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Synthesis of 2,4-disubstituted 3-chlorofurans and the effect of the chlorine substituent in furan Diels–Alder reactions

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Abstract

2,4-Disubstituted 3-chlorofurans were synthesized in 42–69% overall yields by CuCl/bpy-catalyzed halogen atom transfer radical cyclization of 1-substituted 2,2,2-trichloroethyl allyl ethers to 2-substituted 3,3-dichloro-4-(1-chloroalkyl)tetrahydrofurans followed by base promoted dehydrochlorination. Diels–Alder reactions of 4-substituted 2-(2-furyl)-, 2-styryl-, and 2-crotyl-3-chlorofurans with dimethyl acetylenedicarboxylate occurred exclusively on the chlorofurano diene moieties and not on the non-chlorinated furano diene or the chlorinated exocyclic diene alternatives, demonstrating the predominance of the halogen effect in the furan Diels–Alder reaction.

Keywords: 3-Chlorofurans; 3,3-Dichlorotetrahydrofurans; Radical cyclization; Diels–Alder reaction; Dehydrochlorination; Chlorine effect

Halofurans are important building blocks for the synthesis of more complex furans for various applications as the halogen atom can be replaced easily with a variety of groups[1] through halogen–metal exchange[2,3] or transition metal-catalyzed cross-coupling[4] and amination[5] reactions. They are in great demand especially when a substituent is required to be introduced regiospecifically, particularly at the 3- or 4-position in the presence of unsubstituted 2- and/or 5-positions. The synthesis of such furans is not straightforward because other substitution methods, such as electrophilic aromatic substitution and direct metallation generally occur at the 2- and/or 5-positions with the possibility of complications arising due to the problem of regioselectivity. In such a situation, one has to take recourse mostly to ab initio furan synthesis involving cyclization of acyclic and often non-trivial precursors.[1c,6] Other alternatives involving oxazole-Diels–Alder–retro-Diels–Alder methodology,[1c] the substituent-directed β-lithiation of silicon-protected furans[1b] and the intramolecular Diels–Alder reaction of 2-substituted furans (furan-transfer reaction)[1c] are also useful in special cases. However, all these methods are less preferable when a broad synthetic methodology is required, particularly to build a library of variously substituted furans for studying structure–activity relationship.

Further, theoretical calculations and experimental results show that a halogen substituent enhances the rate and efficiency of the furan Diels–Alder reaction and decreases its reversibility.[7] This, the so-called 'halogen effect' has been rationalized in terms of the high propensity of the electronegative halogen atom to attach to a more substituted and thus more electropositive carbon framework. Thus, through a more efficient Diels–Alder reaction[8] or other standard methodologies[9] halofurans may be transformed into a variety of heterocyclic, carbocyclic, acyclic, or aromatic products with a halogen atom handle which can be elaborated further or easily removed.

Bromo- and iodo-furans have served particularly well in substitutions through halogen–metal exchange and cross-coupling reactions and have been used for the synthesis of furanoid and other naturally occurring as well as synthetic bioactive and other potentially useful molecules.[1–5] However, chloro derivatives are more attractive options for industrial applications due to their higher

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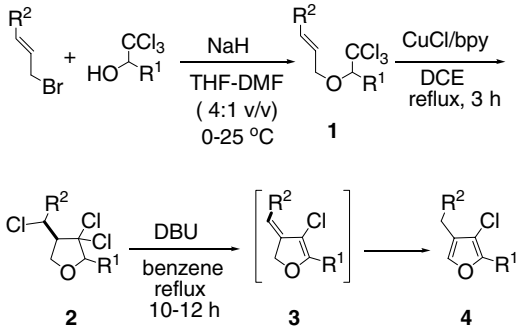
stability and lower cost. Therefore, there is a significant current interest in the replacement of the chlorine atom of chloroarenes with carbon and other groups and considerable success has been realized to bring chloroarenes and chloroheteroarenes into the realm of cross-coupling reactions during the past few years.[10] However, electron-rich chloroheteroarenes, particularly sensitive chlorofurans have hardly been explored.[11] This is partly due to the scarcity of easy routes to chlorofurans, especially 3- or 4-chlorofurans. The reported methods for the synthesis of 3- or 4-chlorofurans have limitations with regard to the yields, general applicability, the number and the nature of the other substituents and the substitution pattern.[12] Most of the methods for the synthesis of trisubstituted chlorofurans are concerned with the synthesis of 2,5-diaryl-3-chlorofurans and do not describe the synthesis of contiguously trisubstituted furans with a chlorine atom at C-3. Recently, we reported the synthesis of 3-substituted 4-chloro and 2,3-disubstituted 4-chlorofurans using CuCl/bpy-catalyzed halogen atom transfer radical cyclization (HATRC) of acetylated chloral allyl hemiacetals as the key step.[12e] Herein, we report an efficient and shorter route for the synthesis of isomeric 2,4-disubstituted 3-chlorofurans, another type of scarcely known β-chlorofurans for which a general method of preparation is not available with only a few examples reported in the literature.[13,14] Some of these compounds possess promising biological activities[14] and appear mostly in patented documents.

The synthesis of 2,4-disubstituted 3-chlorofurans **4** is shown in Scheme 1. Allylation of trichloromethyl carbinols with easily available allylic bromides gave the 1-substituted 2,2,2-trichloroethyl allyl ethers **1**. The trichloromethyl carbinols were easily accessible by reaction of aldehydes with chloroform in the presence of catalytic amounts of DBU[15] or with trichloroacetic acid in DMSO[16] as reported in the literature. Copper-catalyzed HATRC[17] of **1** with CuCl/bpy (1:1 molar mixture, 30 mol %) in refluxing DCE for 3 h occurred in a highly diastereoselective manner to yield tetrahydrofurans **2**, generally in high yields. A one-pot double dehydrochlorination and isomerization of tetrahydrofurans **2** with DBU in refluxing benzene for 10–12 h afforded 2,4-disubstituted 3-chlorofurans **4** in 42–77% overall yields from the trichloroethyl allyl ethers **1** (Table 1).[18] However, the volatile chlorofuran **4a** (entry 1) could be isolated only in poor overall yield (15%) due to loss of material during workup.



Scheme 1. Synthesis of 2,4-disubstituted 3-chlorofurans **4a**–**o**.

Monitoring the progress of the dehydrochlorination reaction by TLC indicated the absence of the starting material after 3 h, however, formation of the furans required 10–12 h at reflux. Plausibly, isofurans **3** are formed first which isomerize to the furans slowly. In the case of 2-(4-nitrophenyl)tetrahydrofuran **2j** (entry 10), complete isomerization to the corresponding furan **4j** required treatment of the mixture of furan and isofuran with a few drops of concd H_2SO_4 in diethyl ether at ambient temperature for 2 h. The dehydrochlorination of the basic tetrahydrofurans **2f** (entry 6) and **2k** (entry 11) was effected by *t*-BuOK/18-crown-6 in refluxing THF instead of DBU to avoid complications in separating them from the excess organic base DBU. This method of dehydrochlorination was also found to give better results for the synthesis of 3-chloro-4-isopropyl-2-(3-tolyl)furan which was prepared in 60% overall yield from the corresponding ether obtained by prenylation of 1-(3-tolyl)-2,2,2-trichloroethanol.

The tetrahydrofurans and furans were purified by column chromatography on silica gel and alumina columns, respectively, with *n*-hexane as the solvent for elution. The solid chlorofurans are fairly stable and the liquid chlorofurans are stable for a few days when stored at low temperatures under a nitrogen atmosphere in hydrocarbon solvents but tend to deteriorate in chlorinated or oxygenated solvents. Their structures were established by IR, ^{1}H, ^{13}C, and DEPT NMR spectroscopy.

Next, we briefly investigated the halogen effect on the furan Diels–Alder reaction. This effect appears to be a general effect applicable to other halogen substituted dienes as well as dienophiles.[7a,19] According to a recent theoretical

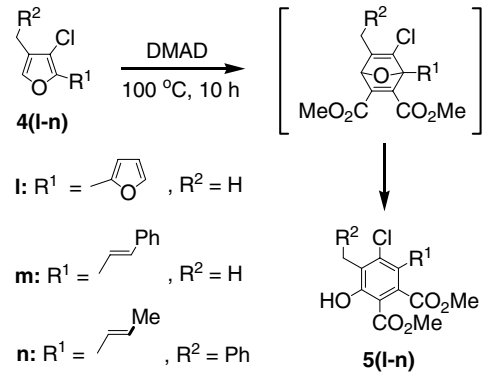
Table 1
Yields of tetrahydrofurans **2a**–**o** and chlorofurans **4a**–**o**

Entry	Ether **1**	R^1	R^2	Yield (%)		
				2[a]	**4**[b]	**4**[c]
1	**a**	*n*-Pr	H	60	25[d]	15
2	**b**	Ph	H	93	74	69
3	**c**	2-$MeOC_6H_4$	H	85	65	55
4	**d**	4-$MeOC_6H_4$	H	87	76	66
5	**e**	3,4-$(MeO)_2C_6H_3$	H	85	71	60
6	**f**	4-$Me_2NC_6H_4$	H	83	73[d]	61
7	**g**	2-ClC_6H_4	H	86	68	59
8	**h**	4-ClC_6H_4	H	87	76	66
9	**i**	3-BrC_6H_4	H	89	72	64
10	**j**	4-$O_2NC_6H_4$	H	90	85	77
11	**k**	2-Pyridyl	H	84	70[d]	59
12	**l**	2-Furyl	H	83	69	57
13	**m**	*E*-PhCH=CH	H	70	60	42
14	**n**	MeCH=CH (major *E*)	Ph	66	65	43
15	**o**	3-MeC_6H_4	Ph	88	65	57

[a] One-step (**1**→**2**).
[b] One-step (**2**→**4**).
[c] Two-steps (**1**→**4**).
[d] Dehydrochlorination of **2** was achieved with *t*-BuOK/18-crown-6 in refluxing THF for 10 h.

calculation,[7a] the halogen effect is more important in the Diels–Alder reaction of halofurans than with halo-substituted cyclic or acyclic hydrocarbon dienes, the maximum effect occurring when the halogen atom is linked to one of the termini of the diene. Accordingly, 2-halofurans have been found to be more reactive than 3-halofurans. However, experimental support for the theoretical predictions through an intramolecular competition between a halofuran diene and a non-halogenated furano diene or a non-furano halodiene has not been reported. The fortuitous availability of the 'twin' dienes **4(l–n)** led us to investigate the Diels–Alder reaction of these compounds. Thus, chlorobifuryl **4l** having a chlorofuran ring and a non-halogenated furan ring, on heating with dimethyl acetylenedicarboxylate (DMAD) at 100 °C for 10 h gave exclusively furylchlorophenol **5l** (Scheme 2) in 74% yield by cycloaddition to the chlorofuran ring. The structure of **5l** was also supported by X-ray crystallography.[20] Similarly, 2-styryl-3-chlorofuran **4m** and 2-crotyl-3-chlorofuran **4n** (predominantly as the *E* isomer) having a chlorofurano diene and a chloro-substituted exocyclic diene moiety, under similar conditions, yielded exclusively styrylchlorophenol **5m** and crotylchlorophenol **5n**, in 65% and 62% yields, respectively,[21] showing the specific participation of the chlorofurano diene in the Diels–Alder reaction.[22]

In conclusion, the present method for the synthesis of 2,4-disubstituted 3-chlorofurans uses readily available starting materials. It is quite general for the synthesis of a variety of 2,4-disubstituted 3-chlorofurans with an alkyl, alkenyl, aryl or heteroaryl substituent at C-2 and a primary or secondary alkyl or benzylic substituent at C-4. In particular, this method would be well suited to a diversity oriented synthesis of 2,3-disubstituted furans with a methyl group at C-4, a structural feature of many natural and bioactive synthetic furans.[1c,6a–d,14d,23] These chlorofurans possessing a chlorine atom in a sterically encumbered position offer a formidable challenge to those interested in cross-coupling reactions. While our results show the predominance of the halogen effect in furan Diels–Alder reactions, conformational and steric effects might also be contributing factors. Further studies with more suitable substrates are required for a more precise conclusion.



Scheme 2. Diels–Alder reaction of chlorofurans **4(l–n)**.

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