Oxetane synthesis via cyclisation of aryl sulfonate esters on polystyrene and PEG polymeric supports

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Abstract—The addition of suitably protected pentaerythritols to polymer supported sulfonyl chloride with subsequent alkoxide formation and intramolecular cyclisation to generate oxetanes is described. This convenient method for the preparation of oxetanes has several advantages over analogous solution phase reactions and the methodology is extended to the preparation and use of a novel PEG-sulfonyl chloride.
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Oxetanes are an important group of cyclic ethers that can be used in synthesis as equivalents for the a[3]-synthon, and undergo a wide range of chemical transformations. As with their three membered ring analogues, the epoxides, they can be self-polymerised under Lewis acid conditions,[1–4] or polymerised through anionic ring opening,[5] to give a range of polyether architectures. They have also been converted into cage molecules for the selective complexation of cations[6] and oxetane moieties are found in many natural products.[7,8] The synthesis of oxetanes has been reported using a number of different strategies,[9] for example, via a [2+2]-photocycloaddition of an alkene and aldehyde,[10] or more frequently the dehydration of 1,3-diols.[11,12] For the later approach, yields are often moderate at best, particularly with acyclic diols.[13]

With the intense interest in these compounds there is a continuing desire to develop facile procedures requiring the minimal purification of products. Therefore, the use of a solid support for the synthesis of sterically hindered, functionalised oxetanes, using the support as a leaving group during the cyclisation step was considered (Scheme 1).

Solid phase organic synthesis (SPOS) has become of increasing importance in the last 10–15 years, largely
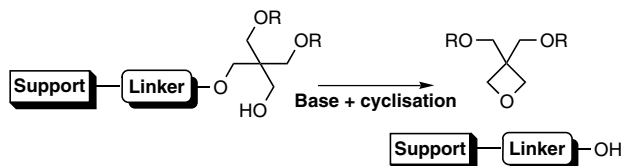
Scheme 1. Solid support cyclisation strategy to oxetanes.

due to the emergence of combinatorial chemistry, which has enabled the parallel synthesis of large libraries of compounds.[14] SPOS has also led to the development of automated synthetic procedures, where the purification following each synthetic step can be achieved using resin-washing procedures.[14] When designing a synthesis on solid support one key consideration is selection of the linker through which the substrate is attached to the support, as well as the type of support. For an application in oxetane synthesis a polymer bound sulfonyl chloride was selected. Herein we describe the use of a polystyrene (PS) resin and the synthesis of a novel PEG-sulfonyl resin for the synthesis of oxetanes.

Sulfonyl chloride (PS bound) is most often used as a nucleophile scavenger (e.g., for amines or alcohols), allowing the simple purification of solution phase reactions. However, as a linker it can also provide a convenient method of attaching a substrate through a free amine or alcohol functionality, which can then be released and modified by nucleophilic attack.[15–17] To the best of our knowledge, there are no reported examples of the cleavage of molecules from this linker via an

intramolecular nucleophilic attack, to form cyclic products. Two pentaerythritol analogues were selected as suitable compounds to investigate this approach: di-*tert*-butyldimethylsilyl pentaerythritol **1** and the monobenzylidene protected pentaerythritol **2**.[18] In order to obtain a direct comparison with the solution phase reaction, the equivalent non-SPOS reaction was initially performed. The monotosylate **3** was readily prepared although the synthesis of **4** proved to be low yielding due to decomposition under the reaction conditions (Scheme 2). Also, as with all such desymmetrisation reactions, the ditosylated compounds together with unreacted starting material were also present in the crude product mixture, and purification by flash column chromatography was required. The alkoxide was then generated in situ, which subsequently formed the oxetane, and was isolated and purified. The use of sodium hydride gave **5** in higher yields, whilst the optimal base to give the oxetane **6** was potassium *tert*-butoxide. The conversion of **1** and **2** into **5** and **6** was achieved in 59% and 6% yield over two steps.

With the results of the solution based oxetane synthesis in hand, we set about modifying the procedure for use on a solid support. Both diols were successfully loaded onto the PS support to give **7** and **8** (**A** is PS, Scheme 3), using pyridine as base and heating at reflux for 16 h, as indicated by a positive result from a bead-staining test.[19]
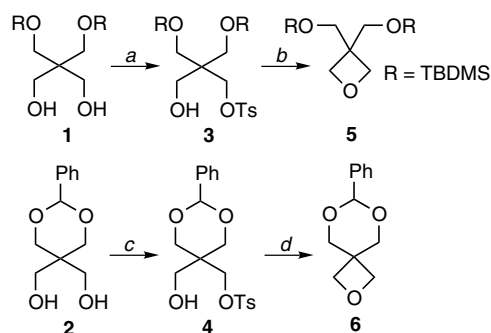
Scheme 2. Reagents and conditions: (a) TsCl, pyridine, reflux, 24 h, 71%; (b) NaH, THF, rt, 3 h, 83%; (c) TsCl, DMAP, pyridine, rt, 16 h, 10%; (d) KO*t*Bu, THF, rt, 3 h, 57%.
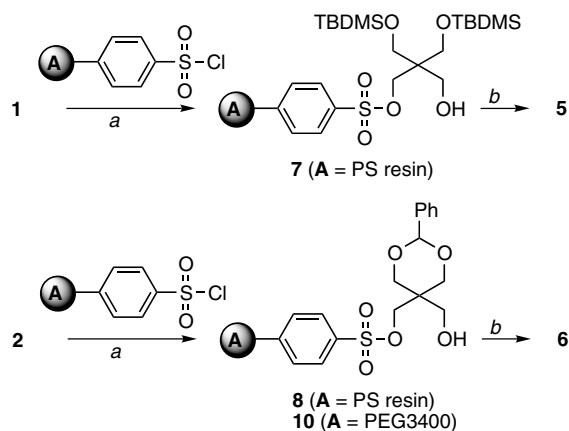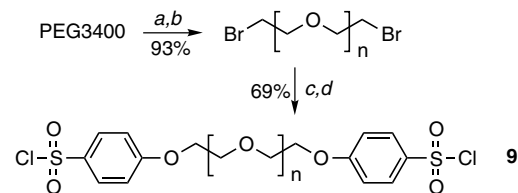

Scheme 3. Reagents and conditions: (a) pyridine, reflux, 16 h; (b) KO*t*Bu.

Interestingly, when the polymer bound alcohols **7** and **8** were treated with sodium hydride no reaction was observed. However, the use of potassium *tert*-butoxide to generate the alkoxide gave **5** and **6** in 96% and 62% yields, respectively, over the two steps. The only purification step required was to remove trace impurities from **5** and **6** by filtration through a short pad of silica.[20]

Whilst the use of a polystyrene resin has many advantages, reactions on the beads are often nontrivial to monitor in detail. In addition, we predicted that a support with a polar environment could influence stabilisation of the alkoxide and the subsequent cyclisation favourably. The synthesis of a sulfonyl chloride linker on a PEG polymer (average mass 3400) was therefore investigated. Soluble polymeric supports of this nature, with applications in liquid-phase organic synthesis (LPOS), can have several advantages over polystyrene based supports:[21] solubility in solvents such as dichloromethane and methanol gives a more solution-like environment for reactions, and also enables the monitoring of polymer bound intermediates by solution ^{1}H NMR spectroscopy. However, their low solubility in other solvents, such as propan-2-ol and diethyl ether, allows ease of purification using simple recrystallisation techniques. The synthesis of the PEG-sulfonyl chloride resin **9** was carried out as detailed below in 64% overall yield, and all steps were readily monitored using solution ^{1}H NMR spectroscopy. The dimesylation of PEG3400 was carried out as previously reported and then conversion to the corresponding dibromide achieved under standard conditions (Scheme 4).[22,23] Reaction with 4-hydroxybenzenesulfonic acid and sodium hydroxide, then treatment with thionyl chloride gave the difunctionalised PEG-sulfonyl chloride resin **9**.[23]

The loading of the pentaerythritol **2** onto **9** required the use of DMAP (stoichiometric) in toluene and the reaction was stirred at rt for 16 h to give **10** (**A** is PEG3400, Scheme 3) containing approximately 30% of a bridged side product, by ^{1}H NMR spectroscopy. The use of alternative reaction conditions led to lower loading levels onto **9**. Despite this, cyclisation and cleavage were readily achieved using potassium *tert*-butoxide to give **6** in 63% yield over the two steps, reflecting the problem with the bridged side products, but highlighting that the cyclisation occurred with **10** in almost quantitative yield. Again, trace impurities were removed from **6** by filtration through a short pad of silica. Since the overall yield was comparable to that for the loading and cyc-

Scheme 4. Reagents and conditions: (a) MsCl, Et₃N, rt, 16 h; (b) LiBr, acetone, reflux, 16 h; (c) 4-hydroxybenzenesulfonic acid, NaOH, *i*PrOH/H₂O, reflux, 16 h; (d) CH₃CN, Soxhlet, CaC₂, 5 h then SOCl₂, DMF, rt, 16 h.

lisation of **2** using the PS resin, it was concluded that the nature of the solid support was not a key issue in this synthesis, however, detailed reaction monitoring was extremely easy using the PEG resin **9**.

In summary, we have developed a straightforward, and synthetically useful method for the formation of oxetanes via a sulfonyl linker on different polymeric supports. This method of forming oxetanes has advantages over the analogous solution phase reactions, both in terms of yield and ease of purification of intermediates and products. The PEG-sulfonyl resin **9** demonstrated clear advantages over PS-supports in terms of reaction monitoring to generate the cyclic ether. Also, these procedures could be used with higher loading resins, expanding the synthetic utility further.[24] It is likely that the methodology can be applied to other 1,3-diols, and for the synthesis of alternative ring sizes.

Acknowledgements

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20. *Procedure for the formation of* **8** *and cyclisation and cleavage to generate* **6**: To a suspension of PS sulfonyl chloride resin (100 mg, 0.20 mmol) in pyridine (5 mL), was added **2** (224 mg, 1.00 mmol), and the reaction mixture was heated at reflux for 16 h. The resin was collected by filtration, washed with CH_2Cl_2 (3×5 mL), DMF (3×5 mL), DMF/H_2O (5:1, 3×5 mL), THF (3×5 mL), and CH_2Cl_2 (3×5 mL), and dried in vacuo to give **8** (102 mg). Unreacted **2** was fully recovered from the filtrate. To a suspension of the loaded resin **8** (50 mg, 0.07 mmol; assuming full loading of **2**) in THF (2 mL) was added potassium *tert*-butoxide (24 mg, 0.21 mmol), and the reaction mixture was shaken at room temperature for 3 h. The resin was collected by filtration, and washed with THF/H_2O (5:1, 3×5 mL), THF (3×5 mL), and CH_2Cl_2 (3×5 mL). The combined filtrates were washed with water (5 mL), dried and evaporated. The crude product was filtered through a short pad of silica in ethyl acetate/hexane (2:3) to give **6** (9 mg, 62%). δ_H (300 MHz; $CDCl_3$) 3.89 (2H, d, *J* 11.0 Hz), 4.27 (2H, s), 4.56 (2H d, *J* 11.0 Hz), 4.77 (2H, s), 5.43 (1H s, C*H*–Ph), 7.31–7.38 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) 38.0 (*C*(CH_2)$_4$), 73.1, 73.8, 81.3, 101.3 (CH–Ph), 126.0, 128.3, 129.0, 137.7.
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23. *Procedure for the formation of* **9**: PEG3400 dimesylate (10.0 g, 2.81 mmol) in acetone (50 mL), and lithium bromide (1.47 g, 16.9 mmol) were heated at reflux for 16 h. The solution was cooled and a white solid removed by filtration. The filtrate was evaporated in vacuo, the crude product dissolved in hot propan-2-ol (50 mL), then cooled to 5 °C. The precipitate formed was collected by filtration, washed with propan-2-ol (10 mL), and Et_2O (50 mL), and dried in vacuo to afford PEG3400 dibromide as a colourless solid (9.86 g, 100%). δ_H (300 MHz; $CDCl_3$) 3.39–3.86 (m, PEG C*H*$_2$), 3.46 (t, *J* 6.3 Hz, C*H*$_2$Br). To a solution of PEG3400 dibromide (8.30 g, 2.35 mmol) in propan-2-ol/water (1:1, 100 mL), was added 4-hydroxybenzenesulfonic acid (mono sodium salt) (5.46 g, 23.5 mmol), and sodium hydroxide (940 mg, 23.5 mmol). The reaction mixture was heated at reflux for 4 d. The solvent was removed in vacuo, and the crude product dissolved in hot propan-2-ol (100 mL), from which an insoluble white solid was removed by filtration. The filtrate was cooled to 5 °C, and the precipitate, which formed collected by filtration. This was washed with propan-2-ol (10 mL), Et_2O (50 mL) and dried in vacuo to afford PEG3400 disulfonic acid sodium salt as a white solid (8.25 g, 93%). δ_H (300 MHz; $CDCl_3$) 3.40–3.85 (m, PEG C*H*$_2$), 4.14 (4H, t, *J* 5.1 Hz, C*H*$_2$OAr), 6.85 (4H, d, *J* 8.7 Hz, Ar–*H*), 7.84 (4H, d, *J* 8.7 Hz, Ar–*H*). PEG3400 disulfonic acid sodium salt (23.2 g, 6.18 mmol), in acetonitrile (500 mL), was then heated at reflux using a Soxhlet apparatus containing calcium carbide (CAUTION: http://ptcl.chem.ox.ac.uk/MSDS/CA/calcium_carbide.html) (2 g) for 5 h under an atmosphere of N_2. The reaction mixture was cooled to rt and thionyl chloride (4.01 mL, 61.8 mmol), and DMF (5 mL) were added and it was stirred for 16 h at rt. The solvent was removed in vacuo and the crude product dissolved in hot propan-2-ol (100 mL). The solution was cooled to 5 °C, and the precipitate formed collected by filtration. The precipitation step was repeated, the combined precipitates washed with propan-2-ol (10 mL), and Et_2O (50 mL), and then dried in vacuo to afford **9** as a white solid (21.6 g, 93%). δ_H (300 MHz; $CDCl_3$) 3.38–3.90 (m, PEG C*H*$_2$), 4.23 (4H, t, *J* 4.6 Hz, C*H*$_2$OAr), 7.07 (4H, d, *J* 9.0 Hz, Ar–*H*), 7.96 (4H, d, *J* 9.0 Hz, Ar–*H*).
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