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REACTIVITY OF MONOTHIO- AND MONOSELENOACETALS TOWARDS OXIDATION IN THE SYNTHESIS OF SUBSTITUTED 2,3-DIHYDROFURANS.

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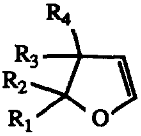
Summary : As a part of a search for mild conditions in the preparation of dihydrofurans, the reactivity of monothio- and monoselenoacetals, prepared from corresponding lactols, towards oxidation has been studied.

The 2,3-dihydrofuran structure is a subunit of interest being widely encountered in various natural products such as clerodin[1] and azadirachtin[2] which embody this highly reactive entity in furofuran or furopyran systems. This moiety is presumed to be responsible for at least part of the biological activity of these molecules. Classical preparation of substituted 2,3-dihydrofurans such as 1 has, hitherto, generally relied on the flash pyrolysis of the lactol-acetate prepared from 2[3-6]. In continuation of our studies towards furofurannic compounds[7], we have seeked a mild, efficient and general method for the preparation of compounds of type 1 and 3 and their substituted analogs.



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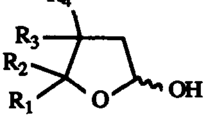

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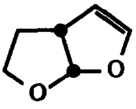

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Our strategy is based on the conversion of the corresponding lactols to sulfide or selenide derivatives[8] followed by oxidation-elimination, a mild and widely used approach to double bond formation. When we started our investigations, there was no published account of such an approach. Two recent reports by Ley et al[9] and Dreiding et al[10] on a similar strategy prompted us to report our own results in this area especially that they reveal some surprising aspect on the reactivity of these compounds.

Entry n°	oxidation conditions	yield	Z in 4' (a)	4
4b X=Se	tBuOOH (1.7 eq.) CH_2Cl_2 20°C 50 h.	(e)	SePh 5%(d)(f)(h)	25%(d)(f)(h)
5b X=Se	tBuOOH (3.5 eq.) CH_2Cl_2 iPr_2NEt 20°C 70h.	(e)	SePh 50%(d)(g)	50%(d)(g)
6b X=Se	tBuOOH 1.7 eq. $Ti(iPrO)_4$ 1 eq. CH_2Cl_2 iPr_2NEt 0°C 25 h.	58%(b)	0%(d)	100%(d)

(a) : All the compounds gave satisfactory infra-red, N.M.R. and mass spectral data.
(b) : Yield calculated on purified products through chromatography on silica-gel
(c) : Ratios calculated on purified products through chromatography on silica-gel.
(d) : Ratios estimated by analysis of ^{1}H N.M.R. spectrum at 200 MHz of the crude reaction mixture.
(e) : The isolation of the components of the reaction mixture has not been attempted therefore the yield cannot be accurately estimated.
(f) : The reaction leads to additional unidentified products.
(g) : The reaction did not proceed further.
(h) : After a further 50 hours the selenide and the dihydrofuran 4 totally disappeared and were converted to unidentified material.

From these results it appears that :

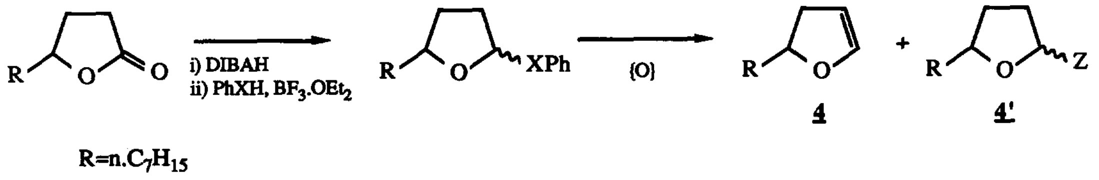
1. In our case, the primary oxidation product (sulfoxide or selenoxide) cannot be isolated. This result contrasts with those of Ley *et al* and Dreiding *et al*.

2. In some cases, elimination may proceed as expected leading to 4. However, if a nucleophilic substrate is present, the products resulting from a nucleophilic substitution predominate (entries 2a,3a,4a,1b,2b,3b). This nucleophilic substitution may occur even with sterically hindered nucleophiles such as t.butanol (entry 3a). This might be interesting as a new glycosylation reaction.

3. The phenylsulfenic or phenylselenenic acids produced in the reaction are easily oxidized into phenylsulfinic or seleninic acids. Phenylsulfinic acid then reacts with the starting sulfoxide (or with the incipient cation therefrom) to produce the corresponding sulfone. Consequently, the intermediate sulfoxide could not be isolated. In contrast, the corresponding selenones are much more difficult to obtain, thus accounting for the formation of the *m*.chlorobenzoate under conditions specified in entry 1b.

4. Diisopropylethylamine has been used to suppress some side-reactions in selenoxide-eliminations[11] such as those observed in entry 4b. Its efficiency was tempered by the easy formation of the corresponding N-oxide in competition with the oxidation of the selenide (entry 5b) or the sulfide (entry 5a).

In a one-pot reaction the commercially available undecanoic acid -lactone, taken as a model, was reduced with diisobutylaluminium hydride and the resulting lactol treated with PhXH (X=S or Se) in the presence of boron trifluoride etherate to form, in excellent yields, 2-heptyl 5-(phenylthio)tetrahydrofuran (87%) and 2-heptyl 5-(phenylseleno)tetrahydrofuran (92%). These were subjected to oxidation-elimination under a variety of reaction conditions. The results are reported in the following table.

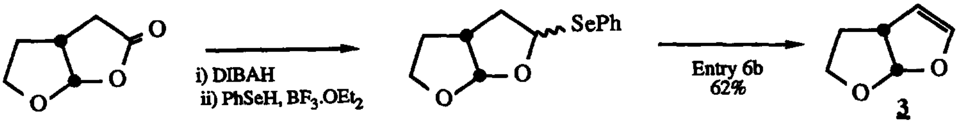


Scheme I

Entry n°	oxidation conditions	yield	Z in 4' (a)	4
1a X=S	mCPBA (1 eq.) CH_2Cl_2 0°C 0.25 h.	64%(b)	SPh 17%(c) SO_2Ph 41%(c) == O 42%(c)	0%(d)
2a X=S	$NaIO_4$ (1.2 eq.) MeOH / H_2O 20°C 0.25 h.	59%(b)	OMe 100%(c)	0%(d)
3a X=S	$NaIO_4$ (1.2 eq.) tBuOH / CH_3CN $Et_3PhN^+Cl^-$ cat. 20°C 140 h.	(e)	OtBu 60%(d) OH 10%(d)(f)	0%(d)
4a X=S	$NaIO_4$ (1.2 eq.) CH_2Cl_2 / H_2O $Et_3PhN^+Cl^-$ cat. 20°C 18 h.	(e)	OH 50%(d)(f)	0%(d)
5a X=S	tBuOOH (1.7 eq.) $PhCH_3$ iPr_2NEt 20°C 50 h.	(e)	SPh 90%(d)(g)	0%(d)(g)
1b X=Se	mCPBA (1 eq.) CH_2Cl_2 -60°C->20°C 0.5 h.	43%(b)	$OCOC_6H_4$mCl 100%(c)	0%(d)
2b X=Se	$NaIO_4$ (1.2 eq.) MeOH/H_2O 20°C 0.25 h.	(e)	OH 45%(d) OMe 55%(d)	0%(d)
3b X=Se	$NaIO_4$ (1.2 eq.) CH_2Cl_2 / H_2O $Et_3PhN^+Cl^-$ cat. 20°C 0.25 h.	(e)	OH 100%(d)	0%(d)

5. The optimal conditions in our case were quite different from those pointed out by Ley et al. They correspond to entry 6b where only very poor nucleophiles are present in the reaction medium and where their effects are attenuated by the presence of the amine.

Those conditions which answer the imperatives we defined when we started this work were succesfully applied to the synthesis of 3 from the corresponding selenide according to scheme II.



Scheme II

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References and notes.

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