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Alkylation of 2-substituted (6-methyl-2-pyridyl)methyl lithium species with epoxides

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Abstract

Substituted (6-methyl-2-pyridyl)methyl lithium 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)methyl lithium derivatives. The trisubstituted epoxide gave low yields of adducts with all (2-pyridyl)methyl lithium species studied. These results are discussed in the context of a proposed synthesis of cananodine.

Cananodine (**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 picolyl lithium 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 of diisopropylamine = 36) for quantitative deprotonation of 2-picoline. Substitution at the α -position of the picoline increases 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’ cuprate¹³ species from the lutidyllithium using 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 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 using *n*-BuLi.

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)methylolithium 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.

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 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).

In order 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)methylolithium 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 Section²²

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 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 minutes 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 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 using *n*-BuLi in the 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, $J = 7.8$, 1H), 6.97 (d, $J = 7.8$, 2H), 5.25 (br s, 1H, OH), 3.66 (m, 1H), 3.00, (ddd, $J = 14.7$, 8.8, 5.4, 1H), 2.92 (ddd, $J = 14.7$, 7.3, 5.4, 1H), 2.56 (s, 3H), 1.93 (dddd, $J = 12.7$, 8.3, 5.4, 2.9, 1H), 1.76 (dddd, $J = 12.7$, 8.8, 7.8, 5.4, 1H), 1.6–1.4 (m, 3H), 1.4–1.2 (m, 7H), 0.86 (t, $J = 6.8$, 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 $(\text{C}_{15}\text{H}_{25}\text{NO}+\text{H})^+$ 236.2014, found 236.2033; Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{NO}$: 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 using 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 work-up 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 using *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, $J = 7.8$, 1H), 6.99 (d, $J = 7.8$, 1H), 6.96 (d, $J = 7.3$, 1H), 3.08 (dd, $J = 15.6$, 6.3, 1H), 2.86 (dd, $J = 15.6$, 2.9, 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, $J = 6.8$, 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 $(\text{C}_{17}\text{H}_{29}\text{NO}+\text{H})^+$ 264.2327, found 264.2331; Anal. Calcd for $\text{C}_{17}\text{H}_{29}\text{NO}$: 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, $J = 7.8$, 1H), 6.99 (d, $J = 7.8$, 2H), 3.16 (dd, $J = 15.1$, 5.4, 2H), 2.65 (dd, $J = 15.1$, 4.9, 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, $J = 7$, 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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Hsieh T-J, Chang F-R, Chia Y-C, Chen C-Y, Chiu H-F, Wu Y-C. *J. Nat. Prod* 2001;64:616–619. [PubMed: 11374955]
2. Total synthesis of (+)-cananodine: Craig D, Henry GD. *Eur. J. Org. Chem* 2006:3558–3561.
3. (a) Lião LM. *Alkaloids* 2003;60:287–343. [PubMed: 14593859] (b) Büchi G, Goldman IM, Mayo DW. *J. Am. Chem. Soc* 1966;88:3109–3133. (c) Cren MC, Defaye G, Fetizon M. *Bull. Soc. Chim. Fr* 1970:3020–3022. (d) Van der Gen A, Van der Linde LM, Witteveen JG. *Recueil Trav. Chim. Pays-Bas* 1972;91:1433–1440. (e) Okatani T, Koyama J, Tagahara K, Suzuta Y. *Heterocycles* 1987;26:595–597. (f) Koyama J, Okatani T, Tagahara K, Suzuta Y, Irie H. *Heterocycles* 1987;26:925–927. (g) Koyama J, Okatani T, Ogura T, Tagahara K, Irie H. *Chem. Pharm. Bull* 1991;39:481–482.
4. Meyer, JA. M.S. Thesis. Bellingham, WA: Western Washington University; 2006.
5. (a) Baldwin JE. *J. Chem. Soc., Chem. Commun* 1976:734–736. (b) Baldwin JE, Kruse LI. *J. Chem. Soc., Chem. Commun* 1977:233–235. (c) Baldwin JE, Lusch MJ. *Tetrahedron* 1982;38:2939–2947.
6. Review: (a) Clark RD, Jahangir A. *Org. React* 1995;47:1–314. Selected examples: (b) Nelson JK, Burns CT, Smith MP, Twamley B, Natale NR. *Tetrahedron Lett* 2008;49:3078–3082. (c) Smith TE, Mourad MS, Velander AJ. *Heterocycles* 2002;57:1211–1217. (d) Smith TE, Balskus EP. *Heterocycles* 2002;57:1219–1225.
7. (a) Pasquinet E, Rocca P, Marsais F, Godard A, Quéguiner G. *Tetrahedron* 1998;54:8771–8782. (b) Diana GD. *J. Med. Chem* 1995;38:1355–1371. [PubMed: 7731021] (c) Crabb TA, Fallah A. *Magn. Res. Chem* 1990;28:431–436. (d) Leighton P, Sanders JKM. *J. Chem. Soc., Perkin Trans 1* 1987:2385–2393. (e) Banting L, Crabb TA, Trethewey AN. *Magn. Res. Chem* 1987;25:352–355. (f) Crabb TA, Jupp PA. *J. Chem. Soc., Perkin Trans 1* 1985:913–918. (g) Jones TH, Highet RJ, Blum MS, Fales HM. *J. Chem. Ecol* 1984;10:1233–1249. (h) Sonnet PE, Oliver JE. *J. Heterocycl. Chem* 1975;12:289–294. (i) Oliver JE, Sonnet PE. *J. Org. Chem* 1974;39:2662–2663. (j) Reinecke MG, Kray LR. *J. Org. Chem* 1964;29:1736–1739. (k) Boekelheide V, Windgassen RJ Jr. *J. Am. Chem. Soc* 1959;81:1456–1459.
8. (a) Crabb TA, Fallah A. *J. Chem. Soc., Perkin Trans 2* 1992:1335–1342. (b) Begley MJ, Crabb TA, Roch OG. *Magn. Res. Chem* 1986;24:292–296.
9. Presented in part at 235th ACS National Meeting; April 6–10; New Orleans, LA. ORGN-356
10. Fraser RR, Mansour TS, Savard S. *J. Org. Chem* 1985;50:3232–3234.
11. Bordwell FG. *Acc. Chem. Res* 1988;21:456–463. (b) Personal communication from Professor Hans J. Reich of unpublished data obtained from Professor Frederick G. Bordwell and coworkers of Northwestern University.
12. Ghera E, David YB, Rapoport H. *J. Org. Chem* 1981;46:2059–2065.
13. Lipshutz BH, Kozłowski J, Wilhelm RS. *J. Am. Chem. Soc* 1982;104:2305–2307.
14. Baker W, Buggle KM, McOmie JFW, Watkins DAM. *J. Chem. Soc* 1958:3594–3603.
15. (a) Taylor SK, DeYoung D, Simons LJ, Vyvyan JR, Wemple MA, Wood NK. *Synth. Commun* 1998;28:1691–1701. (b) Larchevêque M, Debal A. *Synth. Commun* 1980;10:49.
16. Canovese L, Visentin F, Uguagliati P, Chessa G, Pesce A. *J. Organomet. Chem* 1998;566:61–71.
17. Steinreiber A, Mayer SF, Saf R, Faber K. *Tetrahedron: Asymm* 2001;12:1519–1528.
18. Katzenellenbogen JA, Christy KJ. *J. Org. Chem* 1974;39:3315–3318.
19. Kuenzer H, Stahnke M, Sauer G, Wiechert R. *Tetrahedron Lett* 1991;32:1949–1952.
20. Bonner WA. *J. Am. Chem. Soc* 1952;74:1034–1039.
21. Hossain MT, Timberlake JW. *J. Org. Chem* 2001;66:6282–6285. [PubMed: 11559175]
22. For general experimental details, see Supporting Information.

Figure 1.
Relative acidities of 2-picolone derivatives.

Figure 2.
Reductive cleavage of the -SPh group from **5c**.

Table 1

Reaction of lutidyllithium derivatives with 1,2-epoxyoctane.

entry	R	base	additive	product	Yield (%) ^a
1	4a	LDA	none	5a	61
2	4a	LDA	BF ₃ •OEt ₂ ^b	5a	66
3	4a	LDA	HMPA ^c	5a	56
4	4a	BuLi	none	5a	80
5	4a	BuLi	CuCN ^d	5a	89
6	4b	LDA	none	5b	36 ^e
7	4c	LDA	none	5c	68 ^e
8	4c	BuLi	none	5c	70 ^e
9	4d	LDA	none	5d	47 ^e
10	4d	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

Table 2

Reaction of lutidyllithium derivatives with 2-methyl-2,3-epoxynonane.

entry	R	base	additive	product	Yield (%) ^a
1	4a	BuLi	none	8a	40
2	4a	LDA	none	8a	12 ^b
3	4a	LDA	BF ₃ •OEt ₂ ^c	8a	8
4	4a	LDA	HMPA ^d	8a	29
5	4a	BuLi	CuCN ^e	8a	23
6	4c	BuLi	none	8c	9 ^f
7	4c	LDA	none	8c	6 ^f
8	4d	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