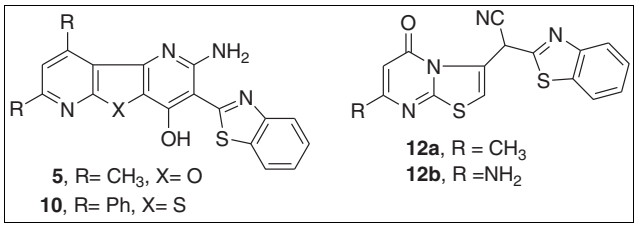
Synthesis of Some New Pyridine and Pyrimidine Derivatives Containing Benzothiazole Moiety

Khaled S. Mohamed,[1] Nayra M. Abdulaziz,[2] and Ahmed A. Fadda[2]*

[1]Engineering Chemistry Department, Higher Institute for Engineering and Technology New Damietta, Egypt
[2]Chemistry Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt
*E-mail: afadda2@yahoo.com

Received October 26, 2011
DOI 10.1002/jhet.1672
Published online in Wiley Online Library (wileyonlinelibrary.com).



A variety of pyridine and pyrimidine rings incorporating benzothiazole moiety were synthesized by reaction of 1-(2-benzothiazolyl)-1-cyano-3-chloroacetone (**1**) with 2-pyridone, 2-thioxopyridine, thiouracil, and 2-thioxopyrimidine derivatives to give compounds 7,9-dimethylfuro[2,3-*b*:4,5-*b*′]dipyridin-4-ol **5**, 4, 6-diphenylthieno[2,3-*b*]pyridin-2-yl **9**, 2-(benzo[*d*]thiazol-2-yl)-2-(7-substituted-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl)acetonitriles **12a** and **b**, pyrimido[2,1-*b*][1,3]thiazepine-3-carboxamide **15**, and benzo[4,5]thiazolo [3,2-*b*]pyridazine-3-one **20**, respectively.

J. Heterocyclic Chem., **50**, 645 (2013).

INTRODUCTION

Synthetic potentiality, as well as the reported biological activity of 2-thioxopyridine [1–3], thieno[2,3-*b*]pyridine [4,5], and pyridothienopyrimidines [6,7], stimulated our interest to synthesize and characterize several derivatives of these ring systems required for several chemical transformation as well as medicinal chemistry programs. In this article, we are interested in the synthesis of 2-(benzo[*d*] thiazol-2-yl)-4-chloro-3-oxobutanenitrile (**1**) as well as to investigate its synthetic potentiality with several reagents to achieve our target.

In recent decades, there has been constant interest in the chemistry of azoles containing benzothiazole fragments as substituents [8]. Among compounds of this type of substances with high and varied biological activity materials [9–15] and a wide spectrum of practical qualities have been found (polymethine dyes, stabilizers of polymeric natural materials), for example, the alkaloid luciferin [2-(2-benzothiazolyl)-Δ^2-thiazoline-4-carboxylic acid] [16].

RESULTS AND DISCUSSION

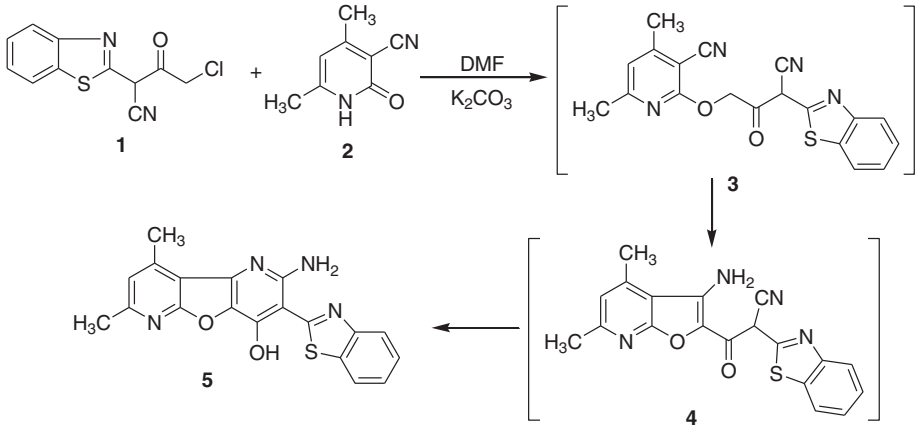
As a continuation of our previous program aimed to synthesize new derivatives of benzothiazole [17–22], the synthesis of substituted fused pyridine ring containing benzothiazole moiety is outlined in Scheme 1.

The corresponding compound **5** was synthesized in good yields by reacting compound **1** with 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**2**) in refluxing dimethylformamide (DMF) in the presence of potassium carbonate as catalyst, instead of the formation of the expected product 3-(3-amino-4,6-dimethylfuro[2,3-*b*]pyridin-2-yl)-2-(benzo[*d*]thiazol-2-yl)-3-oxopropane-nitrile (**4**). The IR spectrum of **5** showed no absorption band in the region between 2000 and 2250 cm^{-1} because of cyano group, and instead, the newly formed NH_2 group has appeared; thus, we can conclude that (CN) group was involved in cyclization step to afford directly compound **5** (Scheme 1). The ^1H NMR showed the presence of two singlet signals at δ 2.54 and 2.68 ppm because of two methyl groups, and no any signals at the region δ 4.0–5.5 ppm because of CH protons; also, the ^1H NMR showed two singlet signals D_2O-exchangeable proton observed at δ 5.89 and δ 6.95 ppm because of OH and NH_2, respectively, besides multiplet at δ 7.0–8.35 ppm because of five aromatic protons. The mass spectrum of **5** showed the molecular ion peak at *m*/*z* 362 (M^+, 13%) that corresponds to the molecular formula $C_{19}H_{14}N_4O_2S$ of the assigned structure. (Schemes 2–5)

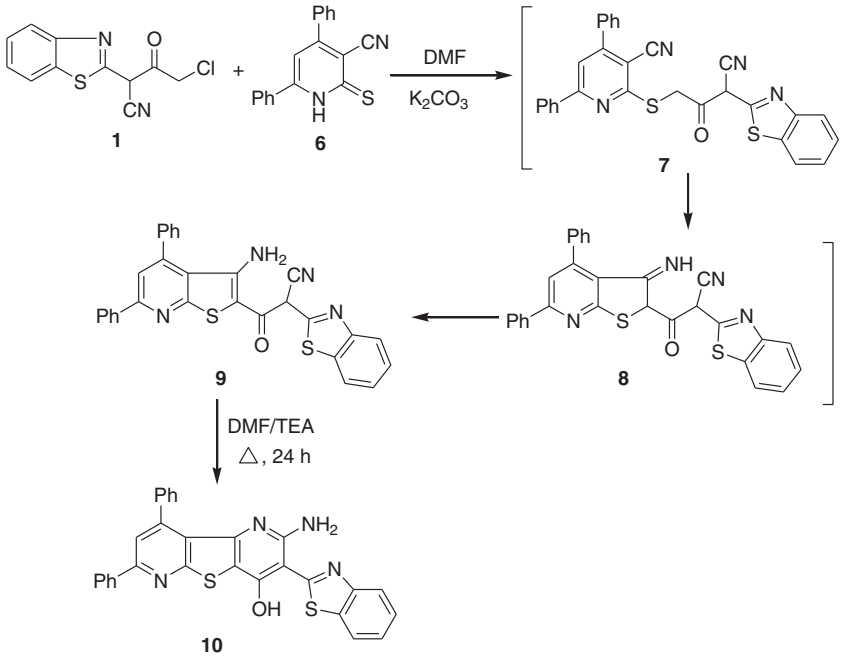
Moreover, it has been found that compound **1** reacted with 4,6-diphenyl-2-thioxo-1,2-dihydropyridine-3-carbonitrile (**6**) in refluxing DMF in the presence of potassium carbonate via the dehydrochlorination followed by cyclization to afford the imino intermediate **8**, which spontaneously aromatized to give the reaction product 3-(3-amino-4,6-diphenylthieno[2,3-*b*] pyridin-2-yl)-2-(benzo[*d*]thiazol-2-yl)-3-oxopropanenitrile (**9**).

The structure of product **9** was established on the basis of their elemental analyses and spectral data (IR, ^1H NMR, and MS). For example, the IR spectrum of compound **9** showed a stretching band at 1658 (C═O), 2205 cm^{-1} (CN), in addition to characteristic bands at 3298 and 3356 cm^{-1} (NH_2). Its ^1H

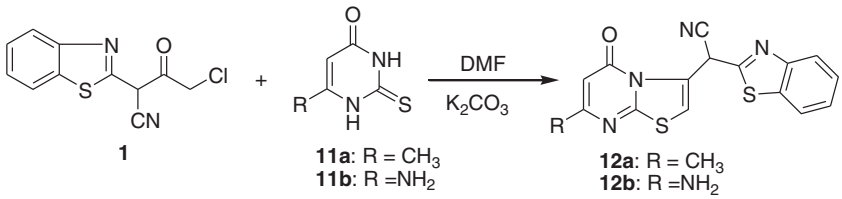
Scheme 1. Synthesis of 7,9-dimethylfuro[2,3-*b*:4,5-*b*′]dipyridin-4-ol **5**.



Scheme 2. Synthesis of 7,9-diphenylthieno[2,3-*b*:4,5-*b*′]dipyridin-4-ol **10**.



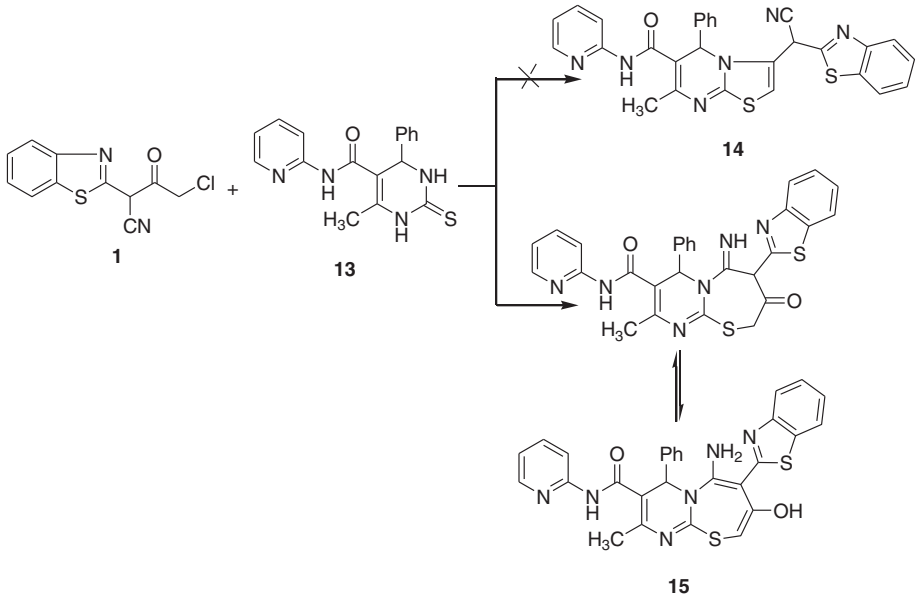
Scheme 3. Synthesis of 2-(benzo[*d*]thiazol-2-yl)-2-(7-substituted-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl)acetonitriles **12a** and **b**.



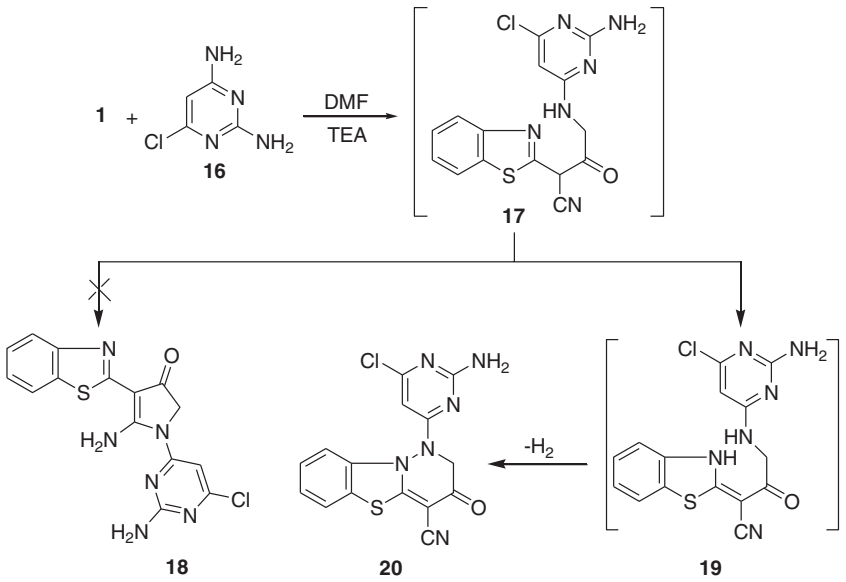
NMR spectrum revealed a singlet at δ 4.88 assignable to the CH proton, broad singlet at δ 5.96, which disappeared upon deuterium exchange, assignable to the NH_2 proton, in addition to the typical signals of the aromatic protons. The mass spectrum of **9** also showed the molecular ion peak at *m*/*z* 502 that gave an additional evidence for the structure elucidation.

Heating of compound **9** in refluxing dry DMF containing a catalytic amount of TEA for further 24 h afforded the

Scheme 4. Synthesis of pyrimido[2,1-*b*][1,3]thiazepine-3-carboxamide **15**.



Scheme 5. Synthesis of benzo[4,5]thiazolo[3,2-*b*]pyridazine-3-one **20**.



corresponding 4,6-diphenylthieno[2,3-*b*]pyridine derivative **10** (Scheme 2). The IR spectrum of **10** showed no absorption band around the region 2000–2250 cm^{-1} because of cyano group, indicating that this group was involved in the cyclization reaction.

The wide applications of diazine compounds as chemotherapeutic agents [23] aroused our interest to synthesize some derivatives of 6-methyl-2-thiouracil (**11a**) and 6-amino-2-thiouracil (**11b**) that might have biological activity as antitumor or antithyroid agents.

Thus, reactions of **1** with **11a** and **11b** in refluxing dimethylformamide in the presence of potassium carbonate led to formation of *S*-alkylated product that cyclized rapidly, through the loss of one molecule of water, to give 2-(benzo[*d*]thiazol-2-yl)-2-(7-methyl-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl)acetonitrile (**12a**) and 2-(7-amino-5-oxo-5*H*-thiazolo[3,2-*a*]pyrimidin-3-yl)-2-(benzo[*d*]thiazol-2-yl) acetonitrile (**12b**) (Scheme 3).

Confirmation of the formation of thiazolo[3,2-*a*]pyrimidine ring in compounds **12a** and **12b** was suggested on the basis of

their IR, ^{1}H NMR, and mass spectra. The IR spectra of compounds **12a** and **12b** revealed the absence of any absorption bands in the region 3050–3350 cm^{-1} belonging to NH group and also the presence of absorption bands in the region ≈1690 cm^{-1} because of stretching vibrations of the exocyclic carbonyl group. The ^{1}H NMR spectrum of **12a** revealed multiplet signals at the lowest field region at δ 7.53–8.18 ppm corresponding to protons of benzothiazole moiety and the proton at C_2 of thiazole ring at δ 6.30 ppm, a singlet signal at δ 6.17 ppm corresponding to proton in position **6**, singlet signal at δ 4.46 ppm because of methine proton, and singlet signal at δ 2.23 ppm because of methyl group.

On the other hand, treatment of **1** with 6-methyl-4-phenyl-*N*-(pyridin-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**13**) in boiling dimethylformamide in the presence of anhydrous potassium carbonate afforded the unexpected structure 7-(benzo[*d*]thiazol-2-yl)-6-imino-2-methyl-8-oxo-4-phenyl-*N*-(pyridin-2-yl)-6,7,8,9-tetrahydro-4*H*-pyrimido[2,1-*b*][1,3] thiazepine-3-carboxamide (**15**) instead of the expected product 3-(benzo[*d*]thiazol-2-yl (cyano) methyl)-7-methyl-5-phenyl-*N*-(pyridin-2-yl)-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carbox-amide (**14**) (Scheme 4).

The correct structure of **15** was deduced from elemental analysis and spectral data. The IR spectrum is in agreement with the proposed structure and reveals no absorption band in the region of 2000–2250 cm^{-1}, which confirms that cyano group was involved in cyclization process and also the presence of absorption bands at 3208, 3300, and 3430 cm^{-1} for NH and NH_2, respectively, and two absorption bands at 1685 and 1705 cm^{-1} because of two carbonyl groups. The ^{1}H NMR spectrum structure **15** reveals a singlet signal at δ 2.34 assignable to the CH_3 protons, singlet signal at δ 4.24 because of CH_2 protons, singlet signal at δ 5.36 ppm because of CH proton in pyrimidine ring, singlet signal at δ 6.44 ppm because of NH_2 protons, broad singlet at δ 8.99 ppm that disappears upon deuterium exchange, assignable to the NH proton, in addition to aromatic protons at δ 7.20–8.40 ppm.

Reaction of **1** with 6-chloropyrimidine-2,4-diamine (**16**) in refluxing dimethylformamide in the presence of catalytic amount of triethylamine resulted in the formation of 1-(2-amino-6-chloropyrimidin-4-yl)-4-cyano-2,3-dihydro-1*H*-benzo[4,5]thiazolo[3,2-*b*]pyridazine-3-one (**20**) (Scheme 5).

Structure **18** was excluded because the IR spectrum revealed stretching frequency of CN at 2189 cm^{-1}. Moreover, the mass spectrum of **20** showed the molecular ion peak at *m/z* 355 ($M^+ - 1$) that agree with the molecular formula $C_{15}H_9ClN_6O_S$ of the assigned structure. Considering the aforementioned data as well as ^{1}H NMR and elemental analysis, structure **20** can be formulated as 1-(2-amino-6-chloropyrimidin-4-yl)-4-cyano-2,3-dihydro-1*H*-benzo[4,5] thiazolo [3,2-*b*]pyridazine-3-one (cf. Experimental section).

EXPERIMENTAL

Melting points were recorded on Gallenkamp electric melting point apparatus (Electronic Melting Point Apparatus, Great Britain, London) and are uncorrected. Infrared spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer (Thermoelectron CO. Egelsbach, Germany) using a KBr wafer technique. The ^{1}H NMR spectra were determined on Varian Gemini 200 MHz (Varian CO., Fort Collins, USA). DMSO-$d_6$was used as solvent, TMS was used as internal standard and chemical shifts were measured in δ ppm. Mass spectra were determined on a GC-MS.QP-100 EX Shimadzu (Japan). Elemental analyses were recorded on Perkin-Elmer 2400 Elemental analyzer at the Microanalytical Center at Cairo University, Cairo, Egypt.

General procedure of the synthesis of 5, 9, 12a, b, and 15. A mixture of **1** (2.5 g, 0.01 mol) and compounds **2** or **6** or **11a** or **11b** or **13** (0.01 mol), respectively, was refluxed in dimethylformamide containing a catalytic amount of potassium carbonate for 8–12 h (TLC controlled). The reaction mixture then was poured onto ice cold water (100 mL) and neutralized with dilute hydrochloric acid. The solid product was collected by filtration, washed with water, and recrystallized from DMF/EtOH mixture to give the corresponding **5**, **9**, **12a**,**b**, and **15**, respectively.

2-Amino-3-(2-benzothiazolyl)-7,9-dimethylfuro[2,3-b:4,5-b′]dipyridin-4-ol (5). Brown crystals; yield (77%); mp >300°C; IR (KBr): ν_{max}, cm^{-1}: 3401, 3388 (NH_2), 3649 (br, OH); ^{1}H NMR (DMSO-d_6): δ 2.54 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 5.89 (s, 1H, OH), 6.95 (s, 2H, NH_2), 7.0–8.35 (m, 5H, aromatic protons); MS: *m/z* 362 (M^+, 13%). *Anal*. Calcd for $C_{19}H_{14}N_4O_2S$ (362.41): C, 62.97; H, 3.89; N, 15.46; S, 8.85%. Found: C, 62.93; H, 3.93; N, 15.49; S, 8.87%.

3-(3-Amino-4,6-diphenylthieno[2,3-b]pyridin-2-yl)-2-(benzo[d]thiazol-2-yl)-3-oxopropane-nitrile (9). Dark brown crystals; yield (35%); mp 290°C; IR (KBr): ν_{max}, cm^{-1}: 3298, 3356 (NH_2), 2205 (CN), 1658 (C═O); ^{1}H NMR (DMSO-d_6): δ 4.88 (s, 1H, CH), 5.96 (s, 2H, NH_2), 7.0–8.35 (m, 15H, aromatic protons); MS: *m/z* 502 (M^+). *Anal*. Calcd for $C_{29}H_{18}N_4OS_2$ (502.61): C, 69.30; H, 3.61; N, 11.15; S, 12.76%. Found: C, 69.36; H, 3.63; N, 11.19; S, 12.82%.

2-(Benzo[d]thiazol-2-yl)-2-(7-methyl-5-oxo-5H-thiazolo[3,2-a]pyrimidin-3-yl)acetonitrile (12a). Brown crystals; yield (69%); mp >300°C; IR (KBr): ν_{max}, cm^{-1}: 2188 (CN), 1690 (CO); ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 4.46 (s, 1H, CH), 6.17 (s, 1H, C_6-H in pyrimidine ring), 6.3 (s, 1H, CH, thiazole ring), 7.53–8.18 (m, 4H, aromatic protons + NH); MS: *m/z* 338 (M^+, 100%). *Anal*. Calcd for $C_{16}H_{10}N_4OS_2$ (338.41): C, 56.79; H, 2.98; N, 16.56; S, 18.95%. Found: C, 56.84; H, 3.05; N, 16.62; S, 19.02%.

2-(Benzo[d]thiazol-2-yl)-2-(7-amino-5-oxo-5H-thiazolo[3,2-a]pyrimidin-3-yl)acetonitrile (12b). Dark yellow; yield (58%); mp 290°C; IR (KBr): ν_{max}, cm^{-1}: 3397, 3389 (NH_2), 2188 (CN), 1685 (CO); ^{1}H NMR (DMSO-d_6): δ 4.48 (s, 1H, CH), 6.01 (s, 1H, C_6-H in pyrimidine ring), 6.3 (s, 1H, CH, thiazole ring), 7.53–8.21 (m, 4H, aromatic protons), 8.6 (s, 2H, NH_2); MS: *m/z* 339 (M^+). *Anal*. Calcd for $C_{15}H_9N_5OS_2$ (339.39): C, 53.08; H, 2.67; N, 20.63; S, 18.90%. Found: C, 53.14; H, 2.71; N, 20.67; S, 18.97%.

6-Imino-7-(benzo[d]thiazol-2-yl)-2-methyl-8-oxo-4-phenyl-N-(pyridin-2-yl)-6,7,8,9-tetra-hydro-4H-pyrimido[2,1-b][1,3]thiazepine-3-carboxamide (15). Dark brown; yield (64%); mp

230°C; IR (KBr): ν_{max}, cm^{-1}: 3300, 3430 (NH_2), 3208 (NH), 1685, 1705 (two C=O); ^1H NMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 3.6 (s, 1H, CH thiazole ring), 4.24 (s, 2H, CH_2), 5.36 (s, 1H, CH-pyrimidine), 6.44 (s, 2H, NH_2), 7.20–8.40 (m, 13H, aromatic protons), 8.99 (s, 1H, NH); MS: *m/z* 537 ($M^+ - 1$). *Anal*. Calcd for $C_{28}H_{22}N_6O_2S_2$ (538.64): C, 62.43; H, 4.12; N, 15.60; S, 11.91%. Found: C, 62.49; H, 4.16; N, 15.66; S, 11.99%.

Synthesis of 2-amino-3-(2-benzothiazolyl)-7,9-diphenylthieno [2,3-b:4,5-b′dipyridin-4-ol (10). Compound **9** (0.01 mol) was heated in refluxing DMF containing a catalytic amount of TEA for 24 h. the reaction mixture was then poured onto water (100 mL) and neutralized with dilute HCl. The solid product was collected and washed with water, dried, and recrystallized from ethanol to give compound **10**. Brownish crystals, yield (65%), mp >300°C, IR (KBr): ν_{max}, cm^{-1}: 3450 (OH), 3350–3330 (NH_2); ^1H NMR (DMSO-d_6): δ 5.35 (s, 1H, OH), 7.41–8.30 (m, 14H, Ar-H), 7.74 (s, 2H, NH_2), 7.84 (s, 1H, C_8-H in pyridine ring); MS: *m/z* 502 (M^+, 100%). *Anal*. Calcd for $C_{29}H_{18}N_4OS_2$ (502.61): C, 69.30; H, 3.61; N, 11.15; S, 12.76%. Found: C, 69.28; H, 3.57; N, 11.09; S, 12.73%.

Synthesis of 1-(2-amino-6-chloropyrimidin-4-yl)-4-cyano-2,3-dihydro-1H-benzo[4,5]thiazolo [3,2-b]pyridazine-3-one (20). A mixture of **1** (2.5 g, 0.01 mol) and 4-chloro-2,6-diaminopyrimidine (2.88 g, 0.01 mol) was refluxed in dimethylformamide containing a catalytic amount of triethylamine (four drops) for 8 h. The reaction mixture was left to cool at room temperature and poured onto ice cold water (100 mL). The solid product was collected by filtration and recrystallized from DMF to give **20**. Yellow crystals; yield (68%); mp 235°C; IR (KBr): ν_{max}, cm^{-1}: 3379, 3369 (NH_2), 2189 (CN) 1688 (C=O); ^1H NMR (DMSO-d_6): δ 4.82 (s, 2H, CH_2), 5.91–7.99 (m, 9H, aromatic protons + NH_2); MS: *m/z* 356 (M^+, 100%). *Anal*. Calcd for $C_{15}H_9ClN_6OS$ (356.79): C, 50.49; H, 2.54; N, 23.55; S, 8.99%. Found: C, 50.54; H, 2.57; N, 23.63; S, 9.06%.

REFERENCES AND NOTES

[1] Adreani, A.; Leani, A.; Ville, G. Eur J Med Chem 2000, 35, 77.

[2] Bekhite, E. A.; Baraka, A. M. Eur J Med Chem 2005, 40, 1405.

[3] Krauze, A.; Vitolina, R.; Garaliene, V.; Stile, L.; Klusa, V.; Duburs, G. Eur J Med Chem 2005, 40, 1163.

[4] Abdel-Rahman, A. E.; Bekhite, E. A.; Al-Tafi, E. A. Pharmazie 2003, 58, 372.

[5] Moloney, G. P. Molecules 2001, 6, 203.

[6] Quintela, J. M.; Prinador, C.; Veiga, C.; Gonzales, L.; Botana, L. M.; Alfonso, A.; Riguera, R. Bioorg Med Chem 1998, 6, 1911.

[7] Quintela, J. M.; Prinador, C.; Gonzales, L.; Parama, A.; Alvares, F.; Sammartin, M. L.; Riguera, R. Eur J Med Chem 2003, 38, 265.

[8] Kelarev, V. I.; Kobrakov, K. I.; Rybina, I. I. Chem Heterocycl Comp (New York, NY, United States) 2003, 39, 1267.

[9] Singh, S. P.; Kodali, D. R.; Prakash, I.; Prakash, Om; Sawney, S. N. Indian J Chem 1984, 23B, 125.

[10] Sawney S. N.; Bansal, O. P. Indian J Chem 1977, 15B, 121.

[11] Sawney, S. N.; Kodali, D. R.; Singh, S. P.; Dhinda, G. S. Indian J Chem 1983, 22B, 584.

[12] Sawney, S. N.; Singh, J.; Bansal, O. P. J Indian Chem Soc 1974, 51, 566.

[13] Sawney, S. N.; Singh, J.; Bansal, O. P. J Indian Chem Soc 1975, 52, 561.

[14] Singh, S. P.; Sehgal, S.; Sharma, P. K. Indian J Chem 1990, 29B, 533.

[15] Khan, R. H.; Rasogi, R. C. J Agr and Food Chem 1990, 38, 1068.

[16] Oka, K.; Kara, S. Heterocycles 1977, 6, 941.

[17] Fadda, A. A.; Zaki, M. E. A.; Samir, K.; Amer, F. A. Phosphorus, Sulfur, Silicon and Rel Elem 2007, 182, 1845.

[18] Fadda, A. A.; Zaki, M. E. A.; Samir, K.; Amer, F. A. Phosphorus Sulfur Silicon Rel Elem 2006, 181, 1815.

[19] Fadda, A. A.; Zaki, M. E. A.; Samir, K.; Amer, F. A. Phosphorus, Sulfur, Silicon and Rel Elem 1999, 155, 59.

[20] Fadda, A. A.; Zaki, M. E. A.; Samir, K.; Amer, F. A. Khim Geterotsikl Soedin (Chem Heterocycl Comp) 2003, 39, 1413.

[21] Fadda, A. A.; Zaki, M. E. A.; Samir, K.; Etman, H. A. Phosphorus, Sulfur, Silicon and Rel Elem 2008, 183, 1801.

[22] Fadda, A. A.; Etman, H. A.; Abdelrazek F. M.; Samir, K.; Ghieth H. M. M. Eur J Chem 2010, 1, 90.

[23] Almerico, A. M.; Tutone, M.; Guarcello, A.; Lauria, A. Bioorg Med Chem Lett 2012, 22, 1000.