A New Route to Substituted Dihydropyrans

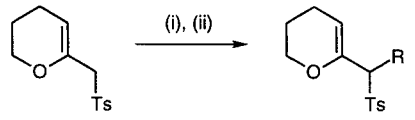
G.L. Edwards,* D.J. Sinclair, C.D. Wasiowych
School of Chemistry, University of New South Wales, Sydney, N.S.W., 2052, Australia
FAX: (+) 61 2 9385 6141E-mail: g.edwards@unsw.edu.au
Received 15 July 1997

Abstract: Deprotonation and subsequent alkylation of 3,4-dihydro-6-(*para*-toluenesulfonylmethyl)-2*H*-pyran gives monoalkylated products in good yields, with excellent α selectivity. The alkylation succeeds not only for reactive haloalkanes, but also for simple primary and secondary alkyl bromides. Desulfonylation with sodium amalgam provides a new and simple route to substituted dihydropyrans.

Cyclic enol ethers are important and versatile structural units in organic methodology which have proved invaluable in a range of natural product syntheses, and there are many methods for their preparation and modification.[1,2] Vinylic deprotonation α to oxygen in the parent systems provides a ready method for the introduction of a variety of substituents; a common entry to this synthetic strategy involves metallation with *tert*-butyllithium.[1] An alternative route involves deprotonation of an α-arenesulfonyl heterocycle and subsequent alkylation; the alkylated intermediate is unstable and readily eliminates arenesulfinic acid to give α-substituted products.[2] These enol ethers are then amenable to cyclisation if a nucleophilic substituent is suitably disposed in the sidechain, opening a route to spiroketals and related compounds.[3] Regio- and stereoselective introduction of a substituent β to the ring oxygen in the cyclic enol ethers can be achieved by hydroboration, an approach that has seen widespread application recently in methodology applicable to polyether marine toxins.[4] In contrast, hydrozirconation of cyclic enol ethers results in combined ring fission and functionalisation, opening the way to a variety of substituted acyclic structures.[5]

Our synthesis of a functionalised, α-substituted dihydropyran (**1**)[6] has allowed us to develop a new and versatile route to these useful entities. This molecule can be viewed not only as an enol ether but also as an allyl sulfone, a species described by Trost[7] as a "chemical chameleon" where the SO_2Ar group allows the allyl unit to react with both electrophiles and nucleophiles. Deprotonation allows regioselective alkylation of the resulting stabilised anion with haloalkanes and carbonyl compounds α to the sulfonyl group, and transition-metal catalysed nucleophilic displacement of the sulfonyl residue can be achieved with organometallic reagents. Therefore the dihydropyran (**1**) seemed an ideal candidate for structural elaboration, and we now wish to report on a new synthesis of alkylated dihydropyrans as part of our programme directed towards the synthesis of new oxygen heterocycles.

Deprotonation of the dihydropyran (**1**) α to the sulfonyl group can be effected with *n*-butyllithium in THF, and subsequent addition of hexamethylphosphoric triamide (HMPA, 1 to 5 equivalents) followed by an alkyl halide gave the α-monoalkylated material in moderate to excellent yields (Scheme 1, Table 1). Indeed, the yields for some alkylations are almost quantitative when calculated against the limited amounts of base employed.[8] It is noteworthy that acceptable yields are obtainable not only with the usual reactive substrates, but also with primary and secondary alkyl halides; only starting material was recovered from an attempted alkylation with *tert*-butyl chloride, presumably as a result of a more favourable elimination taking place. A lower yield (47%) was achieved with the trimethylsilyl-protected propargyl bromide; whether partial deprotection during the alkylation or workup results in loss of lower molecular weight, more volatile, materials is unknown at present.



(**1**) (**2**) to (**7**)

(i) *n*-BuLi (0.8 eq.), THF; (ii) HMPA (1 to 5 eq.), then RX

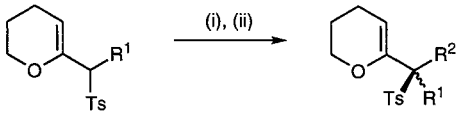
Scheme 1

Table 1

Haloalkane	HMPA (equivalents)	Product	Yield (%)
MeI	5	(**2**)	83
$PhCH_2Br$	5	(**3**)	78
CH_2=$CHCH_2Br$	1[a]	(**4**)	74
n-BuBr	5	(**5**)	70
Me_2CHBr	5	(**6**)	60
$TMSCCCH_2Br$[b]	2[a,c]	(**7**)	47
tert-BuCl	1[d]	—	—

a. 0.9 equivalents of *n*-butyllithium used.
b. 2 equivalents of haloalkane were used in this example; in all other cases only one equivalent was required.
c. 10% DMPU gives a similar yield; higher levels of HMPA lead to reduced yields.
d. Higher levels of HMPA fail to facilitate the alkylation.

A major advantage of this methodology is that the activating sulfonyl group remains in place after the first alkylation, providing scope for introduction of a second alkyl group. It was gratifying to find that deprotonation of the *n*-butyl derivative (**5**) and subsequent alkylation with the activated haloalkane allyl bromide gave the α,α-disubstituted compound (**8**) in 90% yield. Other alkylations (Scheme 2, Table 2) with primary halides gave slightly lower but still acceptable yields, however an attempted second alkylation of compound (**5**) with isopropyl bromide gave no dialkylated material. In these reactions higher levels of base can be used as anion equilibration following the second alkylation is precluded.



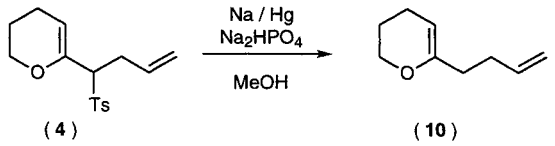
(i) *n*-BuLi (1.0 to 1.1 eq.), THF;
(ii) HMPA (1 eq.), then R^2Br

Scheme 2

Table 2

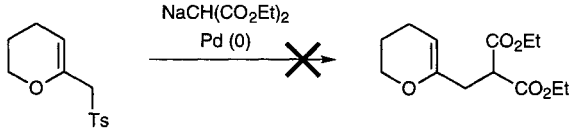
R^1; substrate	R^2Br	Product	Yield (%)
n-C_4H_9; (**5**)	CH_2=$CHCH_2Br$	(**8**)	90%
(**5**)	*n*-BuBr	(**9**)	72%
(**5**)	Me_2CHBr	—	—
CH_2=$CHCH_2$; (**4**)	*n*-BuBr	(**8**)	82%

Removal of sulfonyl groups is best effected reductively, using a variety of reagents such as sodium amalgam and samarium(II) iodide / HMPA.[9] In a representative example, the sulfonyl group was removed reductively using 6% sodium amalgam in buffered methanol giving the substituted dihydropyran (**10**) in 92% yield (Scheme 3). Aluminium amalgam gave only unchanged starting material.



Scheme 3

In principle, the sulfonyl group of an allyl sulfone can also act as a leaving group, and many examples of this nucleophilic displacement in allyl sulfones have been reported using a range of transition metal catalysts.[7,10] While this procedure would suffer the disadvantage of removing the sulfonyl group from the molecule allowing only a single substitution, it could allow the introduction of more highly functionalised sidechains. However all efforts to carry out such a substitution on the dihydropyran (**1**) have thus far failed, with unchanged starting material being recovered in every case (Scheme 4). One explanation for this inertness could be a poor interaction between the electron-rich enol ether and what are, inevitably, electron-rich catalysts [often a d^{10} metal such as Pd(0)].



Scheme 4

Despite its failure to behave as a "chemical chameleon", we believe that the dihydropyran (**1**) is a versatile reagent that provides a convenient and useful new route to α-substituted dihydropyrans. Investigations into its utility for the preparation of more complex heterocyclic structures are continuing.

Acknowledgements: The authors wish to thank the Australian Research Council for generous financial support. Receipt of a Commonwealth Postgraduate Award (by D.J.S.) is also acknowledged.

References and Notes

(1) Shimano, M.; Meyers, A.I. *Tetrahedron Lett.* **1994**, *35*, 7727. Amouroux, R. *Heterocycles* **1984**, *22*, 1489. Kocienski, P.; Yeates, C. *Tetrahedron Lett.* **1983**, *24*, 3905. Boeckman, R.K. Jr.; Bruza, K.J. *Tetrahedron Lett.* **1977**, 4187.

(2) Ley, S.V.; Lygo, B.; Sternfeld, F.; Wonnacott, A., *Tetrahedron* **1986**, *42*, 4333.

(3) For an excellent review, see: Vaillancourt, V.; Pratt, N.E.; Perron, F.; Albizati, K.F. In *The Total Synthesis of Natural Products*; Vol. 8, ApSimon, J., Ed.; John Wiley & Sons, Inc.: New York, 1992; pp 533-691.

(4) Ishihara, J.; Murai, A. *Synlett* **1996**, 363.

(5) Wipf, P.; Xu, W.; Smitrovich, J.H.; Lehmann, R.; Venanzi, L.M. *Tetrahedron* **1994**, *50*, 1935. Cénac, N.; Zablocka, M.; Igau, A.; Commenges, G.; Majoral, J.-P.; Skowronska, A. *Organometallics* **1996**, *15*, 1208.

(6) Edwards, G.L.; Muldoon, C.A.; Sinclair, D.J., *Tetrahedron* **1996**, *52*, 7779.

(7) Trost, B.M.; Organ, M.G.; O'Doherty, G.A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

(8) Optimum conditions are achieved in the first alkylation with addition of less than a full equivalent (0.8 to 0.9 eq.) of *n*-butyllithium; higher amounts lead to contamination of the final product with some polyalkylated materials.
Typical procedure: A solution of the dihydropyran (**1**) (1.00 g, 4.0 mmol) in dry tetrahydrofuran (60 ml) was placed under an argon atmosphere and cooled to -78 °C. *n*-Butyllithium (2.4 ml, 1.5 M solution in hexane, 3.6 mmol) was added dropwise to the stirred solution, and then the temperature was warmed to 0 °C. The temperature was held at 0 °C for 15 min, the mixture was cooled to -78 °C, and then HMPA (0.8 ml, 0.72 g, 4.0 mmol) was added dropwise followed by allyl bromide (0.34 ml, 0.48 g, 4.0 mmol). The solution was allowed to warm to room temperature over a period of 5 h, and the reaction was quenched by the addition of brine (80 ml). The organic layer was separated and the aqueous layer was extracted with ether (3 x 60 ml). The combined organic extracts were washed with brine (200 ml) and then with water (200 ml), dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (10% ethyl acetate / light petroleum) of the crude product gave *3,4-dihydro-6-[1-(para-toluenesulfonyl)but-3-en-1-yl]-2H-pyran* (**4**) as colourless prisms (0.86 g, 74%), m.p. 78-79 °C, (Found: C, 65.9%; H, 7.1%. $C_{16}H_{20}O_3S$ requires C, 65.7%; H, 6.9%). ν_{max} 1280, 1220, 1105, 1080, 1055, 1015, 990, 970, 900, 815, 650, 620 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.65-1.72, m, 2H, H3; 1.90-1.97, m, 2H, H4; 2.44, s, 3H, ArMe; 2.56-2.67, m, 1H, H2'a; 2.71-2.79, m, 1H, H2'b; 3.48, dd, *J* 11.3, 4.1 Hz, 1H, H1'; 3.86-3.74, m, 1H, H2a; 3.79-3.86, m, 1H, H2b; 4.67, t, *J* 4.1 Hz, 1H, H5; 5.05, d(br), *J* 11.3 Hz, 1H, H4'a; 5.11, dd, *J* 15.9, 2.6 Hz, 1H, H4'b; 5.67, ddt, *J* 16.9, 9.7, 7.2 Hz, 1H, H3'; 7.31, d, *J* 8.2 Hz, 2H, ArH; 7.74 ppm, d, *J* 8.2 Hz, 2H, ArH; δ_C (75.5 MHz, $CDCl_3$) 20.4 (C4), 21.6 (ArMe), 21.7 (C3), 29.7 (C2'), 66.3 (C2), 70.5 (C1'), 104.7 (C5), 117.9 (C4'), 129.2 (ArCH), 129.3 (ArCH), 133.2 (C3'), 134.9 (Ar), 144.4 (Ar or C6), 145.6 ppm (C6 or Ar).

(9) Posner, G.H.; Brunelle, D.J. *J. Org. Chem.* **1973**, *38*, 2747. Künzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 1949.

(10) Trost, B.M.; Schmuff, N.R.; Miller, M.J. *J. Am. Chem. Soc.* **1980**, *102*, 5979. Trost, B.M.; Merlic, C.A. *J. Org. Chem.* **1990**, *55*, 1127. Trost, B.M.; Merlic, C.A. *J. Am. Chem. Soc.* **1990**, *112*, 9590. Julia, M.; Righini-Tapie, A.; Verpeaux, J.-N. *Tetrahedron* **1983**, *39*, 3283.