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# Alkylation of Vinyl Sulfones as a Route to 2-Alkylidene Tetrahydrofurans

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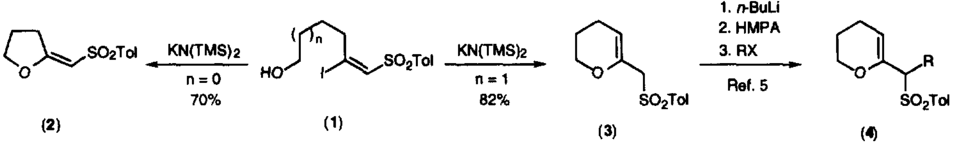
***Abstract:*** Deprotonation of the vinyl sulfone (**2**) with *n*-butyllithium and treatment of the resulting organolithium intermediate with an alkyl halide in the presence of hexamethylphosphoramide (HMPA) gives monoalkylated adducts in 14 to 61% yields. In general, excellent regioselectivity for alkylation α to the sulfone is observed. © 1999 Elsevier Science Ltd. All rights reserved.

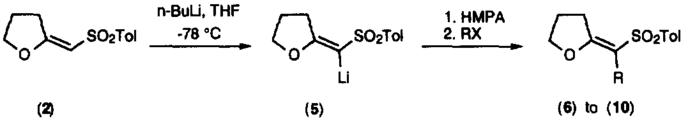
***Keywords:*** Sulfones; Alkylation; Lithiation; Regioselection

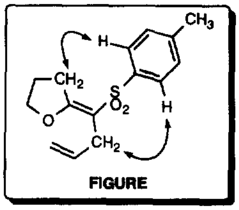
Five- and six-membered oxygen heterocycles with a range of substituents in the "anomeric" position are important substructures in a range of biologically potent natural products. One such group is known collectively as the annonaceous acetogenins;[1] these compounds generally have, as key elements, saturated five- and six-membered heterocycles along with a butenolide "cap". A range of strategies has been developed for the synthesis of these ring systems;[2] recently we[3] and others[4] have developed a methodology (Scheme 1) where β-iodo vinyl sulfones (**1**) are useful intermediates for the preparation of both ring sizes (**2**) and (**3**). Further, we have shown that the dihydropyran intermediate (**3**) can be used as a convenient starting material for the synthesis of a range of substituted dihydropyrans (**4**).[5]



**Scheme 1**

The 2-methylene tetrahydrofuran (**2**) is readily accessible using the β-iodo vinyl sulfone methodology,[3,4] or alternatively by cyclisation of ω-halo β-keto sulfones[6] or ω-hydroxy propargylic sulfones.[7] We believed that deprotonation of this vinyl sulfone and subsequent alkylation[8] would provide a new general route to 2-alkylidene tetrahydrofurans (Scheme 2). Treatment of the vinyl sulfone (**2**) with *n*-butyllithium (1 equiv.) at -78 °C followed by addition of HMPA (1 equiv.) and then the required alkyl halide gave the desired alkylated material.[9] In general, reaction with active (allyl, benzyl), methyl, or primary (*n*-butyl) alkyl halides gave reasonable yields (48 to 61%) of α-monoalkylated products (Table), however attempted alkylation with isopropyl bromide gave a very poor yield (14%).[10] (*E*)-Stereochemistry was assigned on the basis of 2D NOESY experiments; key correlations observed for adduct (**7**) are shown in the Figure. While deprotonation of the vinyl sulfone (**2**) could conceivably occur either α or γ to the sulfur, quenching of the anionic intermediate with $D_2O$ gave a low recovery of starting vinyl sulfone with exclusive α-monodeuteration, suggesting that the vinyllithium species (**5**) is an intermediate.





**FIGURE**

**Scheme 2**

*PII:* S0040-4039(99)00573-0

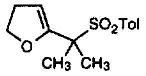
## Table

| Alkyl halide | Product | Yield | (*E*) : (*Z*) |
|---|---|---|---|
| $CH_3I$ | (**6**) | 48%[a] | >95 : <5 |
| $CH_2$=$CHCH_2Br$ | (**7**) | 61% | 92 : 8 |
| $PhCH_2Br$ | (**8**) | 49%[b] | >95 : <5 |
| n-BuBr | (**9**) | 48% | >95 : <5 |
| $(CH_3)_2CHBr$ | (**10**) | 14% | >95 : <5 |

a. Some α,α-dialkylated compound (**11**, 8%) also isolated. See main text.

b. Some α,γ-dialkylated compound (**12**, 5%) also isolated. See main text.

In two cases significant levels of dialkylation have been observed, possibly as a result of deprotonation of the monoalkylated product by the more basic vinyllithium species γ to the sulfone giving a lithio allyl sulfone. A small electrophile ($CH_3I$) gives the second alkylation α to the sulfone (**11**), whereas a more sterically encumbered haloalkane ($PhCH_2Br$) leads to small amounts of γ-alkylation (**12**). Studies on transmetallations, as a potential means to control this reactivity further, are in progress.



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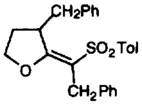

(12)

## References and Notes

1. See: Zeng, L., Ye, Q., Oberlies, N.H., Shi, G., Gu, Z.-M., He, K., and McLaughlin, J.L., *Nat. Prod. Reps.*, **1996**, *13*, 275, and references therein.
2. Eliot, M.C., *Contemp. Org. Synth.*, **1997**, *4*, 238; Boivin, T.L.B., *Tetrahedron*, **1987**, *43*, 3309.
3. Edwards, G.L., Muldoon, C.A., and Sinclair, D.J., *Tetrahedron*, **1996**, *52*, 7779.
4. Short, K.M. and Ziegler, C.B., Jr., *Tetrahedron Lett.*, **1995**, *36*, 355.
5. Edwards, G.L., Sinclair, D.J., and Wasiowych, C.D., *Synlett*, **1997**, 1285.
6. Mussatto, M.C., Savoia, D., Trombini, C., and Umani-Ronchi, A., *J. Chem. Soc., Perkin Trans. I*, **1980**, 260.
7. Dai, W.-M. and Lee, M.Y.H., *Tetrahedron*, **1998**, *54*, 12497.
8. Eisch, J.J. and Galle, J.E., *J. Org. Chem.*, **1979**, *44*, 3279.
9. ***Typical procedure***: *n*-Butyllithium (0.5 ml of a 1.99 M solution in hexanes, 1.0 mmol) was added dropwise to a stirred solution of (*E*)-2-[(*para*-toluenesulfonyl)methylene]tetrahydrofuran (**2**) (0.24 g, 1.0 mmol) in dry THF (15 ml) at -78 °C under an argon atmosphere. After 15 min, HMPA (0.17 ml, 1.0 mmol) was added dropwise, followed by allyl bromide (0.09 ml, 0.13 g, 1.0 mmol) which was added all at once. The solution was allowed to warm to room temperature over 5 h, the reaction was quenched by the addition of brine (20 ml), and the organic layer separated. The aqueous layer was extracted with ether (3 x 15 ml), and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (silica; 10% ethyl acetate/light petroleum) of the crude product gave *(*E*)-2-[1′-(*para*-toluenesulfonyl)-3′-butenylidene]tetrahydrofuran* (**7**) as a colourless oil that eventually solidified to give colourless prisms (0.17 g, 61%), m.p. 70-72 °C (Found: C, 64.4; H, 6.6. $C_{15}H_{18}O_3S$ requires C, 64.7; H, 6.5%). $\nu_{max}$(paraffin) 1635s, 1600m, 1320m, 1300s, 1290m, 1235m, 1205m, 1180s, 1160s, 1130s, 1085m, 1040m, 920m, 820m, 760m, 710m $cm^{-1}$. $\delta_H$ (500 MHz, $CDCl_3$) 2.10 (quintet, *J* 7.4 Hz, 2H, H4), 2.40 (s, 3H, $ArCH_3$), 3.05 (d, *J* 6.2 Hz, 2H, H2′), 3.19 (t, *J* 7.8 Hz, 2H, H3), 4.22 (t, *J* 6.7 Hz, 2H, H5), 4.87 (d(br), *J* 10.0 Hz, 1H, H4′a), 4.93 (dd, *J* 16.4, 1.6 Hz, 1H, H4′b), 5.66 (ddt, *J* 16.4, 10.3, 6.2 Hz, 1H, H3′), 7.26 (d, *J* 8.2 Hz, 2H, ArH), 7.71 (d, *J* 8.2 Hz, 2H, ArH). $\delta_C$ (75.5 MHz, $CDCl_3$) 21.5 ($ArCH_3$), 24.5 (C3), 30.2 (C4 or C2′), 31.2 (C2′ or C4), 72.0 (C5), 109.4 (C1′), 115.3 (C4′), 127.1 (ArCH), 129.4 (ArCH), 134.9 (C3′), 140.0 (Ar), 143.2 (Ar), 169.0 (C2). *m/z* (E.I.) 278 ($M^+$, 6%).
10. This result is in direct contrast to our earlier observation[5] that alkylation of the lithio derivative of allyl sulfone (**3**) with isopropyl bromide gave the α-monoalkylated compound in 60% yield.

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