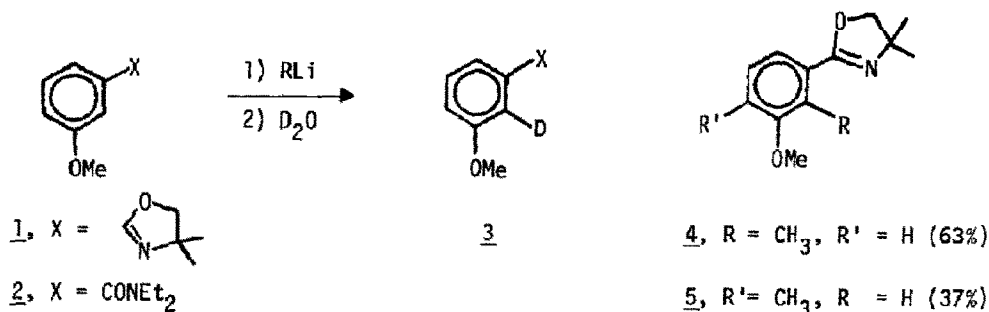


SOLVENT AND BASE STUDIES ON THE SITE OF
 ARYL METALATION OF 2-(3,5-DIMETHOXYPHENYL)-4,4-DIMETHYL-2-OXAZOLINE

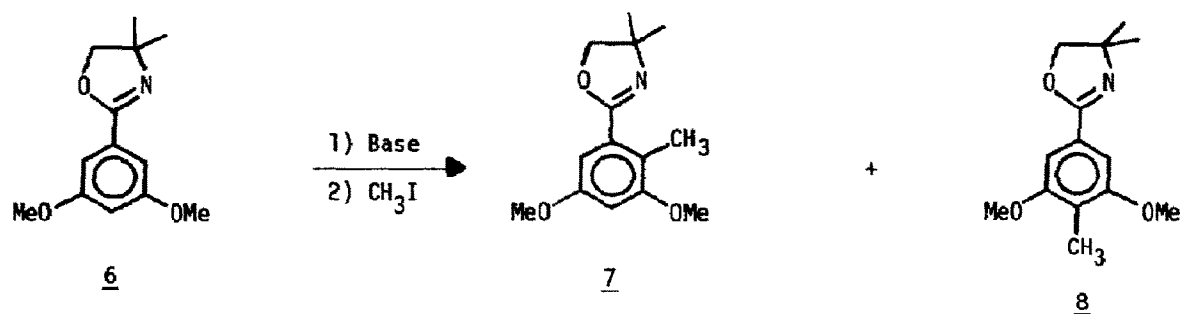
A. I. Meyers* and Walter B. Avila
 Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Summary: The position of metalation and alkylation in aryl oxazolines and diethylamides vary drastically when the base (RLi) and solvents are varied.

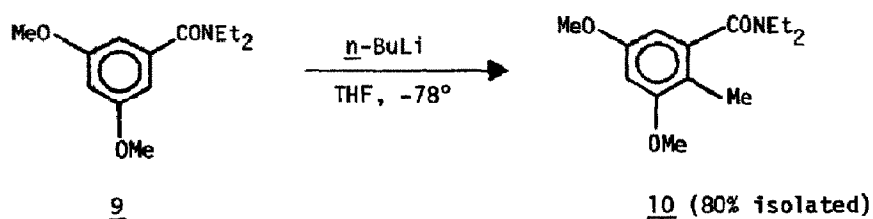
The current interest by a number of laboratories¹ in metalation of aromatic rings activated by various substituents is reflective of the serious need to introduce substituents with a high degree of selectivity. Of equal significance is the effect of variously situated aromatic substituents upon the site of metalation for it is this sort of regioselectivity that determines the value of a synthetic method. During the course of total synthesis of some polynuclear aromatic natural products, we were confronted with metalation problems on methoxy substituted aryl oxazolines and amides and now report that it is possible to direct the metalation by appropriate changes in conditions. The reports that *m*-methoxy aryl oxazolines 1² and the diethyl benzamide 2³ give, with *n*-BuLi (-45°, THF) or *sec*-BuLi-TMEDA (-78°, THF), respectively, only the 2-deuterio product 3 supports the complementary activating effects of both substituents in metalation of the



2-position. However, metalation of 1 with *t*-BuLi (-45°, THF, 1.5 h), followed by CH₃I gave in addition to the expected 2-methyl derivative 4 (63%), the isomeric 4-methyl derivative 5 (37%). This result indicated that variations in base strength (*n*-BuLi vs. *t*-BuLi), steric factors, and other parameters, may override the expected "activating" abilities of the substituents. A study was conducted using the 3,5-dimethoxyphenyl oxazoline 6 which should provide information on kinetic acidity of aryl protons ortho to two activating groups. Based upon previous literature ranking of activating groups in order of their ortho lithiations,¹ it was expected that 7 should be the major isomer.⁴ That this is highly dependent upon the solvent, and nature of the base is dramatically seen from Table 1. Although ether as the solvent gave high ratios of ortho lithiation (7), the total conversion was quite low rendering these conditions synthetically useless.



Use of THF, however, gave high yields of lithiated and subsequently methylated product, but the major product was 8. Thus, a large solvent effect is noted here. Turning to dimethoxyethane as solvent gave a reversal of product composition with 7 predominating. Temperature effects are small with regard to product ratios affecting only the total conversion (96% vs. 77%). The other large effect is due to the nature of the base. In THF under identical conditions, n-butyllithium gives the p-substituted product 8 while a large reversal to the o-substituted product 7 is noted with s-butyllithium. The trend is again reversed by use of t-butyllithium furnishing, although poor conversion, the p-substituted product. Beak has reported¹ that s-BuLi-TMEDA is the base of choice for many metalations on this series. When this base-pair was used in ether, THF, or DME at -78° , the conversions were indeed uniformly high (72-85%) and the ratios of 7 to 8 were 58:46:34, and 93:7, respectively. Thus, DME and s-BuLi-TMEDA were the conditions of choice to achieve the highest ratio of ortho-substitution, whereas n-BuLi, THF, -45° are the optimum conditions for para-substitution. This study also addressed kinetic vs. the thermodynamic metalation product and the reaction ratios were examined after 30 min, 75 min, and 180 min. No change (< was observed in the product distributions. Finally, the diethylbenzamide 9 was metalated (n-BuLi, THF, -78°) and after addition of CH_3I , gave only the ortho-methyl derivative 10 which supports stronger activating ability of this substituent as compared to the oxazoline.¹ Thus, when ortho-substitution is preferred, the diethylamide should be employed in these dimethoxyaryl



systems, whereas, the oxazoline is the derivative of choice for para-substitution. A discussion of the subtle effects of base aggregates, complexing abilities of the substituents, base strength must await further studies, but it is clear that predicting sites of metalation in multiply-substituted aromatics is difficult and should be approached with caution. It is suggested that various conditions such as those employed here be routinely examined when attempting to introduce substituents via lithiated aryls.

Table 1 Ratio of Methylated Oxazolines as a Function of Solvent and Base.

Solvent	RLi ^a	Metalation T ^o ^b	Ratio ^c	Ratio ^{d,f}	
			6/(7 + 8)	7	8
Et ₂ O	<u>n</u> -BuLi	-45	62 (30)	81	19
"	<u>s</u> -BuLi	-45	37 (24) ^e	93	7
THF	<u>n</u> -BuLi	-45	1 (96)	22	78
"	<u>n</u> -BuLi	-78	19 (77)	22	78
"	<u>s</u> -BuLi	-78	10 (87)	67	33
"	<u>t</u> -BuLi	-78	71 (26)	28	72
DME	<u>n</u> -BuLi	-78	2 (98)	85	15
"	<u>s</u> -BuLi	-78	12 (84)	90	10
"	<u>t</u> -BuLi	-78	50 (46)	64	36

a) 1.05 eq RLi added to solution of 6 under N₂ or Argon; b) Reaction mixture stirred for 1.5 h prior to CH₃I addition. Bath removed and stirred for 30 min; c) Ratios determined by vpc (10% SE-52, 60-80 mesh chromsorb W, 6' X 1/4" column, at 180°); d) Determined by a) integration of CH₃-singlet at 2.3 ppm for 7 and 2.1 ppm for 8; b) HPLC analysis which confirmed nmr integration, ether-hexane 1:2 on μ-porosil, flow rate 1-2 ml/min; e) Large amount of s-BuLi addition to C=N link of oxazoline was observed; f) Ratios are rounded off to nearest whole percent.

REFERENCES

1. M. Watanabe and V. Snieckus, J. Am. Chem. Soc., **102**, 1457 (1980); P. Beak and R. A. Brown, J. Org. Chem., **44**, 4464 (1979); A. I. Meyers and K. Lutomski, J. Org. Chem., **44**, 4465 (1979); H. W. Gschwend and H. R. Rodriguez, Org. React., **26**, 1 (1979) and numerous references cited in these reports.
2. A. I. Meyers and E. D. Mihelich, J. Org. Chem., **40**, 3158 (1975). The metalation of 1 was performed (*n*-BuLi, THF, -45°) and treated with CH₃I to give 97% of 4 (CH₃ in place of D). Hydrolysis (6N HCl, reflux, 2h) gave 2-methyl-3-methoxy benzoic acid, mp 141-143°.
3. P. Beak and R. A. Brown, J. Org. Chem., **42**, 1823 (1977).
4. Isolation (tlc) and complete characterization was carried out for 7 [oil, ir (film) 1649 cm⁻¹ nmr (CDCl₃) δ 6.8 (d, 1), 6.5 (d, 1), 4.0 (s), 3.8 (s), 2.30 (s, 3), 1.4 (s)]; 8 [mp 109-110° ir (film) 1659 cm⁻¹; nmr (CDCl₃) δ 7.1 (s, 2), 4.1 (s), 3.8 (s), 2.10 (s, 3), 1.4 (s). Analysis for C, H, N is ±.3%.

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