ChemComm

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

Ram N. Ram* and I. Charles

Department of Chemistry, Indian Institute of Technology, Delhi, Hauz Khas, New Delhi - 110 016, India.
E-mail: rnram@chemistry.iitd.ernet.in

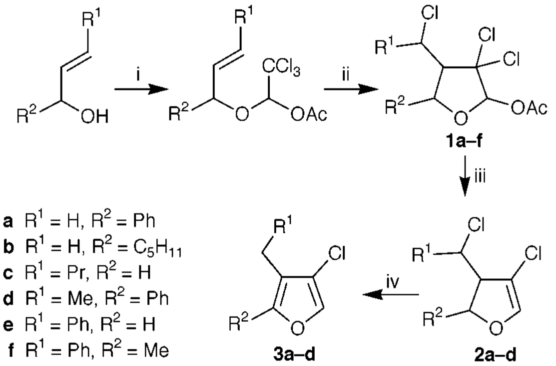
Received (in Cambridge, UK) 8th September 1999, Accepted 1st October 1999

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 $\mathrm{Bu^tOK}$/18-crown-6.

The synthesis of variously substituted furans continues to be of considerable interest[1] due to the presence of the furan nucleus in commercially important pharmaceuticals,[2] flavors[3] 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 reactions[10] led us to use a reaction analogous to the reported[11] $\mathrm{Cu^I}$-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. H_2SO_4 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 $\mathrm{Bu^tOK}$/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 cinnamyl ether by the reaction of trichloroethanol with cinnamyl bromide, followed by CuCl/bipy cyclisation and dehydrochlorination with DBU (Scheme 2).[12]

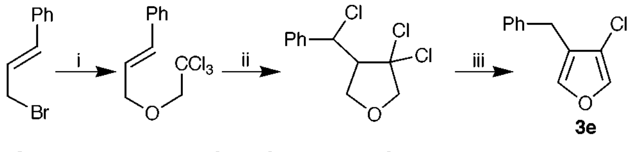


Scheme 1 *Reagents and conditions*: i, CCl_3CHO, 2 h, then Ac_2O, pyridine, DMAP, room temp., overnight; ii, 30 mol% of CuCl/bipy (1 : 1 mixture), 1,2-dichloroethane, reflux, 2 h; iii, Zn, THF, reflux, 4 h; iv, $\mathrm{Bu^tOK}$, 18-crown-6, THF, reflux, 10 h.

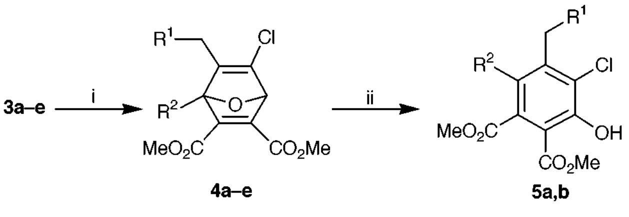
These chlorofurans are fairly stable in hydrocarbon solvents but tend to deteriorate in chlorinated or oxygenated solvents. The decomposition is faster when they are stored as neat liquids.

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 $BF_3\cdot OEt_2$ (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 Nature[13] and are useful synthetic intermediates.[5c,14] This advantage is not



Scheme 2 *Reagents and conditions*: i, CCl_3CH_2OH, K_2CO_3, 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, $BF_3\cdot OEt_2$, 40–50 °C.

This journal is © The Royal Society of Chemistry 1999

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.

Financial assistance by the DST, New Delhi, is gratefully acknowledged.

Notes and references

1 For a general review, see: X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong and H. N. C. Wong, *Tetrahedron*, 1998, **54**, 1955. For some recent examples, see: J. W. Herndon and H. Wang, *J. Org. Chem.*, 1998, **63**, 4564; P. Wipf, L. T. Rahman and S. R. Rector, *J. Org. Chem.*, 1998, **63**, 7132; E. Bures, J. A. Nieman, S. Yu, P. G. Spinazzé, J.-L. J. Bontront, I. R. Hunt, A. Rauk and B. A. Keay, *J. Org. Chem.*, 1997, **62**, 8750; Y. R. Lee, N. S. Kim and B. S. Kim, *Tetrahedron Lett.*, 1997, **38**, 5671.

2 K. Nakanishi, *Natural Products Chemistry*, Kodansha, Tokyo, 1974.

3 *The Chemistry of Heterocyclic Flavouring and Aroma Compounds*, ed. G. Vernin, Ellis Horwood, Chichester, 1982.

4 For review, see: P. Bosshard and C. H. Eugster, *Adv. Heterocycl. Chem.*, 1966, **7**, 378; F. M. Dean, *Adv. Heterocycl. Chem.*, 1982, **30**, 167; D. M. X. Donnelly and M. J. Meegan, *Comp. Heterocycl. Chem.*, 1984, **4**, 657. For recent examples, see: K.-S. Chen and Y.-C. Wu, *Tetrahedron*, 1999, **55**, 1353; A. Arnone, C. D. Gregorio, G. Nasini and O. V. De Pava, *Tetrahedron*, 1998, **54**, 10199.

5 For review, see: (*a*) B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795. For some recent examples, see: (*b*) D. Meng and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 1999, **38**, 1485; (c) R. H. Mitchell, T. R. Ward, Y. Wang and P. W. Dibble, *J. Am. Chem. Soc.*, 1999, **121**, 2601; (*d*) W. E. Noland and B. L. Kedrowski, *J. Org. Chem.*, 1999, **64**, 596; (*e*) J. M. Harris, M. D. Keranen and G. A. O'Doherty, *J. Org. Chem.*, 1999, **64**, 2982; (*f*) A. Padwa, M. A. Brodney, B. Liu, K. Satake and T. Wu, *J. Org. Chem.*, 1999, **64**, 3595; (g) A. Frustner and H. Weintritt, *J. Am. Chem. Soc.*, 1998, **120**, 2817; (*h*) M. Kurosu, L. R. Marcin, T. J. Grinsteiner and Y. Kishi, *J. Am. Chem. Soc.*, 1998, **120**, 6627.

6 T. Bach and L. Krüger, *Tetrahedron Lett.*, 1998, **39**, 1729; M. K. Wong, C. Y. Leung and H. N. C. Wong, *Tetrahedron*, 1997, **53**, 3497; C. Alvarez-Ibarra, M. L. Quiroga and E. Toledano, *Tetrahedron*, 1996, **52**, 4065; S. P. Bew and D. W. Knight, *Chem. Commun.*, 1996, 1007; H. J. Reich and R. E. Olson, *J. Org. Chem.*, 1987, **52**, 2315; L. N. Pridgen and S. S. Jones, *J. Org. Chem.*, 1982, **47**, 1590.

7 C. Zhang, J. Huang, M. L. Trudell and S. P. Nolan, *J. Org. Chem.*, 1999, **64**, 3804; B. H. Lipshutz, P. A. Blomgren and S.-K. Kim, *Tetrahedron Lett.*, 1999, **40**, 197; X. Bei, T. Crevier, A. S. Guram, B. Jandeleit, T. S. Powers, H. W. Turner, T. Uno and W. H. Weinberg, *Tetrahedron Lett.*, 1999, **40**. 3855; B. H. Lipshutz and P. A. Blomgren, *J. Am. Chem. Soc.*, 1999, **121**, 5819; D. W. Old, J. P. Wolfe and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 9722; A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 1998, **37**, 3387; S. Saito, S. Oh-tani and N. Miyaura, *J. Org. Chem.*, 1997, **62**, 8024.

8 (*a*) R. C. Larock and C.-L. Liu, *J. Org. Chem.*, 1983, **48**, 2151 (poor yields); (*b*) Y. Tanabe, K.-i. Wakimura, Y. Nishii and Y. Muroya, *Synthesis*, 1996, 388 (2,5-diaryl-3-chlorofurans); (*c*) D. Obrecht, *Helv. Chem. Acta.*, 1989, **72**, 447 (2-substituted and 2,5-disubstituted 3-chlorofurans); (*d*) N. D. Ly and M. Schlosser, *Helv. Chem. Acta.*, 1977, **60**, 2085 (2-prenyl-3-chlorofuran); (*e*) R. E. Lutz and M. G. Reese, *J. Am. Chem. Soc.*, 1959, **81**, 127 (2,5-diaryl-3-chlorofurans).

9 In fact, we could find no report on 3-substituted 4-chlorofurans and only one report on 2,3-disubstituted 4-chlorofurans in which the formation of two 2,3-disubstituted 4-chlorofuran derivatives has been described. These chlorofurans were obtained as a mixture in poor yields, one of which was characterised only by GC-MS [ref. 8(*a*)].

10 L. Singh and R. N. Ram, *J. Org. Chem.*, 1994, **59**, 710; R. N. Ram and I. Charles, *Tetrahedron*, 1997, **53**, 7335; R. N. Ram and L. Singh, *Tetrahedron Lett.*, 1995, **36**, 5401.

11 J. H. Udding, H. Hiemstra, M. N. A. Van Zanden and W. N. Speckamp, *Tetrahedron Lett.*, 1991, **32**, 3123.

12 Although this scheme seems to be more attractive than Scheme 1, both in the number of steps and overall yields, we were not successful in preparing other trichloroethyl ethers by condensing trichloroethanol with secondary allylic halides.

13 P. F. Schuda, *Top. Curr. Chem.*, 1980, **91**, 75.

14 T. Saito, M. M. Suzuki, T. C. Akiyama, T. Takeuchi, T. Matsumoto and K. Suzuki, *J. Am. Chem. Soc.*, 1998, **120**, 11 633; S. Wadman, R. Whitby, C. Yeates, P. Kocienski and K. Cooper, *J. Chem. Soc., Chem. Commun.*, 1987, 241; A. I. Meyers, C. J. Andres, J. E. Resek, Maureen A. Melaughlin, Charlotte C. Woodall and P. H. Lee, *J. Org. Chem.*, 1996, **61**, 2586; G. Vidari, G. Lanfranchi, P. Sartori and S. Serra, *Tetrahedron: Asymmetry*, 1995, **6**, 2977; H. Kawakami, T. Ebata, K. Okano, K. Matsumoto, K. Koseki and H. Matsushita, Patent; *Chem. Abstr.*, 1994, **120**, 107640g.

Communication 9/07270E