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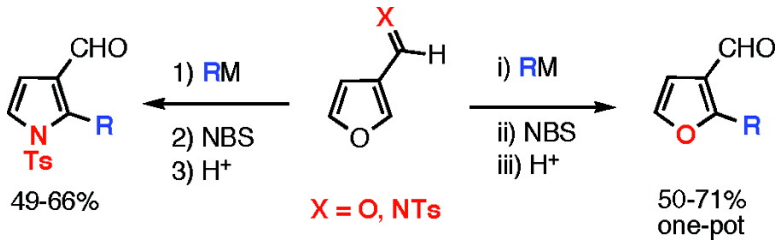

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Addition/Oxidative Rearrangement of 3-Furfurals and 3-Furyl Imines: New Approaches to Substituted Furans and Pyrroles

Ann Rowley Kelly, Michael H. Kerrigan, and Patrick J. Walsh*

P. Roy and Diana T. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

Received December 10, 2007; E-mail: pwalsh@sas.upenn.edu

Abstract: Furans and pyrroles are important synthons in chemical synthesis and are commonly found in natural products, pharmaceutical agents, and materials. Introduced herein are three methods to prepare 2-substituted 3-furfurals starting from 3-furfural, 3-bromofuran, and 3-vinylfurans. Addition of a variety of organolithium, Grignard, and organozinc reagents (M-R) to 3-furfural provides 3-furyl alcohols in high yields. Treatment of these intermediates with NBS initiates a novel oxidative rearrangement that results in the installation of the R group in the 2 position of the 2-substituted 3-furfurals. Likewise, metalation of 3-bromofuran with *n*-BuLi and addition to benzaldehyde provides a furyl alcohol that is converted to 2-phenyl 3-furfural upon oxidative rearrangement. Enantioenriched disubstituted furans can be prepared starting with the Sharpless asymmetric dihydroxylation of 3-vinylfurans. The resulting enantioenriched diols undergo the oxidative rearrangement to furnish enantioenriched 2-substituted 3-furfurals with excellent transfer of asymmetry. This later method has been applied to the enantioselective preparation of an intermediate in Honda's synthesis of the natural product (−)-canadensolide. Mechanistic studies involving deuterium-labeled furyl alcohol suggest that the oxidative rearrangement proceeds through an unsaturated 1,4-dialdehyde intermediate. The alcohol then cyclizes onto an aldehyde, resulting in the elimination of water and rearomatization. On the basis of this proposed mechanism, we found that 3-furyl imines undergo the addition of organometallic reagents to provide furyl sulfonamides. Under the oxidative rearrangement conditions, 2-substituted 3-formyl pyrroles are formed, providing a novel route to these heterocycles. In contrast to the metalation of heterocycles, which often lead to mixtures of regioisomeric products, these new oxidative rearrangements of furyl alcohols and furyl sulfonamides generate only one regioisomer in each case.

1. Introduction

Furans and pyrroles are important constituents of natural products and of pharmaceutical agents.[1−12] Some of the best-selling medications are heterocycles of these types: for instance ranitidine[13] is a furan used to treat stomach ulcers, and atorvastatin (Lipitor)[14] is a pyrrole used to control high cholesterol. Furans and pyrroles are also versatile synthetic intermediates as a result of their high reactivity and facile conversion into a variety of functional groups.[1−6,13,15−18] The value and utility of these heterocycles continues to stimulate research directed toward their synthesis. Despite this effort, the *efficient and selective* synthesis of substituted furans and pyrroles remains a challenge.[8,19−21,3]

A common method to functionalize furans begins with metalation chemistry. Although direct lithiation of furans at C-2 is often readily achieved, halogenation followed by low-temperature metal−halogen exchange is the standard approach to metalate C-3.[22−24] 3-Furyllithiums are highly reactive, and the lithium will migrate from the 3 to the 2 position at low temperatures. As with most organolithiums, lithiated furans exhibit limited functional group compatibility. As an example, Comins and co-workers used a directed metalation to lithiate 3-furfural in the 2 position. To protect the aldehyde and direct

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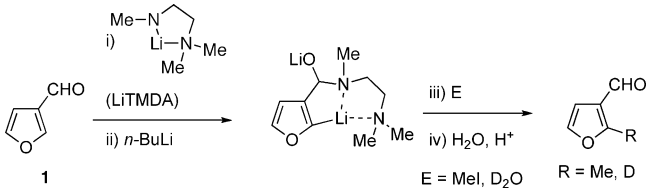
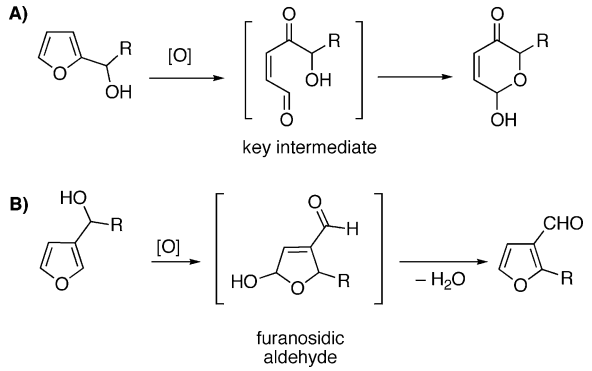
Scheme 1. Synthesis of 2-Substituted 3-Furfurals Using LiTMDA to Form the Directing Group.



Scheme 2. (A) Achmatowicz Reaction and (B) Our Proposed Oxidative Rearrangement of 3-Furyl Alcohols.



the metalation in this process, lithiated trimethylethylene diamine (LiTMDA) was generated, added to 3-furfural, and the resulting adduct metalated with *n*-BuLi (Scheme 1). The lithiated furan was then treated with methyl iodide to generate 2-methyl 3-furfural in 83% yield after hydrolysis of the directing group.[25] This furan alkylation is limited to alkyl halides that will undergo S_N2 substitution over elimination with this bulky organolithium. We have found that D_2O is also a suitable electrophile for preparing the 2-deutero 3-furfural, as outlined below.

Metalation processes, however, can be difficult to control, resulting in lower selectivity, reduced yields, and challenging separations of the desired furan from the unwanted regioisomers. Also, the selectivity of such metalations depends on the metalating reagent and the electrophile.[23] Given the limitations of these methods to generate functionalized heteroaromatics, alternative strategies to prepare these valuable compounds are desirable.

Our approach to the synthesis of substituted furans was inspired by the Achmatowicz reaction (part A of Scheme 2).[26,27] This process, which entails the conversion of 2-furyl alcohols to pyranones under oxidative conditions has been widely utilized in the synthesis of natural products and the preparation of diverse libraries of heterocyclic compounds.[28,29] The mechanism of this oxidative transformation is believed to involve ring-opening to generate an unsaturated 1,4-dicarbonyl intermediate that then cyclizes to the pyranone product. On the basis of this mechanism, we anticipated that 3-furyl alcohols would undergo related oxidative rearrangement to provide furanosidic aldehydes, which could eliminate and rearomatize to provide 2-substituted 3-furfurals (part B of Scheme 2).

Herein, we disclose a novel oxidative rearrangement that enables the selective preparation of diverse 2-substituted 3-furfurals. Beginning with commercially available 3-furfural, the addition of an organometallic reagent generates a furyl alcohol. Oxidative rearrangement of the furyl alcohol with NBS provides the desired 2-substituted 3-furfurals without contamination by other isomers. In this fashion, a variety of substituents can be easily installed at the 2 position. We have extended our oxidative rearrangement to the generation of enantioenriched 2-substituted 3-furfurals and to the formation of 2-substituted 3-formyl pyrroles.

2. Experimental Section

General methods are listed in the Supporting Information.

General Procedure A. Synthesis of Furyl Alcohols from 3-Furfural. 1−Furan-3-yl-propan-1-ol (2a). Under a nitrogen atmosphere, a dry 25 mL flask was charged with 3-furfural (84 μL, 1.0 mmol) and THF (1.0 mL) and cooled to 0 °C. A solution of ethylmagnesium bromide (0.5 mL, 3.0 M in ether, 1.5 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h and quenched with saturated aqueous NH_4Cl. The organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (10% EtOAc in hexanes) to afford the title compound as a colorless oil in 98% yield (123 mg, 0.98 mmol). The ^1H and $^{13}C\{^1H\}$ NMR data for this compound were identical to previously reported literature data.[30]

Synthesis of Furan-3-yl-phenyl-methanol from 3-Bromofuran (2e). Under a nitrogen atmosphere, *n*-BuLi (0.4 mL, 2.5 M in hexanes, 1.0 mmol) was added dropwise to a stirred solution of 3-bromofuran (108 μL, 1.2 mmol) in dry THF (1 mL) at −78 °C. After 15 min, benzaldehyde (101 μL, 1.0 mmol) was added to the solution. The reaction mixture was stirred at −78 °C until completion by TLC and quenched with saturated aqueous NH_4Cl. The organic and aqueous layers were separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography on deactivated silica gel (10% EtOAc in hexanes) to afford the title compound as a colorless oil in 90% yield (157 mg, 0.90 mmol). The ^1H and $^{13}C\{^1H\}$ NMR data for this compound were identical to previously reported literature data.[31]

General Procedure B: Oxidative Rearrangement of Furyl Alcohols. 2-Ethyl-furan-3-carboxaldehyde (3a). A 10 mL flask was charged with 1-furan-3-yl-propan-1-ol (126 mg, 1.0 mmol), THF (4 mL), and H_2O (1 mL). NBS (178 mg, 1.0 mmol) was added to the mixture in two portions (10 min apart) at ambient temperature. The reaction mixture initially turned yellow and later faded to near colorless. The reaction progress was monitored by TLC, and the formation of a new, nonpolar, UV active spot was observed. Upon completion (approximately 4 h), the reaction mixture was treated with 1M $HCl_{(aq)}$ (1 mL, 1 mmol). After stirring for 10 min, the reaction mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the residue was chro-

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matographed on silica gel (5% Et_2O in pentane) to afford the title compound as a yellow oil in 71% yield (88 mg, 0.71mmol). ^1H NMR ($CDCl_3$, 500 MHz): δ 9.96 (s, 1H), 7.31 (d, $J = 1.9$ Hz, 1H), 6.68 (d, $J = 1.9$ Hz, 1H), 2.97 (quartet, $J = 7.8$ Hz, 2H), 1.30 (t, $J = 7.5$ Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$,125 MHz): δ 184.8, 145.0, 142.1, 121.9, 108.1, 20.6, and 12.8; IR (neat) 3123, 2979, 2878, 2743, 1683, and 1575 cm^{-1}. HRMS-CI *m/z* 124.0522 [M^+; Calcd for $C_7H_8O_2$: 124.0524].

General Procedure C: One-Pot Addition/Oxidative Rearrangement with 3-Furfural. 2-Ethyl-furan-3-carboxaldehyde (3a). Under a nitrogen atmosphere, a dry 25 mL flask was charged with 3-furfural (87 μL, 1.0 mmol) and dry THF (1.0 mL) and cooled to 0 °C. A solution of ethylmagnesium bromide (0.5 mL, 3.0 M in ether, 1.5 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h. When the addition reaction was completed by TLC, $HCl_{(aq)}$ (1.5 mL, 1M, 1.5 mmol) was added. THF (7 mL), water (0.5 mL), and NBS (178 mg, 1.0 mmol, in two portions) were then added sequentially at ambient temperature. When the rearrangement was completed by TLC, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (5% Et_2O in pentane) to afford the title compound as a yellow oil in 70% yield (86 mg, 0.70 mmol). The spectral data for this compound were the same as those reported in General Procedure B.

Synthesis of 3-Hex-1-enyl-furan (7). Under a nitrogen atmosphere, $PdCl_2(dppf)\cdot CH_2Cl_2$ (51 mg, 0.063 mmol), (*E*)-hexen-1-ylboronic acid (400 mg, 3.13 mmol), 3-bromofuran (277 μL, 3.13 mmol), and *tert*-butylamine (986 μL, 9.38 mmol) were added to a dry 25 mL round-bottom flask, followed by 2-propanol (10 mL) and water (5 mL). A reflux condenser was attached, and the resulting deep-red solution was refluxed for 4.5 h under N_2 (oil bath ≈ 90 °C). After cooling to room temperature, water (10 mL) was added. Following extraction with Et_2O (3 × 10 mL), the combined organic layers were washed with $HCl_{(aq)}$ (2 mL, 2M), brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Column chromatography on silica gel (0−2.5% EtOAc in hexanes) afforded the title compound in 80% (1.90 g, 11.4 mmol) as a clear liquid. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36 (s, 2H) 6.52 (s, 1H), 6.24 (d, $J = 15.8$ Hz, 1H), 5.96 (dt, $J = 15.8$, 6.9 Hz, 1H) 2.17 (dt, $J = 6.9$ Hz, 6.6 Hz, 2H) 1.40 (m, 4H), 0.94 (t, $J = 7.0$ Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 143.5, 139.5, 131.1, 124.8, 119.4, 107.8, 32.8, 31.7, 22.5, and 14.5; IR (neat) 2958, 2927, 2873, 2859, 1508, and 1466 cm^{-1}. HRMS-CI *m/z* 150.1038 [M^+; Calcd for $C_9H_{10}O_3$: 150.1045].

General Procedure D: Sharpless Asymmetric Dihydroxylation of *trans*-3-Vinylfurans. (1*R*, 2*R*)-1-Furan-3-yl-hexane-1,2-diol (8). In a 100 mL flask, the AD-mix-β (8.47 g) was dissolved in *tert*-butanol (30 mL) and DI H_2O (30 mL) at room temperature followed by the addition of methanesulfonamide (575 mg, 6.05 mmol). After dissolution, the orange solution was cooled to 0 °C and 3-hex-1-enyl-furan (908 mg, 6.05 mmol) was added. After 16 h of stirring at 0 °C, sodium sulfite (9.075 g) was added, and the reaction mixture was warmed to ambient temperature and stirred for 1 h. The reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were washed with KOH (2 N), dried over $MgSO_4$, filtered, and the filtrate was concentrated. Column chromatography on silica gel (10−33% EtOAc in hexanes) afforded the diol product in 86% yield (961 mg, 5.22 mmol) as a clear viscous liquid. $[\alpha]_D^{20} = -3.98°$ ($c = 2.79$, $CHCl_3$, 98% ee); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.46 (s, 1H), 7.43 (s, 1H), 6.42 (s, 1H), 4.46 (dd, $J = 3.2$, 5.9 Hz, 1H), 3.70 (d, $J = 6.2$ Hz, 1H), 2.50 (s, 1H), 2.33 (s, 1H), 1.39 (m, 6H), 0.90 (t, $J = 7.1$ Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$,125 MHz): δ 143, 140.4, 126.1, 108.9, 75.2, 70.5, 32.8, 20.0, 22.8, and 14.2; IR (neat) 3391, 2957, 2934, 2873, 1503, and 1467 cm^{-1}. HRMS-CI *m/z* 167.1064 [$(M-OH)^+$; Calcd for $C_{10}H_{15}O_2^-$: 167.1072].

(*R*)-2-(1-Hydroxy-pentyl)-3-furfural (9). General Procedure B was applied to the diol using (1*R*, 2*R*)-1-furan-3-yl-hexane-1,2-diol (585 mg, 3.18 mmol), THF (12 mL), DI H_2O (3 mL), and NBS (283 mg, 1.59 mmol, in two portions 10 min apart). The yellow solution was stirred for 5 h, quenched with water (10 mL), extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was subject to column chromatography on silica gel (5−20% EtOAc in hexanes), affording the title compound in 68% yield (394 mg, 2.16 mmol). $[\alpha]_D^{20} = -31.09°$ ($c = 2.04$, $CHCl_3$, >99% ee); ^1H NMR ($CDCl_3$, 500 MHz): δ 10.01 (s, 1H), 7.37 (d, $J = 2.0$ Hz, 1H), 6.78 (d, $J = 2.0$ Hz, 1H), 4.96 (t, $J = 6.9$ Hz, 1H), 3.65 (s, 1H), 1.89 (m, 2H), 1.35 (m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 187.1, 165.4, 142.1, 122.7, 110.0, 68.4, 36.1, 27.6, 22.6, and 14.1; IR (film) 3418, 2958, 2863, and 1682 cm^{-1}. HRMS-CI *m/z* 182.0943 [M^+; Calcd for $C_{10}H_{14}O_3$: 182.0943].

Synthesis of (*R*)-1-(3-Hydroxymethyl-furan-2-yl)-pentan-1-ol. Under a nitrogen atmosphere at room temperature, $NaBH_4$ was added to a solution of (*R*)-2-(1-hydroxy-pentyl)-3-furfural (88.6 mg, 0.486 mmol) dissolved in 2-propanol (2 mL, HPLC grade). After stirring for 15 min, the reaction was quenched with H_2O (3 mL) and Et_2O was added (5 mL). The reaction was extracted with Et_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. This material was taken on to the next reaction without purification.

For purposes of characterization, the crude material was run though a plug of silica gel (50% EtOAc in hexanes) to afford the diol in 95% yield. $[\alpha]_D^{20} = 24.03°$ ($c = 3.77$, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.31 (d, $J = 1.8$ Hz, 1H), 6.36 (d, $J = 1.7$ Hz, 1H), 4.78 (t, $J = 7.0$ Hz, 1H), 4.57 (s, 2H), 2.67(s, 1H), 2.38 (s, 1H), 1.90 (m, 2H), 1.39−1.25 (m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 153.4, 141.2, 120.8, 111.5, 67.3, 56.7, 35.7, 27.9, 22.7, and 14.2; IR (film) 3335, 2967, 2933, 2873, 1512, and 1467 cm^{-1}. HRMS-ESI *m/z* 207.0994 [$(M+Na)^+$; Calcd for $C_{10}H_{16}O_3Na$: 207.0997]. The ^1H NMR spectrum and the IR for this compound match those of Honda and co-workers.[32] The ^{13}C NMR was not previously reported.

Synthesis of (*R*)-1-[3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-furan-2-yl]-pentan-1-ol (10). The crude diol (*R*)-1-(3-hydroxymethyl-furan-2-yl)-pentan-1-ol (0.486 mmol), TBSCl (73.2 mg, 0.486 mmol), and imidazole (66.2 mg, 0.972 mmol) were dissolved in CH_2Cl_2 (2 mL) and stirred for 8 h at room temperature under a nitrogen atmosphere. The reaction mixture was quenched with aqueous saturated NH_4Cl and was extracted with Et_2O (15 mL × 3). The combined organic layers were

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dried over $MgSO_4$, filtered, and the filtrate was concentrated under reduced pressure. Column chromatography on silica gel (5−10% EtOAc in hexanes) afforded the title compound in 78% yield (113.1 mg, 0.379 mmol). $[\alpha]_D^{20} = 9.65°$ ($c = 2.07$, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.28 (d, $J = 1.6$ Hz, 1H), 6.29 (d, $J = 1.7$ Hz, 1H), 4.76 (dd, $J_1 = 6.7$, 4.8 Hz, 1H), 4.64 (s, 2H), 2.85 (d, $J = 4.7$ Hz, 1H), 1.88 (m, 2H), 1.44−1.26 (m, 4H), 0.93 (m, 12H), 0.13 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 153.3, 140.7, 120.6 111.2, 67.4, 57.8, 35.7, 27.9, 26.1, 22.8, 18,5, 14.2, −5.08, and −5.10; IR (film) 3412, 2956, 2931, 2856, and 1471 cm^{-1}. HRMS-ESI *m*/*z* 321.1876 [$(M+Na)^+$; Calcd for $C_{16}H_{30}O_3SiNa$: 321.1862]. The ^1H NMR spectrum, IR, and optical rotation for this compound match those of Honda and co-workers.[32] The ^{13}C NMR was not previously reported.

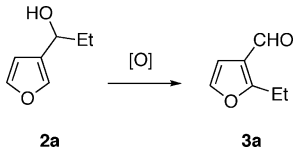
***N*-(1-Furan-3-yl-propyl)-4-methyl-benzene-sulfonamide (12a).** This compound was prepared according to General Procedure A using *N*-furan-3-ylmethylene-4-methyl-benzene-sulfonamide (249 mg, 1.0 mmol), THF (1 mL), and ethyl magnesium bromide (0.5 mL, 3.0 M in ether). The product was chromatographed on silica gel (10% EtOAc in hexanes) to afford the title compound as a colorless oil in 94% yield (262 mg, 0.94 mmol). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.0 (d, 2H, $J =$ 8.1 Hz), 7.26 (m, 3H), 7.10 (s, 1H), 6.10 (s, 1H), 4.30 (m, 1H), 4.23 (q, 1H, $J = 7.0$ Hz), 2.44 (s, 3H), 1.75 (m, 2H), and 0.85 (t, 3H, $J = 7.4$ Hz); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 143.3, 143.2, 139.5, 137.9, 129.4, 127.0, 125.8, 108.3, 51.5, 29.3, 21.5, and 10.1; IR (neat) 3356, 3260, 2923, 1599, 1527, and 1157 cm^{-1}. HRMS-CI *m*/*z* 280.1007 [MH^+; Calcd for $C_{14}H_{18}NO_3S$: 280.1007].

2-Ethyl-1-(toluene-4-sulfonyl)-1*H*-pyrrole-3-carbaldehyde (13a). This compound was prepared by General Procedure B using *N*-(1-furan-3-yl-propyl)-4-methyl-benzene-sulfonamide (278 mg, 1.0 mmol), NBS (178 mg, 1.0 mmol), THF (4 mL), and H_2O (1 mL). After the usual workup, the crude product was purified by column chromatography on deactivated silica gel (0−10% EtOAc in hexanes) to afford the title compound as a yellow oil in 67% yield (186 mg, 0.67 mmol). ^1H NMR ($CDCl_3$, 500 MHz): δ 9.92 (s, 1H), 7.75 (d, 2H, $J = 5.5$ Hz), 7.35 (m, 3H), 6.67 (d, 1H $J = 4.0$ Hz), 3.10 (q, 2H, $J = 10.0$ Hz), 2.47 (s, 3H), and 1.20 (t, $J = 10.0$ Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 187.1, 147.1, 146.9, 136.8, 131.5, 128.5, 125.4, 123.7, 110.0, 22.2, 19.3, and 16.5; IR (neat) 2976, 1724, 1596, 1493, and 1164 cm^{-1}. HRMS-CI *m*/*z* 277.0760 [M^+; Calcd for $C_{14}H_{15}NO_3S$: 277.0773].

3. Results and Discussion

3.1. Development and Optimization of the Oxidative Rearrangement. Our synthesis of 2-substituted 3-furfurals (**3**) begins with the addition of an organometallic reagent to commercially available 3-furfural (**1**). This addition proved to be straightforward, furnishing the furyl alcohols in high yields. The oxidative rearrangement of the resulting furyl alcohols, however, required significant optimization. Utilizing 1-furyl-1-propanol (**2a**) to optimize the oxidation (Scheme 3), we screened various oxidants, oxidant equivalents, and workup procedures. When *m*CPBA, monoperphthalic acid, MMPP, TBHP, and NIS were used, no reaction was observed. Oxidative rearrangement with Br_2 in THF/H_2O and with NCS led to low isolated yields of the desired rearranged products (15−20%).

Scheme 3. Optimization of the Oxidative Rearrangement (Table 1).

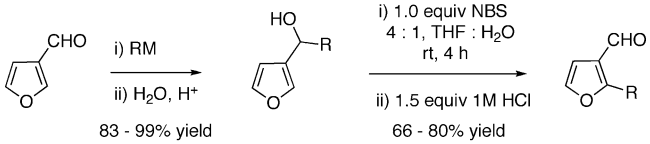


2a **3a**

Table 1. Optimization of the Oxidative Rearrangement with NBS

entry	equiv of NBS	workup	yield (%)
1	1.1	KI, $Na_2S_2O_3$,$NaHCO_3$	50
2	2.0	KI, $Na_2S_2O_3$, $NaHCO_3$	42
3	1.1	KI	30
4	1.1	$Na_2S_2O_3$	51
5	1.1	$NaHCO_3$	29
6	1.1	KI, 1M HCl	25
7	1.1	$Na_2S_2O_3$, 1M HCl	68
8	1.5	1M HCl	70
9	1.1	1M HCl	71
10	1.0	1M HCl	70

Scheme 4. Our Two-step Method for the Synthesis of 2-Substituted 3-Furfurals (Table 2).



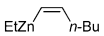
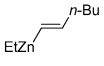
1 **2** **3**

Use of Br_2 in acetone led to consumption of the starting material with the formation of multiple products. Fortunately, higher yields were obtained with NBS, and we focused our efforts on optimization with this reagent.

The conditions for optimization of the oxidative rearrangement are shown in Table 1. Initially we employed 1.1 or 2.0 equiv of NBS in a 4:1 THF/water mixture at room temperature (entries 1 and 2). Under these conditions, the yellow/orange solution became colorless over the 4 h reaction course. Upon consumption of the starting material, the reaction was quenched with successive washings with KI, $Na_2S_2O_3$, and $NaHCO_3$, which is a common workup procedure for Achmatowitz reactions.[29] The yield ranged from 42 to 50% (Table 1, entries 1 and 2). With 1.1 equiv of NBS, alternative workup conditions were examined including evaluating each component of the previous workup individually: KI (entry 3), $Na_2S_2O_3$ (entry 4), or $NaHCO_3$ (entry 5). The yields from these workups were also low. We speculated that basic workup conditions inhibited loss of water and rearomatization of the furanosidic aldehyde; therefore, we examined the affect of acid on the workup. In most cases, acidic workup conditions resulted in increased yields (entries 6−10). When an excess of NBS was used, bromine incorporation into the product was occasionally observed. Further optimization was then performed with 1.0 equiv of NBS (entry 10).

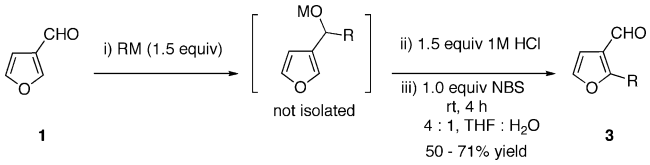
3.2. Oxidative Rearrangement Substrate Scope. To determine the substrate scope of the furan synthesis, we next examined the addition of organolithiums, Grignard, and organozinc reagents to 3-furfural (**1**) (Scheme 4). The resulting furyl alcohols were purified and isolated in high yields (83−99%, Table 2). Although basic, highly reactive organolithium reagents worked well in this process, more functional group tolerant Grignard and organozinc species also provided the furyl alcohols

Table 2. Results for the Two-step and One-pot Synthesis of 2-Substituted 3-Furfurals

entry	organometallic reagent	addition product	addition yield (%)	oxidation product	oxidation yield (%)	two-step yield (%)	one-pot yield (%)
1	EtMgBr	**2a**	98	**3a**	71	70	54
2	*n*-BuLi	**2b**	95	**3b**	66	63	69
3	*i*-PrMgCl	**2c**	91	**3c**	70	64	61
4	$Zn[(CH_2)_4OPiv]_2$	**2d**	83	**3d**	80	66	-
5	PhLi	**2e**	94	**3e**	72	68	70[a]
6	$BrMg(4\text{-}C_6H_4\text{-}Cl)$	**2f**	99	**3f**	72	71	71
7	BrMg(1-Naphthyl)	**2g**	95	**3g**	75	71	66
8	(Allyl)MgBr	**2h**	89	**3h**	73	65	54
9		**2i**	90	**3i**	72	65	50
10		**2j**	93	**3j**	70	65	-
11		**2k**	92	**3k**	70	64	-
12		**2l**	92	**3l**	79	73	65

[a] 5.0 mmol scale

Scheme 5. One-Pot Synthesis of 2-Substituted 3-Furfurals.

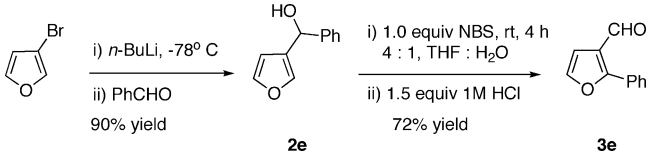


in high yields. The functionalized dialkylzinc reagent $Zn[(CH_2)_4OPiv]_2$ was prepared by Knochel's method and underwent addition to 3-furfural to furnish product in 83% yield.[33] The (*E*)-alkenylzinc reagent was generated by Oppolzer's protocol[34] via hydroboration of the terminal alkyne followed by transmetalation with diethylzinc. The (*Z*)-alkenylzinc reagent was generated by our method[35,36] involving hydroboration of a 1-bromo-1-alkyne, addition of *tert*-butyllithium,[37] and transmetalation of the resulting (*Z*)-vinylborane with diethylzinc. In situ generation and addition of these alkenylzinc reagents to 3-furfural proceeded in 92−93% yield, and no scrambling of the double bond geometry was detected in either product.

With the isolated furyl alcohols in hand, the optimized oxidation conditions (Table 1, entry 10) were utilized in the rearrangement. The conditions proved to be tolerant of a range of functional groups, enabling the installation of alkyl, vinyl, allyl, aryl, and alkynyl groups at the 2 position with yields ranging from 66 to 80% (Table 2). No bromination of the unsaturated side chains or isomerization of the allyl (entry 8) or vinyl (entries 10 and 11) groups were observed with 1.0 equiv of NBS. The combined yields for the two-step addition/oxidative rearrangement process were 63−73%.

We next set out to perform the organometallic addition/oxidative rearrangement sequence in a one-pot tandem reaction (Scheme 5). The advantages of the one-pot procedure are that it is not necessary to isolate the intermediate furyl alcohol and only a single purification is needed. Addition of 1.5 equiv of the organometallic species to 3-furfural was carried out as in Scheme 4; however, rather than workup and isolation of the furyl alcohol, HCl (1M, 1.5 equiv) was added to neutralize the reaction solution. Additional THF and water (4:1) were then introduced into the reaction mixture, followed by 1 equiv of NBS (Scheme 5). After 4 h, the reactions were quenched with additional water and extracted with diethyl ether. As shown in Table 2, the product yields in the one-pot transformation are comparable to, or slightly below, those of the two-step procedure. The one-pot method was unsuccessful with the organozinc reagents. The pivolate protecting group was lost under the conditions of the one-pot procedure, most likely because of the acidic nature of the reaction mixture (entry 4). In the case of the vinyl zinc additions (entries 10 and 11), we speculate that the boron-containing byproducts interfered with the NBS oxidation of the intermediate furyl alcohol.

Scheme 6. Synthesis of 2-Phenyl 3-Furfural.



To explore the potential utility of our method, we examined the scalability of the one-pot synthesis of 2-substituted 3-furfurals. Employing PhLi and 3-furfural on a 5 mmol scale, we were pleased to discover that the reaction proceeded without complication or loss of yield (entry 5, Table 2). To highlight the versatility of our addition/oxidative rearrangement procedure, we also synthesized 2-phenyl 3-furfural by the generation of 3-furyllithium from commercially available 3-bromofuran. Addition of 3-furyllithium to benzaldehyde gave the furyl alcohol **2e** in 90% isolated yield (Scheme 6). The oxidative rearrangement then furnished **3e** in 72% yield.

3.3. Mechanistic Investigations. Several mechanisms for the oxidative rearrangement can be envisioned. Free-radical processes were deemed unlikely because the reaction exhibits similar behavior in the dark and in the light. Of relevance to our oxidative rearrangement, it is known that oxidation of 2,5-disubstituted furans can lead to unsaturated 1,4-dicarbonyl compounds.[38−41] A possible reaction pathway for the oxidative rearrangement begins with bromination of the furan ring of **2** as shown in Scheme 7. We propose that the resulting oxonium ion can undergo the addition of water at the 2 position followed by proton loss, opening of the furan ring, and generation of the key unsaturated 1,4-dialdehyde intermediate. The π system of this unsaturated 1,4-dialdehyde is highly electrophilic and undergoes isomerization about the 2,3 double bond by Michael addition of water, bond rotation, and reformation of the double bond with concomitant elimination of water. Finally, protonation of the carbonyl and attack of the alcohol reforms the heterocycle, generating the furanosidic aldehyde after the proton transfer to the solvent. This intermediate is proposed to undergo acid-catalyzed elimination of water to form the observed 2-substituted 3-furfural (**3**).

(33) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229−8243.
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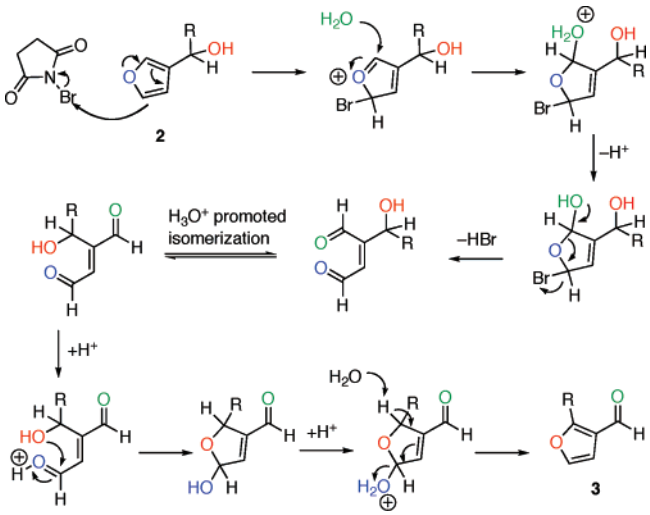
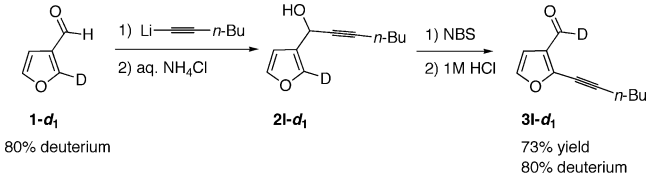
Scheme 7. Possible Reaction Pathway for the NBS-Promoted Oxidative Rearrangement.



Scheme 8. Deuterium Labeling Experiment in the Oxidative Rearrangement.



To probe the mechanism of the oxidative rearrangement, we prepared 2-deutero 3-furfural[42] (**1-*d*$_1$**) using the directed lithiation of Comins and co-workers (Scheme 1).[25] The resulting organolithium was then quenched with D_2O.[23,43] The deuterated product contained 80% deuterium incorporation, as determined by integration of the ^{1}H NMR spectrum. Addition of 1-hexynyllithium, prepared in situ, to 2-deutero 3-furfural (**1-*d*$_1$**) gave the furyl alcohol **2l-*d*$_1$** in 92% yield with no loss of deuterium (Scheme 8, ^{1}H NMR spectroscopy). The oxidation was performed with 1.0 equiv of NBS in THF and H_2O to generate **3l-*d*$_1$**. After rearrangement, it was determined by ^{1}H and ^{13}C-{^{1}H} NMR spectroscopic studies that the deuterium was situated in the aldehydic position (80% incorporation). The outcome of this labeling study supports the reaction pathway proposed in Scheme 7 and the intermediacy of an unsaturated 1,4-dialdehyde or equivalent thereof.

3.4. Synthesis of Enantioenriched 2-Substituted 3-Furfurals. Enantioenriched heterocycles are important building blocks in the pharmaceutical industry, yet their synthesis is often challenging. We envisioned a different approach to the preparation of the oxidative rearrangement precursors than organometallic addition to 3-furfural (Scheme 4) or generation of 3-furyllithium (Scheme 6) that would allow enantioselective introduction of stereogenic centers. Our strategy was to prepare 3-vinyl furans (**4**) and subject them to the Sharpless asymmetric dihydroxylation (AD).[44−46] A series of 3-vinyl furans were prepared and dihydroxylated with AD-mix-β affording the desired diols (**5**) in 78−97% yield with enantioselectivities ≥97% (Scheme 9, Table 3). The oxidative rearrangement was performed using the conditions outlined above to furnish the enantioenriched furan products with good conservation of ee. Only in the case of the aryl substituted derivative was a drop in ee observed (from 98 to 88% ee). This is most likely due to the formation of a stabilized benzylic carbocation from the oxidative rearrangement product.

Scheme 9. AD Route to Chiral Enantioenriched Furyl Alcohols.

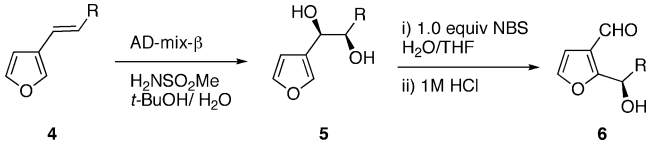


Table 3. Synthesis of Enantioenriched Furans by Asymmetric Dihydroxylation of 3-Vinyl Furans with AD-Mix-β and Oxidative Rearrangement (Scheme 9)

		AD			Rearrangement		
entry	R	product	yield (%)	ee (%)	product	yield (%)	ee (%)
1	CO_2Et	**5a**	78	99	**6a**	63	99
2	CH_2OBn	**5b**	79	>99	**6b**	55	>99
3	cyclohexyl	**5c**	97	97	**6c**	62	97
4	3-C_6H_4-CF_3	**5d**	79	99	**6d**	66	88
5	*t*-Bu	**5e**	89	97	**6e**	59	97

3.5. Enantioselective Synthesis of a Key Intermediate in Route to (−)-Canadensolide. With this method in hand, we sought to demonstrate its utility in natural product synthesis. An interesting natural product target is (−)-canadensolide, which was isolated from *Penicillium canadense* by McCorkindale and co-workers and exhibits antigerminative activity against fungi.[48] Several racemic syntheses[49−54] and syntheses from enantioenriched natural sources[55−61] have been reported. With the exception of Honda's kinetic resolution (KR),[62,32] no syntheses based on asymmetric catalysis have appeared. Honda's enan-

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(53) Lertvorachon, J.; Thebtaranonth, Y.; Thongpanchang, T.; Thongyoo, P. *J. Org. Chem.* **2001**, *66*, 4692−4694.
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(57) Al-Abed, Y.; Naz, N.; Mootoo, D.; Voelter, W. *Tetrahedron Lett.* **1996**, *37*, 8641−8642.
(58) Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 4786−4790.
(59) Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1978**, 3233−3236.
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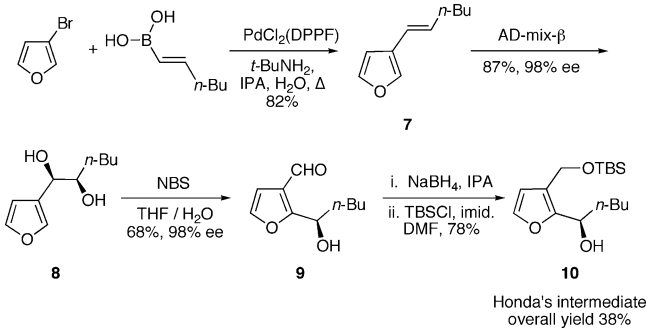
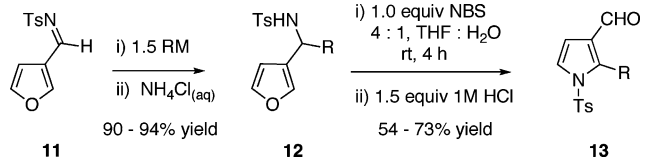
Scheme 10. Our Synthesis of Honda's Furyl Alcohol Intermediate in Route to (−)-Canadensolide.



Scheme 11. Synthesis of 2-Substituted 3-Formyl Pyrroles.



tioenriched furyl alcohol intermediate, which was prepared by KR[63] with the Sharpless−Katsuki catalyst (41%, providing product of >95% ee)[64,65] attracted our attention.[62,32]

To highlight our oxidative rearrangement method, we approached the synthesis of Honda's enantioenriched furyl alcohol intermediate (**10**) as outlined in Scheme 10. A Suzuki cross-coupling[66] of 3-bromofuran with 1-hexenyl-1-boronic acid produced the trans alkene **7** in 82% yield. The Sharpless AD was performed with AD-mix-β to afford the desired diol **8** in 87% yield with 98% ee. Subjecting the diol to our oxidative rearrangement protocol led to the desired 2-substituted 3-furfural intermediate **9** with no loss of ee, as determined by chiral stationary phase HPLC (Scheme 10). From this intermediate, reduction with $NaBH_4$ and selective TBS protection of the primary alcohol led to formation of the furyl alcohol **10** in 78% yield over this two step procedure. The overall yield of our synthesis was 38%, which compares favorably with the 22% yield achieved by Honda. Given the improved yield and high enantiopurity of the furyl alcohol in Scheme 10, coupled with the scalability of the oxidative furan synthesis (Scheme 5), we anticipate that this method will be useful in the synthesis of other natural products.

3.6. Synthesis of 2-Substituted 3-Formyl Pyrroles. On the basis of our oxidative rearrangement mechanism (Scheme 7), we hypothesized that 3-furyl imines (**11**) would undergo a similar rearrangement sequence to form pyrroles (**13**, Scheme 11). To activate the imine toward nucleophilic addition and serve as a protecting group for the resulting pyrrole, we chose to employ *N*-sulfonyl imines. Although deprotection of sulfonamides is quite difficult, the sulfonyl group is an excellent protecting group for pyrroles[67] because it not only moderates the high reactivity of pyrroles but it is easily removed under basic conditions.[68]

Table 4. Synthesis of 2-Substituted 3-Formyl Pyrroles (Scheme 11)

		addition		oxidation	
entry	organometallic reagent	product	yield (%)	product	yield (%)
1	EtMgBr	**12a**	94	**13a**	67
2	*n*-BuLi	**12b**	90	**13b**	67
3	PhLi	**12c**	90	**13c**	70
4	BrMg(2-C_6H_4-Me)	**12d**	91	**13d**	73
5	BrMg(1-Naphthyl)	**12e**	92	**13e**	71
6	(Allyl)MgBr	**12f**	91	**13f**	54
7		**12g**	90	**13g**	72

The addition and oxidative rearrangements of a variety of imine substrates were examined (Scheme 11), and the results are compiled in Table 4. Addition of alkyl (entries 1−2), aryl (entries 3−5), allyl (entry 6), and vinyl (entry 7) organometallic reagents to the furyl imines furnished the desired furyl amines in high isolated yields (90−95%). The oxidative rearrangement of the furyl sulfonamide addition products was performed with NBS under conditions identical to those used in the rearrangement of the furyl alcohols (Table 2). These reactions proceeded smoothly to provide the pyrrole products in 54−73% yield. The addition/oxidative rearrangement route to pyrroles from readily available 3-furfural is a straightforward and practical method to access these valuable heterocycles.

4. Conclusions and Outlook. We have introduced new methods to prepare functionalized 2-substituted 3-furfurals and 2-substituted 3-formyl pyrroles. Unlike prior methods to prepare these fundamental heterocyclic building blocks, our methods enable the synthesis of a range of derivatives that can be isolated free of undesired isomers. Furthermore, in many cases the addition to 3-furfural/oxidative rearrangement can be carried out in a tandem one-pot procedure, circumventing intermediate purification.

The precursors to the oxidative furan rearrangement can be prepared by three approaches: (1) addition of organolithium, Grignard, and organozinc reagents to 3-furfural, (2) addition of 3-furyllithium to aldehydes, and (3) asymmetric dihydroxylation of 3-vinylfurans. The later method enables the synthesis of enantioenriched furan derivatives and has been applied to the generation of an intermediate in Honda's synthesis of the natural product (−)-canadensolide.

Our method for the synthesis of 2-substituted 3-formyl pyrroles begins with the readily prepared sulfonyl imine of 3-furfural. Addition of organometallic reagents generates sulfonamides in high yields. When subjected to oxidative rearrangement conditions, the furyl sulfonamide undergoes pyrrole formation. This method makes possible the generation of alkyl, aryl, vinyl, and allyl substituted pyrroles that would be otherwise difficult to access. Finally, our deuterium labeling studies and the formation of pyrroles from furyl sulfonamides support a proposed mechanism involving oxidative cleavage of the furan ring to an unsaturated 1,4-dialdehyde intermediate. This highly reactive intermediate is not observed but undergoes cyclization to form the observed furan and pyrrole products.

The importance of heterocycles in natural products and medicinal chemistry, coupled with the versatility and scalability of our methods to prepare substituted furans and pyrroles, make

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these methods potentially very useful in target and diversity-oriented synthesis.[69]

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Supporting Information Available: Procedures, full characterization, and stereochemical assignments of new compounds are available (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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