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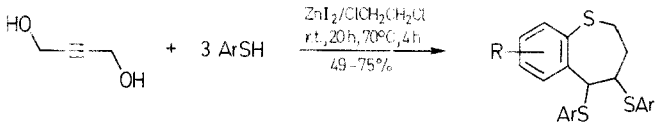
New cyclization products, 4,5-bis(arylthio)-2,3,4,5-tetrahydro-1-benzothiepins, were obtained in good yield by the reaction of 2-butynediol with arenethiols in the presence of zinc iodide. The reaction is assumed to proceed through intramolecular cyclization of a cationic intermediate generated *in situ*.

Base-catalyzed additions of arylthio groups to acetylenic bonds have been reported as typical examples of hitherto known reactions of alkylnols with thiols,[1] 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.[2] To our knowledge, a Lewis acid-catalyzed reaction of alkynols with arenethiols has not yet been reported.[3]

In the course of our synthetic and mechanistic studies on the reactivity and utilization of acetylenic alcohols, especially 2-butyndiols,[4] 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.



1 **2a-g** **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≡C bond of **1**, substitution of one hydroxy group of the intermediate 2-arylthio-2-butene-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.[5] 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-

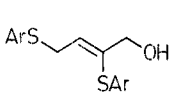
Table. 4,5-Bis(arylthio)-2,3,4,5-tetrahydro-1-benzothiepins **3** from 2-Butynediol (**1**) and Arenethiols **2**

2, 3	Ar	Yield[a,b,c] (%)	n_D^{25}[g]	Molecular Formula[d]	MS (M^+)[e] *m/e*	^{1}H-NMR ($CDCl_3$/TMS)[f] δ, *J*(Hz)
a	C_6H_5	72	oil 1.6600	$C_{22}H_{20}S_3$ (380.4)	380	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, 14H)
b	p-ClC_6H_4	72	oil 1.6597	$C_{22}H_{17}Cl_3S_3$ (483.7)	482	2.04 (m, 1H); 2.43 (m, 1H); 3.18 (m, 2H); 3.53 (d t, 1H, *J* = 10.80, 3.60); 4.32 (d, 1H, *J* = 3.30); 7.17 (m, 11H)
c	p-$CH_3C_6H_4$	75	oil 1.6332	$C_{25}H_{26}S_3$ (422.5)	422	1.96 (m, 1H); 2.34 (s, 9H); 2.52 (m, 1H); 3.12 (m, 2H); 3.54 (d t, 1H, *J* = 11.16/3.24); 4.38 (d, 1H, *J* = 3.24); 7.04 (m, 11H)
d	o-$CH_3C_6H_4$	56	oil 1.6440	$C_{25}H_{26}S_3$ (422.5)	422	2.21 (s, 3H); 2.25 (m, 2H); 2.32 (s, 3H); 2.44 (s, 3H); 3.16 (m, 2H); 3.58 (m, 1H); 4.38 (d, 1H, *J* = 3.24); 7.08 (m, 11H)
e	m-$CH_3C_6H_4$	69	oil 1.6384	$C_{25}H_{26}S_3$ (422.5)	422	2.32 (m, 12H); 3.14 (m, 2H); 3.68 (m, 1H); 4.50 (d, 1H, *J* = 3.24); 7.05 (m, 11H)
f	4-*t*-$C_4H_9C_6H_4$	65	oil 1.5846	$C_{34}H_{44}S_3$ (548.7)	548	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, 11H)
g	2-naphthyl	49	oil 1.6046	$C_{34}H_{26}S_3$ (530.4)	530	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, 20H)

[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 mixture.
[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 FX-90Q.
[g] n_D^{25} recorded on a Shimadzu Bausch & Lomb-3L.

tives have been clearly distinguished by means of ^{1}H-NMR techniques.[5] 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-diarylthio-2-butenols **(4)**, 4-arylthio-4-hydroxylmethyl-3,4-dihydro-2*H*-1-benzothiopyrans **(5)**, and 2,4-bis(arylthio)-butanals **(6)**. For example, in the case of reaction with 4-*t*-butylbenzenethiol **(2f)**, products **3f**, **4f**, **5f**, and **6f** were obtained in yields of 8%, 25%, 8%, and 17%, respectively.



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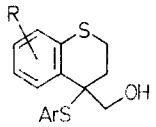

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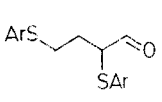

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Each of the products **4**, **5**, and **6** was separated and efficiently transformed to **3** by further reaction with arenethiols and zinc iodide. These results suggest that **3** may be formed by intramolecular cyclization of **4** and **6**, or 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 electrophilic 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.[6]

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**; 0.86 g, 0.01 mol) in dry 1,2-dichloroethane (40 mL) at room temperature under N_2 atmosphere. Stirring is continued for 30 min and to the resultant suspension is added dropwise a solution of 4-chlorobenzenethiol (**2b**; 4.50 g, 0.04 mol) in 1,2-dichloroethane (10 mL). The mixture is stirred for ~ 20 h at room temperature and for 4 h at ~ 70 °C. The reaction is then quenched with water (20 mL), and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with ~ 20% NaOH solution (2 × 50 mL), and dried ($MgSO_4$). 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.

$C_{22}H_{17}Cl_3S_3$ (483.7)	calc.	C 54.77	H 3.52
	found	54.49	3.71

MS: *m/e* = 482 (M^+).

IR (neat, major peaks): ν = 1580, 1480, 1390, 1100, 1015, 825 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 2.04 (m, 1H, 3,3-H_2); 2.43 (m, 1H, 3,3-H_2); 3.18 (m, 2H, 2,2-H_2); 3.53 (d t, *J* = 10.80, 3.60 Hz, 1H, 4-H; 4.32 (d, *J* = 3.30 Hz, 1H, 5-H); 7.17 (m, 11 H_{arom}).

^{13}C-NMR ($CDCl_3$): δ = 30.8 (t, C-3); 33.8 (t, C-2); 54.5 (d, C-4); 66.9 (d, C-5); ~ 130 (C_{arom})

Spectral Data of Compound **4f**:

$C_{24}H_{32}OS_2$ (400.5)

MS: *m/e* = 400 (M^+).

IR (neat): ν = 3375 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.29 (s, 9H, $3CH_3$); 1.32 (s, 9H, $3CH_3$); 1.78 (br. s, 1H, OH); 3.59 (d, *J* = 8.28 Hz, 0.3H, S–CH_2, *E* isomer); 3.89 (d, *J* = 7.20 Hz, 1.7H, S–CH_2, *Z* isomer); 4.00 (br. s, 2H, OCH_2); 5.90 (t t, *J* = 8.28, 1.20, 0.14H, CH=C, *E* isomer); 6.28 (t t, *J* = 7.20, 1.20, 0.86H, CH=H, *Z* isomer); 7.28 (m, 8 H_{arom}).

Spectral Data of Compound **5f**:

$C_{24}H_{32}OS_2$ (400.5)

MS: *m/e* = 400 (M^+).

IR (neat): ν = 3460 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.28 (s, 9H, $3CH_3$); 1.30 (s, 9H, $3CH_3$); 2.00 (m, 2H, 3,3-H_2); 2.38 (t, *J* = 6.48 Hz, 1H, OH); 3.30 (m, 2H, 2,2-H_2); 3.39 (d, *J* = 6.48 Hz, OCH_2); 7.32 (m, 8 H_{arom}).

Spectral Data of Compound **6f**:

$C_{24}H_{32}OS_2$ (400.5)

MS: *m/e* = 400 (M^+).

IR (neat): ν = 1722 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.28 (s, 9 H, $3\,CH_3$); 1.31 (s, 9 H, $3\,CH_3$); 2.00 (m, 2 H, 3,3-H_2); 3.10 (t, J = 7.20 Hz, 2 H, SCH_2); 3.74 (t d, J = 7.20, 3.24 Hz, 1 H, SCH); 7.28 (m, 8 H_{arom}); 9.48 (d, J = 3.24 Hz, 1 H, CHO).

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