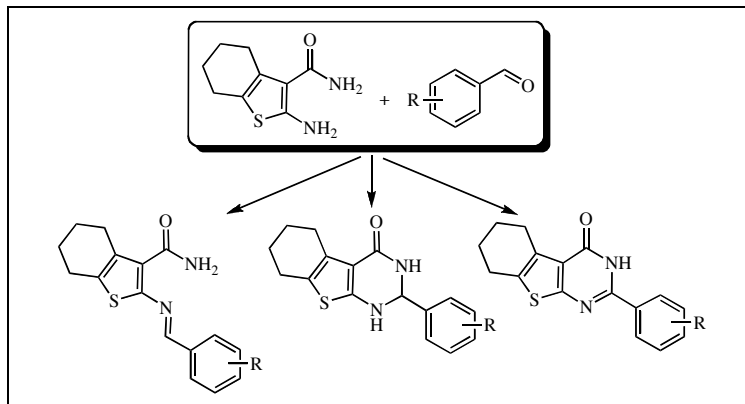


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Transformations of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (Gewald's amide) in the reactions with aromatic aldehydes were studied. Efficient methods for synthesis of three possible types of products: 2-aryl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one, 2-(1-arylmethylidene-amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide and 2-aryl-2,3,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one derivatives were developed. All the products were easily isolated by filtration in very good overall yields. Mutual transformations of these compounds were also studied.

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INTRODUCTION

Excellent synthetic methodology for a variety of substituted 2-aminothiophenes [1-8] has been developed by Gewald and co-workers [1-4]. Application of 2-cyanoacetamide in three-component Gewald reaction [6-9] leads to formation of 2-aminothiophene-3-carboxamides (Gewald's amide) which are 1,5-dinucleophiles applied for synthesis of diverse thieno[2,3-*d*]pyrimidine derivatives [10-19]. The last are known to possess anti-inflammatory, antibacterial, antifungal and antiviral activity [12,14,15]. In addition reactions of such vicinal amino-amides of various structure with aromatic aldehydes are known to lead to three types of products: Schiff bases **1** [20-22], dihydro-4(1*H*)-pyrimidinones **2** [23-27], and 4(3*H*)-pyrimidinones **3** [10-19,27] (Figure 1).

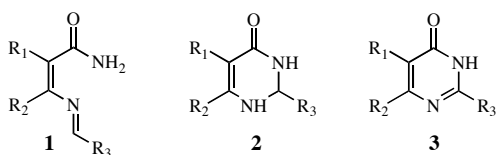


Figure 1.

However, for the case of 2-aminothiophene-3-carboxamides only one type of products **3** was described

[10-19], whereas Schiff bases of type **1** was only isolated as byproducts [22] and thieno[2,3-*d*]pyrimidines of type **2** were not described at all.

RESULTS AND DISCUSSION

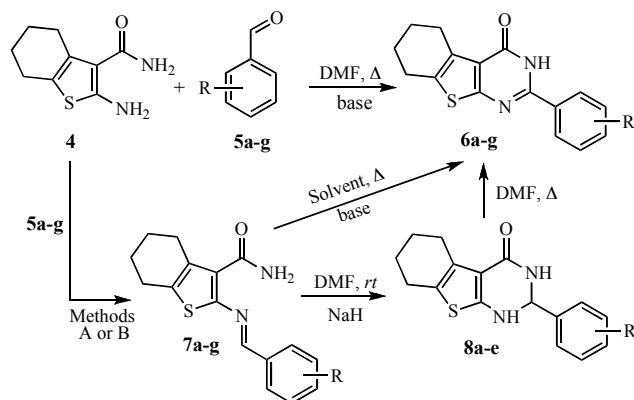
To clarify why not all types of possible products **1-3** are known in the literature we aimed to investigate reactivity of synthetically available 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide [7] **4** (Gewald's amide, Scheme 1) in reactions with aromatic aldehydes **5a-g**.

Heating of Gewald's amide **4** with aromatic aldehydes in ethanol in the presence of HCl [14,15] in our hands led to the desired products **6** in the mixture with byproducts and their purification decreased significantly the isolated yields. Variations of the reaction conditions showed that heating of the reaction mixture in DMF in the presence of piperidine led to the products **6a-g** in good yields and the purification stage was excluded (Scheme 1, Table 1).

During the variation of solvents it was found that refluxing of amino-amide **4** with aldehydes **5a-g** in toluene resulted in formation of Schiff bases **7a-g** in excellent yields (Method A, Table 1). Alternatively, the same compounds were formed in isopropyl alcohol in the presence of catalytic amounts of piperidine under controlled microwave irradiation [28] at 150°C for 5 min

(Method B, Table 1). Fortunately, application of Method B for the synthesis of azomethene **7b** ($R = 4\text{-CH}_3$) gave the desired product in the mixture with minority of derivative **8b**, which was observed in ^1H NMR spectrum of crude reaction product due to the presence of characteristic singlet of C-H of dihydro-4(1*H*)-pyrimidinone ring at 5.63 ppm. Thus, the compounds **8** unknown previously are stable enough and apparently can be isolated.

Scheme 1



Method A: toluene, Δ

Method B: MW 150⁰ C/5min, *i*-PrOH

Solvent: CH_2Cl_2 ; 1,4-dioxane; DMF; toluene.

R: **a** H; **b** 4- CH_3 ; **c** 4- OCH_3 ; **d** 4-Br; **e** 4- $\text{N}(\text{CH}_3)_2$; **f** 2-OH; **g** 4- NO_2

To find proper conditions for the preparative synthesis of compounds **8** we varied solvents and catalysts, time and temperature under microwave irradiation. However, high temperature, strong acidic or basic catalysts under microwave irradiation resulted in the increase of amounts of undesired products **6** in the final reaction mixtures even under inert atmosphere. Consequently, the desired 2-aryl-2,3,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-ones **8** were unstable under applied conditions and transformed into 2-aryl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-ones **6**. Therefore, we switch over to search after suitable conditions for transformation of azomethenes **7** into dihydro-4(1*H*)-pyrimidinones **8**.

The synthesis of derivatives **8a-e** (Scheme 1) was carried out successfully by dissolving of a mixture of azomethenes **7a-e** and sodium hydride in DMF at room temperature followed by dilution with water. Such heterocyclization into dihydro-4(1*H*)-pyrimidinone under the found conditions led to isolation of products **8a-e** in very good yields (Table 1). It should be noted that even mild heating of azomethenes **7a-e** with sodium hydride in the media of different solvents (DMF , 1,4-dioxane, CH_2Cl_2 , toluene) resulted in the formation of the dehydration products **6**. Furthermore, the same products **6** were also readily obtained from azomethenes **7** by refluxing in DMF in the presence of piperidine.

Table 1

Compound	R	Yields ^a , %
6a	H	65
6b	4- CH_3	75
6c	4- OCH_3	80
6d	4-Br	75
6e	4- $\text{N}(\text{CH}_3)_2$	69
6f	2-OH	72
6g	4- NO_2	76
7a	H	91 (95) ^b
7b	4- CH_3	98 (84)
7c	4- OCH_3	95 (95)
7d	4-Br	92 (95)
7e	4- $\text{N}(\text{CH}_3)_2$	89 (91)
7f	2-OH	92 (98)
7g	4- NO_2	98 (97)
8a	H	79
8b	4- CH_3	83
8c	4- OCH_3	86
8d	4-Br	75
8e	4- $\text{N}(\text{CH}_3)_2$	84

^aThe isolated yields.

^bThe yields are given for Method A (B).

Thus, the transformations indicated above show that azomethenes **7** and dihydro-4(1*H*)-pyrimidinone derivatives **8** are intermediates in the reaction pathway from Gewald's amide **4** and aromatic aldehydes **5** to the products of oxidative heterocyclization **6**. However, these intermediates are very unstable under reaction conditions applied for the synthesis of the compounds **6**. This fact, probably, rationalizes the lack of literature data about compounds **7** and **8**.

The structure of the obtained compounds **6-8** was identified by ^1H and ^{13}C NMR spectra. Signals of two NH protons of dihydropyrimidinone **8c** ($R = 4\text{-OCH}_3$) are observed at 7.46 and 7.68 ppm, whereas amide protons of azomethene **7c** are significantly non-equivalent and observed at 7.37 and 8.10 ppm. Chemical shifts of azomethene CH proton and CH proton of dihydro-4(1*H*)-pyrimidinone cycle also differ in values (8.43 ppm for **7c** and 5.63 ppm for **8c**). In ^{13}C NMR spectra carbon signals of these methene groups are also distinguished well (157.4 and 68.3 ppm for CH of **7c** and **8c** correspondingly). In CDCl_3 solution irradiation of this methene proton of derivative **8c** at 5.75 ppm gives a significant Nuclear Overhauser Effect (NOE) on both NH protons at 4.68 and 5.32 ppm, whereas in the case of Schiff base **7c** such NOE is not observed.

In conclusion, in the present work we have studied the transformations of Gewald's amide in the reactions with aromatic aldehydes leading to derivatives of 2-aryl-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one **6**, 2-(1-arylmethylideneamino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide **7** and 2-aryl-2,3,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-

one **8** in very good yields. It was found that azomethenes **7** and dihydro-4(1H)-pyrimidinones **8** were unstable under the conditions which were used for the reactions of Gewald's amides with aromatic aldehydes, however we succeeded in finding the reaction conditions for preparation and identification of these compounds. Thus, we proposed efficient protocols for the synthesis of all three possible products of the investigated reactions.

EXPERIMENTAL

General procedure for the synthesis of 2-aryl-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one derivatives (6). A mixture of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide **4** (2 mmol) and aromatic aldehyde **5** (2.2 mmol) was dissolved in 5 mL of DMF and 0.15 mL of piperidine was added. The reaction mixture was refluxed for 20 – 30 minutes. A yellow crystalline precipitate formed was collected by filtration and washed with ethanol. Yields are listed in Table 1.

Compound **6a**: mp 266–268 °C; ir (potassium bromide): 3401 (NH), 2932 ($\text{C}_{\text{sp}^3}\text{-H}$), 1657 (C=O) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.51–1.99 (m, 4H), 2.73 (s, 2H), 2.89 (s, 2H), 7.38–7.70 (m, 3H), 7.99–8.21 (m, 2H), 12.48 (bs, 1H, NH); *Anal.* Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{OS}$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.55; H, 5.71; N, 9.95.

6b: mp 272–274 °C; ir (potassium bromide): 3401 (NH), 2931 ($\text{C}_{\text{sp}^3}\text{-H}$), 1651 (C=O) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.59–1.91 (m, 4H), 2.36 (s, 3H), 2.74 (s, 2H), 2.89 (m, 2H), 7.31 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H), 12.38 (bs, 1H, NH); *Anal.* Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{OS}$: C, 68.42; H, 6.08; N, 9.39. Found: C, 68.40; H, 6.11; N, 9.37.

6c: mp 265–267 °C; ir (potassium bromide): 3402 (NH), 2930 ($\text{C}_{\text{sp}^3}\text{-H}$), 1648 (C=O) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.58–1.95 (m, 4H), 2.72 (m, 2H), 2.87 (m, 2H), 3.81 (s, 3H), 7.03 (d, J = 9.0 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H), 12.35 (bs, 1H, NH); ^{13}C nmr (125 MHz, DMSO-d_6): δ = 22.6 (CH_2), 23.7 (CH_2), 25.4 (CH_2), 26.4 (CH_2), 56.0 (OCH_3), 114.6, 115.1 (CH), 129.8, 130.8, 131.4 (CH), 136.8, 151.5, 157.4, 163.0, 165.6 (APT); ms (EI, 70 eV): m/z (%) 284 (16), 285 (7), 297 (7), 311 (12), 312 (M^+ , 100), 313 (23), 314 (7); *Anal.* Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.42; H, 5.21; N, 8.88.

6d: mp >300 °C; ir (potassium bromide): 3417 (NH), 2931 ($\text{C}_{\text{sp}^3}\text{-H}$), 1654 (C=O) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.66–1.91 (m, 4H), 2.75 (s, 2H), 2.90 (s, 2H), 7.71 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 12.52 (bs, 1H, NH); *Anal.* Calcd. for $\text{C}_{16}\text{H}_{15}\text{BrN}_2\text{OS}$: C, 52.90; H, 4.16; N, 7.71. Found: C, 53.02; H, 4.14; N, 7.71.

6e: mp 229–231 °C; ir (potassium bromide): 3405 (NH), 2938 ($\text{C}_{\text{sp}^3}\text{-H}$), 1650 (C=O) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.52–1.97 (m, 4H), 2.70 (s, 2H), 2.87 (s, 2H), 4.34 (s, 6H), 6.76 (d, J = 8.9 Hz, 2H), 8.02 (d, J = 8.9 Hz, 2H), 12.10 (bs, 1H, NH); *Anal.* Calcd. for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{OS}$: C, 66.02; H, 6.46; N, 12.83. Found: C, 66.11; H, 6.48; N, 12.85.

6f: mp >300 °C; ir (potassium bromide): 3416 (NH), 2940 ($\text{C}_{\text{sp}^3}\text{-H}$), 1655 (C=O), 1237 (C-O) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.50–1.99 (m, 4H), 2.74 (s, 2H), 2.88 (s, 2H), 6.82–7.09 (m, 2H), 7.39 (tr, J = 7.9 Hz, 1H), 8.10 (d, J = 8.1 Hz,

1H), 12.11 (bs, 1H, NH); *Anal.* Calcd. for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2\text{S}$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.95; H, 5.41; N, 9.35.

6g: mp >300 °C; ir (potassium bromide): 3401 (NH), 2930 ($\text{C}_{\text{sp}^3}\text{-H}$), 1653 (C=O), 1519 (NO_2^{as}), 1343 (NO_2^{s}), 848 ($\text{C}_{\text{ar}}\text{-N}$) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.56–1.97 (m, 4H), 2.74 (s, 2H), 2.89 (s, 2H), 8.28 (d, J = 9.2 Hz, 2H), 8.35 (d, J = 9.2 Hz, 2H), 12.05 (bs, 1H, NH); *Anal.* Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$: C, 58.34; H, 4.59; N, 12.76. Found: C, 58.39; H, 4.50; N, 12.77.

General procedure for the synthesis of 2-(1-arylmethylideneamino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide derivatives (7). *Method A*: The mixture of 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide **4** (2 mmol) and aromatic aldehyde **5** (2.2 mmol) in 5 mL of toluene was refluxed for 15 minutes. After the mixture was cooled the crystalline precipitate formed was filtered off and washed with ethanol (2x1 mL). *Method B*: The mixture of **4** (2 mmol) and aldehyde **5** (2.2 mmol), 0.15 mL of piperidine and 1.5 mL of isopropyl alcohol in a sealed Emrys process vial (for 0.5–2.5 mL of reaction mixture) was irradiated with microwaves at 150 °C for 5 min (for the experiments Emrys™ Creator EXP from Biotage, Uppsala was used, absorption was chosen as “Normal”, the reaction time as “Fixed hold time”, the maximal pressure inside the vial reached 8–10 bar). After the mixture was cooled a yellow crystalline precipitate formed was filtered off and washed with ethanol. Yields are listed in Table 1.

Compound **7a**: mp 176–178 °C; ir (potassium bromide): 3376 (NH), 3178 (NH), 2929 ($\text{C}_{\text{sp}^3}\text{-H}$), 1655 (C=O), 1599 (C=N) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.47–1.95 (m, 4H), 2.54–2.90 (m, 4H), 7.44 (s, 1H, NH_2), 7.46–7.65 (m, 3H), 7.78–7.96 (m, 2H), 8.01 (s, 1H, NH_2), 8.52 (s, 1H); *Anal.* Calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{OS}$: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.01; H, 4.89; N, 9.92.

7b: mp 184–186 °C; ir (potassium bromide): 3400 (NH), 3171 (NH), 2929 ($\text{C}_{\text{sp}^3}\text{-H}$), 1648 (C=O), 1609 (C=N) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.48–1.86 (m, 4H), 2.36 (s, 3H), 2.52–2.82 (m, 4H), 7.31 (d, J = 8.1 Hz, 2H), 7.39 (s, 1H, NH_2), 7.78 (d, J = 8.1 Hz, 2H), 8.05 (s, 1H, NH_2), 8.46 (s, 1H); *Anal.* Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{OS}$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.85; H, 5.52; N, 9.41.

7c: mp 160–162 °C; ir (potassium bromide): 3386 (NH), 3194 (NH), 2931 ($\text{C}_{\text{sp}^3}\text{-H}$), 1626 (C=O), 1600 (C=N) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.57–1.87 (m, 4H), 2.55–2.82 (m, 4H), 3.82 (s, 3H), 7.06 (d, J = 8.7 Hz, 2H), 7.37 (s, 1H, NH_2), 7.85 (d, J = 8.7 Hz, 2H), 8.10 (s, 1H, NH_2), 8.43 (s, 1H); ^1H nmr (200 MHz, deuteriochloroform): δ = 1.56–2.02 (m, 4H), 2.53–2.83 (m, 2H), 2.85–3.13 (m, 2H), 3.88 (s, 3H), 5.75 (bs, 1H, NH), 6.97 (d, J = 8.9 Hz, 2H), 7.74 (d, J = 8.9 Hz), 8.33 (s, 1H), 8.82 (bs, 1H, NH); ^{13}C nmr (125 MHz, DMSO-d_6): δ = 22.6 (CH_2), 23.1 (CH_2), 25.4 (CH_2), 26.4 (CH_2), 56.0 (OCH_3), 115.1 (CH), 128.4, 129.0, 130.8, 131.4 (CH), 136.3, 151.4, 157.4 (CH), 163.0, 165.5 (APT); ms (EI, 70 eV): m/z (%) 220 (9), 241 (11), 253 (6), 254 (6), 266 (12), 268 (13), 296 (28), 297 (72), 298 (12), 314 (M^+ , 100), 315 (20), 316 (8); *Anal.* Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$: C, 64.94; H, 5.77; N, 8.91. Found: C, 65.01; H, 5.85; N, 8.79.

7d: mp 250–252 °C; ir (potassium bromide): 3386 (NH), 3194 (NH), 2931 ($\text{C}_{\text{sp}^3}\text{-H}$), 1630 (C=O), 1600 (C=N), 816 (C-Br) cm^{-1} ; ^1H nmr (200 MHz, DMSO-d_6): δ = 1.53–1.93 (m, 4H), 2.55–2.82 (m, 4H), 7.41 (s, 1H, NH_2), 7.71 (d, J = 8.6 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H), 7.90 (s, 1H, NH_2), 8.48 (s, 1H); ^{13}C nmr (125 MHz, DMSO-d_6): δ = 22.5 (CH_2), 23.0 (CH_2), 25.4 (CH_2), 26.0 (CH_2), 125.9, 131.0, 131.4, 132.3, 132.4, 132.5, 132.7, 135.0, 156.3,

165.5; *Anal.* Calcd. for $C_{16}H_{13}BrN_2OS$: C, 53.20; H, 3.63; N, 7.75. Found: C, 53.24; H, 3.59; N, 7.73.

7e: mp 122-124 °C; ir (potassium bromide): 3380 (NH), 3171 (NH), 2920 (C_{sp^3} -H), 1639 (C=O), 1611 (C=N), 813 (C_{ar} -N) cm^{-1} ; 1H nmr (200 MHz, DMSO- d_6): δ = 1.48-1.92 (m, 4H), 2.57-2.87 (m, 4H), 3.02 (s, 6H), 6.78 (d, J = 9.0 Hz, 2H), 7.28 (s, 1H, NH_2), 7.70 (d, J = 8.7 Hz, 2H), 8.31 (s, 1H), 8.36 (s, 1H, NH_2); *Anal.* Calcd. for $C_{18}H_{19}N_3OS$: C, 66.43; H, 5.88; N, 12.91. Found: C, 66.39; H, 5.90; N, 12.91.

7f: mp 209-211 °C; ir (potassium bromide): 3404 (OH), 3311 (NH), 3245 (NH), 2934 (C_{sp^3} -H), 1640 (C=O), 1611 (C=N), 1575 (NH^{def}), 1434 (NH^{def}) cm^{-1} ; 1H nmr (200 MHz, DMSO- d_6): δ = 1.30-2.03 (m, 4H), 2.49-3.01 (m, 4H), 6.68-7.04 (m, 2H), 7.22-7.44 (m, 1H), 7.50 (s, 1H, NH_2), 7.66 (d, J = 7.9 Hz, 1H), 7.87 (s, 1H, NH_2), 8.63 (s, 1H), 11.79 (s, 1H, OH); *Anal.* Calcd. for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.46; H, 4.75; N, 9.35.

7i: mp 218-220 °C; ir (potassium bromide): 3380 (NH), 2928 (C_{sp^3} -H), 1644 (C=O), 1572 (C=N), 1516 (NO_2^{as}), 1338 (NO_2^s) cm^{-1} ; 1H nmr (200 MHz, DMSO- d_6): δ = 1.49-1.88 (m, 4H), 2.52-2.83 (m, 4H), 7.49 (s, 1H, NH_2), 7.81 (s, 1H, NH_2), 8.11 (d, J = 8.9 Hz, 2H), 8.32 (d, J = 8.9 Hz, 2H), 8.60 (s, 1H); *Anal.* Calcd. for $C_{16}H_{13}N_3O_3S$: C, 58.70; H, 4.00; N, 12.84; Found: C, 58.61; H, 3.96; N, 12.85.

General procedure for the synthesis of 2-aryl-2,3,5,6,7,8-hexahydro[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one (8). A mixture of 2-(1-arylmethylideneamino)-4,5,6,7-tetrahydrobenzo-*b*[1]thiophene-3-carboxamide **7** (2 mmol) and sodium hydride (4 mmol) was dissolved in 2 mL of DMF at room temperature. To the stirring reaction mixture 2 mL of water was poured. A yellow crystalline precipitate formed was filtered off and washed with ethanol (2x1 mL) and hexane (2x2 mL). Yields are listed in Table 1.

Compound **8a**: mp 148-150 °C; ir (potassium bromide): 3387 (NH), 3209 (NH), 2927 (C_{sp^3} -H), 2844 (C_{sp^3} -H), 1639 (C=O) cm^{-1} ; 1H nmr (200 MHz, DMSO- d_6): δ = 1.42-1.85 (m, 4H), 2.44 (s, 2H), 2.62 (s, 2H), 5.68 (s, 1H), 7.26-7.53 (m, 5H), 7.61 (s, 1H, NH), 7.81 (s, 1H, NH); *Anal.* Calcd. for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.51; H, 5.65; N, 9.87.

8b: mp 168-170 °C; ir (potassium bromide): 3375 (NH), 3213 (NH), 2929 (C_{sp^3} -H), 2838 (C_{sp^3} -H), 1634 (C=O) cm^{-1} ; 1H nmr (200 MHz, DMSO- d_6): δ = 1.51-1.86 (m, 4H); 2.44 (s, 2H); 2.64 (s, 2H); 2.28 (s, 3H); 5.63 (s, 3H); 7.16 (d, J = 8.3 Hz, 2H); 7.34 (d, J = 8.3 Hz, 2H); 7.52 (s, 1H, NH); 7.73 (s, 1H, NH); *Anal.* Calcd. for $C_{17}H_{18}N_2OS$: C, 68.42; H, 6.08; N, 9.39. Found: C, 68.37; H, 6.02; N, 9.39.

8c: mp 151-153 °C; ir (potassium bromide): 3344 (NH), 3249 (NH), 2930 (C_{sp^3} -H), 2834 (C_{sp^3} -H), 1629 (C=O) cm^{-1} ; 1H nmr (200 MHz, DMSO- d_6): δ = 1.49-1.83 (m, 4H), 2.45 (m, 2H), 2.64 (m, 2H), 3.73 (s, 3H), 5.63 (s, 1H), 6.92 (d, J = 8.8 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.46 (s, NH, 1H), 7.68 (s, NH, 1H); 1H nmr (200 MHz, deuteriochloroform): δ = 1.47-2.03 (m, 4H), 2.56 (m, 2H), 2.62-3.12 (m, 2H), 3.81 (s, 3H), 4.68 (s, 1H, NH), 5.32 (s, 1H, NH), 5.75 (s, 1H), 6.90 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H); ^{13}C nmr (125 MHz, DMSO- d_6): δ = 22.5 (CH_2), 23.5 (CH_2), 24.3 (CH_2), 25.9 (CH_2), 55.6 (OCH_3), 68.3 (CH), 110.7, 114.0 (CH), 119.4, 128.6 (CH), 132.3, 133.2, 157.0, 159.8, 162.9 (APT); ms (EI, 70 eV): m/z (%) 179 (15), 284 (6), 297 (54), 298 (14), 312 (13), 314 (M+, 100), 315 (31), 316 (8); *Anal.* Calcd. for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91. Found: C, 65.03; H, 5.81; N, 8.95.

8d: mp 186-188 °C; ir (potassium bromide): 3328 (NH), 3182 (NH), 2931 (C_{sp^3} -H), 2834 (C_{sp^3} -H), 1645 (C=O) cm^{-1} ; 1H nmr (200 MHz, DMSO- d_6): δ = 1.45-1.85 (m, 4H), 2.45 (s, 2H), 2.63 (s, 2H), 5.68 (s, 1H), 7.40 (d, J = 8.6 Hz, 2H), 7.57 (d, J = 8.6 Hz, 2H), 7.66 (s, 1H, NH), 7.82 (s, 1H, NH); ^{13}C nmr (125 MHz, DMSO- d_6): δ = 22.5 (CH_2), 23.4 (CH_2), 24.3 (CH_2), 25.9 (CH_2), 67.5 (CH), 110.9, 119.7, 121.9, 129.4, 131.6, 132.3, 141.2, 156.6, 162.6; *Anal.* Calcd. for $C_{16}H_{15}BrN_2OS$: C, 52.90; H, 4.16; N, 7.71. Found: C, 52.92; H, 4.11; N, 7.64.

8e: mp 176-178 °C; ir (potassium bromide): 3378 (NH), 3235 (NH), 2931 (C_{sp^3} -H), 2831 (C_{sp^3} -H), 1625 (C=O), 824 (C_{ar} -N) cm^{-1} ; 1H nmr (200 MHz, DMSO- d_6): δ = 1.51-1.84 (m, 4H); 2.44 (s, 2H); 2.64 (s, 2H); 2.87 (s, 6H); 5.56 (s, 1H); 6.69 (d, J = 9.0 Hz, 2H); 7.26 (d, J = 9.0 Hz, 2H); 7.32 (s, 1H, NH); 7.59 (s, 1H, NH); *Anal.* Calcd. for $C_{18}H_{21}N_3OS$: C, 66.02; H, 6.46; N, 12.83. Found: C, 65.95; H, 6.40; N, 12.86.

REFERENCES

- [1] Gewald, K. *Angew. Chem.* **1961**, 73, 114.
- [2] Gewald, K. *Chem. Ber.* **1965**, 98, 3571.
- [3] Gewald, K.; Schinke, E.; Bottcher, H. *Chem. Ber.* **1966**, 99, 94-98.
- [4] Gewald, K.; Schinke, E. *Chem. Ber.* **1966**, 99, 2712.
- [5] Peet, N. P.; Sunder, S.; Barbuch, R. J. *J. Heterocycl. Chem.* **1986**, 23, 129-134.
- [6] Gewald, K. *Chem. Heterocycl. Comp.* **1976**, 12(10), 1077-1090.
- [7] Sibor, J.; Pazdera, P. *Molecules* **1996**, 1, 157-162.
- [8] Sabnis, R. W.; Rangnekar, D. W.; Sonawane, N. D. *J. Heterocycl. Chem.* **1999**, 36, 333-345.
- [9] Eller, G. A.; Holzer, W. *Molecules* **2006**, 11, 371-376.
- [10] Sauter, F.; Stanetty, P.; Potuzak, H.; Baradar, M. *Monatsh. Chem.* **1976**, 107, 669-673.
- [11] Manhas, M. S.; Amin, S. G. *J. Heterocycl. Chem.* **1977**, 14, 161-164.
- [12] El-Sharief, A. M. Sh.; Micky, J. A. A.; Shmeiss, N. A. M. M.; El-Gharieb, G. *Phosphorus, Sulfur Silicon Relat. Elem.* **2003**, 178(3), 439-452.
- [13] Mohareb, R. M.; Sherif, S. M.; Gaber, H. M.; Ghabrial, S. S.; Aziz Susan, I. *Heteroat. Chem.* **2003**, 14(5), 459-467.
- [14] Wang, Y. D.; Johnson, S.; Powell, D.; McGinnis, J. P.; Miranda, M.; Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2005**, 15(16), 3763-3766.
- [15] Jennings, L. D.; Kincaid, S. L.; Wang, Y. D.; Krishnamurthy, G.; Beyer, C. F.; McGinnis, J. P.; Miranda, M.; Discafani, C. M. and Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2005**, 15(16), 4731-4735.
- [16] Sauter, F.; Jordis, U.; Froehlich, J.; Gewald, K.; Grohmann, F.; Ahmed, E. K. *Ach. Mod. Chem.* **1994**, 131(3-4), 489-498.
- [17] Arya, V. P. *Indian J. Chem.* **1972**, 10, 1141-1150.
- [18] Sharma, S. D.; Verinder, K.; Pradeep, S. *Indian J. Chem. Sect. B.* **1993**, 32(5), 517-525.
- [19] Shishoo, C. J.; Devani, M. B.; Ullas, G. V.; Ananthan, S.; Bhadi, V. S. *J. Heterocycl. Chem.* **1985**, 22, 825-830.
- [20] Coyne, W. E.; Cusic, J. W. *J. Med. Chem.* **1968**, 11(6), 1208-1213.
- [21] Abdel-Jalil, R. J.; Wolfgang, V.; Muhammad, S. *Tetrahedron Lett.* **2004**, 45(17), 3475-3476.
- [22] Ramanathan et al. *J. Indian Chem. Soc.* **1978**, 55, 822-823.
- [23] Moore, J. A.; Sytherland, G. J.; Sowerby, R.; Kelly, E. G.; Palermo, S.; Webster, W. *J. Org. Chem.* **1969**, 34(4), 887.
- [24] Yale, H.L.; Kalkstein, M. *J. Med. Chem.* **1967**, 10, 334-336.

- [25] Lessel, J. *Arch. Pharm.* **1994**, 327, 571-579.
- [26] Guoping, C.; Xiaoliang, X.; Zhifang, L.; William P. W.; Ping, L. *J. Heterocycl. Chem.* **2002**, 39, 1271-1272.
- [27] Dave, K. G.; Shishoo, G. J.; Devani, M. B.; Kalyanaraman, R.; Ananthan, S.; Ullas, G. V.; Bhadti, V. S. *J. Heterocycl. Chem.* **1980**, 17, 1497-1500.
- [28] Kappe, C. O.; Stadler, A. *Microwaves in organic and medical chemistry* In Mannhold, R.; Kubinyi, H.; Folkers, G. (Eds.) *Methods and Principles in Medical Chemistry*, Vol. 25, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2005.