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para-Toluenesulfonyl Iodide as a Convenient, Mild Reagent for the Preparation of Functionalised Cyclic Ethers

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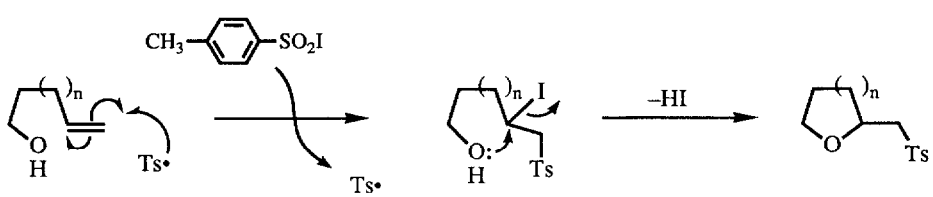
Key Words: cyclic ether; free radical additions; iodocyclisation; sulfone

Abstract: *Free radical addition of para-toluenesulfonyl iodide to alkenols occurs readily to give functionalised β-iodosulfones as single regioisomers. Cyclisation to give cyclic ethers is effected by treatment with potassium carbonate in methanol. An anomalous reaction, where a substituted alkenol cyclises directly to give an iodotetrahydropyran, is also discussed.*

In recent years many natural product syntheses have incorporated, as key strategic elements in the elaboration of complex molecular frameworks, highly stereo- and regio-selective free radical reactions.[1] Of increasing importance is the extension of radical methodology to allow for the introduction, transfer or retention of functionality for further synthetic operations.[2] As a part of a programme directed towards the development of new routes to functionalised oxygenated heterocycles, we elected to investigate the radical addition of *para*-toluenesulfonyl iodide[3] (tosyl iodide, TsI) to unsaturated alcohols and ethers (Scheme), such that the products could be amenable to further ionic reactions. The recently published work of Serra and da Silva Corrêa[4] on novel radical displacement reactions has prompted us to communicate our preliminary results in this area. The different stereoelectronic constraints of free radical *versus* ionic reactions will ensure that our approach complements that of Serra and da Silva Corrêa.[4]

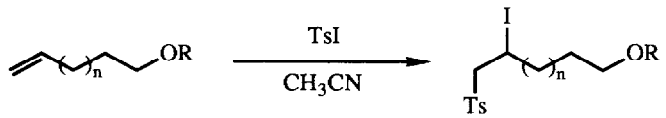


n = 1 (**1**) n = 1 (**3**) n = 1 (**5**)

n = 2 (**2**) n = 2 (**4**) n = 2 (**6**)

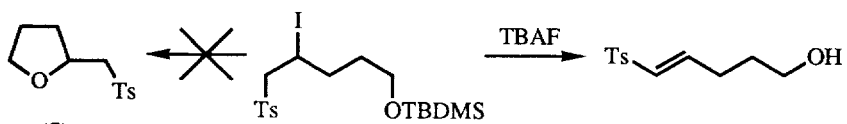
SCHEME

In the first instance, we chose to examine the reaction of simple unsaturated alcohols 4-penten-1-ol (**1**) and 5-hexen-1-ol (**2**) with tosyl iodide. From a mechanistic viewpoint, we considered that initial free radical addition to the alkenes would give β-iodosulfones (**3**) and (**4**) which would then cyclise to provide the cyclic ethers (**5**) and (**6**) directly. Reaction of the unsaturated alcohols with tosyl iodide in acetonitrile under an argon atmosphere occurred readily at room temperature (*ca.* 20°C) to give only the β-iodosulfones (**3**) and (**4**) in quantitative yields, as single regioisomers. There was no evidence of the desired cyclic structures, or of sulfonate esters, in the ^{1}H n.m.r. spectra of the crude reaction products. Chromatography of the β-iodosulfones on silica gel led to partial decomposition; the recovered products were contaminated with up to 20% of the corresponding vinyl sulfones (*vide infra*). The addition reactions required no additional initiation *and proceeded smoothly even when light was excluded*, indicating that homolysis of the weak sulfur–iodine bond occurs at a synthetically useful rate at ambient temperature. This observation is in contrast with reports on radical additions of tosyl bromide[5] and chloride,[6] where supplementary initiation appears necessary.



R = H	n = 1 (**1**)	R = H	n = 1 (**3**)
	n = 2 (**2**)		n = 2 (**4**)
R = TBDMS	n = 1 (**7**)	R = TBDMS	n = 1 (**9**)
	n = 2 (**8**)		n = 2 (**10**)

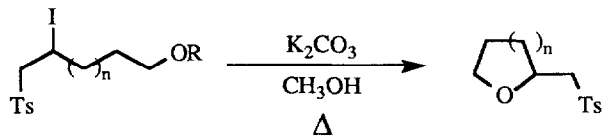
An alternative route was attempted, whereby tosyl iodide was added to *t*-butyldimethylsilyl ethers (**7**) and (**8**) giving the β-iodosulfones (**9**) and (**10**), in the expectation that the incipient alkoxide produced on treatment with tetra-*n*-butylammonium fluoride (TBAF) would displace iodide to give the desired oxacycles (**5**) and (**6**). Instead, treatment of the silyl ether (**9**) gave a mixture of products where the vinyl sulfone (**11**) predominated (J_{trans} 15.1 Hz). Clearly, either fluoride or the intermediate alkoxide led to base-mediated dehydroiodination rather than the desired cyclisation.



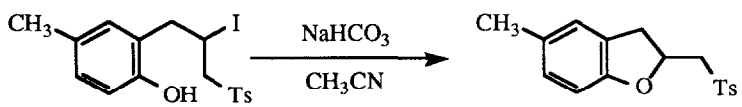
(**5**) (**9**) (**11**)

However, cyclisation was effected by treatment of the hydroxy β-iodosulfones (**3**) and (**4**) with anhydrous K_2CO_3 in boiling methanol, to give the 2-substituted tetrahydrofuran (**5**, 65% yield)[7,8] and pyran (**6**, 54% yield),[7,8,9] respectively. In a similar manner, the silyl ether (**9**) gave the desired cyclic ether (**5**, 42% yield).[7] The spectroscopic data for tetrahydrofuran (**5**) correlated well with that provided by Serra and da Silva Corrêa.[4] This reaction has also been extended to the synthesis of the dihydrobenzofuran (**13**) in

quantitative yield;[7] cyclisation of the phenol (**12**, derived from 2-allyl-*p*-cresol) was accomplished by treatment with $NaHCO_3$ in acetonitrile.

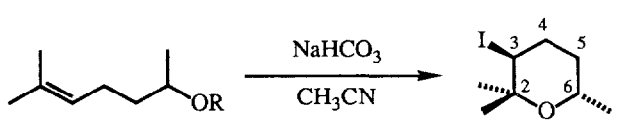


R = H	n = 1	(**3**)	n = 1	(**5**)
	n = 2	(**4**)	n = 2	(**6**)
R = TBDMS	n = 1	(**9**)	n = 1	(**5**)



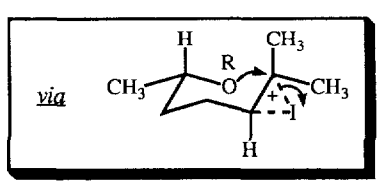
(**12**) (**13**)

An interesting variation in the reactivity of tosyl iodide was discovered when addition to alkenol (**14**) was attempted: instead of the desired β-iodosulfone or heterocyclic product, the only compound to be isolated was the volatile *trans*-iodide (**16**), in 51% yield ($J_{3,4_{ax}}$ 11.7 Hz, $J_{6,5_{ax}}$ 10.9 Hz). In a similar manner the silyl ether (**15**) also gave the iodide (**16**, 48% yield) as the only product, suggesting the involvement of a cationic rather than a radical intermediate. This compound was identical in all respects to that derived from a Bartlett iodocyclisation[10] [alkenol (**14**), I_2, $NaHCO_3$, CH_3CN]. Whereas reaction of tosyl iodide with terminal alkenes gives products which can be formally envisaged (following cyclisation) as reaction with Ts^+, the electron-rich alkenol (**14**) gives a compound where the tosyl iodide apparently behaves as a source of I^+.



R = H (**14**) (**16**)

R = TBDMS (**15**)



We are presently investigating the scope of this procedure for the synthesis of larger rings and for the incorporation of other heteroatoms. The effect of substituents on the stereoselectivity of the ring closure is also being studied, as well as the limits of the novel "dual reactivity" of tosyl iodide as described in this work.

References and Notes

1. Curran, D.P., *Synlett*, 1991, 63.
2. Jasperse, C.P., Curran, D.P., and Fevig, T.L., *Chem. Rev.*, 1991, **91**, 1237.
3. Truce, W.E., Heuring, D.L., and Wolf, G.C., *J. Org. Chem.*, 1974, **39**, 238.
4. Serra, A.C. and da Silva Corrêa, C.M.M., *Tetrahedron Lett.*, 1991, **32**, 6653.
5. Chuang, C.-P. and Ngoi, T.H.J., *Tetrahedron Lett.*, 1989, **30**, 6369.
6. Serra, A.C., da Silva Corrêa, C.M.M., and do Vale, M.L.C., *Tetrahedron*, 1991, **47**, 9463.
7. Yield refers to the overall yield from the corresponding alcohol or silyl ether.
8. Representative n.m.r. data (partial assignment of ^{13}C spectra with DEPT pulse sequence):
   Compound (**5**): δ_H (300 MHz; $CDCl_3$) 1.62-1.71 (m, 1H, ring CH), 1.82-1.92 (m, 2H, ring CH), 2.07-2.17 (m, 1H, ring CH), 2.44 (s, 3H, CH_3), 3.19 (dd, *J* 14.1, 6.1 Hz, 1H, SCH), 3.40 (dd, *J* 14.1, 6.2 Hz, 1H, SCH), 3.68 (dt, *J* 8.5, 6.8 Hz, 1H, H5a), 3.79 (dt, *J* 8.5, 6.8 Hz, 1H, H5b), 4.22 (pentet, *J* 6.5 Hz, 1H, H1), 7.34 (d, *J* 8.3 Hz, 2H, ArH), 7.80 (d, *J* 8.3 Hz, 2H, ArH). δ_C (125 MHz; $CDCl_3$) 21.6 (CH_3), 25.3 (CH_2), 31.6 (CH_2), 61.2 (CH_2), 68.0 (CH_2), 72.9 (OCH), 128.1 (ArCH), 129.8 (ArCH), 137.0 (Ar), 144.6 (Ar).
   Compound (**6**): δ_H (300 MHz; $CDCl_3$) 1.22-1.80 (m, 6H, ring CH), 2.40 (s, 3H, CH_3), 3.07 (dd, *J* 14.5, 3.8 Hz, 1H, SCH), 3.27-3.34 (m, 1H, OCH), 3.30 (dd, *J* 14.5, 7.7 Hz, 1H, SCH), 3.73-3.84 (m, 2H, OCH), 7.30 (d, *J* 8.3 Hz, 2H, ArH), 7.75 (d, *J* 8.3 Hz, 2H, ArH). δ_C (75.5 MHz; $CDCl_3$) 21.2 (CH_3), 22.6 (CH_2), 24.8 (CH_2), 31.0 (CH_2), 61.8 (CH_2), 67.7 (CH_2), 71.9 (OCH), 127.7 (ArCH), 129.2 (ArCH), 137.0 (Ar), 144.0 (Ar).
9. ***Typical procedure:*** *para*-Toluenesulfonyl iodide (1.41 g, 5.0 mmol) was added to a solution of 5-hexen-1-ol (**2**) (0.5 g, 5.0 mmol) in dry acetonitrile (50 ml) under an argon atmosphere. The resulting yellow solution was protected from light and was stirred at room temperature overnight. The solvent was removed and the residue was dissolved in dichloromethane, washed sequentially with aqueous sodium thiosulfate and water, dried ($MgSO_4$) and concentrated under reduced pressure to give the β-iodosulfone (**4**). The β-iodosulfone was dissolved in methanol (50 ml) and anhydrous potassium carbonate (1.2 g, 8.7 mmol) was added. The resulting mixture was heated under reflux for 5 h under an argon atmosphere, and then filtered and concentrated under reduced pressure. The residue was dissolved in dichloromethane, washed with water, dried ($MgSO_4$) and evaporated. Flash chromatography (gradient elution with light petroleum / diethyl ether) gave the cyclic ether (**6**) as a white solid (0.68 g, 54% from 5-hexen-1-ol).
10. Rychnovsky, S.D. and Bartlett, P.A., *J. Am. Chem. Soc.*, 1981, **103**, 3963.

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