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Synthesis of substituted dihydrobenzothiopyrans and dihydrobenzopyrans by cation-mediated cyclisation reactions

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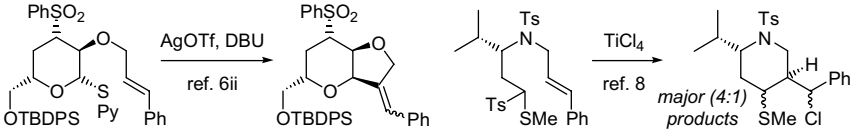
Abstract—Treatment with acid of thiosalicylaldehyde- and salicylaldehyde-derived phenyl 3-phenyl-2-propenyl thioethers and ethers possessing latent oxonium ion functionality triggers simple or tandem cyclisation to give substituted dihydrobenzothiopyrans and dihydrobenzopyrans. Some derivatisation reactions of the products are described.

The synthesis of heterocycles by cyclisation through carbon–carbon bond formation is a strategy complementary to the more classical approach involving reaction of carbon-based electrophilic functional groups with nucleophilic heteroatoms. In this context, cycloaddition,[1] radical cyclisation,[2] ring-closing olefin metathesis[3] and anion-[4] and carbocation-assisted[5] cyclisation reactions all have recently been deployed. We have investigated the formation of oxygen- and nitrogen-containing heterocycles through the intramolecular combination of electron-rich olefins with, respectively, acetal-derived oxocarbenium ions[6] and thionium species derived either by Pummerer reactions of sulfoxides[7] or by ionisation of α-arylsulfonyl thioethers.[8] Some of this work[6b,8] showed that 3-phenyl-2-propenyl groups are effective intramolecular nucleophiles for oxonium and thionium ion electrophiles, with the intermediate benzylic cations resulting from the heterocyclisation process undergoing addition or elimination according to the reaction conditions (Scheme 1).

We became interested in the possibility of synthesising dihydrobenzothiopyrans[9] and dihydrobenzopyrans[10] using this approach, in which the requisite benzylic cationic intermediates generated from substrates **1** and **2** would be stabilised additionally by the sulfur or oxygen atom through which the nucleophilic 3-aryl-2-propenyl group was appended (Scheme 2). This letter reports the results of these investigations.

Substrate **1** was studied first. It was assembled using a simple, four-step sequence beginning from commercially available methyl thiosalicylate.[11] Sulfur alkylation with *E*-1-bromo-3-phenyl-2-propene using guanidinium carbonate in acetone,[12] followed by low-temperature DIBAL-H-mediated ester reduction in CH_2Cl_2 and oxidation of the resulting primary alcohol with PCC[13] gave an intermediate aldehyde. Finally, acid-catalysed acetalisation with trimethyl orthoformate provided **1** in 87% overall yield from methyl thiosalicylate.

A number of reagents and reaction conditions were evaluated for the cyclisation of **1** before tin(II)chloride–chlorotrimethylsilane was identified as the best combination. Thus, treatment of **1** with 2 equiv of TMSCl and substoichiometric $SnCl_2$ in CH_2Cl_2 at 0 °C[14] resulted in



Scheme 1.

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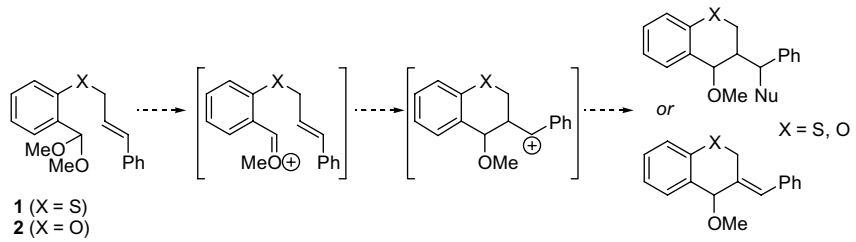
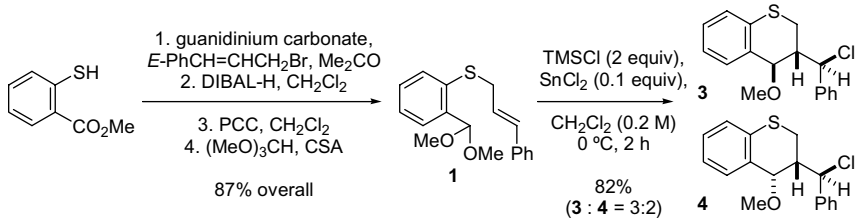


Scheme 2.



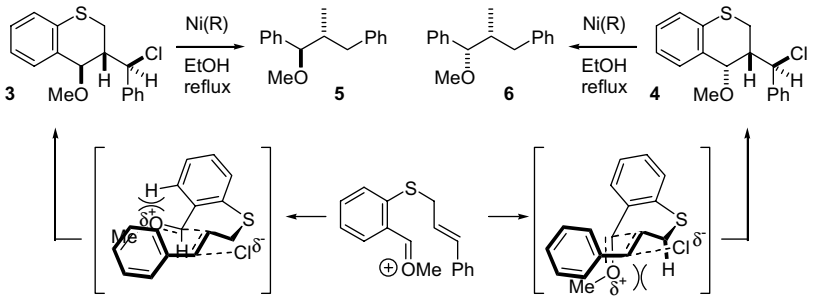
Scheme 3.

the formation of two diastereoisomeric dihydrobenzothiopyrans in a 3:2 ratio and 82% combined yield. Structure **3** was assigned to the major isomeric product by X-ray crystallographic analysis of a single crystal. The minor product was assigned as **4** by X-ray crystallography following oxidation to the corresponding sulfone in quantitative yield using *m*-CPBA in CH_2Cl_2.[15] The synthesis and cyclisation reaction of **1** are shown in Scheme 3.

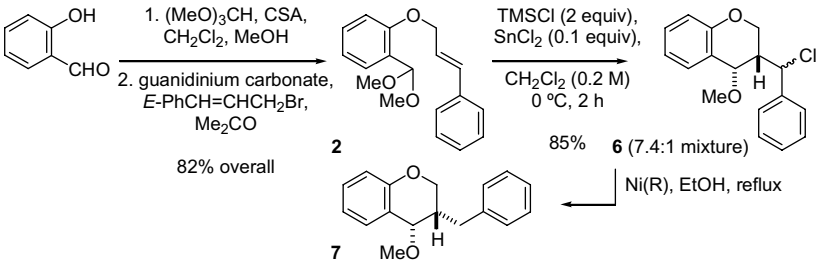
Inspection of structures **3** and **4** reveals that both are products of stereospecific *anti*-addition of the internal oxonium ion and chloride to the *E*-double bond in **1**. That **3** and **4** differed with respect to the newly formed methoxy-bearing stereocentre was further confirmed by the formation of two diastereomers of 1-methoxy-2-methyl-1,3-diphenylpropane on separate treatment with Raney nickel. The lack of stereoselectivity is perhaps indicative of competing interactions of similar magnitude involving the oxonium ion and the *ortho*-hydrogen atom in the reactive conformation leading to **3**, and a pseudoaxial methylene hydrogen atom in that leading to **4** (Scheme 4).

Attention was next turned to the oxygenated analogue **2**. This substrate was readily synthesised by *O*-alkylation of salicylaldehyde dimethyl acetal[16] with *E*-1-bromo-3-phenyl-2-propene using the same conditions as in the synthesis of substrate **1**, providing **2** in 82% yield from salicylaldehyde. Exposure of **2** to the conditions used successfully for substrate **1** resulted in the formation in 85% yield of a 7.4:1 separable mixture of diastereomers **6**. The 3,4-*cis* substitution of the C3 chlorobenzyl and C4 methoxy substituents in **6** followed from the relatively small (4 Hz) vicinal $J_{3,4}$ values (4 and 2 Hz) for the C3 methine signals in the ^{1}H NMR spectra. Treatment of the diastereomeric mixture with Raney nickel gave a *single* dihydrobenzopyran **7**, in contrast to sulfur-containing products **3** and **4**, which had given isomeric products upon desulfurisation–dechlorination. The synthesis of **2** and its cyclisation and derivatisation reactions are depicted in Scheme 5.

The results depicted in Scheme 5 show that in contrast with the cyclisation of **1**, that of **2** exhibited complete selectivity with respect to the stereocentres on the newly formed oxygen heterocycle. This may arise by a lessening of the oxonium–pseudoaxial hydrogen interaction similar to that postulated in the reactive conformation leading to **4** because of the greater C–O–C bond angle. The lack of *anti*-specificity of addition to the double bond may be a consequence of the greater rate of intra-



Scheme 4.



Scheme 5.

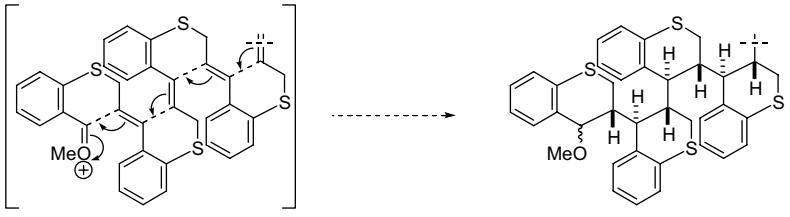
molecular interception of the oxonium ion on account of the shorter C–O bonds appending the 3-phenyl-2-propenyl internal nucleophile.

The final part of our study looked at the possibility of achieving cation-mediated cascade cyclisations using oligomeric substrates related to **1**. Our idea was that a substrate comprising a latent oxonium ion trigger and repeat units of the *E*-3-phenyl-2-propenylthio 'monomer' present in **1** might undergo ionisation followed by a cascade of cyclisation reactions in an *anti*-specific manner as depicted in Scheme 6.

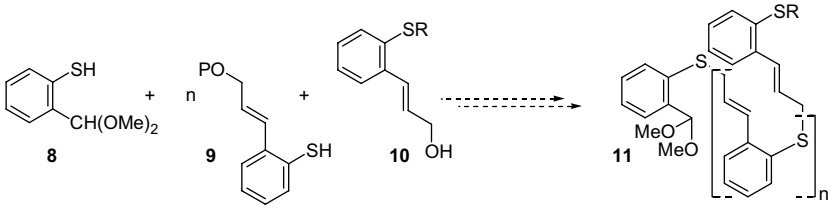
An attractive aspect of this plan was the anticipated ease with which the required substrates **11** would be accessible synthetically, using inherently reactive arenethiol–allylic alcohol combinations. We envisaged initial combination of a head unit **10** with 'monomer' **9** followed by iterative attachment of further units of **9**, and finally a capping fragment **8** possessing the latent cationic centre (Scheme 7).

In order both to assess the chemical feasibility of both the cyclisation reaction and to evaluate the chemistry planned for the assembly of precursors, we elected to synthesise a cyclisation substrate **11** ($n = 1$, R = Bn) corresponding to a simple one-monomer extension of **1**. Head unit **10** (R = Bn) was readily prepared in 62% overall yield by benzylation of methyl thiosalicylate followed by two-step conversion into the aldehyde; Wittig homologation and DIBAL-H reduction completed the synthesis. Compounds **8** and **9** (P = TBDPS) were made from common intermediates again derived from methyl thiosalicylate. Reduction was followed by oxidation to the aldehyde, which simultaneously effected thiol protection through formation of the symmetrical disulfide–aldehyde **12**.[17] This was processed in two separate routes; simple aldehyde protection gave disulfide–acetal **14** in quantitative yield, whilst Wittig homologation[18] followed by ester reduction and allylic alcohol protection gave disulfide–silyl ether **13**. Substrate **11** ($n = 1$, R = Bn) was then easily assembled using disulfide reduction-Mitsunobu chemistry. Treatment of **13** with Bu_3P–H_2O in THF gave thiol **9** (P = TBDPS), and the crude product was coupled with **10** (R = Bn) in the presence of diisopropyl azodicarboxylate (DIAD) to give **15**. Desilylation of **15** under standard conditions and combination with thiol **8**, which had been freshly prepared from **14** using the conditions employed for the generation of **9**, gave **11** ($n = 1$, R = Bn) in good overall yield (Scheme 8).

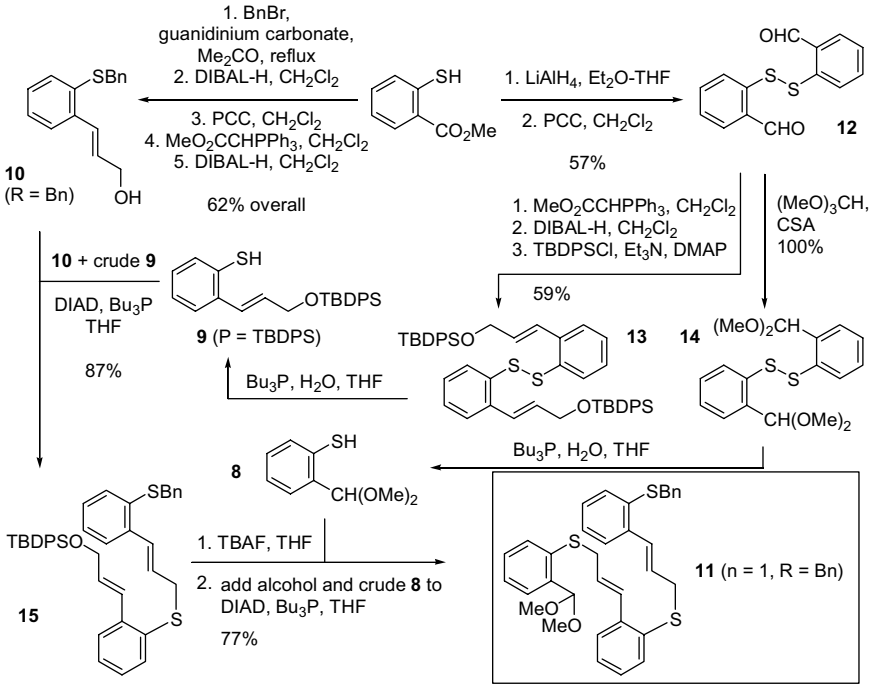
With a robust synthesis of **11** ($n = 1$, R = Bn) in hand, its cyclisation behaviour was studied. Disappointingly, the



Scheme 6.



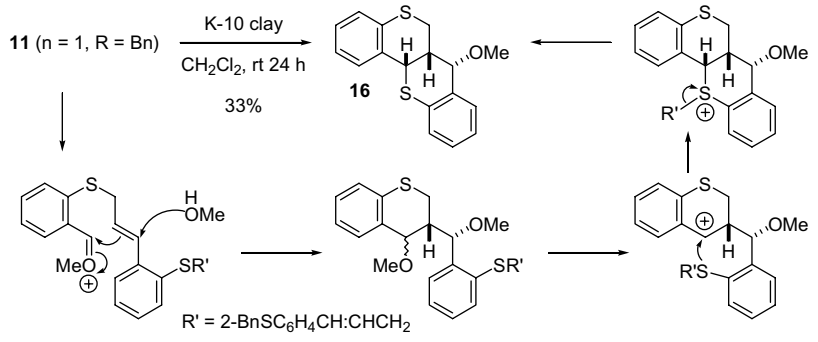
Scheme 7.



Scheme 8.

$SnCl_2$–TMSCl conditions used previously for the cyclisations of **1** and **2** failed to yield significant amounts of ring-closure products, as did a range of other Lewis acid reagent systems. After extensive experimentation it was found that **11** ($n = 1$, R = Bn) underwent cyclisation on treatment with K10 Montmorillonite clay, giving a new product in 33% yield. However, oxidation (*m*-CPBA) to the corresponding sulfone and X-ray crystallographic analysis[15] revealed the structure of the cyclised product to be **16**. Presumably, this unexpected tetracyclic substance is formed by internal trapping of the oxonium ion formed initially, followed by interception of the resulting benzylic cation with a methoxy nucleophile in a fashion similar to the cyclisation of **1**. Subsequently, the product of this mono-cyclisation undergoes a second ionisation followed by intramolecular trapping by the thioether sulfur atom and allylic carbon–sulfur bond scission from the resultant labile sulfonium ion intermediate (Scheme 9).

In conclusion, we have shown that a simple 3-phenyl-2-propenyl thioether derivative of thiosalicylaldehyde dimethyl acetal undergoes efficient, stereospecific—with respect to the nucleophilic double bond—but non-stereoselective cyclisation on treatment with a Lewis acid. A structurally similar ether-containing substrate undergoes completely stereoselective cyclisation, but in a non-stereospecific manner with respect to the substrate double bond. A higher-order cyclisation substrate was synthesised using an iterative strategy, which should prove amenable to the synthesis of higher oligomeric substrates. Attempted cascade cyclisation resulted in carbon–carbon and carbon–sulfur bond formation. Future investigations will focus on the development of modified substrates possessing alternative, less highly oxidised latent cationic functionality, which prohibits the second, unwanted ionisation process, which triggers substrate breakdown by nucleophilic attack through sulfur.



Scheme 9.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tetlet.2005.03.161.

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