl)-2-lithiopyridine[3] and 6-(2-methyl-1,3-dioxolan-2-yl)-2-lithiopyridine in synthetically useful yields.

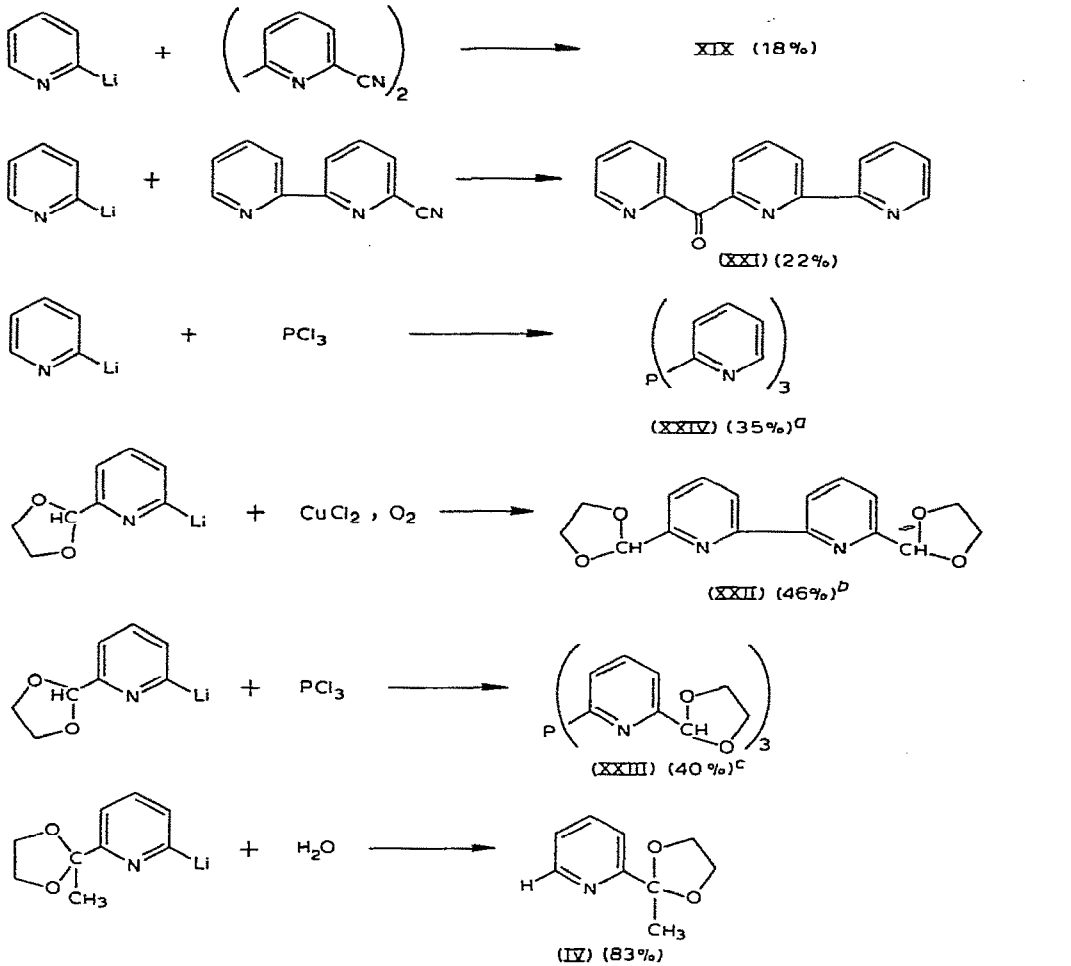
Difficulties in the preparation and use of these reagents at higher reaction temperatures could arise from several sources. The enhanced reactivity of organolithium reagents in the presence of chelating tertiary amines is now a well-recognized phenomenon[12], as is the susceptibility of the pyridine ring to nucleophilic attack at the α-carbon by lithium reagents[13]. Even at lowered temperatures, yields of reactions where a 6-bromo or pyridyl group protects the α-carbon site were invariably found to be higher than in the absence of α-substituents. Yields in comparable reactions of lithio reagents employed in this work decrease in the approximate order I > XII > 2-lithiopyridine > XI.

The reluctance of 6-bromo-2-lithiopyridine to undergo a second metalation* with n-butyllithium affords the opportunity for sequential replacement of two bromine atoms. The preparation of tris(2-aldoximo-6-pyridyl)phosphine[3] via the dioxolanyl-pyridylphosphine XXIII, prepared as shown in Table 3, represents one application. The reactions shown in Tables 1–3 represent other attempts to explore some of the synthetic possibilities inherent in pyridyllithium chemistry. Many of these

* This observation is to be contrasted with the reported formation of the di-Grignard reagent from 2,6-dibromopyridine[14] and, less directly, with the di-lithiation of *m*-dibromobenzene using n-butyllithium[15].

TABLE 3

OTHER SYNTHESES USING LITHIOPYRIDINES



[a] *Cf.* ref. 18 and text. [b] This compound was also prepared by an Ullman coupling reaction employing 2-(1,3-dioxolan-2-yl)-6-bromopyridine[3] and copper powder in hot DMF (yield 9.3% after purification). [c] *Cf.* ref. 3.

reactions were selected in order to afford compounds which might possess useful ligating properties or serve as precursors for the formation of macrocylic ring systems (e.g., XVI and XVII). A few additional comments follow in order to place these reactions in perspective with regard to previous synthetic investigations.

The reactions of 6-bromo-2-acetylpyridine (II) appear to parallel those of the corresponding aldehyde. In both cases, lithiation of the remaining bromo-substituent can be effected after protection of the carbonyl group. Standard organic techniques may further transform products of pyridyllithium reactions, as shown by the formation of tris(6-cyano-2-pyridyl)phosphine from the bromo precursor V by the method of

Case[10]. On the other hand, the attempted lithiation of tris(6-bromo-2-pyridyl)-methyl silane (VII) and reaction with *N,N*-dimethylacetamide followed by aqueous quenching led to complete hydrolysis of the product, so that only 2-acetylpyridine could be recovered. This result confirms recent reports of the facile hydrolysis of the 2-pyridylsilicon bond[16].

Reactions of 2-lithiopyridine with nitriles lead after hydrolysis to about 50% yields of ketones[1]. Reactions of our large lithiopyridines and lithiobipyridyls with α-cyanopyridines and -bipyridyls lead to lower yields of ketones VIII, X, XIX and XXI. Reactions of polypyridyl nitriles with simple lithiopyridines generally give higher yields than the reverse sequence of lithiopolypyridyls and 2-cyanopyridines. The method of Case [10] was found to provide an improved synthesis of 6,6'-dicyano-2,2'-bipyridyl (58% yield; by lit. method[9], 35%). Symmetric pyridyl ketones can be prepared in an alternative way from lithiopyridines and ethyl chloroformate, as shown by the synthesis of bis(6-bromo-2-pyridyl)-ketone (IX).

Difficulty in repeating the synthesis of tri-2-pyridylphosphine (XXIV) from the reaction of 2-lithiopyridine and phosphorous trichloride has been reported [17]. However, we were able to reproduce the work of Plâzek and Tyka[18] and obtained this compound in 35% yield as a viscous oil distilling at 200–215° (0.1 mm) which slowly crystallized from methanol. A 13% yield of 2,2'-bipyridyl was also obtained. In contrast, tris(6-bromo-2-pyridyl)phosphine (V) was obtained in 75% yield in an analogous reaction (Table 1). Tris-[6-(2,2'-bipyridyl)]phosphine[4] (XXV) was obtained from 6-lithio-2,2'-bipyridyl and phosphorus trichloride at −80° (Table 2). In attempted preparations of this compound at −40°, only 6,6'-di(2-pyridyl)-2,2'-bipyridyl[9] (6%) could be isolated. Similarly, only 6,6'-diacetyl-2,2'-bipyridyl (XVII) could be isolated after hydrolysis of the reaction product of 6-(1,3-dioxolan-2-yl)-2-lithiopyridine and phosphorus trichloride formed at −50°. The phosphine XXIII (together with an 8% yield of the byproduct XXII) may be obtained by carrying out the reaction at lower temperatures.

The 6-substituted and 6,6'-disubstituted 2,2'-bipyridyls are a fairly inaccessible class of compounds which have been synthesized primarily via the bromo derivatives[9,10] by addition to the azomethine linkage in 2,2'-bipyridyl[19], and by coupling appropriately substituted pyridines with various reagents[1,9,20]. The difficult direct bromination of 2,2'-bipyridyl[9] (vapor phase, 500°) and the frequently mediocre yields in the coupling of substituted pyridines or bromopyridines have previously inhibited the development of new syntheses involving the bipyridyl functionality. In contrast to 2,6-dibromopyridine, 6,6'-dibromo-2,2'-bipyridyl is cleanly dilithiated in 80% yield, allowing a wide number of transformations. For example, reaction with dimethyl sulfate provides a 50% yield of 6,6'-dimethyl-2,2'-bipyridyl (XVIII). Previous preparations of XVIII by dimerization of 2-picoline have provided at best only a few percent of product[20]. To avoid the necessity for the vapor phase bromination*, coupling reactions leading to bromobipyridyls were investigated. Reactions using copper bronze are unsuitable, as they lead to coupling at all bromo sites. Instead, use was made of the recently developed oxidation of lithium diarylcuprates[21]. In initial

* The gas phase bromination reactions of 2,2'-bipyridyl reported by Burstall[9] were reinvestigated. Yields were determined to be only 15–21% each of 6-bromo-2,2'-bipyridyl and 6,6'-dibromo-2,2'-bipyridyl.

studies, the cuprates were generated by the addition of one equivalent of tetrakis-[iodo(tri-n-butylphosphine)copper(I)][7] to two equivalents of the pyridyllithium species at −78°, with subsequent oxidation with molecular oxygen. Following a report that n-butyllithium was coupled by $CuCl_2$ to give a 50% yield of octane[21c], similar coupling reactions were attempted with pyridyllithium species. Anhydrous $CuCl_2$ was found to react with about three equivalents of 6-bromo-2-lithiopyridine in a highly exothermic reaction at −70°, resulting in a 50% yield of 6,6′-dibromo-2,2′-bipyridyl after air oxidation. The oxygen treatment is thought to be necessary for the oxidative coupling of pyridylcopper(I) species formed in the disproportionation of the transiently produced pyridylcopper(II) species[21c,22]. The possibility of cross-coupling reactions is shown by the one-step synthesis of 6-bromo-2,2′-bipyridyl from 2-lithiopyridine and 6-bromo-2-lithiopyridine in 23% yield (Table I) based on the latter reagent. The utility of the method was further demonstrated by the isolation of 6,6′-bis(1,3-dioxolan-2-yl)-2,2-bipyridyl (XXII) in 46% yield (Table 3) when 6-(1,3-dioxolan-2-yl)-2-lithiopyridine was similarly treated with cupric chloride and oxygen. Hydrolysis of XXII afforded the dialdehyde XVI in essentially quantitative yield. The ease of the reaction and the high yields of substituted bipyridyls makes the $CuCl_2$ coupling reaction highly useful for laboratory scale reactions.

In order to provide a comparison between the coupling scheme described above and the Ullman reaction, VIII was treated with copper bronze in DMF. The coupled product XIX was obtained in only 6.6% yield after a laborious workup. Several other attempts to improve the efficiency of this method met with only marginal success; severe decomposition was observed in every case. Similar results were obtained when 6-(1,3-dioxolan-2-yl)-2-bromopyridine was so treated; XXII was obtained in only 9.3% yield, comparing unfavorably with the 46% yield in the $CuCl_2$ catalyzed coupling reaction.

Although only reactions occurring at the α-position of pyridyl rings have been investigated here, application of the reported methods to other isomeric lithiopyridyl species may well be feasible.

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