Novel Synthesis of 4,5-Bis(arylthio)-2,3,4,5-tetrahydro-1-benzothiepins: Noteworthy Cyclization by the Reaction of 2-Butynediol with Arenethiols in the Presence of Zinc Iodide

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New cyclization products, 4,5-bis(arylthio)-2,3,4,5-tetrahydro-1-benzothiepins, were obtained in good yield by the reaction of 2-butynediol with arenethiols in the presence of zinc iodide. The reaction is assumed to proceed through intramolecular cyclization of a cationic intermediate generated in situ.

Base-catalyzed additions of arylthio groups to acetylenic bonds have been reported as typical examples of hitherto known reactions of alkylnols with thiols, while it has recently been found that the hydroxy group of benzyl and allylic alcohols is efficiently replaced by an arylthio group under catalysis by zinc iodide. To our knowledge, a Lewis acid-catalyzed reaction of alkylnols with arenethiols has not yet been reported.

In the course of our synthetic and mechanistic studies on the reactivity and utilization of acetylenic alcohols, especially 2-butyndiols, we investigated the synthesis of heterocyclic compounds as potential biologically active substances. We now report a novel and convenient synthesis of 4,5-bis(arylthio)-2,3,4,5-tetrahydro-1-benzothiepins (3) from the reaction of 2-butynediol (1) with arenethiols (2) in the presence of zinc iodide.

\[
\text{HO} + 3\text{ArSH} \xrightarrow{2\text{HgClO}_4 \cdot \text{H}_2\text{O} \cdot \text{Et}_2\text{O}, \text{75%}} \xrightarrow{2\text{HCl} \cdot \text{Et}_2\text{O}, \text{65%}} \text{3a-g}
\]

This selective formation of the cyclization product 3 may be assumed to proceed through the stepwise involvement of at least three different types of processes, that is, addition of thiol 2 to the C=O bond of 1, substitution of one hydroxy group of the intermediate 2-arylthio-2-butenyl-1,4-diol by 2, and intramolecular cyclization of a cationic intermediate generated in situ.

The structural assignment of products 3 is based on microanalyses, mass spectra, IR- and \(^1\)H-NMR-spectral data and by comparison of the spectral data with those of dihalobenzothiepins. Although it should be expected that the two vicinal arylthio groups of the tetrahydro-1-benzothiepins 3 may be cis or trans to each other, the products 3 were found to consist of almost only one stereoisomer (GLC, TLC, \(^1\)H-NMR, \(^13\)C-NMR). The analogous isomers of dihalobenzothiepins deriva-
Table. 4,5-Bis(arylio)-2,3,4,5-tetrahydro-1-benzothiepin 3 from 2-Butynediol (1) and Arenethiols 2

<table>
<thead>
<tr>
<th>2, 3</th>
<th>Ar</th>
<th>Yield (a) (%)</th>
<th>nδ (b)</th>
<th>Molecular Formula (c)</th>
<th>MS (M⁺) (d)</th>
<th>δ'H-NMR (CDCl₃/TMS) (e) δ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>C₆H₆</td>
<td>72</td>
<td>oil</td>
<td>C₃H₇N₂S₂ (380.4)</td>
<td>380</td>
<td>2.02 (m, 1H); 2.53 (m, 1H); 3.19 (m, 2H); 3.67 (m, 1H); 4.49 (d, 1H, J = 2.88); 7.19 (m, 1H)</td>
</tr>
<tr>
<td>b</td>
<td>p-C₆H₄Cl</td>
<td>72</td>
<td>oil</td>
<td>C₃H₇N₂S₂Cl (483.7)</td>
<td>482</td>
<td>2.04 (m, 1H); 2.43 (m, 1H); 3.18 (m, 2H); 3.53 (d, 1H, J = 10.80; 3.60; 4.32 (d, 1H, J = 3.30); 7.17 (m, 1H)</td>
</tr>
<tr>
<td>c</td>
<td>p-CH₃C₆H₄</td>
<td>75</td>
<td>oil</td>
<td>C₃H₇N₂S₂ (422.5)</td>
<td>422</td>
<td>1.96 (m, 1H); 2.34 (s, 9H); 2.52 (m, 1H); 3.12 (m, 2H); 3.54 (d, 1H, J = 11.60; 3.24); 4.38 (d, 1H, J = 3.24); 7.04 (m, 1H)</td>
</tr>
<tr>
<td>d</td>
<td>o-CH₃C₆H₄</td>
<td>56</td>
<td>oil</td>
<td>C₃H₇N₂S₂ (422.5)</td>
<td>422</td>
<td>2.21 (s, 3H); 2.25 (m, 2H); 2.32 (s, 3H); 2.44 (s, 3H); 3.16 (m, 2H); 3.58 (m, 2H); 4.38 (d, 1H, J = 3.24); 7.08 (m, 1H)</td>
</tr>
<tr>
<td>e</td>
<td>m-CH₃C₆H₄</td>
<td>69</td>
<td>oil</td>
<td>C₃H₇N₂S₂ (422.5)</td>
<td>422</td>
<td>2.32 (m, 1H); 3.14 (m, 2H); 3.68 (m, 1H); 4.50 (d, 1H, J = 3.24); 7.05 (m, 1H)</td>
</tr>
<tr>
<td>f</td>
<td>4-t-ClC₆H₄ Cl</td>
<td>65</td>
<td>oil</td>
<td>C₃H₇N₂S₂ (548.7)</td>
<td>548</td>
<td>1.28 (s, 9H); 1.29 (s, 18H); 1.96 (m, 1H); 2.50 (m, 1H); 3.14 (m, 2H); 3.64 (m, 1H); 4.46 (d, 1H, J = 3.24); 7.26 (m, 1H)</td>
</tr>
<tr>
<td>g</td>
<td>2-naphthyl</td>
<td>49</td>
<td>oil</td>
<td>C₃H₇N₂S₂ (530.4)</td>
<td>530</td>
<td>2.11 (m, 1H); 2.71 (m, 1H); 3.28 (m, 2H); 3.91 (m, 1H); 4.76 (d, 1H, J = 3.24); 7.39 (m, 1H)</td>
</tr>
</tbody>
</table>

(a) Yield of isolated product.
(b) Under similar conditions, the reaction of 1 with a variety of aliphatic mercaptans resulted in the formation of complex mixtures.
(c) The results in the absence of zinc iodide were: 3, 2%; 4, trace amount.
(d) Satisfactory microanalyses obtained: C ± 0.32, H ± 0.25.
(e) Recorded on a Jeol JMS-07.
(f) Recorded on a Jeol JFX-90Q.
(g) nδ recorded on a Shimadzu Bausch & Lomb-3L.

Aromatic mixtures have been clearly distinguished by means of ¹H-NMR techniques. However, the stereochemistry of 3 could not be definitely established to be either cis or trans from the spectral data of 3.

Addition of 10 vol.% of tetrahydrofuran to the reaction solvent lead to the formation of a mixture of 1-benzothiepin derivatives 3. 2,4-dihydroxy-2-butenols (4), 4-aryliothio-4-hydroxymethyl-3,4-dihydro-2H-1-benzothiepinans (5), and 2-aryliothio-3-butanol (6). For example, in the case of reaction with 4-sec-butylbenzenethiol (2f), products 3f, 4f, 5f, and 6f were obtained in yields of 8%, 25%, 8%, and 17%, respectively.

Each of the products 4, 5, and 6 was separated and efficiently transformed to 3 by further reaction with arenethiols and zinc iodide. These results suggest that 3 may be formed by intramolecular cyclization of 4 and 6, or ring-enlargement of 5. Although a detailed mechanism of the present reaction has not yet been, it may be assumed that 4 is initially formed and that 5 and 6 are intermediates formed by the cationic cyclization of 4 or by double-bond shift to the terminal position, respectively. The compound 3 is then formed by intramolecular cyclization of cationic intermediates generated by electrophile attack of zinc iodide to carbonyl or hydroxy groups.

The present one-pot reaction thus provides a new and convenient method for the synthesis of benzothiepin derivatives which have hitherto been difficult to synthesize.

7-Chloro-4,5-bis(4-chlorophenylthio)-2,3,4,5-tetrahydro-1-benzothiepin (3b): Typical Procedure:

Dried zinc iodide (8.00 g, 0.025 mol) is added to a stirred solution of 2-butynediol (1; 0.80 g, 0.01 mol) in dry 1,2-dichloroethane (40 mL) at room temperature under N₂ atmosphere. Stirring is continued for 30 min. The reaction mixture is then quenched with water and extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with 20% NaOH solution (2 x 50 mL), and dried (MgSO₄). The solvent is removed in vacuo and the residue is purified by column chromatography on silica gel (hexane/acetone, 7:3); yield of 3b: 3.50 g (72%) oil.

C₇H₇N₂S₂ calc. C 54.77 H 3.52 (483.7) found 54.49 3.71

**Spectral Data of Compound 4f:**

C₁₂H₁₄O₂S (400.5)

MS: m/z = 400 (M⁺)

IR (ν, max, cm⁻¹): 3375, 1610, 1540, 1470, 1275, 750

1H-NMR (CDCl₃): δ = 2.04 (m, 1H, 3.24; 7.19 (m, 1H)

13C-NMR (CDCl₃): δ = 30.8 (t, C-3); 33.8 (t, C-2); 54.5 (d, C-4); 66.9 (d, C-5); 130 (C-α)

**Spectral Data of Compound 5f:**

C₂₁H₁₄O₂S (400.5)

MS: m/z = 400 (M⁺)

IR (ν, max, cm⁻¹): 3375, 1610, 1540, 1470, 1275, 750

1H-NMR (CDCl₃): δ = 2.04 (m, 1H, 3.24; 7.19 (m, 1H)

13C-NMR (CDCl₃): δ = 30.8 (t, C-3); 33.8 (t, C-2); 54.5 (d, C-4); 66.9 (d, C-5); 130 (C-α)

**Spectral Data of Compound 6f:**

C₂₁H₁₄O₂S (400.5)

MS: m/z = 400 (M⁺)

IR (ν, max, cm⁻¹): 3375, 1610, 1540, 1470, 1275, 750

1H-NMR (CDCl₃): δ = 2.04 (m, 1H, 3.24; 7.19 (m, 1H)

13C-NMR (CDCl₃): δ = 30.8 (t, C-3); 33.8 (t, C-2); 54.5 (d, C-4); 66.9 (d, C-5); 130 (C-α)
$^1$H-NMR (CDCl$_3$): $\delta = 1.28$ (s, 9H, 3 CH$_3$); $1.31$ (s, 9H, 3 CH$_3$); $2.00$ (m, 2H, 3,3-H$_2$); $3.10$ (t, $J = 7.20$ Hz, 2H, SCH$_2$); $3.74$ (t, $J = 7.20$ Hz, 2H, SCH$_2$); $4.24$ Hz, 1H, SCH$_2$; $7.28$ (m, 8H, arom); $9.48$ (d, $J = 3.24$ Hz, 1H, CHO).

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(1) For the base-catalyzed reaction of acetylenic alcohols with thiols, see:


(3) Patai, S. (ed.) The Chemistry of the Carbon-Carbon Triple Bond,

