Efficient Preparation of 2-Bromo-6-lithiopyridine via Lithium−Bromine Exchange in Dichloromethane

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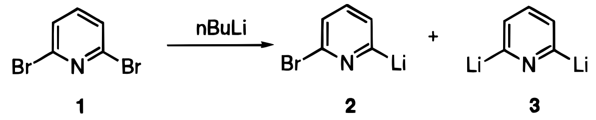
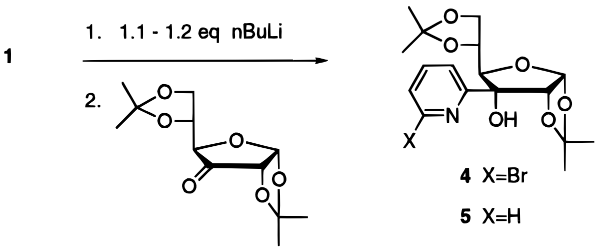
As part of research directed toward synthesis of chiral 2,2′-bipyridines, we required an efficient method for generating 2-bromo-6-lithiopyridine.[1] 2-Bromo-6-lithiopyridine is an important building block in a number of syntheses of biologically important compounds[2] and is also a key intermediate in the synthesis of oligopyridines.[3] Published methods for its preparation utilize the facile lithium−bromine exchange reaction between 2,6-dibromopyridine and butyllithium at low temperature (Scheme 1). Most of these methods involve slow addition of butyllithium (in hexanes) to solutions of 2,6-dibromopyridine in THF[1,4] or ether.[5] In the pioneering work of Gilman, an ether solution of 2,6-dibromopyridine (chilled to −30 °C) is added to butyllithium (also at −30 °C in ether).[5] A more recent method involves addition of 2,6-dibromopyridine to butyllithium at −78 °C in THF.[6]

Since 2,6-dibromopyridine possesses two potential sites for lithium−bromine exchange, the major difficulty associated with these methods is controlling the extent of lithiation. Dilithium−bromine exchange is problematic when excess butyllithium is used to ensure quantitative reaction of 2,6-dibromopyridine,[1,4] but it also occurs in THF with 1.0 equiv of butyllithium.[6] Gilman reported that only monolithiation is observed with excess butyllithium in ether.[5] Cai et al. were unable to reproduce this result and found that lithium−bromine exchange with 2 equiv of butyllithium at −40 °C provided **3** as the major product.[6] Clean monolithiation in THF is accomplished only by inverse addition of 2,6-dibromopyridine to 1.0 equiv of butyllithium at −78 °C.[6] An alternative, but less convenient, method for monolithiation involves treating a suspension of 2,6-dibromopyridine at −60 °C in ether with 1.0 equiv of butyllithium and warming to −40 °C for 15 min.[5] The poor solubility of 2,6-dibromopyridine in ether at −60 °C makes this latter method essentially an inverse addition technique similar to Cai's and is thought to proceed via the intermediacy of **3**. As 2,6-dibromopyridine is dissolved, it initially undergoes dilithium−bromine exchange to form **3**. Once the butyllithium is consumed, the remaining 2,6-dibromopyridine undergoes lithium−bromine exchange with **3** to give monolithiated product **2**.[6]

Scheme 1



Scheme 2



In our hands, complete conversion of 2,6-dibromopyridine to **2** in THF or ether invariably required > 1.0 equiv of butyllithium. Depending on the scale of the reaction, varying amounts of **3** were formed as evidenced by isolation of compound **5** (Scheme 2). We were interested in compound **4** as an intermediate in the synthesis of C_2-symmetric 2,2′-bipyridines.[1] Purification of **4** was complicated by either unreacted **1** or compound **5**. We therefore needed a method for preparing **2** with excess butyllithium which would allow for complete consumption of **1** and also avoid the problem of dilithium−bromine exchange which leads to **5**. Although butyllithium reacts with dichloromethane in THF at −100 °C,[7] there is evidence that vinyllithiums are stable at −78 °C in dichloromethane for several hours.[8] The stability of vinyllithiums in dichloromethane and the fact that solvents profoundly influence the structure and properties of organolithiums[9] led us to examine the use of dichloromethane as solvent for this reaction. We were gratified to find that 2,6-dibromopyridine undergoes remarkably clean lithium−bromine exchange at −78 °C and that dilithiation is much less favorable in dichloromethane than in either THF or ether (Table 1).

To determine the scope of this reaction, we reacted **2** with several electrophiles (Table 2). Yields were uniformly good (68−90%) for all electrophiles examined. The highest yield was observed when **2** was quenched with 2-propanol. Quenching with *i*-PrOD showed no evidence of prior protonolysis even when the solution of **2** was allowed to stand at −78 °C for 12 h prior to quenching. This eliminates the possibility that **2** is quenched via other reactions (Scheme 3).

To the best of our knowledge, this represents the first use of dichloromethane as solvent for a lithium−bromine

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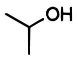
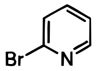
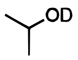
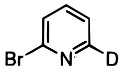
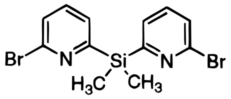
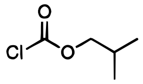
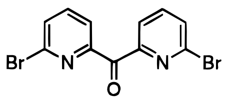
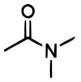
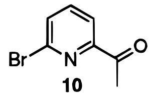
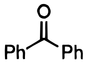
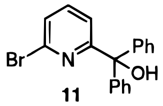
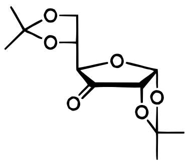
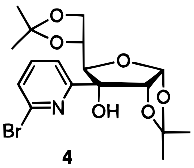
Table 1. Percent Dilithium−Bromine Exchange[a]

equiv of butyllithium[b]	CH_2Cl_2	Et_2O	THF
1.2	1.7 ± 0.4	4.7 ± 0.4	12 ± 1.7
1.5	4.5 ± 1.2	7.6 ± 1.3	27 ± 1.1
2.0	7.7 ± 0.8	13 ± 2.9	44 ± 2.6
2.5	11 ±2.0	28 ± 2.0	56 ± 3.6
3.0	16 ± 3.2	39 ± 2.6	72 ± 9.4

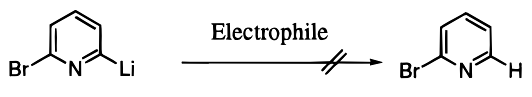
[a] Analyses were run in triplicate. Percentages were determined by ^1H NMR of the crude reaction mixture (C_5H_5N δ 8.6 *vs* C_5H_4BrN δ 8.4). [b] 1.6 M in hexanes.

Table 2. Reaction of 2-Bromo-6-lithiopyridine with Selected Electrophiles in Dichloromethane

entry	electrophile	product	yield (%)
1		 6	90
2		 7	86
3	$(CH_3)_2SiCl_2$	 8	68
4		 9	75
5		 10	70
6		 11	84
7		 4	72

exchange reaction. This may be due to the reactivity of dichloromethane with organolithiums.[7] Butyllithium reacts with dichloromethane in THF or ether to form (dichloromethyl)lithium. In THF, (dichloromethyl)lithium is stable at −100 °C but decomposes to (chloromethyl)carbene when the temperature is allowed to rise above −65 °C. It is considerably less stable in ether and decomposes instantaneously at temperatures as low as −80 °C. This reactivity may have discouraged the use of dichloromethane as solvent for lithium−halogen exchange reactions. In the absence of ethereal solvents, however, we find that butyllithium is remarkably stable in dichloromethane at −78 °C (Scheme 4). A 0.2 M solution of butyllithium in dichloromethane was stirred for 2 h at −78 °C and then quenched with CO_2. Valeric acid was isolated (67%), and analysis of the crude reaction mixture by GC/MS indicated that no dichloroacetic acid was formed. To exclude the possibility that this was due to rapid decomposition of (dichloromethyl)lithium in dichloromethane, we attempted trapping an insipient (chloromethyl)carbene with cyclohexene. No chlorocyclopropanated product **13** was detected.

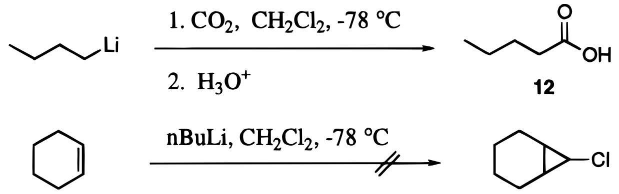
Scheme 3



2 6

Electrophile = CH_2Cl_2, C_4H_9Br, or H_2O

Scheme 4



12 13

In summary, dichloromethane was not observed to react with butyllithium for up to 2 h at −78 °C in the absence of THF or ether. 2,6-Dibromopyridine underwent monolithium−bromine exchange in dichloromethane to give **2** with only minor amounts of **3** formed with excess butyllithium. The efficiency of this method, and the potential utility of non-ethereal solutions of **2**, make this an important addition to the synthetic methodology for 2-substituted pyridines.

Experimental Section

Reactions were performed under a nitrogen atmosphere in flame-dried reaction flasks using standard Schlenk methodology. Dichloromethane was dried over P_2O_5, and THF and ether were dried over sodium benzophenone ketyl. All solvents were freshly distilled under nitrogen prior to use. For flash chromatography,[10] 400−230 mesh silica gel 60 (E. Merck No. 9385) was employed. All compounds described were characterized by ^1H and ^{13}C NMR (TMS/$CDCl_3$) solutions at 200 and 50 MHz, respectively. Compound **1** (recrystallized and dried prior to use) and butyllithium (1.6 M in hexanes) were obtained from Aldrich. Butyllithium was titrated via the method of Juaristi et al.[11] Products **4**,[1] **6**,[12] **9**, and **10**[5] were reported previously and had HRMS data and ^1H and ^{13}C NMR spectra consistent with literature values.

General Method for Lithium−Bromine Exchange in Dichloromethane. A flame-dried reaction flask under nitrogen was charged with **1** (380 mg, 1.60 mmol) and 30 mL of freshly distilled dichloromethane. The resulting solution was chilled to −78 °C (15 min), and butyllithium (1.1 mL of 1.6 M ^{n}BuLi in hexanes, 1.8 mmol, 1.1 equiv) was slowly added. The reaction was allowed to stir for 20 min at −78 °C before quenching with the desired electrophile. The resulting mixture was stirred for 30 min and then warmed to ambient temperature.

(3*R*)-3-(2-Pyridyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5). To a flame-dried reaction vessel (under nitrogen) were added **1** (560 mg, 2.36 mmol) and 10 mL of freshly distilled THF. The resulting solution was chilled to −78 °C. Butyllithium (1.1 mL of 2.5 M ^{n}BuLi in hexanes, 2.8 mmol, 1.2 equiv) was then added dropwise. After addition was complete, the solution was allowed to stir for 1 h. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranos-3-ulose[13] (550 mg, 2.13 mmol) in dry THF was then added. The reaction mixture was allowed to stir for 1 h at

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−78 °C, slowly warmed to ambient temperature, and allowed to stand for 1 h. Solvents were then removed by rotary evaporation at reduced pressure. The crude syrup was dissolved in a minimum volume of CH_2Cl_2 and purified by flash chromatography (30% EtOAc in hexanes). Compounds **4**[1] and **5** were obtained in 65% combined yield (**4**: 490 mg, 1.18 mmol, 50%; **5**: 119 mg, 3.53×10^{-1} mmol, 15%) in $\geqslant$ 95% purity as determined by ^1H NMR.

Spectral data for **5** is provided: ^1H NMR ($CDCl_3$, 500 MHz): δ 8.54 (dd, 1 H, $J = 1, 5$ Hz), 7.73 (dd, 1 H, $J = 1.5, 7.3$ Hz), 7.66 (d, 1 H, $J = 7.8$ Hz), 7.24 (m, 1 H), 6.15 (d, 1 H, $J = 3.4$ Hz), 4.67 (d, 1 H, $J = 3.4$ Hz), 4.21 (d, 1 H, $J = 6.3$ Hz), 3.67 (bs, 1 H), 3.60 (dd, 1 H, $J = 6, 14$ Hz), 3.57 (dd, 1 H, $J = 6, 12$ Hz), 3.32 (dd, 1 H, $J = 6, 7.8$ Hz), 1.68 (s, 3 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 158.70, 148.38, 136.48, 122.93, 121.50, 112.74, 109.00, 105.83, 83.94, 83.37, 81.85, 73.80, 66.02, 26.92, 26.55, 26.51, 25.25. HRMS (FAB, M + H), calcd for $C_{17}H_{24}NO_6$: 338.1604; found: 338.1606.

2-Bromo-6-deuteriopyridine (7). A dichloromethane solution of **2** was generated as described above. The reaction was stirred for 1 h at −78 °C. Deuterated 2-propanol (99 + % D) was then added. After stirring 30 min at −78 °C, the mixture was allowed to warm to ambient temperature and poured onto saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous phase was extracted with two additional portions of dichloromethane. The combined organic layers were dried (Na_2SO_4) and filtered, and solvents were removed at 40 °C under atmospheric pressure. The product was purified via bulb-to-bulb distillation to provide 220 mg of **2** (1.38 mmol, 86%).

^1H NMR ($CDCl_3$): δ 7.60−7.46 (m, 2 H), 7.26 (dd, 1 H, $J = 1, 6$ Hz); ^{13}C NMR ($CDCl_3$): δ 149.94 (t, $J = 28$ Hz), 142.25, 138.58, 128.30, 122.55. HRMS (EI) calcd for $C_5H_3D^{81}BrN$: 159.9569, found: 159.9578; calcd for $C_5H_3D^{79}BrN$: 157.9590, found: 157.9590.

Bis[6-(2-bromopyridyl)]dimethylsilane (8). To a dichloromethane solution of **2** prepared as described above was added $(CH_3)_2SiCl_2$ (0.8 mL of a 1.0 M solution in THF, 0.8 mmol, 0.5 mol equiv). The mixture was allowed to stir for 30 min at −78 °C before warming to ambient temperature. The reaction mixture was then poured onto saturated aqueous $NaHCO_3$ and separated. The aqueous layer was extracted with two additional portions of dichloromethane, and the combined organic layers were dried (Na_2SO_4) and filtered, and solvents were removed at 40 °C under reduced pressure. The crude syrup was dissolved in a minimum volume of CH_2Cl_2 and purified by flash chromatography (5% EtOAc in hexanes). Compound **8** was obtained in 68% yield (202 mg, 5.42×10^{-1} mmol).

^1H NMR ($CDCl_3$): δ 7.55−7.38 (m, 6 H), 0.64 (s, 6 H); ^{13}C NMR ($CDCl_3$): δ 167.71, 143.40, 136.71, 129.18, 127.77, −3.93. HRMS (CI) calcd for $C_{12}H_{12}{}^{81}Br_2N_2Si$: 373.9096, found: 373.9090; calcd for: $C_{12}H_{12}{}^{79}Br^{81}BrN_2Si$ 371.9116, found: 371.9111; calcd for $C_{12}H_{12}{}^{79}Br_2N_2Si$: 369.9136, found: 369.9142.

[6-(2-Bromopyridyl)]diphenylmethanol (11). Benzophenone (296 mg, 1.62 mmol) was added to a dichloromethane solution of **2** prepared as described above. The mixture was allowed to stir for 30 min at −78 °C before warming to ambient temperature. The reaction mixture was then poured onto saturated aqueous $NaHCO_3$ and separated. The aqueous layer was extracted with two additional portions of dichloromethane, the combined organic layers were dried (Na_2SO_4), filtered, and solvents were removed at 40 °C under reduced pressure. The crude reaction mixture was subjected to flash chromatography (5% EtOAc in hexanes). Compound **11** was obtained in 84% yield (457 mg, 1.34 mmol).

^1H NMR ($CDCl_3$): δ 7.53−7.40 (m, 2 H), 7.34−7.26 (m, 10 H), 7.02 (dd, 1 H, $J = 1.2, 7.2$ Hz), 5.55 (s, 1 H); ^{13}C NMR ($CDCl_3$): δ 165.19, 145.36, 140.73, 138.65, 128.12, 128.05, 127.61, 126.85, 121.77, 80.92. HRMS (FAB, M + H) calcd for $C_{18}H_{15}{}^{81}BrNO$: 342.0317, found: 342.0303; calcd for $C_{18}H_{15}{}^{79}BrNO$: 340.0337, found: 340.0323.

Quenching of Butyllithium with CO_2 in Dichloromethane. Butyllithium (1.25 mL of 1.6 M ^{n}BuLi in hexanes) was added dropwise to 15 mL of dichloromethane at −78 °C under nitrogen. The resulting colorless solution was allowed to stir for 2 h at −78 °C. Crushed dry ice (1.0 g, 23 mmol) was added, and the reaction was allowed to warm to ambient temperature. After 1 h the mixture was poured onto 4% HCl and extracted with two volumes of dichloromethane. The combined organic layers were dried over Na_2SO_4 and filtered, and the solvents were removed under reduced pressure. Valeric acid was obtained in 67% isolated yield (136 mg, 1.33 mmol). Aliquots of the crude reaction mixture were removed both before and after aqueous workup and analyzed by GC/MS. No dichloroacetic acid was detected in either sample.

Attempted Trapping of (Chloromethyl)carbene. A flame-dried reaction flask was charged with freshly distilled cyclohexene (80 mg, 1 mmol, dried over CaH_2 before distillation) and dichloromethane (15 mL). The resulting solution was cooled to −78 °C. Butyllithium was then added (1.25 mL of 1.6 M ^{n}BuLi in hexanes, 2.0 mmol). The mixture was allowed to stir for 2 h at −78 °C before quenching with 2-propanol. After warming to ambient temperature the crude reaction mixture was analyzed by GC/MS. No chlorocyclopropanated product **13** was detected.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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