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A Novel Cyclodehydration Reaction of Hydroxy-phenols using Imidate Esters as Leaving Groups

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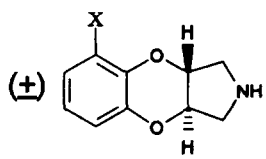
Abstract A mild, efficient and stereospecific intramolecular method for converting hydroxy-phenols into benzodioxans, dihydrobenzopyrans and dihydrobenzofurans *via* imidate esters, and suitable for large scale operation is described.

Tetrahydro-1H-benzodioxino[2,3-c]pyrroles are potent and selective α_2-adrenoreceptor antagonists[1] and the 5-fluoro analogue, Fluparoxan **1** is currently undergoing clinical trials for the treatment of male sexual dysfunction.



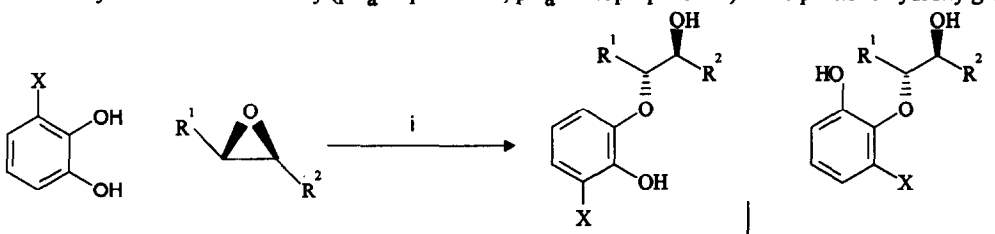
1 X=F

2 X=H

One synthetic route for the preparation of **1, 2** and their analogues using cheap and readily available starting materials involved the condensation of catechols **3** or **4** with *trans*-substituted epoxides **5-7** under basic conditions to give the hydroxy-phenols **8** in good yields. In the case of the substituted catechols, such as **4**, reaction with epoxide **5** gave the two regioisomeric *anti*-hydroxy-phenols **8** and **9** which were separable by chromatography in 48% and 14% yields respectively. Cyclodehydration of **8** (X=H, R^1=R^2= $-CH_2OCH_2Ph$) using the Mitsunobu reaction[2], triphenylphosphine-diethyl azodicarboxylate in refluxing acetonitrile or tetrahydrofuran, or using triphenylphosphine-carbon tetrachloride-triethylamine in refluxing acetonitrile, a variant of the Mitsunobu reaction which has been used[3] for the cyclodehydration of simple alkyl 1,4-diols, the benzodioxan **10** was obtained in 90% yield. Diethyl azodicarboxylate is, however, unstable and potentially explosive and carbon tetrachloride is toxic; furthermore chromatographic separation of the byproducts, triphenylphosphine oxide and diethyl hydrazinedicarboxylate, was necessary which made both of these reactions totally unsuitable for large scale preparations. Another reagent was therefore sought that could effect the cyclisation of **8** efficiently, with complete inversion of configuration and without the disadvantages mentioned above. No cyclisation occurred when polyphosphoric acid trimethylsilyl ester[4] and p-toluenesulphonyl chloride in 2,6-lutidine[5] were employed.

Reaction between Vilsmeier reagents and alcohols provides imidate esters which are known to produce alkyl halides[6] and amides at elevated temperatures. More recently alkyl trichloroacetimidates have found

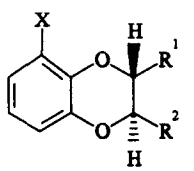
synthetic utility as etherifying[7,8] or esterifying agents[8]. We envisaged that reaction between the Vilsmeier reagent (chloromethylene)dimethylammonium chloride $ClCH{=}NMe_2^+\ Cl^-$ **11** and hydroxy-phenol **8** would provide the alkyl imidate **12** selectively (pK_a of phenol 10, pK_a of isopropanol 18). The phenolic hydroxy group



3 X=H
4 X=F

5 $R^1=R^2=$-CH_2OCH_2Ph
6 $R^1=R^2=$-CH_2OBu^t
7 $R^1=$-CH_2OCH_2Ph
$R^2=$-$CH_2CH_2OCH_2Ph$

8 **9**



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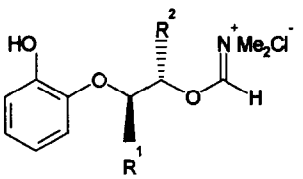
i NaH, EtOH, reflux or K_2CO_3, DMF, 100°C; ii **11**, CH_2Cl_2; Et_3N



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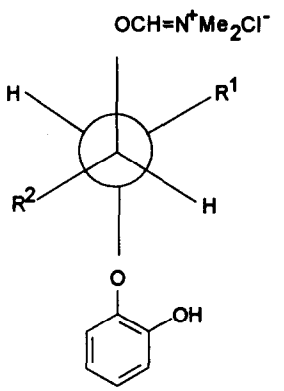


A

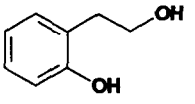
would then be set up for an intramolecular nucleophilic displacement of dimethyl formamide in preference to intermolecular chloride displacement (structure A). Thus reaction of **8** (X=H, $R^1= R^2=$ -CH_2OCH_2Ph) with 1.1 equivalents of **11**, readily prepared from dimethyl formamide and oxalyl chloride, gave exclusively **12** whose structure was confirmed by isolation of its formate ester following hydrolysis. Addition of excess triethylamine

to a dichloromethane solution of the intermediate **12** at room temperature gave the *trans*-benzodioxan **10** (X=H, $R^1 = R^2 = -CH_2OCH_2Ph$) in 78% yield which was identical with the product derived by the Mitsunobu procedure. The absence of the *cis*-isomer of **10** (NMR and GC) indicated that the reaction proceeded with complete inversion of configuration. The reaction was successfully repeated on multi-kilogram quantities in pilot plant operations. This novel cyclisation procedure was then applied to other analogues of **8** which are shown in the table. *t*-Butyl as well as benzyl protecting groups are equally effective under the cyclisation conditions (entries 1 and 2). Cyclisation of **8** and **9** individually or as a mixture provided **10** (entries 3 and 4). The reaction also works well with other hydroxy-phenols such as **13** or **14** providing five- or six- membered rings respectively (entries 6 and 7). Attempts to cyclise the *syn* hydroxy-phenol **17** at room temperature were unsuccessful; however in refluxing chloroform the reaction proceeded slowly and while the intermediate imidate ester was still present after five days, work-up provided the benzodioxan in 35% yield in a ratio of 95:5 **18** : **10** (X=H, $R^1 = R^2 = -CH_2OCH_2Ph$). As anticipated the antiperiplanar disposition of the nucleophile with the leaving group would place the substituent groups R in a severely congested environment (structure B). Consequently the intermolecular chloride displacement starts to compete with the cyclisation and the derived chloride can then react further to provide the small amount of the observed *trans*-benzodioxan.

In conclusion the cyclisation reaction of *anti*-hydroxy-phenols described above is a mild and efficient, one-pot procedure. Furthermore, since it utilises cheap and readily available reagents, the procedure is amenable to large scale operation.

Table

Entry		Substrate	Product	Yield (%)
1	**8**	X=H $R^1 = R^2 = -CH_2OCH_2Ph$	**10**	78
2	**8**	X=H $R^1 = R^2 = -CH_2OBu^t$	**10**	70
3	**8**	X=F $R^1 = R^2 = -CH_2OCH_2Ph$	**10**	77
4	**8 + 9**	X=F $R^1 = R^2 = -CH_2OCH_2Ph$	**10**	77
5	**8**	X=H $R^1 = -CH_2OCH_2Ph$ $R^2 = -CH_2OCH_2CH_2Ph$	**10**	72
6	**13**		**15**	80
7	**14**		**16**	78
8	**17**		**18**	35



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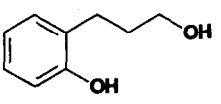

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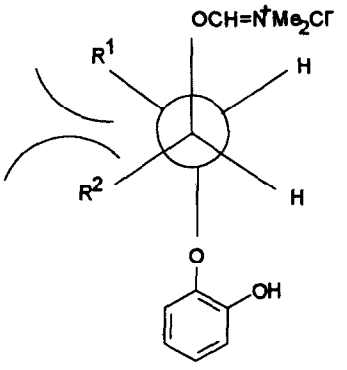

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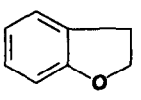

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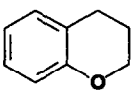

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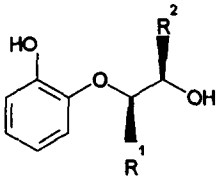

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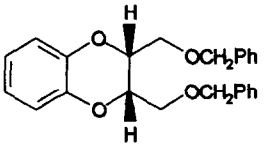

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