

BENZYNE DERIVED FROM ARYLOXAZOLINES. A VERSATILE INTERMEDIATE.

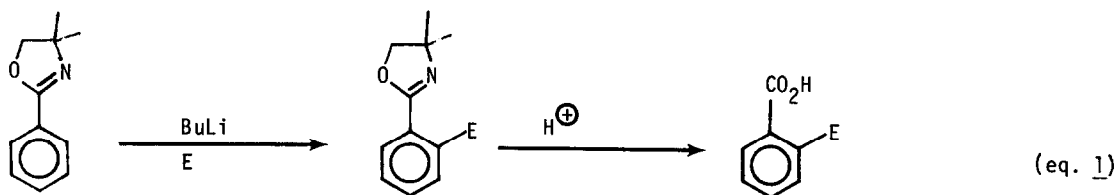
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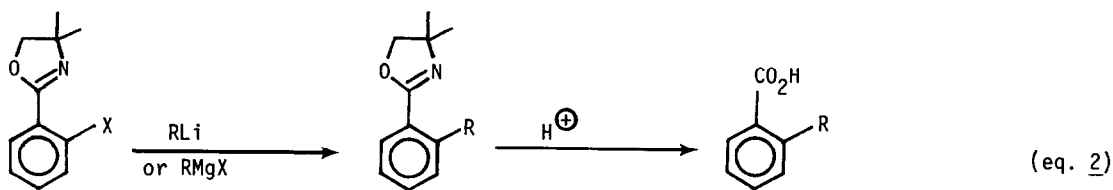
**SUMMARY:** The benzyne derived from *m*-chlorophenyl oxazoline adds nucleophiles regioselectively producing *m*-substituted products. Electrophiles are also trapped furnishing 1,2,3-trisubstituted benzenes.

The synthetic utility of aryloxazolines has been amply demonstrated as a route to *o*-substitution of benzoic acid equivalents by either electrophilic or nucleophilic substitution (eq. 1, 2)<sup>1</sup>. We now report that the benzyne derivative 4 can be readily prepared and displays some highly useful synthetic behavior when treated with either dienes or organolithium reagents.

Electrophilic ortho-substitution



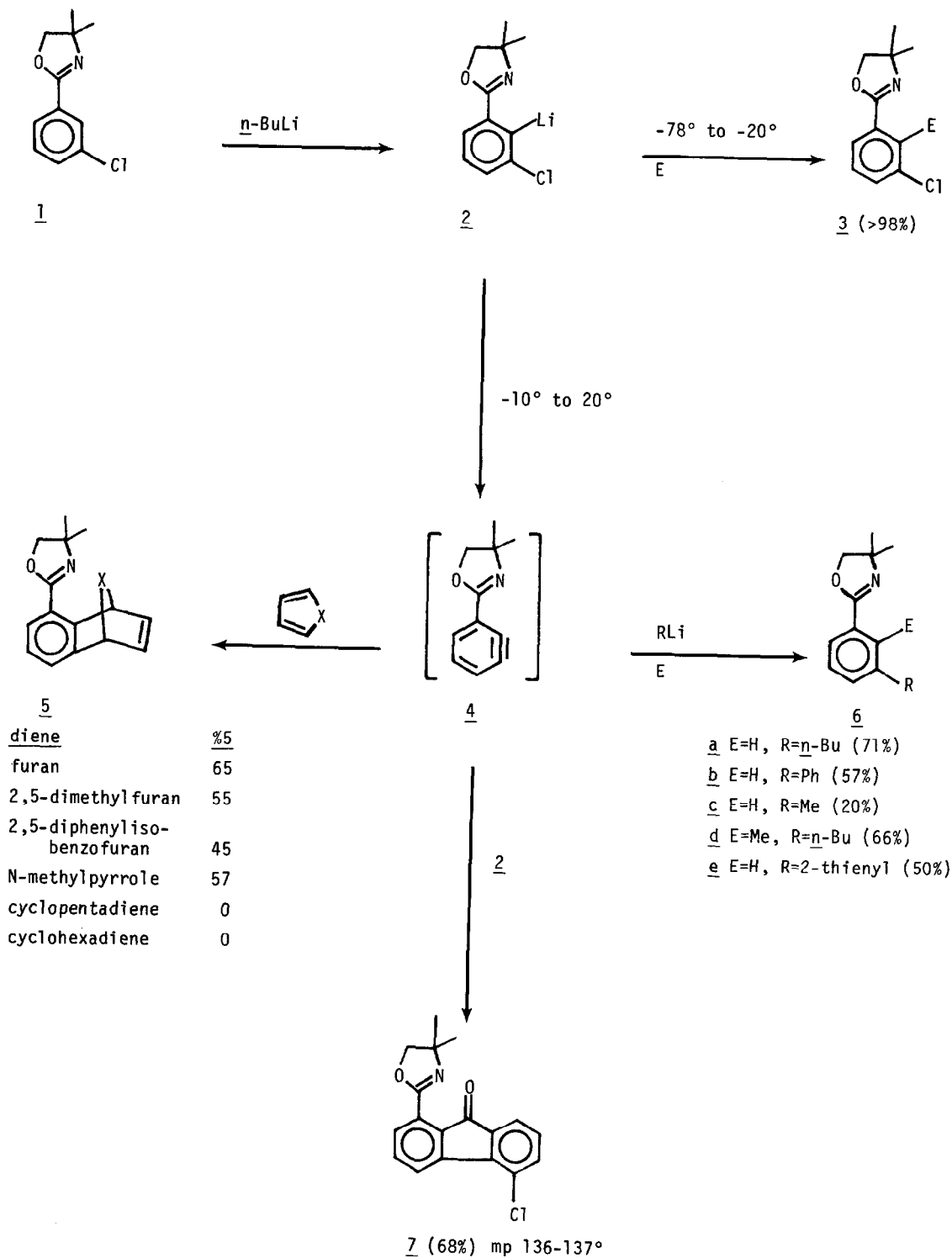
Nucleophilic ortho-substitution



X = MeO, F

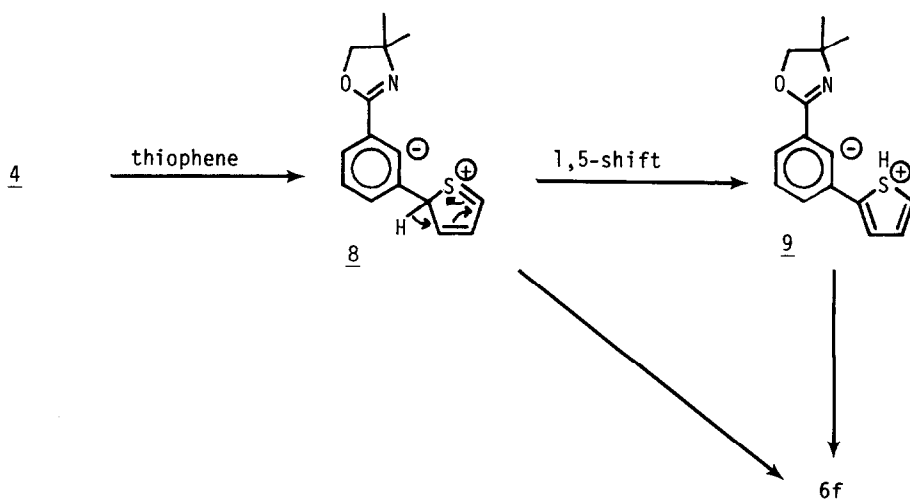
R = alkyl, aryl

The benzyne precursor, 1, was prepared as described previously<sup>2</sup> using *m*-chlorobenzoyl chloride and 2-amino-2-methylpropanol (86%, bp 58°/0.02 mm, IR (film) 1652 cm<sup>-1</sup>). When 1 was treated *n*-butyllithium (THF, -78°) the presence of the 2-lithio salt was confirmed by



addition of methyl iodide ( $E=Me$ ) furnishing a quantitative yield of 2-methyl-3-chlorooxazoline 3. Thus, the 2-lithio salt 2 does not eliminate LiCl at this temperature, contrary to 2-lithio chlorobenzene without additional substituents (LiCl elimination occurs at  $-90^\circ$  to the benzene)<sup>3</sup>. In fact, the 2-lithio salt is stable up to temperatures approaching  $-10^\circ$ , presumably due to the chelation of lithium with the adjacent oxazoline moiety.

However, when 2 is allowed to warm slowly, in the presence of various dienes, to ambient temperatures, cycloaddition takes place<sup>4</sup> providing the adducts 5. Reactions with furans and pyrroles gave satisfactory yields (not optimized) whereas reaction with hydrocarbon dienes gave no cycloadduct but only the fluorenone derivative 7, arising out of self condensation of the benzyne with the lithio salt 2<sup>5</sup>. The latter reaction demonstrates that an organolithium reagent can add regiospecifically to the benzyne and suggested that other organolithium reagents may also follow this course providing an efficient route to *m*-substituted benzoic acid derivatives. This would enhance the versatility of the aryloxazolines for not only reaching *ortho*-substituted benzoic acids (eq. 1, 2) but a route to isomer free *meta*-derivatives. Addition of *n*-butyllithium to the initially prepared solution of the lithio oxazoline 2 at  $-78^\circ$  gives merely a solution of two carbanions and obviously no reaction ensues. As the temperature is allowed to rise to ambient, 2 eliminates LiCl and is transformed *in situ* into the electrophilic-benzyne 4. This event is followed by nucleophilic addition by butyllithium furnishing 6a after hydrolytic quenching as the only product isolated. Thus, the organolithium reagents 6(a-c) enter regiospecifically assisted by the chelation of the ortholithio adduct to the oxazoline<sup>6</sup>. If an electrophile is added at room temperature to a solution of the adduct 6 ( $R=Bu$ ,  $E=Li$ ) then the 1,2,3-trisubstituted benzene 6d is obtained free of any isomers. Reaction of 4 with thiophene did not produce the cycloadduct 5 but instead gave 6e in 50% yield. The high yield for this reaction precluded the *trans*-metallation of thiophene and 2 followed by addition of 2-lithiothiophene to the benzyne 4. The most likely route to 6e may be nucleophilic addition of thiophene to 4 generating 8 which proceeds on to the



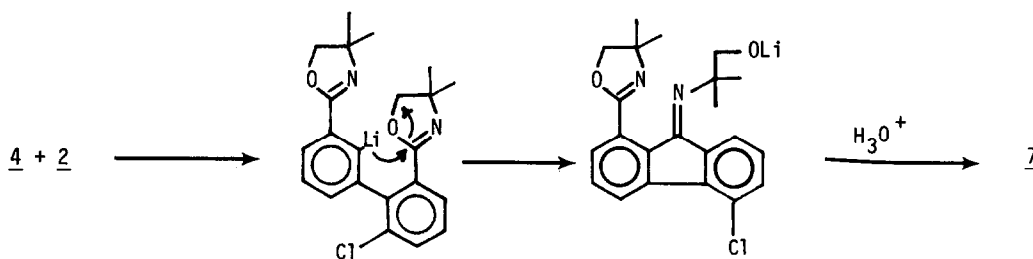
observed product through a 1,5-H shift (9) or direct proton transfer. A related reaction between benzyne and N-methyl indole derivatives has been reported by Kuehne<sup>7</sup> in rather low yields.

The ready generation of the oxazoline benzyne 4 and the preliminary success with various nucleophiles leading to 6 (a-e) now opens a route to m-substituted or 1,2,3 substituted benzene derivatives. Further experiments are in progress to extend this methodology to related systems<sup>8</sup>.

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#### REFERENCES

1. For complete references to this methodology, see A. I. Meyers and W. B. Avila, *J. Org. Chem.* **46**, 3881 (1981). Recent reports on further applications can be seen; J. Novak and C. A. Salemnik, *Tetrahedron Letters* **23**, 258 (1982); A. I. Meyers and R. Gabel, *J. Org. Chem.* **47**, 1982 (in press); A. I. Meyers, K. A. Lutomski, *J. Am. Chem. Soc.* **104**, 1982 (in press); D. J. Cram and J. Wilson, *J. Am. Chem. Soc.* **104**, 1982 (in press).
2. A. I. Meyers, R. Gabel, and E. D. Mihelich, *J. Org. Chem.* **43**, 1372 (1978).
3. H. Gilman and R. D. Gorsich, *J. Am. Chem. Soc.* **78**, 2217 (1956).
4. For a review on benzyne additions to dienes see R. W. Hoffmann, "*Dehydrobenzenes and Cycloalkynes*," Academic Press, N.Y., 1967.
5. Reaction of 4 with 2 undoubtedly proceeds through the intermediates shown.



6. Regiospecific addition to benzyne has been observed (L. Mobius Dissertation, Univ. of Heidelberg, 1965) when a substituent was present ortho to the lithiated benzene.
7. M. E. Kuehne and T. Kitagawa, *J. Org. Chem.* **29**, 1270 (1964).
8. All new compounds gave satisfactory analytical results. The reactions described herein have not yet been optimized.

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