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Synthesis of Substituted Furans Using 1,4-Dioxene

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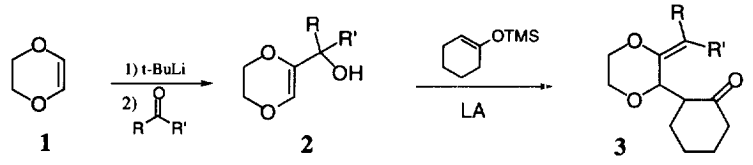
Abstract: Treatment of 2,3-substituted 1,4-dioxanes **4** with catalytic amount of camphorsulfonic acid in dichloromethane at room temperature aforded substituted furans.

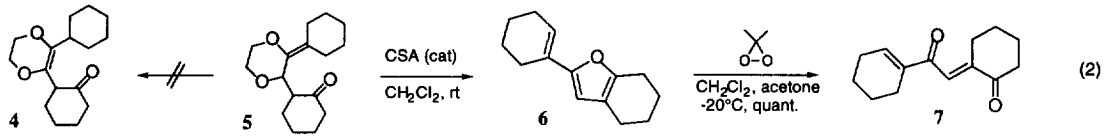
Keywords: 2,3-dihydro-1,4-dioxin, substitued furans, acid-catalyzed cyclodehydration, camphorsulfonic acid.

Furans are important functional groups that can be found in many natural products[1] and have frequently been used as intermediates in organic synthesis.[2] Consequently, the construction of the furan ring has stimulated the continued development of new methods.[3] As part of our general interest in the synthetic applications of 1,4-dioxene (2,3-dihydro-1,4-dioxin) **1**,[4] we recently reported the behaviour of allylic alcohols **2**, readily prepared by the addition of dioxenyllithium to ketones and aldehydes,[5] towards nucleophilic displacement reactions in the presence of a Lewis acid.[6] For instance, **2** reacts with various silyl enol ether such as 1-(trimethylsilyloxy)-cyclohexene in the presence of lithium perchlorate ($LiClO_4$) in ether or a catalytic amount of trimethylsilyl trifluorosulfonate (TMSOTf) in acetonitrile to afford 2,3-disubstituted 1,4-dioxanes **3** in high yields (eq 1). In this communication we report the use of these compounds in a new approach for the preparation of substituted furans under mild conditions.



(1)

This method was found while attempting the synthesis of compounds **4** by acid-catalyzed isomerization of **5**. Thus, treatment of **5** with a catalytic amount (5% equiv) of camphorsulfonic acid (CSA) in dichloromethane at room temperature for 15min provided only one product, isolated in 95% yield after flash chromatography. Contrary to our expectations, its spectral data were not consistent with ketone **4**. In particular, the IR spectrum did not show any signal corresponding to a carbonyl absorption; the ^{13}C NMR spectrum contained resonances for four quaternary sp^2, instead of the two expected for **4**, and two tertiary sp^2. After careful analysis of the ^1H and ^{13}C NMR spectra,[7] structure **6** was assigned to this compound. Oxidation of **6** with *one equivalent* of



(2)

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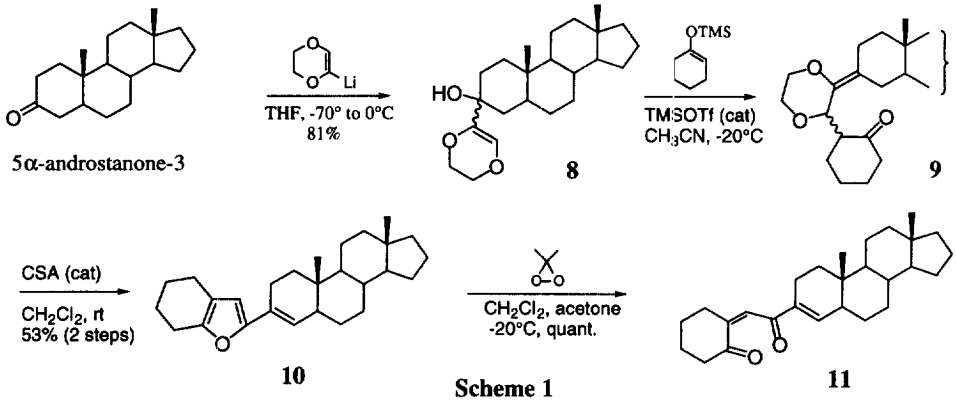
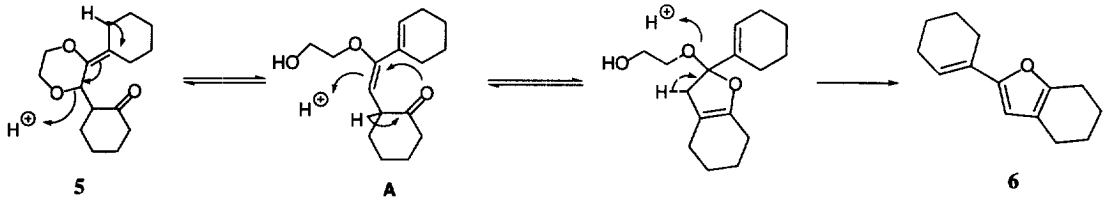
dimethyldioxirane[8] at –20°C provided dienedione **7**[7] in nearly quantitative yield (eq 2). This result, which is in agreement with previous observations on the oxidation of furans,[9] provides a strong support for the structure of **6**.

The ease of this reaction prompted us to investigate it in greater detail, and we therefore prepared the steroid derivative **9**. The addition of 1,4-dioxenyllithium to 5α-androstan-3-one gave allylic alcohol **8** as a separable mixture of 3β and 3α epimers (*ca* 3:2 ratio) in 81% combined yield (Scheme 1). Treatment of the major 3β–OH isomer with 1-(trimethylsilyloxy)-cyclohexene in the presence of TMSOTf (0.05 equiv) in acetonitrile at –30°C to –20°C afforded **9** as a mixture of four isomers wich were unseparable by flash chromatography. Exposure of this crude mixture to a catalytic amount of CSA in CH_2Cl_2 furnished a crystalline compound (53% overall yield) which showed the same spectroscopic data for the furyl moiety as for **6**.[7] The structure **10** was unambiguously assigned by X-ray crystallographic analysis.[10]

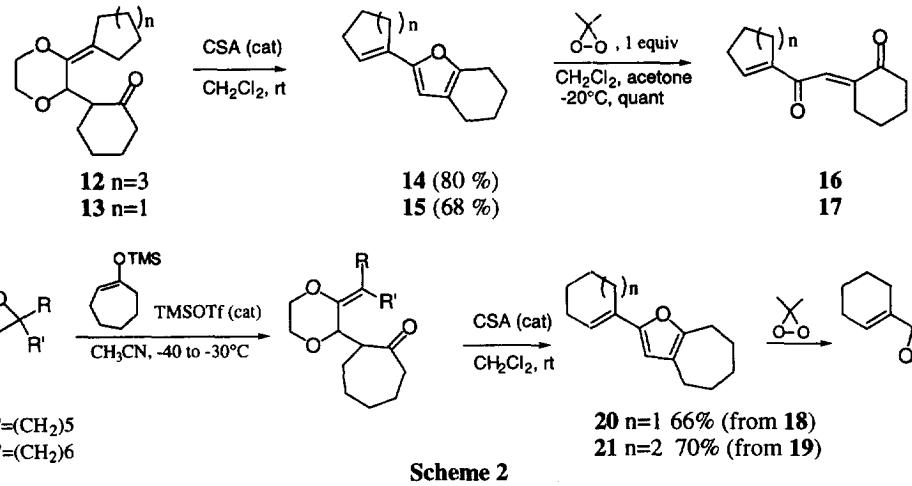


Scheme 1

The formation of the furan ring can be rationalized as illustrated below for the case of **6**. Protonation of the dioxane ring probably occurs first and results in formation of the intermediate **A** which can undergo cyclization followed by aromatization to furnish **6**.

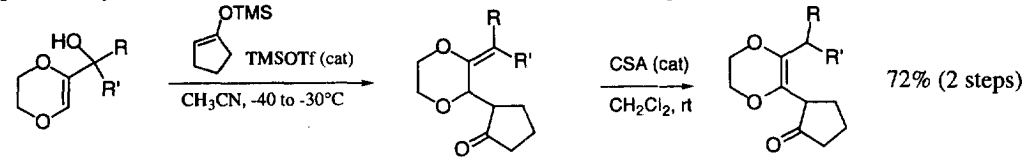


In the same way, cycloheptylidene **12** and cyclopentylidene **13** led to 2-cycloheptenyl- and 2-cyclopentenyl-4,5,6,7-tetrahydro-benzofurans **14** and **15** in 80% and 68% yield respectively (Scheme 2). As for **6**, furans **10**, **14**, and **15** underwent oxidation with dimethyldioxirane to afford dienediones **11**, **16** and **17** respectively in high yield. 2-Cycloalkyl-5,6,7,8-tetrahydro-4H-cyclohepta<b>furans **20** and **21**[7] were also prepared from the readily available tertiary alcohols **18** and **19** in good overall yield (Scheme 2).

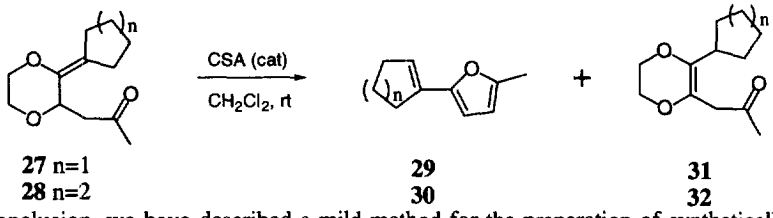


Scheme 2

In contrast, treatment of cyclopentanone derivatives **23** and **24** with CSA under the same conditions as above, gave the 3,4-disubstituted 1,4-dioxenes **25** and **26** as the sole isolated products in high yield (72% yield in two steps from the corresponding allylic alcohols). In this case, the absence of the expected furans is presumably due to the strain which could result from the cyclization process.



When the ketone side chain was linear such as 2-oxo-propyl group in **27** and **28**, the treatment with CSA led to a mixture of furans **29** and **30** along with the 3,4-disubstituted 1,4-dioxenes **31** and **32** in modest overall yield (40-50%).



In conclusion, we have described a mild method for the preparation of synthetically valuable substituted furans from readily accessible 1,4-dioxene and ketones as starting materials.

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7. All new compounds were fully characterized by their spectroscopic and analytical data. Selected compounds: **6**: colorless oil, ^{1}H NMR (200MHz,$CDCl_3$) δ 1.55-1.95 (m, 8H), 2.10-2.30 (m, 4H), 2.39 (t, J=6Hz, 2H), 2.59 (t, J=5.4Hz, 2H), 5.97 (s, 1H), 6.15-6.30 (m, 1H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 153.4 (C), 149.5 (C), 127.5 (C), 120.7 (CH), 118.0 (C), 104.6 (CH), 25.2 (CH_2), 25.0 (CH_2), 23.3 (2 CH_2), 22.6 (CH_2), 22.5 (CH_2), 22.2 (CH_2) ppm. **7**: IR (CCl_4) ν_{max} 1704, 1655 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50-1.65 (m, 4H), 1.75-2.05 (m, 4H), 2.10-2.35 (m, 4H), 2.45-2.70 (m, 4H), 6.23 (s, 1H), 6.75-6.90 (m, 1H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 204.1 (C), 194.6 (C), 148.8 (C), 141.8 (CH), 139.9 (C), 128.8 (CH), 42.9 (CH_2), 35.9 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.8 (CH_2), 22.8 (CH_2), 21.8 (CH_2), 21.7 (CH_2) ppm. **10**: mp 150-153°C (petroleum ether), $[\alpha]_D$ +64 (c 0.42, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (s, 3H), 0.77 (s, 3H), 2.39 (t, J=5.8 Hz, 2H), 2.58 (t, J=6Hz, 2H), 5.98 (s, 1H), 6.12 (d, J=6Hz,1H) ppm. ^{13}C NMR (50.3.6MHz, $CDCl_3$) δ 153.1 (C), 149.6 (C), 126.2 (C), 119.7 (CH), 118.2 (C), 104.7 (CH), 54.6 (CH), 54.3 (CH), 41.4 (CH), 40.8 (C), 40.6 (CH_2), 40.1 (CH2), 39.0 (CH_2), 36.1 (CH), 34.9 (C), 32.3 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 25.7 (CH_2), 23.3 (3CH_2), 22.3 (CH_2), 21.2 (CH_2), 20.6 (CH_2), 17.5 (CH_3), 12.0 (CH_3) ppm. **11**: IR (CCl_4) ν_{max} 1705, 1655, 1548 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.69 (s, 3H), 0.70 (s, 3H), 2.52 (t, J=6.8 Hz, 2H), 2.60 (t, J=6Hz, 2H), 6.23 (s, 1H), 6.71 (d, J=6Hz,1H) ppm. ^{13}C NMR (100.6MHz, $CDCl_3$) δ 204.1 (C), 194.5 (C), 148.6 (C), 140.7 (CH), 138.9 (C), 129.0 (CH), 54.4 (CH), 54.0 (CH), 42.9 (CH_2), 41.0 (CH), 40.9 (CH_2), 40.7 (C), 40.4 (CH_2), 38.8 (CH_2), 35.9 (CH), 35.8 (CH_2), 34.8 (C), 32.0 (CH_2), 28.5 (CH_2), 27.7 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 21.2 (CH_2), 20.5 (CH_2), 17.5 (CH_3), 12.1 (CH_3) ppm. **20**: colorless oil, ^{1}H NMR (400MHz,$CDCl_3$) δ 1.62-1.85 (m, 10H), 2.15-2.25 (m, 4H), 2.45 (t, J=6Hz, 2H), 2.76 (t, J=5.4Hz), 2H), 5.94 (s, 1H), 6.09-6.28 (m, 1H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 152.1 (C), 151.4 (C), 127.2 (C), 122.0 (C), 120.5 (CH), 107.5 (CH), 30.9 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 26.7 (CH_2), 26.2 (CH_2), 25.2 (CH_2), 24.9 (CH_2), 22.5 (CH_2), 22.4 (CH_2) ppm.
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