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REGIOSPECIFIC TETRAHYDROPYRAN-3-ONE ENOLATES. SYNTHESIS AND REACTIVITY OF SILYL ENOL ETHER DERIVATIVES

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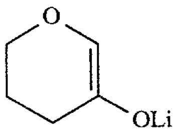
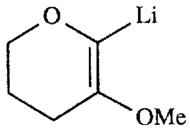
Summary. The synthesis and reactivity of the silyl enol ether (3) is reported. This reagent complements the reactivity of the lithiated enol ether (2) previously used as a synthetic equivalent of the regiospecific tetrahydropyran-3-one enolate (1).

As part of a general study relating to the synthesis of complex tetrahydropyrans, we recently reported that the β-alkoxy alkenyl lithium (**2**) can be used as an effective equivalent of the regiospecific enolate (**1**,R=H).[1] This enolate regioisomer is difficult to obtain in useful yields from the corresponding ketone since the preferred mode of enolization of pyran-3-ones tends to be away rather than towards the ring constrained heteroatom.[2]

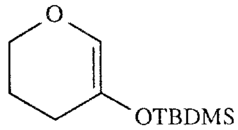
In a more conventional sense, the introduction of silyl enol ethers greatly expanded the synthetic scope of enolate chemistry by providing a means of introducing an electrophile to a ketone under nonequilibrating conditions.[3] Not only do these labile silyl derivatives provide access to the corresponding enolate, but they are also compatible with a range of "S_N1-type" electrophiles in the presence of Lewis acids.[4]



(1)



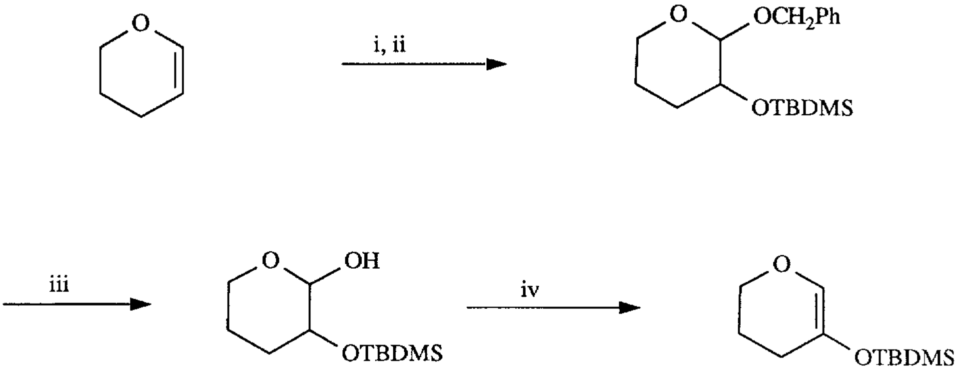
(2)



(3)

A silyl derivative of enolate (**1**) would be anticipated to provide significant advantages over the alkenyl lithium (**2**), the scope of which is limited by the highly basic nature of this species. In this paper we describe the synthesis and reactivity of the t-butyldimethylsilyl(TBDMS) enol ether derivative (**3**).

The synthesis of (**3**) is shown in Scheme 1. The only significant difference between this route and that used to prepare the methoxy precursor of (**2**)[1] was the use of benzyl alcohol rather than methanol in the peracid oxidation of dihydropyran.

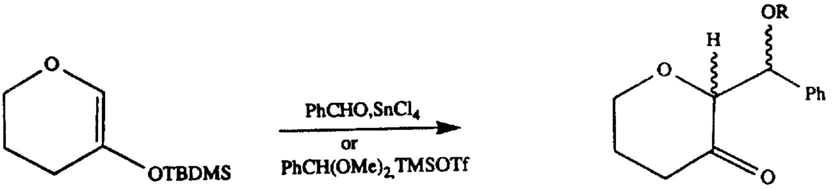


(3)

SCHEME 1. Reagents: i, m-CPBA, $PhCH_2OH$ (58%); ii,TDBMSCl,DBU (94%); iii,H_2 Pd/C (86%); iv,$MeSO_2Cl$, Et_3N (80%).

In this way the corresponding hemiacetal was obtained by hydrogenolysis rather than by acid-catalysed hydrolysis which led to extensive migration and loss of the silyl moiety.

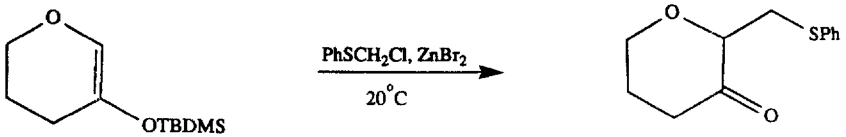
Reaction of benzaldehyde with silyl enol ether (**3**) under Mukaiyama's conditions[5] ($SnCl_4$,CH_2Cl_2,-78°C) was unselective, giving the aldol product (**4a**) in 50% yield as a 3:2 mixture of *syn* and *anti* diastereoisomers. The condensation of (**3**) with benzaldehyde dimethyl acetal in the presence of trimethylsilyl trifluoromethanesulphonate[6] was also examined. Under these conditions a higher level of selectivity was observed with (**4b**) being isolated as a 5:1 mixture of isomers.[7] Phenylthiomethylation[8] of (**3**) was achieved using α-chloromethylphenylsulphide in the presence of $ZnBr_2$ in CH_2Cl_2 at 20°C to give (**5**) in 64% yield.



(3)

(4a), R=H

(4b), R=Me

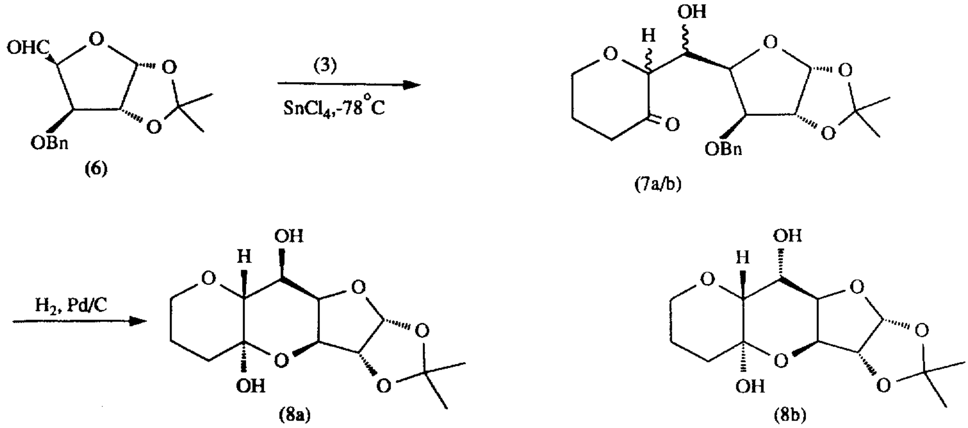


(3)

(5)

Because of their relevance to the synthesis of the herbicidin class of tricyclic nucleosides, we have also studied the reactivity of silyl enol ether (**3**) towards the more complex carbohydrate-derived electrophiles, aldehyde (**6**)[9] and α-chlorosulphide (**9**)[10]

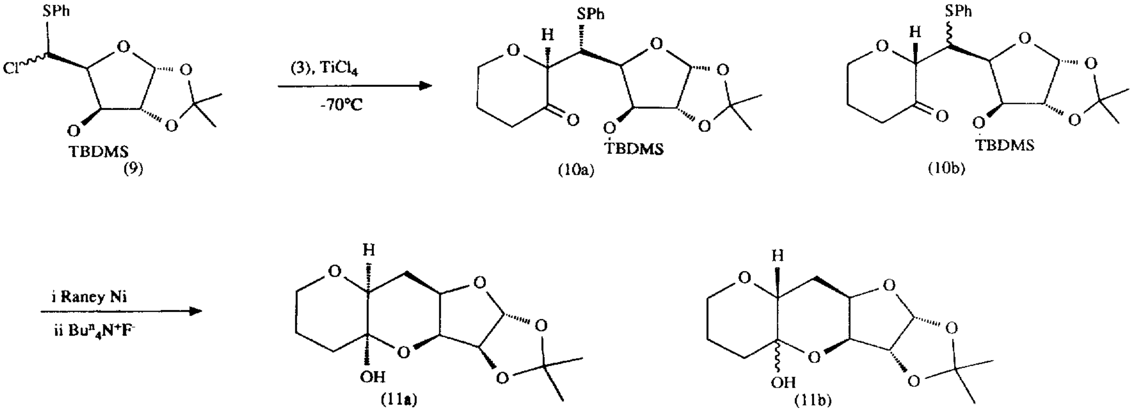
Condensation of (**6**) with silyl enol ether (**3**), using $SnCl_4$ as the Lewis acid of choice, in CH_2Cl_2 at -78°C gave a 1:1 mixture of two inseparable diasteroisomeric aldol adducts (**7a**) and (**7b**) in 35% yield. Hydrogenolysis of this mixture gave a separable mixture of the tetracyclic hemiketals (**8a**) and (**8b**) in 50% yield. The structural assignments of (**8a/b**) are based on extensive ^1H nmr studies.



(6) (7a/b) (8a) (8b)

In the presence of $TiCl_4$ (CH_2Cl_2,-70°C), α-chlorosulphide (**9**) reacted with silyl enol ether (**3**) to give a 4:1 mixture of two diasteroisomers in a combined yield of 70%. The major component (**10a**) was readily separated and the structure of this adduct was established by x-ray crystallographic analysis.[11]

Raney nickel desulphurization of (**10a**) followed by fluoride ion-induced desilylation gave hemiketal (**11a**) in 50% overall yield. This structural assignment was also confirmed by x-ray crystallography.[12] In a similar fashion the other adduct (**10b**) was converted to hemiketal (**11b**), but the stereochemical assignment of the anomeric hydroxyl of this isomer has not been established unambiguously.



(9) (10a) (10b) (11a) (11b)

In summary, the silyl enol ether (**3**) complements the reactivity of the alkenyl lithium (**2**), but the chemistry described above is likely to be applied more readily to the synthesis of more complex tetrahydropyran-3-ones.

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References and Notes

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6. S. Murata, M. Suzuki and R. Noyori, *J. Amer. Chem. Soc.*,**1980**, *102*, 3248.
7. The *syn/anti* assignment of adducts (**4a**) and is based on the magnitude of the coupling constant to the benzylic methine proton ($^3J_{syn}$=3.5Hz, $^3J_{anti}$=7.5Hz). Structural assignments adducts (**4b**) have not been made as yet.
8. For a comprehensive discussion of the Lewis acid-promoted phenylthioalkylation of silyl enol ethers see I. Paterson, *Tetrahedron*, **1988**, *44*, 4207.
9. R.C. Anderson and B. Fraser-Reid, *J. Org. Chem.*, **1985**, *50*, 781
10. Chlorosulphide (**9**) was prepared in three steps (60% overall yield) from 1,2-O-isopropylidene-5-toluene-p-sulphonyl-α-D-xylofuranose, (R.C. Young, P.N. Kent and R.A. Dwek, *Tetrahedron*, **1970**, *26*, 3983) by (i) silylation (TBDMSCl,DBU); ii, PhSH, DBU; iii,N-chlorosuccinimide.
11. Chlorosulphide adduct (**10a**) crystallised (hexane) in space group $P2_12_12_1$ with a=12.071(3), b=12.134(7), c=38.748(10)Å and Dcalcd=1.158gcm^{-3} for Z=8 at room temperature. The asymmetric unit consisted of two discreet molecules of (**10a**), which were identical to each other within experimental error. The structure was solved by direct methods using 1765 reflections with $I \geq 3\sigma I$ and refined by blocked matrix least squares, where each molecule of (**10a**) was treated separately, to final residuals of R=9.2% and R_w=8.39%.
12. Hemiketal (**11a**) crystallised (hexane/ether) in space group $P2_12_12_1$ with a=8.086(2), b=18.193(4), c=9.612(3)Å and Dcalcd=1.306gcm^{-3} for Z=4 at room temperature. The structure was solved by direct methods using 684 reflections with $I \geq 3\sigma I$ and refined by full matrix least squares to final residuals of R=9.94% and R_w=10.50%.

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