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1,3-Dioxolan-2-ylium Cations from Acylfurans: Conversion of Furyl Ketones to Esters Under Nonoxidative Conditions

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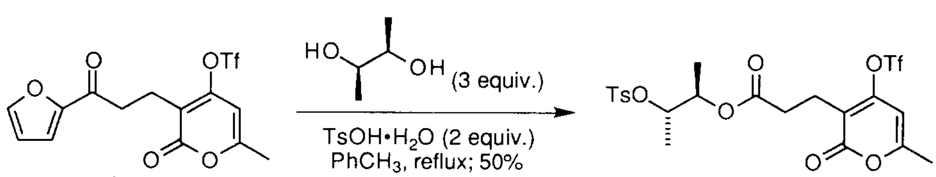
Abstract: Acylfurans **3** furnished tosylated glycol monoesters **5** when treated with 1,2-diols in the presence of an equivalent of TsOH. This process likely occurs via protiodefuranation of the intermediate furyl ketals to form 1,3-dioxolan-2-ylium cations **8**. Subsequent ring-opening via S_N2 nucleophilic displacement by *p*-toluenesulfonate then provides esters **5**. When a 1,3-diol was employed, furan-containing ester **9** was formed instead of the standard product through an apparent aldol dimerization/fragmentation pathway.

Furans are versatile building blocks that have been employed in cycloadditions,[1] oxidative ring openings,[2] nucleophilic additions,[3] and many other chemical transformations[4] that take advantage of the unique properties of this electron-rich aromatic heterocycle. Our interest in the furan subunit has focused on its use as a cycloaddition partner in [4+3]- and [4+4]-cycloadditions.[5] Here we report our serendipitous discovery that ketofurans may form highly reactive 1,3-dioxolan-2-ylium cation[6] intermediates under ketalization conditions via loss of volatile furan. Subsequent nucleophilic opening then provides glycol ester monotosylates.

While studying various auxiliary-based approaches to asymmetric [4+4]-photocycloaddition reactions, we sought to prepare C_2-symmetric ketal derivatives of ketofuran **1**. These substrates could be obtained in good yields under standard protic acid ketalization conditions, but the reactions were sluggish, often requiring up to two days. To increase the rate of the reaction, stoichiometric amounts of *p*-toluenesulfonic acid (TsOH) were employed, shortening the reaction time substantially. However, in this case, ester **2** was the only product observed, and none of the desired ketal product was isolated (eq 1). This unusual result amounts to an acylation of the glycol by **1** with loss of furan, and results in a formal oxidation at the acyl carbon.[7] We now wish to report the general preparation of tosylated glycol monoesters from acylfuran staring materials under nonoxidative ketalization reaction conditions.



1 **2** (1)

To explore the generality of this process, we chose commercially available acetylfuran **3a** and 1-(2'-furyl)-3-phenyl-1-propanone **3b** (easily prepared by aldol condensation between acetylfuran and benzaldehyde, followed by a palladium catalyzed hydrogenation).[8] With these ketofurans in hand, diols **4a-c** were tested using 1.5-3.0

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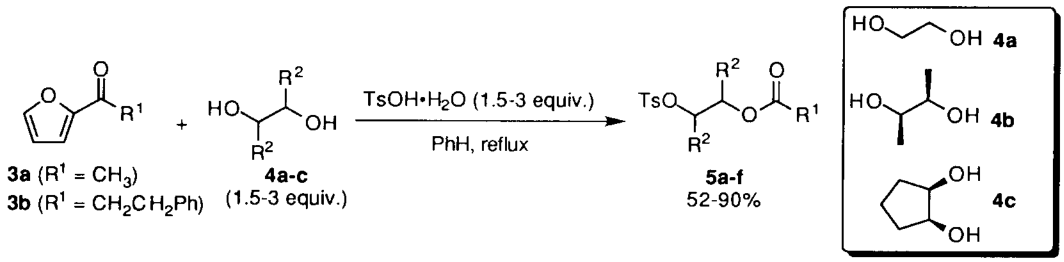
equivalents each of the diol and TsOH in refluxing benzene (equation 2).[9] The results of these reactions are shown in Table 1. All of these reactions were also performed in refluxing toluene, but lower yields of products were observed in all cases. Other acids (acetic acid, triflic acid, methanesulfonic acid) were also examined, but resulted in either no reaction or complete decomposition of the starting substrate.



(2)

Table 1. Preparation of Esters 5 from Ketofurans 3 and Symmetric Diols.[a]

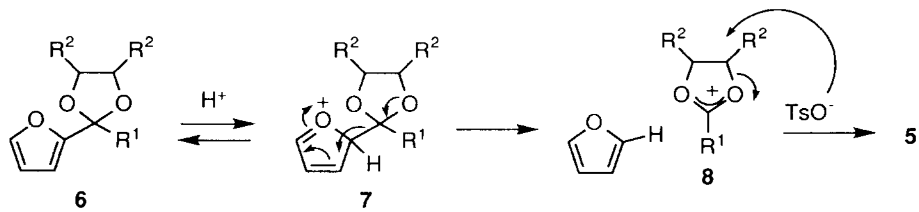
Entry	Ketofuran	R^1	Glycol	R^2	Product	Yield(%)	de(%)[b]
1	**3a**	CH_3	**4a**	H	**5a**	52	--
2	**3b**	CH_2CH_2Ph	**4a**	H	**5b**	77	--
3	**3a**	CH_3	**4b**	CH_3	**5c**	88	87[c]
4	**3b**	CH_2CH_2Ph	**4b**	CH_3	**5d**	90	>95[c]
5	**3a**	CH_3	**4c**	$(CH_2)_3$	**5e**	64	>95
6	**3b**	CH_2CH_2Ph	**4c**	$(CH_2)_3$	**5f**	68[d]	>95

[a]See equation 2 and reference 9. [b]Extent of diol inversion (see text). [c]Only 1.5 equiv. of TsOH and diol were employed. [d]An additional 23% of *trans*-1,2-dihydroxycyclopentane monotosylate was isolated (see text).

All 1,2-diols furnished ester products analogous to **2** when exposed to stoichiometric TsOH, but there was some variation in the efficiency of the transformation. Glycol **4b** (*R,R*-2,3-butanediol) gave the best yields (entries 3 and 4), and required only 1.5 equiv. each of diol and TsOH. In other cases, use of less than three equivalents of either diol or TsOH led to incomplete consumption of **3**. Examples employing *cis*-1,2-dihydroxycyclopentane **4c** (entries 5 and 6) were complicated by the concomitant formation of the ketal derived from **4c** and cyclopentanone, a side-reaction which may account for the requirement for excess diol in these cases.[10] In one case (entry 6), an additional product, *trans*-1-hydroxy-2-tosyloxycyclopentane, was isolated.[11]

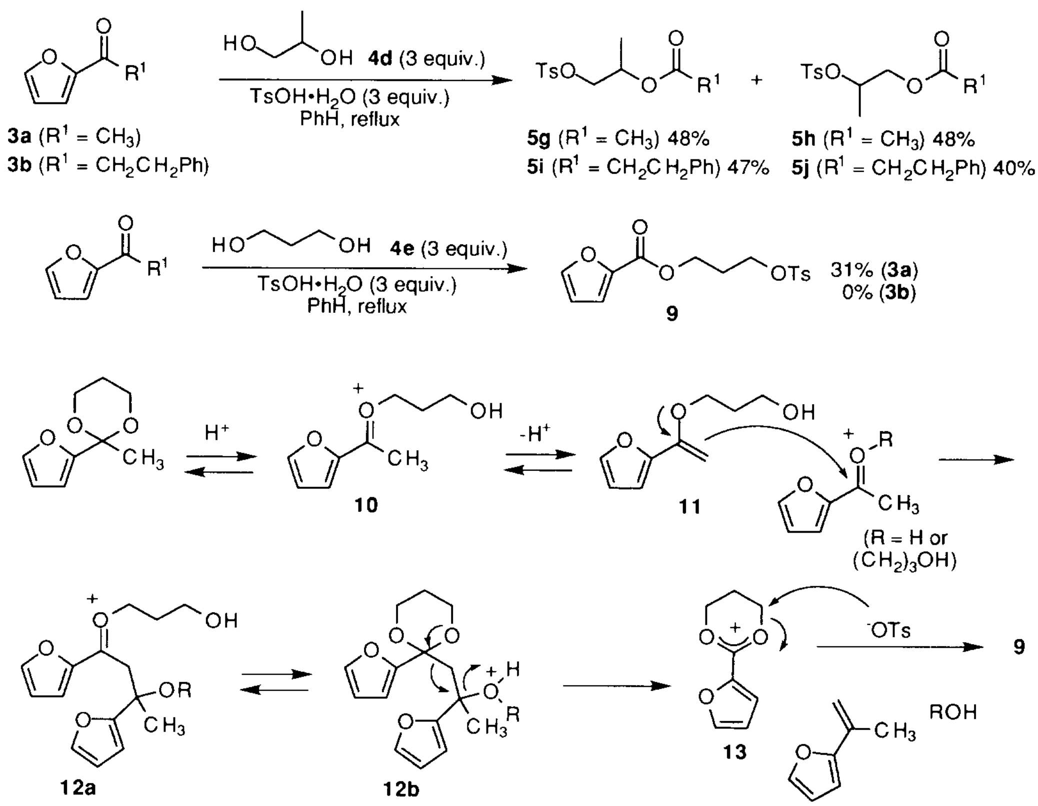
Esters **5** are presumed to form via ketals **6**, which then undergo furan protonation at C-1 to give **7** (Scheme 1). At this point, loss of volatile furan and formation of a highly stabilized 1,3-dioxolan-2-ylium cations **8** can occur.[12,13] Backside nucleophilic displacement by tosylate then opens the ring with inversion at one of the stereocenters to yield the ester products **5**.[14] This mechanism is similar to that proposed for the conversion of diols to bromoacetates using the Moffatt reagent.[15] It is notable that use of simple alcohols (MeOH, EtOH, $Ph(CH_2)_2OH$) led only to recovered starting materials, indicating the importance of a cyclic ketal in this sequence.

Scheme 1



The effect of glycol substitution pattern was also examined, using 1,2-propanediol **4d** and 1,3-propanediol **4e** (Scheme 2). Under the standard conditions, diol **4d** gave high yields of ester products **5g-j**, but with virtually no regioselectivity. In this case steric factors favoring attack at the primary position may be balanced by an electronic preference for attack at the more substituted secondary position. In contrast, 1,3-diol **4e** gave low yields of ester product **9** with **3a** and no reaction with **3b**. The most notable aspect of this result is the retention of the furan ring, suggesting an apparent (and highly doubtful) protiodemethylation. A more reasonable mechanism for the formation of **9** involves equilibration of the propylene ketal with enol ether **11** via **10**, which should be more favorable in the case of a 6-membered ketal.[16] Cationic aldol condensation of **11** with **10** or with protonated **3a** then leads to equilibrating dimeric products **12a** and **12b**. Ketal assisted fragmentation of **12b** would then result in volatile propenylfuran and the highly stabilized 1,3-dioxan-2-yl cation **13**, which then suffers the usual nucleophilic opening to furnish **9**. This mechanism is consistent with the low yield seen with **3a** (theoretical yield = 50%), and the failure of the more highly substituted **3b** to react may be due to greatly diminished rates of enol ether formation and aldol condensation. Excellent precedent for ketal mediated condensations and fragmentations of this sort can be found in the reports of Sakai and coworkers.[17]

Scheme 2



We have described a novel method for converting furyl ketones to esters in the presence of stoichiometric 1,2-diols and TsOH. This formal oxidation at the ketone carbon proceeds through a protiodefuranation of the intermediate ketal to give a 1,3-dioxolan-2-ylium cation which then suffers nucleophilic ring opening. In contrast, use of 1,3-propane diol gives ester products retaining the furan in a process that likely involves an aldol dimerization/fragmentation mechanism. Further aspects of this unusual chemistry will be reported in due course.

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8. The intermediate α,β-unsaturated ketofuran was examined as a third substrate, but proved to be unreactive under all attempted ketalization conditions.
9. A 25 mL round bottom flask equipped with a Dean-Stark trap and a reflux condenser was charged with acetyl furan **3** (0.071 g, 0.64 mmol), $TsOH{\bullet}H_2O$ (0.367 g, 1.93 mmol), ethylene glycol (0.120 g, 1.93 mmol) and benzene (15 mL). The solution was then stirred under N_2 and heated to reflux for 14 h. The dark colored reaction was then cooled, diluted with Et_2O (40 mL) and washed with sat. $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was then dried ($MgSO_4$) and concentrated. The crude yellow oil was purified via column chromatography (silica gel; hexanes/EtOAc 4:1) to yield **5a** (0.086 mg, 0.33 mmol, 52%) as a yellow oil: R_f 0.23 (hexanes/EtOAc 7:3); IR (neat) 1744 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 (br d, J = 8.3 Hz, 2H), 7.35 (br d, J = 8.5 Hz, 2H), 4.31 (s, 4H), 2.44 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) ^{d} 170.5,145.0, 132.6, 129.9(2), 127.9(2), 67.5, 61.5, 21.6, 20.6.
10. Cyclopentanone is believed to arise from competing pinacol rearrangement of **4c** under the reaction conditions.
11. This product may result from transesterification of the initially formed **5f** by excess **4c**. However, none of the expected monoester of **4c** was isolated.
12. Facile protiodesilylations of furylsilanes are well precedented. See: (a) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112. (b) Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439.
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