Unexpected Formation of Benzothiazoles in the Synthesis of New Heterocycles: Benzo-1,2,4-dithiazines

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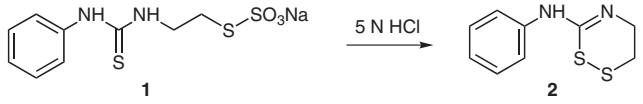
Received 28 November 2007; revised 10 December 2007

Abstract: The synthesis of benzo-1,2,4-dithiazines was investigated presuming a reversible sulfur–sulfur bond formation. 2-Aminothiophenol, when allowed to react with isothiocyanates, provided benzothiazoles. 2,2′-Diaminodiphenyl disulfide underwent cyclizations very readily without any reducing agent to give, according to the reaction conditions, benzothiazoles or benzo-1,2,4-dithiazines. The developed procedure offers a simple and convenient way to prepare the title compounds in very good to excellent yields. Until now, benzo-1,2,4-dithiazines as well as 2,2′-diaminodiphenyl disulfides bearing aminocarbonothioyl groups were unknown.

Key words: benzo-1,2,4-dithiazines, benzothiazoles, cyclizations, heterocycles, sulfur

1,2,4-Dithiazines, six-membered heterocycles containing two sulfur atoms in positions 1 and 2 and a nitrogen atom in the position 4 of the ring, represent a class of compounds that has not been studied much so far. The first report of this kind was based on a reaction between thiourea and Bunte salts, i.e. *S*-alkyl or *S*-aryl thiosulfates, in acidic media and appeared in 1963.[1] Since the corresponding disulfides were previously obtained,[2] a Bunte salt bearing an (aminocarbonothioyl)amino group such as **1** was expected to undergo intramolecular cyclization on treatment with an acid according to Scheme 1.



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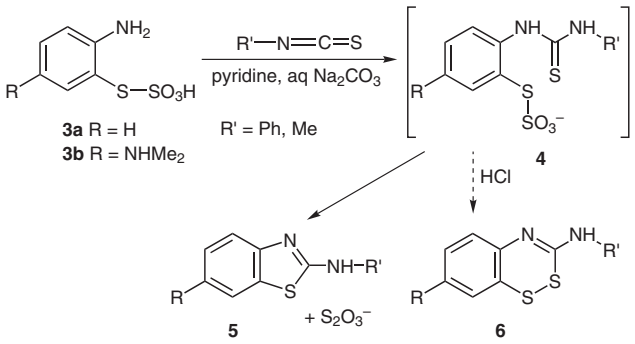
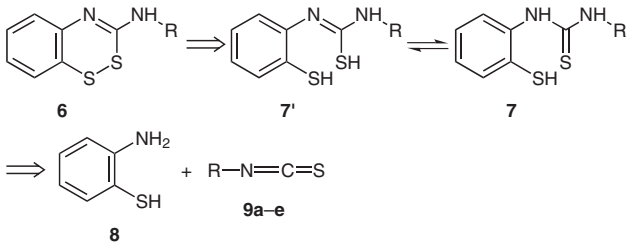
Scheme 1 Cyclization of sodium *S*-{2-[(anilinocarbonothioyl)amino]ethyl} thiosulfate to 1,2,4-dithiazine



Scheme 2 Reactions of *S*-aryl hydrogen thiosulfates with isothiocyanates



Scheme 3 Retrosynthetic analysis of benzo-1,2,4-dithiazines

Indeed, a crude product was formed, from which 3-anilino-5,6-dihydro-1,2,4-dithiazine (**2**) was isolated as a picrate and identified by CHNO elemental analysis. Attempts to release the free base were unsuccessful. A similar transformation of *S*-aryl hydrogen thiosulfates was supposed to lead to benzo-1,2,4-dithiazines **6**. However, neither the presumed benzo-1,2,4-dithiazines nor 2-[(aminocarbonothioyl)amino]phenyl thiosulfates **4** resulted from reactions of *S*-2-aminophenyl hydrogen thiosulfate (**3a**) and its 5-dimethylamino derivative **3b** with phenyl and methyl isothiocyanates (Scheme 2).

Instead of the desired products, benzothiazole derivatives **5** were obtained in almost quantitative yields accompanied by large amounts of the thiosulfate anion, which were determined by iodometric analysis.[1]

Current knowledge on benzo-1,2,4-dithiazine synthesis is quite limited because, except for the brief notes mentioned above, there is only one more report available in the literature; in this, Heller showed that **3b** provides the corresponding benzothiazole-2-thione with carbon disulfide in aqueous ammonia.[3]

The aim of this work was to find a suitable and reliable approach to this new class of compounds. Once benzo-1,2,4-dithiazines are prepared, we assume that the formation of the sulfur–sulfur bond could be reversible and, on this basis, their application, e.g. as free-radical scavengers, in various fields of industry may follow.

We considered the formation of benzo-1,2,4-dithiazines **6** by an oxidative cyclization of intermediates **7** generated in a reaction of 2-aminothiophenol (**8**) with isothiocyanates **9** (Scheme 3).

The reaction of **8** with benzoyl and acetyl isothiocyanate (**9a** and **9c**) has already been described; Uher[4] obtained *N*-benzoyl- and *N*-acetyl-*N*′-(2-sulfanylphenyl) thioureas

SYNTHESIS 2008, No. 8, pp 1297–1305
Advanced online publication: 10.04.2008
DOI: 10.1055/s-2008-1067008; Art ID: Z27707SS

(**7a** and **7c**) as solids precipitated from benzene solutions within several days in 42% and 54% yield, respectively.

Taking into account that benzene has serious adverse effects on human health, our initial experiments were carried out in acetone at temperatures near 0 °C. First, the reaction of **8** with **9a** afforded 2-benzoylaminobenzothiazole (**5a**). A possible explanation may consist in the more polar solvent used. The lower temperature and shorter reaction time in our case were expected to support the isolation of **7a**.

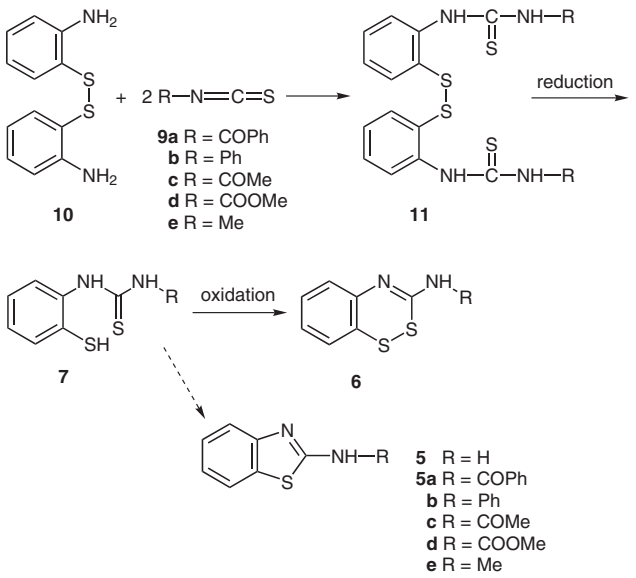
When **8** and **9a** were used in a 1:2 ratio, the substitution should occur on both the nitrogen and the sulfur since there is a lone electron pair on both these atoms available for nucleophilic reactions. Despite a sufficient amount of benzoyl isothiocyanate (**9a**), only a complex mixture arose. Subsequent basic hydrolysis was intended to release the thiourea **7a**, however, **5a** and 2-aminobenzothiazole (**5**) were formed instead. The unsubstituted derivative **5** was identical to that given by basic hydrolysis of **5a**. When the same procedure was undertaken with methoxycarbonyl isothiocyanate (**9d**), only 2-aminobenzothiazole (**5**) was obtained.

In all experiments, acyl isothiocyanates were prepared in situ from ammonium thiocyanate and the corresponding acyl chlorides. Quantities of acyl chlorides were calculated on the assumption of their 60% conversion into acyl isothiocyanates; ammonium thiocyanate was used in 10% additional excess. 2-Aminothiophenol required purification by vacuum distillation since it is readily oxidized to 2,2′-diaminodiphenyl disulfide (**10**) even by air oxygen. The solid residue from the distillation was recrystallized to provide **10** as a yellow crystalline compound.

The above mentioned mixture, produced in the reaction of **8** with **9a** in a 1:2 ratio, might also contain derivatives of disulfide **10** besides N-substituted and N,S-disubstituted 2-aminothiophenol. Use of freshly distilled **8**, sufficiently protected from air during all operations, would certainly reduce or prevent its formation. The same disadvantage, however, applies to all reactions with thiols and thiophenols.

In the next part, we chose 2,2′-diaminodiphenyl disulfide (**10**) as the starting compound. Although its transformation into benzo-1,2,4-dithiazines **6** requires an additional step, i.e. a reduction of the sulfur–sulfur bond (Scheme 4), this approach could represent a simple procedure involving relatively well-defined reaction mixtures. Moreover, **10** is much easier and more convenient to handle and is less harmful than 2-aminothiophenol (**8**; skin, eye and lung irritant).

Surprisingly, reactions of 2,2′-diaminodiphenyl disulfide (**10**) with isothiocyanates **9a–e** afforded the corresponding benzothiazole derivatives **5a–e**. These products were formed without any reducing agent present in the reaction mixture. The various conditions examined (solvent, temperature, base) are summarized in Table 1.



Scheme 4 Transformation of 2,2′-diaminodiphenyl disulfide (**10**) into benzo-1,2,4-dithiazines **6**

Table 1 Reaction Conditions and Yields of Pure Benzothiazole Derivatives Obtained from 2,2′-Diaminodiphenyl Disulfide (**10**) and Isothiocyanates **9a–e**

Entry	Product	R	Solvent	Temp (°C)	Yield (%)	Other conditions
1	**5a**	COPh	acetone	0	93	solid disulfide
2			$CHCl_3$	r.t.	40	*cf.* Method C
3	**5b**	Ph	acetone	r.t.	34	–
4			acetone	r.t.	44	1:4[a]
5			MeOH	65	49	Et_3N
6			EtOH	78	55	–
7			$CHCl_3$	r.t.	22	Et_3N
8			$CHCl_3$	r.t.	66	–
9			toluene	r.t.	82	–
10	**5c**	COMe	acetone	r.t.	22	–
11			$CHCl_3$	r.t.	59	–
12	**5d**	COOMe	acetone	0	10[b]	–
13			$CHCl_3$	r.t.	48[c]	–
14	**5e**	Me	EtOH	r.t.	83	–
15			$CHCl_3$	r.t.	35	–

[a] The ratio of starting compounds **10** to **9b**.
[b] In addition to benzothiazole, substituted 2,2′-diaminodiphenyl disulfide (17%) was isolated.
[c] Yield of benzothiazole containing unreacted isothiocyanate.

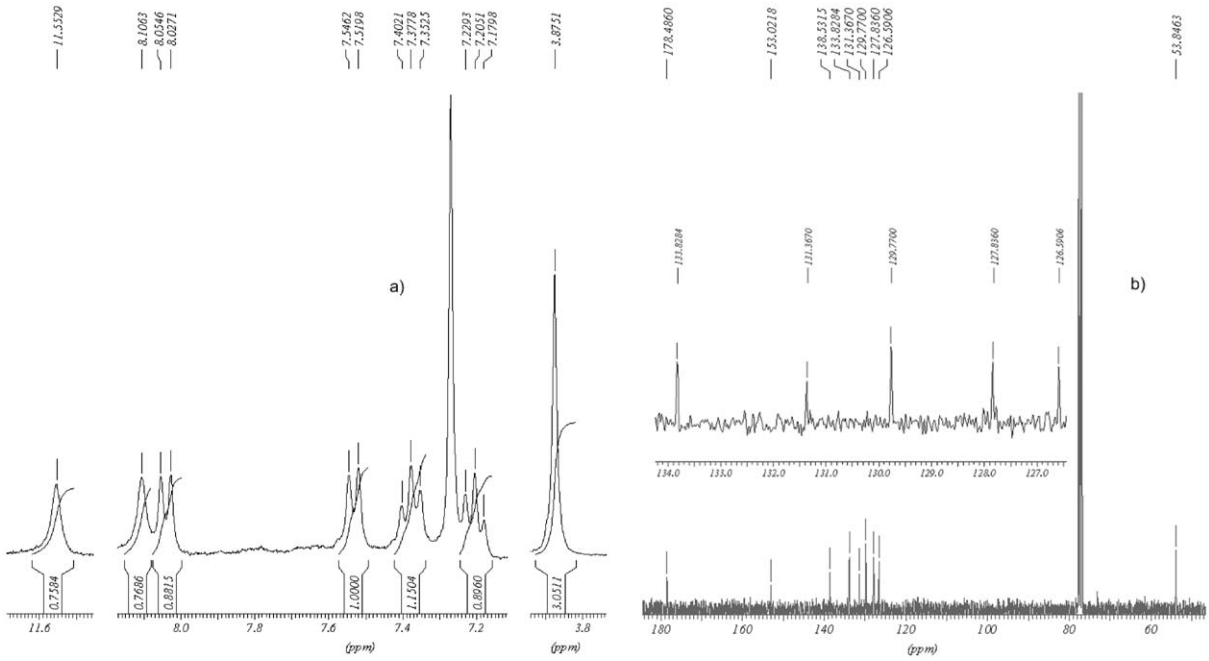


Figure 1 ^{1}H NMR (a) and ^{13}C NMR (b) spectra of 2,2′-di[(methoxycarbonylamino)carbonothioyl]aminodiphenyl disulfide (**11d**) in $CDCl_3$

In the case of phenyl isothiocyanate (**9b**), the use of reagents in a 1:4 ratio (**10** to **9b**) did not considerably increase the yield in comparison with the same experiment in a 1:2 ratio. When triethylamine was applied as a base in chloroform, the isolated quantity of 2-phenylaminobenzothiazole (**5b**) was even two-thirds lower than in its absence. In this context, the reaction in boiling methanol should provide a yield significantly higher than the observed 49%; however, 55% was achieved in boiling ethanol. Apparently, higher temperatures still have a positive effect upon the transformation in polar solvents; nevertheless, a very good yield (82%) was obtained at room temperature in toluene. The reaction of 2,2′-diaminodiphenyl disulfide (**10**) with acetyl isothiocyanate (**9c**) at room temperature also led to better results in chloroform than in acetone.

During the experiment with methoxycarbonyl isothiocyanate (**9d**) in acetone, the intermediate **11d** was trapped and separated as a colorless crystalline compound. Although the reaction was carried out at a temperature near 0 °C, the initially yellow solution turned gradually dark as a consequence of significant decomposition (TLC). **11d** was isolated together with the corresponding benzothiazole derivative **5d**; yields of both were, unfortunately, low, being 17% and 10%, respectively.

The purification of 2,2′-di[(methoxycarbonylamino)carbonothioyl]aminodiphenyl disulfide (**11d**) was quite smooth since it was either only slightly soluble or even insoluble in common organic solvents (acetone, acetonitrile, methanol, dichloromethane, carbon tetrachloride, benzene, acetic acid) and water except pyridine and trifluoroacetic acid. In spite of the low solubility, ^{1}H and ^{13}C NMR spectra could be recorded in $CDCl_3$ solution (Figure 1a,b).

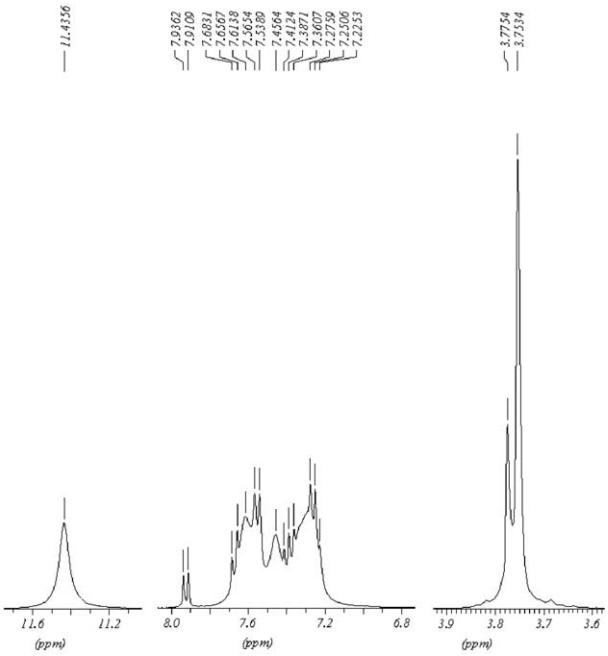


Figure 2 ^{1}H NMR spectrum of **11d** in DMSO-d_6 recorded immediately

In DMSO-d_6, however, **11d** underwent an immediate conversion (Figure 2). After a few days, all the solid dissolved and the NMR spectra (Figure 3) were almost identical to those of 2-methoxycarbonylaminobenzothiazole (**5d**; Figure 4).

Similarly, melting of **11d** was accompanied by a rapid solidification and the resulting crystals took the shape of needles characteristic of **5d**; the subsequent sublimation at 205 °C confirmed the conversion of **11d** into **5d**.

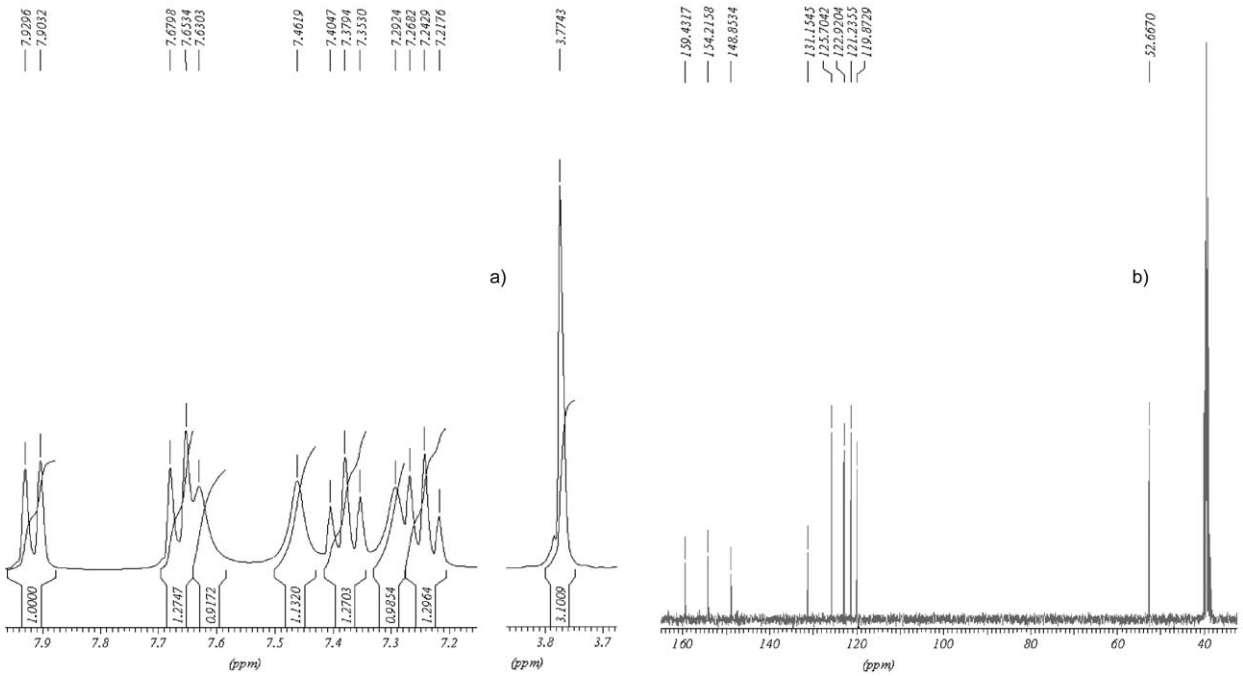


Figure 3 ^{1}H NMR (a) and ^{13}C NMR (b) spectra of **11d** in DMSO-d_6 recorded after a few days

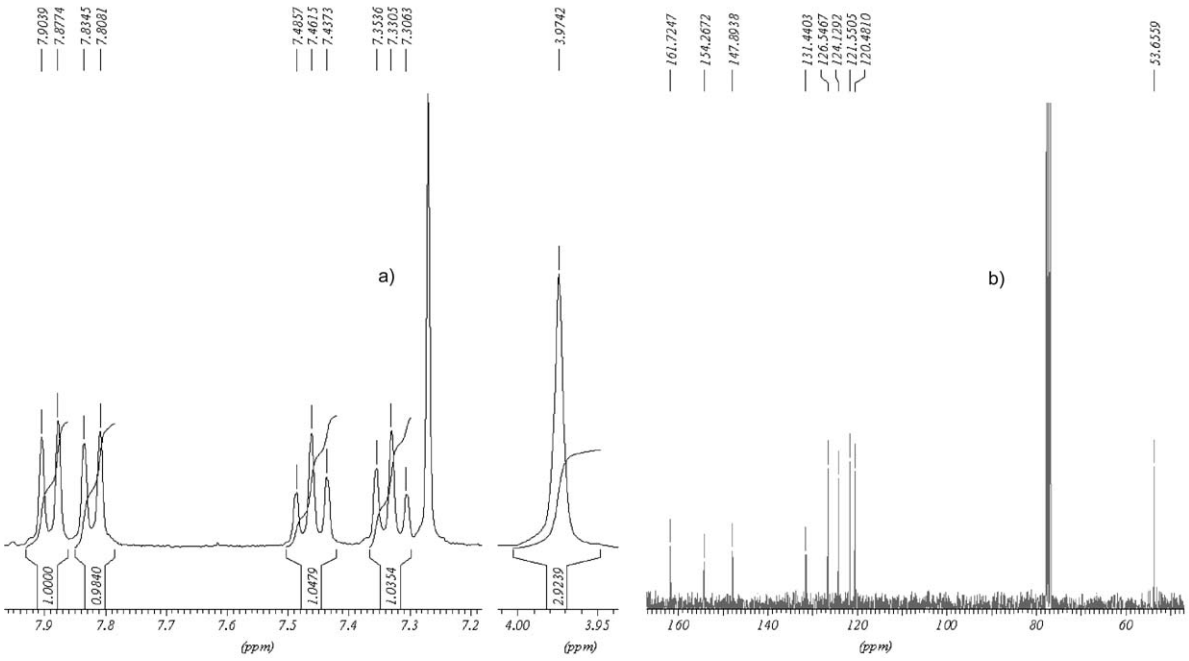


Figure 4 ^{1}H NMR (a) and ^{13}C NMR (b) spectra of **5d** in $CDCl_3$

Attempts at mass spectra measurements obviously failed; the expected molecular peak at *m*/*z* 482 was not even detected. On the contrary, the most intensive peak (100%) appeared at *m*/*z* 208, i.e. as expected for **5d**. Nevertheless, 2,2′-di[(methoxycarbonylamino)carbonothioyl]aminodiphenyl disulfide (**11d**) was stable enough to be stored at room temperature for several months without any significant changes in its infrared spectrum. It is the only substituted 2,2′-diaminodiphenyl disulfide bearing aminocarbonothioyl groups that is known so far. In the context of our work, it represents important evidence that the reaction follows the desired pathway as shown in Scheme 4.

According to Table 1, the experiments with methyl isothiocyanate (**9e**) and benzoyl isothiocyanate (**9a**) proceeded very well in polar solvents at room temperature and in an ice bath, respectively. The yields achieved (83% **5e**, 93% **5a**) were the highest in the whole series. In contrast, the above-mentioned reaction of **9a** with 2-aminothiophenol (**8**) provided only 54% of **5a** under the same conditions.

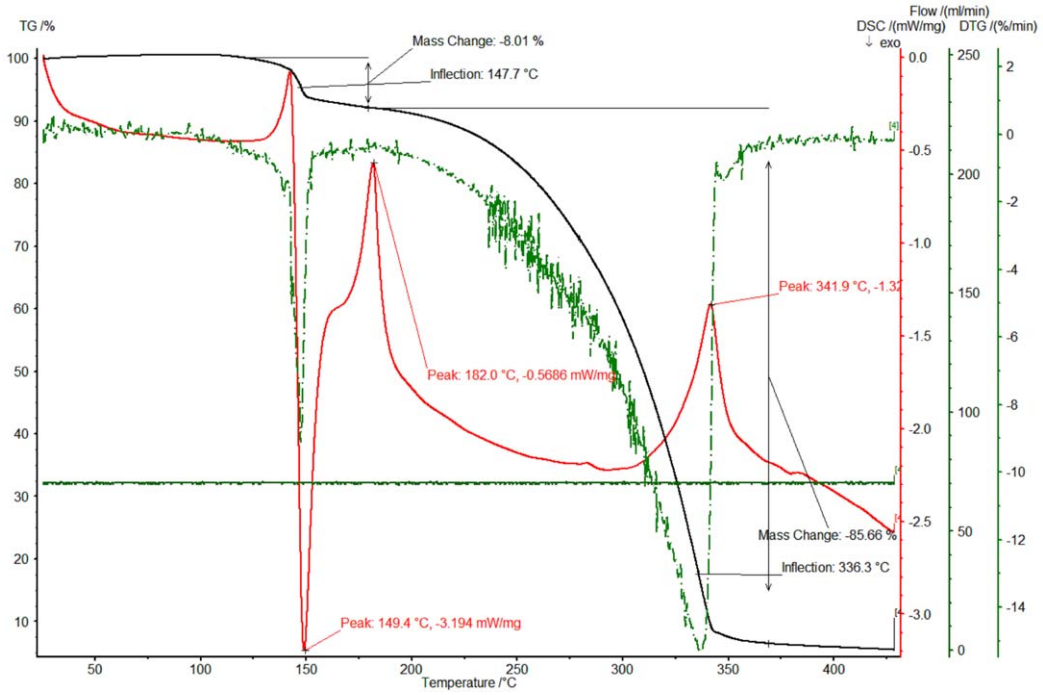


Figure 5 Thermal analysis of 2-benzoylaminobenzo-1,2,4-dithiazine (**6a**)

All benzothiazole derivatives prepared were identified by IR, ^{1}H and ^{13}C NMR spectroscopy. In the course of their mass spectra measurements, a fragment of *m*/*z* 96 was always revealed. Although its intensity varied between 40% (**5**) and 18% (**5b**) decreasing even below 10% (**5a**, **5c**), it is a common feature for all benzothiazole derivatives of this series, and may be assigned the formula C_5H_4S.

Methyl derivative **5e** gave an intense peak at *m*/*z* 135, corresponding to benzothiazole unsubstituted in position 2. An ion at *m*/*z* 108 probably belongs to C_6H_4S; fragmentation to 2-aminobenzothiazole (**5**) including its descendents (*m*/*z* 123; C_6H_5NS) was not observed. 2-Phenylaminobenzothiazole (**5b**) did not follow any of the mentioned pathways; the respective peaks were almost undetectable.

A characteristic behavior of acyl derivatives, i.e. splitting off the acyl groups, was noticed in the mass spectra of **5a**, **5c** and **5d**. Moreover, benzoyl derivative **5a** evolved carbon monoxide under the formation of 2-phenylaminobenzothiazole (**5b**; *m*/*z* 226); methoxycarbonyl derivative **5d** eliminated methanol affording 2-isothiocyanatobenzothiazole (*m*/*z* 176).

As stated above, the reaction of 2,2′-diaminodiphenyl disulfide (**10**) with isothiocyanates **9** was believed to provide benzo-1,2,4-dithiazines **6**. However, the competitive cyclization to benzothiazoles occurred to a large extent. To explain its possible mechanism, additional experiments with selenium analogues have been performed and these results will be reported in a forthcoming paper.

Two different products were isolated from the reaction of **10** with **9a** in chloroform. Immediately after the reagents were combined, about half of the suspension was taken and briefly boiled, giving **5a** again. Another solid **6a**, obtained from the remaining portion kept at room temperature, showed very similar but not identical spectroscopic properties. It was identified by IR, ^{1}H and ^{13}C NMR spectroscopy; since the sole distinction between benzothiazoles and benzo-1,2,4-dithiazines is the number of sulfur atoms, only slight variances have to be expected. All data were recorded under the same conditions as those of 2-benzoylaminobenzothiazole **5a**.

Comparison of ^{13}C NMR spectra of **5a** and the new compound **6a** revealed that the number of carbons was equal but the chemical shifts were up to 1 ppm higher or lower. The most significant difference (3.15 ppm) was found between ^{13}C NMR signals of C=N; peaks at 167.36 ppm (**5a**) and 165.91 ppm represented the carbonyl groups and also carbons with the highest chemical shift in both cases. This indicated that (di)benzoylthiourea **11b** was not present since its thiocarbonyl group would appear at a higher ppm value. Moreover, assignment of the particular signals proved a displacement of one of the aromatic carbons, which was detected among the quaternary carbons. The structure of benzothiazole **5a** was, in consequence, rather unlikely. Based on these data, the above-mentioned substance **6a** was most properly identified as the desired 2-benzoylaminobenzo-1,2,4-dithiazine. Very good compliance with a predicted ^{13}C NMR spectrum was found as well.

The structure of **6a** was further confirmed by means of thermal analysis. Melting of 2-benzoylaminobenzo-1,2,4-dithiazine (**6a**) was observed at 147–150 °C (*cf.* 188–190 °C for **5a**). In agreement with this, thermal analysis showed that an endothermic process took place at this temperature (Figure 5).

Melting was accompanied by 8% mass loss, i.e. by a solvent evaporation. As most of the acetone would certainly

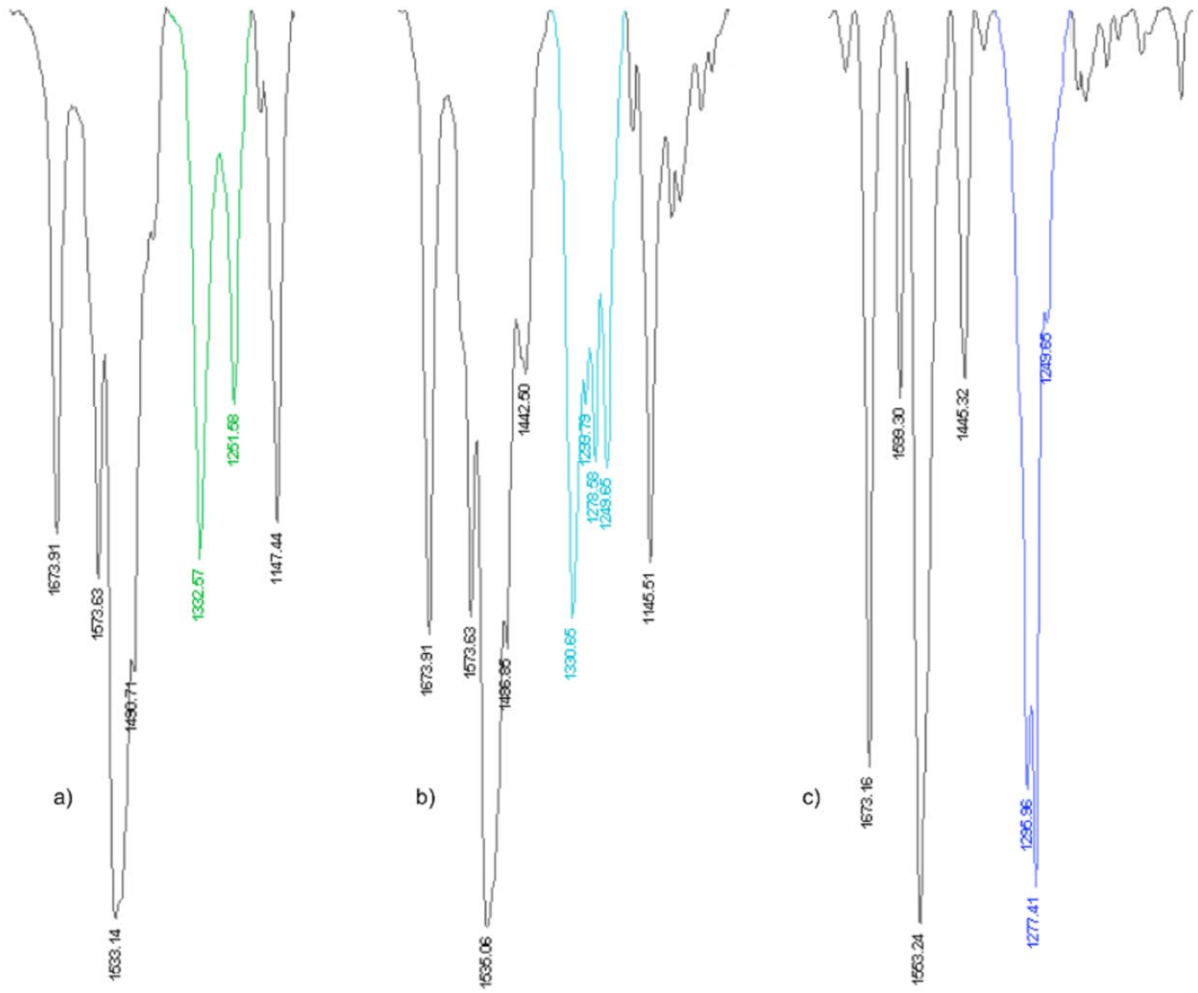


Figure 6 IR spectrum (detail) of (a) pure 2-benzoylaminobenzo-1,2,4-dithiazine (**6a**); (b) **6a** showing the first traces of decomposition; (c) pure 2-benzoylaminobenzothiazole (**5a**)

have been removed at much lower temperatures, the acetone molecules left must have been trapped in the crystals. Subsequent rearrangement of bonds and/or resolidification occurred without any mass change and, finally, complete decomposition took place.

Besides the reaction in chloroform, **6a** was also prepared in acetone at –20 to –30 °C. A well-chilled 2,2′-diaminodiphenyl disulfide solution was treated with **9a** without exceeding –20 °C and kept at this temperature overnight. Compound **6a** precipitated as an insoluble pale solid in yields of 80–93%. In comparison with the above-mentioned reaction, which, unfortunately, led only to benzothiazole derivatives, this procedure was much more reliable. Moreover, very good to excellent yields could be achieved.

2-Benzoylaminobenzo-1,2,4-dithiazine (**6a**) is a relatively stable crystalline substance. However, when stored at room temperature, the following changes in its infrared spectrum took place within two weeks (Figure 6).

Figure 6 shows that **6a** underwent slow decomposition to **5a**. It thus became clear why attempts at mass spectra measurements failed regardless of sample freshness. The molecular peak was detected (0.4%) but the signal of **5a** at *m*/*z* 254 was much more intense (25%).

None of the transformations described was carried out in the presence of a reducing agent. In spite of this, the cyclization of the substituted disulfides **11** occurred very readily. Disulfide **11d** was the only intermediate trapped and identified. According to the reaction conditions, benzothiazoles **5a**–**e** or benzo-1,2,4-dithiazine (**6a**) were isolated. The five-membered rings were, however, preferred over their six-membered counterparts since they were obtained to a much larger extent and, in addition, the conversion of **6a** into **5a** was observed. Nevertheless, benzo-1,2,4-dithiazine (**6a**) was a relatively stable solid and its formation was proved in a number of experiments. It might be presumed, therefore, that the other derivatives are also available in the same way.

The aim of this work, i.e. the synthesis of the new heterocycles benzo-1,2,4-dithiazines, was achieved. The procedure is simple and convenient, and gives very good to excellent yields. Moreover, the substituted disulfide **11d**, which has not been previously described, was isolated and

identified. The properties of other benzo-1,2,4-dithiazine derivatives, with special attention to the reversibility of the sulfur–sulfur bond formation, are the subject of further research.

All chemicals and solvents used are commercially available. Reaction conversions were monitored by TLC on Silufol UV 254 in Et_2O. IR spectra were recorded on an ATI Mattson Genesis spectrometer, NMR spectra on a Bruker Avance 300 spectrometer and mass spectra on a Trio 1000 spectrometer equipped with a direct inlet probe. ^{13}C NMR spectra were also predicted using ACD/CNMR Spectrum Generator. The thermal analysis was carried out on a Netzsch STA 449 C instrument in an Al_2O_3 crucible at a heating rate of 10 °C/min and at a flow rate of anhydrous synthetic air of 70 mL/min. Melting points were determined on a Kofler hot stage and are uncorrected.

Reaction of 2-Aminothiophenol (8) with Benzoyl Isothiocyanate (9a) in 1:1 Ratio

Compound **8** (36.3 g, 0.29 mol) was added dropwise to a solution of **9a** in anhydrous acetone (400 mL) prepared from NH_4SCN (40.1 g, 0.53 mol) and benzoyl chloride (67.5 g, 0.48 mol). The reaction mixture was stirred in an ice bath until a yellow solid precipitated. After filtration, the solid was dissolved in MeOH, insoluble residues were removed and the solution was evaporated to dryness to give pure 2-benzoylaminobenzothiazole (**5a**).

Yield: 39.6 g (54%); mp 188–190 °C (Lit.[4] 188 °C, Lit.[5] 189–190 °C).

IR (KBr): 3170 (ν, NH), 3057 (ν, ArH), 1673 (ν, C=O), 1599 (ν, CN), 1553 (δ, NH), 1445, 1296, 1277, 753 (γ, Ar), 702 (γ, Ar) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.23 (t, *J* = 7.4 Hz, 1 H, ArH), 7.38 (t, *J* = 7.4 Hz, 1 H, ArH), 7.49–7.61 (m, 3 H, ArH), 7.69 (d, *J* = 7.9 Hz, 1 H, ArH), 7.90 (d, *J* = 7.6 Hz, 1 H, ArH), 8.15–8.17 (m, 2 H, ArH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 119.55 (Ar), 121.24 (Ar), 122.47 (Ar), 125.43 (Ar), 128.15 (2 × Ar), 128.18 (2 × Ar), 131.71 (Ar), 131.86 (5-C), 134.28 (13-C), 148.84 (4-C), 161.88 (C=N), 167.36 (C=O).

MS (EI, 30 eV): *m*/*z* (%) = 77 (74), 105 (100), 226 (64), 254 (72) $[M]^+$.

Reaction of 8 with 9a in 1:2 Ratio Followed by Basic Hydrolysis

Freshly distilled **8** (5.0 g, 0.04 mol) was added dropwise to a solution of **9a** in anhydrous acetone (66 mL) prepared from NH_4SCN (11.7 g, 0.15 mol) and benzoyl chloride (19.7 g, 0.14 mol). The reaction mixture was stirred in an ice bath until a yellow solid precipitated. After filtration, the solid was dried in air to give the crude product (10.5 g).

The crude material obtained above (0.4 g) was added to 5% K_2CO_3 solution in 65% MeOH (10 mL). Under ultrasound activation, the yellow suspension turned pale. The solid was filtered off and identified as **5a**; the solution was treated with charcoal. After filtration, H_2O was added, MeOH was evaporated and other crystals were precipitated by AcOH. These were identical to 2-aminobenzothiazole (**5**) obtained by a basic hydrolysis of **5a** as follows:

5a (0.3 g, 1.2 mmol) was boiled with KOH (0.1 g, 1.3 mmol) in EtOH (15 mL) until only one compound was detected in the reaction mixture (TLC). H_2O was then added and EtOH was evaporated to give pure **5**, which was filtered off and dried at 40 °C under reduced pressure.

Yield: 0.1 g (56%); mp 126–129 °C (Lit.[6a] 126–128 °C, Lit.[6b] 129 °C).

IR (KBr): 3398 (ν, NH_2), 3060 (ν, ArH), 1643 (ν, CN), 1531, 1448, 1106, 1018, 743 (γ, Ar) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.00 (t, *J* = 7.6 Hz, 1 H, ArH), 7.20 (t, *J* = 7.6 Hz, 1 H, ArH), 7.33 (d, *J* = 7.9 Hz, 1 H, ArH), 7.63 (d, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 117.62 (Ar), 120.65 (2 × Ar), 125.24 (Ar), 130.86 (5-C), 152.71 (4-C), 166.30 (C=NH).

MS (EI, 30 eV): *m*/*z* (%) = 96 (40), 123 (29), 150 (100) $[M]^+$.

Reaction of 8 with Methoxycarbonyl Isothiocyanate 9d in 1:2 Ratio Followed by Basic Hydrolysis

Freshly distilled **8** (15.4 g, 0.12 mol) was added dropwise to a solution of **9d** in anhydrous acetone (200 mL) prepared from NH_4SCN (36.0 g, 0.47 mol) and methyl chloroformate (40.6 g, 0.43 mol). The reaction mixture was stirred in an ice bath until a pale solid precipitated. After filtration, the solid was washed with toluene and dried in air to give the crude product (15.1 g).

The crude material obtained above (0.4 g) was added to 5% K_2CO_3 solution in 65% MeOH (25 mL) and, under ultrasound activation, slowly disappeared (monitored by TLC). The solution was then evaporated to dryness, H_2O was added and the solid was extracted with CH_2Cl_2. The organic layer was dried with anhydrous Na_2SO_4 and evaporated to dryness to give pure **5** (0.14 g).

2,2′-Diaminodiphenyl Disulfide (10)

As 2-aminothiophenol **8** is quite sensitive to air oxygen, it was purified by a vacuum distillation (60–70 °C/1–2 mmHg) to give pure **10** as a yellow crystalline compound.

Mp 91–93 °C (Lit.[7a] 91–92 °C, Lit.[7b] 93 °C).

IR (KBr): 3381 (ν, NH_2), 3064 (ν, ArH), 1624 (ν, CN), 1473, 1306, 1246, 1155, 752 (γ, Ar), 700, 669 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.35 (s, 2 H, NH_2), 6.61 (t, *J* = 7.5 Hz, 1 H, ArH), 6.72 (d, *J* = 7.8 Hz, 1 H, ArH), 7.15–7.21 (m, 2 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 115.37 (Ar), 118.34 (Ar), 118.87 (CS), 131.72 (Ar), 136.92 (Ar), 148.77 (CN).

MS (EI, 30 eV): *m*/*z* (%) = 80 (54), 124 (100), 248 (46) $[M]^+$.

Reactions of 2,2′-Diaminodiphenyl Disulfide (10) with 9a

Method A (Table 1, entry 1): Compound **10** (2.0 g, 8.1 mmol) was added to a solution of **9a** in anhydrous acetone (15 mL) prepared from NH_4SCN (2.4 g, 31.5 mmol) and benzoyl chloride (4.0 g, 28.2 mmol). The reaction mixture was stirred in an ice bath until yellow crystals precipitated. After filtration, the crystals were dried in air to give pure **5a** (3.8 g, 93%).

Method B: The same quantities of reagents as described above were used. A solution of **9a** was added dropwise to **10** dissolved in anhydrous acetone (15 mL) under continuous stirring at –20 to –30 °C. The reaction mixture was then kept at –20 °C overnight. The precipitated pale solid was filtered off, thoroughly washed with acetone and dried in air to give pure 2-benzoylaminobenzo-1,2,4-dithiazine (**6a**).

Yield: 3.7–4.3 g (80–93%); mp 147–150 °C.

IR (KBr): 3411, 1674 (ν, C=O), 1574 (ν, CN), 1533 (δ, NH), 1333, 1252, 1147, 756 (γ, Ar), 704 (γ, Ar) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.31–7.36 (m, 1 H, ArH), 7.44–7.49 (m, 1 H, ArH), 7.54–7.59 (m, 2 H, ArH), 7.63–7.68 (m, 1 H, ArH), 7.79 (d, *J* = 7.9 Hz, 1 H, ArH), 8.00 (d, *J* = 7.6 Hz, 1 H, ArH), 8.12–8.15 (m, 2 H, ArH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 120.09 (Ar), 121.50 (Ar), 123.51 (Ar), 125.98 (Ar), 128.09 (2 × Ar), 128.43 (2 × Ar), 131.24

(6-C), 131.74 (14-C), 132.66 (Ar), 147.97 (5-C), 158.73 (C=N), 165.91 (C=O).

Method C: A solution of **9a** in anhydrous acetone (10 mL), prepared from NH_4SCN (1.2 g, 15.8 mmol) and benzoyl chloride (2.0 g, 14.1 mmol), was evaporated to dryness, partially dissolved in $CHCl_3$ (30 mL) and added dropwise to a solution of **10** (1.0 g, 4.0 mmol) in $CHCl_3$ (15 mL). The reaction mixture was immediately divided into two parts. One was allowed to react at r.t.; no heat evolution was observed. The second was briefly boiled. **6a** and **5a**, respectively, were obtained.

Method D (Table 1, entry 2): In contrast to the procedure described in Method C above, the solution of **10** was added dropwise to a suspension of **9a** in $CHCl_3$ (15 mL). The reaction mixture was stirred at r.t. until a yellow solid precipitated. After filtration, the solid was dried in air to give pure **5a** (0.82 g, 40%).

Reactions of 2,2′-Diaminodiphenyl Disulfide (10) with Phenyl Isothiocyanate (9b)

Method A (Table 1, entry 3): Compound **9b** (5.4 g, 40.3 mmol) was added dropwise to a solution of **10** (5.0 g, 20.2 mmol) in acetone (30 mL). The reaction mixture was stirred at r.t. until a colorless solid precipitated. After filtration, the solid was washed with acetone and dried in air to give pure 2-phenylaminobenzothiazole (**5b**).

Yield: 3.1 g (34%); mp 161–164 °C (Lit.[8a] 161 °C, Lit.[8b] 163 °C).

IR (KBr): 3190 (ν, NH), 3057 (ν, ArH), 1626 (ν, CN), 1569 (δ, NH), 1450, 1273, 1250, 1225, 746 (γ, Ar), 717 (γ, Ar) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 7.02 (t, *J* = 7.4 Hz, 1 H, ArH), 7.15 (t, *J* = 7.6 Hz, 1 H, ArH), 7.30–7.39 (m, 3 H, ArH), 7.60 (d, *J* = 8.0 Hz, 1 H, ArH), 7.79 (d, *J* = 7.7 Hz, 3 H, ArH), 10.44 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 117.76 (2 × Ar), 119.14 (Ar), 120.96 (Ar), 122.01 (Ar), 122.21 (Ar), 125.80 (Ar), 128.93 (2 × Ar), 129.93 (5-C), 140.59 (11-C), 152.05 (4-C), 161.55 (C=N).

MS (EI, 30 eV): *m*/*z* (%) = 96 (18), 225 (100) $[M - H]^+$, 226 (71) $[M]^+$, 227 (20) $[M + H]^+$.

Method B (Table 1, entry 4): Compound **10** (1.5 g, 6.1 mmol) in acetone (15 mL) and **9b** (3.3 g, 24.2 mmol) were used in the same procedure as described in Method A above to give pure **5b** (1.2 g, 44%).

Method C (Table 1, entry 5): Using the same quantities of **10** and **9b** as in Method A, a suspension in MeOH (60 mL) was prepared. Under stirring at r.t., Et_3N (0.7 g, 7.2 mmol) was added and, since no heat evolved, the reaction mixture was boiled for 2 h. When allowed to cool down, a solid precipitated within several hours. Pure **5b** (4.5 g, 49%) was obtained by filtration.

Method D (Table 1, entry 6): Similarly to Method C, **10** (1.5 g, 6.1 mmol) was boiled with **9b** (1.6 g, 12.1 mmol) in EtOH (10 mL) for 1 h. The solid precipitated by cooling was filtered off, washed with EtOH and dried in air to give pure **5b** (1.5 g, 55%).

Method E (Table 1, entry 7): Compounds **10** (1.0 g, 4.0 mmol) and **9b** (1.1 g, 8.1 mmol) were dissolved in $CHCl_3$ (15 mL). Since only starting materials were detected (TLC) in the reaction mixture after 2 d at r.t., Et_3N (0.8 g, 8.1 mmol) was added. The precipitated solid was filtered off and washed with $CHCl_3$ to give pure **5b** (0.4 g, 22%).

Method F (Table 1, entry 8): The procedure described in Method E was repeated without the addition of Et_3N. After 4 d, a solid precipitated (H_2S evolution was observed). After filtration, the solution was partially evaporated and the second crop crystallized. Both were washed with $CHCl_3$ to give pure **5b** (1.2 g, 66%).

Method G (Table 1, entry 9): The same quantities of **10** and **9b** as used in Method E were allowed to react in toluene (30 mL). After 5 d at r.t., a solid precipitated; only starting compounds were detected (TLC) in the reaction mixture. After filtration, the solid was washed with toluene to give pure **5b** (1.5 g, 82%).

Reactions of 2,2′-Diaminodiphenyl Disulfide (10) with Acetyl Isothiocyanate (9c)

Method A (Table 1, entry 10): A solution of **10** (0.3 g, 1.2 mmol) in anhydrous acetone (5 mL) was added to a solution of **9c** in anhydrous acetone (5 mL) prepared from NH_4SCN (0.35 g, 4.6 mmol) and acetyl chloride (0.3 g, 4.2 mmol). The reaction mixture was stirred at r.t. and a pale solid precipitated from the brown solution within 24 h. The solid was filtered off and dried in air to give pure 2-acetylaminobenzothiazole (**5c**).

Yield: 0.1 g (22%); mp 185–189 °C (Lit.[9a] 186 °C, Lit.[9b] 187–189 °C).

IR (KBr): 3062 (ν, ArH), 2960 (ν, CH_3), 2855, 1695 (ν, C=O), 1603 (ν, CN), 1548 (δ, NH), 1446, 1369, 1274, 758 (γ, Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (s, 3 H, CH_3), 7.35 (t, *J* = 7.4 Hz, 1 H, ArH), 7.46 (t, *J* = 7.4 Hz, 1 H, ArH), 7.77 (d, *J* = 7.9 Hz, 1 H, ArH), 7.85 (d, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.69 (CH_3), 120.38 (Ar), 121.90 (Ar), 124.33 (Ar), 126.68 (Ar), 131.92 (5-C), 147.48 (4-C), 160.32 (C=N), 169.11 (C=O).

MS (EI, 30 eV): *m*/*z* (%) = 43 (68), 150 (100), 192 (56) $[M]^+$.

Method B (Table 1, entry 11): A solution of **9c** in anhydrous acetone (10 mL), prepared from NH_4SCN (1.2 g, 15.8 mmol) and acetyl chloride (1.1 g, 14.1 mmol), was evaporated to dryness. The residue was partially dissolved in $CHCl_3$ (10 mL) and added dropwise to a solution of **10** (1.0 g, 4.0 mmol) in $CHCl_3$ (15 mL). The resulting suspension gradually dissolved under stirring at r.t. Within 48 h a solid crystallized (H_2S evolution was observed). The solid was removed and the solution was partially evaporated. The precipitated crystals were filtered off and dried in air to give pure **5c** (0.9 g, 59%).

Reactions of 2,2′-Diaminodiphenyl Disulfide (10) with Methoxycarbonyl Isothiocyanate (9d)

Method A (Table 1, entry 12): A solution of **10** (1.8 g, 7.3 mmol) in anhydrous acetone (10 mL) was added dropwise to a solution of **9d** in anhydrous acetone (15 mL), prepared from NH_4SCN (2.0 g, 26.6 mmol) and methyl chloroformate (2.3 g, 24.2 mmol), under stirring in an ice bath. The initially yellow solution turned gradually dark and a solid slowly precipitated. The solid was filtered off and dissolved in acetone. An insoluble colorless portion was removed and identified as 2,2′-di[(methoxycarbonylamino)carbonothioyl]aminodiphenyl disulfide (**11d**; 0.6 g, 17%). The acetone solution was partially evaporated; another colorless solid was filtered off and dried in air to give pure 2-methoxycarbonylaminobenzothiazole (**5d**; 0.3 g, 10%).

2,2′-Di[(methoxycarbonylamino)carbonothioyl]aminodiphenyl Disulfide (11d)

Mp 172–173 °C.

IR (KBr): 3044 (ν, ArH), 1728 (ν, C=O), 1577 (ν, CN), 1530 (δ, NH), 1405, 1342, 1238, 1175, 1038, 768 (γ, Ar) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 3.88 (s, 3 H, CH_3), 7.21 (t, *J* = 7.4 Hz, 1 H, ArH), 7.38 (t, *J* = 7.4 Hz, 1 H, ArH), 7.53 (d, *J* = 7.9 Hz, 1 H, ArH), 8.04 (d, *J* = 8.3 Hz, 1 H, ArH), 8.11 (s, 1 H, NH), 11.55 (s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 53.85 (CH_3), 126.59 (Ar), 127.84 (Ar), 129.77 (Ar), 131.37 (CS), 133.83 (Ar), 138.53 (CN), 153.02 (C=O), 178.49 (C=S).

2-Methoxycarbonylaminobenzothiazole (5d)
Mp 206–208 °C (sublimation) (Lit.[10] 210 °C).

IR (KBr): 2852 (ν, CH_3), 1730 (ν, C=O), 1610 (ν, CN), 1572 (δ, NH), 1452, 1302, 1279, 1250, 760 (γ, Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.97 (s, 3 H, CH_3), 7.33 (t, *J* = 7.1 Hz, 1 H, ArH), 7.47 (t, *J* = 7.3 Hz, 1 H, ArH), 7.82 (d, *J* = 7.9 Hz, 1 H, ArH), 7.89 (d, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.66 (CH_3), 120.48 (Ar), 121.55 (Ar), 124.13 (Ar), 126.55 (Ar), 131.44 (5-C), 147.89 (4-C), 154.27 (C=N), 161.72 (C=O).

MS (EI, 30 eV): *m/z* (%) = 59 (93), 64 (38), 77 (26), 96 (24), 105 (100), 108 (42), 122 (36), 136 (74), 149 (54), 176 (58), 208 (86) $[M]^+$.

Method B (Table 1, entry 13): A solution of **9d** in anhydrous acetone (10 mL), prepared from NH_4SCN (1.2 g, 15.8 mmol) and methyl chloroformate (1.3 g, 14.1 mmol), was evaporated to dryness. The residue was partially dissolved in $CHCl_3$ (10 mL) and added dropwise to a solution of **10** (1.0 g, 4.0 mmol) in $CHCl_3$ (15 mL). The resulting suspension gradually dissolved under stirring at r.t. A solid precipitated within 4 d (H_2S evolution was observed) was filtered off, washed with $CHCl_3$ and dried in air to give **5d** (0.8 g, 48%) containing unreacted isothiocyanate.

Reactions of 2,2′-Diaminodiphenyl Disulfide (10) with Methyl Isothiocyanate (9e)
Method A (Table 1, entry 14): A suspension of **10** (3.0 g, 12.1 mmol) in EtOH (30 mL) was treated with solid **9e** (1.8 g, 24.2 mmol). The reaction mixture was stirred at r.t.; a clear solution was formed within 48 h. Afterwards, sulfur (0.3 g) precipitated and was removed. The solution was partially evaporated; another solid crystallized and was filtered off, washed with EtOH and dried in air to give pure 2-methylaminobenzothiazole (**5e**).

Yield: 3.3 g (83%); mp 141–142 °C (Lit.[11a] 140–141 °C, Lit.[11b] 142–143 °C).

IR (KBr): 3061 (ν, ArH), 2867 (ν, CH_3), 1606 (ν, CN), 1572 (δ, NH), 1450, 1280, 1254, 1224, 752 (γ, Ar) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.10 (s, 3 H, CH_3), 7.09 (t, *J* = 7.6 Hz, 1 H, ArH), 7.31 (t, *J* = 7.6 Hz, 1 H, ArH), 7.53 (d, *J* = 7.9 Hz, 1 H, ArH), 7.61 (d, *J* = 7.9 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.84 (CH_3), 118.61 (Ar), 121.04 (Ar), 121.42 (Ar), 126.14 (Ar), 130.40 (5-C), 152.55 (4-C), 169.33 (C=N).

MS (EI, 30 eV): *m/z* (%) = 69 (31), 82 (24), 96 (28), 108 (35), 135 (66), 163 (51) $[M - H]^+$, 164 (100) $[M]^+$, 165 (31) $[M + H]^+$.

Method B (Table 1, entry 15): The same quantities of **10** and **9e** as used in Method A were allowed to react in $CHCl_3$ (30 mL). After several days at r.t., the solution was partially evaporated; precipitated crystals were filtered off and the solution was further evaporated to crystallize another solid. Both were washed with $CHCl_3$ and dried in air to give pure **5e** (1.4 g, 35%) and sulfur (0.2 g).

Acknowledgment

This work was supported by the Grant Agency of the Czech Republic (Grant No. 203/01/1333).

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