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THE REGIOSPECIFIC LITHIATION OF AROMATIC ACETALS

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Abstract The dimethylacetal of benzaldehyde and some 3, 3,4 and 3,4,5 oxygenated derivatives thereof are regiospecifically deprotonated at the 2-position by alkyl lithiums. The resulting aryl lithiums provide various 2-substituted benzaldehydes in moderate to excellent yields.

Following the pioneering work of Hauser,[1] several investigators have established that regiospecific deprotonation of aromatic systems ortho to an existing substituent may be accomplished with alkyl lithiums. The success of these 'ortho-lithiations' have been attributed in the main to intramolecular coordination of the lithium with a lone pair of electrons in the substituent. A great variety of such ortho-directing substituents have been employed,[2] but among these only one report[3] involved the use of a modified aromatic aldehyde. In that instance the cyclohexylimine of piperonal was observed to deprotonate at the 2-position exclusively, and the resulting 2-lithio derivative was intercepted with a variety of electrophiles. The yields of 2-substituted aldehydes were moderate and the reaction failed with the cyclohexylimines of veratraldehyde and m-anisaldehyde. This was attributed to steric inhibition by the freely rotating methyl group. The process, however, represented a significant advance in the methodology for the preparation of 1,2-methylenedioxy-3,4-disubstituted benzene derivatives and has been exploited in the synthesis of many benzylisoquinoline alkaloids.[4]

The ready availability of aromatic aldehydes and the obvious desirability of retaining the aldehyde function as a handle for further synthetic manipulation led us to search for other aldehyde derivatives which could be similarly deprotonated. Dimethyl acetals of aromatic aldehydes are easily prepared, stable to the conditions of lithiation, and the acetyl moiety retained or hydrolyzed at will after the reaction. The dimethyl acetal moiety was therefore investigated as a directing group in ortho-lithiation.

The results[5] of our experiments with eleven dimethyl acetals are summarized in the table. Diethyl ether was generally the best solvent for these lithiations although tetrahydrofuran and dimethoxyethane can also be used. For comparison purposes all experiments reported in the table were carried out in diethyl ether and the products were isolated as the aldehyde after brief exposure of the reaction products to dilute acid. In most instances the dimethyl acetal may be isolated if so desired.

Lithiation when observed took place ortho to the acetal group and with acetals in 1, 2, 4 and 9 the more stable anion resulting in 1,2,3,4-substitution (in 1, 2 and 4) or 1,2,3-substitution (in 9) was produced. Acetals of veratraldehyde 2 and trimethyl gallaldehyde 3 are lithiated in high yield in contrast to the earlier experience[3] with cyclohexylimines of such compounds. Acetals 9-11 are only deprotonated with t-BuLi and even then products are only obtained in low to moderate yields. This is understandable in terms of the lower acidity of the aromatic protons in such compounds. In spite of repeated efforts under a variety of conditions no significant aromatic lithiation could be induced in substrates with a substituent ortho to the acetal (compounds 5-8). One possible explanation is that complexation of the lithium with the acetal oxygen atoms for ortho-deprotonation is sterically inhibited, altered or disfavoured in some way by the ortho substituent in these instances. In fact compound 7 with n-butyl lithium provided a small amount of the benzyl ether 12. The gradual disappearance of the acetal proton in the p.m.r. spectrum of the reaction mixture suggested slow nucleophilic displacement of a methoxyl group by the butyl anion. Furthermore, acetal 8 showed no tendency to lithiate on the ortho-methyl group.

The results reported above thus provide a facile entry to 2,3 and 2,3,4-substituted benzaldehydes. The use of such intermediates in the synthesis of benzylisoquinoline alkaloids and other natural products is now being actively explored. The results obtained with acetal 4 are of particular significance for the development of a simple, unambiguous synthesis of alkaloids like petaline 13 and caseadine 14 which contain the unusual 7-methoxy-8-hydroxy substitution pattern in one benzene ring.

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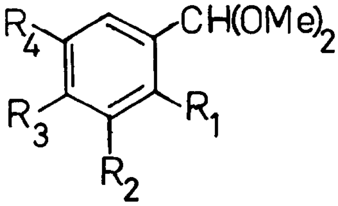
Refererences

1. F. N. Jones, M. F. Zinn, and C. R. Hauser, J. Org. Chem. 28, 663 (1963).
2. D. W. Slocum and C. A. Jennings, J. Org. Chem. 41, 3653 (1976), and references therein.
3. F. E. Ziegler and K. W. Fowler, J. Org. Chem. 41, 1564 (1976).
4. B. C. Nalliah, D. B. MacLean, H. L. Holland and R. Rodrigo, Can. J. Chem. 57, 1545 (1979).
5. All new compounds prepared in this study were fully characterized by elemental analysis and spectroscopic methods.



1 $R_1 = R_4 = H, R_2 + R_3 = OCH_2O$

2 $R_1 = R_4 = H, R_2 = R_3 = OMe$

3 $R_1 = H, R_2 = R_3 = R_4 = OMe$

4 $R_1 = R_4 = H, R_2 = OCH_2OCH_3, R_3 = OMe$

5 $R_1 = R_2 = OMe, R_3 = R_4 = H$

6 $R_1 = R_4 = OMe, R_2 = R_3 = H$

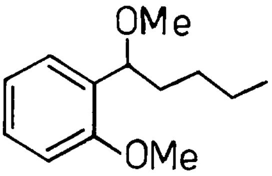
7 $R_1 = OMe, R_2 = R_3 = R_4 = H$

8 $R_1 = Me, R_2 = R_3 = R_4 = H$

9 $R_1 = R_3 = R_4 = H, R_2 = OMe$

10 $R_1 = R_2 = R_4 = H, R_3 = OMe$

11 $R_1 = R_2 = R_3 = R_4 = H$



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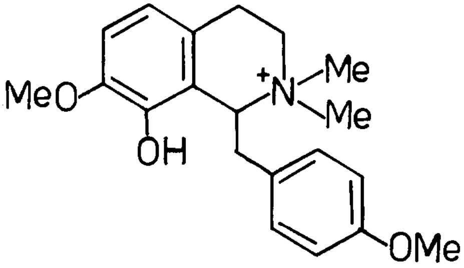

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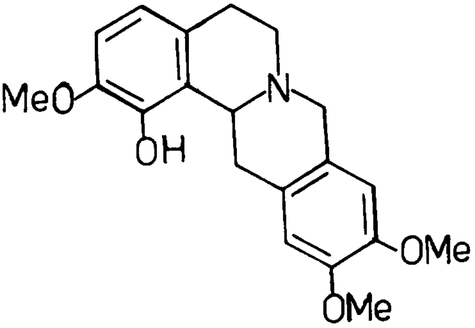

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Acetal	Organolithium	Temperature	Electrophile	Yield of Aldehyde (%)
1	n-BuLi	-78° → 0°	D_2O	> 90[a]
			CO_2	60-80
	t-BuLi	-78°	D_2O	> 90[a]
			CO_2	70-85
			CH_3OCOCl	74
2	n-BuLi	-78°	D_2O	> 90[a]
			CO_2	81
			CH_2O	85
3	n-BuLi	-23°	D_2O	> 90[a]
			CH_3I	68
			CO_2	48
	t-BuLi	-23°, 0°	D_2O	> 95[a]
			CH_3I	95
4	n-BuLi	0°	D_2O	> 95[a]
			CH_3I	84[b]
			DMF	88[b]
5	n-BuLi, n-BuLi-TMEDA	0°, 23°, -78°	CH_3I	no reaction
	t-BuLi	0°, -23°, -78°	CH_3I	complex mixture
6	n-BuLi, n-BuLi-TMEDA	0°, -23°	CH_3I	no reaction
	t-BuLi	0°, -23°, -78°	CH_3I	complex mixture
7	n-BuLi	0°, -23°, -78°	CH_3I	complex mixture
	n-BuLi-TMEDA	0°	CH_3I	no reaction
	t-BuLi	-23°, -78°	CH_3I	complex mixture
		-97°	CH_3I	no reaction
8	n-BuLi, n-BuLi-TMEDA	0°, -23°, -78°	CH_3I	complex mixture
	t-BuLi	-78°	CH_3I	complex mixture
9	n-BuLi	0°, -23°, -78°	CH_3I, D_2O	complex mixture
	t-BuLi	0°, -78°	CH_3I	40[a]
			CO_2	22
10	n-BuLi, n-BuLi-TMEDA	-23°	CH_3I	complex mixture
	t-BuLi	-23°	CH_3I	68
			CO_2	41
11	n-BuLi, t-BuLi	-78°	CH_3I	no reaction
	n-BuLi, n-BuLi-TMEDA	25°, 0°, -23°	CH_3I	complex mixture
	t-BuLi	-78° → 0°	CH_3I	34

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[a] by p.m.r. estimation.

[b] isolated as phenolic aldehydes.

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