Pergamon

Tetrahedron Letters, Vol. 36, No. 41, pp. 7531-7534, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01524-8

Stereoselective Synthesis of 2,5-Dialkyl-3-(phenylsulfonyl) Tetrahydrofurans via Cyclisation of *Z*-Sulfonyl-substituted Homoallylic Alcohols

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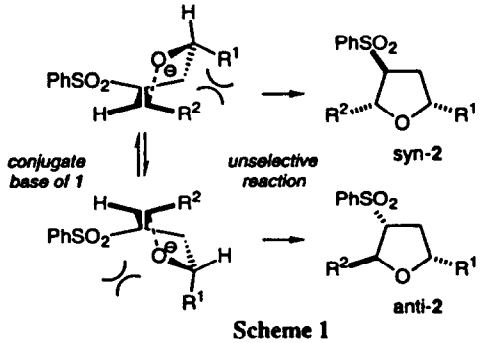
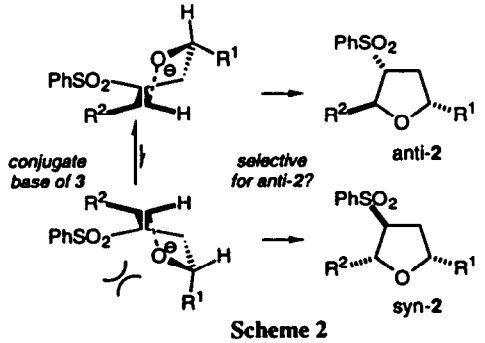
Abstract: *Z*-Sulfonyl-substituted homoallylic alcohols **3** underwent highly anti-selective base-mediated 5-*endo*-trig cyclisation reactions to give 2,5-dialkyl-3-phenylsulfonyl tetrahydrofurans anti-**2**. A simple steric model is proposed to account for the high selectivities. Tetrahydrofuran **2g** was efficiently and stereoselectively sulfenylated at the 3-position to give **6**, which was subjected to an oxidation–syn-elimination sequence to give unsaturated cyclic sulfone **7**. Treatment of **6** with Lewis acid in the presence of soft carbon nucleophiles gave the products of rearrangement followed by trapping.

We have been looking at 5-*endo*-trig cyclisation reactions[1] for the stereoselective synthesis of 2,5-dialkyl-3-(phenylsulfonyl) tetrahydrofurans. We reported previously[2] that treatment of *E*-sulfonyl-substituted homoallylic alcohols **1** with *t*-BuOK–*t*-BuOH in THF gave 2,5-dialkyl-3-phenylsulfonyl tetrahydrofurans **2** in mostly good yields but with poor selectivities for the 2,5-syn versus the 2,5-anti isomers. This was attributed to repulsive steric interactions of similar magnitudes in the two competing reactive conformations (Scheme 1). In a search for a more efficient variant of this process, we reasoned that the *Z*-cyclisation substrates **3** might undergo more selective cyclisations. Examination of the analogous transition-state models pointed towards the absence of substantial non-bonded interactions only in the conformation leading to the 2,5-anti disubstituted tetrahydrofuran (Scheme 2). We report in this Letter the preparation and highly selective 5-*endo*-trig cyclisation



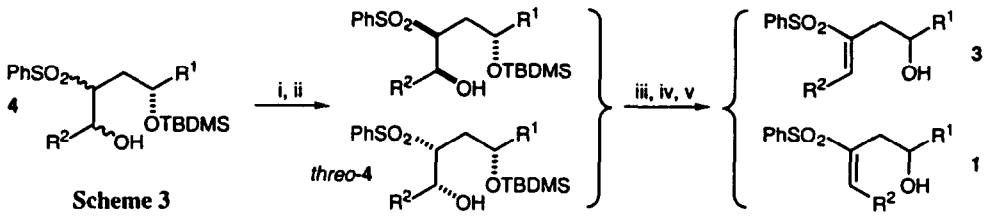
Scheme 1



Scheme 2

reactions of *Z*-sulfonyl-substituted homoallylic alcohols **3**. We report also some reactions for the elaboration of one of the syn-**2** products which demonstrate the synthetic utility of the sulfonyl group post-cyclisation.

Our synthetic route to *Z*-substrates **3** differed from the approach previously used[2] in terms of the leaving group involved in the elimination step leading to the vinylic sulfone moiety. Thus, oxidation of the diastereomeric mixtures of adducts **4**[3] and threo-selective[4] reduction of the resulting β-ketosulfones with $NaBH_4$–$CeCl_3$[5] gave diastereomerically enriched **4**. These were tosylated and subjected to E2-type elimination[6] followed by desilylation to give predominantly *Z*-sulfones **3**, which could be separated from small amounts of **1**[7] by HPLC (Scheme 3, Table 1).



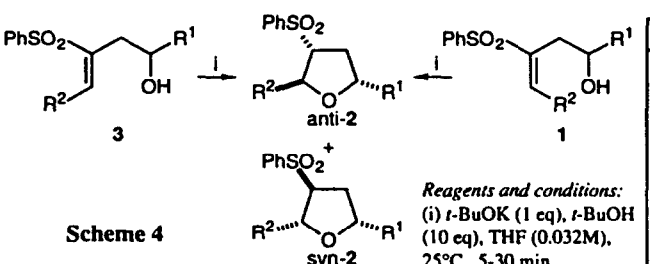
Scheme 3

Reagents and conditions: (i) PDC, 4Å molecular sieves, CH_2Cl_2 (0.1M), rt, 3 h; (ii) $NaBH_4$ (2 eq), $CeCl_3$ (1 eq), MeOH (0.4M), rt, 1 h; (iii) *n*-BuLi (1 eq), TsCl (1.5 eq), THF (0.2M), 0°C; (iv) NaOEt (2 eq), EtOH (0.1M), rt; (v) HF, MeCN (0.1M), rt.

Table 1. Synthesis of Cyclisation Substrates

Entry	R^1	R^2	Yield of threo-4[8]	Yield of **3** + **1**[9]	Ratio of **3** : **1**[10]
a	Ph	*i*-Pr	89	66	10:1
b	CH_2OBn	*c*-C_6H_{11}	84	66	2.5:1
c	Ph	*t*-Bu	66	65	3:1
d	Ph	Me	86	51	1:1
e	H	$BnOCH_2CHMe$	63	56	4:1

Our previous studies[2] of cyclisation reactions of the *E*-substrates **1** had shown that *t*-BuOH was essential for clean, high-yielding tetrahydrofuran formation. With substrates having R^2 bulkier than methyl, isomerisation to the thermodynamically more stable allylic sulfones had been observed.[11] In the present work, it was found that an increase of the amount of *t*-butanol from 5 to 10 equivalents reduced the extent of this side-reaction, and these conditions were subsequently adopted as standard.[12] Exposure to the standard conditions of the *Z*-substrates **3a**, **3b** and **3f**[2] (R^1 = Me, R^2 = *i*-Pr) possessing substituents on the γ-position of the vinylic sulfone electrophilic moiety resulted in rapid, high-yielding formation of anti-**2a**, anti-**2b** and anti-**2f** with high selectivities. Identical transformation of *E*-isomers **1a** and **1b** gave syn-**2a** and syn-**2b** in lower yields, but with similarly high selectivities. In contrast, reaction of the *iso*-butyl-substituted vinylic sulfone **3c** gave mostly syn-**2c**, as was the case for the *E*-isomer **1c**; the syn-selectivity was higher for the latter transformation. This stereoconvergence was most pronounced for substrates **1d** and **3d**; identical mixtures of syn- and anti-**2d** were formed on treatment of both isomers with base in the usual way (Scheme 4, Table 2). These results suggest that *Z*-vinylic sulfones **3** which are not branched at the γ-position undergo competitive isomerisation to **1** prior to cyclisation; the lower yields of **2** reflect the increased amounts of allylic sulfones formed in these cases.[13]



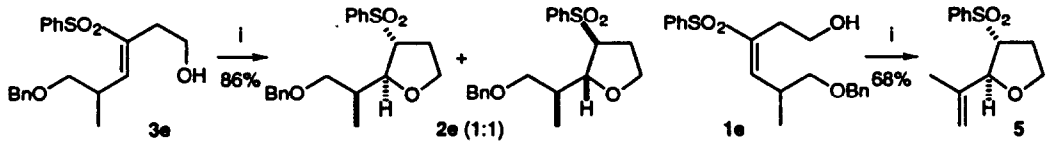
Scheme 4

Reagents and conditions: (i) *t*-BuOK (1 eq), *t*-BuOH (10 eq), THF (0.032M), 25°C, 5-30 min.

Table 2. Cyclisation Reactions of **3** and **1**

Substrate	Yield of **2**	Ratio of syn-:anti-**2**
3a	83	1:10
1a	67	10:1
3b	87	1:10
1b	69	10:1
3c	53	2:1
1c	47	4:1
3d	57	2:1
1d	62	2:1
3f	86	1:8

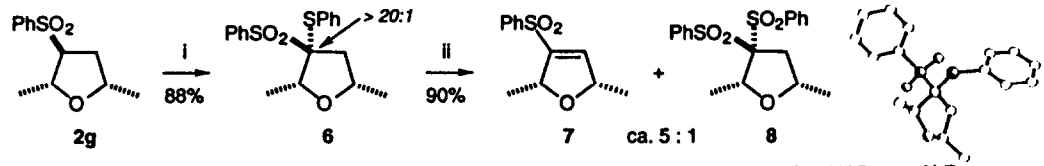
Cyclisation of substrate **3e** was carried out to probe the effect on cyclisation stereochemistry of a stereocentre positioned exo- with respect to the incipient heterocycle. The precursor **4e** was made via a modified sequence in which the conjugate adduct of thiophenol and acrolein was reduced to the primary alcohol, protected as the TBDMS ether, and oxidised to the sulfone prior to lithiation and addition to 3-benzyloxy-2-methylpropanal. Exposure of **3e** to the standard cyclisation conditions gave a 1:1 mixture of the two possible diastereomers of **2e** (Scheme 5). Notably, reaction of the *E*-isomer **1e** gave the alkenyltetrahydrofuran **5**, presumably by elimination of benzyloxide ion to form the sulfonyldiene prior to cyclisation.



Reagents and conditions: (i) *t*-BuOK (1 eq), *t*-BuOH (10 eq), THF (0.032M), 25°C, 30 min.

Scheme 5

Some derivatisation reactions of tetrahydrofuran **2g**[2] were examined in order to utilise the diverse reactivity of the phenylsulfonyl group for further transformations. Low-temperature deprotonation followed by addition of co-solvent and diphenyldisulfide and low-temperature proton quench resulted in highly selective formation of the crystalline tetrahydrofuran **6** in which the phenylsulfenyl moiety was oriented syn with respect to the 2-methyl group (Figure).[14] Exposure of **6** to peracid gave directly the unsaturated cyclic sulfone **7** together with a small amount of the disulfone **8** (Scheme 6). We presume that the unusually low temperature at which the syn-elimination took place stems from relief of steric crowding in the putative intermediate sulfoxide.



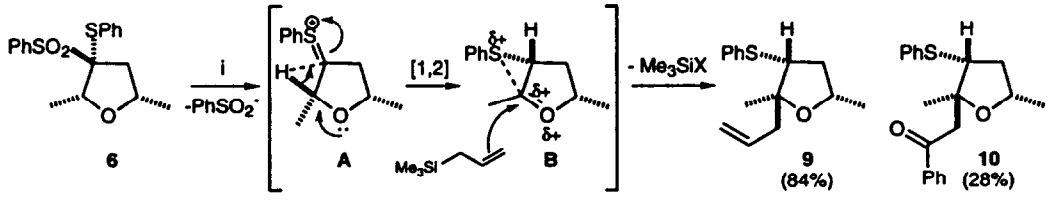
Reagents and conditions: (i) *n*-BuLi, THF, -93°C; DMPU (10% v/v), then PhSSPh (1.5 eq), -93°C→-78°C, then AcOH–THF (1 eq); (ii) CH_3CO_3H (10 eq), CH_3CO_2H–H_2O, CH_2Cl_2, rt, 12 h.

Scheme 6

X-Ray structure of **6**

Figure

We have investigated also some Lewis acid-mediated reactions of sulfone **6**. We reasoned that treatment of **6** with oxaphilic reagents would give a thionium ion, and that this would react with soft carbon nucleophiles.[15] Addition of aluminium trichloride to a mixture of **6** and acetophenone TBDMS enol ether gave in low yield ketone **10**. However, the analogous reaction using allyltrimethylsilane as the nucleophilic trap gave in high yield the thioether **9**.[16] We propose a mechanistic pathway in which the inductively destabilised thionium ion **A** formed initially undergoes a [1,2]-hydride shift to give the anchimerically stabilised isomeric structure **B**.[17] Subsequent nucleophilic attack occurs anti- with respect to the neighbouring thioether group (Scheme 7).



Reagents and conditions: (i) $AlCl_3$ (1.1 eq) added to **6** + allyltrimethylsilane, CH_2Cl_2, -78°C, 5 min.

Scheme 7

In summary, base-mediated 5-*endo*-trig cyclisation reactions of Z-sulfonyl-substituted homoallylic alcohols possessing γ-substituents on the vinylic sulfone moiety give anti-2,5-disubstituted tetrahydrofurans with excellent selectivities. The reaction of a substrate possessing a stereocentre at the γ-position was completely unselective. With less highly substituted substrates, isomerisation followed by syn-selective cyclisation is a significantly competitive process. We are currently seeking to apply the anti-selective cyclisation reaction to the synthesis of a fragment of the acyltetronic acid-containing ionophore tetronasin, and we are exploring alternative nucleophilic traps in the thionium–oxonium ion rearrangement reaction of **6**. The results of these studies will be reported in due course.

ACKNOWLEDGEMENTS

We thank the SERC (Quota Studentship to A. M. S.), and the SERC/EPSRC and The Wellcome Foundation Ltd (Earmarked/CASE Studentship to N. J. I.) for financial support of this research. We acknowledge support from the Wolfson Foundation for the establishing of the Wolfson Centre for Organic Chemistry in Medical Science.

REFERENCES AND NOTES

1. For the first example of tetrahydrofuran formation via 5-*endo*-trig cyclisation of sulfonyl-substituted homoallylic alcohols, see: Auvray, P.; Knochel, P.; Normant, J.-F. *Tetrahedron Lett.* **1985**, *26*, 4455.
2. Craig, D.; Smith, A. M. *Tetrahedron Lett.* **1992**, *33*, 695.
3. Alcohols **4** were prepared by nucleophilic ring-opening of epoxides by lithio(phenylsulfonyl)methane, protection of the resulting secondary alcohols using TBDMS triflate–pyridine, and further α-deprotonation and reaction with aldehydes: see reference 2.
4. The threo-selectivity may be rationalised using the Cram or Felkin–Anh models, treating the sulfonyl group as the largest α-substituent.
5. The use of $CeCl_3$ consistently gave cleaner, more rapid reduction reactions than $NaBH_4$ alone. L-Selectride®[6] was effective only for substrates having R^2 = Me.
6. Julia, M.; Launay, M.; Stacino, J.-P.; Verpeaux, J.-N. *Tetrahedron Lett.* **1982**, *23*, 2465.
7. In some cases the threo:erythro ratio of tosylates was not accurately reflected in the Z:E ratio of olefins formed on elimination. Varying small amounts of the products of elimination followed by addition of ethanol across the vinylic sulfone double bond were obtained. These species would undergo E1cB rather than E2 elimination, and their intermediacy might account for the diminished Z:E ratios in these instances.
8. All yields herein are cited as percentages of isolated, purified materials which gave satisfactory ^1H, ^{13}C nmr and ir spectra, and which showed low-resolution ms and either elemental combustion analysis or high-resolution ms characteristics in accord with the assigned structures. The yields of threo-**4** are for the two steps from the initial threo/erythro mixtures of **4**.
9. The yields of **3** + **1** are for the three steps from threo-**4**.
10. Determined by ^1H nmr.
11. For example, **1** (R^1 = Me, R^2 = *i*-Pr) and **1** (R^1 = Me, R^2 = CH_2OBn) underwent rapid, quantitative isomerisation to give diastereomeric mixtures of *allylic* sulfones on treatment with *t*-BuOK–THF in the presence of 5 equivalents of *t*-BuOH.
12. Substrate **3** (R^1 = Ph, R^2 = *n*-C_6H_{13}) gave only allylic sulfone under the standard cyclisation conditions.
13. A referee has suggested that the observation of allylic sulfone and tetrahydrofuran in the same reaction indicates that the former is an intermediate in the formation of the latter. This need not be the case: the conjugate base of **3** could be trapped with proton exclusively at the γ-position under the reaction conditions, and might yield the isomerised product only on external protic quench. We have not subjected the corresponding allylic sulfones to the present cyclisation conditions.
14. We thank Dr D. J. Williams and Ms A. M. Z. Slawin of this department for this determination.
15. Simpkins, N. S. *Tetrahedron Lett.* **1988**, *29*, 6787.
16. Compound **9**: δ_H (250 MHz, $CDCl_3$) 7.50-7.20 (5H, m, PhS), 5.85 (1H, m, H_2C=C*H*), 5.06 (1H, br d, J 10 Hz, *H*$_2$C=CH), 4.98 (1H, br d, J 16 Hz, *H*$_2$C=CH), 3.98 (1H, m, C*H*CH$_3$), 3.59 (1H, dd, J 11.5, 7 Hz, C*H*SPh), 2.48-1.16 (3H, m, allylic CH_2 and one ring CH_2), 1.72 (1H, m, other ring CH_2), 1.26 (3H, s, Me), 1.25 (3H, d, J 7 Hz, Me).
17. For a recent example of an analogous [1,5]-shift, see: Cox, P. J.; Griffin, A. M.; Newcombe, N. J.; Lister, S.; Ramsay, M. V.; Alker, D.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1443.

(*Received in UK* 20 *July* 1995; *accepted* 11 *August* 1995)