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THE USE OF NOVEL ARENE-CHROMIUM COMPLEXES TO ACHIEVE THE REGIOCONTROLLED ALKYLATION OF 1,4-BENZODIOXINS

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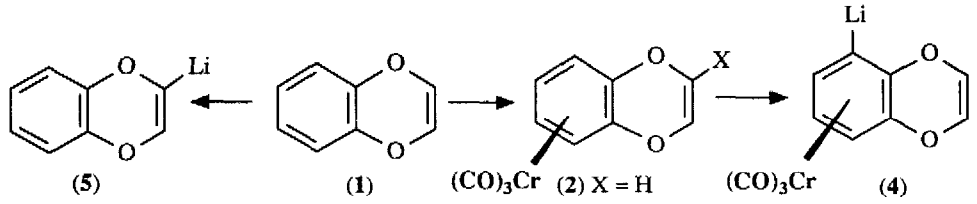
Summary:- The novel formation of an η^6-arene tricarbonylchromium complex of benzodioxin (1) allows, via metalation and alkylation, functionalisation at the C-5 position in contrast to such reactions proceeding at C-2 in the uncomplexed molecule.

Recently there has been an increase in interest in the chemistry of benzodioxins[1-7], stimulated by studies into their pharmacological profile, which indicate that they are of potential medicinal value. Most of this work has centred upon functionalising the 2-position of this oxygen heterocycle, as typified by a recent report of ours upon a simple and efficient method for preparing 2-alkenyl and 2-aryl substituted benzodioxins[8].

However it would also be of value to be able to functionalise other positions with equal facility. Unfortunately the greater acidity of the protons at C-2 and C-3 restrict the use of an obvious aryl metalation strategy for functionalisation on the aryl ring (unless one initially blocks these positions by means of a lengthy protection sequence). Additionally the enhanced nucleophilicity of these positions places a similar restriction on the use of an electrophilic substitution approach. Despite these limitations the first option may be possible since there are methods available for increasing the relative acidity of aryl protons, one of which involves the formation of an η^6-arene metal complex[9]. We now describe how such an approach allows regiochemical control in the alkylation of benzodioxin.

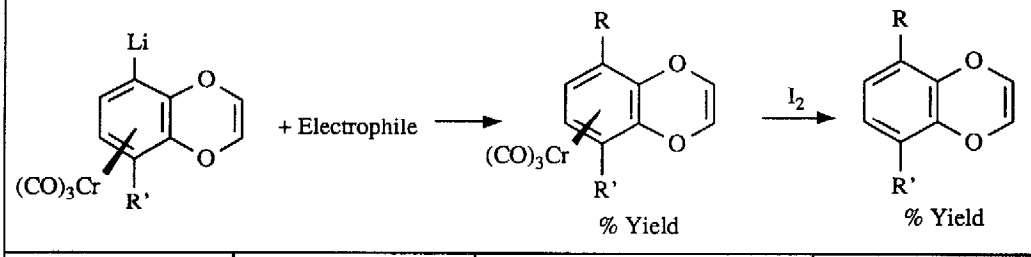
Reaction of benzo-1,4-dioxin (**1**) with chromium hexacarbonyl gives a modest 41% yield of the η^6-arene chromium complex (**2**)[10], with only a slight increase in yield (46%) being seen in a similar reaction of the



2-trimethylsilyl derivative (**3**). Not unexpectedly the reaction showed no trace of complexation in the hetero ring, since there is substantial evidence[11] to indicate the non aromaticity of this ring. Reaction of the chromium complex (**2**) with n-BuLi forms a yellow solution, corresponding to the aryl lithium (**4**). Reaction with a range of electrophiles (**TABLE**) gives exclusively a series of 5-substituted derivatives in modest yield, each of which is readily oxidatively decomplexed to form the useful 5-substituted benzo-1,4-dioxin. These

results contrast and complement the reaction of the uncomplexed benzodioxin which forms the 2-lithio species (**5**) only. The position of lithiation in the aryl ring is presumably controlled by an ortho stabilisation effect, which can, as shown, be extended to the formation and alkylation of a 5,8-dilithio compound (**6**).

TABLE



		% Yield	% Yield
R' = H	Me_3Si — Cl	R = $SiMe_3$ R' = H	R = $SiMe_3$ R' = H
		46 %	77 %
R' = H	$PhCH_2$ – Br	R = CH_2Ph R' = H	R = CH_2Ph R' = H
		51 %	69 %
R' = H		R = Me_2COH R' = H	R = Me_2COH R' = H
		38 %	73 %
R' = Li	$PhCH_2$ – Br	R = R' = CH_2Ph	R = R' = CH_2Ph
(**6**)	(2 equiv.)	52 %	78 %

The use of arene metal complexes to control the regiochemistry of substituted benzenes is now well established[12] and its use for controlling the regiochemistry of alkylation in benzodioxins offers considerable scope for achieving selective substitution of these useful compounds. For instance one can readily conceive of now being able to introduce up to four different groups into positions 2, 3, 5, and 8 of this nuclei, which will be of great value in future studies.

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9. For a recent example of the alkylation of indoles in this manner see:- Beswick, P.J; Greenwood, C.S; Mowlem, T.J; Nechteval, G; Widdowson, D.A. *Tetrahedron*, **1988**, 44, 7325.
10. All new compounds gave satisfactory analytical and/or spectroscopic data. The position of alkylation was determined by examination of the aryl signals in the ^{13}C and ^{1}H high field nmr spectrum. In all reactions the careful examination of crude reaction mixtures showed the presence of only one alkylated product in every case.
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