Generation and Synthetic Applications of (3-Pyridinylchloromethyl)lithium

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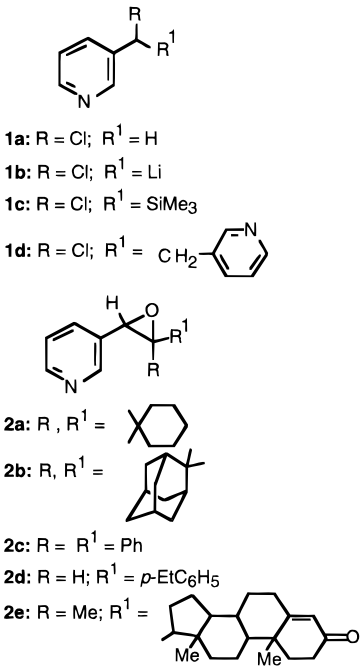
No longer only the subject of mechanistic interest, α-haloorganolithiums, also called halocarbenoids, have become increasingly important since the pioneering work by Kobrich in the 1960s.[1] Due to the improvement of preparative techniques, these organolithiums have become valuable synthetic intermediates which are reasonably stable at low temperatures and can be trapped with electrophiles.[2] α-Haloalkyl-,[3] α-halocyclopropyl-,[4] α-haloalkylidene-,[5] and α-haloallyl-[6] lithiums have been extensively studied and used in synthetic organic chemistry. The utility of the products obtained in the reactions of the above α-haloorganolithiums is that they still contain one or more halogens which make them available for further synthetic elaborations. (α-Halobenzyl)lithiums have received much less attention, probably because of their tendency to give the "homocoupling" reaction and α-elimination. Examples of the formation of α,*β*-diarylethyl chloride, presumably derived from the interaction of the chlorobenzyl anion with its precursor benzyl chloride, have been reported.[7] The α-elimination of hydrogen halide from benzyl halides, in the presence of powerful bases, to give carbenes is a well-known process.[8] These observations indicate that the tendency of (benzylhalomethyl)lithiums to give homocoupling and α-elimination precludes their possible use in C−C bond-forming reactions with electrophiles other than benzyl halides. The only known example of coupling is that of the trimethylsilylation of (benzylchloromethyl)lithium and (benzylbromomethyl)lithium with Me_3SiCl.[9]

As part of a research project concerning the reactions and synthetic applications of (heteroarylhaloalkyl)lithiums,[10−13] we have studied the reactions of a benzylic-like α-chloroorganolithium, such as (3-pyridinylchloromethyl)lithium,[14] with electrophiles.

Lithiation of 3-(chloromethyl)pyridine **1a** with lithium diisopropylamide (LDA) at −78 °C gave a dark brown solution, which very likely contains the lithiated species **1b**. Attempts, however, to trap **1b** by addition of Me_3SiCl failed. We just recovered the "homocoupling" products **1d** and **4** together with traces of the expected 3-[(trimethylsilyl)methyl]pyridine (**1c**), as verified by GC-MS. Compound **1c** did form, almost quantitatively, when **1b** was generated from **1a** in the presence of Me_3SiCl (Barbier conditions).[15] Moreover, (pyridinylchloromethyl)lithium **1b** proved to be reasonably stable at −78 °C to be trapped by a number of other electrophiles, even under Grignard conditions.[15] Indeed, treatment of **1b**, soon after its generation, with cyclohexanone led to the formation of epoxide **2a** in an excellent yield. Similarly,



1b reacted with adamantanone, benzophenone, and *p*-ethylbenzaldehyde affording epoxides **2b**, **2c**, and **2d**, respectively (Table 1). The reaction with *p*-ethylbenzaldehyde was stereoselective and gave the epoxide **2d** having the *E* configuration.[16] The reaction of **1b** with *trans*-androsterone led to the steroidal epoxide **2e** as a

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(14) (3-Pyridinylchloromethyl)lithium (**1b**) actually has to be considered an α-halocarbanion, whereas (2-pyridinylchloromethyl)lithium (See ref 11) has a large character of an aza-enolate as suggested by spectroscopic data reported for similar species: Hogen-Esch, T. E.; Jenkins, W. L. *J. Am. Chem. Soc.* **1981**, *103*, 3666.
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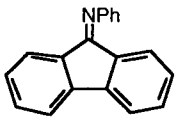
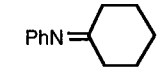
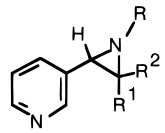
Table 1. Reactions of (3-Pyridinylchloromethyl)lithium (1b) with Electrophiles at 78 °C in THF

Electrophile	Reaction product (% yield)[a,b]
Me_3SiCl	**1c** (>95)[c]
cyclohexanone	**2a** (90)
adamantanone	**2b** (90)
benzophenone	**2c** (85)
p-ethylbenzaldehyde	**2d** (58)
trans-androsterone	**2e** (55)
PhN=CHPh	**3a** (92)
$PhCH_2N$=CHPh	**3b** (88)
	**3c** (41)
PhN=C(Me)Ph	**3d** (30)
	**3e** (40)

a) Yields were not optimized and refer to isolated, purified compounds; b) Reactions carried out under Grignard conditions; c) Reaction carried out under Barbier conditions.

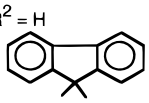
mixture of *Z* and *E* isomers. The synthesis of this sort of pyridinyl epoxides, which have been studied in medicinal chemistry for their cytotoxic activity,[17] has been reported and it was based on the Darzens reaction of 3-pyridinyl carboxaldehyde with chloroacetone[17] and chloroacetonitrile.[18] Yields, however, were poor (26−37%).

Lithiated intermediate **1b** adds also to Schiff's bases to give reasonable to excellent yields of the novel aziridines **3a**−**e**. In particular, the reaction with unsymmetrical imines proceeded with very high *E* diastereoselectivity.[19]



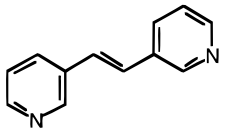
3a: R = R^1 = Ph; R^2 = H

3b: R = Bz; R^1 = Ph; R^2 = H

3c: R = Ph; R^1, R^2 = 

3d: R = R^1 = Ph; R^2 = Me

3e: R = Ph; R^1, R^2 = 



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In conclusion, in this paper we have shown that (pyridinylchloromethyl)lithium **1b**, differently from (chloro- and (bromobenzyl)lithium, which have a bias to undergo "homocoupling" and α-elimination, is sufficiently stable at low temperature to be trapped by electrophiles. The reactions of **1b** with carbonyl coumponds and Schiff's bases represent a useful tool for the preparation of functionalized pyridines.

Experimental Section

^{1}H-NMR spectra were recorded on 60, 90, 200, and 300 MHz spectrometers; chemical shifts are reported in parts per million (δ) from an internal TMS standard using $CDCl_3$ as solvent. IR spectra were recorded on a Perkin-Elmer spectrometer Model 598. GC analyses were carried out with a Hewlett-Packard MP-5890 series II gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.); GC-MS spectrometry analyses were performed on a gas chromatograph equipped with a mass selective detector operating at 70 eV (EI). Melting points were uncorrected. Flash chromatographies were performed with Merck 230−400 mesh silica gel. All reactions were conducted in oven-dried glassware under a nitrogen atmosphere.

Materials. THF of commercial grade was purified by distillation (twice) from sodium wires in N_2 atmosphere. Petroleum ether refers to the 40−60 °C boiling fraction. 3-(Chloromethyl)-pyridine (**1a**), is sold as the hydrochloride (Aldrich) from which it can be obtained upon treatment with 10% NaOH solution.

All other chemicals were of commercial grade and used without further purification or, if necessary, purified by distillation or crystallization prior to use. Microanalyses were performed on a C,H,N analyzer.

Generation of the (3-Pyridinylchloromethyl)lithium (1b) and Trapping with Electrophiles. The reaction with benzophenone is described: to diisopropylamine (2.4 mmol) in 10 mL of THF was added at 0 °C 1 mL of 2.4 M n-BuLi. The solution was cooled at −78 °C and then treated dropwise with a solution of **1a** (0.256 g, 2.0 mmol) and benzophenone (0.440 g, 2.4 mmol) in 10 mL of THF. After 1 h at −78 °C the reaction mixture was allowed to warm to rt and quenched with aqueous NH_4Cl. Extraction with ether (3 × 25 mL), drying over Na_2SO_4, and evaporation of the solvent under reduced pressure left a residue that was column chromatographed (silica gel, petroleum ether/diethyl ether: 8.5/1.5 as eluent) to give **1c** (85% yield).

The new compounds showed the following data:

(3-Pyridinylchloromethyl)trimethylsilane 1c: oil. ^{1}H-NMR ($CDCl_3$) δ 0.1 (s, 9H), 4.32 (s, 1H), 7.1−8.7 (m, 4H). MS *m*/*z* 199 (M^+, 64), 156 (30), 106 (5), 73 (100). Anal. Calcd for $C_9H_{14}ClNSi$: H, 7.08; C, 54.12; N, 7.01. Found: H, 7.11; C, 54.20; N, 7.11.

3′-(3-Pyridinyl)cyclohexanespiro-2′-oxirane (2a): mp 88−90 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ 1.2−1.8 (m, 10H), 3.97 (s, 1H), 7.25−8.75 (m, 4H). MS *m*/*z* 189 (M^+, 60), 188 (31), 160 (19), 108 (100), 92 (95). IR ($CHCl_3$) ν 3035, 2930, 2850, 1600, 1445, 1260 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO$: H, 7.99; C, 76.16; N, 7.40. Found: H, 7.88; C, 76.22; N, 7.32.

3′-(3-Pyridinyl)adamantanespiro-2′-oxirane (2b): mp 130−32 °C (EtOH) ^{1}H-NMR ($CDCl_3$) δ 1.10−2.20 (m, 14H), 4.0 (s, 1H), 7.2−8.8 (m, 4H). MS *m*/*z* 241 (M^+, 100), 240 (19), 91 (23), 77 (12). IR ($CHCl_3$) ν 3035, 2920, 2850, 1595, 1450, 1420, 1090 cm-^{1}. Anal. Calcd for $C_{16}H_{19}NO$: 7.94; C, 79.63; N, 5.80. Found: H, 7.86; C, 79.73; N, 5.72.

2′,2′-Diphenyl-3′-(3-pyridinyl)oxirane (2c): mp 101−103 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ 4.47 (s, 1H), 7.10−8.7 (m, 14H). MS *m*/*z* 273 (28), 272 (18), 165 (100). IR ($CHCl_3$) ν 3050, 3030, 2960, 1595, 1580, 1260 cm^{-1}. Anal. Calcd for $C_{19}H_{15}NO$: H, 5.53; C, 83.49; N, 5.12. Found: H, 5.60; C, 83.58; N, 5.06.

2′-(4-Ethylphenyl)-3′-(3-pyridinyl)oxirane (2d): mp 47−8 °C (petroleum ether). ^{1}H-NMR ($CDCl_3$) δ 1.2 (t, 3H, *J* = 7 Hz), 2.7 (q, 2H, *J* = 7 Hz), 3.82−3.97 (2d, 2H, *J* = 1.8 Hz), 7.1−8.7 (m, 8H). MS *m*/*z* 225 (M^+, 29), 224 (21), 196 (100), 117 (43). Anal. Calcd for $C_{15}H_{15}NO$: H, 6.71; C, 79.97; N, 6.22. Found: H, 6.75; C, 79.90; N, 6.12.

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2′-Methyl-2′-(*trans*-17-androsterone)-3′-(3-pyridinyl)oxirane (2e): oil. ^{1}H-NMR ($CDCl_3$) δ 0.7−2.6 (m, 29H), 4.65 (s, 1H), 5.8 (s, 1H), 7.3−8.75 (m, 4H). IR ($CHCl_3$) ν 3020, 2970, 2875, 1660, 1450, 1230 cm^{-1}. Anal. Calcd for $C_{26}H_{33}NO$: H, 8.86; C, 83.15; N, 3.73. Found: H, 8.80; C, 83.30; N, 3.70.

***N*-Phenyl-2′-phenyl-3′-(3-pyridinyl)aziridine (3a):** mp 102−104 °C (EtOH, petroleum ether). ^{1}H-NMR ($CDCl_3$) δ 3.73−3.85 (2d, 2H, J = 6.1 Hz), 6.8−8.7 (m, 14H). MS m/z 272 (M^+,-59), 271 (100), 168 (44), 167 (51), 77 (31). IR ($CHCl_3$) ν 3035, 2980, 1600, 1485, 1410, 1270 cm^{-1}. Anal. Calcd for $C_{19}H_{16}N_2$: H, 5.92; C, 83.79; N, 10.29. Found: H, 6.00; C, 83.84; N, 10.20.

***N*-Benzyl-2′-phenyl-3′-(3-pyridinyl)aziridine (3b):** oil. ^{1}H-NMR ($CDCl_3$) δ 3.15−3.35 (AB system, two doublets, 2H, J = 14 Hz), 4.45−4.70 (2d, 2H, J = 6.5 Hz), 7.0−8.6 (m, 14H). MS m/z 286 (M^+, 2), 194 (100), 181 (5), 116 (12). Anal. Calcd for $C_{20}H_{18}N_2$: H, 6.33; C, 83.88; N, 9.78. Found: H, 6.40; C, 83.98; N, 9.70.

***N*-Phenyl-3′-(3-pyridinyl)fluorenespiro-2′-aziridine (3c):** mp 136−138 °C. ^{1}H-NMR ($CDCl_3$) δ 4.36 (s, 1H) 6.1−8.75 (m, 17H). MS m/z 346 (M^+, 100), 345 (44), 268 (46), 267 (39), 239 (40). IR ($CHCl_3$) ν 3060, 3035, 2960, 1600, 1485, 1250 cm^{-1}. Anal. Calcd for $C_{25}H_{18}N_2$: H, 5.24; C, 86.68; N, 8.09. Found: H, 5.34; C, 86.78; N, 7.98.

***N*-Phenyl-2′-phenyl-2′-methyl-3′-(3-pyridinyl)aziridine (3d):** oil. ^{1}H-NMR ($CDCl_3$) δ 1.30 (s, 3H), 3.35 (s, 1H), 7.20−8.7 (m, 14H). MS m/z 286 (M^+, 39), 285 (50), 194 (96), 180 (100). IR ($CHCl_3$) ν 3060, 3030, 2980, 1600, 1450, 1245 cm^{-1}. Anal. Calcd for $C_{20}H_{18}N_2$: H, 6.34; C, 83.88; N, 9.78. Found: H, 6.40; C, 83.92; N, 9.68.

***N*-Phenyl-3′-(3-pyridinyl)cyclohexanespiro-2′-aziridine (3e):** oil. ^{1}H-NMR ($CDCl_3$) δ 1.3−2.0 (m, 10H), 3.33 (s, 1H), 6.9−8.9 (m, 9H). MS m/z 264 (M^+, 26), 263 (12), 235 (15), 221 (16), 172 (100). IR ($CHCl_3$) ν 3060, 2960, 2850, 1600, 1450, 1250 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_2$: H, 7.62; C, 81.78; N, 10.60. Found: H, 7.70; C, 81.84; N, 10.45.

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