Antitumour benzothiazoles. Part 2.[1] Formation of 2,2'-diaminobiphenyls from the decomposition of 2-(4-azidophenyl)benzazoles in trifluoromethanesulfonic acid

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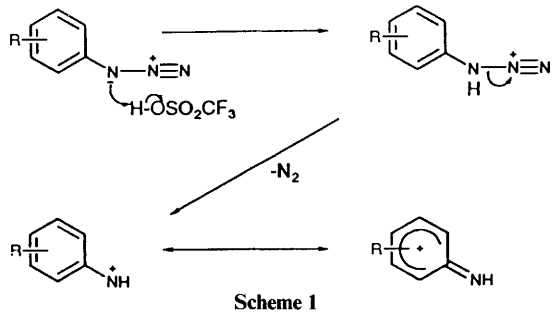
Decomposition of 2-(2-azidophenyl)- and 2-(3-azidophenyl)-benzothiazoles in trifluoromethanesulfonic acid generates π-carbocations. These reactive intermediates have been trapped by triflate anion with the nucleophile substituting *para* to the original azido group to yield triflate-substituted arylamines. 2-(4-Azidophenyl)-benzothiazoles and -benzoxazoles behave differently: triflate-substituted arylamines are accompanied by symmetrical or unsymmetrical benzazolyl-substituted 2,2'-diaminobiphenyls as major products. These biphenyls have been identified by their characteristic ^1H and ^{13}C NMR spectra. 2,2'-Diaminobiphenyls are formed by initial C–C coupling interactions between the π-carbocations and undecomposed 2-(4-azidophenyl)benzazoles and not by benzidine-type rearrangements as originally proposed. Symmetrical 2,2'-diaminobiphenyls have been oxidized by (diacetoxyiodo)benzene to give novel benzazolyl-substituted benzo[*c*]cinnolines.

Introduction

We have shown previously that polyhydroxylated 2-phenylbenzothiazoles combine some of the structural attributes of hydroxylated flavones, isoflavones and oestrogenic and antioestrogenic stilbenes and exhibit a broad, but mechanistically undefined, spectrum of activities against human tumour cell lines.[1] Moreover, 2-(4-aminophenyl)benzothiazoles display subtle and selective effects against certain breast cancer cell lines *in vitro* and *in vivo*.[2] In an effort to gain insights into potential routes for metabolism of the bioactive 2-(aminophenyl)benzothiazoles we were interested to track the fate of the nitrenium species, generated from the azidophenyl analogues of these amines, in the presence of nucleophiles.

The decomposition of aryl azides in strong acids such as trifluoromethanesulfonic acid (TFSA) is initiated by heterolysis of the protonated azide to generate mesomeric π-carbocation↔arylnitrenium species (Scheme 1). The synthetic utility



Scheme 1

of intramolecular reactions of azides where group R is a *meta*-substituent bearing a pendant nucleophile has been exploited especially by Abramovitch [3] and the subject has been reviewed.[4] When TFSA is employed in an anhydrous solvent mixture of trifluoroacetic acid (TFA) containing trifluoroacetic anhydride (TFAA) at 0 °C the π-carbocations can be intercepted by triflate anion at *ortho*- or *para*-positions to the (incipient) amine. We have shown that the triflate group can be introduced adjacent to a very bulky substituent, often in high yield.[5,6]

We also reported in a preliminary communication [7] that 2-(4-azidophenyl)benzothiazoles decompose in TFSA/TFA/TFAA ('triflic mixture') at 0 °C to afford benzothiazolyl-substituted 2,2'-diaminobiphenyls of a type not previously reported in aryl azide decompositions. The formation of these biphenyls raises intriguing mechanistic questions. We now report in full the results of our extensive studies on the decompositions of 2-(azidophenyl)benzothiazoles and their extension into the related benzoxazole series.

Results and discussion

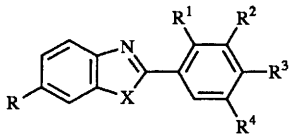
Synthesis of azidophenylbenzazoles

The starting nitrophenylbenzothiazoles **1–5** required for this work were prepared by two general routes: either direct condensation of 2-aminobenzenethiol with nitrocarboxylic acids or acid chlorides, or Jacobson cyclisation of nitro-substituted thiobenzanilides with alkaline potassium ferricyanide.[1] Reduction of the nitro compounds with tin(II) chloride in ethanol furnished the amines **6–10**. Alternatively, the amines **6–8** and 2-(4-aminophenyl)benzoxazole **11** could be prepared in one step from 2-aminobenzenethiol or 2-aminophenol, respectively, and aminobenzoic acids in polyphosphoric acid at 210 °C. The azides **13–19** were then formed from the amines by conventional diazotisation–azidation.

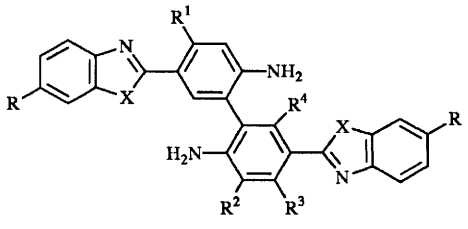
Decompositions of 2-(azidophenyl)benzazoles

Decomposition of the azide **13** in triflic mixture, followed by ice–aqueous ammonia quench and chromatographic fractionation, yielded the triflate-substituted amine **20** (67%) together with minor amounts of the trifluoroacetylamine **21** and the aminophenol **22**. The trifluoroacetylamine was prepared independently from **20** and TFAA and the phenol by hydrolysis of **21** in boiling 10% aqueous potassium hydroxide. Phenol **22**, isolated from the original reaction mixture, is probably generated from **20** during the quenching process.

Decomposition of the azide **14** in triflic mixture furnished a 70% yield of the triflate **23**, together with trifluoromethylsulfonamide **24** and phenol **25** by-products. The sulfonamide **24** arises from an intermolecular O→N triflate rearrangement of the



	X	R	R^1	R^2	R^3	R^4
1	S	H	NO_2	H	H	H
2	S	H	H	NO_2	H	H
3	S	H	H	H	NO_2	H
4	S	H	F	H	NO_2	H
5	S	H	Cl	H	NO_2	H
6	S	H	NH_2	H	H	H
7	S	H	H	NH_2	H	H
8	S	H	H	H	NH_2	H
9	S	H	F	H	NH_2	H
10	S	H	Cl	H	NH_2	H
11	O	H	H	H	NH_2	H
12	S	Me	H	H	NH_2	H
13	S	H	N_3	H	H	H
14	S	H	H	N_3	H	H
15	S	H	H	H	N_3	H
16	S	Me	H	H	N_3	H
17	S	H	F	H	N_3	H
18	S	H	Cl	H	N_3	H
19	O	H	H	H	N_3	H
20	S	H	NH_2	H	H	OSO_2CF_3
21	S	H	$NHCOCF_3$	H	H	OSO_2CF_3
22	S	H	NH_2	H	H	OH
23	S	H	OSO_2CF_3	H	H	NH_2
24	S	H	OH	H	H	$NHSO_2CF_3$
25	S	H	OH	H	H	NH_2
26	S	H	H	OSO_2CF_3	NH_2	H
27	S	Me	H	OSO_2CF_3	NH_2	H
28	S	H	F	H	NH_2	OSO_2CF_3
29	S	H	Cl	H	NH_2	OSO_2CF_3
30	S	H	Cl	OSO_2CF_3	NH_2	H
31	S	H	H	OH	$NHSO_2CF_3$	H
32	S	Me	H	OH	$NHSO_2CF_3$	H
33	S	H	F	H	$NHSO_2CF_3$	OH
34	S	H	H	OSO_2CF_3	$NHCOCF_3$	H
35	S	Me	H	OSO_2CF_3	$NHCOCF_3$	H
36	S	H	F	H	$NHCOCF_3$	OSO_2CF_3
37	S	H	H	OH	NH_2	H
38	S	Me	H	OH	NH_2	H
39	S	H	F	H	NH_2	OH



	X	R	R^1	R^2	R^3	R^4
40	S	H	H	H	H	H
41	S	H	H	OSO_2CF_3	H	H
42	S	Me	H	H	H	H
43	S	Me	H	OSO_2CF_3	H	H
44	S	H	F	H	F	H
45	S	H	F	H	H	F
46	O	H	H	H	H	H

primary reaction product **23**, and the phenol **25** is an artefact produced during work-up.

In the cases of those azides where the position *para* to the azido group is occupied by a benzazolyl residue, simple triflate-substituted arylamines were only minor products following triflic mixture treatment; instead, 2,2′-diaminobiphenyl compounds were significant and, in some cases, major products. Thus, the azide **15** afforded a mixture of the simple triflate **26** (12%) and the biphenyls **40** (29%) and **41** (23%). In a similar manner the azide **16** gave a comparable mixture of triflate **27** (14%) and biphenyls **42** (32%) and **43** (18%).

The 2-(4-azido-2-halogenophenyl)benzothiazoles **17** and **18** differed markedly in their decomposition profiles in triflic mixture. 2-(4-Azido-2-fluorophenyl)benzothiazole **17** gave the expected triflate **28** (31%) together with two isomeric biphenyls **44** (11%) and **45** (8%), neither of which had incorporated a triflate group. In contrast, 2-(4-azido-2-chlorophenyl)benzothiazole **18** afforded two isomeric triflate-substituted arylamines **29** (18%) and **30** (25%), but no 2,2′-diaminobiphenyls were detected despite careful chromatographic fractionation of the reaction mixture. Anomalously, 2-(4-azidophenyl)benzoxazole **19** with triflic mixture gave no triflate-substituted arylamines, but a high yield (66%) of the symmetrical 2,2′-diaminobiphenyl **46** was isolated.

Proof of the structure of the aforementioned compounds comes from their chemical transformations and especially their highly characteristic ^1H and ^{13}C NMR spectra (Tables 1 and 2) and FAB mass spectra. The arylamines **26**–**28**, bearing a triflate substituent in the *ortho* position, rearranged to trifluoromethylsulfonamides **31**–**33**, respectively, in boiling 10% aqueous potassium hydroxide, converted into the trifluoroacetylamines **34**–**36**, respectively, with TFAA in TFA and hydrolysed to the aminophenols **37**–**39**, respectively, in 80% sulfuric acid.

The 'dimeric' structure of the 2,2′-diaminobiphenyl **40** was initially suggested by the FAB mass spectrum and the symmetrical nature confirmed by the presence of only 13 distinct carbons in the ^{13}C NMR spectrum. The biphenyls **40** and **46** also formed symmetrical diacetyl-derivatives **47** and **48** with acetic anhydride. Significantly, the biphenyls **40**, **42** and **46**

Table 1 Spectroscopic properties of nitro-, amino- and azido-phenylbenzazoles[a]

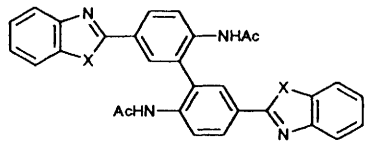
Compound	ν_{max}/cm^{-1}	δ_H 4-H	5-H	6-H	7-H	2′-H	3′-H	4′-H	5′-H	6′-H	Others[b]	m/z (M^+)
4	3448, 1529, 1342, 809, 769	8.00, d (7.6)	7.59, td (8.0, 1.2)	7.50, td (8.1, 1.3)	8.21–8.11, m	(F)	8.21–8.11, m	(NO_2)	8.21–8.11, m	8.73–8.67, m		274
5	3420, 1511, 1352 890, 756, 724	8.01, d (8.0)	7.59, td (7.9, 1.3)	7.50, td (8.0, 1.4)	8.18, d (8.0)	(Cl)	8.44, d (2.3)	(NO_2)	8.26, dd (8.8, 2.3)	8.57, d (8.8)	6.40	290
6	3464, 1612, 1580, 1492, 745	7.87, d (7.7)	7.45, td (7.6, 1.2)	7.35, td (7.5, 1.2)	7.96, d (7.9)	(NH_2)	6.81–6.73, m	7.22, td (6.4, 1.9)	6.81–6.73, m	7.70, d (7.8)	($2\,H$, NH_2)	226
7	3434, 3311, 3212, 1605, 1482, 762	7.89, d (8.5)	7.51–7.34, m		8.05, d (7.7)	7.51–7.34, m	(NH_2)	6.80, dd (8.0, 2.3)	7.26, t (7.7)	7.51–7.34, m	3.84 ($2\,H$, NH_2)	226
8	3457, 3296, 3181, 1604, 1474, 827	7.88, d (7.7)	7.45, td (7.2, 1.3)	7.33, td (7.3, 1.2)	8.00, d (7.1)	7.75, d (8.6)	6.66, d (8.7)	(NH_2)	6.66, d (8.7)	7.75, d (8.6)	3.67 ($2\,H$, NH_2)	226
9	3431, 3329, 3208, 1625, 1432, 755	7.90, d (7.7)	7.47, td (8.1, 1.2)	7.34, td (8.1, 1.1)	8.04, d (8.2)	(F)	6.47, dd (13.1, 2.2)	(NH_2)	6.57, dd (8.6, 2.3)	8.20, t (9.0)	4.12 ($2\,H$, NH_2)	244
10	3455, 3299, 1602, 1432, 1262, 757	7.90, d (7.9)	7.48, td (7.2, 1.3)	7.37, td (7.3, 1.2)	8.06, d (7.7)	(Cl)	6.80, d (2.4)	(NH_2)	6.68, dd (8.6, 2.4)	8.11, d (8.6)	4.03 ($2\,H$, NH_2)	260
11[c]	3472, 3322, 3186, 1614, 1454, 742	7.69–7.64, m	7.36–7.28, m		7.69–7.64, m	7.87, d (8.6)	7.67, d (8.6)	(NH_2)	7.67, d (8.6)	7.87, d (8.6)	6.02 ($2\,H$, NH_2)	210
13	2122, 1578, 1299, 1280, 967, 751	7.93, d (7.3)	7.53–7.47, m	7.39, t (7.9)	8.09, d (8.1)	(N_3)	7.33–7.30, m	7.53–7.47, m	7.33–7.30, m	8.44, dd (7.8, 1.7)		252
14	2093, 1606, 1481, 1306, 1281, 726	7.90, d (8.0)	7.36–7 m		8.08, d (8.0)	7.78, d (1.2)	(N_3)	7.12, dd (8.5, 1.4)	7.36–7.53, m	7.80, dd (7.7, 1.2)		252
15	2121, 1605, 1478, 1285, 762	7.83, d (7.8)	7.43, td (8.1, 1.3)	7.31, td (8.1, 1.3)	8.04–7.97, m	8.04–7.97, m	7.07, d (8.7)	(N_3)	7.07, d (8.7)	8.04–7.97, m		252
16	3462, 2116, 1284, 816	7.61, d (0.7)	7.26, dd (8.4, 1.5)	(CH_3)	7.90, d (8.3)	7.99, d (8.7)	7.05, d (8.7)	(N_3)	7.05, d (8.7)	7.99, d (8.7)	2.46, s ($3\,H$, CH_3)	266
17	3450, 2107, 1615, 1432, 1288, 760	7.92, d (7.7)	7.51, td (7.4, 1.0)	7.40, td (7.3, 1.1)	8.09, d (8.1)	(F)	6.87, dd (11.7, 2.1)	(N_3)	6.97, dd (8.6, 2.1)	8.42, t (8.3)		270
18	2101, 1600, 1301, 1263, 736	7.95, d (7.3)	7.54, td (7.6, 0.9)	7.43, td (8.1, 1.0)	8.12, d (8.2)	(Cl)	7.20, d (2.3)	(N_3)	7.08, dd (8.6, 2.3)	8.30, d (8.5)		286
19	3422, 2120, 1618, 1493, 1283, 744	7.63–7.59, m	7.42–7.35, m		7.81–7.71, m	8.28, d (8.8)	7.20, d (8.8)	(N_3)	7.20, d (8.8)	8.28, d (8.8)		236

[a] Solvent for ^1H NMR: $CDCl_3$; coupling constants (Hz) are in parentheses. [b] All NH_2 signals appeared as broad singlets, exchangeable with D_2O. [c] Solvent: [$^2H_6$]DMSO.

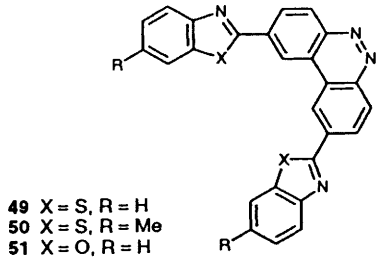
Table 2 ^{1}H NMR spectral data (δ values) of azide decomposition products **20**–**39**

Compound	4-H	5-H	6-H	7-H	2′-H	3′-H	4′-H	5′-H	6′-H	Others[a]
20	7.89, d (7.3)	7.48, td (7.8, 1.5)	7.39, td (7.2, 1.1)	7.98, d (8.0)	(NH_2)	6.78, d (9.0)	7.11, dd (9.0, 2.8)	(OSO_2CF_3)	7.56, d (2.8)	6.60 (2 H, NH_2)
21	7.98, d (7.7)	7.60, t (7.3)	7.53, t (7.5)	8.05, d (7.7)	($NHCOCF_3$)	8.92, d (9.3)	7.45, dd (9.3, 2.8)	(OSO_2CF_3)	7.80, d (2.7)	14.10 (1 H, NH)
22	7.87, d (7.8)	7.45, t (7.1)	7.35, t (8.1)	7.97, d (8.0)	(NH_2)	6.71 (8.7)	6.81, dd (8.7, 2.6)	(OH)	7.20, d (2.6)	8.84 (1 H, OH)[b] 6.67 (2 H, NH_2)[b]
23	7.97, d (7.6)	7.57, td (8.2, 1.3)	7.47, td (8.0, 1.3)	8.17, d (8.0)	(OSO_2CF_3)	7.26, d (8.9)	6.79, dd (8.9, 2.9)	(NH_2)	7.38, d (2.9)	4.20 (2 H, NH_2)
24[b]	8.07, d (7.9)	7.57, t (7.5)	7.48, t (7.5)	8.18, d (7.8)	(OH)	7.19, d (8.9)	7.38, dd (8.9, 2.6)	($NHSO_2CF_3$)	8.32, d (2.6)	11.76 (1 H, OH) 9.70 (1 H, NH)
25[b]	8.02, d (8.0)	7.53, t (7.4)	7.43, t (7.1)	8.12, d (7.8)	(OH)	6.82, d (8.7)	6.72, dd (8.7, 2.5)	(NH_2)	7.38, d (2.6)	10.69 (1 H, OH) 4.9 (2 H, NH_2)
26	7.88–7.81, m	7.48, t (7.7)	7.36, t (7.6)	8.02, d (8.1)	7.96, d (1.8)	(OSO_2CF_3)	(NH_2)	6.90, d (8.5)	7.88–7.81, m	4.12 (2 H, NH_2)
27	7.66, s	7.31–7.26, m	(CH_3)	7.90, d (8.3)	7.94, d (1.9)	(OSO_2CF_3)	(NH_2)	6.91, d (8.5)	7.84, dd (8.4, 1.9)	4.27 (2 H, NH_2) 2.49, s (3 H, CH_3)
28	7.91, d (7.4)	7.51, td (7.5, 1.0)	7.39, td (7.5, 1.0)	8.08, d (8.2)	(F)	6.67, d (11.9)	(NH_2)	(OSO_2CF_3)	8.31, d (6.7)	4.39 (2 H, NH_2)
29	7.93, d (7.5)	7.52, t (8.0)	7.41, t (8.0)	8.09, d (8.3)	(Cl)	6.99, s	(NH_2)	(OSO_2CF_3)	8.26, s	4.32 (2 H, NH_2)
30	7.92, d (8.0)	7.48, td (7.5, 1.4)	7.42, td (7.4, 1.3)	8.06, d (7.6)	(Cl)	(OSO_2CF_3)	(NH_2)	6.86, d (8.8)	8.12, d (8.8)	4.43 (2 H, NH_2)
31[b]	8.06, d (8.0)	7.58–7.42 m		8.15, d (7.9)	7.70, d (1.7)	(OH)	($NHSO_2CF_3$)	7.37, d (8.3)	7.58–7.42, m	10.5 (1 H, OH)
32[b]	7.65, d (1.4)	7.39–7.35, m	(CH_3)	7.95–7.92, m	7.95–7.92, m	(OH) 7.29, d	($NHSO_2CF_3$)	7.50, dd (8.2, 2.0)	7.39–7.35, m	8.35 (1 H, NH) 2.47, s (3 H, CH_3)
33	8.07, d (8.0)	7.56, t (7.5)	7.45, t (7.5)	8.15, d (8.0)	(F)	(13.1) (OSO_2CF_3)	($NHSO_2CF_3$)	(OH)	7.72, d (7.1)	
34	7.92, d (7.7)	7.54, td (7.2, 1.2)	7.44, td (8.0, 1.3)	8.11–8.07, m	8.21, d (1.9)	(OSO_2CF_3)	($NHCOCF_3$)	8.41, d (8.7)	8.11–8.07, m	8.29 (1 H, NH)
35	7.71, s	7.35, dd (8.4, 1.4)	(CH_3)	7.96, d (8.3)	8.19, d (1.9)	8.37, d	($NHCOCF_3$)	8.39, d (8.6)	8.06, dd (8.6, 2.0)	8.26 (1 H, NH) 2.51, s (3 H, CH_3)
36	7.98, d (7.6)	7.57, td (7.8, 1.2)	7.47, td (7.5, 1.2)	8.14, d (8.1)	(F)	(11.8)	($NHCOCF_3$)	(OSO_2CF_3)	8.57, d (6.4)	8.34 (1 H, NH)
37[b]	7.90, d (7.9)	7.49–7.32, m		8.02, d (7.9)	7.49–7.32, m	(OH)	(NH_2)	6.69, d (8.1)	7.49–7.32, m	9.58 (1 H, OH) 5.35 (2 H, NH_2)
38	7.40, s	7.25–7.30, m	(CH_3)	7.77, d (8.3)	7.81, s	(OH)	(NH_2)	6.66, d (8.0)	7.25–7.30, m	9.53 (1 H, OH) 5.30 (2 H, NH_2)
39[b]	7.94, d (8.1)	7.49, t (7.5)	7.37, t (7.5)	8.06, d (8.3)	(F)	6.50, d (13.6)	(NH_2)	(OH)	7.62, d (7.2)	9.58 (1 H, OH) 5.70 (2 H, NH_2)

[a] All OH, NH and NH_2 signals appeared as broad singlets exchangeable with D_2O. [b] Solvent: [$^2H_6$]DMSO; solvent for other compounds: $CDCl_3$.

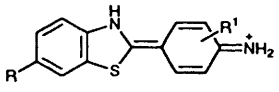


47 X = S
48 X = O



49 X = S, R = H
50 X = S, R = Me
51 X = O, R = H

were oxidised to 2,9-disubstituted benzo[*c*]cinnolines **49–51**, respectively, by (diacetoxyiodo)benzene (DAIB) in dry toluene in 60–70% yields which convincingly corroborates the proposed structures of the starting biphenyls. In addition, all the colourless 2-(4-aminophenyl)benzothiazoles and benzothiazolyl-substituted biphenyls with a free 4-amino group gave deep yellow solutions in 2 mol dm^{-3} hydrochloric acid; these bathochromic shifts may be accounted for by the extended conjugation of quinonoid mesomers of general structure **52**. No



52

such shifts were seen in 2-phenylbenzothiazoles bearing amino groups in *ortho* or *meta* positions in the 2-phenyl residue.

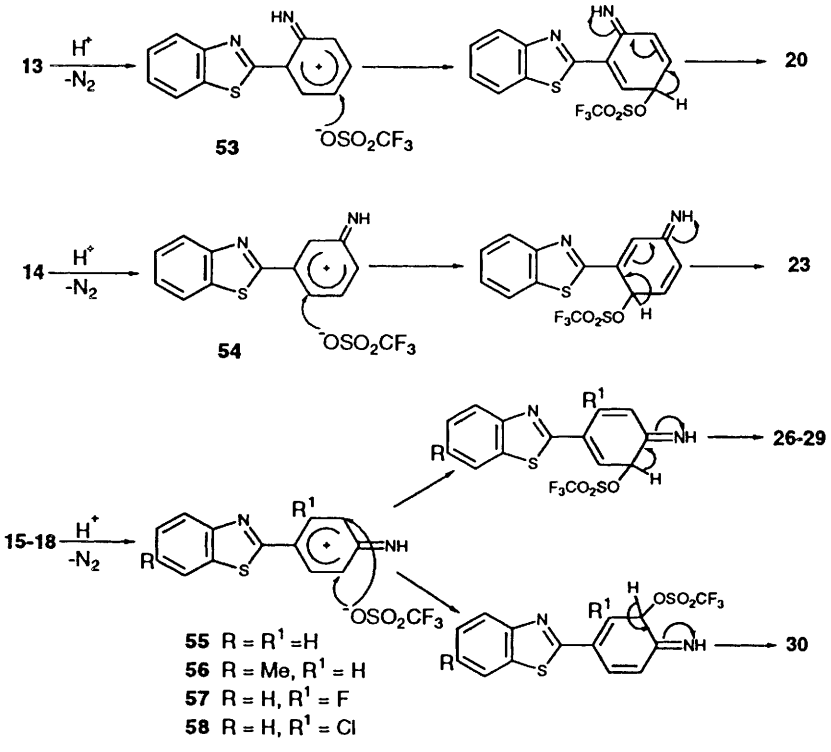
Mechanism of formation of triflate-substituted 2-(aminophenyl)-benzothiazoles

The generation of the π-carbocations **53–58** from the precursor azides **13–18** in triflic mixture, followed by their interception with triflate anion, accounts for the formation of simple triflate-substituted arylamines (Scheme 2). Despite careful chromatographic fractionation of the reaction mixtures from the decomposition of azides **13** and **14**, only triflates **20** and **23**, derived from nucleophile intrusion *para* to the incipient amine, were detected although the reason for this preference is not clear. The efficiency of conversion of 2-(3-azidophenyl)benzothiazole **14** into amine **23** is notable in that the triflate group is juxtaposed to the bulky benzothiazolyl moiety. When the *para* position is blocked, as in the azides **15–18**, the π-carbocations **55–58** must perforce be intercepted by triflate *ortho* to the incipient amine, but this is an unfavourable outcome as biphenyls now become substantial products. In the case of 2-(4-azido-2-chlorophenyl)benzothiazole **18**, products **29** and **30**, from introduction of triflate at both *ortho* positions of the π-carbocation **58**, were formed in a 2:3 ratio. Disappointingly, no participation of the hetero-atoms of the thiazole nucleus, potentially leading to ring-expansion reactions, was involved in product formation.

As an alternative tactic to generate the carbocation **53** and products derived therefrom, the indazolo[3,2-*b*]benzothiazole **59**, formed by thermolysis of azide **13**,[8] was treated with TFSA at 25 °C but no ring-opening (Scheme 3) of the indazolobenzothiazolium cation **60** was effected and only unchanged **59** was recovered on basification of the reaction mixture. Also, an attempt to extend π-carbocation capture to alternative nucleophiles was unsuccessful. Thus, when 2-(3-azidophenyl)-benzothiazole **14** was decomposed in triflic mixture containing tetraethylammonium halides (halide = F, Cl, Br), sodium halides (halide = Cl, Br) or a representative carbon nucleophile (diethyl malonate) no incorporation of halide or malonate was observed and only the triflate **23** was isolated in 65–75% yields. In addition, no decomposition of this azide occurred in acetic, trifluoroacetic or 100% phosphoric acid at 25 °C.

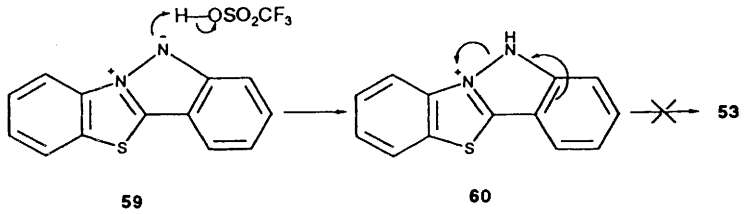
Mechanism of formation of 2,2′-diaminobiphenyls

Our original (tentative) proposal to explain the formation of these products from 2-(4-azidophenyl)benzothiazoles [7] involved an N–N intermolecular coupling to generate hydrazo intermediates, followed by an *ortho*-benzidine rearrangement.



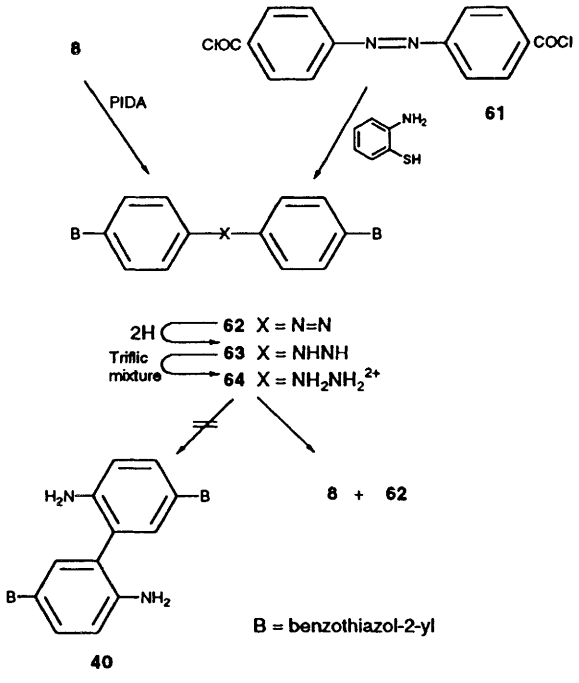
55 R = R¹ = H
56 R = Me, R¹ = H
57 R = H, R¹ = F
58 R = H, R¹ = Cl

Scheme 2



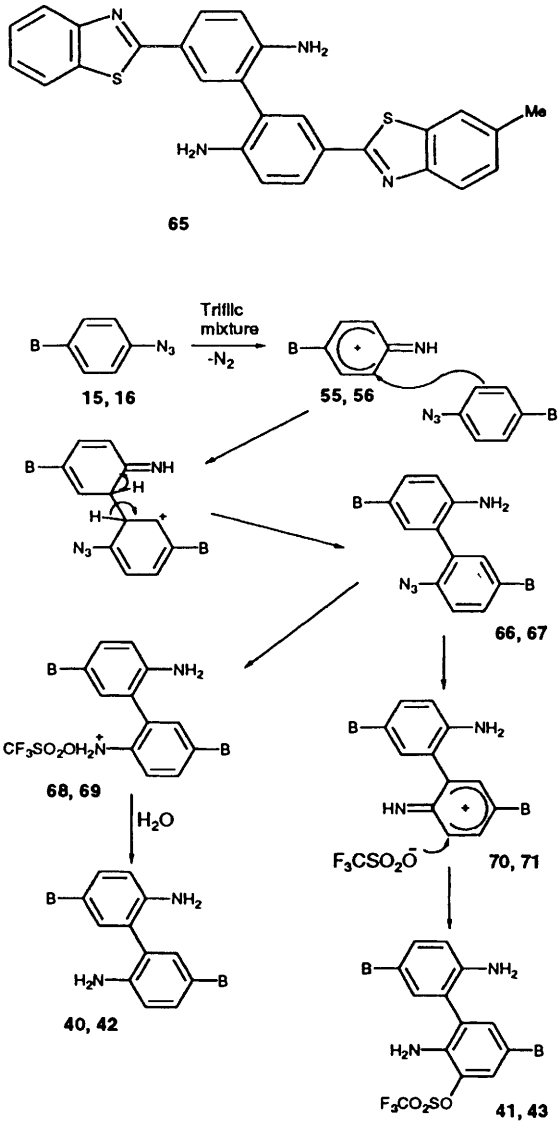
Scheme 3

This mechanism is no longer tenable in the light of further experimentation. Thus, 4,4′-bis(benzothiazol-2-yl)azobenzene **62** was synthesised either by direct oxidation of amine **8** with DAIB in dry toluene at 25 °C or by condensation of the acid chloride **61** with 2-aminobenzenethiol in boiling pyridine. Reduction of the azobenzene with tin(II) chloride–hydrochloric acid gave the hydrazobenzene **63** (*note:* not the benzidine rearrangement product **40**). Also, the (presumed) diprotonated species **64** did not rearrange to the expected diaminobiphenyl **40** in hot triflic mixture or mineral acids: instead, disproportionation occurred and the products were the amine **8** and the azobenzene **62** (Scheme 4). A similar disproportionation has been reported in 4,4′-diiodohydrazobenzene **63** (B = I).[9]



Scheme 4

Both aryl azides[10] and hydroxylamines[11] yield biphenyls when decomposed in TFSA in the presence of *neutral* aromatic substrates (*e.g.* benzene, anisole, nitrobenzene). Similarly, the reductive phenylation of nitroarenes can be accomplished using zinc dust–TFSA in benzene.[12] C–C couplings between carbocations **55** and **56**, generated from azides **15** and **16**, respectively, and amines **8** and **12** cannot be involved in the pathway to 2,2′-diaminobiphenyls **40** and **42** since these amines would be protonated in the triflic mixture and poor substrates for electrophilic substitution. Moreover, simple arylamines have been recorded as only very minor by-products in TFSA-induced aryl azide decompositions[13,14] (*cf.* photo- and thermal degradations).[4] Consistent with these reports decomposition of 2-(4-azidophenyl)benzothiazole **15** in TFSA alone at 0 °C in the present work gave < 5% of the amine **8**, insufficient to account for the observed yields of biphenyls. This conclusion was confirmed when azide **15** was decomposed in triflic mixture in the presence of a molar equivalent of the amine **12**, or



Scheme 5

alternatively, azide **16** was decomposed in the presence of amine **8**; the 'crossed' biphenyl **65** was not formed in either case.

A mechanism which accounts for the formation of biphenyls from azides **15** and **16** is summarised in Scheme 5. Coupling between π-carbocations **55** and **56**, generated from the azide substrates and *undecomposed* azides, could afford transient 2-amino-2′-azidobiphenyls **66** and **67**, respectively, which are subsequently processed by two routes. One pathway leads to the symmetrical biphenyls **40** and **42**, possibly *via* protonated *O*-trifluoromethylsulfonylhydroxylamines **68** and **69** formed by interception of nitrenium mesomers with TFSA which are subsequently hydrolysed to amines during work-up; the second pathway leads to the triflate-substituted 2,2′-diaminobiphenyls **41** and **43** after intermediate generation of further π-carbocation reactive species **70** and **71** as previously described in Scheme 2.

The crystal structure of 5,6-dimethoxy-2-(4-methoxyphenyl)-benzothiazole shows that the bulky sulfur atom imposes a twist angle of 21° about the pivotal C–C bond.[15] The absence of biphenyl products from the decomposition of 2-(4-azido-2-chlorophenyl)benzothiazole **18** may be due to a steric effect of the bulky chloro (relative to fluoro) group which increases the twist angle between the benzothiazole moiety and the reactive π-carbocation centre and inhibits bimolecular interaction, except by the relatively compact triflate anion. The significantly higher yield of biphenyl **46**, obtained from 2-(4-azidophenyl)-benzoxazole **19** is consistent with this hypothesis since the smaller oxygen atom would allow for the achievement of greater coplanarity in the transition state leading to biphenyl products.

Experimental

All mps were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured in KBr on a Mattson 2020 GALAXY Series FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on Bruker AC250 or ARX250 spectrometers Mass spectra and accurate mass measurements were recorded on an AEI MS-902 or a VGMicromass 7070E spectrometer.

2-(4-Aminophenyl)-6-methylbenzothiazole **12** was purchased from Aldrich Chemical Co. Ltd.

Synthesis of 2-(nitrophenyl)benzothiazoles 1–5

To a solution of the appropriate nitrobenzoyl chloride (0.03 mol) in pyridine (20 cm^3) was added dropwise 2-amino-benzenethiol (0.03 mol). Usually the reaction was exothermic but for the synthesis of the 2-(4-nitrophenyl)benzothiazoles **3–5** reaction mixtures were heated under reflux for 1 h. The resulting mixtures were cooled to 25 °C and poured into water (200 cm^3). Precipitates were filtered off, washed with water and recrystallised from methanol or ethanol. Yields and physical characteristics of products were as follows: **1**, 82%, mp 124–126 °C (lit.,[16] mp 122–123 °C); **2**, 80%, mp 182–184 °C (lit.,[17] mp 186.8–187.3 °C); **3**, 74%, mp 229–231 °C (lit.,[17] mp 233 °C); 2-(2-*fluoro*-4-*nitrophenyl*)*benzothiazole* **4**, 76%, mp 195–197 °C (Found: C, 56.7; H, 2.35; N, 10.4. $C_{13}H_7FN_2O_2S$ requires C, 56.9; H, 2.55; N, 10.2%); 2-(2-*chloro*-4-*nitrophenyl*)*benzothiazole* **5**, 74%, mp 180–182 °C (Found: C, 53.7; H, 2.3; N, 9.4. $C_{13}H_7ClN_2O_2S$ requires C, 53.7; H, 2.4; N, 9.6%).

Synthesis of 2-(aminophenyl)benzazoles 6–11

(1) A mixture of the appropriate 2-(nitrophenyl)benzothiazole **1–5** (0.015 mol) and tin(II) chloride dihydrate (0.075 mol) in absolute ethanol (50 cm^3) was stirred and refluxed under nitrogen for 4 h. After evaporation of ethanol, ethyl acetate (100 cm^3) was added to the residue and the organic layer was washed with 2 mol dm^{-3} aqueous sodium hydroxide (3 × 100 cm^3), water (2 × 100 cm^3) and dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was recrystallised from ethanol to afford the appropriate amine. Yields and physical characteristics of products were as follows: **6**, 85%, mp 140–142 °C (lit.,[18] mp 126.7–127.7 °C); **7**, 95%, mp 143–144 °C (lit.,[19] mp 145 °C); **8**, 90%, mp 155–157 °C (lit.,[20] mp 155–157 °C); 2-(4-*amino*-2-*fluorophenyl*)*benzothiazole* **9**, 85%, mp 164–165 °C (Found: C, 63.7; H, 3.6; N, 11.3. $C_{13}H_9FN_2S$ requires C, 63.9; H, 3.7; N, 11.5%); 2-(4-*amino*-2-*chlorophenyl*)*benzothiazole* **10**, 93%, mp 100–101 °C (Found: C, 59.7; H, 3.4; N, 10.6. $C_{13}H_9ClN_2S$ requires C, 59.9; H, 3.48; N, 10.7%); **11**, 85%, mp 176–178 °C (lit.,[21] mp 180 °C).

(2) The amines **6–8** were also prepared from 2-aminobenzenethiol and 2-, 3- and 4-aminobenzoic acids, respectively, in polyphosphoric acid at 210 °C for 4 h, and the amine **11** similarly from 2-aminophenol and 4-aminobenzoic acid. Yields of these reactions ranged 57–65%.

Synthesis of 2-(azidophenyl)benzazoles 13–19

A fine suspension of the precursor 2-(aminophenyl)benzazole (0.01 mol) in 5 mol dm^{-3} hydrochloric acid (100 cm^3) was diazotised at 0–5 °C with sodium nitrite (0.012 mol) in water (2 cm^3). The reaction mixture was left to stir for 20 min, then sodium azide (0.04 mol) in water (5 cm^3) was added to it dropwise and the mixture was stirred for a further 2 h at 0–5 °C. After basification with 2 mol dm^{-3} aqueous sodium hydroxide to pH 7, the precipitate was filtered off, washed with water and dried. Purification by flash chromatography on silica gel using EtOAc–hexane (1:3) as the eluent gave the title compounds. Yields and physical characteristics of products were as follows: **13**, 92%, mp 118–120 °C decomp. (lit.,[16] mp 133–134 °C decomp.); 2-(3-*azidophenyl*)*benzothiazole* **14**, 96%, mp 72–74 °C decomp. (Found: C, 61.7; H, 3.4; N, 22.6. $C_{13}H_8N_4S$ requires C, 61.9; H, 3.2; N, 22.2%); 2-(4-*azidophenyl*)*benzothiazole* **15**, 90%, mp 158–160 °C decomp. (Found: C, 61.6; H, 3.4; N, 22.4. $C_{13}H_8N_4S$ requires C, 61.9; H, 3.2; N, 22.2%); 2-(4-azidophenyl)-6-methylbenzothiazole **16**, 72%, mp 132–134 °C decomp. (lit.,[22] mp 133.5 °C); 2-(4-*azido*-2-*fluorophenyl*)*benzothiazole* **17**, 84%, mp 121–123 °C decomp. (Found: C, 57.7; H, 2.6; N, 20.3. $C_{13}H_7FN_4S$ requires C, 57.8; H, 2.6; N, 20.7%); 2-(4-*azido*-2-*chlorophenyl*)*benzothiazole* **18**, 69%, mp 119–122 °C (Found: C, 54.7; H, 2.6; N, 19.3. $C_{13}H_7ClN_4S$ requires C, 54.45; H, 2.4; N, 19.5%); 2-(4-*azidophenyl*)*benzoxazole* **19**, 72%, mp 132–133 °C decomp. (Found: C, 65.9; H, 3.6; N, 23.3. $C_{13}H_8N_4O$ requires C, 66.1; H, 3.4; N, 23.7%).

The spectroscopic data of all nitro-, amino- and azido-phenylbenzothi(or ox)azoles **1–19** are summarised in Table 1.

General procedure for the decomposition of 2-(azidophenyl)-benzazoles 13–19

The azide (1 g) was added in small portions to a mixture of TFSA (4 cm^3), TFA (5 cm^3) and TFAA (1 cm^3) at 0 °C. After being stirred at 0 °C for 30 min, then at room temperature for 18 h, the reaction mixture was basified with ice–aqueous ammonia and extracted with ethyl acetate. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. This gave a dark residue which was separated on silica gel (see below). The ^1H NMR data of the pure products are listed in Table 2.

Decomposition of 2-(2-azidophenyl)benzothiazole 13. Chromatographic fractionation of the products using EtOAc–hexane (1:4) as the eluent afforded 2-(2-*amino*-5-*trifluoromethylsulfonyloxyphenyl*)*benzothiazole* **20** (67%), mp 98–100 °C (EtOH) (Found: C, 44.7; H, 2.2; N, 7.7%; M^+, 374. $C_{14}H_9F_3N_2O_3S_2$ requires C, 44.9; H, 2.4; N, 7.5%; *M*, 374); ν_{max}/cm^{-1} 3483, 1618, 1500, 1407, 1223, 1204, 1138, 903, 870, 756 and 652; 2-(2-*trifluoroacetamido*-5-*trifluoromethylsulfonyloxyphenyl*)*benzothiazole* **21** (5%), mp 153–155 °C (MeOH) (Found: M^+, 470. $C_{16}H_8F_6N_2O_4S_2$ requires *M*, 470); ν/cm^{-1} 3430, 1718, 1558, 1420, 1206, 1189, 1164, 1142, 995, 922, 868 and 755; and 2-(2-*amino*-5-*hydroxyphenyl*)*benzothiazole* **22** (13%), mp 210–212 °C (Found: C, 64.3; H, 4.0; N, 11.3%; M^+, 242. $C_{13}H_{10}N_2OS$ requires C, 64.4; H, 4.2; N, 11.6%; *M*, 242), ν/cm^{-1} 3328, 1498, 1446, 1237, 1196, 1157, 994, 909, 845 and 753.

Trifluoroacetylation of **20** (0.31 g) with TFAA at room temperature gave **21** (0.37 g, 95%), hydrolysis of which with a 10% solution of potassium hydroxide in methanol and water gave **22** (83%).

Decomposition of 2-(3-azidophenyl)benzothiazole 14. A dichloromethane extract of the decomposition products was concentrated and furnished a precipitate of 2-(2-*hydroxy*-5-*trifluoromethylsulfonamidophenyl*)*benzothiazole* **24** (7%), mp 178–179 °C (Found: C, 44.7; H, 2.3; N, 7.7%; M^+, 374. $C_{14}H_9F_3N_2O_3S_2$ requires C, 44.9; H, 2.4; N, 7.5%; *M*, 374); ν_{max}/cm^{-1} 1658, 1500, 1177, 1150, 1074, 992, 762 and 610. The soluble fraction was chromatographed using EtOAc–hexane (3:7) as the eluent to give 2-(5-*amino*-2-*trifluoromethylsulfonyloxyphenyl*)*benzothiazole* **23** (70%), mp 87–89 °C (Found: C, 45.2; H, 2.8; N, 7.8%; M^+, 374. $C_{14}H_9F_3N_2O_3S_2$ requires C, 44.9; H, 2.4; N, 7.5%; *M*, 374); ν_{max}/cm^{-1} 3464, 3330, 1637, 1502, 1404, 1209, 1164, 1134, 860, 763 and 641; and 2-(5-*amino*-2-*hydroxyphenyl*)*benzothiazole* **25** (5%), mp 172–175 °C (Found: M^+, 242. $C_{13}H_{10}N_2OS$ requires *M*, 242); ν/cm^{-1} 3414, 1597, 1498, 1439, 1253, 1194, 994 and 755.

Decomposition of 2-(4-azidophenyl)benzothiazole 15. Chromatography [EtOAc–hexane (2:3)] of the reaction mixture afforded 2-(4-*amino*-3-*trifluoromethylsulfonyloxyphenyl*)*benzothiazole* **26** (12%), mp 192–195 °C (Found: C, 44.75; H, 2.65; N, 7.9%; M^+, 374. $C_{14}H_9F_3N_2O_3S_2$ requires C, 44.9; H, 2.4; N, 7.5%; *M*, 374); ν/cm^{-1} 3465, 3376, 1637, 1481, 1408, 1206, 1139, 905, 818 and 758; 2,2′-*diamino*-5,5′-*bis*(*benzothiazol*-2-*yl*)*biphenyl hydrate* **40** (29%), mp 305–307 °C (Found: C, 67.0; H, 4.0; N, 11.8; S, 13.8%; M^+, 450.0970. $C_{26}H_{18}N_4S_2{\cdot}H_2O$ requires C, 66.6; H, 4.3; N, 12.0; S, 13.7%; $M - H_2O$, 450.0973); ν/cm^{-1} 3468, 3362, 1619, 1468, 1434, 1306, 1226, 756 and 726; $\delta_H([^2H_6]DMSO)$ 8.03 (d, 2 H, *J* 7.8, benzothiazolyl 7-H, 7′-H), 7.92 (d, 2 H, *J* 7.8, benzothiazolyl 4-H, 4′-H), 7.86 (dd, 2 H, *J* 2.2 and 8.5, 4-H, 4′-H), 7.73 (d, 2 H, *J* 2.2, 6-H, 6′-H), 7.46 (t, 2 H, *J* 7.5, benzothiazolyl 5-H, 5′-H), 7.35 (t, 2 H, *J* 7.7, benzothiazolyl 6-H, 6′-H), 6.94 (d, 2 H, *J* 8.5, 3-H, 3′-H) and 5.52 (br s, 4 H, 2 × NH_2, exchangeable with D_2O); $\delta_C([^2H_6]DMSO)$ 168.7, 154.7, 150.0, 134.7, 130.9, 129.1, 127.1, 125.3, 123.1, 122.8, 122.7, 121.9 and 116.0; and 2,2′-*diamino*-5,5′-*bis*(*benzothiazol*-2-*yl*)-3-*trifluoromethylsulfonyloxybiphenyl* **41** (23%), mp 185 °C (dec) [Found: C, 54.3; H, 3.0; N, 9.1%; $(M + H)^+$, 599.0493. $C_{27}H_{17}F_3N_4O_3S_3$ requires C, 54.2; H, 2.9; N, 9.4%; *M* + H, 599.0493]; ν_{max}/cm^{-1} 3465, 3387, 1625, 1473, 1420, 1221, 1138, 921, 756, 726 and 601; $\delta_H(CDCl_3)$ 8.08–7.99 (m, 5 H), 7.96 (d, 1 H, *J* 1.9), 7.90 (d, 2 H, *J* 7.9), 7.54–7.34 (m, 4 H), 6.93 (dd, 1 H, *J* 1.5 and 7.5), 4.40 (br s, 2 H, NH_2, exchangeable with D_2O) and 4.10 (br s, 2 H, NH_2, exchangeable with D_2O); $\delta_C(CDCl_3)$ 168.0, 166.1, 154.4, 154.2, 147.1, 140.0, 137.2, 135.1, 135.0, 130.8, 130.5, 130.1, 126.9, 126.6, 126.3, 125.5, 125.1, 125.0, 124.7, 123.4, 123.1, 122.0, 121.9, 121.5, 121.2 and 116.2.

2-(3-Hydroxy-4-trifluoromethylsulfonamidophenyl)benzothiazole 31

The amine **26** (0.1 g) was refluxed with 10% aqueous potassium hydroxide (15 cm^3) and methanol (10 cm^3) for 2 h and the product was extracted into ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give **31** (0.078 g, 78%), mp 235–237 °C (Found: C, 44.75; H, 2.4; N, 7.35%; M^+, 374. $C_{14}H_9F_3N_2O_3S_2$ requires C, 44.9; H, 2.4; N, 7.5%; *M*, 374); ν_{max}/cm^{-1} 3353, 1480, 1447, 1390, 1210, 1137, 954 and 752.

2-(4-Trifluoroacetamido-3-trifluoromethylsulfonyloxyphenyl)-benzothiazole 34

The amine **26** (0.1 g) was treated with TFAA (2 cm^3) at room temperature and the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give the *benzothiazole* **34** (0.085 g, 68%) (Found: C, 40.6; H, 2.1; N, 11.15%; M^+, 470. $C_{16}H_8F_6N_2O_4S_2$ requires C, 40.85; H, 1.7; N, 10.85%; *M*, 470); ν_{max}/cm^{-1} 3448, 3304, 1720, 1531, 1417, 1220, 1162, 1138, 912, 831, 765 and 616.

2-(4-Amino-3-hydroxyphenyl)benzothiazole 37

(1) The amine **31** (0.078 g) was treated with 80% sulfuric acid (4 cm^3) at 175 °C for 1 h. The reaction mixture was poured into water, neutralised with 5 mol dm^{-3} aqueous sodium hydroxide and extracted with ethyl acetate. The combined extract was washed with water, dried ($MgSO_4$) and evaporated to yield the *aminophenol* **37** (0.042 g, 83%), mp 215–217 °C (Found: M^+, 242. $C_{13}H_{10}N_2OS$ requires *M*, 242); ν_{max}/cm^{-1} 3398, 1613, 1477, 1439, 1306, 1227 and 756.

(2) The same hydroxyphenylbenzothiazole **37** (94%) was formed when the triflate ester **34** was hydrolysed with 10% aqueous potassium hydroxide in a mixture of methanol and water (1:1).

Decomposition of 2-(4-azidophenyl)-6-methylbenzothiazole 16

Chromatographic fractionation of the reaction mixture (EtOAc–petroleum ether) afforded the following: 2-(4-*amino*-3-*trifluoromethylsulfonyloxyphenyl*)-6-*methylbenzothiazole* **27** (14%) [eluting with EtOAc–light petroleum (1:4)], mp 147–149 °C (Found: C, 46.2; H, 3.1; N, 7.5%; M^+, 388.0163. $C_{15}H_{11}F_3N_2O_3S_2$ requires C, 46.4; H, 2.8; N, 7.2%; *M*, 388.0163); ν_{max}/cm^{-1} 3364, 1627, 1487, 1410, 1211, 1141 and 828; 2,2′-*diamino*-5,5′-*bis*(6-*methylbenzothiazol*-2-*yl*)*biphenyl* **42** (32%) [eluting with EtOAc–light petroleum (1:1)], mp 309–312 °C [Found: C, 70.1; H, 4.5; N, 11.95%; $(M + H)^+$, 479.1364. $C_{28}H_{22}N_4S_2$ requires C, 70.3; H, 4.6; N, 11.7%; *M* + H, 479.1364]; ν_{max}/cm^{-1} 3465, 3368, 1619, 1475, 1452, 1401, 1306, 1225, 1154 and 818; $\delta_H([^2H_6]DMSO)$ 7.85 (d, 2 H, *J* 2.2, H-6, H-6′), 7.82–7.78 (m, 4 H, 4-H, 4′-H, benzothiazolyl 4-H, 4′-H), 7.70 (d, 2 H, *J* 2.1, benzothiazolyl 7-H, 7′-H), 7.28 (dd, 2 H, *J* 1.3 and 8.4, benzothiazolyl 5-H, 5′-H), 6.93 (d, 2 H, *J* 8.5, 3-H, 3′-H), 5.49 (br s, 4 H, 2 × NH_2, exchangeable with D_2O) and 2.43 (s, 6 H, 2 × CH_3); $\delta_C([^2H_6]DMSO)$ 167.6, 152.9, 149.8, 135.0, 134.8, 130.8, 128.9, 128.5, 123.2, 122.5, 122.4, 122.1, 116.0 and 21.9; and 2,2′-*diamino*-3-*trifluoromethylsulfonyloxy*-5,5′-*bis*(6-*methylbenzothiazol*-2-*yl*)*biphenyl* **43** (18%) [eluting with EtOAc–light petroleum (3:7)], mp 222 °C (dec.) (from $CHCl_3$–EtOH) [Found: C, 55.5; H, 3.5; N, 9.2%; $(M + H)^+$, 627.0806. $C_{29}H_{21}F_3N_4O_3S_3$ requires C, 55.6; H, 3.35; N, 8.9%; *M* + H, 627.0806]; ν_{max}/cm^{-1} 3439, 1626, 1475, 1420, 1402, 1218, 1150 and 813; $\delta_H(CDCl_3)$ 8.05 (d, 1 H, *J* 1.9), 8.01–7.88 (m, 5 H), 7.69 (s, 2 H), 7.34–7.29 (m, 2 H), 6.92 (d, 1 H, *J* 8.3), 4.37 (br s, 2 H, NH_2, exchangeable with D_2O), 4.07 (br s, 2 H, NH_2, exchangeable with D_2O) and 2.51 (s, 6 H, 2 × CH_3); $\delta_C(CDCl_3)$ 167.0, 165.2, 152.6, 152.5, 146.9, 139.8, 137.1, 135.7, 135.3, 135.2, 135.1, 130.6, 130.3, 129.8, 128.4, 128.2, 126.4, 124.9, 124.6, 122.8, 122.5, 121.8, 121.7, 121.5, 120.9, 116.1 and 21.9.

2-(3-Hydroxy-4-trifluoromethylsulfonamidophenyl)-6-methylbenzothiazole 32

The amine **27** (0.1 g) was refluxed with 10% aqueous potassium hydroxide (15 cm^3) and methanol (10 cm^3) for 0.5 h and the product was extracted into ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give *benzothiazole* **32** (75%) (Found: C, 46.7; H, 3.1; N, 7.5%; M^+, 388. $C_{15}H_{11}F_3N_2O_3S_2$ requires C, 46.4; H, 2.8; N, 7.2%; *M*, 388); ν_{max}/cm^{-1} 3446, 1605, 1447, 1385, 1230, 1206, 1139, 806 and 619.

6-Methyl-2-(4-trifluoroacetamido-3-trifluoromethylsulfonyloxyphenyl) benzothiazole 35

The amine **27** (0.1 g) was treated with TFAA (2 cm^3) at room temperature and the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give **35** (65%) (Found: C, 43.0; H, 2.0; N, 6.2%; M^+, 472. $C_{17}H_{10}F_6N_2O_4S_2$ requires C, 43.2; H, 2.1; N, 5.9%; *M*, 472); ν_{max}/cm^{-1} 3430, 1716, 1535, 1422, 1289, 1215, 1165, 1137, 923, 826 and 620.

2-(4-Amino-3-hydroxyphenyl)-6-methylbenzothiazole 38

Hydrolysis of **35** in boiling 10% aqueous potassium hydroxide gave **38** (85%) (Found: M^+, 256. $C_{14}H_{12}N_2OS$ requires *M*, 256); ν_{max}/cm^{-1} 3440, 1618, 1482, 1447, 1400, 1302, 1225 and 808.

Decomposition of 2-(4-azido-2-fluorophenyl)benzothiazole 17

According to the general procedure, the reaction products were dissolved in dichloromethane. The precipitate formed was filtered off and identified as 2,2′-*diamino*-4,4′-*difluoro*-5,5′-*bis*(*benzothiazol*-2-*yl*)*biphenyl* **44** (11%), mp 348–350 °C (Found: C, 64.5; H, 3.6; N, 11.8%; M^+, 486. $C_{26}H_{16}F_2N_4S_2$ requires C, 64.2; H, 3.3; N, 11.5%; *M*, 486); ν_{max}/cm^{-1} 3463, 3357, 1624, 1460, 1430, 1252, 1165 and 763; $\delta_H([^2H_6]DMSO)$ 8.08 (d, 2 H, *J* 7.9, benzothiazolyl 7-H, 7′-H), 7.79 (d, 2 H, *J* 8.8, 6-H, 6′-H), 7,93 (d, 2 H, *J* 8.1, benzothiazolyl 4-H, 4′-H), 7.48 (t, 2 H, *J* 8.0, benzothiazolyl 5-H, 5′-H), 7.37 (t, 2 H, *J* 7.8, benzothiazolyl 6-H, 6′-H), 6.70 (d, 2 H, *J* 14.3, 3-H, 3′-H) and 5.87 (br s, 4 H, 2 × NH_2, exchangeable with D_2O).

The soluble products were chromatographed to give 2-(4-*amino*-2-*fluoro*-5-*trifluoromethylsulfonyloxyphenyl*)*benzothiazole* **28** (31%) [eluting with EtOAc–hexane (1:4)], mp 146–148 °C (light petroleum–$CHCl_3$) (Found: C, 43.0; H, 2.3; N, 7.4%; M^+, 392. $C_{14}H_8F_4N_2O_3S_2$ requires C, 42.85; H, 2.0; N, 7.1%; *M*, 392); ν_{max}/cm^{-1} 3469, 3379, 1638, 1408, 1234, 1209, 1138, 871 and 760; 2-(2-*fluoro*-4-*trifluoroacetamido*-5-*trifluoromethylsulfonyloxyphenyl*)*benzothiazole* **36** (1.1%) [eluting with EtOAc–hexane (1:4)], mp 144–147 °C (from MeOH) (Found: M^+, 434. $C_{16}H_{10}F_4N_2S_2O_4$ requires *M*, 434); ν_{max}/cm^{-1} 3424, 1736, 1629, 1548, 1428, 1215, 1176, 1137, 916, 871, 851, 762 and 623; and 2,2′-*diamino*-4,6′-*difluoro*-5,5′-*bis*(*benzothiazol*-2-*yl*) *biphenyl* **45** (8%) [eluting with EtOAc–hexane (1:1)], mp 238–240 °C (from $CHCl_3$) [Found: C, 64.0; H, 3.2; N, 11.8%; $(M + H)^+$, 487.0863. $C_{26}H_{16}F_2N_4S_2$ requires C, 64.2; H, 3.3; N, 11.5%; *M* + H, 487.0863]; ν_{max}/cm^{-1} 3400, 1625, 1460, 1430, 1316, 1254, 1166 and 757; $\delta_H(CDCl_3)$ 8.36 (t, 1 H, *J* 8.4), 8.28 (d, 1 H, *J* 8.1), 8.09 (d, 1 H, *J* 7.9), 8.00 (d, 1 H, *J* 7.8), 7.92–7.86 (m, 2 H), 7.52–7.43 (m, 2 H), 7.36 (t, 2 H, *J* 7.6), 6.74 (d, 1 H, *J* 8.6), 6.67 (d, 1 H, *J* 12.8), 4.22 (br s, 2 H, NH_2, exchangeable with D_2O) and 3.59 (br s, 2 H, NH_2, exchangeable with D_2O).

2-(2-Fluoro-5-hydroxy-4-trifluoromethylsulfonamidophenyl)-benzothiazole 33

The amine **28** (0.1 g) was heated in boiling 10% aqueous potassium hydroxide (15 cm^3) and methanol (10 cm^3) for 0.5 h and the rearranged product was extracted into ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give **33** (75%) (Found: C, 43.05; H, 2.3; N, 7.45%; M^+, 392. $C_{14}H_8F_4N_2O_3S_2$ requires C, 42.85; H, 2.0; N, 7.1%; *M*, 392); ν_{max}/cm^{-1} 3416, 1621, 1523, 1430, 1288, 1203, 1185, 1134, 757 and 630.

2-(4-Amino-2-fluoro-5-hydroxyphenyl)benzothiazole 39

Hydrolysis of either the triflate ester **36** with 10% aqueous potassium hydroxide or the trifluoromethylsulfonamide **33** with 80% sulfuric acid at 175 °C for 0.5 h afforded *hydroxyphenylbenzothiazole* **39** in 75 and 85% yields, respectively (Found: C, 59.9; H, 3.2; N, 10.95%, M^+, 260. $C_{13}H_9FN_2OS$ requires C, 60.0; H, 3.5; N, 10.8%; *M*, 260); ν_{max}/cm^{-1} 3407, 1628, 1434, 1308, 1210, 1147 and 756.

Decomposition of 2-(4-azido-2-chlorophenyl)benzothiazole 18

Chromatographic fractionation of the products using EtOAc–hexane (1:4) as the eluent afforded 2-(4-*amino*-2-*chloro*-5-*trifluoromethylsulfonyloxyphenyl*)*benzothiazole* **29** (25%), mp 153–154 °C (from light petroleum–$CHCl_3$) [Found: C, 41.4; H, 1.8; N, 6.65%; M^+, 408 (410). $C_{14}H_8ClF_3N_2O_3S_2$ requires C, 41.1; H, 2.0; N, 6.85%; *M*, 408 (410)]; ν_{max}/cm^{-1} 3450, 3368, 1637, 1408, 1232, 1209, 1138, 852, 759 and 615; and 2-(4-*amino*-2-*chloro*-3-*trifluoromethylsulfonyloxyphenyl*)*benzothiazole* **30** (18%) [Found: C, 40.9; H, 1.9; N, 6.5%; M^+, 408 (410). $C_{14}H_8ClF_3N_2O_3S_2$ requires C, 41.1; H, 2.0; N, 6.85%; *M*, 408 (410)]; ν_{max}/cm^{-1} 3402, 1627, 1406, 1231, 1132, 887, 851, 758 and 658.

2,2′-Diamino-5,5′-bis(benzoxazol-2-yl)biphenyl 46

Azide **19** (1.4 g) was treated with TFSA (7 cm^3) in TFA (8 cm^3) and TFAA (1.5 cm^3) according to the general procedure. The crude product chromatographed on silica gel using EtOAc–hexane (1:1) as the eluent to give a buff solid (0.82 g, 66%), mp 176–179 °C [Found: C, 74.2; H, 4.1; N, 13.1%; $(M + H)^+$ 419. $C_{26}H_{18}N_4O_2$ requires C, 74.6; H, 4.3; N, 13.4%; *M* + H, 419]; ν_{max}/cm^{-1} 3381, 3330, 3205, 1619, 1485, 1454, 1243, 1140 and 744; $\delta_H([^2H_6]DMSO)$ 7.97 (dd, 2 H, *J* 1.9 and 8.5, 4-H, 4′-H), 7.84 (d, 2 H, *J* 1.9, 6-H, 6′-H), 7.37–7.29 (m, 4 H, benzoxazolyl 5-H, 5′-H, 6-H, 6′-H), 7.70–7.67 (m, 4 H, benzoxazolyl 4-H, 4′-H, 7-H, 7′-H), 6.79 (d, 2 H, *J* 8.5, 3-H, 3′-H) and 5.62 (br s, 4 H, 2 × NH_2, exchangeable with D_2O); $\delta_C([^2H_6]DMSO)$ 164.2, 150.8, 150.4, 142.9, 131.3, 129.1, 125.3, 125.1, 122.9, 119.7, 116.0, 114.6 and 111.2.

2,2′-Bis(acetamido)-5,5′-bis(benzothiazol-2-yl)biphenyl 47

Acetylation of the biphenyl **40** with acetic anhydride at room temperature gave **47** (92%), mp 325–327 °C (MeOH) (Found: C, 67.1; H, 4.0; N, 10.6%; M^+, 534. $C_{30}H_{22}N_4O_2S_2$ requires C, 67.4; H, 4.1; N, 10.5%; *M*, 534); ν_{max}/cm^{-1} 3408, 2924, 1698, 1618, 1508, 1409, 1256, 1215, 1090 and 906; $\delta_H([^2H_6]DMSO)$ 9.19 (s, 2 H, 2 × NH, exchangeable with D_2O), 8.18–8.14 (m, 4 H, 4-H, 4′-H, benzothiazolyl 7-H, 7′-H), 8.07 (d, 2 H, *J* 7.5, benzothiazolyl 4-H, 4′-H), 8.02 (d, 2 H, *J* 2.1, 6-H, 6′-H), 7.94 (d, 2 H, *J* 8.5 3-H, 3′-H), 7.56 (dt, 2 H, *J* 1.3 and 7.6, benzothiazolyl 5-H, 5′-H), 7.47 (dt, 2 H, *J* 1.3 and 7.6, benzothiazolyl 6-H, 6′-H) and 1.90 (s, 6 H, 2 × CH_3); δ_C(TFA) 175.4, 172.2, 140.8, 140.5, 132.6, 131.1, 130.8, 130.6, 129.7, 129.6, 127.8, 124.0, 123.1, 117.5 and 21.6.

2,2′-Bis(acetamido)-5,5′-bis(benzoxazol-2-yl)biphenyl 48

Acetylation of the biphenyl **46** with acetic anhydride at room temperature gave **48** (89%), mp 285–287 °C (MeOH) (Found: C, 71.55; H, 4.4; N, 11.0%; M^+, 502. $C_{30}H_{22}N_4O_4$ requires C, 71.7; H, 4.4; N, 11.15%; *M*, 502); ν_{max}/cm^{-1} 3414, 3307, 1675, 1585, 1510, 1453, 1304, 1242 and 745; $\delta_H([^2H_6]DMSO)$ 9.21 (s, 2 H, 2 × NH, exchangeable with D_2O), 8.24 (dd, 2 H, *J* 1.6 and 8.4, 4-H, 4′-H), 8.12 (d, 2 H, *J* 1.6, 6-H, 6′-H), 7.99 (d, 2 H, *J* 8.5, 3-H, 3′-H), 7.83–7.79 (m, 4 H, benzoxazolyl 4-H, 4′-H, 7-H, 7′-H), 7.47–7.39 (m, 4 H, benzoxazolyl 5-H, 5′-H, 6-H, 6′-H) and 1.90 (s, 6 H, 2 × CH_3); $\delta_C([^2H_6]DMSO)$ 169.8, 162.9, 151.1, 142.5, 140.1, 132.3, 131.1, 128.2, 126.4, 126.3, 125.8, 123.5, 120.6, 111.8 and 24.1.

2,9-Bis(benzothiazol-2-yl)benzo[*c*]cinnoline 49

A mixture of **40** (0.09 g) and DAIB (0.013 g) in dry toluene (15 cm^3) was stirred at 25 °C for 2 days. The solvent was removed under reduced pressure, the product was adsorbed on silica gel (2 g) and chromatographed using EtOAc–hexane (1 : 1) as the eluent to give pale yellow crystals of the benzocinnoline **49** (0.06 g, 62%), mp 316 °C (dec.) (Found: C, 70.2; H, 2.85; N, 12.2%; M^+, 446.0664. $C_{26}H_{14}N_4S_2$ requires C, 69.95; H, 3.1; N, 12.55%; *M*, 446.0660); ν_{max}/cm^{-1} 1614, 1426, 1314, 1143, 1091, 759 and 724; $\delta_H(CDCl_3)$ 9.53 (d, 2 H, *J* 1.8, 1-H, 10-H), 8.94, (d, 2 H, *J* 8.6, 4-H, 7-H), 8.67 (dd, 2 H, *J* 1.7 and 8.6, 3-H, 8-H), 8.28–8.24 (m, 2 H, benzothiazolyl 7-H, 7′-H), 8.08–8.04 (m, 2 H, benzothiazolyl 4-H, 4′-H) and 7.64–7.51 (m, 4 H, benzothiazolyl 5-H, 5′-H, 6-H, 6′-H); δ_C(TFA) 169.5, 143.6, 142.1, 133.8, 132.7, 132.3, 131.9, 131.4, 131.0, 127.5, 124.2, 123.6 and 118.9.

2,9-Bis(6-methylbenzothiazol-2-yl)benzo[*c*]cinnoline 50

The biphenyl **42** was subjected to DAIB oxidation as described above to give the *benzocinnoline* **50**, mp 305–307 °C (Found: C, 70.8; H, 4.1; N, 12.1%; M^+, 474.0958. $C_{28}H_{18}N_4S_2$ requires C, 70.9; H, 3.8; N, 11.8%; *M*, 474.0973); ν_{max}/cm^{-1} 3441, 2924, 2854, 1606, 1459, 1137 and 831; $\delta_H(CDCl_3)$ 9.33 (d, 2 H, *J* 1.5, 1-H, 10-H), 8.82 (d, 2 H, *J* 8.6, 4-H, 7-H), 8.54 (dd, 2 H, *J* 1.6 and 8.6, 3-H, 8-H), 8.07 (d, 2 H, *J* 8.4, benzothiazolyl 4-H, 4′-H), 7.75 (d, 2 H, *J* 1.2, benzothiazolyl 7-H, 7′-H), 7.38 (dd, 2 H, *J* 1.2 and 8.4, benzothiazolyl 5-H, 5′-H) and 2.55 (s, 6 H, 2 × CH_3); $\delta_C(CDCl_3)$ 165.9, 152.6, 146.1, 136.7, 136.5, 136.0, 132.5, 128.8, 128.7, 123.6, 121.8, 121.4, 120.6 and 22.0.

2,9-Bis(benzoxazol-2-yl)benzo[*c*]cinnoline 51

The biphenyl **46** was subjected to DAIB oxidation to give the *benzocinnoline* **51**, mp 331–333 °C (Found: C, 75.15; H, 3.3; N, 13.15%; M^+, 414.1110. $C_{26}H_{14}N_4O_2$ requires C, 75.4; H, 3.4; N, 13.5%; *M*, 414.1117); ν_{max}/cm^{-1} 3061, 1619, 1543, 1413, 1384, 1243, 1213, 1141, 1059, 882 and 744; $\delta_H(CDCl_3)$ 9.62 (d, 2 H, *J* 1.5, 1-H, 10-H), 8.96 (d, 2 H, *J* 8.6, 4-H, 7-H), 8.79 (dd, 2 H, *J* 1.6 and 8.6, 3-H, 8-H), 7.98–7.90 (m, 2 H, benzoxazolyl 4-H, 4′-H), 7.78–7.74 (m, 2 H, benzoxazolyl 7-H, 7′-H) and 7.53–7.40 (m, 4 H, benzoxazolyl 5-H, 5′-H, 6-H, 6′-H); $\delta_C(CDCl_3)$ 161.8, 151.5, 146.3, 142.4, 132.8, 130.4, 128.6, 126.7, 125.6, 121.8, 121.3, 121.0 and 111.4.

4,4′-Bis(benzothiazol-2-yl)diphenyldiazene 62

(1) A mixture of the diphenyldiazene acid chloride **61** (1.5 g) (prepared from the corresponding dicarboxylic acid)[23] and 2-aminobenzenthiol (1.26 g, 0.01 mol) in pyridine (10 cm^3) was stirred at 135 °C for 6 h. The precipitate was filtered off, washed with water and recrystallised from nitrobenzene to furnish metallic orange crystals (1.51 g, 69%), mp 308–310 °C (Found: C, 69.5; H, 3.5; N, 12.25%; M^+, 448. $C_{26}H_{16}N_4S_2$ requires C, 69.6; H, 3.6; N, 12.5%; *M*, 448); ν_{max}/cm^{-1} 3050, 1476, 1432, 1409, 1384, 1314, 1251, 1221, 1106, 964, 854, 753, 725, 696, 621, 564 and 528; $\delta_H(CDCl_3)$ 8.22 (d, 4 H, *J* 8.5, 2-H, 2′-H, 6-H, 6′-H), 8.05 (m, 6 H, *J* 8.5, 3-H, 3′-H, 5-H, 5′-H and benzothiazolyl 7-H, 7′-H), 7.88 (d, 2 H, *J* 7.9, benzothiazolyl 4-H, 4′-H), 7.47 (m, 2 H, benzothiazolyl 5-H, 5′-H) and 7.37 (m, 2 H, benzothiazolyl 6-H, 6′-H); δ_C(TFA) 173.3, 156.4, 140.4, 131.1, 129.7, 129.6, 129.5, 127.4, 125.0, 123.0 and 117.5.

(2) A mixture of amine **8** (2.5 g, 0.011 mol) and DAIB in dry toluene (150 cm^3) was stirred at 25 °C for 2 days. The precipitate was filtered off, washed with diethyl ether and water and finally crystallised from nitrobenzene to give the same azo compound **62** (1.1 g).

1,2-Bis[4-(benzothiazol-2-yl)phenyl]diazane 63

(1) The azo compound **62** (1.18 g, 2.631 mmol) was, reduced with tin(II) chloride dihydrate (5.4 g, 22.16 mmol) in 10 mol dm^{-3} hydrochloric acid (24 cm^3) at 25 °C for 2.5 h. The reaction mixture was basified with 2 mol dm^{-3} NaOH and extracted several times with ethyl acetate. The organic phase was washed with 2 mol dm^{-3} NaOH (2 × 150 cm^3) and water (2 × 150 cm^3), dried ($MgSO_4$) and the solvent was evaporated. The crude hydrazobenzene was crystallised twice from EtOAc–$CHCl_3$ (2 : 1) to give a pale yellow powder (0.5 g, 42%), mp 275–277 °C (Found: C, 69.1; H, 3.7; N, 12.1%; M^+, 450. $C_{26}H_{18}N_4S_2$ requires C, 69.3; H, 4.0; N, 12.4%; *M*, 450); ν_{max}/cm^{-1} 3347, 3260, 3057, 3024, 1605, 1483, 1435, 1384, 1314, 1268, 1225, 1177, 1117, 966, 825, 755, 726, 693 and 632; δ_H([H_6]DMSO) 8.54 (s, 2 H, NHNH, exchangeable with CD_3OD), 8.02 (d, 2 H, *J* 7.1, benzothiazolyl 4-H, 4′-H), 7.94–7.83 (m, includes d, 6 H, *J* 8.6, 3-H, 3′-H, 5-H, 5′-H and benzothiazolyl 7-H, 7′-H), 7.46 (t, 2 H, *J* 7.7, benzothiazolyl 5-H, 5′-H), 6.87 (t, 2 H, *J* 7.6, benzothiazolyl 6-H, 6′-H) and 2.48 (d, 4 H, *J* 8.8, 2-H, 2′-H, 6-H, 6′-H); δ_C(TFA) 173.8, 155.4, 139.9, 130.6, 130.1, 128.4, 128.0, 122.7, 116.3, 115.7 and 112.8.

(2) The same diphenyldiazane **63** (85%) was obtained by catalytic hydrogenation of the diphenyldiazene **62** in acetic acid over 10% palladium on charcoal catalyst at 50 psi† of hydrogen (30 h).

Disproportionation of the diphenyldiazane 63

(1) The diphenyldiazane **63** (0.2 g) was treated with triflic mixture according to the general procedure for the decomposition of azido compounds at 0 °C, followed by stirring at room temperature for 6 h and basification with ice–aqueous ammonia. Products were extracted with ethyl acetate. After evaporation of the solvent, the residue was adsorbed onto silica gel and chromatographed [EtOAc–hexane (1 : 2), EtOAc–MeOH (1 : 1)] to afford the amine **8** and the azobenzene **62** which were identical (mp, TLC and NMR) with authentic products.

(2) The diphenyldiazane **63** (0.2 g) was dissolved in hot ethyl acetate (200 cm^3) (under nitrogen). 5 mol dm^{-3} Sulfuric acid (15 cm^3) was added dropwise at reflux temperature. The mixture was stirred (1 h), cooled and neutralised with cold 2 mol dm^{-3} aqueous sodium hydroxide. The organic phase was washed with water, dried ($MgSO_4$) and the solvent was removed. TLC examination of the mixture revealed the presence of the amine **8** and diphenyldiazene **62**.

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† psi = 6.89 kPa.

References

1 Part 1, M. F. G. Stevens, C. J. McCall, P. Lelieveld, P. Alexander, A. Richter and D. E. Davies, *J. Med. Chem.*, 1994, **37**, 1689. This paper was also designated Part 23 in the series 'Structural Studies on Bioactive Compounds.'
2 M. F. G. Stevens, C. J. McCall and P. Lelieveld, *International Application*, PCT/GB94/01883.
3 R. A. Abramovitch, P. Chinnasamy, K. Evertz and G. Huttner, *J. Chem. Soc., Chem. Commun.*, 1989, 3.
4 E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, 1988, **88**, 298.
5 M. F. G. Stevens, W. K. Chui and M. A. Castro, *J. Heterocycl. Chem.*, 1993, **30**, 849.
6 E. A. Bliss, R. J. Griffin and M. F. G. Stevens, *J. Chem. Soc., Perkin Trans. 1*, 1989, 2217.

7 M. A. Castro and M. F. G. Stevens, *J. Chem. Soc., Chem. Commun.*, 1992, 869.
8 I. M. McRobbie, O. Meth-Cohn and H. Suschitzky, *Tetrahedron Lett.*, 1976, 929.
9 H. J. Shine and J. P. Stanley, *J. Org. Chem.*, 1967, **32**, 905.
10 H. Takeuchi and K. T. Takano, *J. Chem. Soc., Perkin Trans. 1*, 1986, 611.
11 T. Ohta, R. Machida, K. Takeda, Y. Endo, K. Shudo and T. Okamoto, *J. Am. Chem. Soc.*, 1980, **102**, 6385.
12 T. Okamoto, K. Shudo and T. Ohta, *J. Am. Chem. Soc.*, 1975, **97**, 7184.
13 R. A. Abramovitch, R. Jeyaranan and K. Yannakopoulou, *J. Chem. Soc., Chem. Commun.*, 1985, 1107.
14 R. A. Abramovitch, M. Cooper, S. Iyer, R. Jeyaranan and J. A. R. Rodriguez, *J. Org. Chem.*, 1992, **47**, 4819.
15 P. C. Yates, C. J. McCall and M. F. G. Stevens, *Tetrahedron*, 1991, **47**, 6493.
16 D. Hawkins, J. M. Lindley, I. M. McRobbie and O. Meth-Cohn, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2387.
17 M. T. Bogert and H. B. Corbitt, *J. Am. Chem. Soc.*, 1926, **48**, 783.
18 D. W. Hein, R. J. Alheim and J. J. Leavitt, *J. Am. Chem. Soc.*, 1957, **79**, 427.
19 H. Rivier and J. Zeltner, *Helv. Chim. Acta*, 1937, **20**, 691.
20 R. S. Varma and S. Chauhan, *Ind. J. Chem.*, 1988, **27B**, 438.
21 P. B. Tripathy and E. Jena, *J. Inst. Chem. (India)*, 1970, **42**, 65.
22 T. Tsunoda, S. Maeda and Y. Hata, *Jpn. Kokai Tokkyo Koho*, 7394, 419 (*Chem. Abstr.*, 1974, **80**, 102348p).
23 M. L. Tomlinson, *J. Chem. Soc.*, 1946, 756.

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