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Preparation of 2-Lithiotetrahydropyrans: Kinetic and Thermodynamic Generation of Alkyllithium Reagents

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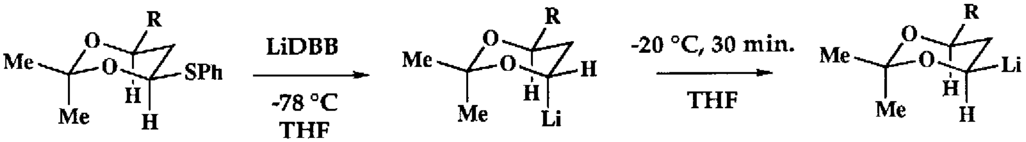
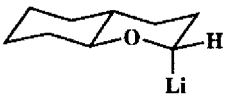
Summary: Both axial and equatorial 2-lithiotetrahydropyrans are readily prepared from 2-(phenylthio)-tetrahydropyrans. Axial 2-lithiotetrahydropyrans are formed selectively on reducing 2-(phenylthio)-tetrahydropyrans with lithium di-*tert*-butylbiphenylide, and equatorial 2-lithiotetrahydropyrans are formed selectively by thermal equilibration of the axial isomers.

As part of a research program directed towards the synthesis of polyene macrolide antibiotics, we are interested in the chemistry of stereodefined 1,3-diol synthons **2ax** and **2eq**, shown below. In our initial approach to these alkyllithium reagents, we had occasion to examine a strategy first suggested by Cohen[1] for controlling the stereochemistry of 2-lithiotetrahydropyrans. Our results show that the axial or equatorial 2-lithiotetrahydropyrans can be prepared with very high selectivity from a common precursor.

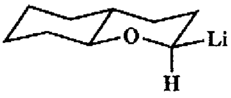


1eq **2ax** **2eq**

In two seminal papers,[1] Cohen showed that 2-(phenylthio)tetrahydropyrans are effective precursors to 2-lithiotetrahydropyrans[2] and that, for conformationally biased rings, the axial 2-lithiotetrahydropyran is the kinetic product.[3] He also examined the equilibration of axial 2-lithiotetrahydropyrans and found that it was possible to epimerize the initially formed axial alkyllithium **3ax** to a more stable equatorial alkyllithium **3eq** (87 : 13 ratio)[4] but that no epimerization was observed with *trans*-2-lithio-4-methyltetrahydropyran (**4ax**, *vide infra*). The alkyllithium **3ax** has a conformationally locked pyran ring, where the lithium is forced into an axial position, but alkyllithium **4ax** is conformationally mobile and can ring flip to the equatorial alkyllithium **5**, thus removing the driving force for epimerization. To summarize, axial 2-lithiotetrahydropyrans were available with good selectivity, but epimerization to the equatorial 2-lithiotetrahydropyran proceeded with moderate selectivity and was only applicable to conformationally locked pyrans.

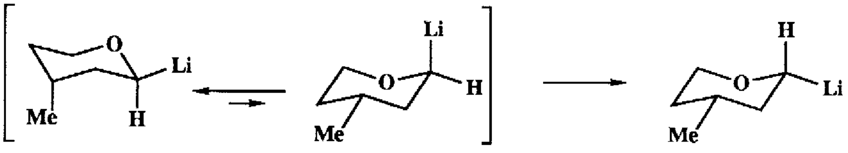


3ax



3eq

We began our investigation by examining the reduction of *cis*-4-thiophenyl-1,3-dioxane **1eq** (R=*i*-Pr). Lithium di-*tert*-butylbiphenylide (LiDBB)[5] was used as the reducing agent for all of the reactions described herein; it leads to higher yields and cleaner reductions than those reported for lithium 1-(dimethylamino)-



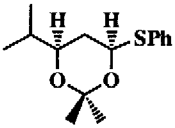
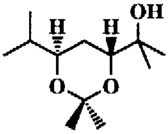
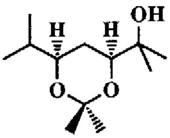
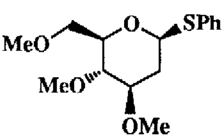
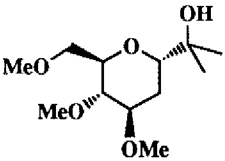
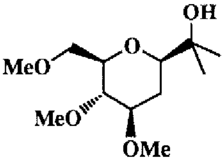
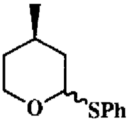
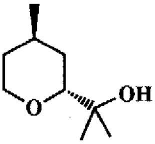
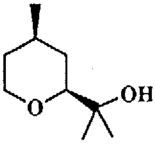
5 4ax 4eq

naphthalenide[1] or lithium naphthalenide.[6] Reduction of **1eq** (R=*i*-Pr) at -78 °C in THF followed by addition of acetone gave a 98.3 to 1.7 ratio of axial and equatorial products[7] in a combined yield of 78% (Table, entry 1c). Reduction of the corresponding *trans*-4-thiophenyl-1,3-dioxane **1ax** (R=*i*-Pr) followed by addition of acetone gave the same ratio (98 to 2). Thus, in accord with previous reports,[1,8] the stereochemistry of the alkyllithium is independent of the stereochemistry of the starting material. Epimerizations were performed by generating the alkyllithium solution as above and then transferring the reaction flask to a constant temperature bath for 30-60 minutes, returning the flask to a -78 °C bath, and adding acetone. The epimerization results are strongly dependent upon the temperature. At -30 °C the ratio of equatorial to axial acetone adducts is only 1.6:1 (entry 1a), whereas at -20 °C the ratio has improved to 20:1 (entry 1b). TMEDA has no effect on the rate of epimerization.[1,9] The major side reaction is competitive deprotonation of THF, which accounts for the drop in yield with increasing temperature. We chose -20 °C as the best balance between selectivity and yield and prepared the equatorial adduct with 96:4 selectivity in 54% yield (entry 1d). By reduction and optional epimerization, both axial alkyllithium **2ax** and equatorial alkyllithium **2eq** can be prepared in good yield from a common precursor. Further work with these 1,3-diol synthons will be reported elsewhere.

We were struck by the exceptionally high selectivity with which either axial or equatorial alkyllithiums could be generated from readily available thiophenol derivatives and decided to explore the generality of this sequence. Phenyl 3,4,6-tri-O-methyl-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (**6**)[10] (entry 2) and 4-methyl-2-(thiophenyl)tetrahydropyran (**4**, Li=SPh)[11] (entry 3) were chosen as test cases because stereodefined alkyllithium reagents have great potential in C-glycoside synthesis[12] and because of the lack of epimerization found by Cohen with *trans*-2-lithio-4-methyltetrahydropyran (**4ax**)[1] respectively. The reactions were performed as described above and are presented in the Table. The pyranoside epimerization ratios (entry 2) are comparable to those of the 1,3-dioxane system (entry 1.) The kinetically formed alkyllithium gives a 97.7 to 2.3 ratio of axial to equatorial products in 81% combined yield (entry 2c); epimerization of the alkyllithium for 45 minutes at -20 °C leads to a 98.8 to 1.2 ratio of equatorial and axial products in 59% yield (entry 2d.)[13] The epimerization is noticeable at -30 °C and proceeds rapidly at -20 °C. Both the axial and equatorial pyranosyllithium species derived from **6** are readily available by these procedures.

In stark contrast the *trans*-2-lithio-4-methyltetrahydropyran (**4ax**) is formed selectively on reduction, but, even at -15 °C, the epimerization is slow. After 30 minutes at -20 °C the axial acetone adduct is still the major product (entry 3b), and competitive deprotonation of THF begins to dramatically reduce the yield. Apparently the presence of the more stable ring conformation **5** reduces the effective concentration of the axial alkyllithium **4ax** and dramatically reduces the rate of epimerization. Assuming the equatorial position is overwhelmingly preferred by the lithium substituent the *cis*-2-lithio-4-methyltetrahydropyran (**4eq**) should still be thermodynamically favored over **5** by ~ 1.79 Kcal/mole[14] which would give a 96 to 4 ratio at 20 °C. The epimerization does not lack driving force; rather the rate of inversion is slow relative to the rate of protonation by THF. A more effective epimerization could be achieved by reducing the rate of the protonation reaction. After several fruitless attempts to prepare LiDBB in less acidic solvents, we found that the rate of deprotonation in THF/hexane mixtures is dramatically reduced.[15] The rate of epimerization is also reduced but to a lesser extent. Epimerization can be accomplished by preparing **4ax** in a 25% THF/ 75% hexanes solvent mixture and then warming the solution to +20 °C for 20 minutes before cooling to -78 °C and quenching the resulting alkyllithium **4eq** with acetone. This procedure gives the equatorial adduct with 92 to 8 selectivity in good yield (entries 3d.)

Table: Synthesis and Trapping of Axial and Equatorial 2-Lithiotetrahydropyrans.^{a}

Entry	Starting Material Equilibration Conditions	Axial Product	Equatorial Product Ratio(Axial:Equatorial)^b	Yield^c
				
1 a	-30 °C, 30 min		38 : 62	(63%)
b	-20 °C, 30 min		5 : 95	(52%)
c	**no epimerization**^{e}		**98.3 : 1.7**	**78%**
d	**-20 °C, 30 min**		**4.2 : 95.8**	**54%**
				
2 a	-30 °C, 30 min		85 : 15	(63%)
b	-20 °C, 30 min		6.5 : 93.5	(50%)
c	**no epimerization**^{e}		**97.7 : 2.3**	**81%**
d	**-20 °C, 45 min**		**1.2 : 98.8**	**59%**
				
3 a	-30 °C, 30 min		89 : 11	(58%)
b	-20 °C, 30 min		70 : 30	(33%)
c	**no epimerization**^{e}		**96.8 : 3.2**	**53%** (90%)^d
d	**+20 °C, 20 min; 25% THF/Hex**		**4.8 : 95.2**	**30%** (55%)^d

a) The reactions were performed as described in the text. The alkyllithium concentrations are ~0.025M. b) The ratios were determined by capillary GC. c) Small scale reactions (~20 mg) are given in plain type, and the combined GC yields (given in parentheses) are calculated using *n*-dodecane as an internal standard. **Preparative reactions with isolated yields are given in bold type.** d) The isolated yield in this case is low due to the volatility of the product. e) The alkyllithium reagents were generated at -78 °C for 5-10 min and then trapped with acetone.

We have found that 2-(thiophenyl)tetrahydropyrans are excellent precursors to axial 2-lithiotetrahydropyrans, which in turn can be efficiently epimerized to the more stable equatorial 2-lithiotetrahydropyrans. Thus, both axial and equatorial 2-lithiotetrahydropyrans can be prepared from a common precursor with excellent selectivity. By using THF/hexane solvent mixtures, even conformationally mobile 2-lithiotetrahydropyrans can be epimerized. This strategy should be applicable to the synthesis of pyran rings in systems ranging from ionophores to C-glycosides.[16]

References and Footnotes

1. Cohen, T. ; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130; Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900. See also Lin, M.-T. Ph.D. thesis, University of Pittsburg, 1984.

2. The reduction of alkyl phenyl sulfides to alkyllithiums was reported by Screttas: Screttas, C. G.; Screttas, M. M. *J. Org. Chem.* **1978**, *43*, 1064; Screttas, C. G.; Screttas, M. M. *J. Org. Chem.* **1979**, *44*, 713.

3 Still has demonstrated that α-alkoxyorganolithiums are configurationally stable at low temperature, and trapping with acetone is expected to proceed with retention of configuration. Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. The question of retention verses inversion in alkyllithium reactions is discussed in the following references: Glaze, W. H.; Selman, C. M.; Ball, A. L. Jr.; Bray, L. E. *J. Org. Chem.* **1969**, *34*, 641; Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842; Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263; Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265; Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G.A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211.

4 Compound **3ax** was epimerized at -30 °C with TMEDA in THF for an unspecified length of time (ref 1).

5. Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

6. Reduction of **6** with lithium naphthalide (vs. LiDBB) gave inferior yields and many more side products.

7. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and high resolution MS. The stereochemical assignments for entries 2 and 3 were based on literature assignments of the kinetic products (ref. 1 and ref. 8) and were consistant with the ^{1}H and ^{13}C NMR spectra. The stereochemical assignments in entry 1 were based on ^{1}H NMR analysis: the anomeric proton in the equatorial product is axial (3.58 ppm; $J = 2.7, 11.6$ Hz), whereas the corresponding proton in the axial product is not consistant with a chair conformation (3.54 ppm; $J = 6.4, 9.8$ Hz).

8. Lancelin, J.-M.; Morin-Allory, L.; Sinay, P. *J. Chem. Soc., Chem. Commun.*, **1984**, 355. Beau, J.-M.; Sinay, P. *Tetrahedron Lett.* **1985**, *26*, 6185.

9. A series of reactions was performed using the same procedure as entries 1a and 1b, but with three equivalents of TMEDA added before the reduction. The resulting ratios (axial : equatorial) are 35:65 (-30 °C); and 16:84 (-20 °C).

10. Prepared as an 87% β to 13% α mixture (ref 8).

11. Prepared as a 66% to 34% mixture of **4ax** (Li=SPh) and **4eq** (Li=SPh) as described in ref. 1..

12. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930. Lesimple, P.; Beau, J.-M.; Sinay, P. *J. Chem. Soc., Chem. Commun.*, **1985**, 894. Beau, J.-M.; Sinay, P. *Tetrehedron Lett.* **1985**, *26*, 6193. Beau, J.-M.; Sinay, P. *Tetrahedron Lett.* **1985**, *26*, 6185.

13. **Alkyllithium Equilibration:** A dry flask under nitrogen was charged with 100.2 mg of **6**, a crystal of 1,10-phenanthroline, and 10 mL of dry THF and cooled in a dry ice/acetone bath. A hexane solution of n-BuLi was added until the solution turned brown, and then a ~0.2 M solution of LiDBB (ref. 5) was added dropwise until the green color persisted. After 5 minutes the reaction flask was transferred to a -20 °C constant temperature bath and allowed to stand for 45 minutes. The flask was returned to the dry ice bath and 74 µL of acetone was added. After 10 minutes the reaction was allowed to warm to room temperature and then quenched (NH_4Cl solution), extracted (3 x EtOAc), dried (Na_2SO_4), and concentrated. Chromatography (SiO_2, 70%-100% EtOAc/hexanes) gave 49.0 mg (59%) of the equatorial adduct as a slightly yellow oil.

14. This is the *pseudo*-A-value for methyl at the 4-position of a tetrahydropyran ring, calculated using Still's Macromodel program (version 2.0).

15. The kinetics for deprotonation of THF by n-BuLi are 1st order in BuLi and 2.5th order in THF: Honeycutt, S. C. *J. Organometal. Chem.* **1971**, *29*, 1. The kinetics for epimerization are apparently < 2.5th order in THF.

16. This work was supported by research funds of the Graduate School of the University of Minnesota.

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