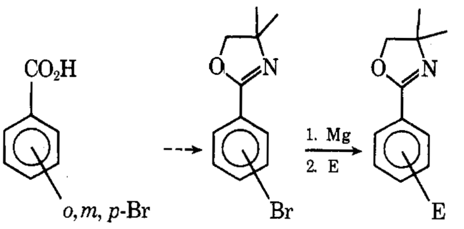
Communications

Oxazolines. XVII. Regioselective Metalation of 2-Aryl Oxazolines. A Route to Polydeuteriobenzoic Acids

Summary: The ortho-lithiation of 2-aryl oxazolines with *n*-BuLi has been shown by deuterium incorporation studies to provide a source of deuteriated benzoic acids.

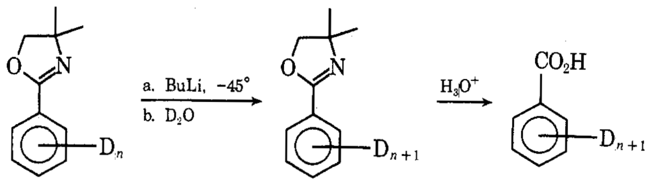
Sir: We recently reported[1] a method for the elaboration of bromobenzoic acids via the Grignard reagent of their 4,4-dimethyl-Δ^2-oxazoline derivatives, I (eq 1). We wish to describe an extension of this work which obviates the need for the ortho bromo substituent and enables the preparation of polysubstituted benzoic acid derivatives through consecutive metalations of the aromatic ring.

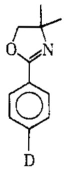
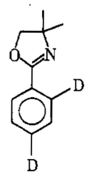
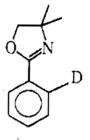
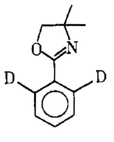
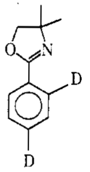
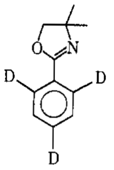
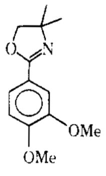
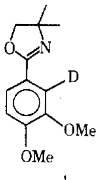
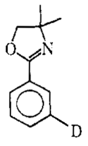
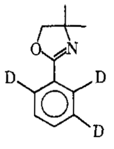


I II (1)

It is well known that anisole and benzamides undergo metalation with organolithium reagents predominantly in the ortho position.[2] Precoordination of the lithium base with the adjacent lone pairs followed by abstraction of the adjacent ortho proton has been proposed as a possible

Table I
Deuteration of Phenyl Oxazolines



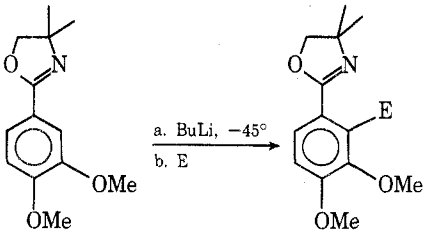
Entry	Oxazoline[a]	Conditions[b]	Product[c] (%)[d]	Benzoic acid	
				% yield[d]	Deuterium ratio[e] $d_0:d_1:d_2:d_3:d_4$
1		A	 (90)	76	0:9:100:6:0
2		B	 (90)	82	0:13:100:5:0
3		B	 (92)	79	0:0:21:100:7
4		A	 (95)	71	3:100:13:0:0
5		C	 (88)	77	0:4:44:100:11

[a] Oxazolines were prepared as previously described.[1] Monodeuterio compounds were conveniently obtained by halogen–metal exchange of the bromides with *n*-BuLi (THF, −78°) followed by D_2O quenching.
[b] Method A, stirred with 1.1 equiv of *n*-BuLi for 1.5 hr and quenched at −45° with D_2O; method B, stirred with 1.1 equiv of *n*-BuLi for 6 hr before quenching at −45°; method C, oxazoline sequentially subjected to conditions A and B.
[c] Deuterium incorporation was complete within the limits of NMR spectroscopy.
[d] Yields are for distilled or recrystallized materials.
[e] Mass spectral data at 70 eV.

mechanism. We now report the rapid and efficient metalation of oxazolines II (E = D) with n-BuLi in THF at −45°. Table I shows a series of experiments run to determine the extent and position of metalation. The ease of metalation and the high selectivity observed are particularly noteworthy. The low temperature employed both limits unwanted side reactions[3] and provides a large isotope effect enabling selective hydrogen abstraction[4] (entries 2, 3, and 5). Entry 4 illustrates the ability to have other substituents on the ring. In this case, the 3-methoxy group enhances metalation in the 2 position through participation of its lone pairs in the coordination step.

The following procedure is illustrative. To 0.405 g (2.3 mmol) of 2-(4-deuteriophenyl)-4,4-dimethyl-Δ^2-oxazoline in 30 ml of THF under N_2 at −45° (Dry Ice–chlorobenzene bath) was added 1.1 ml of 2.3 M n-BuLi in hexane (2.6 mmol, 1.1 molar equiv) and the solution was stirred for 1.5 hr. Excess D_2O (1–2 ml) was then added; the mixture was allowed to warm to ambient temperature and poured into ether. After washing, drying ($MgSO_4$), and concentration there was obtained a clear oil which on distillation (bulb to bulb, pot temperature 60° at 0.05 mmHg) afforded 0.365 g (90%) of 2-(2,4-dideuteriophenyl)-4,4-dimethyl-Δ^2-oxazoline, pure by NMR analysis. Direct hydrolysis of this material in 20 ml of 4.5 N HCl (reflux, 4 hr) gave 0.195 g (76%) of fine needles (mp 121°) after recrystallization from water. The benzoic acids obtained in this manner were all analyzed for deuterium content by mass spectral techniques (Table I). The desired deuteriobenzoic acids were formed in 80–87% isotopic yield except for entry 5 which was performed in sequence in a single vessel. In this instance the trideuteriobenzoic acid was obtained in 63% isotopic yield. These experiments have not been optimized and further effort should produce higher yields of the intended deuterio derivatives.

In addition to deuteration, other electrophiles were added to the o-lithiated aryl oxazolines. As expected,[2] substituted derivatives were obtained in high yields.[5] Thus III, after addition of n-butyllithium, was treated with dimethyl disulfide or N-chlorosuccinimide and furnished IV [92%; oil; ir (film) 1655 cm^{-1}; NMR (CCl_4) δ 7.2 (d, 1), 6.7 (d, 1), 4.0 (s, 2), 3.9 (s, 6), 2.4 (s, 3), 1.33 (s, 6)] and V [90%; oil; ir (film) 1650 cm^{-1}; m/e (70 eV) 270 (M$^+$), 272 (M + 2); NMR ($CDCl_3$) δ 7.5 (d, 1), 6.9 (d, 1), 4.1 (s, 2), 3.9 (s, 3), 3.8 (s, 3), 1.4 (s, 6)].



III

IV, E = SMe
V, E = Cl

The versatility of oxazolines to serve as precursors to a variety of functional groups[6] amplifies the usefulness of these reactions and we are currently applying the above findings to the preparation of aromatics present in natural products.

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References and Notes

(1) A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 3787 (1974).
(2) B. J. Wakefield, "The Chemistry of Organolithium Compounds", Pergamon Press, Elmsford, N.Y., 1974, Chapter 3.
(3) At higher temperatures, the butyllithium will slowly add to the C═N link of the oxazolines giving rise to small quantities of 2-(n-butyl)-2-aryl oxazolidines.
(4) K_H/K_D is calculated to be 14 at −45° from the equation $K_H/K_D = e^{(1200/1.99\times T)}$
(5) A recent report by Gschwend et. al [*J. Org. Chem.*, **40**, 2008 (1975)] has also described metalation of aryl oxazolines and subsequent elaboration with a number of electrophiles.
(6) Acids and esters, ref 1; ketones, A. I. Meyers and E. M. Smith, *J. Org. Chem.*, **37**, 4289 (1972), and C. Lion and J. E. Dubois, *Tetrahedron*, **29**, 3417 (1973); aldehydes, I. C. Nordin, *J. Heterocycl. Chem*, **3**, 531 (1966).

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Reduction of Organic Halides by the System Titanocene Dichloride–Magnesium

Summary: A titanocene dichloride–magnesium system reduces organic halides under mild conditions and in good yield.

Sir: The chemical reactivity of titanocene, generated by the reduction of titanocene dichloride (I), has been the subject of considerable interest.[1] Recent evidence[1e,2] suggests the following scheme for the reduction of I with sodium under argon.

$$\text{I} \rightarrow (\pi\text{-Cp})_2\text{TiCl} \rightarrow \underset{\text{II}}{[(\pi\text{-Cp})_2\text{Ti}]_{1-2}} \rightarrow$$
$$[(\pi\text{-Cp})(C_5H_4)\text{TiH}]_2 \rightarrow [(\pi\text{-Cp})(C_5H_4)\text{TiH}]_x$$

Titanocene,[3] or its dimer (i.e., II), has been implicated in the various reductions induced by this system.[1c,e,f]

It has been shown[4] that the organotitanium species generated by the action of powdered magnesium on I reduces molecular nitrogen. Presumably the action of magnesium on I proceeds via a sequence similar to that shown above. We have investigated the reactions of the titanocene dichloride–magnesium system with organic halides and found that they are reduced in good yield.

The reducing system was generated by the addition of excess finely powdered magnesium to a stirred solution of I under argon. A color change from the characteristic red color of I to green, then black, was noted.[4] The compound to be reduced was rapidly added to this system at 0°. The reaction was then immediately quenched by the addition of the resultant mixture to water. The product was isolated by ether extraction.

The efficiency of this reducing system is illustrated by the reduction of azo compounds.[5] The reductions of diethyl azodicarboxylate (75%), dimethyl azodicarboxylate (77%), diphenyl azodicarboxylate (67%), and azobenzene (75%) are representative and proceed in the yields specified.

It should be noted that the azo compounds were recovered unchanged from exposure to magnesium powder alone under identical conditions. Furthermore, comparable yields of hydrazo products were obtained by filtering the reducing system to remove the unreacted magnesium prior to the addition of the azo compounds.