POLYORGANOMETALLIC HETEROCYCLES. * 2,6-DILITHIOPYRIDINE

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Summary

Metal—halogen exchange between 2,6-diiodo- and 2,6-dibromopyridine and two equivalents of n-butyllithium gives 2,6-dilithiopyridine. On quenching with either carbon dioxide followed by esterification, methanol or dimethyl disulfide the dilithio compound gives a methyl 2,6-pyridinedicarboxylate, pyridine, or 2,6-dithiomethylpyridine, respectively. A convenient procedure for halogen—halogen exchange is also described.

Introduction

It has been previously demonstrated, as early as 1933, that monohalopyridines undergo metal—halogen exchange to generate the corresponding Grignard [2—9] or organolithium [10—15] reagents. These intermediates have been subsequently employed in the preparation of numerous simple substituted pyridines, thus confirming the intermediacy of the organometallics. Proost and Wibaut [16,17] reported the successful preparation of 2,6-pyridine bis(magnesium bromide) from 2,6-dibromopyridine via application of Grignard's entrainment procedure [18,19]; proof of this bis-organomagnesium intermediate rested on trapping procedures utilizing either benzaldehyde [16] or allyl bromide [17].

Attempted preparation of dilithiopyridines was first reported by Gilman et al. [13], in which either 2,6- or 3,5-dibromopyridine was subjected to excess butyllithium in diethyl ether at —30°C, however only monosubstituted products were detected. With increased reaction temperatures the yields of monocarboxylated products decreased and no products resulting from di(metal—halogen) exchange were found. These results are consistent with the facts that (1) pyridyllithiums generally decompose above —30°C [14]; (2) at elevated

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* For the previous article in this series see ref. 1.

temperatures n-butyllithium adds to the pyridine nucleus [20]; and (3) metal—halogen exchange in these systems is complete (>90%) after 15 minutes at —30°C [12]. Recent studies conducted with 2-bromo-6-lithiopyridine [21—24] have avoided, citing Gilman's unsuccessful results, attempts to prepare 2,6-dilithiopyridine.

Interestingly with benzene or electron-rich heterocycles, metal—halogen (or hydrogen) exchange has afforded convenient entry into 1,2-, 1,3-, and 1,4-dilithiobenzene [25—28], 2,5-dilithiothiophene [29,30], 2,5-dilithiofuran [30,31], and 2,5-dilithio-N-methylpyrrole [30,32,33]. Even with activated electron-poor heterocycles, Abramovitch et al. have reported the intermediacy of substituted 2,6-dilithiopyridine N-oxides, based on product analysis [34—36].

However, even though numerous workers have attempted the preparation 2,6-dilithiopyridine, we herein report the first evidence of its intermediacy in an organic reaction.

Results and discussion

2,6-Dibromopyridine (I) was treated with 2.2 molar equivalents of n-butyllithium in diethyl ether at —80°C, followed by carboxylation and esterification with methanol and anhydrous HBr. The main (60%) product was methyl 6-bromopicolinate (II) along with traces of 2-bromopyridine (<5%), and unchanged I (32%) [24]. Reduction of the reaction temperatures to —100°C and the use of 5—7 equivalents of n-butyllithium afforded similar results under identical trapping conditions [24].

Since 2,6-dichloropyridine is resistance to metal—halogen exchange [37] and I is converted to II via monometalation (III) under these conditions, 2,6-diiodopyridine (IV) was prepared. 2,6-Dichloropyridine was treated with excess sodium iodide in refluxing concentrated hydroiodic acid for 12 h to give (42%) of 2,6-diiodopyridine (IV), as colorless needles. The NMR spectral data for IV exhibited a triplet at δ 6.98 ppm for the 4-pyridyl hydrogen and a doublet at δ 7.73 ppm for the 3,5-pyridyl hydrogens. Mass spectral data showed the molecular ion at 331 (100%) with major fragments at 204 ($M^+ - 127$), 127 (I^+), and 77 (C_5H_3N). When IV was treated with 3.8 equivalents of n-butyllithium in tetrahydrofuran (THF) at —90°C, facile metal—halogen exchange occurred to generate 2,6-dilithiopyridine (V) which was trapped with carbon dioxide at —90°C to give, after esterification, dimethyl 2,6-pyridinedicarboxylate (VI) and 2-carbomethoxypyridine-6-carboxylic acid (VII). No halogenated products were isolated from the reaction.

After the successful generation of V, the metal—halogen exchange of I was reinvestigated, except using THF as the solvent. Di(metal—halogen) exchange occurred and diester VI was isolated. A second unexpected product, methyl 6-chloropicolinate, was obtained via monometallation and halogen—halogen exchange under prolonged HCl catalyzed esterification conditions. Similar halogen—halogen exchange has been demonstrated even under these mild conditions [24]. This successful metal—halogen exchange for I in THF supports the enhanced solubilizing properties of THF over diethyl ether for simple organolithiums; other examples as well as explanations for this enhancement are

available [38].
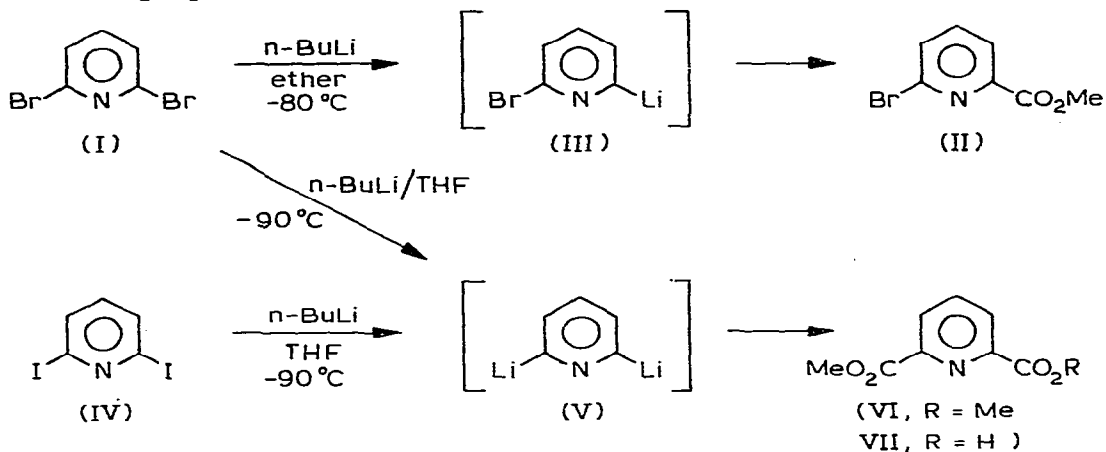
The diminished yields from carboxylation-esterification procedure are mechanical in origin and do not reflect the actual quantity of V generated in the reaction.

Isolation of VI and VII confirmed the presence of V; however in view of the low product yields alternate trapping procedures were conducted. Quenching the metalation reaction with methanol at —90°C afforded a mixture of pyridine and 2-bromopyridine in 52—58% and 7—12% yields, respectively. Further trapping of V with dimethyl disulfide gave 2,6-dithiomethoxypyridine and 2-bromo-6-thiomethoxypyridine in 36—40% and 26—28% yield, respectively.

Since I was reported [16,17] to give the bis-Grignard reagent, generated under rather severe reaction conditions, and the products from their trapping experiments could be rationalized via other routes, we repeated the reaction of I with magnesium and ethyl bromide in diethyl ether according to the procedure of Proost and Wibaut [17]. Instead of using benzaldehyde or allyl halide, standard trapping by carboxylation and subsequent esterification was conducted.
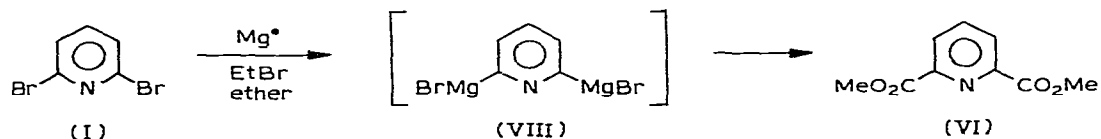
Besides unchanged dibromide (I) and 2-ethylpyridine, the desired diester VI was isolated in yields approximate to those of the above procedure. Thus 2,6-pyridine bis(magnesium bromide) (VIII) can be generated, and is quite stable at ambient temperatures. This however, greatly contrasts the thermal instability of V above ca. —80°C.

Both 2-lithiopyrimidine (IX) and 1,2,3-triazine (X) are isoelectronic with 2,6-dilithiopyridine. Thus, it is interesting to note that 2-bromopyridine has been shown not to undergo metal—halogen exchange to give IX, upon treatment with n-butyllithium (in ether) even at 110°C [39]. Also as of 1977, the related triazine X has not be synthesized [40]; however, theoretical calculations indicate that this ring system has some degree of electron delocalization [41].

Reactions of these pyridine bis-organometallics will be considered in detail elsewhere.

Experimental

All melting points were taken in capillary tubes with a Thomas—Hoover Uni-Melt melting point apparatus and were uncorrected. NMR spectra were obtained in $CDCl_3$ solutions with Me_4Si, as the internal standard ($\delta = 0$ ppm) and recorded on a Varian Associates A-60A spectrometer. Mass spectra were obtained on a Hewlett Packard Model 5986 GC/MS system. Infrared (IR) spectra were recorded on a Perkin—Elmer 621 spectrometer. Elemental analysis was performed by Mr. R. Seab in these laboratories.

2,6-Diiodopyridine
A mixture of 2,6-dichloropyridine (14.8 g, 0.1 mol) and sodium iodide (20 g) in hydroiodic acid (75 ml, d 1.7) was refluxed for 12 h under nitrogen according to the procedure of [42]. Pure 2,6-diiodopyridine was recrystallized from ether, as colorless needles: m.p. 185—186°C (lit. [43] m.p. 183°C); 13.8 g; (42%). NMR δ (ppm) 6.98 (t, 4-Pyr-H, J 8.5 Hz, 1H), 7.73 (d, 3,5-Pyr-H, J 8.5 Hz, 2H); Mass spectrum (70 eV) 331 (M^+, rel. int. = 100%), 204 ($M^+ -127$, 46.5), 127 (I^+, 18.6), 77 (C_5H_3N, 20.6); IR (KBr) 3010, 1540, 1408, 1120, 975, 785 cm^{-1}. (Found: C, 18.61; H, 0.87; N, 4.38. $C_5H_3I_2N$ calcd.: C, 18.31; H, 0.90; N, 4.22.)

Methyl 2,6-Pyridinecarboxylate via 2,6-Dilithiopyridine
Method A from 2,6-diiodopyridine. An anhydrous THF solution (125 ml) of 2,6-diiodopyridine (3.31 g, 0.10 mol) was cooled to —95°C (petroleum ether/liquid nitrogen bath) under an argon atmosphere, then n-butyllithium (17 ml, 0.038 mol, Foote, hexane) was added. The solution was stirred for 4 h with the temperature being strictly maintained below —89°C. At the end of this period, the golden slurry was rapidly poured onto carbon dioxide (70 g) and stirred. After warming to room temperature, the green slurry was concentrated in vacuo to afford an oily residue, which was dissolved in water (50 ml) and extracted several times with methylene chloride. This organic extract was dried and concentrated in vacuo to give an unidentified oil: 550 mg; NMR δ 0.60—1.80 ppm (br, m). The aqueous layer was concentrated in vacuo to give a solid, which was slurried in anhydrous methanol, saturated with gaseous HCl, and refluxed for 24 h under nitrogen. After concentration, the oily residue was dissolved in water, adjusted to pH 7 with solid potassium carbonate, and extracted with methylene chloride. The combined organic extracts were dried and chromatographed on silica gel eluting with acetone to give a colorless solid, which was recrystallized from acetone to give colorless crystals of methyl 2,6-pyridinedicarboxylate: 115 mg (6%); m.p. 118—121°C (lit. [44] m.p. 124—125°C); NMR δ (ppm) 3.91 (s, CO_2Me, 6H), 8.20 (m, pyr-H, 3H).

The aqueous layer was adjusted to pH 2 with concentrated HCl, then extracted with methylene chloride. The combined extract was dried, and concentrated to give a pink solid, 2-carbomethoxypyridine-6-carboxylic acid: 50 mg (3%); m.p. 144—146°C (lit. [45] m.p. 151°C); 50 mg; NMR δ (ppm) 4.07

(s, CO_2Me, 3H), 8.00—8.53 (m, pyr-H, 3H), 9.39 [s, CO_2H, (exchanged with D_2O), 1H].

Method B from 2,6-dibromopyridine. The above reaction (Method A) was repeated except 2,6-dibromopyridine (2.37 g, 0.01 mol) was used, in tetrahydrofuran as solvent. Fractional crystallization from petroleum ether afforded the colorless crystalline methyl 2,6-pyridinedicarboxylate (150 mg (8%), m.p. 117—120°C) and methyl 6-chloropicolinate: 520 mg (30%); m.p. 78—81°C; NMR δ (ppm) 4.02 (s, CO_2Me, 3H), 7.63 (dd, 3-Pyr-H, J 8.0, 2.0 Hz, 1H), 7.92 (t, 4-Pyr-H, J 8.0, 2.0 Hz, 1H), 8.11 (dd, 5-Pyr-H, J 8.0, 2.0 Hz, 1H); mass spectrum (70 eV) 171 (M^+, 3.8), 141 (M^+ —30, 32.2), 136 (M^+ —35, 9.2), 113 (M^+ —58, 100), 76 (C_5H_2N, 35.5). (Found: C, 49.15; H, 3.64; N, 7.93. $C_7H_6ClNO_2$ calcd.: C, 49.16; H, 3.50; N, 8.19).

Method C. Trapping of 2,6-dilithiopyridine with methanol. 2,6-Dibromopyridine (4.7, 0.02 mol) in THF (20 ml) was treated with n-butyllithium (31 ml, 0.076 mol, 2.4 M in hexane) under the conditions described in Method B. After stirring for 4.5 h, the reaction mixture was rapidly quenched with a chilled THF solution (20 ml) of anhydrous methanol (6.4 g, 0.2 mol). The temperature rose briefly to —78°C but was quickly returned to —90°C. The quenched reaction mixture was stirred for 6 h, while slowly warming to room temperature. Then, the mixture was concentrated by fractional distillation collecting only the material that boiled below 60°C. The residue was slurried in hot petroleum ether/diethyl ether, then filtered. The ethereal filtrate was concentrated and the liquid residue was analyzed by vapor phase chromatography [(10% OV-210, Chromosorb Q 100/120)], which indicated the presence of pyridine and 2-bromopyridine. This mixture was distilled (b.p. 60—90°C) to afford pyridine (52—58%) along with low boiling solvents. The residue was column chromatographed eluting with ethyl acetate to afford 2-bromopyridine (7—12%).

Method D. Trapping of 2,6-dilithiopyridine with dimethyl disulfide. The reaction (Method C) was repeated except using dimethyl disulfide (9.4 g, 0.01 mol) in THF (40 ml) to quench the reaction. After work-up, and removal of the low boiling solvents, a mixture (2.55 g, b.p. 98—112°C (3 mm)) of 2,6-dithiomethoxypyridine (36—40%; mass spectrum (70 eV) 173 (M^+ +2, 8.0), 172 (M^+ +1, 12.2), 171 (M^+, 80.5), 156 (M^+ —15, 8.5), 138 (M^+ —33, 22.7), 125 (M^+ —46, 17.3), 109 (M^+ —62, 29.1), 97 (M^+ —74, 27.9), 45 (HCS, 100)) and 2-bromo-6-thiomethoxypyridine (26—28%; mass spectrum (70 eV) 206 (M^+ +3, 10.9), 205 (M^+ +2, 96.2), 203.9 (M^+, 100), 203 (M^+ —1, 76.6), 202 (M^+ —2, 78.2), 157 (M^+ —47, 35.6), 109 (M^+ —95, 34.7), 78 (C_5H_4N, 43.1)) was isolated and analyzed by VPC/MS.

2,6-Pyridine(magnesium bromide) was synthesized, by the procedure of Proost and Wibaut [16,17], from ethyl bromide (23.1 g, 0.22 mol) magnesium (4.86 g, 0.20 g-atm), and 2,6-dibromopyridine (9.6 g, 0.04 mol) in anhydrous ether (100 ml). After the period of reflux, the mixture was cooled and then poured into carbon dioxide (100 g) with rapid stirring. The solvent was evaporated to give a white solid, which was slurried in water (100 ml) and the pH was adjusted to ca. 6 with concentrated HCl. A tan solid was filtered and recrystallized to give unchanged starting dibromide: m.p. 114—115°C. The filtrate was extracted with dichloromethane and the combined extract was dried with anhydrous magnesium sulfate, and concentrated in vacuo to afford an oil

(2.62 g), which was shown to be a mixture of I (500 mg), 2-ethylpyridine (400 mg) and propionic acid. The pH of the filtrate was adjusted to 1 with concentrated HCl, then concentrated in vacuo to give a solid residue which was dried at 130° C for 24 h in vacuo. This residue was slurried in anhydrous methanol (200 ml) and gaseous HBr added. After the mixture was refluxed for 12 h, the mixture was worked-up as above to give a white solid (1.0 g) which was recrystallized from hexane/diethyl ether to give methyl 2,6-pyridinedicarboxylate: 90 mg (1.2%), m.p. 113—118°C.

Acknowledgement

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