One-Pot Stereoselective Synthesis of Pyrano[3,2-*c*]benzothiopyrans: A New Generation and [4+2] Cycloaddition of *ortho*-Thioquinonemethides

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Received 16 December 2004

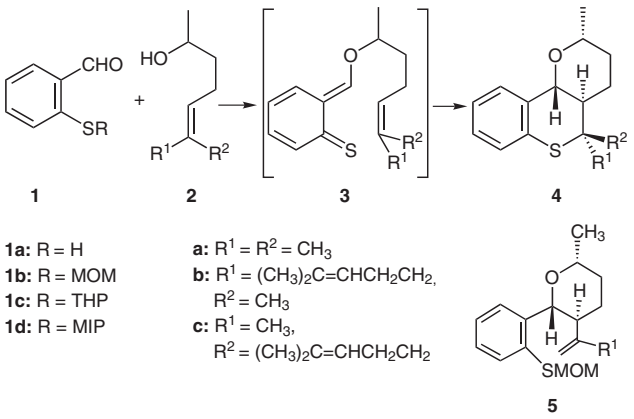
Abstract: Pyrano[3,2-*c*]benzothiopyrans are synthesized from thiosalicylaldehyde derivatives and unsaturated alcohols in the presence of trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid with complete *trans*-stereoselectivity via intramolecular [4+2] cycloaddition of *ortho*-thioquinonemethides. A more efficient generation and cycloaddition of *ortho*-thioquinonemethides with Lewis acid is also described.

Key words: stereoselective synthesis, [4+2] cycloaddition, Lewis acid, sulfur, heterocycles

In the past decades, a number of studies on pyrans and benzopyrans have been reported while those of their sulfur-containing analogs are rare.[1,2] It is only lately that the studies of benzothiopyrans have attracted attention of a number of research groups.[3] To the best of our knowledge there are relatively few reports touched upon the synthesis of polycyclic pyranobenzothiopyrans.[2b,4] As a result of advances in both synthetic chemistry and biology, there is now an increased demand for an efficient and convenient synthetic method for sulfur-containing polycyclic compounds.[5] On the other hand, intramolecular Diels–Alder reaction is useful in the construction of fused polycyclic compounds, but this reaction finds few application for the sulfur-containing systems.

As an extension of our recent studies on the *trans* stereoselective synthesis of pyrano[3,2-*c*]benzopyrans from salicylaldehydes and 5-methyl-4-hexen-2-ol,[6] we anticipated that polycyclic pyranobenzothiopyran **4** would be prepared stereoselectively via *ortho*-thioquinonemethides (**3**),[2,7] generated in situ from thiosalicylaldehyde derivative **1** and olefinic alcohol **2** (Scheme 1). Here we report a new generation of *ortho*-thioquinonemethides with acid catalyst and an efficient one-pot *trans* stereoselective synthesis of pyranobenzothiopyrans.

We initially used thiosalicylaldehyde methoxymethyl ether (**1b**) as the substrate, because thiosalicylaldehyde (**1a**) was reported to be intractable and extremely susceptible to air-oxidation.[8] The reaction of **1b** and 6-methyl-5-hepten-2-ol (**2a**) was carried out at room temperature in the presence of trimethyl orthoformate (1.2 equiv) and *p*-toluenesulfonic acid (0.2 equiv) to give tricyclic compound **4a** (54%) along with a minor amount of substituted tetrahydropyran **5a** (18%, Table 1, entry 1). The structures of **4a**[4] and **5a**[9] were easily confirmed by their ^{1}H NMR and ^{13}C NMR spectra. It is worthwhile to note that **4a** had B/C-*trans* ring junction in high stereoselectivity. The stereoselectivity of this reaction can be explained on the basis of steric repulsion in the *exo*-transition state of the thiatriene system.[6b]



Scheme 1

In the cases of increased reaction temperature or prolonged reaction time, **4a** was obtained as the sole product; no formation of **5a** was observed (Table 1, entries 3 and 4). Furthermore, we found that **5a** was completely converted into **4a** at a temperature above 50 °C in the presence of acid catalyst in benzene. These results suggested two possible mechanisms for the formation of **4a** from **2a** (Scheme 2), a concerted mechanism (path 1) which involved *ortho*-thioquinonemethide **3** and a stepwise one (path 2) which involved two cationic species (**A** and **B**).

It then became necessary to thoroughly clarify the stereospecificity of this cycloaddition reaction from synthetic and mechanistic points of view. For this purpose, we synthesized a stereoisomeric pair of alcohols **2b** and **2c** from geraniol and nerol,[6b] respectively. These alcohols were reacted with thiosalicylaldehyde **1b** to give a mixture of tricyclic compounds **4b**,**c**, and substituted tetrahydropyran **5b** at room temperature for a prolonged period

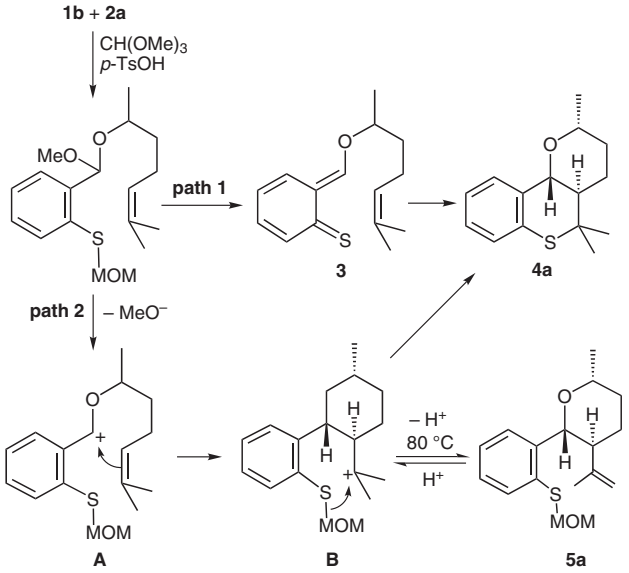
SYNLETT 2005, No. 3, pp 0469–0472
Advanced online publication: 04.02.2005
DOI: 10.1055/s-2005-862379; Art ID: U32004ST

or under reflux in benzene within a short time (Table 1, entries 5, 6 and 9). Similarly, we observed the conversion of **5b** to a mixture of **4b** and **4c** under the same conditions as described above.

Table 1 Reactions of Thiosalicylaldehydes with *p*-TsOH

Entry	1	2	Conditions	Products (yield, %)	
1	**1b**	**2a**	25 °C, 13 h	**4a** (54)	**5a** (18)
2	**1b**	**2a**	80 °C, 15 min	**4a** (56)	**5a** (13)
3	**1b**	**2a**	80 °C, 35 min	**4a** (68)	–
4	**1b**	**2a**	110 °C, 10 min[a]	**4a** (67)	–
5	**1b**	**2b**	25 °C, 18 h	**4b** (32), **4c** (10)	**5b** (18)
6	**1b**	**2b**	80 °C, 35 min	**4b/4c** (48:22:30)[b]	**5b**
7	**1b**	**2b**	80 °C, 3 h	**4b** (43), **4c** (18)	–
8	**1b**	**2b**	110 °C, 30 min	**4b** (42), **4c** (19)	–
9	**1b**	**2c**	25 °C, 24 h	**4b** (19), **4c** (12)	**5b** (6)
10	**1c**	**2a**	25 °C, 5.5 h	**4a** (72)	–
11	**1c**	**2b**	25 °C, 4 h	**4b** (42)	–
12	**1c**	**2b**	80 °C, 15 min	**4b** (59)	–
13	**1c**	**2c**	80 °C, 45 min	**4c** (50)	–
14	**1d**	**2a**	80 °C, 45 min	**4a** (<10)	–

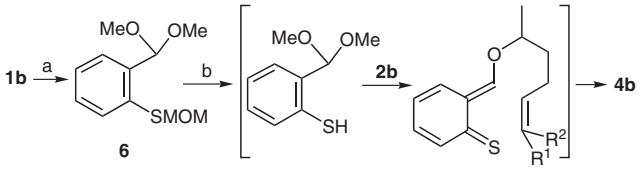
[a] Reaction in toluene.
[b] The ratio was determined by GC.



Scheme 2

Since the presence of relatively stable methoxymethyl protective group seemed to lead to the preferential formation of cation at the benzylic position (**A**, Scheme 2), we then tried to overcome the problem by removing the methoxymethyl group before elimination of the methoxy group in order to promote the formation of *ortho*-thioquinonemethide (Scheme 3).

In the presence of a catalytic amount of *p*-toluenesulfonic acid and a small amount of methanol, **1b** reacted with trimethyl orthoformate at room temperature to give acetal **6**[10] quantitatively. Then, the isolated acetal **6** reacted with **2b** in benzene–methanol at 50–60 °C to furnish **4b** as a single tricyclic compound in 35% yield.



Scheme 3 a) $CH(OMe)_3$, *p*-TsOH, MeOH, benzene, r.t., 10 min, quant; b) *p*-TsOH, benzene–MeOH, 50–60 °C, 2 h, then **2b**, 45 min, 35%.

In order to synchronize the deprotection of the SH protective group with elimination of methoxy group at the benzylic position, we used more labile 2-tetrahydropyranyl as a protective group for SH of thiosalicylaldehyde. The results are shown in Table 1 (entries 10–13). The reaction of **1c** and (*E*)-alcohol **2b** afforded *trans*-tricyclic **4b** as a single cyclic product, at room temperature in 42% yield (Table 1, entry 11). By comparing with the reaction as shown in entry 5, Table 1, this experiment suggested strongly that the reaction proceeded solely via a concerted intramolecular [4+2] cycloaddition of *ortho*-thioquinonemethide (**3**). Increasing the reaction temperature improved the yields of **4b** or **4c** (Table 1, entries 12 and 13). The use of thiosalicylaldehyde 1-methyl-1-methoxy ethyl (MIP) ether (**1d**) decreased the yield of **4a** (Table 1, entry 14).

Lewis acids such as $AlCl_3$, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$ and $Yb(OTf)_3$ have been found to be more efficient for the generation and cycloaddition of *ortho*-quinonemethides than Brønsted acids.[11,12] In the line with our continued interest on the use of $BF_3{\cdot}OEt_2$ for studies on *ortho*-quinonemethides, we then studied the generation of *ortho*-thioquinonemethides utilizing $BF_3{\cdot}OEt_2$. The results are shown in Table 2.

The reaction of **2a** with **1b** proceeded within 30 minutes to give tricyclic compound **4a** in 96% yield (Table 2, entry 1). No formation of substituted pyran **5a** was observed at all. This catalytic system was successfully applied to reactions of alcohol **2b** and **2c** with **1b**. The reaction proceeded smoothly at room temperature, to give only a single tricyclic product **4b** and **4c**, respectively (Table 2, entries 2 and 3). Again, no formations of substituted pyran compounds were observed. These somewhat decreased

Table 2 Reactions of Thiosalicylaldehydes with $BF_3{\cdot}OEt_2$

Entry	1	2	Conditions	Product	Yield (%)
1	**1b**	**2a**	r.t., 15 min	**4a**	96
2	**1b**	**2b**	r.t., 50 min	**4b**	66
3	**1b**	**2c**	r.t., 2 h	**4c**	50
4	**1c**	**2a**	r.t., 30 min	**4a**	95
5	**1c**	**2b**	r.t., 40 min	**4b**	90
6	**1c**	**2c**	r.t., 60 min	**4c**	89

yields were due to the recovery of **1b**. It is worthwhile to note that the reaction utilizing **1c** and **2a–c** lead to the corresponding **4a–c**, as single cyclic products in excellent yields (Table 2, entries 4–6). In these intramolecular cycloaddition reactions the Lewis acid served not only to accelerate the reaction but also to promote the cleavage of the protective groups, methoxymethyl or 2-tetrahydropyranyl, furnishing *ortho*-thioquinonemethides.

In conclusion, we have described a *trans* stereoselective synthesis of pyrano[3,2-*c*]benzothiopyrans from thiosalicylaldehyde derivatives and unsaturated alcohols in the presence of trimethyl orthoformate and acid catalyst via intramolecular [4+2] cycloaddition of *ortho*-thioquinonemethides. We have also found that $BF_3{\cdot}OEt_2$ is a very effective acid catalyst for the generation and the reaction of *ortho*-thioquinonemethides.

General Procedure for the Cycloaddition Reactions

A flask was charged with alcohol (10 mmol), thiosalicyclaldehyde derivative (12 mmol), and trimethyl orthoformate (12 mmol), and then acid catalyst (2 mmol) was dropped into the reaction mixture. The mixture was stirred at r.t. (or 80 °C, 110 °C) and monitored by TLC. The reaction mixture was treated with 10% aq NaOH (in the case of $BF_3{\cdot}OEt_2$, the reaction was treated with H_2O), and the organic layer was separated. The aqueous layer was extracted with Et_2O, and the combined organic layer was washed with brine, dried over anhyd $MgSO_4$, and concentrated in vacuo to give crude products, which were purified by silica gel chromatography.

Compound **4b**: ^{1}H NMR (400 MHz, C_6D_6): δ = 0.93 (m, 1 H), 1.10 (m, 1 H), 1.21 (s, 3 H), 1.22 (d, *J* = 6.1 Hz, 3 H), 1.32–1.46 (m, 2 H), 1.52–1.67 (m, 2 H), 1.57 (s, 3 H), 1.66 (s, 3 H), 1.97 (m, 1 H), 2.14 (m, 1 H), 2.33 (m, 1 H), 3.30 (dqd, *J* = 2.2, 6.1, 11.7 Hz, 1 H), 4.23 (d, *J* = 10.3 Hz, 1 H), 5.11 (tt, *J* = 1.5, 7.1 Hz, 1 H), 6.96 (ddd, *J* = 1.5, 7.3, 7.8 Hz, 1 H), 7.00 (ddd, *J* = 1.5, 7.3, 7.8 Hz, 1 H), 7.17 (m, 1 H), 7.89 (dd, *J* = 1.5, 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 18.0, 22.4, 23.1, 24.1, 24.9, 26.1, 33.8, 41.1, 44.1, 48.8, 74.0, 76.8, 124.3, 124.4, 126.7, 127.9, 128.1, 131.7, 133.0, 134.2.

Compound **4c**: ^{1}H NMR (400 MHz, C_6D_6): δ = 1.00–1.06 (m, 2 H), 1.09 (s, 3 H), 1.22 (d, *J* = 6.1 Hz, 3 H), 1.34 (m, 1 H), 1.50–1.68 (m, 3 H), 1.52 (s, 3 H), 1.61 (s, 3 H), 2.02–2.08 (m, 2 H), 2.56 (m, 1 H), 3.31 (dqd, *J* = 2.2, 6.1, 11.7 Hz, 1 H), 4.30 (d, *J* = 10.3 Hz, 1 H), 5.06 (tt, *J* = 1.5, 7.1 Hz, 1 H), 6.90 (ddd, *J* = 1.5, 7.3, 7.8 Hz, 1 H), 6.98 (ddd, *J* = 1.5, 7.3, 7.8 Hz, 1 H), 7.12 (dd, *J* = 1.5, 7.8 Hz, 1 H), 7.85 (dd, *J* = 1.5, 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 17.7, 22.2, 23.6, 24.6, 24.8, 25.8, 34.0, 35.2, 48.3, 48.9, 74.0, 76.3, 124.4, 124.8, 126.3, 127.8, 128.8, 131.5, 133.3, 134.1.

Acknowledgment

We are sincerely grateful to Dr. Hiroko Suezawa of Yokohama National University, for carrying out NOE measurements. This work was supported in part by a Grant-in-Aid for Scientific Research (B) No. 09450339, 13555252, and Grant-in-Aid for Scientific Research on Priority Areas No. 14044029 from the Ministry of Education, Science, Sport and Culture, Japan.

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(9) Compound **5a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.1 Hz, 3 H), 1.45 (m, 1 H), 1.50 (s, 3 H), 1.71–1.80 (m, 2 H), 1.92 (m, 1 H), 2.47 (ddd, *J* = 2.9, 10.0, 11.5 Hz, 1 H), 3.42 (s, 3 H), 3.67 (dqd, *J* = 2.0, 6.1, 11.1 Hz, 1 H), 4.60 (m, 2 H), 4.85 (d, *J* = 11.2 Hz, 1 H), 4.93 (d, *J* = 11.2 Hz, 1 H), 4.95 (d, *J* = 10.0 Hz, 1 H), 7.21 (ddd, *J* = 1.7, 7.3, 7.6 Hz, 1 H), 7.23 (ddd, *J* = 1.5, 7.3, 7.6 Hz, 1 H), 7.43 (dd, *J* = 1.7, 7.6 Hz, 1 H), 7.56 (dd, *J* = 1.5, 7.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 22.2, 30.7, 33.7, 48.5, 56.1, 74.4, 78.6, 79.5, 112.3, 127.2, 127.6, 128.0, 131.6, 135.5, 141.4, 145.8.

(10) Compound **6** was purified by silica gel column chromatography, and was characterized by NMR.

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