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A CYCLIZATION-TRAPPING ROUTE TO CARBOCYCLIC AND HETEROCYCLIC BENZYLIC SULFONES

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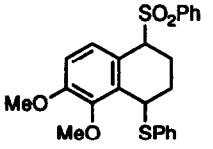
Abstract: Acetals of 4-arylbutyraldehydes and 3-aryloxy-, 3-arylamino- and 3-arylthiopropionaldehydes react with Na-sulfinates in formic or trifluoroacetic acid to give good yields of the corresponding 4-(sulfonyl) substituted tetralins, tetrahydroquinolines, chromans and thiochromans.

During the course of synthetic studies[2] on the pseudopterosin family of diterpenes, we required tetralin derivatives such as **1**, bearing oxidatively differentiated sulfur moeities at C-1 and C-4. Our initial route[2a] required six steps and used a standard intramolecular Friedel-Crafts reaction to prepare the tetralone **2**, the final step being the reaction of the corresponding tetralol with $PhSO_2Na$ in HCO_2H. This route to benzylic sulfones was originally employed as a mechanistic test for the intermediacy of carbonium ions[3] and has also found preparative use.[4] Related reactions with thiols have been utilised for the degradation and structure elucidation of complex lignans[5] and constitute a useful route to benzylic sulfides.[6] We have now devised a novel, shorter route to **1** and we have extended this chemistry to heterocyclic systems: we report our preliminary results in this paper.



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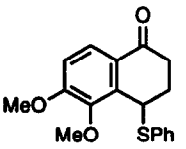

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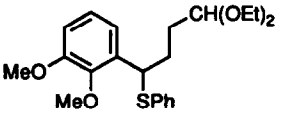

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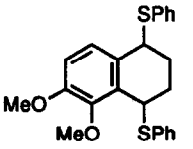

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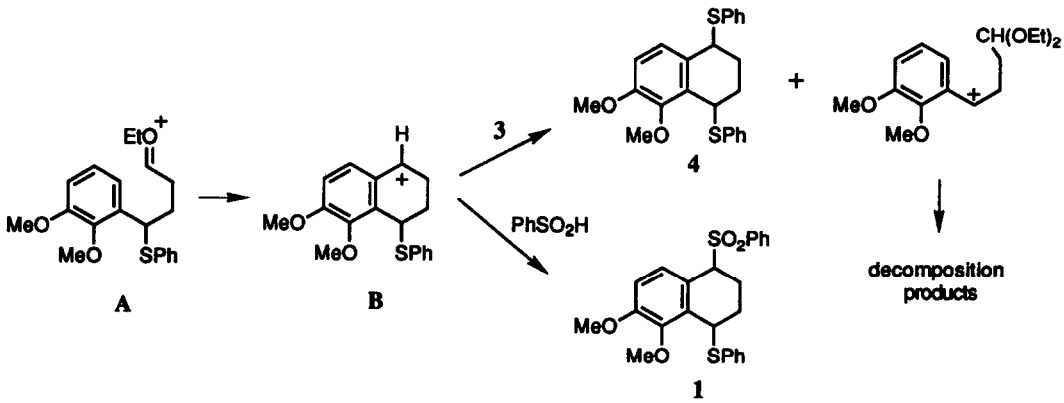
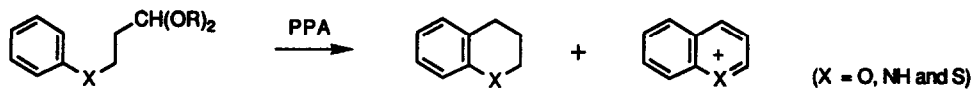
Anticipating that the acid-catalysed reaction between a sulfinic acid and an appropriately substituted 4-phenylbutyraldehyde acetal might be either reversible or slow under conditions where a benzylic carbonium ion, derived *via* cyclisation of the acetal, could be trapped to give the corresponding sulfone, we prepared the acetal **3** ($2,3\text{-}(MeO)_2C_6H_3CH_2Cl$ + PhSNa, then BuLi; $ICH_2CH_2CH(OEt)_2$, -70° to RT).[7] Gratifyingly, **3** reacted with 2 eq. of $PhSO_2Na$ in HCO_2H (RT, 6 h) to give **1** in 84% isolated yield. When the sulfinate salt was omitted, a modest yield of the bis-(phenylthio) compound **4** separated, leaving a complex mixture in the liquors. These results are consistent with the processes shown in **Scheme 1**. The initially formed, acyclic oxocarbonium ion **A** cyclises efficiently, and the product then affords the tetralin-1 cation **B**, for which various reaction pathways are available. In the absence of any traps (e.g. in the reaction of 6-methoxy-1-tetralol with acid), dimer formation is observed[8] by virtue of reaction between the

carbonium ion and the electron-rich styrene derivative formed by proton loss. In the case of **3** the phenylthio group is transferred, resulting in the stable thioether **4** plus mixtures presumably derived from the educt carbonium ion. *With sulfinate present, the ion B is cleanly trapped to produce the benzylic sulfone.* Compounds **1** and **4** were predominantly the *trans* isomers, and gave identical disulfone samples upon oxidation.



Scheme 1

Applying the reaction to substrates of general structure Ar-X-$CH_2CH_2CH(OEt)_2$ formed heterocyclic systems; the trapping by the sulfinate ion avoided the extensive redox disproportionation which has characterised previous acid-induced cyclisations[9] of these precursors (**Scheme 2**):



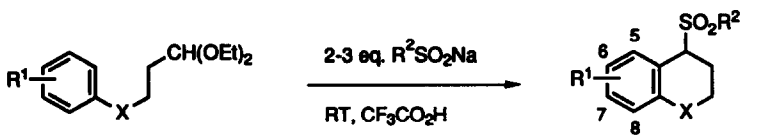
Scheme 2

Table 1 shows that such cyclizations conducted under mild conditions in the presence of sulfinic acid salts afford good to excellent yields of the corresponding 4-(sulfonyl) substituted chromans, thiachromans and tetrahydroquinolines. Formic acid was a satisfactory medium, but in general, higher yields with shorter reaction times were obtained by adding the substrate in CH_2Cl_2 to the sulfinate salt in neat CF_3CO_2H. Highly electron-rich systems were the exception, as noted for the preparation of the 7-methoxy compound **12**, where HCO_2H gave the better result. In the absence of sulfinate salts, multicomponent mixtures and/or oligomeric materials were formed. A typical procedure is as follows:

4-(4-Methylphenyl)sulfonyl-3,4-dihydrobenzo-[b]-pyran (7). Sodium *p*-toluenesulfinate hydrate (4.0 g, ~19 mmol) was stirred at RT in CF_3CO_2H (25 mL) for 15 min, then cooled in ice and 3-phenoxy-1,1-diethoxypropane (1.57 g, 7 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The ice bath was removed and stirring was continued for 0.5 h. After dilution with CH_2Cl_2, the mixture was washed with H_2O followed by

aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated. Recrystallization from CH_2Cl_2-hexanes gave the pure sulfone **7** (1.77 g; 87 %) as fibrous needles, mp 124-126 °C. ^1H NMR ($CDCl_3$): δ 2.23 (m, 1), 2.45 (s, 3), 2.51 (m, 1), 4.1-4.4 (m, 3), 6.8-6.9 (m, 2), 7.12 (d, 1, J = 9 Hz), 7.2-7.3 (m, 1), 7.32 (d, 2, J = 8 Hz) and 7.63 (d, 2, J = 8 Hz). Anal. Calcd. for $C_{16}H_{16}O_3S$: C, 66.65; H, 5.59. Found: C, 66.44; H, 5.59.

Table 1. Synthesis of 4-(Sulfonyl) Chromans, Tetrahydroquinolines and Thiachromans.

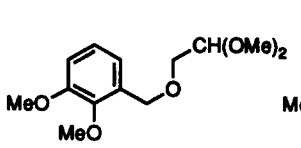


5 **6 - 12**

Product	X	R^1	R^2	t (h.)	Yield, %[a]	mp, °C
6	O	H	Ph	0.5	91	83-86[b]
7	O	H	p-Tol	0.5	87	124-126
8	O	H	Me	0.5	76	79-81
9	S	H	Ph	2.0	73	150-152
10	O	6-Cl	Ph	1.0	87	102-104
11	O	6-OMe	Ph	0.25	92	91-93
12	O	7-OMe	Ph	0.25	78[c]	103-105
13	NSO_2Ph	7-OMe	Ph	1.0	92[d]	(note d)

Notes: a. Isolated yield (based on the acetal) of chromatographically pure or recrystallized product.
b. Reported[10] mp 86.5-87 °C
c. In HCO_2H at 5°C. Reactions in TFA gave larger amounts of by-products. The 7-methoxy isomer **12** was the major product, and was isolated by direct crystallization after the usual workup.
d. A 6:1 mixture of the (non-crystalline) 7- and 5-methoxy isomers.[11]

Other systems are accessible by this cyclization-trapping process: reaction of the acetal **14** with TFA-$PhSO_2Na$ afforded the isochroman **15**, mp 153-155 °C, in high yield. Limited success with different trapping agents in these processes underscores the greater generality of the sulfone method: although sulfide **16** was obtained cleanly from the appropriate 4-methoxy acetal and PhSH in TFA, the chloro analog **17** was formed in admixture with 4-$ClC_6H_4OCH_2CH_2CH(SPh)_2$ and other compounds, reflecting irreversible intermolecular trapping prior to cyclisation when the latter step is relatively slow. Similarly, in TFA containing Et_3SiH (4 eq.), the 4-methoxy acetal afforded a 1:1 mixture of **18** and **19**, and the 4-chloro acetal gave "acyclic" product **20** exclusively. When the methoxy acetal was added to TFA alone, insoluble resinous materials were produced. Allyltrimethylsilane (in HCO_2H) was not a satisfactory trap. However, the foregoing sulfones were readily converted to 4-allyl compounds: **21** was isolated in 88% yield after treating **7** with $EtAlCl_2$ and excess CH_2=$CHCH_2SiMe_3$.



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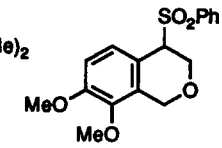

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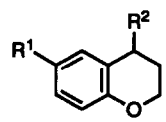
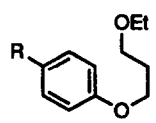
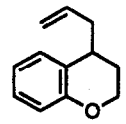


16 R^1 = OMe, R^2 = SPh
17 R^1 = Cl, R^2 = SPh
18 R^1 = OMe, R^2 = H



19 R = OMe
20 R = Cl



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The ability of benzylic sulfones to react in this fashion[2a] and also to undergo alkylation[2a,12] and acylation[10] *via* the derived carbanions enhances the synthetic potential of these carbocyclic and heterocyclic cyclization-trapping products. We will report at a later date on the extension of this chemistry to other substitution patterns and ring systems.

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11. Samples of the pure isomers were separated and characterised spectroscopically. Major, 7-methoxy isomer, ^{1}H NMR ($CDCl_3$): δ 1.72 (m, 1), 2.27 (m, 1), 3.73 (m, 1), 3.80 (s, 3), 4.04 (t, 1, J = 4.2 Hz), 4.12 (m, 1), 6.62 (dd, 1, J = 8.6, 2.5 Hz) and 7.1-7.7 (m, 12H). Minor, 5-methoxy isomer, ^{1}H NMR ($CDCl_3$): δ 1.95 (m, 1), 2.93 (m, 1), 3.10 (s, 3), 4.2-4.5 (m, 2), 4.76 (br. d, 1, J = 4.9 Hz), 6.28 (d, 1, J = 8.1 Hz), 7.14 (t, 1, J = 8.5 Hz), 7.3-7.7 (m, 9) and 7.90 (d, 2, J = 9.2 Hz).
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