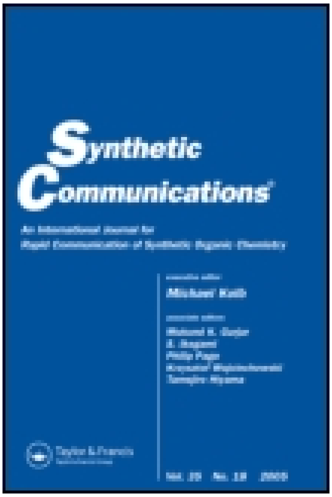

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Unexpected Aromatization of 2-Acetoxy-3,3-dichloro-4-(α-chloroalkyl)tetrahydrofurans to 3-Alkyl-4-chlorofurans with NaI/DMF

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Abstract: An unexpected aromatization of 2-acetoxy-3,3-dichloro-4-(α-chloroalkyl)tetrahydrofurans to 3-alkyl-4-chlorofurans occurs on heating with sodium iodide in dimethylformamide (DMF) at 120 °C.

Keywords: Aromatization; β-Chlorofurans; Dechloroacetoxylation; Dehydrochlorination; Sodium iodide; Tetrahydrofurans

Variously substituted furans are frequently found in many biologically active natural products,[1] pharmaceuticals,[2] and flavor and fragrance compounds.[3] Furthermore, they are also used as versatile intermediates in many synthetic pathways leading to aromatic, alicyclic, and acyclic compounds.[4] Because of the utilities of furans, a variety of methods using cyclic and acyclic precursors have been devised for their synthesis.[5,6] Among them, relatively few reports deal with the preparation of β-mono-, di-, or trisubstituted furans with either or both the α-positions unsubstituted. This is because these furans need to be prepared from suitably substituted acyclic compounds, as direct electrophilic substitution or lithiation of furan ring occurs at the α-position(s). Because many naturally occurring bioactive compounds have these substitution patterns, the direct synthesis of such furans assumes considerable importance. In this respect, the synthesis of β-halo-substituted furans would be more useful because direct replacement of the halo group would give a

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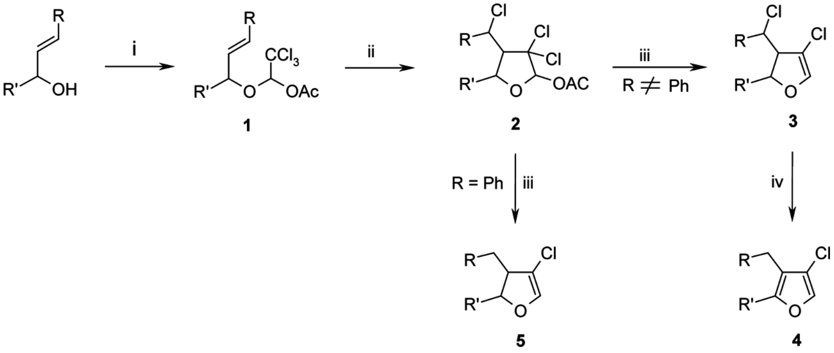
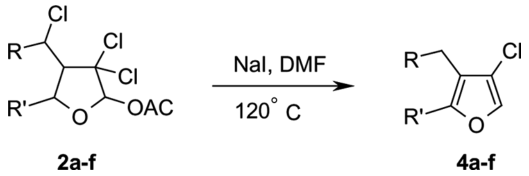
variety of β-substituted furans. Both iodo- and bromo-furans have been well utilized for this purpose by replacing the halo group with a variety of carbon groups such as alkyl, alkenyl, alkynyl, aryl, heteroaryl, formyl, and acyl groups.[4,7–11] There is considerable current interest in the chloro group replacement reactions of chloroarenes and chloroheteroarenes[12] because chloro compounds are, in general, less expensive and more stable than their bromo and iodo counterparts. However, not only are relatively few general methods known to prepare β-chlorofurans, but also these methods have their own limitations with respect to the yields, the nature of other substituents, and the substitution patterns.[13–16] Recently, Karpov et al.[17] have reported an elegant one-pot synthesis of 3-chloro- and 3-iodofurans by a modified Sonogashira coupling of acid chlorides with tetrahydropyranyl (THP)-protected propargyl alcohols. The THP-protected γ-hydroxy alkynones thus formed undergo sequential acid-induced deprotection, addition of sodium halide, and cyclocondensation to give the 2-substituted-4-halofurans or 2,5-disubstituted-4-halofurans in one step. These furans can be isolated or the iodofurans can be made to undergo Suzuki coupling with boronic acid in the same pot. However, this procedure gives furans that lack a substituent at the 3-position.

Recently, we reported[18] a new method to prepare 3-substituted- and 2,3-disubstituted-4-chlorofurans from easily accessible allylic alcohols using CuCl/bipy-catalyzed chlorine atom transfer radical cyclization of the protected hemiacetals (**1**) as the key step (Scheme 1).

However, during the dechloroacetoxylation with Zn/THF, the tetrahydrofurans with a tertiary or benzylic chloro substituent in the side



Scheme 1. Reagents and conditions: i. CCl_3CHO, 2 h, then Ac_2O, pyridine, DMAP (30 mol%), rt, overnight; ii. CuCl/bpy (30 mol%, 1:1 mixture), 1,2-dichloroethane, reflux, 2 h; iii. Zn, THF, reflux, 4 h; iv. t-BuOK/18-Crown-6, THF, reflux, 10 h.



2a-f **4a-f**

Scheme 2. Aromatization of tetrahydrofurans **2**.

chain at the 3-position, such as **2** (R = Ph), gave the dihydrofurans **5** by reductive dechlorination of the side chain, thus terminating the sequence for further conversion to the chlorofurans **4**. As a solution to this problem, we considered using some other reagents with low reducing ability. Thus, sodium iodide with its known efficacy in dechlorotrifluoroacetoxylation[19] and related reactions[20] was chosen as an alternative reagent for this purpose. We were gratified to observe that when the reaction was done by heating the tetrahydrofurans **2** with NaI (5 equivalents) in DMF at about 120 °C for 4 h, it led not only to the expected dechloroacetoxylation but also to an unexpected and much welcomed dehydrochlorination and aromatization by double bond shift, all in one step, to give the desired *β*-chlorofurans **4** in 23–46% yields (Scheme 2, Table 1). The low yields of *β*-chlorofurans could be reconciled by the advantages offered by this method over the earlier method.[18] All the products were characterized by IR and ^{1}H NMR spectral analysis and by comparison with the authentic samples including their Diels–Alder reaction products with dimethyl acetylenedicarboxylate.[18] The chlorofurans were found to be fairly stable in hydrocarbon solvents but tend to deteriorate in chlorinated or oxygenated solvents even during the course of recording their ^{13}C NMR spectra.

Table 1. Aromatization of tetrahydrofurans **2** by NaI/DMF

S. no.	Tetrahydrofuran **2**	R	R′	4-Chlorofuran **4** yield (%)
1	**a**	H	Ph	41
2	**b**	H	n-C_5H_{11}	38
3	**c**	n-C_3H_7	H	23
4	**d**	CH_3	Ph	39
5	**e**	Ph	H	46
6	**f**	Ph	CH_3	43

It was not possible to detect or isolate the expected dechloroacetoxylation product or any isofuran intermediate even when the reaction was done for shorter duration, at lower temperatures, or both. When the dihydrofuran **3d** was heated with NaI (5 equivalents) in DMF, the aromatization occurred and took about the same time (4 h) for completion as taken by the tetrahydrofurans **2** to give the chlorofuran **4d** in better yield (60%). No reaction occurred when the tetrahydrofuran **2d** or the dihydrofuran **3d** was heated in DMF at 120 °C in the absence of NaI, though a few special types of chlorosteroidal compounds have been reported to aromatize on heating in DMF at reflux.[21] Thus, an iodide ion seems to be required for the dechloroacetoxylation and probably also for replacement of the side-chain chloro group with iodo group to facilitate the dehydrohalogenation.

EXPERIMENTAL

General Procedure

NaI (1.5 g, 10 mmol) was added to a solution of tetrahydrofuran **2** (2 mmol) in 10 ml of DMF. The reaction mixture was protected from atmospheric moisture with a calcium chloride guard tube and heated to 120 °C in an oil bath for 4 h. The solution was cooled, diluted with 50 ml of equivolume mixture of petroleum ether–diethyl ether, and washed successively with water (2 × 50 ml), 5% sodium thiosulphate solution (10 ml), and brine (10 ml). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product thus obtained was chromatographed on an alumina column using *n*-hexane as the eluent to obtain the 4-chlorofuran **4** as a colorless oil.

Spectral Data

4-Chloro-3-methyl-2-phenylfuran (4a): IR: ν_{max}3057 (m), 2922 (s), 2850 (m), 1482 (s), 1431 (m), 737 (s), 698 (s) cm^{-1}. ^1H NMR: δ 2.24 (s, 3H), 7.24–7.44 (m, 4H), 7.59–7.61 (m, 2H) ppm.

4-Chloro-3-methyl-2-pentylfuran (4b): IR: ν_{max}2976 (s), 1644 (w), 1484 (m), 1396 (m), 1260 (w), 1148 (s), 1070 (s), 930 (m), 742 (m) cm^{-1}. ^1H NMR: δ 0.90 (t, $J = 6.89$ Hz, 3H), 1.13–1.37 (m, 4H), 1.58 (quintet, $J = 7.35$ Hz, 2H), 1.9 (s, 3H), 2.51 (t, $J = 7.4$ Hz, 2H), 7.21 (s, 1H) ppm.

3-Butyl-4-chlorofuran (4c): IR: ν_{max}2925 (s), 1604 (s), 1509 (s), 1451(s), 1233 (s), 1214 (s), 1146 (s), 1015 (s), 917 (s), 726 (s) cm^{-1}.

^{1}H NMR: δ 0.93 (t, $J = 7.24$ Hz, 3H), 1.38 (sextet, $J = 7.27$ Hz, 2H), 1.55 (quintet, $J = 7.44$ Hz, 2H), 2.39 (t, $J = 7.6$ Hz, 2H), 7.16 (s, 1H), 7.37 (s, 1H) ppm.

4-Chloro-3-ethyl-2-phenylfuran (4d): IR: $\nu_{\max}$3036 (s), 2924 (m), 1603 (s), 1508 (s), 1479 (s), 1146 (s), 1014 (s), 916 (s), 727 (s), 676 (s) cm^{-1}. ^{1}H NMR: δ 1.37 (t, $J = 7.53$ Hz, 3H), 2.80 (q, $J = 7.52$ Hz, 2H), 7.38–7.54 (m, 2.1H), 7.69–7.72 (m, 1.3H) ppm.

3-Benzyl-4-chlorofuran (4e): IR: $\nu_{\max}$3008 (m), 2880 (m), 1504 (s), 1060 (s), 920 (s), 730 (s), 706 (s) cm^{-1}. ^{1}H NMR: δ 3.66 (s, 2H), 6.99 (m, 1H), 7.10–7.24 (m, 5H), 7.31 (d, $J = 1.69$ Hz, 1H) ppm.

3-Benzyl-4-chloro-2-methylfuran (4f): IR: $\nu_{\max}$2957 (s), 2872 (s), 1663 (w), 1456 (s), 1377 (m), 1037 (s), 763 (m), 698 (s) cm^{-1}. ^{1}H NMR: δ 2.17 (s, 3H), 3.70 (s, 2H), 7.15–7.28 (m, 6H) ppm.

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