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Alkylation of 2-Substituted (6-Methyl-2-pyridyl)methyllithium Species with Epoxides

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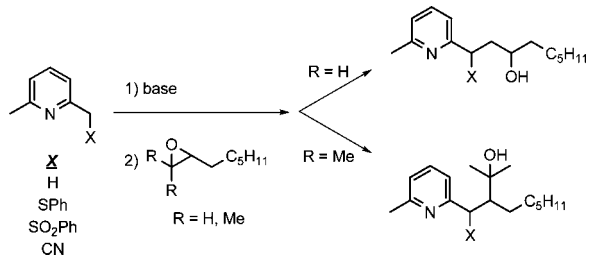
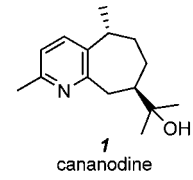
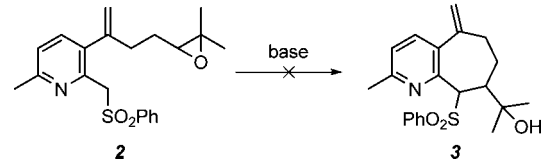


Substituted (6-methyl-2-pyridyl)methyllithium species were reacted with 1,2-epoxyoctane and 2-methyl-2,3-epoxynonane. The monosubstituted epoxide reacted efficiently with lutidyllithium and a number of 2-substituted (6-methyl-2-pyridyl)methyllithium derivatives. The trisubstituted epoxide gave low yields of adducts with all (2-pyridyl)methyllithium species studied. These results are discussed in the context of a proposed synthesis of cananodine.

Cananondine (**1**) is a guaipyridine alkaloid isolated from the fruits of *Cananga odorata* shown to inhibit the growth of two hepatocellular carcinoma cell lines.[1,2] The guaipyridines are a small class of natural products whose syntheses have not been extensively studied.[3] As part of our ongoing efforts toward the synthesis of cananodine, we planned an intramolecular epoxide opening to form the seven-membered carbocycle of the natural product. A color change consistent with the formation of an α-pyridyl anion was observed when epoxy sulfone **2** was treated with either *n*-BuLi or LDA in THF, but we were unable to isolate any of the cyclized product **3**. The majority of starting **2** was recovered in every case.[4] Since the planned 7-*exo*-tet cyclization does not run afoul of Baldwin's rules for ring closure,[5] we concluded that the sulfone-stabilized anion is not nucleophilic enough and/or the trisubstituted epoxide is too hindered to be a competent electrophile.

Lateral lithiation of heterocyclic systems for subsequent functionalization is a powerful synthetic tool.[6] The literature offers limited insight as to the solution of the present problem, however, as there are only a scattering of examples of α-pyridyl anions reacting with ethylene oxide, simple monosubstituted,[7] or disubstituted epoxides.[8] We have found no examples of a reaction of an α-pyridyl anion with a trisubstituted epoxide, nor have we found any examples of reactions with epoxides where the α-pyridyl carbon bears an acidifying group. Thus, we engaged in a directed study to address the questions raised above in the context of intermolecular reactions of α-substituted lutidyllithium species with epoxides.[9]





Amide bases have been used to generate picolyllithium species,[7a,b] but more often *n*-BuLi or PhLi is used for this purpose.[7c−k] The pK_a value of 2-picoline has been determined to be 34 (Figure 1).[10] This makes *n*-BuLi or PhLi (pK_a(butane) ≈ 50; pK_a(benzene) = 43) the obvious choice over LDA (pK_a(diisopropylamine) = 36) for quantitative deprotonation of 2-picoline. Substitution at the α-position of the picoline increases

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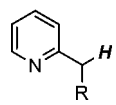
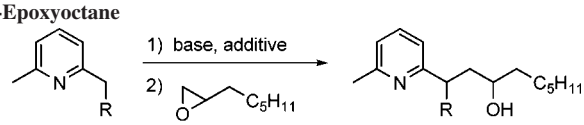


R	pK_a
H	34
Ph	28.2
SO_2Ph	20.5

FIGURE 1. Relative acidities of 2-picoline derivatives.

TABLE 1. Reaction of Lutidyllithium Derivatives with 1,2-Epoxyoctane



4 **5**

entry		R	base	additive	product	yield (%)[a]
1	**4a**	H	LDA	none	**5a**	61
2	**4a**	H	LDA	$BF_3 \cdot OEt_2$[b]	**5a**	66
3	**4a**	H	LDA	HMPA[c]	**5a**	56
4	**4a**	H	BuLi	none	**5a**	80
5	**4a**	H	BuLi	CuCN[d]	**5a**	89
6	**4b**	CN	LDA	none	**5b**	36[e]
7	**4c**	SPh	LDA	none	**5c**	68[e]
8	**4c**	SPh	BuLi	none	**5c**	70[e]
9	**4d**	SO_2Ph	LDA	none	**5d**	47[e]
10	**4d**	SO_2Ph	BuLi	none	**5d**	74[e]

[a] Isolated yields of purified **5**. [b] 1 equiv. [c] 2 equiv. [d] 0.5 equiv. [e] Mixture of diastereomers.

acidity dramatically, however, as seen for 2-benzylpyridine and 2-(methylphenylsulfonyl)pyridine (Figure 1).[11] Indeed, the conjugate base of 2-(methylphenylsulfonyl)pyridine has been reported to be unreactive toward alkyl halides and Michael acceptors.[12] Given that our ultimate goal is an intramolecular epoxide opening, we were mindful of the compatibility of the chosen base with epoxide functionality. Thus, we explored the use of both LDA and *n*-BuLi as bases and the use of various acidifying groups at the α-position.

Addition of 2,6-lutidine (**4a**) to a solution of LDA in THF at −78 °C resulted in a deep reddish solution, characteristic of the picolyl-type lithium species. Addition of 1,2-epoxyoctane provided a good yield of the adduct **5a**[7g] after workup and purification (Table 1, entry 1). Use of boron trifluoride as an additive did not dramatically improve the yield of **5a** (entry 2), but did decrease the reaction time from 12−18 h to 15 min. HMPA as an additive offered no advantages (entry 3). Using *n*-BuLi instead of LDA resulted in a somewhat higher yield of **5a** (entry 4), and formation of a "higher order" cuprate[13] species from the lutidyllithium with 0.5 equiv of CuCN gave the highest yield of **5a** (entry 5).

Three acidifying groups on the α-position of lutidine were tried: cyano, thiophenyl, and sulfonylphenyl. These groups were chosen based on ease of substrate preparation and the options available for eventual removal of the acidifying group after reaction with the epoxide. Of these, the cyano substrate **4b**[14] was least effective in reacting with epoxyoctane (entry 6). The yield of **5b** was diminished by formation of side products including lactone **6**, which is formed by intramolecular attack of the intermediate alkoxide or hydroxyl group on the nitrile.[15]

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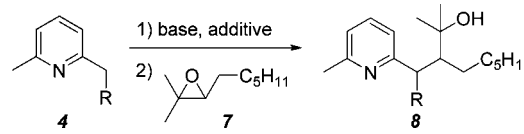
TABLE 2. Reaction of Lutidyllithium Derivatives with 2-Methyl-2,3-epoxynonane

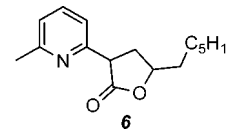


4 **7** **8**

entry		R	base	additive	product	yield (%)[a]
1	**4a**	H	BuLi	none	**8a**	40
2	**4a**	H	LDA	none	**8a**	12[b]
3	**4a**	H	LDA	$BF_3 \cdot OEt_2$[c]	**8a**	8
4	**4a**	H	LDA	HMPA[d]	**8a**	29
5	**4a**	H	BuLi	CuCN[e]	**8a**	23
6	**4c**	SPh	BuLi	none	**8c**	9[f]
7	**4c**	SPh	LDA	none	**8c**	6[f]
8	**4d**	SO_2Ph	BuLi	none	**8d**	0

[a] Isolated yields of purified **8**. [b] Dialkylated product **10** (8%) also isolated. [c] 1 equiv. [d] 2 equiv. [e] 0.5 equiv. [f] Mixture of diastereomers.

Thiophenyl-substituted substrate **4c**[16] was successfully deprotonated with either *n*-BuLi or LDA to give similar yields of adduct **5c** after reaction with 1,2-epoxyoctane (entries 7 and 8). The sulfonylphenyl substrate **4d** gave modest yields of adduct **5d** (entry 9) when LDA was used as base, but the yield of **5d** was significantly improved with use of *n*-BuLi.



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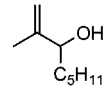
We next examined reactions of lutidyllithium with the trisubstituted epoxide 2-methyl-2,3-epoxynonane (**7**)[17] (Table 2). Deprotonation of **4a** with *n*-BuLi followed by addition of the epoxide gave a modest yield of adduct **8a** (entry 1). Use of LDA to deprotonate **4a** gave a much lower yield of **8a** along with dialkylated product **10** (8%) and a mixture of unreacted **7** and allylic alcohol **9**[18] (1:1 ratio, 50%) (entry 2). Use of boron trifluoride and HMPA as additives with LDA did not improve the yield of **8a**, but did prevent the formation of **10**. In both of these cases, however, a similar amount of unreacted **7** and allylic alcohol **9** was isolated as before (55% and 60%, respectively, entries 3 and 4). Use of a higher order cuprate derived from **4a** also gave a relatively poor yield of **8a**. The thiophenyl-substituted derivative **4c** gave very low yields of adduct **8c**, regardless of base used (entries 6 and 7), and the sulfonylphenyl-containing substrate **4d** failed to produce **8d** after deprotonation with *n*-BuLi and reaction with epoxide **7** (entry 8).

Clearly the trisubstituted epoxide **7** is a much poorer electrophile than 1,2-epoxyoctane in the reaction with (6-methyl-2-pyridyl)methyllithium species. The dominant reaction path is epoxide elimination to produce **9**. These results, within the context of our planned synthesis of cananodine, suggest a monosubstituted epoxide should be employed in the attempted cyclization.



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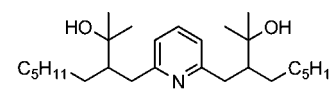

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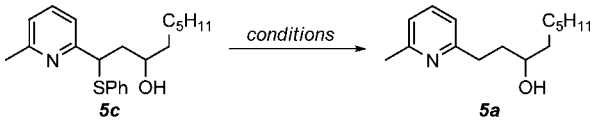
As for the nature of the acidifying group in the α-position of the pyridine for the planned intramolecular reaction, our results indicate the sulfur-containing substituents will be more useful



Conditions	Yield (%)
SmI_2, HMPA, THF	42
Raney, Ni, EtOH	75
LDBB, THF	62

FIGURE 2. Reductive cleavage of the −SPh group from **5c**.

than the nitrile. Furthermore, the thiophenyl group is preferable to the sulfonylphenyl group if LDA is to be used in the intramolecular reaction (Table 1, compare entries 7 and 9).

To gain further insight as to the suitability of the thiophenyl substituent for the cananodine synthesis, we explored methods to reductively cleave this group from adduct **5c**. Samarium(II) iodide,[19] Raney nickel,[20] and lithium di-*tert*-butylbiphenylide (LDBB)[21] all successfully converted **5b** to **5a**, but Raney nickel gave the highest yield and the cleanest product mixture (Figure 2).

To summarize, the reaction of lutidyllithium with 1,2-epoxyoctane provides good yields of adducts, with slightly higher yields obtained when using *n*-BuLi versus LDA to generate the alkyllithium species. (6-Methyl-2-pyridyl)methyllithium species substituted in the α-position with a thiophenyl or sulfonylphenyl group also react effectively with 1,2-epoxyoctane, while the cyano-substituted substrate was less effective. In contrast, a trisubstituted epoxide was a poor electrophile for all picolyl-type lithium species studied. These results suggest a monosubstituted epoxide is more likely to be successful in an intramolecular reaction required for our planned synthesis of cananodine.

Experimental Section.[22]

1-(6-Methylpyridin-2-yl)nonan-3-ol (5a). A 25-mL round-bottomed flask under argon was charged with LDA (3.0 mmol, prepared from diisopropylamine and *n*-BuLi in ∼15 mL of THF) and cooled in a dry ice/2-propanol bath. 2,6-Lutidine (0.35 mL, 0.322 g, 3.0 mmol) was added dropwise to the flask. The solution turned red, and after 15 min the dry ice bath was removed and the flask allowed to warm to room temperature. The flask was then recooled in the dry ice slush bath, 1,2-epoxyoctane (0.46 mL, 0.38 g, 3.0 mmol) was added, and the solution was allowed to slowly warm to room temperature overnight. Saturated NH_4Cl solution was then added and the mixture was extracted with ether (3 × 15 mL). The combined organic layers were washed with saturated NH_4Cl and brine before drying over Na_2SO_4. After solvent evaporation, the crude product was purified by radial chromatography (1:1 hexanes: ethyl acetate on a 2 mm silica rotor, 7.5 mL/min flow rate) to provide **5a** as a pale yellow oil (0.429 g, 61%). When this procedure was repeated with *n*-BuLi in place of LDA, **5a** was isolated in 80% yield after chromatographic purification. IR (neat) 3344 (br), 1594, 1578, 1458, 1376, and 1061 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, J = 7.8 Hz, 1H), 6.97 (d, J = 7.8 Hz, 2H), 5.25 (br s, 1H, OH), 3.66 (m, 1H), 3.00, (ddd, J = 14.7, 8.8, 5.4 Hz, 1H), 2.92 (ddd, J = 14.7, 7.3, 5.4 Hz, 1H), 2.56 (s, 3H), 1.93 (dddd, J = 12.7, 8.3, 5.4, 2.9 Hz, 1H), 1.76 (dddd, J = 12.7, 8.8, 7.8, 5.4 Hz, 1H), 1.6−1.4 (m, 3H), 1.4−1.2 (m, 7H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.3, 137.1, 120.6, 120.0, 71.6, 37.9, 36.0, 35.1, 31.9, 29.5, 25.9, 24.1, 22.6, and 14.1. HRMS (FAB) calcd for $(C_{15}H_{25}NO + H)^+$ 236.2014, found 236.2033. Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.33; H, 10.94; N, 5.91.

2-Methyl-3-((6-methylpyridin-2-yl)methyl)nonan-2-ol (8a). The procedure used for the preparation of **5a** was followed with use of LDA (3.0 mmol), 2,6-lutidine (**4a**) (0.35 mL, 0.322 g, 3.0 mmol), and 2-methyl-2,3-epoxynonane (**7**) (0.469 g, 3.0 mmol). Extractive workup and flash chromatography (gradient elution 15:1 hexanes:ethyl acetate to 1:2 hexanes:ethyl acetate) provided, in order of elution, unreacted **7** (0.114 g, 24%), allylic alcohol **9**[18] (0.120 g, 26%), unreacted **4a** (0.153 g, 48%), tertiary alcohol **8a** (0.092 g, 12%), and dialkylated product **10** (0.098 g, 8%) as a mixture of diastereomers. When this procedure was repeated with *n*-BuLi in the place of LDA, **8a** was isolated in 40% yield after chromatographic purification. Data for **8a**: IR (neat) 3400 (br), 1594, 1578, and 1159 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 1H), 6.96 (d, J = 7.3 Hz, 1H), 3.08 (dd, J = 15.6, 6.3 Hz, 1H), 2.86 (dd, J = 15.6, 2.9 Hz, 1H), 2.56 (s, 3H), 1.76 (m, 1H), 1.47 (m, 1H), 1.34 (s, 3H), 1.25 (m, 9H), 1.17 (s, 3H), 0.86 (t, J = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 157.3, 137.1, 120.7, 120.5, 71.9, 49.1, 37.4, 31.8, 30.7, 30.6, 29.4, 28.5, 25.9, 23.9, 22.6, and 14.1. CI-MS (MeOH) *m/z* 264 (M + H, 28), 247 (18), and 246 (100). HRMS (FAB) calcd for $(C_{17}H_{29}NO + H)^+$ 264.2327, found 264.2331. Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10; N, 5.32. Found: C, 77.12; H, 11.39; N, 5.42.

Data for **10**: ^1H NMR (500 MHz, $CDCl_3$) major diastereomer δ 7.49 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 7.8 Hz, 2H), 3.16 (dd, J = 15.1, 5.4 Hz, 2H), 2.65 (dd, J = 15.1, 4.9 Hz, 2H), 1.86 (m, 2H), 1.45 (m, 2H), 1.30 (s, 6H), 1.3−1.1 (m, 20H), 1.15 (s, 6H), 0.83 (t, J = 7 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) major diastereomer δ 161.2, 137.1, 120.7, 71.9, 50.0, 38.1, 31.7, 31.6, 29.7, 29.4, 28.7, 25.4, 22.6, and 14.1. CIMS (MeOH) *m/z* 420 (M + H, 48), 402 (52), 385 (56), and 59 (100).

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Supporting Information Available: Additional experimental procedures, compound characterization data, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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