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New Synthesis of 2,3-Disubstituted and 2,2,3-Trisubstituted 2*H*-1-Benzothiopyran Derivatives

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Abstract: A new, versatile synthesis of 2,3-disubstituted and 2,2,3-trisubstituted 2*H*-1-benzothiopyran derivatives is described. The key step involves the cyclization of 3-(2-*tert*-butylthiophenyl)-prop-2-en-1-ols to 2*H*-1-benzothiopyrans. A mechanism for the key step is proposed. Copyright © 1996 Elsevier Science Ltd

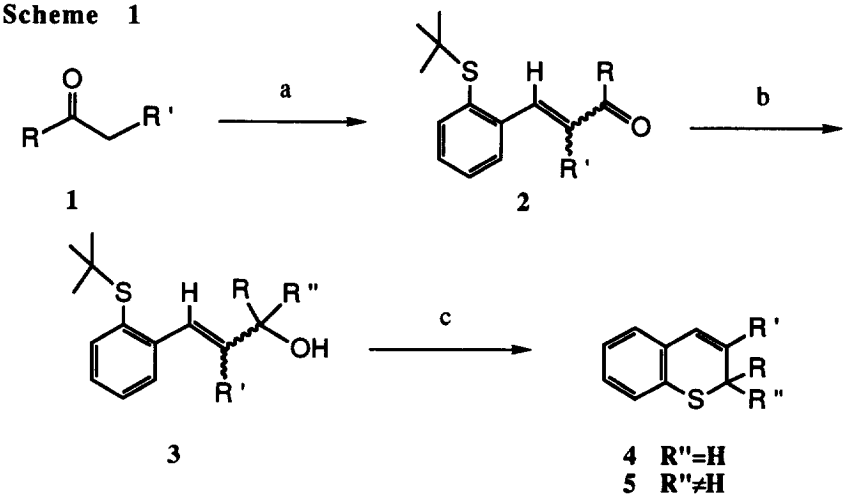
2*H*-1-Benzothiopyrans are used as bioisosters of 2*H*-1-benzopyrans and could be considered as potential biologically active agents. For example, sulfur analogs of 2,2-disubstituted 2*H*-1-benzopyran (precocenes) have been synthesized for their insecticidal activities.[1] Herein, we wish to report a novel route for the preparation of 2,3-disubstituted and 2,2,3-trisubstituted 2*H*-1-benzothiopyran derivatives.

A survey of the literature revealed that 2*H*-1-benzothiopyrans were prepared via the condensation of thiophenol with acrylic acid derivatives to produce thiochromanones which were then reduced to thiochromanols and dehydrated.[1,2] 2*H*-1-Benzothiopyrans are also prepared by the reaction of (2-mercaptophenyl)-methyltriphenylphosphonium bromide with 2-haloketones in the presence of a base in moderate yield.[3] In some cases, preparation of starting materials (acrylic acids or 2-haloketones) are necessary for both syntheses. Moreover, to our knowledge, the synthesis of 2,2,3-trisubstituted 2*H*-1-benzothiopyrans (alkyl and/or aryl groups) has not been reported. In order to develop an efficient method for the preparation of such benzothiopyrans, we considered the cyclization of 3-(2-*tert*-butyl-thiophenyl)-prop-2-en-1-ols **3** in acidic medium via the generation of allylic carbocation intermediate as one of the potential retrosynthetic pathways.

Scheme 1 outlines our synthetic route for 2*H*-1-benzothiopyrans **4** and **5**, while Table 1 summarizes the results obtained. Condensation of 2-*tert*-butylthio-benzaldehyde[4] with the sodium enolate of substituted methylketones **1** in tetrahydrofuran gave a mixture of (*E*,*Z*)-α,β-unsaturated ketones **2**.[5] Reaction was complete at -78°C to rt except when R,R'=Ph which required refluxing. Reduction of α,β-unsaturated ketones **2** with 1 equivalent of lithium aluminum hydride in tetrahydrofuran gave allylic alcohols **3** (R''=H) which were cyclized with trifluoroacetic acid (6-7 equiv) in dichloromethane to yield 2,3-disubstituted 2*H*-1-benzothiopyrans **4**. The scope of this synthesis was demonstrated by combination of alkyl and/or phenyl groups (R and R'). The yield (32%) of the cyclization was low

when alkyl groups were used. However, when the reaction was performed at low temperature (-20°C), the yield increased to 82%. 1,2-Addition of methyllithium (3 equiv) to α,β-unsaturated ketone **2c** in tetrahydrofuran gave the corresponding allylic alcohol **3** (R"=Me) which was cyclized to afford 2,2,3-trisubstituted 2*H*-1-benzothiopyran **5c** (Table 1, entry 5).

Scheme 1



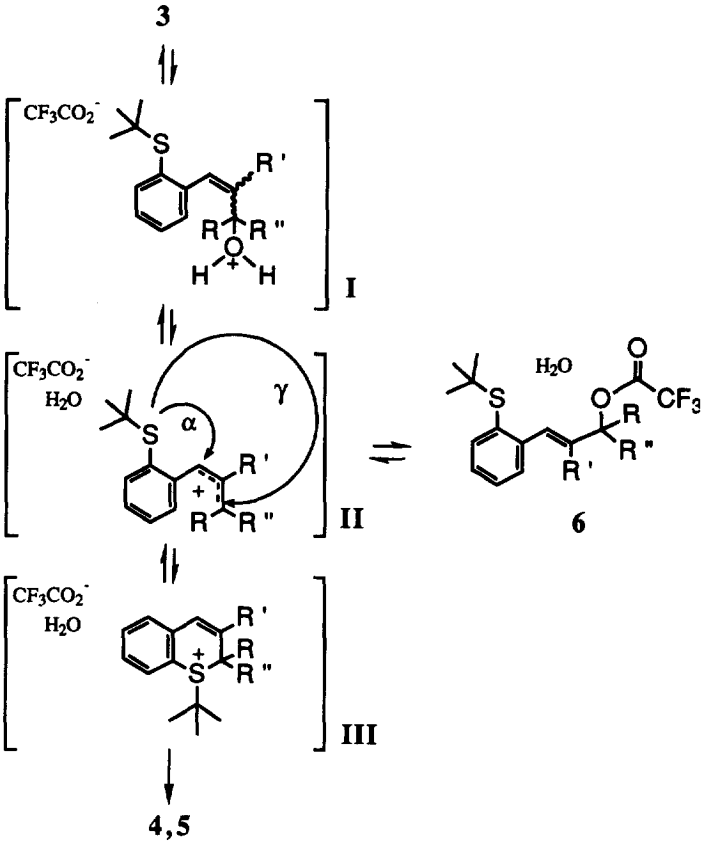
a) NaN[(Si(CH$_3$)$_3$]$_2$, 2-*tert*-butylthiobenzaldehyde, THF, -78°C to rt (or reflux); b) LAH, THF, 0°C for R"=H or R"Li, THF, -78°C to rt for R"≠H; c) TFA:CH_2Cl_2 (1:20), 0°C, 30 min.

Table 1. Synthesis of 2,3-disubstituted and 2,2,3-trisubstituted 2*H*-1-benzothiopyrans **4** and **5**

Entry	R	R'	R"	Product[a]	*E*:*Z*[b] crude 2	Yield(%)[c] 2	3	4(5)
1	Ph	Ph	H	**4 a**	37:63	78	84	88
2	Ph	Me	H	**4 b**	97:3	63	85	93
3	Et	Ph	H	**4 c**	57:43	26[d]	84	68[e]
4	Et	Me	H	**4 d**	>98:2	68	88	32[f]
5	Et	Ph	Me	**5 c**	57:43	26[d]	73	27[g]

[a]Compounds **4** and **5** gave satisfactory ^{1}H NMR, ^{13}C NMR and mass spectra, which are consistent with the assigned structure. [b]*E*:*Z* ratio was determined by the ^{1}H NMR analysis of *tert*-butyl protons and NOE NMR experiments[5]. [c]Isolated yield. [d]The yield was 70% and the *E*:*Z* ratio was 83:17 when the Knoevenagel reaction was used (piperidine, toluene, 2 equiv of aldehyde, 10 days). [e]The reaction time was 2.5 h. [f]The yield increased to 82% by conducting reaction at -20°C for 20 h. [g]Optimization of this yield at low temperature was unsuccessful.

Scheme 2



We have proposed a possible mechanism for the cyclization reaction (Scheme 2). We have shown that both (*E*,*Z*) isomers of allylic alcohols **3** gave 2*H*-1-benzothiopyrans **4** and **5**. The preceding observation strongly supports the formation of the allylic carbocation intermediate **II**. At this stage, we wanted to know if the protected or unprotected thiophenol was involved in this process. Only the starting material was recovered when either the α,β-unsaturated ketone (*E*)-**2a** or (*Z*)-**2a** was treated with the standard cyclization conditions. This experiment showed that the loss of the *tert*-butyl group from thiophenol occured after formation of allylic carbocation intermediate **II**. This observation suggests the presence of 2*H*-1-benzothiopyranium intermediate **III**. The solvolytic products **6c,d** could be isolated from the crude reaction mixture during the cyclization of (*E*)-allylic alcohols **3c,d** to 2*H*-1-benzothiopyrans **4c,d**.[6] However, the presence of the intermediate **6** was not observed during the cyclization of allylic alcohols **3a,b** even at low temperature.[7] Moreover, we observed that both allylic alcohols (*E*)-**3c** and (*Z*)-**3c**

gave the same (*E*)-allylic trifluoroacetate **6c** upon treatment with trifluoroacetic acid. The presence of the allylic trifluoroacetate intermediate **6** can be explained by the trapping of the allylic carbocation intermediate **II** by trifluoroacetate anion. This solvolysis phenomena could be explained by the high reactivity of the allylic carbocation intermediates **IIc,d** (R=Et) (compare with **IIa,b** (R=Ph)).

In summary, we propose the present cyclization mechanism as follows: the protonation of allylic alcohols **3** gives intermediate **I** which is transformed to allylic carbocation intermediate **II** which is in equilibrium with the (*E*)-allylic trifluoroacetate **6**. The intramolecular attack of sulfur atom at the γ-position[8] of the carbocation **II** gives the 2*H*-1-benzothiopyranium intermediate **III**. The desired 2*H*-1-benzothiopyrans **4** and **5** are then obtained after the loss of isobutylene.

In conclusion, a highly efficient synthesis of 2*H*-1-benzothiopyrans has been described. The scope and limitations of the present work are in progress and will be reported elsewhere.

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References and Notes

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(5) (*E,Z*)-α,β-Unsaturated ketones **2** could be separated by chromatography. The stereochemistry of the double bond of α,β-unsaturated ketones **2** was determined via the NOE experiments. Irradiation of the vinyl proton of compounds **2a-d** showed a NOE with the benzoyl (ortho) protons (**2a,b**) or the methylene protons (**2c,d**) and thus, the (*E*)-isomer of ketones **2** was assigned.
(6) For example, the cyclization reaction of alcohol **3d** was conducted at -40°C. According to ^{1}H NMR spectra, the crude contains a (2:3) mixture of the starting (*E*)-allylic alcohol **3d** and the corresponding (*E*)-allylic trifluoroacetate **6d**.
(7) The low temperature experiments suggest the increasing order of reactivity of the (*E,Z*)-allylic alcohols **3** as follows: **3c** < **3d** << **3a** < **3b**.
(8) The attack at the α-position gives benzothiete derivatives which were not observed.

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