

Synthesis of 3-substituted and 2,3-disubstituted 4-chlorofurans

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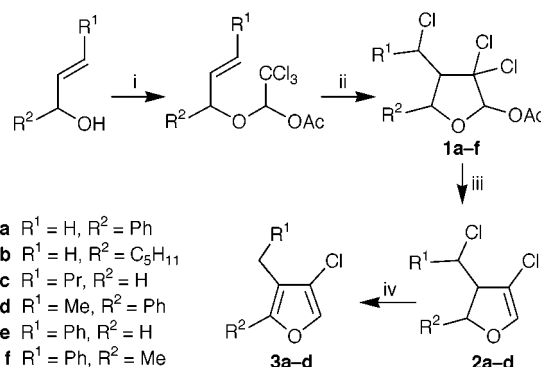
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A simple method for the synthesis of 3-substituted and 2,3-disubstituted 4-chlorofurans is described which involves CuCl/bipy-catalysed regioselective cyclisation of 1-acetoxy-2,2,2-trichloroethyl allyl ethers followed successively by dechloroacetoxylation with Zn dust and tandem dehydrohalogenation–aromatisation with Bu^tOK/18-crown-6.

The synthesis of variously substituted furans continues to be of considerable interest¹ due to the presence of the furan nucleus in commercially important pharmaceuticals,² flavors³ and a variety of naturally occurring biologically active compounds.⁴ Furans also serve as useful synthetic intermediates for the synthesis of aromatic, alicyclic and acyclic molecules.⁵ Since furans undergo electrophilic substitution and lithiation at the 2- and 5-positions, bypassing any of these positions to substitute the 3- and/or 4-positions is not straightforward. Therefore, β -mono-, di- and tri-substituted furans having either or both of the 2- and 5-positions unsubstituted are generally synthesised *via* acyclic routes. If the substituent happens to be a functional group, particularly at the 3- and/or 4-position(s), a variety of furans can be prepared by simple functional group transformations, thus widening the scope of the synthesis. In this respect, bromo and iodo groups have served particularly well by undergoing replacement with alkyl, alkenyl, alkynyl, aryl, heteroaryl, formyl and acyl groups.^{5a,6} Since the chloro compounds, in general, are less expensive and more stable, there is considerable current interest in the replacement of the chloro group of aryl and vinyl chlorides with carbon groups.⁷ However, there are very few reported methods for the preparation of 3- and/or 4-chlorofurans.⁸ Furthermore, these methods have their own limitations with regard to yields,^{8a} the nature of the other substituents^{8b,e} and the substitution pattern.^{8b–e,9} Therefore, herein we disclose a simple, new and broader route to prepare 3-substituted and 2,3-disubstituted 4-chlorofurans, which also complements the few reported methods for 3- and/or 4-chlorofuran synthesis.

Our interest in the chemistry of reactive aldehydes and metal-ion-promoted reactions¹⁰ led us to use a reaction analogous to the reported¹¹ Cu^I-catalysed cyclisation of β -chloroethyl allyl ethers as the key step for the present synthesis. Thus, chloral hemiacetals, prepared by simply mixing chloral with readily accessible allylic alcohols, after protection as acetates, underwent regioselective cyclisation with CuCl/bipy, as expected, to afford the tetrahydrofurans **1a–f**. Dechloroacetoxylation of **1a–d** with Zn dust gave the 2,3-dihydrofurans **2a–d** as stereoisomeric mixtures in 61–81% overall yields. Dehydrochlorination of **2a–d** with KOH/EtOH followed by isomerisation of the crude isofurans with catalytic amounts of conc. H₂SO₄ and purification thereafter by column chromatography (silica gel, *n*-hexane) furnished the 4-chlorofurans **3a–d** in 31–65% overall yields (starting from the allyl alcohols). When the dehydrochlorination was performed with Bu^tOK/18-crown-6/THF, tandem isomerisation of isofurans was observed, giving the 4-chlorofurans **3a–d** in better overall yields (51–74%) (Scheme 1).

During dechloroacetoxylation, reduction of the benzylic chloro group was observed in the case of **1e–f**. The 4-chlorofuran **3e** was, however, prepared in 81% overall yield by a simple modification involving preparation of trichloroethyl



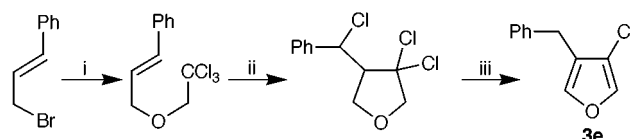
Scheme 1 Reagents and conditions: i, CCl₃CHO, 2 h, then Ac₂O, pyridine, DMAP, room temp., overnight; ii, 30 mol% of CuCl/bipy (1:1 mixture), 1,2-dichloroethane, reflux, 2 h; iii, Zn, THF, reflux, 4 h; iv, Bu^tOK, 18-crown-6, THF, reflux, 10 h.

cinnamyl ether by the reaction of trichloroethanol with cinnamyl bromide, followed by CuCl/bipy cyclisation and dehydrochlorination with DBU (Scheme 2).¹²

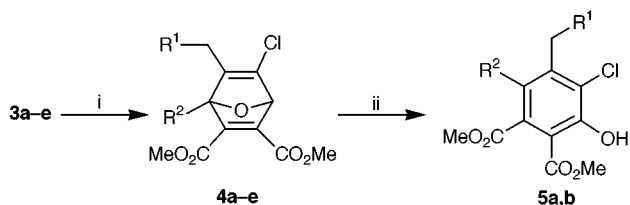
These chlorofurans are fairly stable in hydrocarbon solvents but tend to deteriorate in chlorinated or oxygenated solvents. The decomposition is faster when they are stored as neat liquids.

All the compounds have been characterised by IR, NMR and mass spectral studies. The chlorofurans **3** were also characterised by their transformation into the Diels–Alder adducts **4** on reaction with dimethyl acetylenedicarboxylate. In the case of **3a**, the reaction proceeded further to give the phenol **5a** under the reaction conditions used (neat, 100 °C, 10 h). The furan **3b** gave a mixture of the cycloadduct **4b** and the phenol **5b**, which was completely converted into the phenol **5b** on slight warming with BF₃·OEt₂ (Scheme 3).

An additional advantage of the present method of furan synthesis is that it can be used to prepare 2,3-dihydrofurans as well, which, like furans, are also widely distributed in Nature¹³ and are useful synthetic intermediates.^{5c,14} This advantage is not



Scheme 2 Reagents and conditions: i, CCl₃CH₂OH, K₂CO₃, acetone, reflux, 6 h; ii, 30 mol% of CuCl/bipy (1:1 mixture), 1,2-dichloroethane, reflux, 2.5 h; iii, DBU, benzene, reflux, 3 h.



Scheme 3 Reagents and conditions: i, DMAD, 100 °C, 10 h; ii, BF₃·OEt₂, 40–50 °C.

available with the existing methods of β -chlorofuran synthesis. We expect that in the present method of furan synthesis the chloro group might provide a branching point in the synthetic tree at the 2,3-dihydrofuran or furan stage or later during synthetic applications, to give access to a variety of di-, tri- and tetra-substituted furans and other interesting molecules.

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