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Facile synthesis and desulfurization of 5-(phenylthio)pyrano-[3,2-*c*][1]benzopyrans starting from 5-phenylthio-4-penten-1-ols and salicylaldehyde via in situ intramolecular cycloaddition of substituted *o*-quinonemethides

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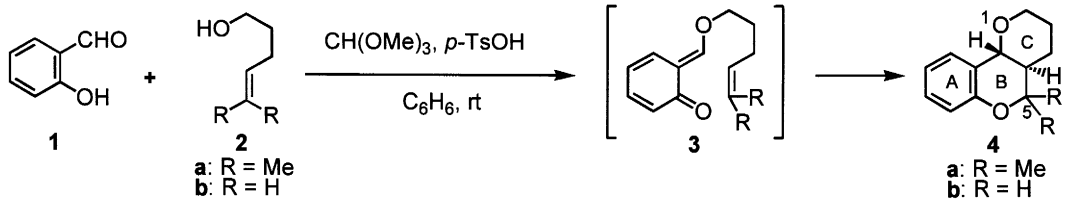
Abstract

5-(Phenylthio)pyrano[3,2-*c*][1]benzopyrans (**6**) were successfully synthesized in high yield by the reaction of 5-phenylthio-4-penten-1-ol (**5**) and salicylaldehyde (**1**) in benzene in the presence of *p*-toluenesulfonic acid and trimethyl orthoformate. *trans,trans*-Isomer **6a** and *cis,cis*-isomer **6d** were produced as major products from (*E*)-**5** and (*Z*)-**5**, respectively. Treatment of **6a** with lithium 4,4′-di-*tert*-butylbiphenyl or Raney Ni (W-4) lead to *trans*-pyrano[3,2-*c*][1]benzopyran **4b** which is very difficult to make by direct cycloaddition using unsubstituted 4-penten-1-ol (**2b**).

Keywords: cycloaddition; intramolecular Diels–Alder reaction; *o*-quinonemethide; 5-(phenylthio)pyrano[3,2-*c*][1]benzopyran; pyrano[3,2-*c*][1]benzopyran.

We have been investigating the generation and reaction of *o*-quinonemethides under mild conditions in order to widen their application in organic synthesis.[1] Previously, we reported that salicylaldehyde (**1**) reacted with alcohol **2a** in benzene in the presence of *p*-TsOH and trimethyl orthoformate at room temperature to give *trans*-**4a** in high yield as a single stereoisomer (Scheme 1).[2]



Scheme 1.

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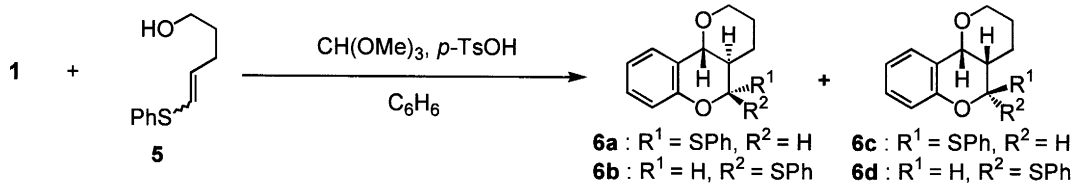
In general, the cycloaddition between various salicylaldehydes and 5-methyl-4-alken-1-ols proceeds very efficiently; however, the reaction between **1** and 4-penten-1-ol (**2b**) does not take place at all, even in refluxing benzene for 5 days.[3] The failure of the reaction with **2b** may be attributed to the low electron density at the olefinic moiety, as can be predicted from the mechanistic character of inverse electron demanded [4+2] cycloaddition.[1] We then anticipated that unsubstituted pyranobenzopyran **4b** may be obtained by employing phenylthio-substituted olefinic alcohol **5** instead of **2b** followed by desulfurization of the primary cyclization product. Furthermore, we were interested in the reactivity and stereochemical nature of the cycloaddition of disubstituted olefins.

Simple radical addition of thiophenol to 4-pentyn-1-ol afforded 5-phenylthio-4-pentenol **5** as a ca. 1:1 mixture of (*E*)- and (*Z*)-isomers.[4] The individual stereoisomers were prepared by the stereoselective hydrogenation of 5-(phenylthio)-4-pentyn-1-ol or its THP ether.[5]

The cycloaddition reactions were carried out by stirring a solution of alcohol **5** (1.0 mmol), aldehyde **1** (1.2 mmol), trimethyl orthoformate (1.2 mmol), and *p*-TsOH (0.2 mmol) in benzene. The reaction proceeded smoothly and the products **6a**–**d** were isolated by silica gel column chromatography and were characterized by spectroscopic data. The product **6a** was easily isolated by silica gel column chromatography; however, the others were difficult to separate from each other. The results are summarized in Table 1.[6]

Table 1
Reaction of salicylaldehyde (**1**) with alcohol **5**



entry	alcohol **5** *E* / *Z*	conditions temp	conditions time	combined yield (%)	isomer ratio of product **6** **6a**	**6b**	**6c**	**6d**
1	52 : 48	rt	5 h	80	67	5	3	25
2	52 : 48	rt	15 h	86	69	4	5	22
3	52 : 48	reflux	15 min	83	74	6	4	16
4	86 : 14	rt	23 h	93	91	6	0	3
5	86 : 14	reflux	15 min	89	87	2	2	9
6	0 : 100	rt	25 h	65	31	4	3	62
7	0 : 100	reflux	15 min	85	31	14	5	50

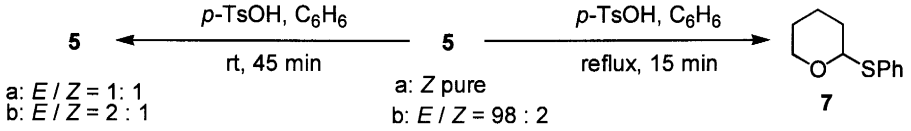
Reaction of salicylaldehyde with a 52:48 mixture of (*E*)- and (*Z*)-alcohols **5** afforded a mixture of tricyclic stereoisomers **6a**–**d** in 80% combined yield at room temperature, the isomeric ratio of **6** not being correlated with that of **5** (entry 1). A long reaction period (entry 2), or high reaction temperature (entry 3), did not greatly affect the diastereomer ratio of the products. Reaction of **1** with a 86:14 mixture of (*E*)- and (*Z*)-**5** afforded tricyclic compounds **6a** as a major product at room temperature (entry 4) and similar behavior was observed in refluxing benzene (entry 5). Interestingly, reaction of **1** with pure (*Z*)-**5** afforded a considerable amount of **6a** as well as **6d** at both temperatures (entries 6 and 7).

Since the intramolecular cycloaddition by this method usually proceeds through an *exo* transition state, such unusual stereoselectivities should be significant enough to attract much attention from both

synthetic and mechanistic viewpoints. To shed light on the unusual stereoselectivity of this cyclization, we investigated the isomerization behavior of **5** and **6**.

First, tricyclic compounds **6a** and **6d** were heated in benzene at reflux in the presence of *p*-TsOH. According to ^{1}H NMR measurements, **6a** isomerized slowly to give a ca. 1:1 mixture of **6a** and **6b** after 36 h, whereas **6d** completely changed to **6c** in 5 h. According to the molecular orbital calculations (AM1, kcal/mol),[7] **6c** (−25.42) has less heat of formation energy than **6d** (−21.49), and that of **6b** (–25.67) is very close to that of **6a** (−25.40). These data suggest that both **6a** and **6d** are the kinetic products of the cycloaddition reaction. It is worth noting that the above isomerization took place only at the C-5 carrying the phenylthio group, absolutely not at the B/C ring junction.

Next, we examined the isomerization of alcohol **5** (Scheme 2). The (*E*)- or (*Z*)-**5** was isomerized to a mixture of (*E*)- and (*Z*)-isomers at room temperature, and 2-(phenylthio)tetrahydro-2*H*-pyran **7** was obtained from both the alcohols under refluxing conditions.



Scheme 2.

The reaction between **1** and the (*E*)- and (*Z*)-mixtures of **5** was monitored by ^{1}H NMR spectra in benzene-d_6 at room temperature. Compound **6a** was generated rapidly, whereas **6d** was generated in less than 5% of **6a** at the early stage. It was observed that (*E*)-**5** was consumed rapidly, whereas (*Z*)-**5** remained until a later stage of the reaction.

Therefore, the stereochemical outcome of the cycloaddition reaction mentioned before could be rationalized as follows. (*E*)-**5** and (*Z*)-**5** afforded **6a** and **6d** as major products, respectively; however, **6a** was also obtained from the reaction of pure (*Z*)-**5** with **1**, as a result of the isomerization of (*E*)-**5** to (*Z*)-**5** under the reaction conditions (Scheme 2).

The characteristic feature of the cycloaddition could be accounted for by assuming four transition state models **TS-1** (*E-exo*), **TS-2** (*E-endo*), **TS-3** (*Z-exo*), and **TS-4** (*Z-endo*) in the concerted mechanism (Fig. 1). In general, *exo*-type transition states **TS-1** and **TS-3** may be more favored, and this is the case for the reactions of alkyl substituted olefin. On the other hand, vinyl sulfide **5** afforded **6a** and **6d** as major products through **TS-1** and **TS-4**. Coefficient values calculated by the AM1 method are shown in Fig. 2.[7] These results indicate that transition states are stabilized by an interaction between the sulfur atom and the carbonyl carbon of *o*-quinonemethide in *exo*-type **TS-1** and *endo*-type **TS-4**, whereas **TS-2** and **TS-3** have no orbital interaction.[8] Consequently, vinyl sulfide would prefer **TS-1** and **TS-4** to provide **6a** and **6d**.

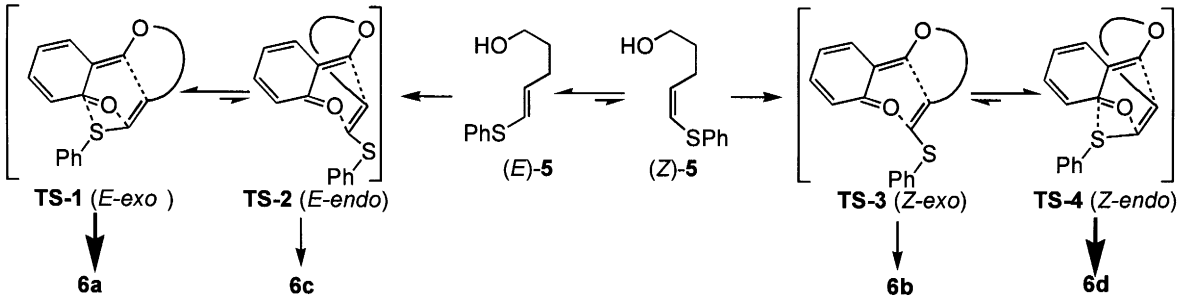


Fig. 1.

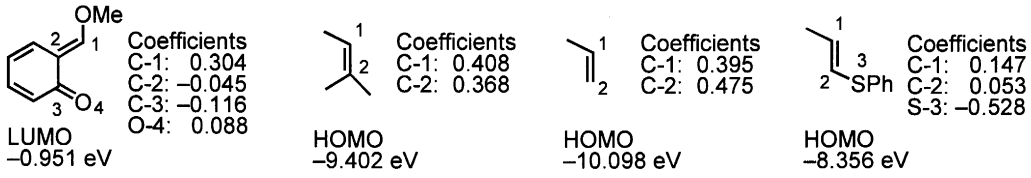
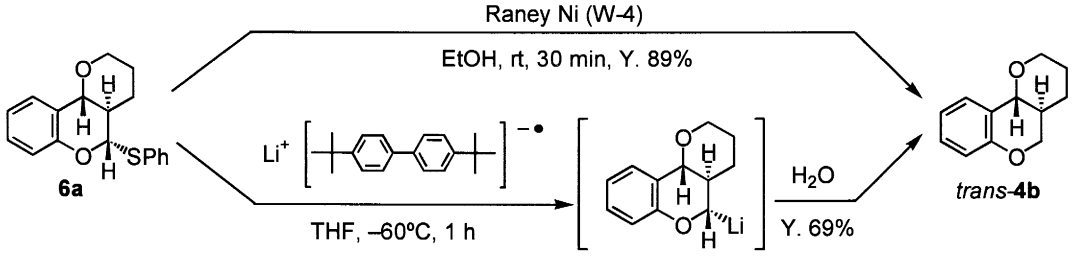


Fig. 2.

As mentioned earlier, direct cycloaddition of **1** and **2b** does not take place at all. Therefore, if the C-5 thiophenyl group of **6** can be removed efficiently, this approach should become a useful method for producing **4b**. Phenylthio-substituted compound **6a** was treated with Raney Ni (W-4)[9] in ethanol at room temperature to give tricyclic compound **4b** as a single stereoisomer in high yield (Scheme 3).[10] The same product was also obtained by treatment of **6a** with LiDBB[11] prepared from 4,4′-di-*tert*-butylbiphenyl and lithium metal.



Scheme 3.

In summary, we have found that the reaction of (*E*)- and (*Z*)-alcohols **5** with **1** furnished phenylthio-substituted tricyclic compounds **6a** and **6d**, respectively, as major products in high yields, and that **6d** can be efficiently isomerized to the more thermodynamically stable isomer **6c**. By desulfurization of **6a**, unsubstituted product **4b** was easily obtained, which was difficult to make from the reaction of **1** with **2b**. As phenylthio-substituted compounds can be reductively lithiated, as shown in Scheme 3 for example, which makes them useful intermediates for a variety of transformations, the present method should be applicable to the synthesis of substituted pyranobenzopyrans in natural products.

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4. Reaction of 4-pentyn-1-ol and thiophenol using AIBN as a radical initiator in benzene at reflux afforded alcohol **5** as a mixture of (*E*)- and (*Z*)-isomers in 80% yield. Cf. Miyake, H.; Yamamura, K. *Bull. Chem. Soc. Jpn*. **1988**, *61*, 3752.

5. To a solution of 4-pentyn-1-ol tetrahydropyranyl (THP) ether in THF was added hexane solution of *n*-butyllithium, followed by a THF solution of $PhS(Ph)(Me)S^{+}I^{-}$ to furnish 5-(phenylthio)-4-pentyn-1-ol THP ether. This was reduced with $LiAlH_4$ in THF at room temperature to give a 86:14 mixture of the corresponding (*E*)- and (*Z*)-olefins, which was treated with pyridinium *p*-toluenesulfonate (PPTS) in methanol to give a mixture of (*E*)- and (*Z*)-**5** in 88% yield. 5-(Phenylthio)-4-pentyn-1-ol THP ether was treated with PPTS in methanol to give the parent alcohol in 95% yield, which was reacted with trimethylaluminum followed by diisobutylaluminum hydride to give pure (*Z*)-**5** in 42% yield. Cf. (a) Ma, S.; Negishi, E. *Tetrahedron Lett*. **1997**, *38*, 3829. (b) Kabanyane, S. T.; MaGee, D. I. *Can. J. Chem*. **1992**, *70*, 2758. (c) Krief, A.; Kenda, B.; Remacle, B. *Tetrahedron* **1996**, *52*, 7435.
6. All compounds were purified by silica gel column chromatography, and were characterized by spectroscopic means. Physical properties and selected ^1H NMR spectral data (in $CDCl_3$, 270 MHz, δ; TMS=0) are as follows. Compound **6a**: mp. 120–121°C (hexane–EtOAc; colorless crystals) 1.36 (m, 1H), 1.68–1.88 (m, 3H), 2.30 (m, 1H), 3.61 (m, 1H), 4.16 (m, 1H), 4.26 (d, *J*=10.2 Hz, 1H), 5.29 (d, *J*=10.9 Hz, 1H), 6.90 (d, *J*=8.3 Hz, 1H), 6.94 (dd, *J*=7.3, 7.6 Hz, 1H), 7.17 (dd, *J* =7.3, 8.3 Hz, 1H), 7.25–7.33 (m, 3H), 7.36 (d, *J*=7.6 Hz, 1H), 7.60 (dd, *J*=1.7, 7.9 Hz, 2H). Compound **6b**: (colorless oil; 60% pure) 1.70–2.06 (m, 3H), 2.27–2.38 (m, 2H), 3.71 (m, 1H), 4.18 (m, 1H), 4.50 (d, *J*=10.9 Hz, 1H), 5.67 (d, *J*=4.0 Hz, 1H), 6.85 (d, *J*=8.3 Hz, 1H), 7.00 (t, *J*=7.6 Hz, 1H), 7.24–7.34 (m, 4H), 7.47 (d, *J* =7.6 Hz, 1H), 7.53 (dd, *J*=1.7, 7.9 Hz, 2H). Compound **6c**: (colorless oil; 90% pure) 1.60–1.88 (m, 3H), 2.00 (m, 1H), 2.28 (m, 1H), 3.64–3.68 (m, 2H), 4.87 (d, *J*=4.3 Hz, 1H), 5.68 (d, *J*=5.9 Hz, 1H), 6.89 (d, *J*=7.6 Hz, 1H), 7.00 (t, *J*=7.6 Hz, 1H), 7.20–7.59 (m, 7H). Compound **6d**: (colorless oil; 80% pure) 1.61–1.89 (m, 3H), 1.96 (m, 1H), 2.54 (m, 1H), 3.47 (m, 1H), 3.63 (m, 1H), 4.98 (d, *J*=5.9 Hz, 1H), 5.50 (d, *J*=2.3 Hz, 1H), 6.90 (d, *J*=8.3 Hz, 1H), 7.00 (t, *J*=7.3 Hz, 1H), 7.20 (dd, *J*=7.3, 8.3 Hz, 1H), 7.25–7.40 (m, 3H), 7.43 (d, *J*=7.3 Hz, 1H), 7.55 (dd, *J*=1.7, 7.9 Hz, 2H).
7. The calculations were performed by using CAChe work system version 4.1.1 (PM3 and AM1).
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10. Compound **4b**: mp 83–84°C (hexane–EtOAc; colorless crystals) δ 1.24 (m, 1H), 1.68–2.04 (m, 4H), 3.68 (dt, *J*=3.0, 11.5 Hz,1H), 3.88 (t, *J*=11.5 Hz, 1H), 4.16 (dd, *J*=3.6, 10.9 Hz, 1H), 4.18 (t, *J*=10.9 Hz, 1H), 4.20 (d, *J*=9.9 Hz, 1H), 6.77 (d, *J*=8.2 Hz, 1H), 6.90 (dd, *J*=7.3, 7.6 Hz, 1H), 7.14 (dd, *J*=7.3, 8.2 Hz, 1H), 7.39 (d, *J*=7.6 Hz, 1H).
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