Agric. Chem. Biotechnol. **44**(1), 20-22 (2001)

Regioselective Benzylic Thioether Formation from Polyhydroxy Stilbene

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Received November 11, 2000

We have attempted to synthesize polyhydroxy stilbene compounds through the benzyl thioether moiety. During synthesis, we unexpectedly observed that demethylation of the compound under $AlCl_3$ in ethanethiol resulted in a regioselective addition of thiol to the double bond as well as complete demethylation. We report on the regioselective short synthesis for general structure and its structural identification.

Key words : *Regioselective, thioether, stilbene.*

Recently, new approaches toward asthma drug therapy, as exemplified through the leukotriene D4 (LTD4) receptor antagonists development, have brought forth a wide range of potential drug candidates. Of the several LTD4 antagonists going through clinical evaluations (Fig. 1), the benzyl thioether moiety acts as a key functional group.[1,2] As a separate development through plant material screening of potential LTD4 antagonists, we were previously able to show that polyhydroxy stilbenes such as resveratrol possess strong antagonistic activities.[3] In light of these findings, we have attempted to synthesize polyhydroxy stilbene compounds through the benzyl thioether moiety **1**.

During the process of synthesis (Fig. 2), we unexpectedly observed that demethylation of compound **5** under $AlCl_3$ in ethanethiol resulted in regioselective addition of thiol to the double bond as well as complete demethylation, yielding the desired benzyl thioether attachment to the polyhydroxy phenyl group. We report here on the regioselective short synthesis for general structure **1** and its structural identification.

Materials and Methods

General Procedure. Infrared spectra were recorded on a Perkin Elmer Paragon 2000 FT-IR spectrometer. NMR spectra were obtained on a Bruker Avance 400 (9.4 T) instrument in $CDCl_3$. For the ^{1}H-NMR experiments, 16 transients were acquired with 1 sec relaxation delay using 32 K data points, and the 90° pulse was 9.7 usec, with spectral width of 4,000 Hz. For the ^{13}C-NMR and DEPT experiments, 512 transients were acquired with a 2 sec relaxation delay using 64K data points, and the 90° pulse was 9.8 usec with spectral width of 22,000 Hz. Two-dimensional spectra were acquired with 2048 data points in t_2 and 256, in t_1 increments. The COSY spectrum was collected through the magnitude method.[4] HMQC and HMBC spectra were collected through the methods

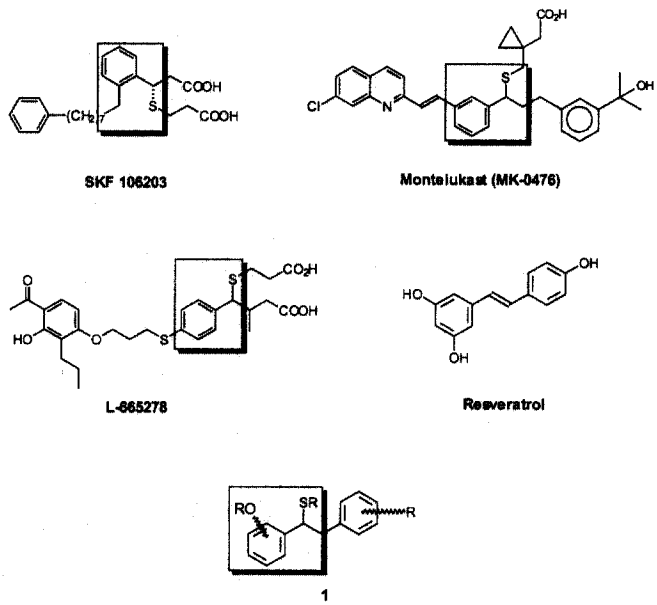

Fig. 1. Typical benzyl thioether in LTD4 antagonists and polyhydroxystilbene.

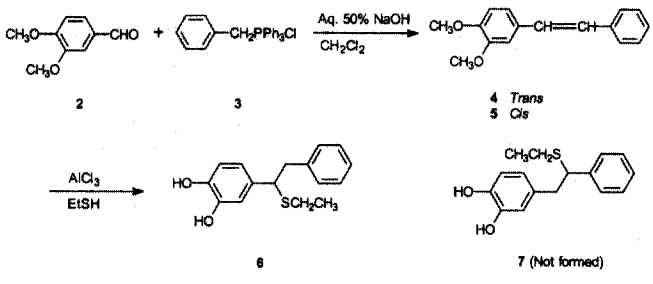

Fig. 2. Synthetic scheme for benzylthioether 6.

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Abbreviations: LTD4, leukotriene D4; DEPT, distortionless enhancement of polarization transfer; COSY, correlated spectroscopy; HMQC, heteronuclear mutiple quantum coherence; HMBC, heteronuclear mutiple bonded connectivity.

described by Bax[5] and Summers[6], respectively. The delay for the long ranged coupling of HMBC was 70 msec. Analytical thin-layer chromatography was performed using precoated silica gel 60 F_{254} plates, and the silica gel used for flash column chromatography was supplied from Merck (230-400 mesh, 60A).

Synthesis of dimethoxy stilbene (4, 5). 3,4-Dimethoxy benzaldehyde **2** (4 g, 24 mmol) and phosphonium salt **3** (12.4g, 32 mmol) were dissolved in 20 mL of CH_2Cl_2. To the above solution, a 40% aqueous solution of NaOH (20 mL) was added, and the resulting suspension was stirred for 4 h at room temperature. The organic layer was extracted using CH_2Cl_2, and combined organic layers were dried over $MgSO_4$. Filtration and evaporation gave a residue which was separated through flash chromatography to give *trans* **4** (1.8 g) and *cis* **5** (2.7 g) isomers.

Compound 4: IR (KBr pellet) 809.9, 958.4, 1026.5, 1139.7, 1155.4, 1225.7, 1267.6, 1464.4, 1514.6, 1591.9, 3447.6, 4691.5; EI/MS (m/z) calc = 240.3, exp = 240.0; ^{1}H-NMR (400 MHz, $CDCl_3$) 3.88 (3 H, s), 3.93 (3 H, s), 6.84 (1 H, d, J = 8.2 Hz), 7.00 (1 H, d, J = 16.3 Hz), 7.03-7.06 (3 H, m), 7.24 (1 H, t, J = 4.4 Hz), 7.35 (2 H, t, J = 7.8 Hz), 7.50 (2 H, d, J = 8.2 Hz) ; ^{13}C-NMR (100 MHz, $CDCl_3$) 55.87 (q), 55.94 (q), 108.72 (d), 111.20 (d), 119.89 (d), 126.27 (d), 126.81 (d), 127.30 (d), 128.46 (d), 128.66 (d), 130.45 (s), 137.51 (s), 148.92 (s), 149.11 (s).

Compound 5: IR (KBr pellet) 450.0, 536.0, 616.3, 696.4, 767.4, 808.5, 869.0, 918.2, 1025.9, 1133.2, 1174.6, 1267.8, 1417.0, 1463.1, 1513.6, 1598.5, 2834.7, 2933.3, 3004.1, 3549.5; EI/MS (m/z) calc = 240.3, exp = 240.0; ^{1}H-NMR (400 MHz, $CDCl_3$) 3.58 (3 H, s), 3.84 (3 H, s), 6.52 (2 H, d, J = 12.2 Hz), 6.72 (1 H, d, J = 8.2 Hz), 6.76 (1 H, d, J = 2.0 Hz), 7.18 (1 H, m), 7.26-7.28 (4 H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 55.91 (q), 55.98 (q), 108.77 (d), 111.25 (d), 119.94 (d), 126.32 (d) 126.85 (d), 127.34 (d), 128.50 (d), 128.70 (d), 130.49 (s), 137.56 (s), 148.97 (s), 149.15 (s).

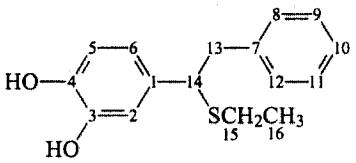
Synthesis of benzyl thioether 6. To a stirred solution of aluminum trichloride (6.7 g, 25 mmol) in ethanethiol (12 mL), stilbene **5** (1.68 g, 10 mmol) was added under an ice-bath condition. The reaction mixture was warmed to room temperature and stirred for 3 h. It was subsequently poured into dilute HCl and extracted using CH_2Cl_2. The organic layers were washed with brine and dried over Na_2SO_4. After flash chromatographic separation, benzyl thioether **6** (1.29 g) was obtained as a pure compound.

Compound 6: IR (KBr pellet) 513.1, 699.6, 748.0, 808.5, 870.7, 917.5, 976.4, 1112.1, 1191.9, 1249.6, 1281.3, 1352.7, 1453.0, 1500.0, 1519.2, 1599.4, 1621.2, 2926.0, 2966.1, 3319.4; EI/MS (m/z) calc = 274.4, exp = 274.0; ^{1}H-NMR (400 MHz, $CDCl_3$) 1.11 (3 H, t, J = 7.4 Hz), 2.28 (2 H, m), 3.07 (2 H, m), 3.94 (1 H, dd, J = 8.4, 6.5 Hz), 6.63 (1 H, dd, J = 8.1, 2.1 Hz), 6.71 (1 H, d, J = 8.1 Hz), 6.83 (1 H, d, J = 2.1 Hz), 7.05 (2 H, m), 7.05 (3 H, m) ; ^{13}C-NMR (100 MHz, $CDCl_3$) 14.8 (q), 25.7 (t), 43.7 (t), 51.2 (d), 115.2 (d), 115.5 (d), 121.3 (d), 126.7 (d), 128.6 (d), 129.6 (d), 135.4 (s), 139.4 (s), 143.0 (s), 143.9 (s).

Results and Discussion

The Wittig reaction between **2** and **3** under a two-phase solvent system[7] gave *trans* (**4**) and *cis* (**5**) stilbenes that were separable. (ratio = **2** : **3**) The major *cis* isomer showed a coupling

Table 1. The NMR data and assignments of the compound 6.



d13C	CHn DEPT	d1H of directly attached protons HMQC	assignments
14.8	q	1.11(t, J = 7.4 Hz)	C16
25.7	t	2.28(m)	C15
43.7	t	3.07(m)	C13
51.2	d	3.94(dd, J = 8.4, 6.5 Hz)	C14
115.2	d	6.83(d, J = 2.0 Hz)	C2
115.5	d	6.72(d, J = 8.1 Hz)	C5
121.3	d	6.63(dd, J = 8.1, 2.1 Hz)	C6
126.7	d	7.15(m)	C10
128.6	d	7.18(m)	C9, C11
129.6	d	7.03(m)	C8, C12
135.4	s		C1
139.4	s		C7
143.0	s		C4
143.9	s		C3

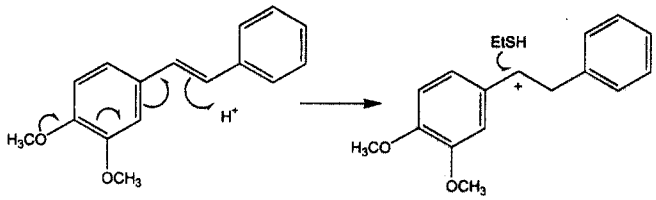


Fig. 3. Reaction mechanism through carbocation formation.

constant at the double bond of $J = 12.2$ Hz, and the minor *trans* isomer at $J = 16.3$ Hz. These methoxy groups were deprotected to give polyhydroxy stilbenes. Several methods for cleavage of phenyl-methyl ether have been reported.[8] When **5** was treated with fused pyridine hydrochloride under the elaborated temperature of 200°C, only decomposed product could be obtained. An attempt to demethylate compound **5** with boron tribromide (BBr_3) gave a mixture of monomethylated and fully demethylated products.[9] Rather unexpectedly, demethylation of **5** under $AlCl_3$ in ethanethiol gave a regioselective addition of thiol to the double as well as complete demethylation to yield the desired benzyl thioether in polyhydroxy phenyl group. Even though addition of thiols to styrenes[10] under various Lewis acids such as $TiCl_4$ and $AlCl_3$ have been reported, the methoxy groups remained intact. To our knowledge, this is the first report stating that $AlCl_3$ in ethanethiol system gives not only thiol addition but also demethylation in stilbenes.

Demethylation of **5** under $AlCl_3$ in ethanethiol gave a single product **6.** Several NMR experiments such as DEPT, HMQC, HMBC, and COSY were carried out to identify the structure **6**. The resonance assignments are listed in Table 1. The two methyl groups shown in starting material **5** disappeared, confirming the demethylations. ^{13}C-NMR peaks at 14.8 and 25.7 ppm indicated that product **6** included an ethyl group. The substituted position of the ethylthio group was determined based on HMBC. The mass spectrum of **6** gave a molecular weight peak at 274.0, identifying the compound **6** as hydroxybenzyl thioether.

In addition reaction of ethanethiol to stilbene under a Lewis acid, the p bond is deleted and a carbocation is formed. In the present case, carbocation formation may have occurred regioselectively. A complexation between thiol and $AlCl_3$ gives a proton to the styrene to form a stable carbocation at the benzylic position with an electron-donating group such as OCH_3 (Fig. 3). The regioselective carbocation formation appears to be responsible for the production of a corresponding regioselective benzylic thioether derivatives.

Acknowledgment. This work was supported by Korean Ministry of Health and Welfare Grant (HMP-97-D4-0020).

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