An Unexpected Result of the Reaction of Benzothioamide Derivatives with 2-Aryl-2-bromoacetonitriles

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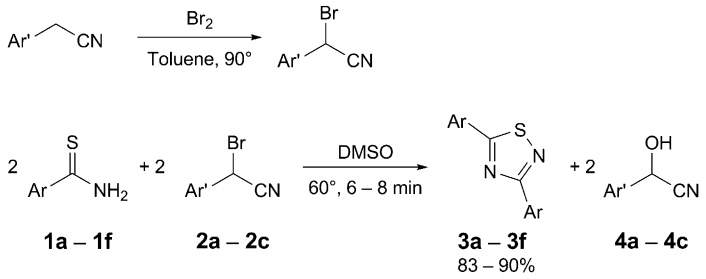
Unexpectedly, in the reaction of 2-bromo-2-phenylacetonitrile derivatives with 2 mol-equiv. of benzothioamide in DMSO, 3,5-diaryl-1,2,4-thiadiazoles were obtained in excellent yields (83–90%) and in short reaction times (5–10 min). It is found that, in DMF, a quite different reaction takes place and 2,5-diaryl-1,3-thiazol-4-amines are formed as the main products.

Introduction. – In continuation of our research in developing novel synthetic routes for the preparation of sulfur heterocycles using thioamides [1–14], we report here on unexpected and unprecedented results of the reaction of benzothioamide with 2-bromo-2-phenylacetamide derivatives in DMSO and/or DMF.

Results and Discussion. – It was found that a mixture of benzothioamides **1** and 2 mol-equiv. of an 2-bromo-2-phenylacetamide derivative **2** at 60° in DMSO leads to the corresponding 3,5-diaryl-1,2,4-thiadiazoles **3** in short time (6 min; *Scheme 1*) with an efficient conversion (83–90% yield).

Scheme 1

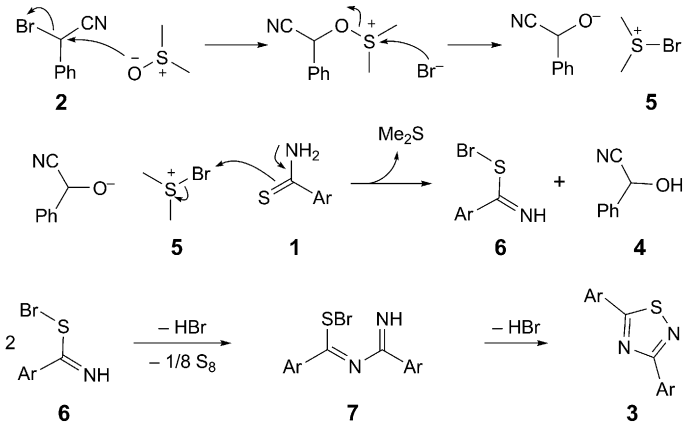


1a – 1f **2a – 2c** **3a – 3f** 83 – 90% **4a – 4c**

The study was started by examining the reaction of 3-bromobenzenecarbothioamide (**1a**) as a test substrate with 2-bromo-2-phenylacetonitrile (**2a**) in DMSO. Fortunately, the course of the reaction could be followed even visually. At the outset of the reaction, a yellow color is visible due to presence of the benzothioamide in the mixture. After 2 min heating at 60°, the mixture turns orange and then changes to red within a further 3 min heating. Finally, a rapid and exothermic reaction takes place within 1 min leading to the corresponding 3,5-bis(3-bromophenyl)-1,2,4-thiadiazole (**3a**) in 90% yield.

A mechanism for the reaction is proposed based on a report of *Takikawa et al.* [9] (*Scheme 2*). It seems that the bromo(dimethyl)sulfonium ion (**5**), formed by reaction of DMSO with **2**, is the active intermediate in the reaction. Meanwhile, benzothioamide **1** undergoes an *S*-bromination with this reactive intermediate to produce, after loss of Me_2S, **6**, which, after releasing HBr and sulfur affords the *S*-brominated compound **7**. Finally, this undergoes intermediate cyclization to the corresponding 3,5-diaryl-1,2,4-thiadiazole **3**, alongside elimination of HBr.

Scheme 2



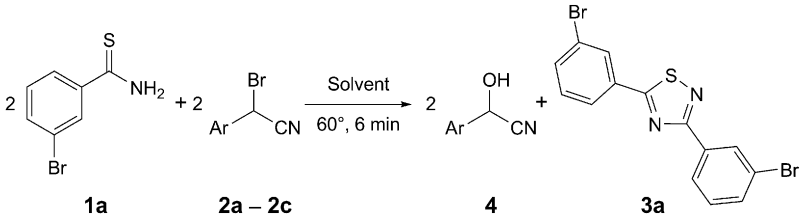
As shown, DMSO has a vital function in the course of the reaction because it plays the role as reagent and solvent. The proposed mechanism was supported by isolation of mandelonitrile as by-product. Fortunately, mandelonitrile was soluble in the reaction media, and the corresponding thiadiazole precipitated as fine crystals. To isolate the pure product, cold MeOH was added, and the mixture was filtered. Compounds **2** with three differently substituted phenyl groups were reacted with benzothioamide **1** to assess the effect of the substituents on the course of the reaction. The results are compiled in *Table 1*.

Six different benzothioamide derivatives, **1a**–**1f**, were probed to evaluate the scope of this new synthetic approach. The results are collected in *Table 2*.

Unexpectedly, a different result was obtained, when the reaction of 4-chlorobenzenecarbothioamide (**1g**) with 2-bromo-2-phenylacetonitrile (**2a**) was carried out in a small amount of DMF as solvent. In this case, the reaction proceeded at room temperature leading to 2-(4-chlorophenyl)-5-phenyl-1,3-thiazol-4-amine (**8a**) as the major product (84% yield). As shown in the mechanism proposed in *Scheme 3*, formation of compound **8a** can be attributed to a different pathway followed under this condition.

Conclusions. – In summary, an unexpected result of the reaction of benzothioamide derivatives with 2-bromo-2-phenylacetonitrile in different solvents was observed. The novel reaction could be successfully employed for the mild, rapid, and efficient conversion of benzothioamide derivatives to the corresponding thiadiazoles or thiazol-

Table 1. *Preparation of Compound* **3a** *from* **1a** *and* **2a**–**2c**.

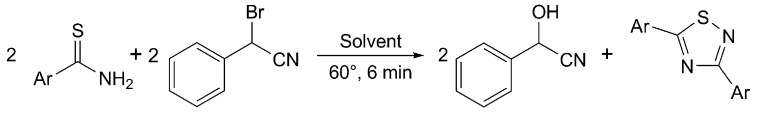


1a **2a – 2c** **4** **3a**

Entry	**2**	Ar	Solvent	Yield[a]) [%]
1	**2a**	Ph	DMSO	90
2	**2a**	Ph	Dioxane	16
3	**2b**	4-Cl–C_6H_4	DMSO	88
4	**2b**	4-Cl–C_6H_4	Dioxane	17
5	**2c**	4-NO_2–C_6H_4	DMSO	80
6	**2c**	4-NO_2–C_6H_4	Dioxane	12

[a]) Pure isolated products.

Table 2. *Oxidative Cyclization of Benzothioamides Using 2-Bromo-2-phenylacetonitrile* (**2a**)



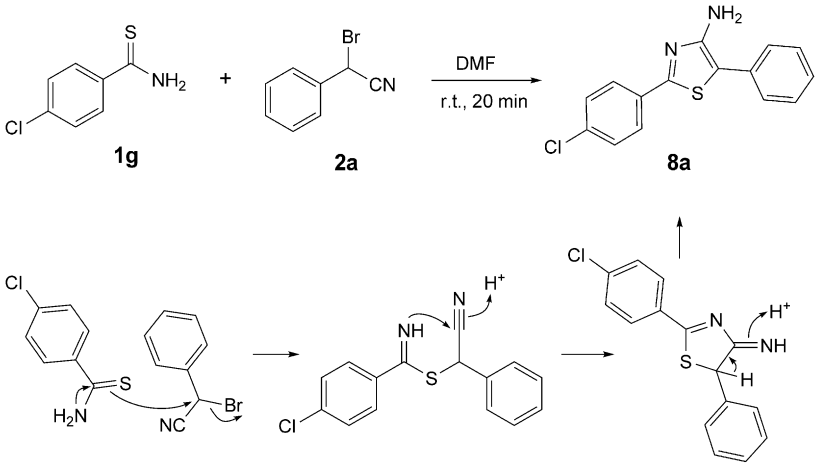
1a – 1f **2a** **4** **3a – 3f**

Entry	Ar	**1**	Time [min]	Product **3**[a])	Yield[b]) [%]
1	3-Br–C_6H_4	**1a**	6	**3a**	90
2	4-Br–C_6H_4	**1b**	6	**3b**	90
3	2-Cl–C_6H_4	**1c**	8	**3c**	88
4	3-Cl–C_6H_4	**1d**	7	**3d**	89
5	4-F–C_6H_4	**1e**	8	**3e**	83
6	2,4-Cl_2–C_6H_3	**1f**	8	**3f**	85

[a]) All products were characterized by ^{1}H- and ^{13}C-NMR spectroscopy. [b]) All yields refer to pure isolated products.

4-amines depending on the choice of solvent. The significance of the presented method lies in the simplicity of performing the reaction and the isolation of the product. To the best of our knowledge, the method also seems to be one of the simplest and the fastest routes for the preparation of 3,5-diaryl-1,2,4-thiadiazoles and/or 2,5-diarylthiazol-4-amines so far investigated.

Scheme 3



Experimental Part

General. All solvents were dried and distilled before use according to standard procedures. M.p.: in sealed capillaries; uncorrected. Anal. TLC: silica gel (SiO_2; *Merck 60 F_{254}*) coated on aluminum plates; visualization by UV and with aq. $KMnO_4$ soln. IR Spectra: *UR-20* spectrometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra in $CDCl_3$ and (D_6)DMSO on *Bruker AMX-500* spectrometers: δ in ppm rel. to Me_4Si as internal standard, J in Hz.

Caution: All experiments should be carried out in an efficient hood to avoid exposure to very unpleasant Me_2S vapors. All 2-bromo-2-phenylacetonitriles are highly lachrymatory, and skin-irritant compounds should be handled with great care.

General Procedure for the Preparation of 2-Bromo-2-phenylacetonitriles **2**. In a 100-ml round-bottom flask, phnelyacetonitrile derivative (50 mmol) in dry toluene (50 ml) was dissolved and heated to 90°. Thereafter, Br_2 (52 mmol, 8.32 g, 2.67 ml) was added dropwise during 20 min with vigorous stirring. Heating was continued for a further 40 min. Then, the mixture was cooled to r.t., washed with $NaHCO_3$ soln. (5%, 2 × 25 ml), and then with H_2O (2 × 50 ml). The org. phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure to obtain the 2-bromo-2-phenylacetronitrile derivative.

General Procedure for the Preparation of 3,5-Diaryl-1,2,4-thiadiazoles **3a**–**3e**. Benzothioamide **1** (3 mmol) and **2** (1.5 mmol) was dissolved in DMSO (1 ml) and heated at 60° for the times noted in *Table 2*. After completion of the reaction (TLC) and cooling to ambient temp., the mixture was poured into MeOH/H_2O 85:15 (4 ml), and the resulting crystals of the product were filtered, washed with MeOH/H_2O 1:1 (2 × 5 ml), and dried to obtain pure compound as white crystals.

General Procedure for the Preparation of 2,5-Diarylthiazol-4-amines **8**. Benzothioamide **1** (3 mmol) and **2** (3 mmol) were dissolved in DMF (1 ml) and stirred at r.t. for 20 min. Thereafter, the mixture was poured into H_2O (5 ml), and the crude precipitated product was filtered. The product was purified by crystallization from AcOEt/Et_2O to afford compound **8** as deep yellow crystals.

3,5-Bis(3-bromophenyl)-1,2,4-thiadiazole (**3a**). Yield: 533 mg (90%). White crystals. IR: 2941, 2857, 1581, 763. ^1H-NMR: 8.51 (*s*, 1 H); 8.32 (*d*, J = 8.7, 1 H); 8.21 (*s*, 1 H); 7.93 (*dd*, J = 8.4, 1.5, 1 H); 7.68 (*ddd*, J = 8.4, 1.5, 0.8, 1 H); 7.60–7.68 (*m*, 2 H); 7.35–7.42 (*m*, 2 H). ^{13}C-NMR: 186.8; 172.4; 134.9; 134.5; 133.4; 130.8; 130.3; 126.9; 126.1; 123.4; 122.9. Anal. calc. for $C_{14}H_8Br_2N_2S$ (396.10): C 42.45, H 2.04, N 7.07, S 8.10; found: C 42.28, H 1.99, N 7.15, S 8.31.

3,5-Bis(4-bromophenyl)-1,2,4-thiadiazole (**3b**). Yield: 534 mg (90%). White crystals. IR: 2985, 2843, 1593, 775. ^1H-NMR: 8.24 (*d*, J = 8.5, 2 H); 7.90 (*d*, J = 8.5, 2 H); 7.66 (*d*, J = 6.9, 2 H); 6.64 (*d*, J = 6.9,

2 H). ^{13}C-NMR: 187.2; 172.9; 132.8; 131.6; 129.8; 129.5; 128.8; 126.6; 125.1. Anal. calc. for $C_{14}H_8Br_2N_2S$ (396.10): C 42.45, H 2.04, N 7.07, S 8.10; found: C 42.30, H 2.01, N 7.10, S 8.25.

3,5-Bis(2-chlorophenyl)-1,2,4-thiadiazole (**3c**). Yield: 404 mg (88%). White crystals. IR: 2976, 2854, 1580, 784. ^{1}H-NMR: 7.40 – 7.42 (*m*, 2 H); 7.46 – 7.48 (*m*, 2 H); 7.55 – 7.60 (*m*, 2 H); 8.05 (*td*, *J* = 7.2, 2.2, 1 H); 8.65 (*td*, *J* = 7.2, 2.1, 1 H). ^{13}C-NMR: 126.8; 127.5; 129.6; 130.7; 130.8; 130.9; 132.1; 132.3; 133.3; 133.8; 173.2; 183.1. Anal. calc. for $C_{14}H_8Cl_2N_2S$ (307.20): C 54.74, H 2.62, N 9.12, S 10.44; found: C 54.51, H 2.45, N 9.05, S 10.55.

3,5-Bis(3-chlorophenyl)-1,2,4-thiadiazole (**3d**). Yield: 410 mg (89%). White crystals. IR: 2995, 2813, 1590, 751. ^{1}H-NMR: 7.43 – 7.49 (*m*, 3 H); 7.52 – 7.54 (*m*, 1 H); 7.90 (*d*, *J* = 7.6, 1 H); 8.07 (*s*, 1 H); 8.27 (*d*, *J* = 7.0, 1 H); 8.39 (*s*, 1 H). ^{13}C-NMR: 125.7; 126.4; 127.3; 128.5; 130.0; 130.6; 132.0; 132.1; 134.3; 134.8; 135.5; 172.5; 186.9; Anal. calc. for $C_{14}H_8Cl_2N_2S$ (307.20): C 54.74, H 2.62, N 9.12, S 10.44; found: C 54.60, H 2.51, N 9.10, S 10.61.

3,5-Bis(4-fluorophenyl)-1,2,4-thiadiazole (**3e**). Yield: 341 mg (83%). White crystals. IR: 2998, 2855, 1602, 771. ^{1}H-NMR: 7.16 – 7.24 (*m*, 4 H); 8.05 (*ddd*, *J* = 11.9, 5.2, 2.8, 2 H); 8.38 (*ddd*, *J* = 12.2, 6.7, 3.3, 2 H). ^{13}C-NMR: 115.7; 116.5; 129.6; 130.4; 163.2; 163.9; 165.2; 166.0; 172.8; 187.0. Anal. calc. for $C_{14}H_8F_2N_2S$ (274.29): C 61.30, H 2.94, N 10.21, S 11.69; found: C 61.21, H 2.80, N 10.02, S 11.80.

3,5-Bis(2,4-dichlorophenyl)-1,2,4-thiadiazole (**3f**). Yield: 478 mg (85%). White needles. IR: 2971, 2839, 1597, 769. ^{1}H-NMR: 7.40 (*dd*, *J* = 8.4, 2.1, 1 H); 7.47 (*dd*, *J* = 8.7, 2.1, 1 H); 7.58 (*d*, *J* = 2.1, 1 H); 7.62 (*d*, *J* = 2.1, 1 H); 8.04 (*d*, *J* = 8.4, 1 H); 8.57 (*d*, *J* = 8.7, 1 H). ^{13}C-NMR: 120.7; 127.2; 128.1; 130.3; 130.8; 131.4; 133.1; 134.2; 134.4; 136.3; 136.4; 138.0; 173.2; 182.3. Anal. calc. for $C_{14}H_6Cl_4N_2S$ (376.09): C 44.71, H 1.61, Cl 37.71, N 7.45, S 8.53; found: C 44.60, H 1.54, N 7.37, S 8.74.

2-(4-Chlorophenyl)-5-phenyl-1,3-thiazol-4-amine (**8a**). Yield: 695 mg (81%). Yellow crystals. IR: 3330, 3276, 3039, 1615, 825. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 7.85 – 7.87 (*d*, *J* = 8.4, 2 H); 7.53 – 7.55 (*m*, 4 H); 7.38 – 7.42 (*t*, *J* = 7.6, 2 H); 7.20 – 7.24 (*t*, *J* = 7.6, 1 H); 5.80 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 160.5; 154.3; 134.8; 132.8; 132.3; 129.7; 129.5; 127.4; 126.3; 126.1; 106.1. Anal. calc. for $C_{15}H_{11}ClN_2S$ (286.78): C 62.82, H 3.87, N 9.77, S 11.18; found: C 62.59, H 4.10, N 9.43, S 10.90.

5-(4-Chlorophenyl)-2-phenyl-1,3-thiazol-4-amine (**8b**). Yield: 720 mg (84%). Yellow crystals. IR: 3337, 3265, 3052, 1617, 761. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 7.85 – 7.87 (*m*, 2 H); 7.54 – 7.57 (*m*, 2 H); 7.45 – 7.50 (*m*, 5 H); 4.42 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 132.8; 132.3; 131.1; 129.8; 129.7; 129.5; 129.3; 128.0; 126.1. Anal. calc. for $C_{15}H_{11}ClN_2S$ (286.78): C 62.82, H 3.87, N 9.77, S 11.18; found: C 62.48, H 3.99, N 9.55, S 10.81.

2,5-Bis(4-chlorophenyl)-1,3-thiazol-4-amine (**8c**). Yield: 700 mg (73%). Yellow crystals. IR: 3424, 3341, 3018, 1596, 754. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 7.86 – 7.88 (*d*, *J* = 8.4, 2 H); 7.54 – 7.57 (*m*, 4 H); 7.45 – 7.48 (*d*, *J* = 8.4, 2 H); 6.62 (*s*, 2 H). ^{13}C-NMR (100 MHz, (D$_6$)DMSO): 162.3; 147.5; 135.5; 132.5; 131.6; 130.3; 129.9; 129.6; 129.5; 127.7; 114.2; Anal. calc. for $C_{15}H_{10}Cl_2N_2S$ (321.22): C 56.09, H 3.14, N 8.72, S 9.98; found: C 55.89, H 3.36, N 9.43, S 10.90.

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