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LITHIATION OF 6-METHOXY 1,4-BENZODIOXAN: FUNCTIONALIZATION AT THE 5-POSITION

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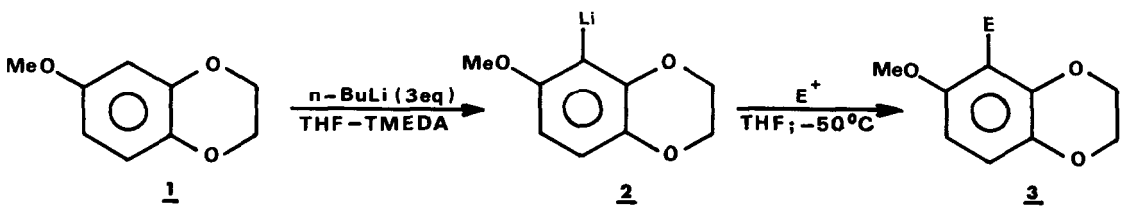
Summary: 6-Methoxy 1,4-benzodioxan 1 undergoes O-lithiation with n-butyllithium to give the intermediate lithio derivative 2. Reaction of 2 with various electrophiles affords 5-substituted 6-methoxy 1,4-benzodioxans 3.

The 1,4-benzodioxan structure is present in many natural products such as neolignans[1] and several synthetic derivatives exhibiting biological activity[2]. However despite extensive work in this area the introduction of substituents on the aromatic nucleus of 1,4-benzodioxans remains somewhat difficult owing to the formation of structural isomers[3].

In connection with studies directed toward the synthesis of various coumarins, we needed 6-alkoxy and 6-hydroxy 1,4-benzodioxans substituted at the 5 position. We describe here the preparation of such compounds from the 6-methoxy 1,4-benzodioxan 1 readily obtained from the commercialy available 6-amino 1,4 benzodioxan[4].

Deprotonation of alkyl aryl ethers with strong bases is a well established procedure[5].However the formation of the lithio derivative 2 by treatment of 1 with n-butyllithium is still problematic and requires definite conditions of temperature. Low temperatures ($< -50°C$) give incomplete deprotonation whereas higher ones ($> -30°C$) induce a cleavage of the benzodioxan ring[6]. However the treatment of 1 at - 50°C with three equivalents of n-butyllithium in tetrahydrofuran in the presence of six equivalents of N,N,N',N'-tetramethylenediamine (TMEDA)[7] readily affords the lithio derivative 2. This carbanion subsequently reacts, at - 50°C, with various electrophiles (6 equivalents) to give compounds 3 in fair to excellent yields[8]. The results are summarized in the table.



1 2 3

Replacement of the methoxy group by methoxyethoxymethyl (MEM) or methoxymethyl (MOM) produces an important lowering of the yields.

Table: Preparation of compounds 3

	Electrophile	Yield[(a)]	m.p.	E in product
a	D_2O	80	oil	D
b	MeI	72	38	Me
c	Me_3SiCl	92	oil	Me_3Si
d	Me_2CO[(b)]	44	oil	Me_2COH
e	Ph_2CO	72	143	Ph_2COH
f	$(CH_2)_5$ CO	82	oil	$(CH_2)_5COH$
g	Me_2N-CHO	66[(c,d)]	124	CHO
h	$CH_3(CH_2)_6CHO$	87	oil	$CH_3(CH_2)_6CHOH$
i	PhCHO	84	oil	PhCHOH

(a) Yield of pure product isolated by silica gel column chromatography. Not optimized; (b) 51% of starting material 1 recovered; (c) in those reaction conditions, n-BuLi does not react significantly with the formed aldehyde 3g; (d) N-formyl piperidine as electrophilic reagent gives 60% yield.

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(8) All compounds 3 gave IR, ^{1}HNMR and Microanalyses consistent with the assigned structures.

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