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The Cyclosulfonylation Reaction: A Comment on the Radical Reactions of 4-Pentenyl Tosylate

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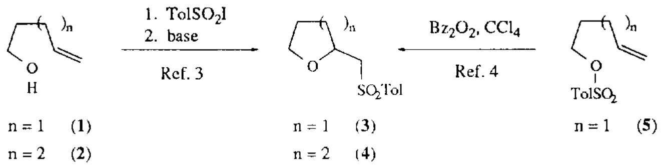
Abstract: Attempted free radical rearrangement of the *para*-toluenesulfonyl ester of 4-penten-1-ol in carbon tetrachloride gives only the simple Kharasch 1,2-adduct, instead of the 2-substituted tetrahydrofuran as claimed by Serra and da Silva Corrêa.

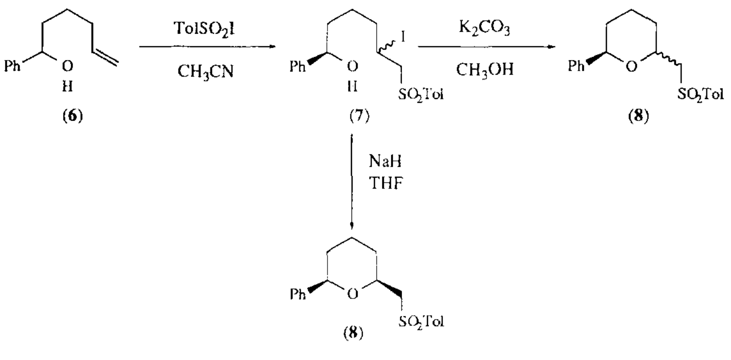
The widespread distribution of natural products containing rings of various sizes has led to the development of a diversity of synthetic routes to heterocyclic compounds with a range of substitution patterns; one key strategic approach involves cyclofunctionalisation procedures that give, ultimately, cyclic products with the incorporation of additional functionality that can be exploited for further transformations.[1,2] In recent *Letters*, we[3] and others[4] have reported cyclisation reactions (Scheme 1) that give heterocyclic products with appended sulfonyl residues that could prove useful for subsequent stuctural elaboration. While the method of Serra and da Silva Corrêa[4] is reported to provide the tetrahydrofuran (**3**) in quantitative yield from the tosylate (**5**), our procedure[3] allows access to the saturated pyran (**4**) as well as the furan (**3**) in reasonable yields.



SCHEME 1

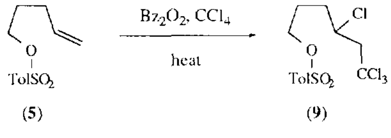
Initially, it was our intention to develop the *para*-toluenesulfonyl iodide (tosyl iodide) based methodology[3] into an efficient diastereoselective heterocyclic synthesis. Thus, addition of tosyl iodide to the substituted alcohol (**6**) gave the expected β-iodo sulfone (**7**) in excellent yield as a *ca.* 1:1 mixture of diastereoisomers; the chiral centre is obviously too far removed from the intermediate radical to affect the course of the iodine atom abstraction in the chain-carrying step. Cyclisation using potassium carbonate[3] gave the desired 2,6-disubstituted tetrahydropyran (**8**) as a *ca.* 1:1 mixture of diastereoisomers (Scheme 2). Likely explanations for the lack of diastereoselectivity are that ring closure is occurring either by simple S$_N$2 displacement of iodide, or alternatively that elimination of HI giving a vinylsulfone precedes conjugate addition where rapid protonation of the intermediate α-sulfonyl carbanion leads to a kinetic product which cannot equilibrate under these conditions.[5]

A report by Mandai and coworkers[6] on similar, sulfoxide-based molecules indicated that the use of a stronger base could solve the problem. Indeed, an excess of sodium hydride in THF allowed ring closure and equilibration to take place and the product (**8**) was isolated as a 27:1 (*cis:trans*) mixture of diastereoisomers. A similar ratio was observed upon equilibration of the 1:1 mixture (obtained from the cyclisation using K_2CO_3/CH_3OH) using NaH. Sodium hydride can likewise be used for the two-step cyclofunctionalisation of unsubstituted 4-penten-1-ol (**1**) and 5-hexen-1-ol (**2**), with yields of the 2-substituted heterocycles (**3**) and (**4**) of up to 70% over two steps (from alkenol) being achievable.

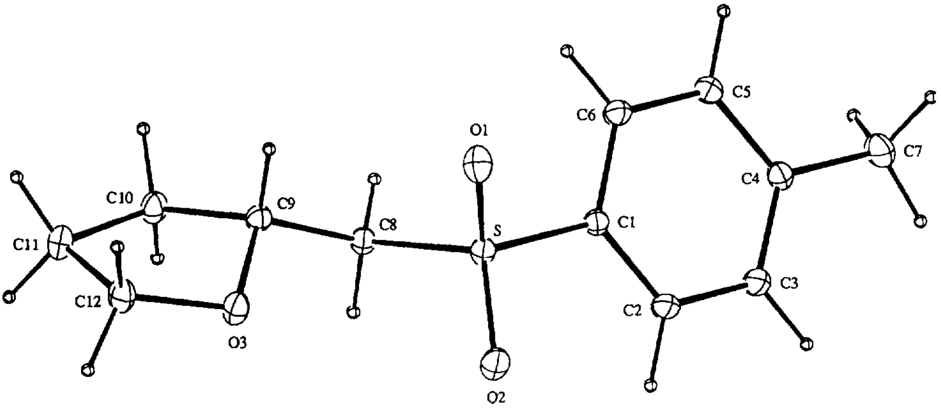


SCHEME 2

We were interested to compare this diastereoselectivity with the results that could be achieved using the procedure of Serra and da Silva Corrêa,[4] and therefore commenced to investigate a variant on their sealed-tube conditions which would allow reactions to be conducted at atmospheric pressure. Thus, treatment of 4-penten-1-yl tosylate (**5**) with benzoyl peroxide in boiling CCl_4 under an argon atmosphere[7] gave a waxy solid which, on first inspection, appeared to be the desired heterocycle (**3**). The ^1H n.m.r. spectrum showed absorptions consistent with a product containing a tosyl group, low field protons as expected for CH_2O, and an ABX system required for an α-sulfonyl CH_2 group with an adjacent chiral centre. However comparison with the spectrum of the product derived from our tosyl iodide method indicated that the compounds were quite different. While 2D COSY experiments revealed the same proton-proton correlations for each sample, reexamination of the published ^{13}C n.m.r. data indicated one significant difference: our assignments[3] of C2 (72.9) and C5 (61.2 or 68.0 p.p.m. - the latter being the most likely value) differed from those of Serra and da Silva Corrêa[4] [C2 (56.65) and C5 (69.29)]. Measurement of the ^{13}C n.m.r. spectrum for the Serra and da Silva Corrêa compound generally agreed with their reported results, however we also observed an additional, unreported quaternary carbon resonance at 96.5 p.p.m., which was close to (but distinct from)[8] CCl_4. In addition, the mass spectrum of this compound gave a molecular ion with a complex isotope pattern consistent with a molecule containing four chlorine atoms. It is our belief that this compound, rather than being a cyclic structure, is instead the simple 1,2-adduct (**9**) resulting from addition of $Cl–CCl_3$ across the double bond (the Kharasch reaction);[9] the signal at 96.5 p.p.m. corresponds well with a $C–CCl_3$ group [*cf.* $ClCH_2CH_2CCl_3$, δ_C 96.3 p.p.m.],[10] and the carbon resonance at 56.65 p.p.m. is consistent with a –CHCl– group.[11] In our hands, attempted reaction of tosylate (**5**) under sealed tube conditions likewise gave the acyclic product (**9**), and use of a solvent (benzene, with experiments carried out both at atmospheric pressure and under sealed tube conditions) that would not be expected to participate in the reaction gave only unchanged starting material. Cyclic material corresponding to the product obtained using our tosyl iodide method was never obtained in our laboratories using the procedure of Serra and da Silva Corrêa.

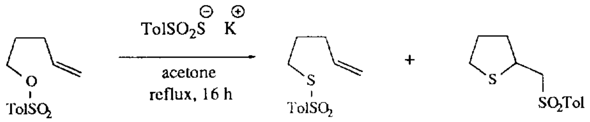


Confirmation that the product derived by cyclisation of the tosyl iodide adduct of pentenol (**1**) is indeed the heterocycle (**3**) was obtained by single crystal X-ray diffraction (Figure);[12] while the structural features themselves are unremarkable [for instance, the S–O bond lengths were 1.436(2) and 1.438(2)Å and the O–S–O and C–S–C angles 118.6(1) and 104.6(1)°, respectively], determination of the structure demonstrates that an unexpected rearrangement has not intervened in the two-step cyclofunctionalisation of the alkenol. We believe that our procedure, involving radical addition of tosyl iodide to an alkenol (requiring neither external initiation nor protection of the hydroxyl group) and subsequent cyclisation under mild conditions, provides a simple and convenient route to these functionalised oxacycles.



FIGURE

In contrast to the failure of the cyclo-etherification, the rearrangement reaction (also reported by Serra and da Silva Corrêa)[4] of the corresponding thiotosylate (**10**) proceeds to give the tetrahydrothiophen (**11**); in fact, our preparations of the starting thiotosylate under the prescribed conditions (acetone, reflux, 16 h)[4] gave products which were contaminated with significant quantities of the heterocycle [with typical yields of products being 33% of thiotosylate (**10**) and 45% of thiophen (**11**)]. A purified sample of the thiotosylate (**10**) isomerised on standing in the laboratory (approx. one month) to give the tetrahydrothiophen (**11**) quantitatively. Spectroscopic data (including a 2D COSY experiment which revealed the required proton-proton correlations) were consistent with the heterocyclic structure (**11**); interestingly, the α-sulfonyl CH_2 group of (**11**) now appears as a simple doublet (δ 3.33 p.p.m., ^3J 6.8 Hz) in the ^1H spectrum despite the adjacent chiral centre. We are currently exploring the scope of this simple cyclisation reaction for the preparation of a range of sulfur heterocycles.



(5) (10) (11)

References and Notes

1. Boivin, T.L.B., *Tetrahedron*, 1987, **43**, 3309.
2. Harding, K.E. and Tiner, T.H., in "Comprehensive Organic Synthesis". Volume 4, Chapter 1.9, pp. 363-421. Editors: M.F. Semmelhack (volume); B.M. Trost and I. Fleming (series); Pergamon Press: Oxford 1991; .
3. Edwards, G.L. and Walker, K.A., *Tetrahedron Lett.*, 1992, **33**, 1779.
4. Serra, A.C. and da Silva Corrêa, C.M.M., *Tetrahedron Lett.*, 1991, **32**, 6653.
5. We thank Professor R. Rickards, Australian National University, for this suggestion.
6. Mandai, T., Ueda, M., Kashiwagi, K., Kawada, M., and Tsuji, J., *Tetrahedron Lett.*, 1993, **34**, 111.
7. Typically, a solution of the pentenyl tosylate (**5**) (0.50 g, 2.1 mmol) in carbon tetrachloride (10 ml) was heated to boiling under an argon atmosphere. A solution of benzoyl peroxide (50 mg) in carbon tetrachloride (5 ml) was added portionwise (0.5 ml aliquots) to the boiling solution over 10 h, and heating was then continued for a further 15 h. The reaction mixture was washed with aqueous sodium bisulfite (5%), dried ($MgSO_4$) and evaporated under reduced pressure. Flash chromatography (silica gel; ethyl acetate/light petroleum, 1:9) gave 4,6,6,6-tetrachlorohex-1-yl *para*-toluenesulfonate (**9**) (0.66 g, 80%) as a waxy solid, m.p. 30-32 °C (Found: C, 39.7; H, 4.3. $C_{13}H_{16}Cl_4O_3S$ requires C, 39.6; H, 4.1.%). ν_{max} 1355s, 1175s cm^{-1}[SO_2 asym and sym]. δ_H($CDCl_3$, 500 MHz) 1.79-1.88, m, 2H; 1.93-2.07, m, 2H; 2.46, s, 3H, $ArCH_3$; 3.07, dd, J_{gem} 15.6, ^3J 4.5 Hz, 1H, CH_aCCl_3; 3.26, dd, J_{gem} 15.6, ^3J 5.7 Hz, 1H, CH_bCCl_3; 4.09-4.11, m, 2H, CH_2O; 4.19-4.24, m, 1H, CHCl; 7.36, d, ^3J 8.3 Hz, 2H, ArH; 7.79, d, ^3J 8.3 Hz, 2H, ArH. δ_C($CDCl_3$, 75 MHz)[*Published data from reference 4 are provided for comparison*] 21.6(CH_3) [*21.45*], 25.7(CH_2) [*25.45*], 34.9(CH_2) [*34.65*], 56.8(CH) [*56.65*], 62.1(CH_2) [*61.77*], 69.4(CH_2) [*69.29*], 96.5(CCl_3) [—], 127.9(ArCH) [*127.63*], 129.9(ArCH) [*129.77*], 133.0(Ar) [*132.73*], 144.9(Ar) [*144.77*].
   M^+ observed at *m/z* 392/394/396/398 for $C_{13}H_{16}Cl_4O_3{}^{32}S$.
8. This was determined by addition of CCl_4 to the sample and remeasurement of the spectrum.
9. Walling, C. and Huyser, E.A., *Org. Reactions*, 1963, **13**, 91.
10. Velichko, F.K., Dostovalova, V.I., Kuzmina, N.A., Fedin, E.I., and Freidlina, R.Kh., *Org. Mag. Res.*, 1975, **7**, 46.
11. Velichko, F.K., Chukovskaya, E.C., Dostovalova, V.I., Kuzmina, N.A., and Freidlina, R.Kh., *Org. Mag. Res.*, 1975, **7**, 361.
12. *Crystal data*: $C_{12}H_{16}O_3S$, M 240.3, monoclinic, space group $P2_1/c$, a 5.643(1), b 15.420(2), c 14.058(2)Å, β 103.508(9)°, V 1189.3(4)Å^3, D_c 1.34 g cm^{-3}, Z 4, μ_{Cu} 22.95 cm^{-1}. Crystal size 0.16 by 0.20 by 0.28 mm, $2\theta_{max}$ 140°, min. and max. transmission factors 0.53 and 0.74. The number of reflexions was 1946 considered observed out of 2247 unique data, with R_{merge} 0.017 for 82 pairs of equivalent hk0 data. Final residuals R, R_w were 0.043, 0.065 for the obsereved data. Full details have been deposited at the Cambridge Crystallographic Data Centre.

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