

SELECTIVE DEMETHYLATION OF 3,4-DIMETHOXYBENZALDEHYDE

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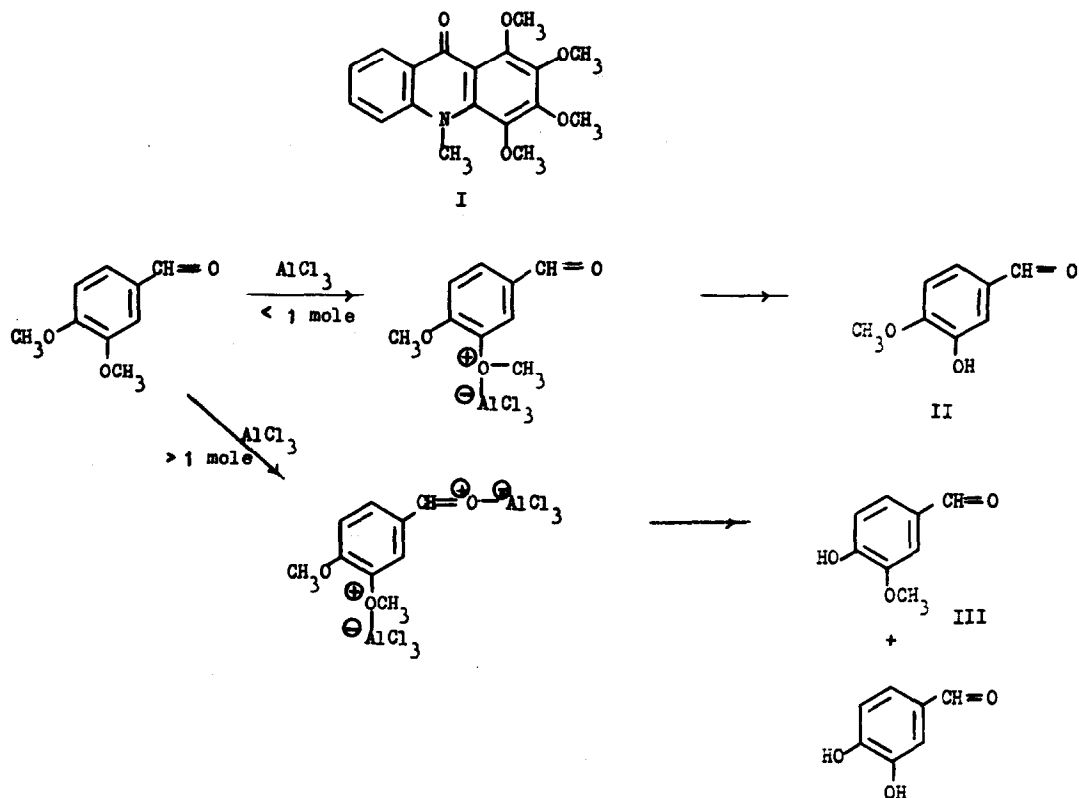
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A recent report by Brossi (1) on the selective acid-catalysed demethylation of the methoxyl group substituted meta to a carbonyl function prompts this report of similar work. We were interested in developing a method for the selective, stepwise demethylation of the acridone alkaloid melicopicine, (I), and chose to use veratraldehyde as a model compound to study the effect of varying the demethylating agent, solvent, and temperature.

The use of Lewis acids, such as aluminium chloride, boron trichloride, boron tribromide and pyridinium hydrochloride was first studied. In agreement with the work of Brossi (1), it was found that with less than one equivalent of the Lewis acid, the product was almost exclusively isovanillin, II, formed by demethylation of the meta-methoxyl group. However, as the relative concentration of the Lewis acid increased, the proportion of vanillin, III, also increased, until at 1.5 moles the monodemethylated material was almost exclusively vanillin. It would thus appear that with higher proportions of the Lewis acid a different demethylation mechanism takes over. An alternative explanation, namely that isovanillin once formed was then more rapidly demethylated than either veratraldehyde or vanillin was ruled out by partially demethylating a mixture of vanillin and isovanillin, when the products were vanillin 26%, isovanillin 25%, and dihydroxybenzaldehyde 49%.

We suggest that Lewis acids preferentially co-ordinate with the most electron-rich ethereal oxygen atom first, and only with excess Lewis acid does co-ordination with the aldehyde occur:-



The results obtained with Lewis acids are tabulated below.

TABLE 1

Demethylation of Veratraldehyde with Lewis Acids

Reagent		Relative % Vanillin II <sup>a</sup>	Relative % Isovanillin III <sup>a</sup>	Relative % Dihydroxy-Benzaldehyde <sup>a</sup>
AlCl <sub>3</sub> <sup>b</sup>	0.5 moles <sup>c</sup>	-	100	-
	0.7	5	95	-
	1.0	35	55	10
	1.5	78	3	19
	2.0	65	2	33
BCl <sub>3</sub> <sup>d</sup>	0.5	-	100	-
	1.5	84	7	9

BBr <sub>3</sub> <sup>e</sup>	0.5	5	95	-
	1.5	50	-	50
Pyridine. HCl <sup>f</sup>	0.25	46	54	-
	0.5	42	39	19
	1.0	-	-	100

<sup>a</sup> Determined by v.p.c. on a 6' SE-100 column at 180°.

<sup>b</sup> In benzene, 40 mins at 90°.

<sup>c</sup> Relative to veratraldehyde.

<sup>d</sup> In light petroleum, 3 hr at 10°.

<sup>e</sup> In benzene, 3 hr at 80°.

<sup>f</sup> 5 min at 180°.

The demethylation of veratraldehyde with diphenylphosphide anion (2) was then studied. It was anticipated that nucleophilic attack would selectively occur at the methoxyl group para to the aldehyde group; in fact the site of attack was dependent on solvent and the cationic species present. The results are tabulated in Table 2.

TABLE 2

Demethylation of Veratraldehyde by Diphenylphosphide anion

Cation	Solvent	Relative %		
		Vanillin	Isovanillin	Dihydroxy-Benzaldehyde
Li <sup>+</sup> , Al <sup>+++ a</sup>	THF <sup>b</sup>	95	5	-
Li <sup>+</sup> , Al <sup>+++ a</sup>	ether <sup>c</sup>	-	100	-
Li <sup>+</sup> d	THF	-	100	-
Li <sup>+</sup> d	ether	-	100	-
Li <sup>+</sup> d	DMF	-	100	-
Na <sup>+</sup> e	THF	f		
Na <sup>+</sup> e	ether	-	100	-

- a Prepared from equivalent amounts of  $\text{LiAlH}_4$  and diphenylphosphine
- b 4 hr at  $60^\circ$
- c 4 hr at  $35^\circ$
- d Prepared from lithium and diphenylphosphine
- e Prepared from sodium and diphenylphosphine
- f Only traces of simple demethylated products were obtained, containing only isovanillin by v.p.c.

We are unable, at present, to offer any satisfactory explanation for the results observed. Several other instances (3,4,5,6) may be cited where the superior co-ordinating properties of tetrahydrofuran for metal ions, prevent those ions forming a complex with the substrate. Although this offers an explanation for differences in runs 1 and 2, it does not offer any explanation for the nucleophilic attack at the more electron-rich methyl group. The observation by Mallion and Mann (7) that the demethylation is slower in the presence of  $\text{Al}^{+++}$  suggests that in the presence of  $\text{Al}^{+++}$ , a different species is reacting.

We conclude that the demethylation of methyl ethers with diphenylphosphide anion is not a simple  $\text{SN}_2$  process (8) and are directing further work in this direction.

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