Low-valent titanium mediated synthesis of hydroxystilbenoids: Some new observations

U Shadakshari, S Rele, S K Nayak & S Chattopadhyay

Bio-Organic Division, Bhabha Atomic Research Centre, Mumbai 400 085, India

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A series of phenolic stilbenoids possessing different numbers and positions of hydroxylations, partial methoxyl substituents and nature of olefinic moieties has been synthesized by McMurry coupling. It is found that the McMurry coupling of the phenolic aldehydes furnishes the dihydrostilbenes via an "in situ" hydrogenation, while the phenolic ketones give the stilbenes. Interestingly, the study also reveals that the low-valent titanium reagent (TiCl₄-Zn-THF) could selectively depyranylate phenolic -OTHP function without affecting alcoholic -OTHP group.

Results and Discussion

Although the preparative routes to stilbenes are numerous, very few reports on the synthesis of hydroxyl- or methoxystilbenes are known. Given that the radical scavenging activities of the hydroxystilbenes are not significantly governed by their olefinic geometry, we envisaged that an easy access to these compounds would be extremely useful for their antioxidant screening. The low-valent titanium (LVT)-mediated reductive coupling of carbonyls (McMurry olefination) appeared most convenient for this. Hence, in continuation of our work on the reaction, a series of the target compounds were synthesized following the LVT route as shown in Schemes I-III. The synthesis was aimed at providing the stilbenoids with varied structural features such as number of hydroxyl/methoxyl substituents, their relative positions and nature of substitution of the double bond etc and the required compounds were synthesized as well-defined E/Z-mixtures.

The obvious way of synthesizing the hydroxystilbenes via the LVT-route is the dimerization of the suitable phenolic carbonyl compounds. However, when the reaction was carried out with the LVT reagent [TiCl₄-Zn-THF (reagent-A)] using 1a and 1b as the substrates, besides the desired hydroxystilbenes 2a and 2b, the corresponding dihydro compounds 3a and 3b were also obtained (Scheme I, Table I, entries 1, 2). On the other hand, the reaction proceeded smoothly with the phenolic ketone 1c furnishing the...
stilbene 2c as the sole product in 65% yield (Table I, entry 3). Thus, it was apparent that while McMurry coupling of phenolic ketones provides the stilbenes, the phenolic aldehydes furnish the stilbenes along with their in situ hydrogenated products. Earlier, with some sterically crowded aryl ketones, McMurry coupling was reported to produce the dihydro-

ostilbenes. However, the present study revealed that the in situ hydrogenation is also possible without any steric congestion, when a free phenolic functionality is present in the substrate\(^\text{10}\).

Since the hydroxylaldehydes were not suitable precursors for the disubstituted hydroxystilbenes by the LVT method, the coupling was carried out with
some methoxy compounds, 1d-1f which furnished the methoxystilbenes 2d-2f in good yields (Table I, entries 4-6). The stereochemical compositions of the 2b, 2d-f were evaluated from the integration of the methoxyl resonances in their respective 1H NMR spectra. The methoxyl resonances are reported to appear upfield for the E-stilbenes compared to those of the Z-compounds11. For 2c, the E/Z ratio was deduced from the integration of its benzylic methyl resonances. For 2a, however, the analysis was carried out with the corresponding methoxyl derivative, prepared by methylation of its phenolic groups with K2CO3-Me2SO4.

Thus, the methods discussed above were efficient for the synthesis of the methoxylated stilbenes from which the target polyphenolic compounds could be obtained easily. However, they were unsuitable for preparing the partially methoxylated congeners, which constitute an impressive array of important natural antioxidants. It was envisaged that the LVT-mediated coupling of the tetrahydropyranyl protected phenolic aldehydes would be a suitable alternative for this class of stilbenes.

With this aim, compound 4a, prepared by pyranylation [3,4-dihydropyran (DHP)/pyridinium p-toluene sulfonate (PPTS)] of 1a was subjected to reductive coupling (Scheme II) in the presence of reagent-A. This directly afforded the target compound 2a (Table II, entry 1) via an in situ removal of the THP groups of the coupled product. Similar reaction with the THP protected compound, 4b (Table II, entry 2) also gave the hydroxystilbene 2b. Compound 4b was prepared by pyranylation of 1b as done for 4a. In order to study the generality of the protocol, LVT-mediated depyranylation of a simple phenolic substrate 4c and an aliphatic substrate 4d were also attempted using the reagent-A. Deprotection of 4c proceeded smoothly yielding 4e in high yield (Table II, entry 3), although 4d could not be deprotected under the same conditions. Thus, it is concluded that the LVT reagent-A can deprotect the aromatic THP protected ethers efficiently without affecting the aliphatic ethers.

The syntheses of the unsymmetrical stilbenes were accomplished via the cross-coupling reaction (Scheme III, Table III). Thus, the reagent-A mediated coupling of the resorcinol derivative 1e with 4a furnished 2g. Likewise, coupling of 4a with 4b provided the resveratrol congener 2h. As anticipated, the product ratios of these reactions followed statistical distributions. In these cases also, the geometric compositions of the hydroxystilbenes were evaluated by analysis of their respective 1H NMR spectra12.

The methoxylated stilbenes 2d-2g obtained via the Schemes I and III were subsequently converted to the required hydroxy compounds 2d'-2g' via a BBr3 catalyzed demethylation (Scheme IV).

### Experimental Section

Reagents were used as received. Analytical and preparative TLC was performed using silica gel 60 F254 (Merck) coated plates and visualized by UV light. Melting points (uncorrected) were determined on a Fischer-Johns Melting Point apparatus. The IR spectra were scanned (KBr) on a Nicolet FT-IR Impact 410 instrument. The 1H NMR spectra were recorded on a Bruker AC 200 200 MHz spectrometer. Anhydrous reactions were carried out under argon atmosphere and using freshly dried solvents.

### Table I — Reductive coupling of methoxy/hydroxy aldehydes to stilbenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (hr)</th>
<th>Product</th>
<th>Product (1H NMR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>22</td>
<td>2a (38, 70:30)</td>
<td>3a (32)</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>22</td>
<td>2b (36, 60:40)</td>
<td>3b (40)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>6</td>
<td>2e (65, 65:35)</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>22</td>
<td>2d (72, 50:50)</td>
<td>--</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>22</td>
<td>2c (70, 50:50)</td>
<td>--</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>22</td>
<td>2f (74, 50:50)</td>
<td>--</td>
</tr>
</tbody>
</table>

*Isolated yields. Determined by 1H NMR.

### Table II — Deprotection of aromatic O-THP group with LVT (reagent - A)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>2a (65)</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>2b (68)</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>4e (95)</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>--</td>
</tr>
</tbody>
</table>

*Isolated yields.

### Table III — LVT-mediated synthesis of mixed stilbenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrates</th>
<th>Symm. Stilbenes</th>
<th>Unsymm. Stilbenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1e + 4a</td>
<td>2a (19), 2e (25)</td>
<td>2g (22, 52:48)</td>
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<tr>
<td>2</td>
<td>4a + 4b</td>
<td>2a (15), 2b (20)</td>
<td>2h (25, 55:45)</td>
</tr>
</tbody>
</table>

*Isolated yields. Determined by 1H NMR.
General procedure for LVT-mediated dimerization of carbonyls. A dry argon-filled three-necked round-bottom flask was charged with anhydrous THF (40 mL), TiCl$_4$ (4.0 mmol) and Zn (13.2 mmol). The mixture was refluxed for 3 hr with stirring when the reaction mixture changed from violet to black. To the LVT reagent thus prepared, was added the appropriate aldehyde/ketone (1.0 mmol) in THF (5 mL) and the reaction mixture was refluxed under stirring for the period specified in Tables. After the completion of the reaction (cf. TLC), the reaction mixture was diluted with hexane-acetate mixture (2:3) and passed through a pad of celite. The organic layer was washed with water and brine, and dried (Na$_2$SO$_4$). Removal of solvent followed by preparative TLC (silica gel) furnished the respective products.

1,2-Bis(4-hydroxyphenyl)ethylene 2a: mp 259 °C; IR: 3449 (OH), 3004 (aromatic C-H), 2960, 2860, 1608, 1514, 1469, 1328, 816 cm$^{-1}$; $^1$H NMR (CD$_2$OD): δ 6.78-6.88 (m, 6H, 2×CH$_2$); Anal. Calcd for C$_{14}$H$_{12}$O$_2$: C, 79.25, H, 5.66%. Found: C, 79.42, H, 5.84%.

1,2-Bis(3-methoxy-4-hydroxyphenyl)ethylene 2b: mp 210 °C (lit.$^{12a}$ mp 212–15 °C); IR: 3449 (OH), 3004 (aromatic C-H), 2960, 2860, 1608, 1514, 1469, 1238, 816 cm$^{-1}$; $^1$H NMR (CD$_2$OD): δ 3.78 and 3.89 (two s, 6H, 4×0CH$_3$), 6.62-6.68 (m, 3H, 3×H-3, 2×H-5, 2×olefinic protons), 7.32-7.37 (m, 4H, 2×H-2, 2×H-6); Anal. Calcd for C$_{14}$H$_{12}$O$_2$: C, 79.25, H, 5.66. Found: C, 79.42, H, 5.84%.

1,2-Bis(3-methoxy-4-hydroxyphenyl)ethane 3a$^{12b}$: IR: 3381 (OH), 3020 (aromatic C-H), 1621, 1514, 1464, 1360, 1238, 917, 815 cm$^{-1}$; $^1$H NMR (CD$_2$OD): δ 2.27 (s, 3H, 2×CH$_3$), 4.25 (d, J = 7.5 Hz, 4H, 6×H); 6.78 (d, J = 8.0 Hz, 4H, H-3, H-3', H-5, H-5'); 7.18 (d, J = 8.0 Hz, 4H, H-2, H-2', H-6, H-6').

1,2-Bis(3-methoxy-4-hydroxyphenyl)ethane 3b: IR: 3379 (OH), 3013 (aromatic C-H), 2916, 1607, 1518, 1471, 1372, 1237, 820 cm$^{-1}$; $^1$H NMR (CD$_2$OD): δ 2.29 (s, 4H, 2×CH$_2$), 3.87 (s, 6H, 2×OCH$_3$), 6.62-6.68 (m, 3H, 3×H, 3×ArH); Anal. Calcd for C$_{16}$H$_{16}$O$_4$: C, 69.88, H, 6.74%. Found: C, 69.88, H, 6.74%.

2,3-Bis(4-hydroxyphenyl)1,2-butene 2c: mp 128-29°C (lit.$^{12c}$ mp 153–54 °C); IR: 3380 (OH), 3100 (aromatic C-H), 2988, 1605, 1513, 1450 cm$^{-1}$; $^1$H NMR (CD$_2$OD): δ 3.90 (s, 6H, 3-OCH$_3$, 3'-OCH$_3$), 3.94 (s, 6H, 4-OCH$_3$, 4'-OCH$_3$), 6.46-7.06 (m, 8H, ArH, olefinic protons).

2,3-Bis(3,4-dimethoxyphenyl)1,2-butene 2d: mp 125°C (lit.$^{13c}$ mp 139-40°C); IR: 3061 (aromatic C-H), 3005, 2953, 1604, 1496 cm$^{-1}$; $^1$H NMR (CD$_2$OD): δ 3.87 (s, 6H, 2×OCH$_3$, Z-isomer), 3.92 (s, 6H, 2×OCH$_3$, E-isomer), 6.86-7.11 (m, 8H, ArH, olefinic protons).

2,3-Bis(3,5-dimethoxyphenyl)1,2-butene 2e: mp 139-40°C (lit.$^{13c}$ mp 139-40°C); IR: 3061 (aromatic C-H), 3005, 2953, 1604, 1496 cm$^{-1}$; $^1$H NMR (CD$_2$OD): δ 3.87 (s, 6H, 2×OCH$_3$, Z-isomer), 3.92 (s, 6H, 2×OCH$_3$, E-isomer), 6.86-7.11 (m, 8H, ArH, olefinic protons).

2,3-Bis(2,4,5-trimethoxyphenyl)1,2-butene 2f: IR: 3052 (aromatic C-H), 2953, 1608, 1460, 1378, 1242, 960 cm$^{-1}$; $^1$H NMR (CD$_2$OD): δ 3.89 (s, 18H, 6×OCH$_3$), 6.75-6.93 (m, 3H, ArH, olefinic proton, olefinic proton.
General procedure for demethylation. To a stirred and cooled (−40°C) solution of the compound (2 mmols) in dry CH₂Cl₂ (10 mL) was slowly injected BBr₃ (4 mmols). After stirring at −40°C for 2 hr, the reaction was quenched with aqueous saturated NaHCO₃ solution. The organic layer was separated, washed with water and brine and dried. The product obtained on removal of solvent in vacuo, was purified by preparative TLC (30% EtOAc in hexane) to yield the pure demethylated products.

1,2-Bis(3,4-dihydroxyphenyl)ethylene 2d': mp 211°C [lit.⁴ mp 241°C (dec.)]; IR: 3364 (OH), 2945, 1608, 1595, 1513, 1449, 1378, 1247, 960, 832 cm⁻¹; ¹H NMR (CDCl₃): δ 7.31-7.34 (m, 3H, ArH, olefinic proton), 7.31-7.34 (m, 3H, ArH, olefinic proton).

1,2-Bis(3,5-dihydroxyphenyl)ethylene 2e': mp 290°C [lit.⁴ mp 320-23°C]; IR: 3364 (OH), 2945, 2832, 2503, 1449, 1419, 1114, 1030 cm⁻¹; ¹H NMR (CDCl₃): δ 6.68-6.72 (m, 5H, H-2, H-2', H-4, H-4', 1 × olefinic proton), 7.32-7.37 (m, 3H, H-6, H-6', 1 × olefinic proton).

1,2-Bis(2,4,5-trihydroxyphenyl)ethylene 2f': IR: 3380 (OH), 2925, 1610, 1460, 1378, 1242, 960 cm⁻¹; ¹H NMR (CDCl₃): δ 6.78-6.95 (m, 3H, ArH, olefinic protons, E-isomer), 7.12-7.28 (m, 3H, ArH, olefinic protons, Z-isomer). Anal. Calcd for C₁₅H₁₂O₄: C, 60.87, H, 4.35. Found: C, 60.78, H, 4.47%

3, 4',5',5'-Tetrahydroxystilbene 2g': mp 230°C (lit.¹² mp 253-55°C); IR: 3395 (OH), 2945, 2832, 2596, 2521, 1661, 1449, 1417, 1116, 1032 cm⁻¹; ¹H NMR (CDCl₃): δ 6.27-6.66 (m, 6H, H-2, H-2', H-3', H-4, H-5', 1 × olefinic proton), 6.71-6.92 (m, 3H, H-6, H-6', 1 × olefinic proton).

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**References**


