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THE REACTION OF HETEROCYCLIC LITHIO SALTS WITH STYRENE OXIDE

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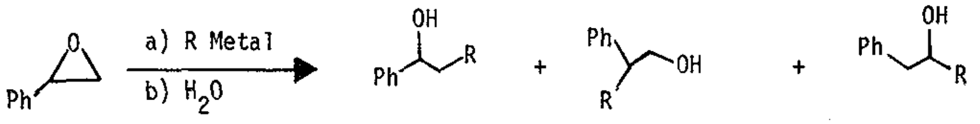
A study of temperature and reaction duration for several heterocyclic lithio salts on styrene oxide has led to reaction conditions which allow high yields of SN_2 ring opening.

The reaction of RMgX[1] and R_2Mg[2] with styrene oxide has been reported to give no alkylation at the primary carbon (leading to 1) but only products derived from attack at the benzylic carbon (2) and addition to phenylacetaldehyde (3). On the other hand, organolithiums[3] and cuprates[3] gave mixtures containing only 50-60% of 1 along with 40-50% of 2, whereas sodiomalonic ester gave only 40% 1 and 60% 2.[4] It is therefore clear that products of the type 1 are not readily available by direct ring opening of styrene oxides. During our studies on lithio carbanions of various heterocycles as precursors to aldehydes,[5,6] and other carbonyl compounds,[7] we had the opportunity to evaluate several systems with regard to their ring opening of styrene oxide. The lithio salts (7) of 2-methyl-2-thiazoline (4), 2,4,4-trimethyl-2-oxazoline (5), and 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine (6) were generated using n-butyllithium (1.05 equiv) at -78° in THF solvent. In each case styrene oxide was



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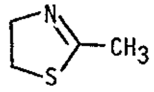
added at -78° and the temperature of reaction was varied (from -78° to r.t.) to afford the alkylated heterocycles 8 and 9. Hydrolysis (3N HCl, 30 min, 95°) of the mixture produced the butyrolactone 10 as the predominant product (80-97%). The ratios of γ-phenylbutyrolactones 10 and β-phenyl lactones 11 are directly related to primary and benzylic attack, respectively. A study of the isomer ratio of 10 and 11 was carried out as a function of temperature and although 4 and 6 did not show any dependency, reactions of 5 with styrene oxide varied somewhat. The optimum conditions were found to be at -45° for 5-7 h which resulted in a ratio of 94-97% 10.



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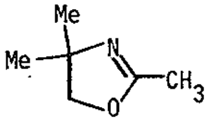

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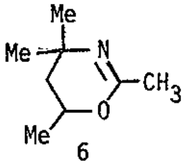

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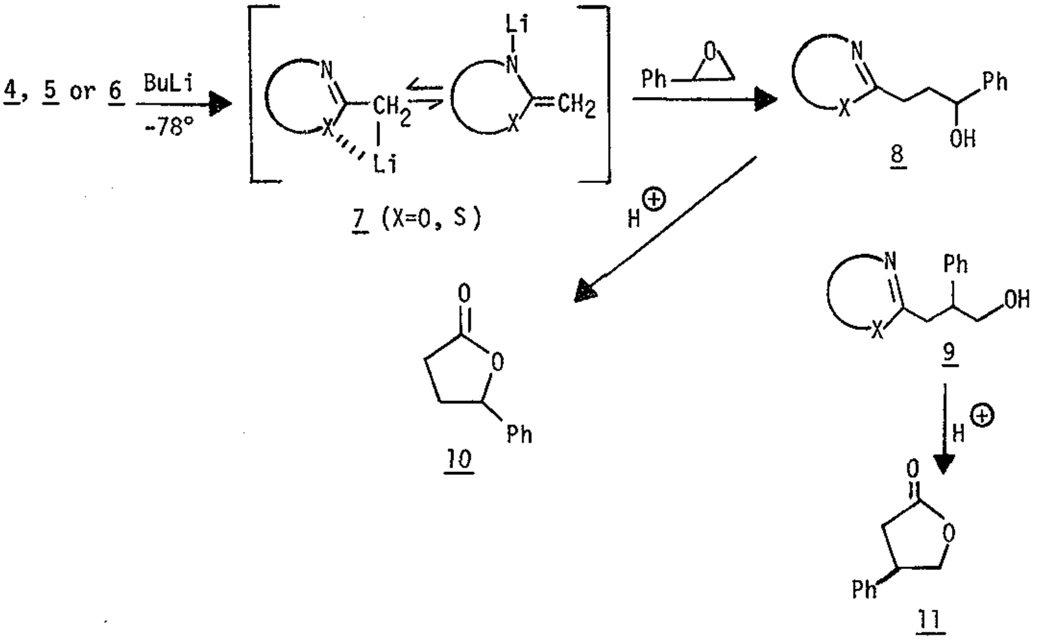

The reaction stoichiometry also proved important in that using an excess of

TABLE 1 Reaction of 4, 5, and 6 with styrene oxide under various conditions

Lithio Salt	Epoxide[c] (equiv)	Rxn T°	Rxn time(h)	Quench T°	Lactones[d] % 10	%11	Total Yield, %[b]
4[a]	1.1	-60	5	25°	85	15	66
6[a]	1.1	-78 → 25	5	25°	89	11	61
6	1.1	-45	5	-45°	89	11	62
5	1.1	-78 → 25	2	25°	90	10	66
5	0.95	-78 → 25	2	25°	80	20	56
5	1.1	-45	6	25°	97	3	65
5	1.1	-45	5	-15°	96	4	58
5	1.1	-45	7	-45	94	6	51
5	1.1	-78 → 25	5	25°	94	6	80[e]

a) Changing time, temperature, stoichiometry gave essentially same ratios of 10 and 11; b) Overall yields based upon 4, 5, or 6; c) Added neat to the anion at the indicated temperature; d) Ratios determined by glc using 9% FFAP on chromsorb P (6' X 0.25') at 190°. Retention times were 36.8 min (10) and 38.8 min (11) with He flow rate of 38 cc/min; e) The lithio salt of 5 was complexed with 1.0 equiv of TMEDA prior to addition of styrene oxide.

the carbanion increased significantly the amount of benzylic attack. Finally, if the lithio salt of 5 is complexed with tetramethylethylenediamine (TMEDA), the amount of 11 is only 6% and the yield of lactones is highest (80%). These experiments seem to indicate that a delicate balance exists between lithium coordination to the oxygen and rate of nucleophilic attack. The rate of nucleophilic attack on the epoxide is slow at temperatures below -45° where the lithium-oxygen bond is weak.[8] On the other hand, lithio-coordination to the oxygen is stronger above these temperatures and even though nucleophilic attack (at the primary carbon) is more rapid, the formation of the incipient benzylic carbonium ion leads to 11. When TMEDA is employed, *the solvation of the lithio cation is very pronounced making* 5 *a stronger* nucleophile and at the same time tying up the lithium cation so that complexation with the oxygen lone pair on the epoxide is diminished. This leads to higher yields of lactone 10 and 11 which contains only 6% of 11. The value of these lithio salts in synthesis lies mainly in the fact that they are sufficiently nucleophilic at temperatures considerably lower than organolithiums, Grignards, sodio carbanions, and organo cuprates, to effect the desired reactions and at the same time minimize the extent of lithium coordination to the epoxide and hence ring opening and/or rearrangements. It should now be possible to utilize aryl-substituted epoxides in a variety of synthetic transformations which require SN_2 regioselectivity.[9,10]

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8. No reaction of 4, 5 or 6 took place with styrene oxide at -78° as determined by quenching with water at this temperature after 1 or 7 h.
9. A number of epoxides have been treated under these conditions to form butyrolactones and these will be reported in a full paper in due course.
10. This work was supported by the National Institutes of Health.

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