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Aminoalkoxide-Mediated Formation and Stabilization of Phenylpyridyllithium: Straightforward Access to Phenylpyridine Derivatives

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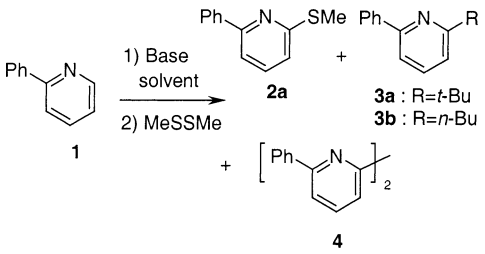
Abstract: It is shown that lithium aggregates promoted the efficient metalation of phenylpyridines and stabilization of phenylpyridyllithium. The BuLi−LiDMAE superbase prevented dimerization or nucleophilic addition encountered with *t*-BuLi or *n*-BuLi. The reported selective pyridine ring lithiation of 2-, 3-, and 4-phenylpyridine α to nitrogen opens a straightforward access to their derivatives.

Phenylpyridines and their derivatives are important compounds[1] for their agrochemical[2] and pharmaceutical[3] applications. Functional phenylpyridines have been prepared by metal-catalyzed cross-coupling of substituted aryl and pyridyl partners,[4] amino−dienes ring closure processes,[5] or modification of the parent phenylpyridines. The latter methodology refers essentially to substitution of the phenyl group, particularly with 2-phenylpyridine **1** whose ortho-aromatic activated C−H bond is easily cleaved by transition metal complexes.[6]

On the other hand, the functionalization of the pyridyl group has been far less studied. A zirconium-mediated C−H activation via nitrogen complexation has been reported leading to introduction of some substituents α to nitrogen.[7] Aryl groups were also coupled in low yield at the 6-position via nucleophilic addition of aryllithiums.[8] Curiously, metalation of unsubstituted phenylpyridines by lithium reagents, a widely used methodology to introduce functionalities onto heterocycles, has not been mentioned yet. Our laboratory has reported a new reagent (BuLi−LiDMAE) for the selective α lithiation of pyridine derivatives in apolar solvents (hexane or toluene).[9] The regioselectivity was a consequence of a cooperative chelation of lithium by pyridine nitrogen and lithium dimethylaminoalkoxide (LiDMAE).[10] We have now investigated if such a reagent could promote the metalation of the pyridine ring of phenylpyridines.

TABLE 1. Reaction of 1 with Lithium Bases[a]



base (equiv)	conditions	yield, % 2a[b]	3[b]	4[b]
LDA (2−4)	THF, −78 °C, 1 h			
LTMP (4)	THF, −78 °C, 1 h			
t-BuLi (1.2)	THF, −78 °C, 1 h		15 (**3a**)	
t-BuLi (1.2)	Et_2O, −78 °C, 1 h			25
t-BuLi (1.2)	hexane, 0 or −78 °C, 1−3 h			
n-BuLi (2−4)	THF, −78 °C, 1 h		24 (**3b**)	
n-BuLi (2−4)	hexane, 0 or −78 °C, 1−3 h		2 (**3b**)	
n-BuLi-TMEDA (2)	hexane, 0 °C, 1 h		17 (**3b**)	
n-BuLi−LiDMAE (2)	hexane, 0 °C, 1 h	75[c]		
n-BuLi−LiDMAE (3)	hexane, 0 °C, 1 h	>99[c]		

[a] All reactions performed on 2 mmol (310 mg) of **1**. [b] GC yields. For each run the remaining part is unreacted **1**. [c] Reaction of MeSSMe (3−7.2 mmol) performed at −78 °C in the same solvent as used for metalation.

We first studied the lithiation of 2-phenylpyridine **1**. As no data were available about this reaction, we also examined the reactivity of **1** toward some commonly used lithium bases (Table 1).

The less basic lithium dialkylamides did not metalate **1** in THF even when used in excess, implying the use of stronger bases such as *n*-BuLi or *t*-BuLi. Unfortunately, none of these reagents led to the expected compound **2a** with main recovery of unreacted **1**. In hexane, no metalation occurred and n-BuLi led to limited nucleophilic addition product **3b** while in THF addition products **3a**,**b** were substantial. The reactivity of *t*-BuLi in Et_2O was of interest since no addition product was detected, and dimer **4** was produced in 25% yield. This indicated that lithiation actually occurred at C-6 of the pyridine ring and the formation of **4** could be explained by nucleophilic addition of the lithio derivative onto the azomethine bond of unreacted **1** before introduction of electrophile. The metalation was next attempted with *n*-BuLi−TMEDA in hexane expecting an increase of basicity of *n*-BuLi as well

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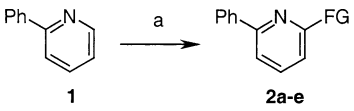
TABLE 2. Preparation of C-6 Substituted 2-Phenylpyridines[a]

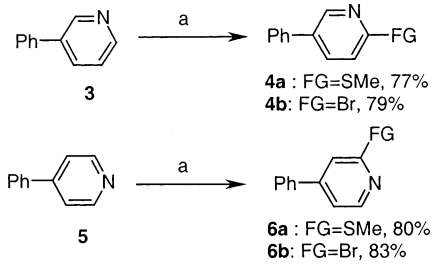


(a) (i) BuLi-LiDMAE (3 equiv.), hexane, 0°C, 1h.
(ii) Electrophile (3.6 equiv.), hexane, -78°C to r.t.

electrophile	product	FG	yield,[b] %
MeSSMe	**2a**	SMe	92
C_2Cl_6	**2b**	Cl	81
CBr_4	**2c**	Br	89
$ClSnBu_3$	**2d**	$SnBu_3$	72
$ClPPh_2$	**2e**	PPh_2	55[c]

[a] All reactions performed on 2.66 mmol (412 mg) of **1**. [b] Isolated yields after column chromatography (hexanes−AcOEt mixtures). [c] Air-sensitive **2e** has been fully oxidized (H_2O_2) into the corresponding phosphine oxide and analyzed as such.

SCHEME 1. Metalation of 3- and 4-Phenylpyridine[a]



[a] Reagents and conditions: (a) (i) BuLi−LiDMAE (3 equiv for **3**; 4 equiv for **5**), hexane, 0 °C, 1 h; (ii) MeSSMe or CBr_4 (3.6 equiv for **3**; 4.8 equiv for **5**), hexane, −78 °C to rt.

as a stabilization of pyridyllithium by diamine. Only addition product **3b** was obtained in this case with low conversion of **1**.

On the other hand, the reaction with BuLi−LiDMAE in hexane at 0 °C induced the unprecedented clean C-6 lithiation of the pyridine ring. Compound **2a** was obtained as a single product in good to excellent yield in sharp contrast with standard alkyllithiums.

To illustrate the scope of this new lithiation process, we performed the condensation of some typical electrophilic reagents (Table 2).

We next examined the ability of our reagent to metalate the other phenylpyridine isomers **3** and **5** whose, from our knowledge, direct lithiation has not been reported (Scheme 1). As shown **3** and **5** were efficiently lithiated α to nitrogen and functionalities could be introduced in very good yields at this position. While the selective C-2 lithiation obtained with **5** could be expected, more interesting was the exclusive lithiation at C-6 of **3**. Indeed, no regiosiomer resulting from a lithiation at C-2 was detected. Curiously, with **5** a larger amount of base had to be used to ensure completion of reaction. An explanation could be the slight solubility of **5** in hexane.

In summary we have shown that BuLi−LiDMAE is a powerful base for the direct pyridine ring metalation of 2-, 3-, and 4-phenylpyridines offering a straightforward access to derivatives. This work also revealed the ability of lithium aggregates to prevent dimerization by efficient stabilization of phenylpyridyllithium.

Experimental Section

Et_2O, THF, and hexane were distilled and stored on sodium wire before use. 2-Dimethylaminoethanol was distilled under nitrogen and stored on molecular sieves. *t*-BuLi was used as a 1.5 M solution in pentane. *n*-BuLi was used as a 1.6 M solution in hexanes. LDA and LTMP were prepared respectively by reaction of diisopropylamine and 2,2,6,6-tetramethylpiperidine with *n*-BuLi in THF.

Procedure for lithiation of phenylpyridines 1 or 3. A solution of 2-dimethylaminoethanol (0.8 mL, 8 mmol) in hexane (10 mL) was cooled at 0 °C and treated dropwise with *n*-BuLi (10 mL, 16 mmol). After 30 min at 0 °C, a solution of appropriate phenylpyridine (412 mg, 2.66 mmol) in hexane (5 mL) was added dropwise. After 1 h at 0 °C, the red brown reaction mixture was cooled to −78 °C and treated with a solution of appropriate electrophile (9.6 mmol) in hexane (5 mL). After 1 h at −78 °C the temperature was allowed to raise to room temperature. The hydrolysis was then performed at 0 °C with H_2O. The organic layer was then extracted twice with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. The crude products **2** or **4** were then purified by column or radial chromatography with hexane/AcOEt mixtures as eluent.

2a. Column chromatography (95:5 hexanes/AcOEt) yielded **2a** (592 mg, 92%) as a yellow oil. ^{1}H NMR δ_H 2.67 (s, 3H), 7.13 (d, J = 7.6 Hz, 1H), 7.39−7.56 (m, 5H), 8.05 (br d, J = 8 Hz, 2H). ^{13}C NMR δ_C 13.3, 115.6, 120.2, 126.9, 128.8, 129.2, 136.6, 156.1, 159.5 ppm. MS (EI) *m*/*z* 201 (M^+, 100), 200 (68), 155 (28), 154 (49), 127 (20), 77 (14), 51 (23). Anal. Calcd for $C_{12}H_{11}NS$: C, 71.60; H, 5.51; N, 6.96. Found C, 71.51; H, 5.62; N, 7.12.

4a. Radial chromatography (95:5 hexanes/AcOEt) yielded **4a** (409 mg, 77%) as a yellow oil. ^{1}H NMR δ_H 2.61 (s, 3H), 7.22 (br d, J = 7.4 Hz, 1H), 7.55−7.60 (m, 5H), 7.71 (dd, J = 7.4 and 0.7 Hz, 1H), 8.68 (d, J = 0.7 Hz, 1H). ^{13}C NMR δ_C 13.5, 113.1, 121.5, 126.9, 127.9, 129.1, 129.2, 134.5, 147.9, 163.5 ppm. MS(EI) *m*/*z* 202 (M^+ + 1, 17), 201 (M^+,100), 200 (46), 168 (26), 154 (30), 77 (18), 51 (18). Anal. Calcd for $C_{12}H_{11}NS$: C, 71.60; H, 5.51; N, 6.96. Found C, 71.74; H, 5.41; N, 7.05.

Procedure for Lithiation of 4-Phenylpyridine 5. The procedure used with **1** and **3** was modified as follows: **5** (310 mg, 2 mmol) was added as a solid through a powder addition funnel.

6a.[11] Radial chromatography (95:5 hexanes/AcOEt) yielded **6a** (320 mg, 80%) as a yellow oil. ^{1}H NMR δ_H 2.52 (s, 3H), 7.16 (dd, J = 5.4 and 1.6 Hz, 1H), 7.36−7.49 (m, 4H), 7.55 (d, J = 1.6 Hz, 1H), 7.61 (m, 1H), 8.45 (dd, J = 5.5 and 0.8 Hz, 1H). ^{13}C NMR δ_C 13.4, 113.1, 115.5, 117.8, 119.3, 127.1, 127.2, 128.6, 129.2, 138.1, 149.9, 160.7 ppm. MS (EI) *m*/*z* 201 (M^+, 100), 200 (60), 155 (44), 127 (21), 77 (15), 51 (18).

Supporting Information Available: Characterization data for compounds **2b**−**e**, **4b**, and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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