SYNTHESIS OF 2-SUBSTITUTED 2,3-DIHYDRO-1,4-BENZOTHIAZINE-3-THIONES *VIA* IMINOPHOSPHORANES

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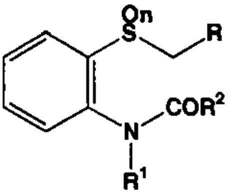
Abstract- 2-(Substituted methylsulfanyl)anilines (**5**) were treated with triphenylphosphine dibromide to yield iminophosphoranes (**6**), whose aza-Wittig reaction with carbon disulfide gave 2-(substituted methylsulfanyl)phenyl isothiocyanates (**8**). Cyclization of **8** by strong bases afforded 2-substituted 2,3-dihydro-1,4-benzothiazine-3-thiones (**10**).

Readily available 2-aminobenzenethiol derivatives (**1**),[1] (**2**),[2] and (**3**)[2] have been used for the preparation of 4*H*-1,4-benzothiazines, their monooxides, and their dioxides. The cyclization to 1,4-benzothiazines proceeded through the intramolecular attack of the carbanion adjacent to sulfur at the carbonyl or imine carbons. 2-Methylsulfanylphenyl carbodiimides (**7**) and isothiocyanates (**8**) may cyclize similarly on treatment with bases to give 1,4-benzothiazines. These heterocumulenes seem to be derived *via* aza-Wittig reaction[3] of *N*-(2-methylsulfanylphenyl)iminophosphoranes (**6**). Recently, we have reported that 2-substituted 1,3-benzothiazoles were easily prepared from **6** (R=H) and acid chlorides in one step.[4] As an



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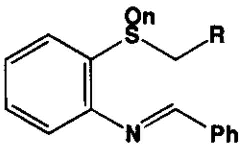

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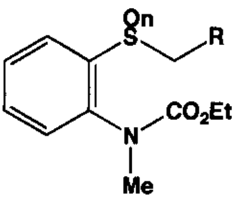

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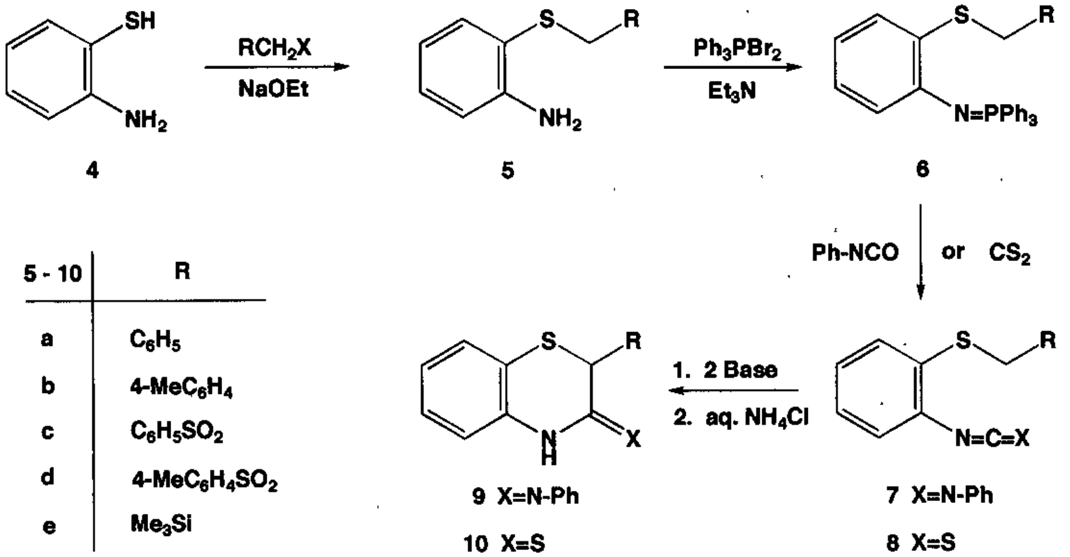
extension of this work we have studied the preparation of **7** and **8**, and their cyclization to 1,4-benzothiazines.

2-Methylsulfanylanilines (**5a-e**) were prepared in a usual manner by the reaction of 2-aminobenzenethiol (**4**) with benzyl chlorides, arylsulfonylchloromethanes, and (chloromethyl)trimethylsilane. Iminophosphoranes (**6a-e**) were obtained according to the literature method[5] from **5** and triphenylphophine dibromide in the presence of triethylamine in boiling benzene in 73-86% yields. In a preliminary experiment to prepare 2-phenyl-3-phenylimino-2,3-dihydro-1,4-benzothiazine (**9**, R=Ph), the aza-Wittig reaction of **6a** with phenyl isocyanate was carried out to obtain the precursor, *N*-(2-benzylsulfanyl)phenyl-*N* '-phenylcarbodiimide (**7a**). However, **7a** could not be isolable due to inseparable by-products formation. On the other hand, the aza-Wittig reaction of **6a** with carbon disulfide proceeded cleanly in boiling toluene to give isothiocyanate (**8a**) in 70% yield. It showed a characteristic isothiocyanate absorption at 2050 cm^{-1} in the ir spectrum. Other isothiocyantes (**8b-e**) were similarly prepared in 48-93% yields, and the physical and spectral data are shown in Tables 1 and 2, respectively. Cyclization of **8** to 2-substituted 1,4-benzothiazine-4-thiones (**10**) would be achieved by generation of stabilized carbanions adjacent to sulfur[6] followed by nucleophilic attack at the isothiocyanate group. In the case of 2-methylsulfanylphenyl isothiocyanate (**8**, R=H) cyclization to **10** (R=H) with strong bases failed, resulting in the formation of complex mixtures. However, when the substituents which could stabilize the carbanion more strongly were introduced, the cyclization occurred to give the expected benzothiazines (**10**). Thus, benzyl (**8a**) and 4-methylbenzyl derivatives (**8b**) gave **10a** (61%) and **10b** (52%),



5 - 10	R
a	C_6H_5
b	$4\text{-}MeC_6H_4$
c	$C_6H_5SO_2$
d	$4\text{-}MeC_6H_4SO_2$
e	Me_3Si

respectively, when they were treated with LDA in THF at -78°C and then room temperature. Synthesis of 2- substituted 1,4-benzothiazine-3-thiones are scarcely known in the literature: they were derived from the corresponding 1,4-benzothiazin-3-ones which were obtained from 2-aminobenzenethiols and 2-haloethanoates,[7] and their condensed products, 1,2,4-triazolo[3,4-*c*]-1,4-benzothiazines, are reported to show antianxiety activity.[8] The carbanions stabilized by both sulfur and sulfone[9] also gave the corresponding 1,4-thiazines (**10c**, 62%) and (**10d**, 50%), the latter being cyclized more smoothly by the use of sodium hydride. Recent studies on the mixed organosulfur-silicon compounds[10] prompted us to examine the reactivity of **8e**. However, it gave only a mixture of the expected **10e** (8%) and the desilylated **10f** (R=H, 10%), which was separated by column chromatography. All the structures of the products were confirmed on the basis of the analytical and spectral data as shown in Tables 1 and 2.

Table 1. Physical Properties of Compounds (6, 8, and 10)

Compound	Yield (%)	mp (°C)	Molecular Formula	Analysis (%)					
				Calcd			Found		
				C	H	N	C	H	N
6a	73	185-187	$C_{31}H_{26}NPS$	78.32	5.51	2.95	78.63	5.69	2 98
6b	78	206-208	$C_{32}H_{28}NPS$	78.49	5.76	2.86	78.57	6.00	2 65
6c	86	176-178	$C_{31}H_{26}NO_2PS_2$	68.99	4.85	2.59	69.20	5.05	2.67
6d[a]	85	139-149	$C_{32}H_{28}NO_2S_2P$	69.41	5.09	2.52	70.89	5 55	2.39
6e	81	150-152	$C_{28}H_{30}NPSSi$	71.30	6.41	2.96	71.10	6.72	3 01
8a	70	40-42	$C_{14}H_{11}NS_2$	65.35	4.30	5.44	65.54	4.39	5.04
8b	87	62-64	$C_{15}H_{13}NS_2$	66.38	4.82	5.16	66.71	4.90	4.91
8c	48	105-107	$C_{14}H_{11}NO_2S_3$	52.31	3.44	4.35	52.09	3.47	4.08
8d	51	73-75	$C_{15}H_{13}NO_2S_3$	53.70	3.90	4.17	53.69	3.86	4.11
8e	93	oil	$C_{11}H_{15}NS_2Si$	52.12	5.95	5.52	52.32	5.89	5.70
10a	61	228 (decomp.)	$C_{14}H_{11}NS_2$	65.33	4.30	5.44	65.53	4.48	5.24
10b	52	185 (decomp.)	$C_{15}H_{13}NS_2$	66.38	4.82	5.16	66.24	4.81	5.07
10c	62	181 (decomp.)	$C_{14}H_{11}NO_2S_3$	52.31	3.44	4.35	52.29	3.51	4.11
10d	50	195 (decomp)	$C_{15}H_{13}NO_2S_3$	53 70	3.90	4.17	53.82	4.10	4.11
10e	8	148 (decomp.)	$C_{11}H_{15}NS_2Si$	52 12	5.96	5.52	51.66	5.69	5.63

[a] It was difficult to obtain the analytically pure sample.

Table 2. Spectral Data of Compounds (6, 8, and 10)

Compound	Ms m/z (%)	Ir (KBr)[b] cm^{-1}	^{1}H-Nmr δ
6a	475 (M$^+$, 80) 442 (100), 183 (62)	1570, 1470, 1435 1325, 1110, 1020	4.10 (s, 2H), 6.43 -7.92 (m, 24H) (CDCl$_3$)
6b	489 (M$^+$, 73) 456 (100), 352 (53)	1560, 1460, 1430 1330, 1100, 1015	2.32 (s, 3H), 4.13 (s, 2H), 6.42-7.84 (m, 23H) (CDCl$_3$)
6c	539 (M$^+$, 12) 398 (100), 263 (63)	1570, 1430, 1290 1100, 1015, 1000	4.68 (s, 2H), 6.37-7.79 (m, 24H) (CDCl$_3$)
6d[c]	553 (M$^+$, 9) 398 (60), 277 (100)	1570, 1460, 1435 1315, 1110, 1020	2.35 (s, 3H), 4.65 (s, 2H), 6.35-7.79 (m, 23H) (CDCl$_3$)
6e	471 (M$^+$, 58) 266 (100), 183 (48)	1560, 1455, 1430 1335, 1245, 1100	0.20 (s, 3H), 2.13 (s, 2H), 6.20-7.88 (m, 19H) (CDCl$_3$)
8a	257 (M$^+$, 40) 224 (29), 91 (100)	2050, 1575, 1490 1450, 1270, 1230	4.10 (s, 2H), 7.03-7.53 (m, 9H) (CDCl$_3$)
8b	271 (M$^+$, 100) 238 (20), 105 (100)	2070, 1560, 1500 1425, 1070, 920	2.32 (s, 3H), 4.09 (s, 2H), 7.09-7.30 (m, 8H) (CDCl$_3$)
8c	321 (M$^+$, 8) 180 (100), 136 (22)	2100, 1575, 1440 1370, 1290, 1135	4.35 (s, 2H), 7 18-7.95 (m, 9H) (CDCl$_3$)
8d	335 (M$^+$, 11) 257 (9), 180 (100)	2100, 1580, 1465 1380, 1290, 1160	2.44 (s, 3H), 4.32 (s, 2H), 7.18-7.82 (m, 8H) (CDCl$_3$)
8e	253 (M$^+$, 8) 238 (17), 73 (100)	2950, 2050, 1580 1460, 1440, 1245	0.20 (s, 9H), 2.13 (s, 2H), 7.08-7.37 (m, 4H) (CDCl$_3$)
10a	257 (M$^+$, 91) 224 (100), 91 (74)	3170, 1595, 1520 1475, 1380, 1105	5.36 (s, 1H), 7.14 (s, 9H), 13.00 (br s, 1H) (DMSO-d$_6$)
10b	271 (M$^+$, 92) 238 (74), 105 (100)	3150, 1500, 1465 1430, 1365, 1100	2.20 (s, 3H), 5.38 (s, 1H), 7.01-7.37 (m, 8H), 13.00 (s, 1H) (DMSO-d$_6$)
10c	321 (M$^+$, 18) 180 (100), 77 (68)	3250, 1515, 1475 1360, 1310, 1140	6.12 (s, 1H), 7.10-7.78 (m, 9H), 12.90 (s, 1H) (DMSO-d$_6$)
10d	335 (M$^+$, 19) 180 (100), 136 (37)	3150, 1590, 1535 1475, 1380, 1320	2.38 (s, 3H), 6.07 (s, 1H), 7.05-7.63 (m, 8H), 12.95 (s, 1H) (DMSO-d$_6$)
10e	253 (M$^+$, 42) 148 (10), 73 (100)	3130, 1495, 1460 1420, 1340, 1240	0.08 (s, 9H), 3.54 (s, 1H), 6.79-7.28 (m, 4H), 9.62 (br s, 1H) (DMSO-d$_6$)

[a] The ir spectra of **8e** was taken with a liquid film.

EXPERIMENTAL

Melting points were determined with a MRK MEL-TEMP II and are uncorrected. Ir spectra were recorded on a JASCO A-102 spectrophotometer. Mass and ^{1}H-nmr spectra were taken with a JEOL JMS DX-300 spectrometer and a JEOL GSX-400 spectrometer, respectively. Microanalyses were performed with a YANACO CHN-Corder MT-5.

2-(Benzylsulfanyl)aniline (**5a**)[11] and 2-trimethylsilylmethylsulfanylaniline (**5e**)[2] were prepared according to the literatures.

2-(*p*-Tolylmethylsulfanyl)aniline (5b)

This compound was prepared in a similar manner as **5a** in 46% yield: bp 156-157°C / 2 mm Hg; ir (neat) 3440, 3350, 3010, 2930, 1595, 1475, 1445, 1295 cm^{-1}; ms m/z (%) 229 (M$^+$, 100), 124 (18), 105 (100); ^{1}H-nmr (CDCl$_3$) δ 2.30 (s, 3H), 3.85 (s, 2H), 4.25 (br s, 2H), 6.70-7.25 (m, 8H). *Anal.* Calcd for $C_{14}H_{15}NS$: C, 73.31; H, 6.59; N, 6.10. Found: C, 73.08; H, 6.56; N, 6.00.

2-(Phenylsulfonylmethylsulfanyl)aniline (5c)

2-Aminobenzenethiol (37.5 g, 0.30 mol) was dissolved into a stirred solution of NaOEt (23.8 g, 0.35 mol) in EtOH (300 ml) under nitrogen atmosphere, and the mixture was stirred at room temperature for 1 h. After a solution of chloromethyl phenyl sulfone[12] (57.2 g, 0.30 mol) was added at once, the mixture was heated under reflux for 18 h. Evaporation of the solvent left a solid, which was washed with water (300 ml) and then with hot water (300 ml). The solid was recrystallized from benzene-hexane to give **5c** (50.3 g, 60%): mp 109-111°C; ir (KBr) 3350, 1600, 1470, 1440, 1290, 1140, 1115 cm^{-1}; ms m/z (%) 279 (M$^+$, 22), 138 (100), 94 (61); ^{1}H-nmr (CDCl$_3$) δ 4.25 (s, 2H), 4.35 (br s, 2H), 6.57-7.91 (m, 9H). *Anal.* Calcd for $C_{13}H_{13}NO_2S_2$: C, 55.88; H, 4.69; N, 5.01. Found: C, 56.21; H, 4.73; N, 4.76.

2-(*p*-Toluenesulfonylmethylsulfanyl)aniline (5d)

This compound was prepared in a similar manner as **5c** in 36% yield: mp 118-120°C (benzene-hexane); ir (KBr) 3475, 3360, 1595, 1480, 1280, 1140, 1080 cm^{-1}; ms m/z (%) 293 (M$^+$, 27), 138 (100), 94 (53); ^{1}H-nmr (CDCl$_3$) δ 2.44 (s, 3H), 4.19 (s, 2H), 4.38 (br s, 2H), 6.56-7.75 (m, 8H). *Anal.* Calcd for $C_{14}H_{15}NO_2S_2$: C, 57.31; H, 5.15; N, 4.77. Found: C, 57.49; H, 5.21; N, 4.70.

2-Benzylthio-*N*-triphenylphosphoranylideneaniline (6a)

To a stirred solution of triphenylphosphine (26.2 g, 0.10 mol) in dry benzene (200 ml) was added a solution of bromine (16.0 g, 0.10 mol) in dry benzene (200 ml) dropwise at 0-5°C. The reaction mixture was stirred for additional 1 h and then warmed to room temperature. To this solution was added at once a mixture of **5a** (21.5 g, 0.10 mol) and triethylamine (20.2 g, 0.20 mol) in dry benzene (100 ml). The reaction mixture was then heated under reflux for 20 h. After cooling, the precipitates of triethylammonium bromide were filtered off, and the filtrate was condensed *in vacuo* . The crude product separated out was collected by filtration and recrystallized from benzene-hexane to give **6a** (34.7 g, 73%). Other iminophosphoranes (**6b-e**) were prepared in a similar manner.

2-(Benzylsulfanyl)phenyl isothiocyanate (8a)

Carbon disulfide (10 ml, 170 mmol) was added dropwise to a solution of **6a** (7.13 g, 15 mmol) dissolved in hot dry toluene (50 ml) under nitrogen atmosphere, and the mixture was heated under reflux for 24 h. After evaporation of the solvent *in vacuo* the residue was treated with hot hexane (80 ml) and then cooled. Triphenylphosphine thioxide separated out was removed by filtration, and evaporation of the filtrate left an oily residue. It was purified by column chromatography on silica gel with an eluent of benzene-hexane to give the product (**8a**) (2.73 g, 70%), which was recrystallized from hexane. Other isothiocyanates (**8b-e**) were prepared in a similar manner.

2-Phenyl-2,3-dihydro-1,4-benzothiazine-3-thione (10a)

To a solution of lithium diisopropylamide (5.0 mmol) [prepared from diisopropylamine (0.78 ml, 5.5 mmol) and butyllithium (3.0 ml of 1.64 M hexane solution, 5.0 mmol)] in dry THF (40 ml) was added dropwise a solution of **8a** (510 mg, 2.0 mmol) in dry THF (10 ml) at -78°C with stirring under nitrogen atmosphere. The color of the reaction mixture turned wine-red. It was stirred at -78° for 20 h and then at room temperature for 8 h. After quenching with saturated aqueous ammonium chloride, the mixture was extracted with benzene, and the extract was dried over $MgSO_4$. Evaporation of the solvent left a solid, which was recrystallized pyridine-ethanol to give **10a** (320 mg, 61%). Other benzothiazinethiones (**10b, c, e**) were prepared in a similar manner. The mixture of **10e** and **10f** (10%, mp 127-129°C; lit.,[13] mp 128°C) was separated by column chromatography on silica gel with an eluent of $CHCl_3$.

2-(*p*-Toluenesulfonyl)-2,3-dihydro-1,4-benzothiazine-3-thione (10d)

To a suspension of NaH in oil (60%) (160 mg, 4.0 mmol) in dry THF (40 ml) was added dropwise a solution of **8d** (670 mg, 2.0 mmol) at room temperature with stirring under nitrogen atmosphere. After stirring for 24 h at room temperature, the mixture was quenched with saturated aqueous NH_4Cl and extracted with benzene. The organic layer was dried over $MgSO_4$, and the solvent was removed *in vacuo* to give a solid, which was recrystallized from ethyl acetate-methanol to afford **10d** (330 mg, 50%).

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