

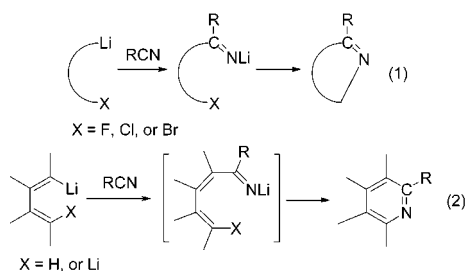
Novel Cycloaddition of Nitriles with Monolithio- and Dilithiobutadienes

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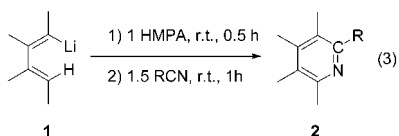
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Received March 18, 2002

The addition of organolithium compounds to nitriles predominantly forms *N*-lithioketimines,¹ which afford ketones or imines upon hydrolysis, and may be used as reactive intermediates for synthesis of *N*-substituted imines.^{2,3} Although intramolecular trapping of the *N*-lithioketimines is very attractive for constructing important *N*-containing heterocycles such as pyridine derivatives, few useful reports have appeared. The conventional way to achieve such syntheses is via subsequent intramolecular nucleophilic substitution of organohalides (eq 1, X = F, Cl, or Br).⁴ Herein we would like to report two novel and synthetically useful reaction patterns of organolithium compounds with nitriles affording pyridine derivatives as the final products (eq 2, X = H or Li).

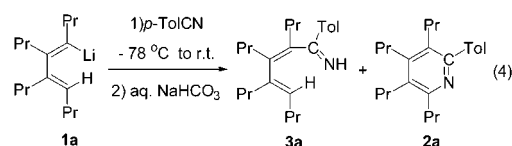


Lithiation of 1-iodo-1,3-dienes with 2 equivalents of *t*-BuLi gave their corresponding 1-lithio-1,3-dienes **1** in quantitative yields as monitored by GC.⁵ Addition of 1 equiv of HMPA (hexamethylphosphoramide) and 1.5 equiv of a nitrile to the above in situ-generated monolithium reagent caused an immediate reaction to afford the pyridine derivatives **2** in high yields (eq 3). Representative

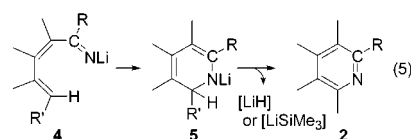


examples of pyridines **2** thus prepared are given in Table 1. 1,2,3,4-Tetrasubstituted 1-lithio-1,3-diene **1a** reacted with nitriles (A: *p*-tolunitrile, B: 4-methoxybenzonitrile, C: benzonitrile) to afford pyridines **2a–c** in high isolated yields. Tetrahydroisoquinolines **2d** and **2e** could be readily prepared in 85 and 75% isolated yields, respectively, from the reactions of **1b** and **1c** with benzonitrile. It is interesting to note that the pyridine derivative **2a** and the desilylated product **2e** are formed in the reaction mixtures without hydrolysis, as demonstrated by NMR.

To investigate the reaction mechanism, an experiment demonstrated in eq 4 was carried out from $-78\text{ }^{\circ}\text{C}$ to room temperature. After the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min, hydrolysis afforded the linear imine **3a** in 64% isolated yield along



with <5% of the pyridine derivative **2a**. With temperature increasing, **3a** decreased while **2a** increased (Table 2). Finally, **3a** disappeared completely, and **2a** was formed as the only final product in 98% yield. On the basis of these observations, a possible reaction mechanism is given in eq 5. The *N*-lithioketimines **4** are formed as



the first intermediates, which undergo intramolecular lithiation–cyclization to afford **5**. Elimination of LiH or LiSiMe_3 (R' = SiMe_3) gives rise to the final pyridine derivatives **2**.

Very interestingly, when 1,4-dilithio-1,3-dienes **6**, generated in situ by lithiation of their corresponding 1,4-diiodo-1,3-dienes,^{6,7} were treated with nitriles in the presence of HMPA, pyridine

Table 1. Formation of Pyridine Derivatives from 1-Lithio-1,3-dienes and Nitriles

Monolithio compound 1	Nitrile	Product 2	Yield of 2 / ^a %
1a	A ^b	2a	98 (87)
1a	B ^c	2b	92 (78)
1a	C ^d	2c	91 (77)
1b	C	2d	93 (85)
1c	C	2e	(75)

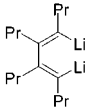
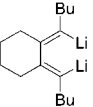
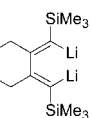
^a GC yields. Isolated yields are given in parentheses. ^b *p*-Tolunitrile. ^c 4-Methoxybenzonitrile. ^d Benzonitrile.

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Table 2. Formation of Linear Imine **3a** and Pyridine **2a**

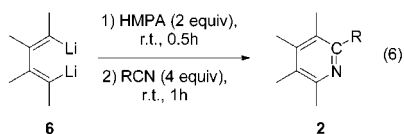
$T/^\circ\text{C}$	t/min	yield of 3a /%	yield of 2a /%
-78	15	70 (64)	<5
-60	30	23	54
-60	60	10	86
0	30	<3	95
rt	30	0	98

Table 3. Formation of Pyridine Derivatives from 1,4-Dilithio-1,3-dienes and Nitriles

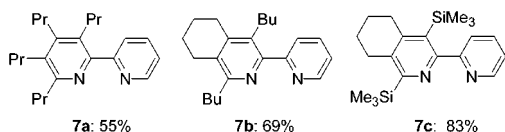
Dilithio compound 6	Nitrile	Product 2	Yield of 2 /% ^a
	A	2a	85 (63)
6a	B	2b	95 (80)
6a	C	2c	87 (62)
	C	2d	89 (73)
	C	2e ^b	(66)

^a GC yields. Isolated yields are given in parentheses. ^b Desilylation took place in the workup procedure.

derivatives **2** were also formed as the final products in high isolated yields (eq 6). Both the monolithio compounds **1** and the dilithio

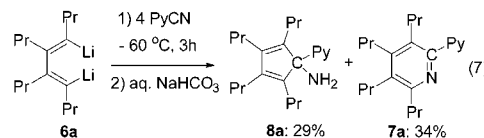


compounds **6** gave the same products **2**. Results are given in Table 3. When 2-cyanopyridine was used, its reaction with **6a**, **6b**, and **6c** afforded 2,2'-bipyridine derivatives **7a**, **7b**, and **7c** in 55, 69, and 83% isolated yields, respectively.⁸



It is noteworthy that substituted 1,3,5-triazines,^{1,2} the self-cyclotrimerization products of nitriles, were formed as byproducts in these reactions. Therefore, at least 3 equiv of nitriles should be used to ensure high-yield formation of pyridines **2** from **6**. On the contrary, formation of substituted 1,3,5-triazines was not observed in cases of 1-lithio-1,3-dienes **1**. No dihydropyridines or related intermediates were observed in the reaction mixtures before workup

as determined by NMR. In fact, NMR spectra show that the pyridine derivatives have been already formed in the reaction mixture. When the reaction of **6a** with 2-cyanopyridine was carried out at -60°C in the presence of HMPA, cyclopentadienylamine **8a** was isolated in 29% yield, along with 34% yield of **7a** (eq 7). Unlike the case



of monolithio compounds **1**, no linear imines were observed in cases of dilithio compounds **6** even at lower temperatures. All these observations suggest that, although the same pyridines are formed as the final products, the reaction mechanisms for the formation of **2** from **1** might be different from those for the formation of **2** from **6**. Further investigation to elucidate the reaction mechanisms and further applications of these novel and synthetically useful reactions are in progress.

Acknowledgment. This work was partially supported by the Natural Science Foundation of China and the Major State Basic Research Development Program (G2000077502-D). Cheung Kong Scholars Program and Qiu Shi Science and Technologies Foundation are gratefully acknowledged. Mr. Yuxing Zhao, Mr. Zhuo Gao, and Miss Jun Yan carried out some experimental work.

Supporting Information Available: Experimental details, characterization data, copies of ^1H and ^{13}C NMR spectra for all isolated compounds and IR spectra of **3a** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA0262176