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THE SYNTHESIS OF 1,2,3-TRISUBSTITUTED BENZENES.

FURTHER COMMENTS ON BENZYNES DERIVED FROM ARYL OXAZOLINES

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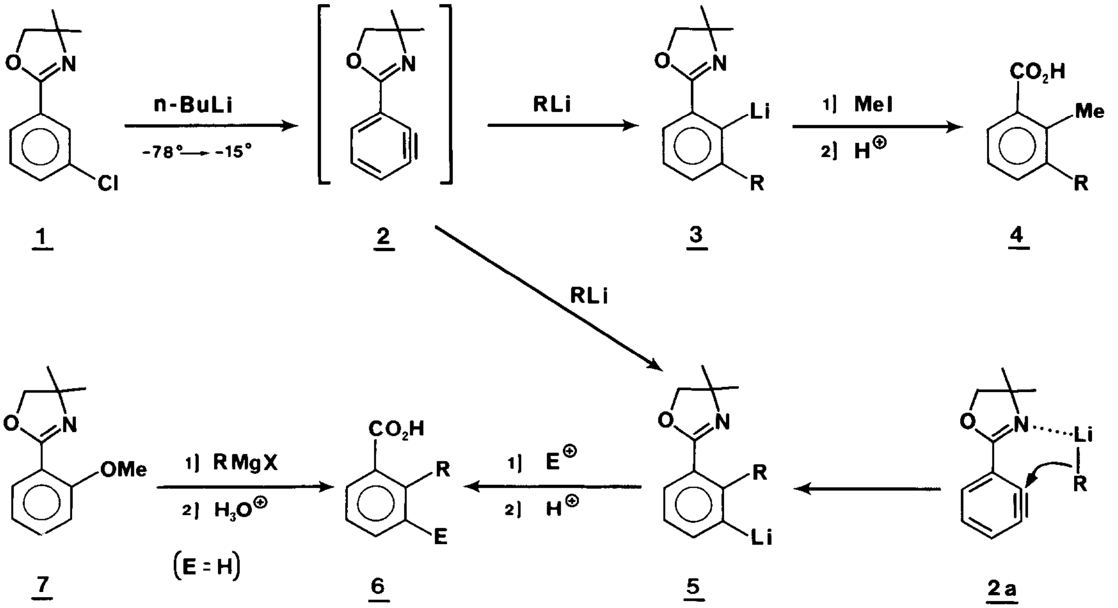
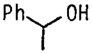
Summary: Further investigation of organolithium addition to the 2,3-benzyne of aryl oxazolines reveals that addition takes place to give the 3-lithio (kinetic) and/or 2-lithio (thermodynamic) products depending on the nature of the organolithium reagent.

We recently reported that 2-(m-chlorophenyl)-2-oxazoline (1), when treated with organolithium reagents, generates the benzyne 2 which reacts further with organolithiums furnishing the 2-lithio adducts, 3[1]. Trapping the latter with methyl iodide and hydrolysis was reported to give 3-substituted-2-methylbenzoic acids, 4. We must now report that, after closer examination of this process, the products are not primarily derived from 3, but in most cases are



those derived from 5. Thus, addition of 3.0 equiv of n-butyllithium to 1 (pentane, -78°, 30 min) and slowly allowing the temperature to rise to 20° (30 min) gave the lithio product 5. The electrophile was added and stirring continued for the time indicated in Table 1. Quenching in abs. EtOH was followed by ether extraction, drying, and chromatography producing the (2,3-disubstituted phenyl) oxazoline which was hydrolyzed to the pure 2,3-disubstituted benzoic acid 6 in good overall yields.

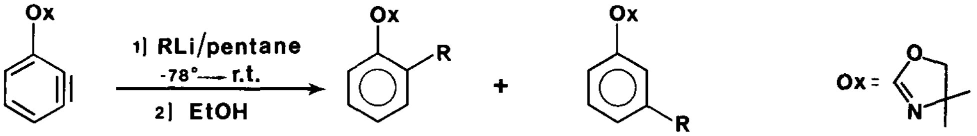
TABLE 1. Reaction of 2-(m-chlorophenyl)-2-oxazoline 1 with n-BuLi and Electrophiles to Give Benzoic Acids 6 (R=n-Bu)

E^+ (time)	E	% Yield 6^a (overall from 1)
EtOH (1 min)	H	70
MeI (20 h)	Me	68
$(CH_2O)_x$ (5 h)	CH_2OH	58
$HCONMe_2$ (15 min)	CHO	57^b
PhCHO (20 min)		57^b
PhCOCl (25 min)	PhC=O	53

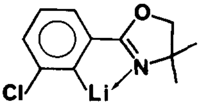
a) The alkylated oxazolines were heated at reflux in 4.5 N hydrochloric acid for 12-15 h.

b) Obtained as the methyl ester of 6 by treatment of the crude acid with 6.0 equiv of CH_2N_2 in ether.

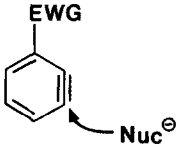
From the benzoic acids obtained, it can be seen that the addition of n-butyllithium to 2 occurred, not as previously reported to 3, but gave instead 5 due to the kinetic effect of the n-butyllithium complexing to the benzyne containing oxazoline 2a. The regiochemistry of addition was confirmed by an independent synthesis using 7, n-butylmagnesium bromide followed by proton quench[2] and hydrolysis to give 6 (E=H, R=n-Bu) which was identical in every respect to the product obtained from 5 (R=n-Bu) followed by proton quench. Our original erroneous assignment of this addition product (to give 3 and 4) was due to reliance only on proton spectra. However, ^{13}C-NMR clearly showed[3] that the n-butyllithium added to 2 to give 5 as the major intermediate with the product from 3 produced in only 11% yield. Chromatography (flash, MPLC, or radial) provides pure, isomer free, material. The fact that the butyllithium addition to 2 proceeded to give only 11% of the 2-lithio adduct 3 indicates that initial chelation to the oxazoline is the predominant factor responsible for the regioselectivity. In order to assess the importance of initial chelation to 2 prior to nucleophilic addition, a series of organolithiums were added to the benzynes 2 and mixtures of 8 and 9 were isolated in yields shown below. The ratios of 8 and 9 were determined by gas chromatography or high pressure liquid chromatography (the balance of the material being mainly starting material, 1). Considerable amounts of 3-aryl products 9 accompany the reaction particularly when 2-lithio ethylbenzene and 2-lithioanisole are employed. The former may be the result of steric effects hindering entry into the 2-position of 2 while the latter (2-lithioanisole) is the result of methoxyl chelation to lithium competing with the chelation to the oxazoline. However, when a strongly chelated lithio compound (2-lithio-3-chlorophenyloxazoline) is introduced, the addition proceeds exclusively to 9[4].



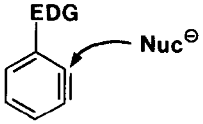
2 8 9

RLi	%8 (via VPC)	%9
n-BuLi	70	11
s-BuLi	46	12
PhLi	48	24
o-EtC_6H_4Li	38	31
o-$MeOC_6H_4Li$	46	33
	0	49

Based on the regiochemistry of addition to benzynes, it is well known[5] that nucleophilic addition proceeds as in A when an electron withdrawing group (EWG) is present while B is the mode of addition for electron donating groups (EDG) except for those cases where steric factors interfere. This is due mainly to thermodynamic control in the addition which leads to the most stable carbanion (chelation to the EWG) and hence the position of the lithium cation. The present results confirm that a kinetic process is operating which can reverse the regiochemistry. The initial complexation of the organolithium reagent to a strong electron donor (e.g. oxazoline) irrespective of the strong electron withdrawing properties of the oxazoline will cause addition to occur in a manner depicted by B. The solvent used to maximize this effect was pentane (or hexane) which poorly solvates the organolithium



A



B

reagent. When THF or ether was employed as solvent, a variety of products including mixtures of 2- and 3-substituted oxazolines 8 and 9 respectively were formed. The yields were invariably poor making these solvents unsuitable for use. On the other hand, large aggregates of the organolithium will undoubtedly be present in hydrocarbon solvents and sterically influence the addition (B) such that considerable amounts of the reaction path follows route A. Further studies on this interesting and useful phenomenon are in progress in an effort to increase the regioselectivity and expand this process to other nucleophiles.

REFERENCES AND NOTES

1. A. I. Meyers and W. F. Rieker, Tetrahedron Letters 23, 2091 (1982).
2. A. I. Meyers, R. Gabel, and E. D. Mihelich, J. Org. Chem. 43, 1372 (1978).
3. For 2-substituted aryl oxazoline 8 (R = Bu) the methylene carbon adjacent to oxygen appeared at 78.6, whereas the corresponding methylene carbon in 9 appeared at 75.7. This is a reflection of the degree of coplanarity between the oxazoline and the benzene ring. The structures for 8 and 9 were assigned by the ^{1}H-chemical shifts (100 MHz) of both the aromatic and oxazoline protons.
4. The fluorenone reported in reference 1 was produced exclusively. Since this report, the structure of the fluorenone has been confirmed by single crystal x-ray analysis, thus firmly supporting addition to the 3-position of the benzyne.
5. R. W. Hoffmann, "Dehydrobenzenes and Cycloalkynes," Academic Press, N.Y. (1967).

ACKNOWLEDGMENT

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