Pergamon

Tetrahedron Letters, Vol. 36, No. 40, pp. 7327-7328, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01510-8

Selective Lithiation of Phloroglucinol Mixed Alkyl Ethers. The Synthesis of Pseudoaspidinol-B.

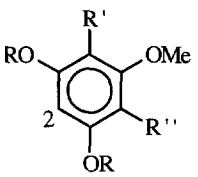
Aija Halonen and Tapio A. Hase*

Department of Chemistry, University of Helsinki
P.O. Box 55, 00014 UNIVERSITY, Finland

Abstract: The title reaction is regioselective with the methyl di-*t*-butyl ether (**4**) but not with the di-*i*-propyl analogue (**3**).

The directed ortho lithiation reaction[1] is a versatile method for preparing highly substituted aromatic compounds that may be difficult to obtain by more classical techniques. Using appropriate substituents and protecting groups it is possible to add a new substituent to a required ring site with a very high selectivity.[2] The acylphloroglucinols, a major group of secondary metabolites occurring in ferns, lichens and certain higher plants,[3] offer a good target for studies of lithiation of variously protected phloroglucinols. The lithiation (and polylithiation) of the parent 1,3,5-trimethoxybenzene has been shown[4] to proceed reasonably well but it is clear that other starting materials would be more convenient if one or two of the target acylphloroglucinol hydroxyls are free. We demonstrate here an entry to such unsymmetrical acylphloroglucinols, using pseudoaspidinol-B (**1**)[5] as an example.

For the desymmetrization of the commercially available 5-methoxyresorcinol (**2**), we expected that derivatization to the di-*i*-propylether (**3**) would provide sufficient steric congestion at C-2 to favour lithiation at C-4 or C-6 (which are equivalent). Metalations of *m*-dialkoxybenzenes, including the di-*i*-propoxy derivative, have been studied previously[6] but these test substrates lacked any further alkoxy substituents on the ring. It was also assumed that the ultimate cleavage of the *i*-propyl groups would be possible in preference to the methoxy group.[7] In the event, lithiation (*n*-BuLi) of **3** and reaction with an electrophile (MeI, Et_2SO_4, or butanal) gave ca. 1:3 mixtures of C-2/C-4 products in 45-72% yield, showing that two *i*-propoxy groups *meta* to each other do not give full protection for the intermediate site towards lithiation and/or for the subsequent alkylation. The size or nature of the electrophile did not have any effect on the C-2/C-4 isomer ratio which presumably means that once formed the two lithio intermediates do not interconvert.

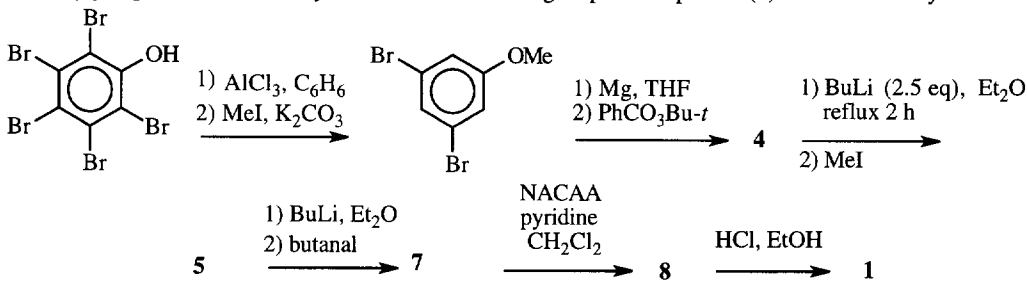


	R	R'	R''
1	H	Me	$COCH_2CH_2CH_3$
2	H	H	H
3	Pr-*i*	H	H
4	Bu-*t*	H	H
5	Bu-*t*	Me	H
6	Bu-*t*	Me	D
7	Bu-*t*	Me	$CHOH\text{-}CH_2CH_2CH_3$
8	Bu-*t*	Me	$COCH_2CH_2CH_3$

Failing to obtain sufficient site selectivity by *i*-propyl blocking, a natural next choice was to use *t*-butyl groups. There are a number of reports[6,8] where simple *t*-butoxybenzenes were tested for lithiation but the *t*-butoxy group was said to be decomposed during the metalation. In view of our success with these derivatives (see below) we suspect that the previous failures may have been due to the use of acidic work-up conditions or perhaps even chromatography on silica which we discovered was also incompatible with these sensitive compounds. On the other hand, the increased lability of the *t*-butyl groups would of course be very helpful when carrying out the final deprotection step.

In our hands, the various literature procedures[9] for the *t*-butylation of phenolic hydroxyl groups were completely unsuccessful when tested on **2**. The required di-*t*-butylether (**4**) was obtained by the double

grignardization[10] and reaction with *t*-butylperbenzoate[11] of 3,5-dibromoanisole, available from pentabromophenol by an electrophilic aromatic *retro*-bromination.[12] Lithiation and methylation of (**4**) gave (**5**) in high yield and with almost complete regioselectivity, there being less than 2 % of the unwanted isomer. The two *t*-butoxy groups thus very efficiently shield the ring site that they flank on both sides. As mentioned above, the product (**5**) could not be purified by flash chromatography and was carried as such over the next steps. For the introduction of the acyl group, **5** was lithiated and treated with a variety of acylating reagents, including the nitrile and the *N*-methoxy-*N*-methylamide.[13] These attempts were unsuccessful, perhaps owing to the easy deprotonation of these electrophiles. A control reaction with D_2O as the electrophile (giving **6** in 84 % recovery and 80 % isotopic purity) showed that the problem was indeed in the acylation step and not the lithiation step and that the lithiation of **5** (and **4**) is fully regioselective. Lithio-**5** was thus reacted with butanal to give the alcohol **7** which was oxidized to the ketone **8** using the NACAA (nicotinic-chromic anhydride) oxidant.[14] The *tert*-butyl blocking groups were removed by treatment with acid to give pseudoaspidinol (**1**) in 22% overall yield from **4**.



We feel that the above approach offers distinct advantages over the more traditional syntheses of pseudoaspidinols and related compounds.[15] Although overall yields remain modest, the formation and difficult separations of regioisomers are avoided in contrast to the previous syntheses that rely on methoxycarbonyl blocking of the ring site ortho to two hydroxyls.

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(*Received in UK* 2 *June* 1995; *revised* 8 *August* 1995; *accepted* 11 *August* 1995)