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A new application of the "mild thiolation" concept for an efficient three-step synthesis of 2-cyanobenzothiazoles: a new approach to *Firefly*-luciferin precursors

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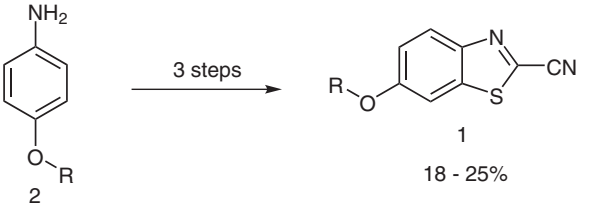
An easy, low cost and upscalable three-step synthesis of *Firefly* luciferin precursors is presented. The 6-alkoxy-2-cyano-benzothiazoles (**1**) were synthesized starting from easily available *O*-alkylated 4-aminophenoles (**2**) via a mild thiolation, Jacobsen cyclization and dehydratization sequence.



Keywords: sulfur; mild thiolation; luciferin; heterocycles; ethers

1. Introduction

2-Cyanobenzothiazoles (**1**) are important building blocks for natural products, functional dyes and innovative materials. *Firefly* luciferin (**3**), a natural product, is of outstanding importance in these areas. The substance was found in the beetle *Photinus pyralis* and is known to be a part of the most efficient chemiluminescence systems nowadays. For that reason, it plays a major role in applications used for medicinal diagnostics (*1*), biochemistry and forensic trace analysis (*2*) (Figure 1).

6-Methoxy-2-cyano-benzothiazole (**1a**) plays a key role as a precursor for preparations of **3**. The first synthesis starting from *p*-anisidine (**2a**) was published in 1961 (*3*). More than 30 years later, Toya *et al.* (*4*) presented a one-step access to **1a** which employed the commercially available 2-amino-6-methoxybenzothiazole (**4**) (Scheme 1). In subsequent years, a large number

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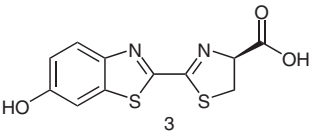
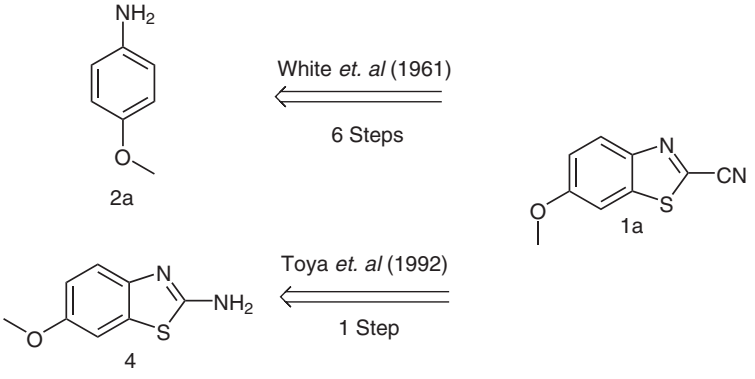


Figure 1. *Firefly*-luciferin.



Scheme 1. Classical synthesis of the precursor molecule (**1a**).

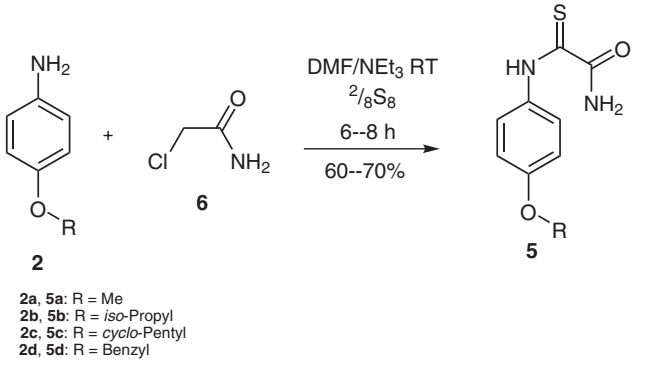
of modified protocols, mostly patents, were published (*5a*, *5b*). However, a new approach for the synthesis of the *Firefly* precursor (**1a**) remains desirable. This paper presents a substantially improved protocol for the synthesis of (**1a**) with a far superior "scalability" and more favorable cost basis. This new procedure is easily applicable not only in a research and teaching laboratory setting, but also in an industrial environment.

The synthesis presented here is related to the method used by Seto *et al.* (*6*). However, the advantage here lies in the formation of the thioamide (**5**) a simple, low cost, one-pot procedure. Whereas the established protocol uses the costly trichloroacetamide in a low yielding procedure with hydrogen sulfide to react with *p*-anisidine (**2a**), the new process takes advantage of the reaction of low-cost chloroacetamide (**6**) with elemental sulfur and base to afford the thioamide (**5**) in good yields (60–70 %). In larger-scale preparation, in the range of 100 g of **2a**, the yield of the Seto method is comparable (*7*) to ours. Nonetheless, with an increase in scale, there are clearly disadvantages in the Seto method when compared with the new procedure presented here.

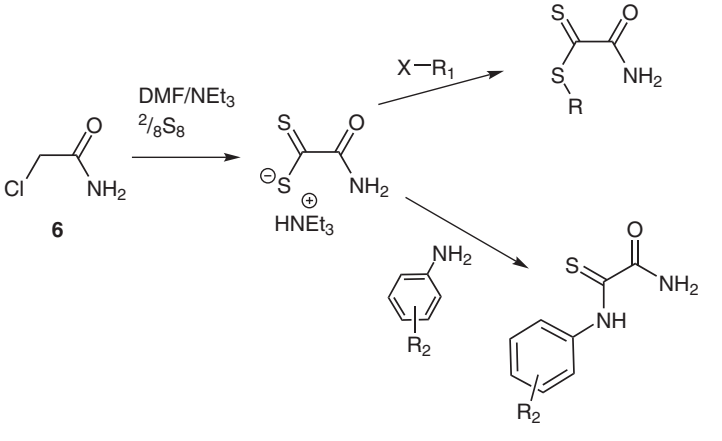
2. Results and discussion

O-Alkylated 4-aminophenols (**2**), which are commercially available or synthesized by simple alkylation reactions (*8*) (Scheme 2: R = Me, *i*-Prop, *cyclo*-pentyl, benzyl), are the starting point of the synthesis. They can easily be transformed with chloroacetamide (**6**) into thioamides (**5**). This procedure, known as "mild thiolation" (*9*), requires a CH-acidic substrate (**6**), elemental sulfur and a base. Working in a polar aprotic solvent (DMF, DMSO), the preactivated sulfur is able to selectively oxidize CH2 groups. Extensive investigations about the "mild thiolation" were the subject of papers in the 1980s (*10*). The authors showed that a mixture of sulfur and triethylamine in DMF is best suited for the oxidative conversion of CH-acidic compounds to their dithiocarboxylic acid derivatives under mild conditions. On the one hand, the triethylammonium salts of the corresponding dithiocarboxylic acid produced can be converted directly in

a one pot procedure to their alkyl dithiocarboxylates (*11*) via alkylation. On the other hand, the corresponding thioamides are formed if a primary or secondary amine is present (*12*) in the reaction mixture (Scheme 2). In our approach, using the amines of type **2**, the method allowed a direct route to a series of substituted thioxoacetamides (**5a**–**d**). From numerous test reactions, the combination of DMF and triethylamine were proven conditions for the planned transformations. Thus, the aminophenol ethers (**2a**–**d**) were converted in a smooth reaction (6–8 h, room temperature) to their corresponding thioamides (**5a**–**d**) (Scheme 3). According to the literature, changes in the substitutions pattern of the aromatic amine lead to adjustments in the reaction conditions (*10*).



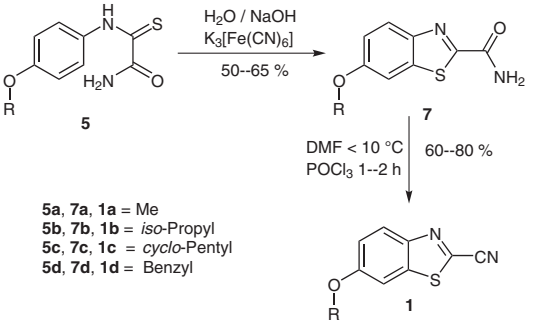
Scheme 2. The "mild thiolation" concept as one-pot reaction yielding thioamides (**5**).



Scheme 3. The "mild thiolation" concept in general.

A major advantage is that the thioamides (**5a**–**d**) can be cyclized to the corresponding benzothiazoles (**7a**–**d**) without further purification. The excess of sulfur that might still remain in the products can be completely filtered off by dissolving (**5a**–**d**) in a basic aqueous solution. The cyclization reaction was carried out with a basic aqueous solution of (**5**) and $K_3[Fe(CN)_6]$ (*13a*, *13b*). Test reactions showed that this reagents offers the best yields and, in addition, easy work up of the resulting products (Scheme 4).

The final dehydratization reaction of the amide was carried out under mild conditions (*14*) in dry DMF with $POCl_3$ below room temperature which leads to better yields of (**1**) than the previously used method (*6*). Attempts to introduce the nitril group prior to the "mild thiolation" step failed completely. Most likely, the *in situ* formed nucleophilic sulfur species attack



Scheme 4. Cyclization to benzothiazoles (**7**) and their dehydratization to the final products (**1**).

the nitrile group forming dithioxalicacid diamides (*15*) which could be detected by thin-layer chromatography (TLC).

The protection of the phenolic OH-group is of major importance in this synthetic approach. Although the OH-group remained unchanged during the thiolation reaction, a subsequent selective alkylation as well as an *ortho*-cyclization failed after the thioamide was formed. The commonly used methylether moiety needs harsh reaction conditions to get cleaved (*16*) so it is far from being an applicable protecting group. First results showed that other ways of cleaving the methyl ether also affect the nitrile group. Therefore, different ethers were considered as protecting groups. The literature shows (*17a*, *17b*) that these derivatives are cleaved easier while keeping nitrile groups in the molecule unchanged.

3. Conclusion

The "mild thiolation" of chloroacetamide (**6**) in the presence of an aminophenol ether (**2**) constitutes an easy way of preparing thioxalicacid amides (**5**). They can easily be cyclized to yield the corresponding alkoxy substituted benzothiazole (**7**) without further purification steps. The final dehydratization led to 2-cyano-6-alkoxy-benzothiazoles (**1**) in good yields and high purities. The synthetic approach shown here presents an easy and efficient way to produce *Firefly*-luciferin precursor molecules. In our opinion, the synthesis can easily be upscaled to 100 g approaches.

4. Experimental

All solvents were of ACS reagent grade or better unless otherwise noted. All reactions were carried out under atmospheric pressure without special need for an inert atmosphere. Unless otherwise stated, there was no special need to exclude moisture. The reagents were purchased from Sigma-Aldrich, Alfa Aesar or Roth. TLC was performed on glass plates coated with silica gel 60. Visualization was observed by UV light at 254 nm or 366 nm.

^{1}H and ^{13}C NMR spectra for all compounds were acquired in DMSO-d_6, $CDCl_3$ and acetone-d_6 on a Bruker AC 250 operating at (250 and 63 MHz, respectively). Chemical shifts (δ) are reported in parts per million (ppm) and referenced with the residual undeuterated solvent. The mass spectra were recorded on a MAZ 95 XL and an FINNIGAN MAT SSQ 710 with electron impact (EI) and on a Waters Acquity ultra-performance liquid chromatography (UPLC) coupled to a quadrapole time-of-flight micro-mass spectrometer (Waters) equipped with electrospray ionization (ESI) in a positive ion mode. Column: BEH C18 UPLC column (2.1 mm, 1.7 μm; Waters). All melting points were measured on a Galen III Boetius System and are uncorrected.

4.1. *General procedure for the preparation of thioamides (5a–d) starting from amines (2a–d) using the "mild thiolation" concept*

To a mixture of 0.5 mol of amine (**2**), 1 mol of sulfur (32.0 g) and 80 ml of triethylamine in 500 mL DMF, 0.55 mol (51.4 g) of chloroacetamide (**6**) was added slowly in a way that the temperature did not exceed 30°C. The reaction mixture was stirred for 8 h and poured into 5 l of water. After filtration, the product was obtained as a yellow powder with elemental sulfur impurities. The powder can be used for the next synthesis step without further purification. For analysis, a sample was taken up in a small portion of acetone filtered and evaporated *in vacuo*. Recrystallization gave the pure compounds in yields of 73–65%.

4.1.1. *2-(4-Methoxyphenylamino)-2-thioxoacetamide (**5a**)*

Yellow solid, m.p. 187–189°C (water–ethanol); yield 70%; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.76 (s, 3H, OCH_3); 6.97 (d, 2H, ArH); 7.89 (d, 2H, ArH); 8.08 (s, 1H, NH); 8.13 (s, 1H, NH); 12.01 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 55.8; 114.1; 125.2; 132.0; 158.0; 162.8; 185.3; MS (m/z, ESI): 211.055 [M + H]; $C_9H_{10}N_2SO_2$ (210.25); Calcd. C 51.41, H 4.79, N 13.32, S 15.25; found C 51.35, H 4.70, N 13.40, S 15.38.

4.1.2. *2-(4-iso-Propoxyphenylamino)-2-thioxoacetamide (**5b**)*

Yellow solid, m.p. 127–128°C (water–ethanol), yield 66%; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.25 (d, 6H, CH_3); 4.60 (hep, 1H, CH); 6.94 (d, 2H, ArH); 7.8–7.92 (m, 2H, ArH); 8.08 (s, 1H, NH); 8.13 (s, 1H, NH); 11.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ (ppm): 22.2; 69.9; 115.6; 125.1; 131.6; 156.3; 162.7; 184.8; MS (m/z, EI): 238 [M]; 196; 152 [Basepeak]; 120; 108; 94; 81; 65; $C_{11}H_{13}N_2SO_2$ (237.30); Calcd. C 55.68, H 5.52, N 11.81, S 13.51; found C 55.56, H 5.48, N 11.74, S 13.68.

4.1.3. *2-(4-Cyclopentyloxyphenylamino)-2-thioxoacetamide (**5c**)*

Yellow solid, m.p. 149–150°C (water–ethanol), yield 73%; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.5–1.75 (m, 6H, CH_2); 1.8–2.0 (m, 2H, CH_2); 4.75–4.85 (m, 1H, CH); 6.88–6.95 (m, 2H, ArH); 7.85–7.93 (m, 2H, ArH); 8.08 (s, 1H, NH); 8.13 (s, 1H, NH); 11.98 (s, 1H, NH);^{13}C NMR (DMSO-d_6) δ (ppm): 24.1; 32.7; 79.3; 115.4; 125.0; 131.5; 156.4; 162.6; 184.9; MS (m/z, EI): 265 [M+1]; 264 [M/Basepeak]; 263 [M–1]; 196; 195; 188; 152; 151; 126; 108; 69; 45; $C_{13}H_{16}N_2SO_2$ (264.34); Calcd. C 59.07, H 6.10, N 10.60, S 12.13; found C 58.98, H 6.08, N 10.54, S 12.38.

4.1.4. *2-(4-Benzyloxyphenylamino)-2-thioxoacetamide (**5d**)*

Yellow solid, m.p. 158–159°C (ethanol–acetone), yield 65%; ^{1}H NMR (DMSO-d_6) δ (ppm): 5.12 (s, 2H, CH_2); 7.05 (d, 2H, ArH); 7.2–7.5 (m, 5H, ArH); 7.90 (d, 2H, ArH); 8.1 (s, 1H, NH); 8.14 (s, 1H, NH); 12.02 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 69.9; 115.0; 125.1; 128.2; 128.3; 128.9; 132.1; 137.3; 157.1; 162.7; 185.3; MS (m/z, EI): 286 [M]; 285 [M–1]; 210; 195; 150; 122; 108; 91 [Basepeak]; 65; 45; $C_{15}H_{14}N_2SO_2$ (286.35); Calcd. C 62.92, H 4.93, N 9.78, S 11.20; found C 62.84, H 4.88, N 9.68, S 11.42.

4.2. *General procedure for the Jacobsen cyclization reaction of the thioamides (5a–d) yielding benzothiazoles (7a–d)*

Thioamide (20 mmol) was dissolved in the necessary amount of 10% NaOH. The mixture was filtered to obtain a sulfur-free yellow solution. This solution was added dropwise to 60 mmol (19.7 g) of $K_3[Fe(CN)_6]$ dissolved in 150 ml of water. After the addition, the reaction mixture was stirred for one additional hour. In the case of thioamide **5d**, the solution was heated to 60°C for 3 h. The formed precipitate was filtered off and washed with water until the filtrate was colorless. The pale yellow product was dried *in vacuo* and used for the next reaction step without further purification. For analysis, samples were recrystallized from ethanol–DMF.

4.2.1. *6-Methoxybenzothiazol-2-carboxamide (**7a**)*

White solid, m.p. 258°C (subl.), yield 65%; ^{1}H NMR (DMSO-d_6) δ (ppm): 3.86 (s, 3H, OCH_3); 7.20 (dd, 1H, ArH, $^3J = 9$ Hz, $^4J = 2.5$ Hz); 7.76 (d, 1H, ArH, $^3J = 2.5$ Hz); 7.99 (d, 1H, ArH, $^3J = 9$ Hz); 8.36 (s, 2H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 55.4; 104.3; 116.6; 124.2; 137.8; 146.8; 158.0; 161.0; 161.7; MS (m/z, ESI): 209.029 [M + H]. $C_9H_8N_2O_2S$ (208.24); Calcd. C 51.91; H 3.87; N 13.45; S 15.40; found C 51.88, H 3.77, N 13.50, S 15.25.

4.2.2. *6-iso-Propoxybenzothiazol-2-carboxamide (**7b**)*

White solid, m.p. >360°C (subl.), yield 63%; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.39 (d, 6H, CH_3, $^3J = 6.0$ Hz); 4.63 (m, 1H, CH, $^3J = 6.0$ Hz); 7.13 (dd, 1H, ArH, $^4J = 2.0$ Hz, $^3J = 9.0$ Hz); 7.37 (d, 1H, ArH, $^4J = 2.0$ Hz); 7.94 (d, 1H, ArH, $^3J = 9.0$ Hz). ^{13}C NMR (DMSO-d_6) δ (ppm): 21.9; 70.8; 106.0; 118.5; 125.1; 139.1; 147.3; 157.4; 160.0; 162.3; MS (m/z, ESI): 237.071 [M + H]. $C_{11}H_{12}N_2O_2S$ (236.29); Calcd. C 55.91; H 5.12; N 11.86; S 13.57; found C 55.88, H 5.07, N 13.60, S 13.29.

4.2.3. *6-cyclo-Pentyloxybenzothiazol-2-carboxamide (**7c**)*

White solid, m.p. >360°C (subl.), yield 63%; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.5–2.0 (m, 8H, CH_2); 4.89 (m, 1H, CH); 7.1–7.2 (m, 1H, ArH); 7.70 (s, 1H, ArH); 7.9–8.0 (m, 1H, ArH); 8.34 (s, 1H; NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 24.1; 32.7; 80.0; 106.8; 118.4; 125.1; 138.6; 147.4; 157.3; 161.9; 162.3; MS (m/z, ESI): 263.77 [M + H]. $C_{13}H_{14}N_2O_2S$ (262.33); Calcd. C 59.52; H 5.38; N 10.68; S 12.22; found C 59.46; H 5.20; N 10.50; S 12.30.

4.2.4. *6-Benzyloxybenzothiazol-2-carboxamide (**7d**)*

White solid, m.p. >360°C (subl.), yield 60%; ^{1}H NMR (DMSO-d_6) δ (ppm): 5.19 (s, 2H, CH_2); 7.24–7.5 (m, 6H, ArH); 7.84 (d, 1H, ArH, $^4J = 2.5$ Hz); 7.96 (s, 1H, NH); 7.99 (d, 1H, ArH, $^3J = 9$ Hz); 8.36 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ (ppm): 70.4; 106.4; 117.9; 125.2; 128.3; 128.5; 129.0; 137.0; 138.6; 147.8; 158.0; 161.9; 162.7; MS (m/z, EI): 285 [M + 1]; 284 [M]; 165; 122; 91 [Basepeak]; 65. $C_{15}H_{12}N_2O_2S$ (284.33); Calcd. C 63.36; H 4.25; N 9.85; S 11.28; found C 63.30; H 4.20; N 9.78; S 11.15.

4.3. *General method for converting amides (7a–d) into nitriles (1a–d)*

A solution of 21 mmol of amide (**7**) in 150 ml of DMF was cooled to 5°C. To this solution, 4 ml of $POCl_3$ were added dropwise keeping the temperature below 10°C. After all $POCl_3$ was added, the

mixture was stirred for 2 h while reaching room temperature. After the reaction was completed (monitored by TLC), the reaction mixture was poured into 500 ml of ice water. The precipitate formed was filtered off and washed with $NaHCO_3$ solution and water. The product was dried *in vacuo* and recrystallized to give white solids.

4.3.1. *6-Methoxybenzothiazol-2-carbonitrile (**1a**)*

White solid, m.p. 125°C (heptane), yield 65%; ^{1}H NMR (acetone-d_6) δ (ppm): 3.95 (s, 3H, OCH_3), 7.32 (dd, 1H, ArH, $^3J = 9.1$ Hz, $^4J = 2.5$ Hz); 7.78 (d, 1H, ArH, $^4J = 2.5$ Hz); 8.1 (d, 1H, ArH, $^3J = 9.1$ Hz). ^{13}C NMR (acetone-d_6) δ (ppm): 55.6; 103.7; 113.2; 118.6; 125.4; 133.5; 137.7; 146.8; 160.6; MS (m/z, ESI): 191.026 [M + 1]. $C_9H_6N_2OS$ (190.22); Calcd. C 56.83; H 3.18; N 14.73; S 16.86; found C 56.77; H 3.15; N 14.66; S 16.75.

4.3.2. *6-iso-Propoxybenzothiazol-2-carbonitrile (**1b**)*

White solid, m.p. 215°C subl., yield 60%; ^{1}H NMR (acetone-d_6) δ (ppm): 1.37 (d, 6H, CH_3, $J = 6$ Hz); 4.79 (m, 1H, CH, $J = 6$ Hz); 7.29 (dd, 1H, ArH, $^4J = 2.5$ Hz, $^3J = 9$ Hz); 7.78 (d, 1H, ArH, $^4J = 2.5$ Hz); 8.06 (d, 1H, ArH, $^3J = 9$ Hz). ^{13}C NMR (acetone d_6) δ (ppm): 21.1; 70.7; 105.5; 113.2; 119.6; 125.5; 133.3; 137.8; 146.6; 158.9; MS (m/z, EI): 218 [M]; 176 [Basepeak]; 147; 124; 96; 69; 43. $C_{11}H_{10}N_2OS$ (218.27); Calcd. C 60.53; H 4.62; N 12.83; S 14.69; found C 60.44; H 4.58; N 12.60; S 14.49.

4.3.3. *6-cyclo-Pentyloxybenzothiazol-2-carbonitrile (**1c**)*

White solid, m.p. 78–79°C (heptane), yield 60%; ^{1}H NMR (DMSO-d_6) δ (ppm): 1.62–2.10 (m, 8H, CH_2); 4.80–4.90 (m, 1H, CH); 7.19 (dd, 1H, ArH, $^4J = 2.5$ Hz, $^3J = 9$ Hz); 7.31 (d, 1H, ArH, $^4J = 2.5$ Hz); 8.05 (d, 1H, ArH, $^3J = 9$ Hz). ^{13}C NMR (DMSO-d_6) δ (ppm): 24.0; 32.8; 80.4; 104.6; 113.3; 119.5; 125.76; 132.9; 137.39; 146.5; 159.1; MS (m/z, ESI): 245.07 [M + H]. $C_{13}H_{12}N_2OS$ (244.31); Calcd. C 63.91; H 4.95; N 11.47; S 13.12; found C 63.85; H 4.90; N 11.28; S 12.99.

4.3.4. *6-Benzyloxybenzothiazol-2-carbonitrile (**1d**)*

White solid, m.p. 139–140°C (heptane), yield 80%; ^{1}H NMR (DMSO-d_6) δ (ppm): 5.18 (s, 2H, CH_2); 7.2–7.5 (m, 7H, ArH); 8.1 (d, 1H, ArH, $^3J = 9$ Hz). ^{13}C NMR (DMSO-d_6) δ (ppm): 70.8; 104.3; 113.2; 119.0; 125.9; 127.5; 128.4; 128.8; 133.5; 135.8; 137.4; 147.0; 159.5; MS (m/z, EI): 267 [M + 1]; 266 [M]; 92; 91; 65. $C_{15}H_{10}N_2OS$ (266.32); Calcd. C 67.65; H 3.78; N 10.52; S 12.04; found C 67.70; H 3.81; N 10.37; S 11.91.

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