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OXAZOLINES AS ACTIVATING GROUPS IN AROMATIC SUBSTITUTION. NUCLEOPHILIC DISPLACEMENT OF o-FLUORO SUBSTITUENTS BY ORGANOMETALLICS AND LITHIO AMIDES.

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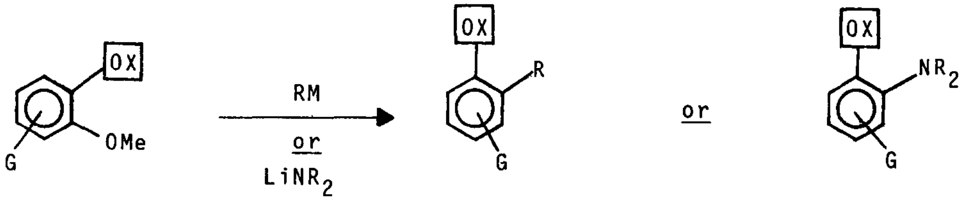
Nucleophilic displacements of aryl fluorides are well known to occur readily in the presence of strong electron withdrawing substituents (NO_2, RCO, CF_3, CN).[1] Intramolecular flourine displacements are also known and have provided interesting routes to a variety of alkaloids[2] and related heterocycles.[3] The above processes were all performed using oxygen and nitrogen nucleophiles and there are virtually no synthetically useful replacements of fluorine involving organometallic nucleophiles leading to C-C bonds. The studies by Semmelhack involving π-(fluorobenzene)chromium carbonyls and carbon nucleophiles leading to substituted aromatics is one noteworthy exception.[4]

We have recently reported that o-methoxyaryl oxazolines 1 react readily with Grignard or organolithium reagents (RM)[5] as well as lithio amides[6] furnishing the substituted aromatics 2 and 3, respectively. This facile process possesses



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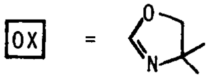
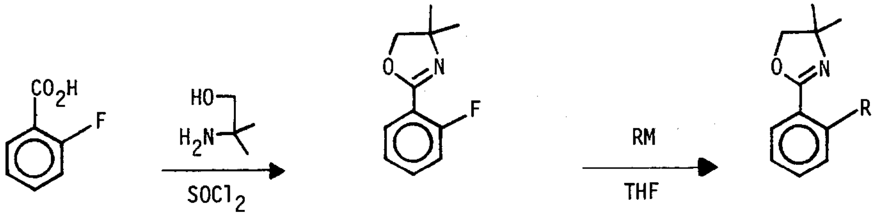
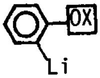
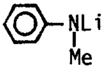
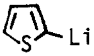


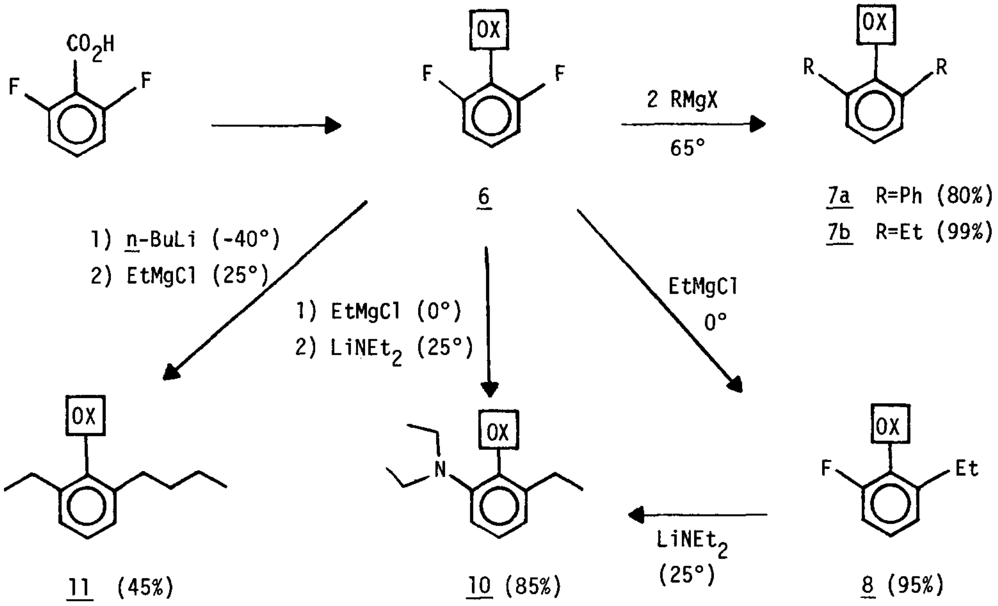
considerable potential in aromatic nucleophilic substitution and also opens a route to unsymmetrically substituted biaryls. It was felt that the o-fluoro substituent would be equally, if not better, suited for this task if the suggested mechanism[5,6] was indeed correct. We now report that the fluoro substituent is cleanly displaced by various lithium or magnesium (but not sodium or potassium) nucleophiles. Conversion of o-fluorobenzoic acid to the oxazoline 4[7] (78% on a 30 g scale, bp 78-81° [1.2 torr]) was followed by treatment with a variety of organolithium reagents and Grignard reagents in THF as outlined above to give generally excellent yields of substituted products 5. The use of benzyl, alkyl, and 1,3-dithianyl lithium reagents (or Grignards) produced low yields (0-17%) of 5 along with starting materials. Similar behavior was previously noted using the o-methoxyaryl oxazoline 1.[5] It appears that delocalized lithio or magnesio anions are not sufficiently tight ion pairs to allow substitution to occur efficiently.[5]



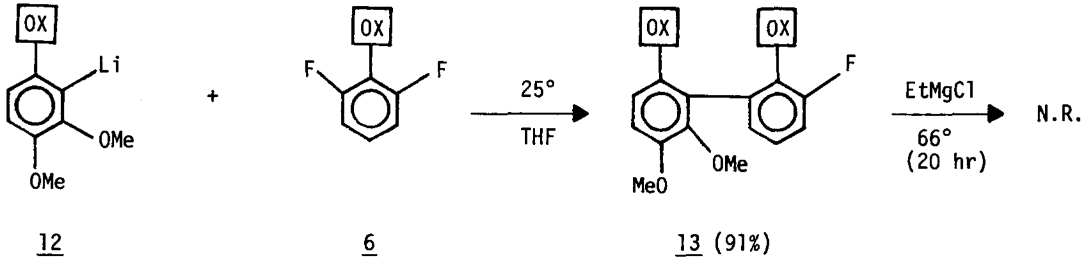
4 5

RM	T°	Time	%5[8]
n-BuLi	-45	2 hr	92
EtMgCl	25	1.5 hr	95
$LiN(i\text{-}Pr)_2$	0	4 hr	70
	-40	7.5 hr	96
	65	16 hr	98
	65	16 hr	30
$LiNEt_2$	25	20 hr	95

By employing 2,6-difluorobenzoic acid as a starting material, conversion to the oxazoline 6 was accomplished in the usual manner[7] (84%, bp 61-65° [0.02 torr]).



In an attempt to introduce two substituents ortho to the oxazoline, 3.0 equiv of phenyl or ethylmagnesium halide was added (THF, reflux) and good yields of the 2,6-disubstituted product, 7a and 7b, were obtained. The introduction of the second substituent requires higher temperatures (>20°) due to steric crowding of the two ortho gruops. Thus, mono-substitution to 8 was very efficient when performed below 0°. This behavior suggested that it should be feasible to introduce two different substituents. This indeed proved to be the case as seen by the clean conversion to 10 and 11. The lower yield of the latter is not to be taken as any significant limitation since none of these reactions have yet been optimized. In another case, it was found that the order of introduction of the two organometallics may be a critical factor. Thus, the lithiated oxazoline 12 coupled smoothly with 6 to afford the biaryl 13[8] but when reaction with ethyl-



magnesium chloride was attempted, no reaction occurred. However, if the smaller group was introduced first (ethyl), the process may prove successful. This and other aspects of this unusual aromatic methodology are currently under investigation.[10]

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REFERENCES

1. H. Bader, A. R. Hansen, and F. J. McCarty, J. Org. Chem., 31, 2319 (1966).
2. D. L. Coffen, D. A. Katonak, and F. Wong, J. Am. Chem. Soc., 96, 3966 (1974); D. L. Coffen and F. Wong, J. Org. Chem., 39, 1765 (1974).
3. A. Walser, T. Flynn, and R. I. Fryer, J. Heterocyclic Chem., 12, 737 (1975) and other references cited.
4. M. F. Semmelhack and H. T. Hall, J. Am. Chem. Soc., 96, 7091 (1974).
5. A. I. Meyers and E. D. Mihelich, J. Am. Chem. Soc., 97, 7383 (1975).
6. A. I. Meyers and R. Gabel, J. Org. Chem., 42, 2653 (1977).
7. A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, J. Org. Chem., 39, 2787 (1974).
8. All yields are of isolated material and these gave spectral and elemental analyses consistent with their structure.
9. A full discussion of the limitations to methoxy substitution in these compounds is presented in an article currently in press; A. I. Meyers, R. Gabel and E. D. Mihelich, J. Org. Chem. (1977).
10. See accompanying paper.