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METALLATION OF RIGID 2-ARYL-1,3-DIOXANES

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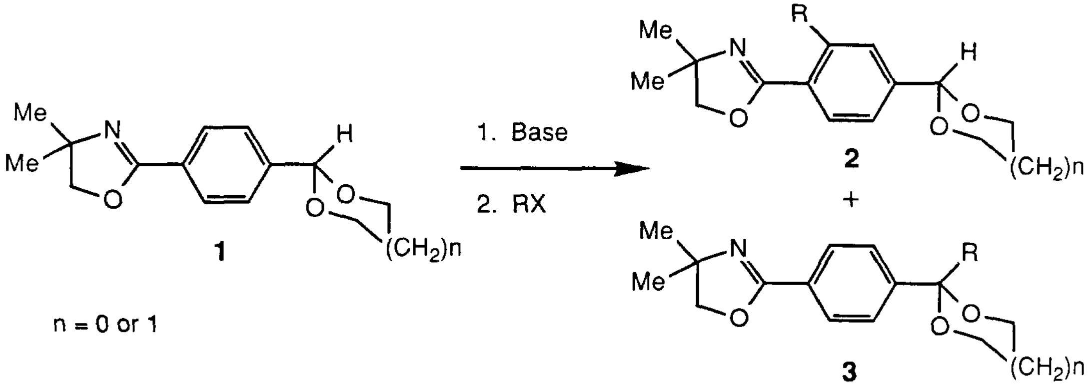
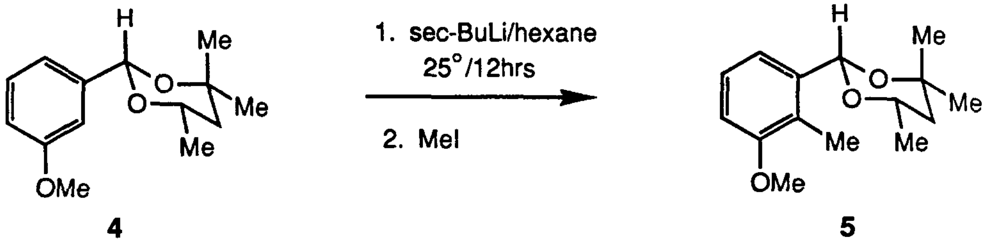
Abstract: Regioselective metallation and alkylation/acylation of 2-aryl-1,3-dioxanes was achieved in high yield.

In 1979, Meyers and Campbell [1] described the utility of 2-aryl acetals as acyl anion equivalents. This finding was successfully extended to a very efficient process for achieving regioselective metallation of appropriately substituted aryl acetals. When the aryl moiety contained an electron withdrawing oxazoline group in the para position (e.g., 1) it was demonstrated[1,2] that regioselective deprotonation of the acetal or the aromatic ring could be achieved by judicious choice of the acetal group and base. With conformationally flexible acetals the kinetic acidity of the acetal hydrogen was shown to be greater than that of the aromatic hydrogens ortho to the oxazoline ring.



Interestingly, conformationally biased 1,3-dioxanes, with a fixed acetal hydrogen (2-H) in the axial orientation, were found to undergo regioselective deprotonation on the aromatic ring ortho to the oxazoline. It was concluded that selective deprotonation of the acetal was feasible only when the acetal hydrogen (2-H) could adopt an equatorial orientation. These experimental observations were consistent with Eliel's work[3] on 1,3-dithianes, stereoelectronic effects[4] and ab initio calculations reported by Lehn[5].

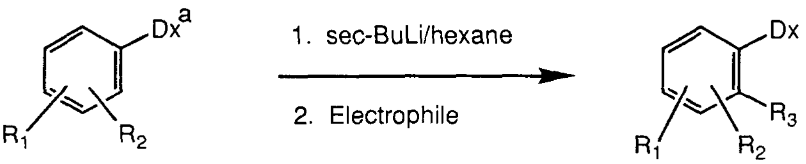
We were interested in extending the experimental evidence reported by Meyers and co-workers[1,2] to non-oxazoline containing aryl acetals. A number of methods have been reported for the ortho metallation of suitably protected aryl aldehydes[6,7], latent aryl aldehydes[8], and in-situ protected aryl aldehydes[9] but none of these offered any obvious advantages over aryl dioxanes. 4,4,6-Trimethyl-2-phenyl-1,3-dioxane 4 was chosen as the acetal to investigate the acidity difference between an axial (2-H) acetal and an aryl hydrogen because 4 could be easily formed under thermodynamic conditions[10] thereby providing only one of the two possible diastereomers. Also, the two equatorial methyl groups at C-4 and C-6 are sufficient to bias the conformation of the dioxane ring in a chair form in which the acetal proton would remain in the least acidic axial orientation.

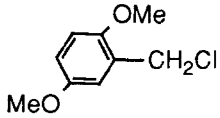
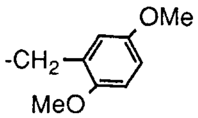
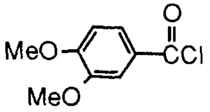
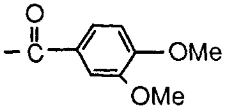


After several experiments, 4 was metallated (sec-BuLi) and alkylated (methyl iodide) exclusively at the C-2 position of the aromatic ring providing 5 in an 80% overall yield. Table 1 illustrates the utility of 4,4,6-trimethyldioxanes in directing ortho metallation of aryl aldehydes. The best yields were obtained with sec-butyl lithium as base and hexane as solvent. Stronger bases, ethereal solvents and longer reaction times generally lead to lower yields. The best yields were obtained with 3- and 3,4-oxygen substituted aryl dioxanes.

Metallation always occurred, as expected, in the 2-position of 3-oxygen substituted aryl dioxanes. Also, consistent with the literature[7], no metallation occurred when the aryl dioxane contained a substitutent in the 2-position. The dioxane can be easily removed under acidic conditions to provide the corresponding aldehyde [11]. Also, direct oxidation of the dioxane to the corresponding benzoic acid is feasible using Jones reagent[12].

TABLE 1



	Aryl acetal R_1	 R_2	Electrophile	Product[b] R_3	Yield (%)[c]
1.	H	3-OMe	a. MeI	-Me	90
			b. $PhCH_2Br$	$-CH_2Ph$	98
			c. CO_2	$-CO_2H$	85
			d. DMF	-CHO	80
			e. 		85
			f. 		95
2.	H	4-OMe	MeI	-Me	85
3.	H	2-OMe	MeI	-Me	0
4.	H	H	MeI	-Me	68
5.	3-OMe	4-OMe	a. MeI	-Me	85
			b. CO_2	$-CO_2H$	80
			c. $PhCH_2O\overset{O}{\overset{\|}{C}}Cl$	$-CO_2CH_2Ph$	65
6.	3,4-OCH_2O-		MeI	-Me	98
7.	2-Me-3,4-OCH_2O-		MeI	-Me	0

a) Dx= 2-aryl substituted-4,4,6-trimethyl-1,3-dioxane

b) All structural assignments are consistent with nmr, ir and CH&N analyses

c) Yields are isolated yields corrected for recovered starting material. The conversion routinely exceeded 85 %.

The following is a general procedure:

Sec-Butyl lithium (2 mmole) was slowly added via syringe to a cold suspension (-40^{O}C) of aryl acetal (1 mmole) in hexane (20 ml). The hetereogenous mixture was allowed to warm to 25^{O}C and stirring continued until anion formation was complete (4 to 12 hrs). The preformed orange anion was recooled to -40^{O} and quenched by careful addition of the electrophile (3 mmol) over 30 min. The reaction mixture was slowly allowed to warm to 25^{O}C and stirred until complete (4-12 hrs). Dilution with water followed by extractive isolation (ethyl acetate) and chromatography (silica gel, hexane/ethyl acetate) provided the desired substituted aryl acetals in the indicated yields (Table 1).

The results reported herein illustrate an efficient method for obtaining 2,3 and 2,3,4-substituted aryl dioxanes.

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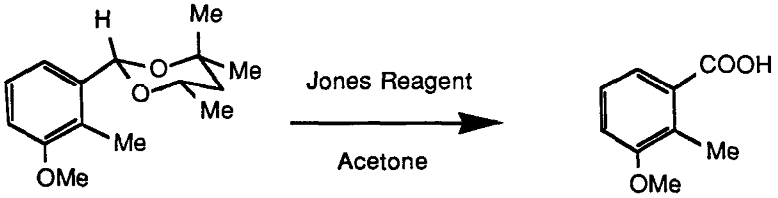
11. The dioxanes were prepared and hydrolyzed as described in References 1 and 2.
12.



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