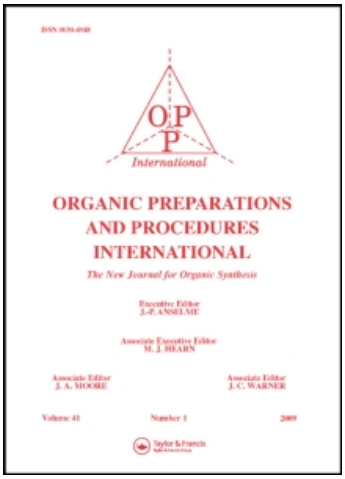

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MONOMETHYLATION OF 3,4-DIHYDROXYBENZALDEHYDE AS AN ALTERNATE ROUTE TO ISOVANILLIN

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the residual oil was purified by column chromatography over silica gel to give pure N-desmethyl mesoridazine (3b, 2.98 g, 40%) as an oil, ^{1}H NMR: δ 1.00-2.10 (m, 9H, addition of D_2O causes it to collapse to a multiplet of 8H, C_3-H_2, C_4-H_2, C_5-H_2, piperidinyl CH_2, NH), 2.30-3.27 (m containing S(O)CH_3 spike at 2.70, 6H, C_2-H, C_6-H_2, S(O)CH_3), 4.03 (app t, J = 7.0 Hz, 2H, phenothiazinyl CH_2), 6.77-7.50 (m, 7H, ArH); EIMS: m/z (rel. int.) 372 (3, $M^{+\cdot}$), 84 (100). A solution of the oil in dry ethanol was treated with benzenesulfonic acid in ethanol and the besylate salt crystallized as white solid, mp. 145-147°, lit.[1] mp. 142-144°.

Anal. Calcd. for $C_{26}H_{30}N_2O_4S_3$: C, 58.87; H, 5.66; N, 5.28; S, 18.11
Found: C, 58.57; H, 6.00; N, 4.94; S, 18.12

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MONOMETHYLATION OF 3,4-DIHYDROXYBENZALDEHYDE AS AN ALTERNATE ROUTE TO ISOVANILLIN

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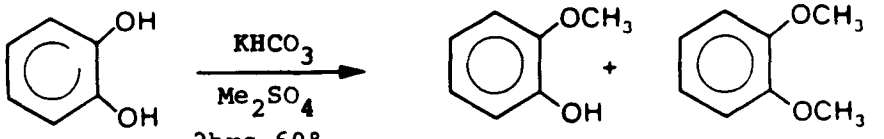
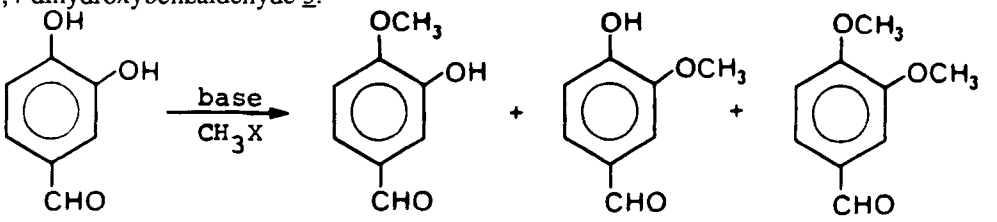
Numerous studies from our laboratory have dealt with alkylations under solid-liquid phase transfer catalysis (PTC) conditions without solvent.[1] The very selective monomethylation of

o-catechol thus led to an attractive preparation of guaiacol using very simple and mild conditions,[2] which constitutes an improved route when compared with the procedures described in a number of patents.[3]



97:3 (72% yield)

Since the conversion of natural vanillin 1 into isovanillin 2 (whose sweetening power is greater) is a problem of current interest, we now report the formation of 2 by monomethylation of 3,4-dihydroxybenzaldehyde 3.



3 2 1 4

Under solid-liquid PTC conditions in the absence of added organic solvent, we tested the following conditions: a) K_2CO_3, $KHCO_3$ or KOH as base, b) Aliquat 336[4] as transfer agent and c) CH_3I as methylating reagent (relative amounts = 1:1:1). After exploratory experiments, the main results obtained at 85° for 5 hrs are as follows.

Conditions	2(%)	1(%)	4(%)
K_2CO_3 (1 eq.)	57	0	14
$KHCO_3$ "	59	0	20
KOH "	50[a)]	0	20
KOH (2.5 eq.)	0	0	98

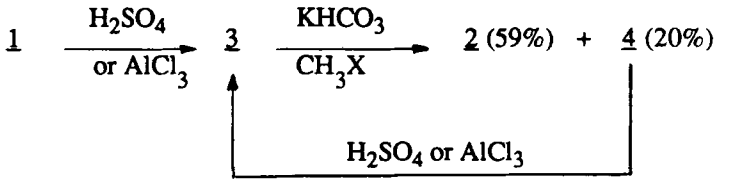
a) In all experiments, yields were only slightly decreased (for instance, 47% in this case) when Aliquat was omitted.

We thus obtained isovanillin 2 selectively as the unique monoalkylated product. It is only accompanied by veratraldehyde 4, from which the separation of 2 is very easy (after acid-base treatment). This observation constitutes a major progress since all previous attempts for selective alkylations were unsuccessful.[5,6] The currently used route to isovanillin 2 from vanillin 1 consists of previous methylation to veratraldehyde 4,[5,7] followed by monodemethylation using H_2SO_4[8] or $AlCl_3$.[9] Unfortunately, this procedure (Scheme 1) leads to a mixture of products 1, 2 and 3 and consequently to a laborious separation of isovanillin 2.

$$1 \xrightarrow[CH_3X]{\text{base}} 4 \xrightarrow[\text{or } AlCl_3]{H_2SO_4} 2 + 3$$

Scheme 1

On the basis of our results, one can now propose a new route to isovanillin 2 (Scheme 2) from 3,4-dihydroxybenzaldehyde 3, which can be itself previously generated from vanillin 1 after demethylation. In this procedure, after removal of 2 (by acid-base treatment), veratraldehyde 4 can be recycled to the starting material 3 by complete demethylation.



Scheme 2

EXPERIMENTAL SECTION

Isovanillin from 3,4-Dihydroxybenzaldehyde.- 3,4-Dihydroxybenzaldehyde 3 (50 mmoles) was mixed with the stoichiometric amount of finely ground potassium carbonate (or potassium hydrogen carbonate). The mixture was then added to methyl iodide (1 mol. eq) containing 2% mol. Aliquat 336, in the absence of any solvent. The mixture was shaken vigorously for 5 min at room temperature and then left in an oil bath at 85° for 5 hrs. The organic products were removed by elution with Et_2O or CH_2Cl_2 after filtration through 4-5 g of Florisil (which retains mineral salts and the catalyst). Analysis was performed by vpc with internal standard (column: Carbowax 20M, 1m; $p(N_2)$ = 2 kg; oven temperature = 210°). Isovanillin was separated from veratraldehyde 4 by extraction with a diluted sodium carbonate solution followed by acidification of the aqueous phase with diluted HCl.

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A CONVENIENT SYNTHESIS OF 2,3-DIBROMOANTHRACENE

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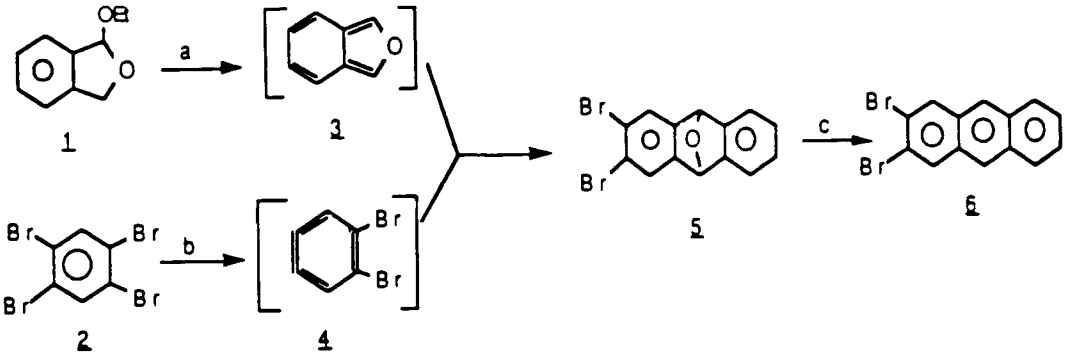
Arynes are useful transient synthetic intermediates which can readily undergo facile Diels-Alder cycloadditions with a variety of dienophiles such as isobenzofurans, furans, pyrroles and butadienes.[1,2]



a) LDA/Et_2O b) MeLi/Et_2O c) Zn/$TiCl_4$/THF or $Fe_2(CO)_9/C_6H_6$

Potential precursors of these arynes are o-dibromoarenes. One such previously unknown arene is 2,3-dibromoanthracene which was recently prepared by Lin and Chou[3] by a three-step procedure. The method of these authors required an autoclave and drastic reaction conditions. The present communication reports the synthesis of the title compound under mild reaction conditions in two steps utilizing the Diels-Alder addition of isobenzofuran (3) and 4,5-dibromobenzyne (4). Thus, the cycloaddition of isobenzofuran (3) and benzyne 4 was conducted according to the procedure of Crump et al.[4] The acetal 1 was treated with methyllithium and a catalytic amount of diisopropylamine followed by treatment with 1,2,4,5-tetrabromobenzene (2) and methyllithium to yield 2,3-dibromo-9,10-epoxy-9,10-