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Lithiation of 2-Chloromethylpyridine: Synthesis of 2-Oxiranyl Pyridines

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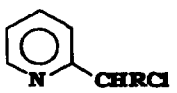
Abstract: Deprotonation of 2-chloromethylpyridine **1a** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C gives a red solution of 2-pyridylchloromethyllithium **1b**, which reacts with carbonyl compounds furnishing oxiranes **2**.

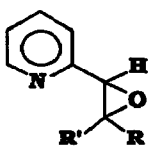
Epoxides are widely recognised as extremely versatile synthetic intermediates: the high degree of ring strain makes them highly reactive and permits a number of nucleophilic ring openings, Lewis acid promoted rearrangement and isomerisation reactions.[1] The ready accessibility of a large variety of oxiranes further contributes to their usefulness.

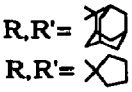
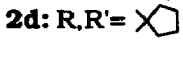
Among the many substituted pyridines have been made available by known procedures,[2-4] the synthesis oxiranyl pyridines of the kind **2**, which appear to be of considerable synthetic potential for the elaboration of pyridines in the side chain, has not been much pursued sofar.[5] Our attempts to prepare this sort of epoxides by direct epoxidation of the relevant pyridyl alkenes by using m-ClPBA failed, due to the preferred N-oxidation,[6] as reported also for other nitrogen containing heteroaromatics.[7] Cyclisation of pyridyl substituted bromohydrins might be envisaged as a route to pyridyl substituted oxiranes. However, such a cyclization meets with the drawback of the need each time of the appropriate 2-pyridyl alkene.[8]

In the present communication we report the first general synthesis of oxiranyl pyridines **2** based on the lithiation of 2-chloromethylpyridine **1a** and subsequent reaction with carbonyl compounds.[13]

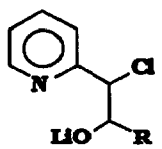


1a: R=H
1b: R=Li
1c: R=Me



2a: R=R'=Ph
2b: R=R'=Me
2c: R,R'= 
2d: R,R'= 

2e: R,R'=
2f: R=H; R'=Ph
2g: R=H; R'=m-Cl-C_6H_4
2h: R=H; R'=p-CF_3-C_6H_4



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Lithiation of commercially available 2-chloromethylpyridine **1a**[9] with LDA in THF at -78°C furnished a dark red solution of the organolithium **1b** that could be trapped with MeI to give **1c**. The rather easy generation of **1b**[10] by lithiation of **1a** is to be ascribed to the stabilizing effect of both the chlorine and the heterocyclic group to the carbanionic species.[11] The reaction of **1b** with benzophenone afforded a good yield of the epoxide **2a**. Similarly the reaction of **1b** with acetone, adamantanone, cyclopentanone and cyclohexanone furnished epoxides **2b**, **2c**, **2d** and **2e** respectively (See table).

The reaction works well also with aldehydes. Indeed, **1b** reacts with benzaldehyde, m-chlorobenzaldehyde and p-trifluoromethylbenzaldehyde providing satisfactory yields of oxiranes **2f**, **2g** and **2h** respectively.

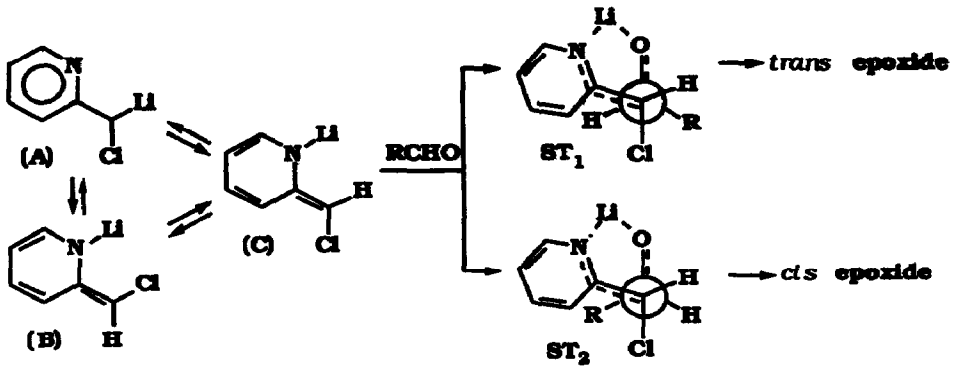
Table. Reactions of **1b** with electrophiles (E) in THF at -78°C under Nitrogen.

E	Product(% yield)[a]	E	Product(%yield)[a]
MeI	**1c** (70)	Cyclohexanone[c]	**2e** (60)
Ph_2CO[b]	**2a** (60)	C_6H_5CHO[d]	**2f** (40)
Me_2CO[c]	**2b** (70)	m-ClC_6H_4CHO[d]	**2g** (30)
Adamantanone[b]	**2c** (75)	p-$CF_3C_6H_4CHO$[d]	**2h** (50)
Cyclopentanone[c]	**2d** (65)		

a) Yields calculated on isolated, purified compounds. b) Reaction carried out by adding to the LDA solution first the carbonyl compound and immediately after the solution of **1a**. c) Reaction carried out by adding **1a** to LDA and soon after the carbonyl compound. d) Reaction carried out by adding the solution of **1a** and the carbonyl compound to LDA.

The oxiranes **2** are the likely result of the nucleophilic addition of **1b** to the carbonyl compound to give lithium chloroalkoxides **3** that rapidly undergo ring closure to **2**. Interestingly, the reaction of **1b** with aldehydes takes place with excellent diastereoselectivity yielding the *trans* oxiranes,[12] as would be predicted from the least sterically encumbered transition state model for the addition step. Indeed, assuming that **1b** exists as the forms (**A**), (**B**) and (**C**) and that form (**C**) is the reactive one, the observed *trans* stereoselection might be explained considering that transition state **ST1**, arising from an re/si face matching between the form (**B**) and the aldehyde and leading to the *trans* isomer, is favored over transition state **ST2** (re/re or si/si face matching) which experiences a larger steric compression as illustrated in the scheme below.

To conclude, the one presented here is the first general synthesis of 2-pyridyl oxiranes. The method counts on the availability of 2-chloromethylpyridine **1a** and on its easy lithiation to the Darzens-type reagent **1b**, which appears to be susceptibile of further application for the synthesis of other small ring heterocycles, such as aziridines and oxetanes. Work is in progress to this end.



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References:

1. a) Rao A. S., Paknikan S. K., Kirtane J. G., *Tetrahedron*, **1983**, 39, 2323; b) Smith J. G., *Synthesis*, **1984**, 629.
2. a) Brody F., Rudy P. R., In "*Pyridine and Its Derivatives*"; Klingsberg, E., Ed., Interscience, New York, **1960**; Vol. 14, Part I, Chapter 2; b) Boodman N. S., Hawtorne J.O., Masciantonio P. X., Simon A. W., in "*Pyridine and Its Derivatives*", Abramovich R.A., Ed., Wiley-Interscience, New York, **1972**; Vol.14, Supplement Part 1, Chapter 2.
3. Newkome J. R., Paudler W. W., *Contemporary Heterocyclic Chemistry*, Wiley, New York, **1982**.
4. *Pyridine and Its Derivatives*, Newkome G. R., Ed., Wiley, New York, **1984**, Vol. 14, Part 5.
5. Kloc K., Kubicz E. and Mlochowsky J., *Heterocycles*, **1984**, 22, 2517 and Refs. therein.; Ribereau MM. P., Nevers G., Queguiner G., Pastour P., *C. R. Acad. Sc. Paris*, **1975**, t. 280, Serie C-293.
6. Scriven E. F. V., "*Pyridines and their Benzoderivative: Reactivity at Ring Atoms*" in *Comprehensive Heterocyclic Chemistry*, Ed. Alan R. Katritzky and Charles W. Rees, Pergamon Press, New York, Vol. 2, Part 2A, pg. 184 and Refs therein.
7. Takahashi S. and Kano H., *Chem. Pharm. Bull.*, **1969**, 17, 1598; Anderson H. J., Barnes D. J. and Khan Z. M., *Can. J. Chem.*, **1964**, 42, 2375.
8. The synthesis of 2-pyridyl ethylene oxide has been reported starting from 2-vinylpyridine: Hanzlik R. P., Edelman M., Michaely W. J., and Scott G., *J. Am. Chem. Soc.*, **1976**, 98, 1952.
9. 2-Chloromethylpyridine **1a** is sold as hydrochloride (Aldrich) from which it can be obtained upon treatment with NaOH solution. It was purified by distillation prior to use.
10. Once generated, if **1b** is allowed to warm to RT and then quenched with aqueous sat NH4Cl a number of products form among which the 1,2-dipyridyl ethene, the homocoupling product $PyCHClCH_2Py$ and the "trimer" $PyCH_2CH(CHClPy)Py$.

11. An example of heterosubstituted α-haloorganolithium generated by lithiation of the corresponding heterosubstituted alkyl halide has been recently reported: Florio S. and Troisi L., *Tetrahedron Lett.*, **1992**, 33, 7953.

12. Actually, we isolated just one isomer and its low coupling constant between the epoxy ring hydrogens seem to suggest the trans configuration, as observed in similar cases. See: Florio S., Ingrosso G., Ronzini L. and Epifani E., *Tetrahedron*,**1991**, 47, 3365.

13. **General Procedure:** To diisopropylamine (2.4 mmole) in 10 ml of THF was added at O°C 1ml of 2.4M n-BuLi. The solution was cooled at -78°C and then added dropwise with a solution of **1a** (0.256 g, 2.0 mmole) and benzophenone (0.440 g, 2.4 mmole) in 10 ml of THF. After 1h at -78°C the reaction mixture was allowed to warm to RT and quenched with aqueous NH_4Cl. Extraction with ether (3x25 ml), drying over Na_2SO_4 and evaporation of the solvent under reduced pressure left a residue that was column chromatographed (silica gel, E.P./E.E.: 8.5/1.5 as eluent) to give diphenylpyridyl oxirane **2a** (60% yield).
The new compounds showed the following data:
1c: ^{1}H-NMR ($CDCl_3$) δ: 1.93 (d, 3H, J=7Hz); 5.25 (q, 1H, J=7Hz); 7.20-8.90 (m,4H). MS m/e: 141(M^+, 2), 106(100), 78(19), 51(11). Anal. Calcd. for C_7H_8ClN: C, 59.38; H, 5.69; N, 9.89. Found: C, 59.44; H, 5.71; N, 9.86. **2a**: ^{1}H-NMR($CDCl_3$) δ: 4.7 (s,1H); 7.20-7.70 (m, 13H); 8.70(d, 1H). MS m/e : 273 (M^+, 22), 256 (100), 244 (63), 165 (87). Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.5; N, 5.12. Found: C, 83.00; H, 5.8; N, 4.9. **2b**: ^{1}H-NMR($CDCl_3$) δ: 1.25 (s,3H); 1.4 (s,3H); 4.95 (s,1H); 7.25-8.80(m,4H). Anal. Calcd. for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.49; H, 7.39; N,9.35. **2c**: ^{1}H-NMR ($CDCl_3$) δ: 1.25-2.25 (m,14H); 4.1 (s,1H); 7.20-8.80 (m,4H). MS m/e : 241 (M^+, 12) 224 (5) 212 (100). Anal. Calcd. for $C_{17}H_{19}NO$: C,79.6; H, 7.93; N, 5.8. Found: C, 78.4; H, 8.2; N, 5.4. **2d**: ^{1}H-NMR ($CDCl_3$) δ: 1.30-2.25 (m, 8H); 4.27 (s,1H); 7.20-8.85 (m, 4H). MS m/e: 175 (M^+,7), 174 (17), 158 (100), 146 (70), 130 (68), 80 (100). Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.48; N, 7.99. Found: C, 76.5; H, 7.29: N, 7.8. **2e**: ^{1}H-NMR ($CDCl_3$) δ: 1.30-2.00 (m, 10H); 4.08 (s,1H); 7.25-8.80 (m, 4H). MS m/e: 189(M^+,7), 172(100), 160(34), 146(36), 108(54). Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; H, 7.98; N, 7.4. Found: C, 76.0; H,7.8; N, 7.3. **2f**: ^{1}H-NMR ($CDCl_3$) δ: 5.25(d,1H, J=4.2 Hz); 5.48(d,1H, J=4.2 Hz); 7.20-8.80 (m, 9H). MS m/e:197(M^+,2), 196(2), 180(14), 168(100). Anal. Calcd. for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.1. Found: C, 78.9; H, 5.7; N, 7.7. **2g**: ^{1}H-NMR ($CDCl_3$, 300MHz) δ: 3.98(d,1H, J=1.86 Hz); 4.02(d,1H, J=1.86 Hz); 7.21-7.35(m, 6H); 7.67-7.73(dt, 1H); 8.58(d,1H). MS m/e: 231(M^+,2), 202(100), 167(36), 89(15), 78(11). Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.4; H, 4.35; N, 6.05. Found: C, 67.36; H, 4.32; N, 6.02. **2h**: ^{1}H-NMR ($CDCl_3$, 300 MHz)) δ: 4.01(d, 1H, J=1.67 Hz); 4.12(d, 1H, J=1.67 Hz); 7.20-7.68(m, 6H); 7.69-7.75(dt,1H); 8.60(d,1H). MS m/e: 265(M^+,3), 246(10), 236 (100). Anal. Calcd. for $C_{14}H_{10}F_3NO$: C, 63.4; H, 3.8; N, 5.28. Found: C, 63.44; H, 3.76; N, 5.25.

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