Behavior of 2-cyano-3-(dimethylamino)-*N*-(4-phenylthiazol-2-yl)-acrylamide towards some nitrogen nucleophiles

Samir Bondock,* Abd El-Gaber Tarhoni, and Ahmed A. Fadda

Department of Chemistry, Faculty of Science, Mansoura University, ET-35516 Mansoura, Egypt
E-mail: Bondock@mans.edu.eg

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Abstract

The versatile, hitherto unreported 2-cyano-3-(dimethylamino)-*N*-(4-phenylthiazol-2-yl)-acrylamide **2** was synthesized and allowed to react with hydroxylamine, hydrazine and guanidine to afford regioselectively the isoxazole **4**, pyrazole **6** and pyrimidine **8** derivatives, respectively. The reaction of **2** with thiourea and / or ethyl glycinate in a basic medium afforded the regioisomeric pyrimidinethione **9** and 3,5-dioxo-1,4-diazepine-6-carbonitrile **14**. Compound **2** reacts also with 2-amino-4-phenylthiazole, 2-amino-4-methylpyridine, 2-aminotetrazole, 2-aminobenzothiazole and 2-aminobenzimidazole to give the corresponding bridgehead nitrogen heterocycles namely thiazolo[3,2-*a*]pyrimidine **18**, tetrazolo[1,5-*a*]pyrimidine **19**, pyrimido [2,1-*b*]benzothiazole **21**, and pyrido[1,2-*a*]benzimidazole **23**. The mechanistic aspects for the formation of the newly synthesized compounds is discussed.

Keywords: Thiazoles, enaminonitriles, *N*-nucleophiles, heterocycles

Introduction

Enaminonitriles are versatile reagents and their chemistry has recently received a considerable attention as precursors to, otherwise not readily obtainable heteroaromatics.[1-10] Several novel syntheses of azoles, azines, and azoloazines utilizing enaminonitriles as starting components have been reported by Elnagdi and coworkers.[11-14] On the other hand, the considerable biological and medicinal activities of thiazoles and those linked to different heterocycles through a carboxamide linkage initiated a considerable recent interest in the development of syntheses of these molecules.[15-19] These compounds were found to be associated with a wide range of chemotherapeutic activities.[20] In continuation of our interest in the synthesis of heterocycles containing a thiazole moiety[21-28], we report herein the results of our study of the reactions of an enaminonitrile **2** with several nitrogen nucleophiles. The aim of the present paper is to present an

efficient synthesis of novel 2-heteroaryl-thiazoles, which have not been reported hitherto. The results of screening of their biological activity will be reported in due course.

Results and Discussion

The starting material, 2-cyano-*N*-(4-phenylthiazol-2-yl)acetamide **1**[29] used in this study was prepared in a quantitative yield using a modified literature procedure by heating 2-amino-4-phenylthiazole in dry toluene with 1-cyanoacetyl-3,5-dimethylpyrazole as cyanoacetylating agent.[30,31] Treatment of **1** with dimethylformamide-dimethylacetal (DMF-DMA) in refluxing toluene afforded the corresponding enaminonitrile **2**. The structure of **2** has been assigned as a reaction product on the basis of analytical and spectral data. The IR spectrum displayed absorption bands at 3230 cm^{-1} due to NH function, at 2196 cm^{-1} due to conjugated C≡N function, at 1668 cm^{-1} due to amidic C=O function. The ^{1}H-NMR spectrum (DMSO–d_6) exhibited two sharp singlet signals at δ 3.27 ppm and 3.33 ppm assignable to *N*,*N*-dimethylamino protons, another two singlet signals at δ 7.57 and 8.07 ppm specific for thiazole-H5 proton and methine proton, respectively, a multiplet signal at δ 7.20-7.95 ppm region owing to aromatic protons, and a broad singlet signal at δ 11.44 ppm due to NH proton. The mass spectrum showed a molecular ion peak at *m/z* = 298, corresponding to a molecular formula $C_{15}H_{14}N_4OS$.

The behavior of the enaminonitrile **2** towards some *N*-nucleophiles to attain polyfunctionally substituted azoles, azines, and related fused systems linked to a thiazole moiety through a carboxamide linkage of potential pharmaceutical interest, has been investigated.

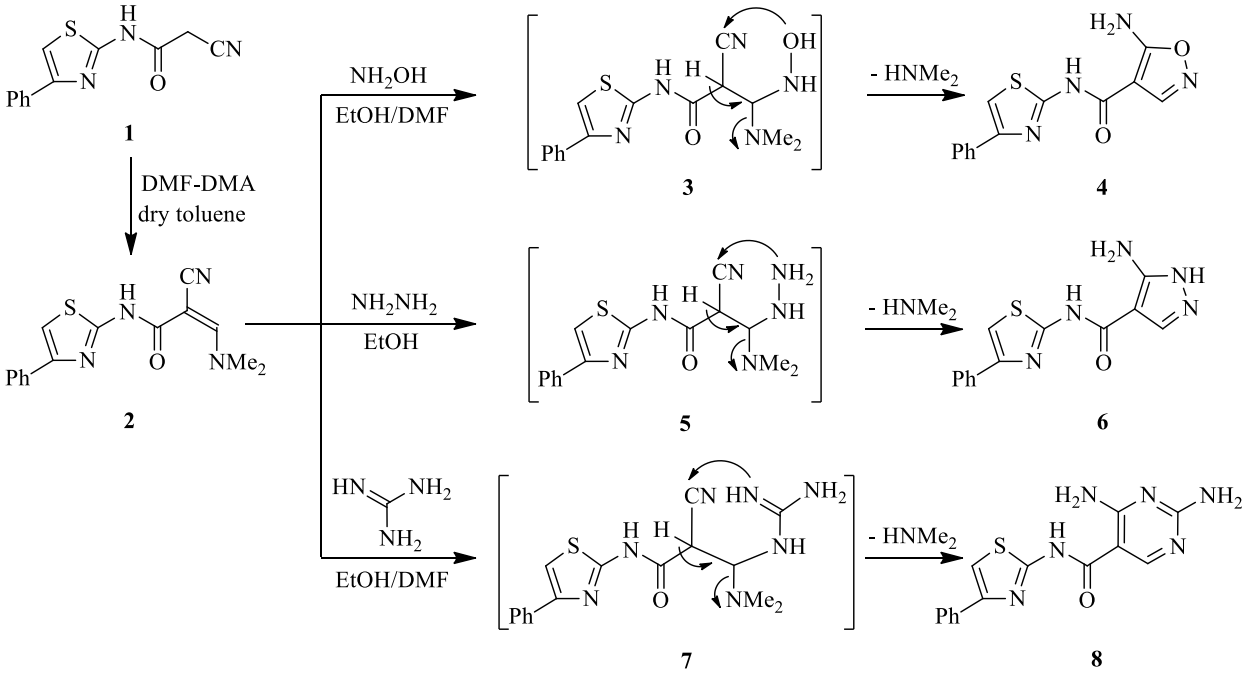
Treatment of **2** with hydroxylamine hydrochloride in refluxing ethanol - dimethylformamide (1:1) mixture in the presence of anhydrous potassium carbonate afforded an orange product which was identified as 5-amino-*N*-(4-phenylthiazole-2-yl)-isoxazole-4-carboxamide **4**. The spectral data of the isolated product was in complete agreement with structure **4**. The IR spectrum revealed the lack of an absorption band corresponding to a conjugated C≡N function and showed absorption bands at 3405, 3345, 3234, and 1666 cm^{-1} corresponding to NH_2 , NH, and amidic C=O functions, respectively. The ^{1}H NMR spectrum (DMSO–d_6) showed two broad singlet signals at δ 5.86 and 11.44 ppm and two sharp singlet signals at δ 7.56 and 8.88 ppm characteristic of NH_2, NH, thiazole-H5, and isoxazole-H3 protons respectively, beside a multiplet signal at δ 7.28–8.00 ppm region distinctive for aromatic protons. The mass spectrum showed a molecular ion peak at *m/z* = 286, corresponding to molecular formula $C_{13}H_{10}N_4O_2S$.

The 5-aminopyrazole **6** was achieved as a sole product by heating the enaminonitrile **2** with hydrazine hydrate in ethanol. Inspection of ^{1}H-NMR spectrum enabled establishing structure **6** for this pyrazole derivative since the pyrazole H-3 appeared as a singlet at δ 8.23 ppm. We could not trace in the ^{1}H-NMR spectrum any signals for the tautomeric 3-aminopyrazole as this could reveal pyrazole-H5 as a doublet. The mass spectrum of **6** showed a molecular ion peak (M^+) at *m/z* = 285 corresponding to a molecular formula $C_{13}H_{11}N_5OS$.

Similarly, the enaminonitrile **2** reacted with guanidine in a mixture of ethanol and dimethylformamide (2:1) containing anhydrous potassium carbonate under reflux to yield in good yield, a product that was identified as 2,4-diamino-*N*-(benzothiazol-2-yl)pyrimidine-5-

carboxamide **8**. The structure of compound **8** was assigned on the basis of the elemental analysis and spectral data. The IR spectrum showed absorption bands at 3382–3122 cm^{-1}, corresponding to two NH_2 and NH functions, and at 1664 cm^{-1} due to amidic C=O function. The ^{1}H-NMR spectrum (DMSO–d_6) revealed two broad singlet signals at δ 6.53 and 8.67 ppm assignable to two NH_2 protons, a singlet signal at δ 8.79 ppm characteristic to pyrimidine-H6 proton, an aromatic multiplet at δ 7.31–7.96 ppm, and another broad singlet signal at δ 11.51 ppm due to NH proton. The mass spectrum showed a molecular ion peak (M^+) at *m/z* = 312, corresponding to a molecular formula $C_{14}H_{12}N_6OS$.

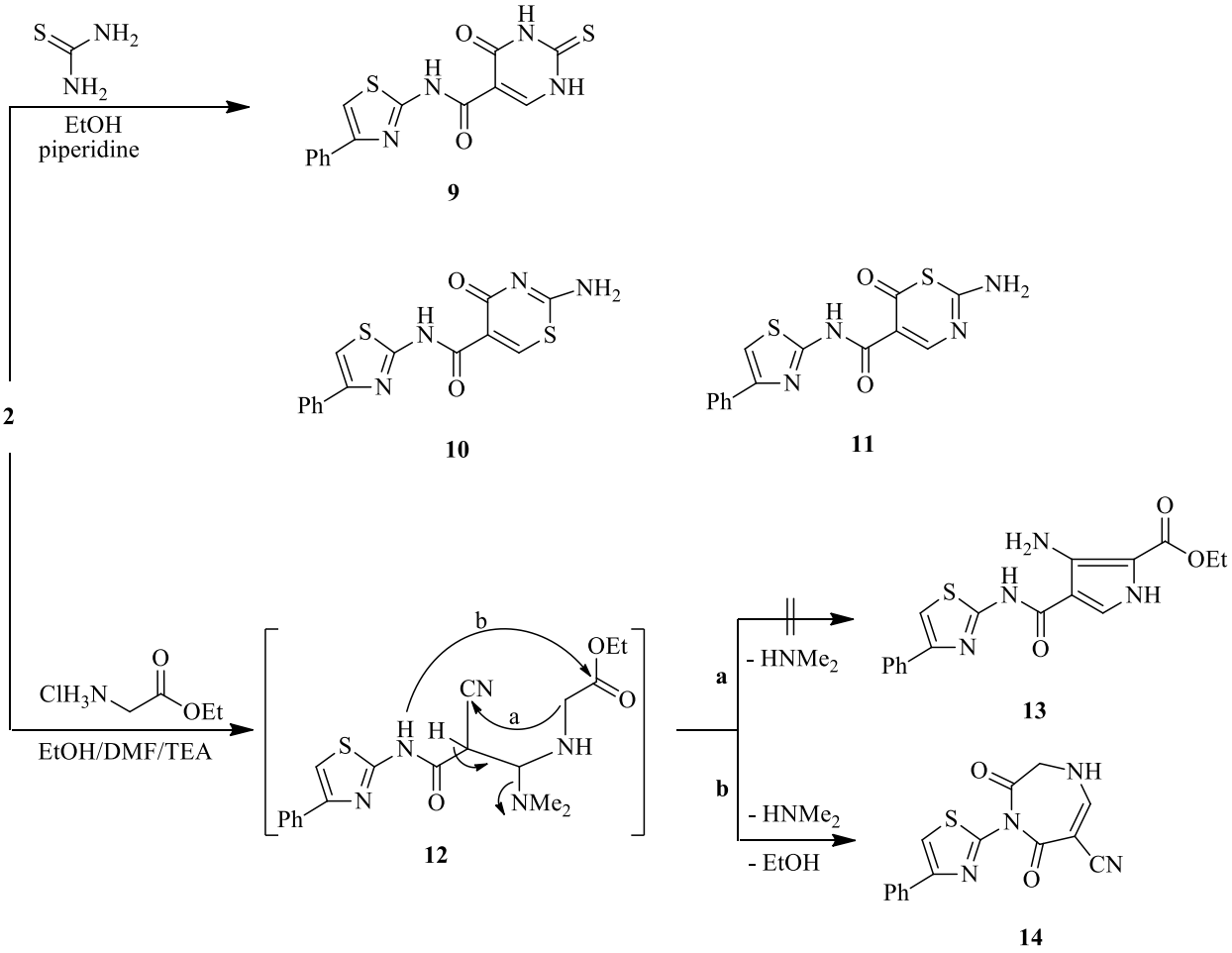
Formation of compounds **4**, **6** and **8** is assumed to take place *via* a Michael type addition of the amino group of the hydroxylamine, hydrazine and guanidine to the activated double in compound **2** to form the non-isolable intermediates **3**, **5** and **7** which readily undergo intramolecular cyclization followed by loss of dimethylamine molecule to form the target compounds (Scheme 1).



Scheme 1. Synthesis of isoxazole **4**, pyrazole **6** and pyrimidine **8** derivatives.

The site selectivity in cycloaddition of some nitrogen ambident nucleophiles with the enaminonitrile **2** was also studied. Thus, reaction of **2** with thiourea in refluxing ethanol containing a catalytic amount of piperidine afforded a single product (as examined by TLC) for which three isomeric cycloadducts **9**, **10** and **11** seemed possible (Scheme 2). However, the pyrimidinethione **9** was assigned for the reaction product on the basis of its elemental analysis and spectral data. The IR spectrum lacked an absorption band due to a nitrile function and revealed absorption bands at 3395-3162, 1670, 1635, and 1279 cm^{-1} characteristic to three NH,

two amidic C=O, and C=S functions, respectively. The ^{1}H-NMR spectrum (DMSO–d_6) exhibited no signal due to NH_2 protons which was attributed to either structures **10** or **11** and displayed a doublet signal at δ 8.22 ppm with coupling constant (*J* = 6.8 *Hz*) assignable to pyrimidine-H6 proton, three broad singlet signals at δ 8.98, 11.02 and 11.74 ppm, specific for three NH protons, in addition to an aromatic multiplet in the region δ 7.21–7.96 ppm. Moreover, its ^{13}C-NMR spectrum revealed 12 carbon types, the most important signals being displayed at δ 175.7, 166.7, and 165.5 characteristics for C=S, acyclic amide, and cyclic amide carbonyl carbons, respectively. The mass spectrum showed a molecular ion peak (M^+) at *m/z* = 330 which is in an agreement with the molecular formula $C_{14}H_{10}N_4O_2S_2$.



Scheme 2. Synthesis of pyrimidinethione **9** and 3,5-dioxo-1,4-diazepine-6-carbonitrile **14**.

It is interesting in this connection that the reaction of **2** with ethyl glycinate hydrochloride in a boiling mixture of ethanol and dimethylformamide containing triethylamine as a catalyst does not afford the pyrrole derivative **13**, as could have been expected in analogy to the formation of **9**. Actually, the product of this reaction was identified on the basis of its spectral data as 3,5-

dioxo-4-(4-phenylthiazol-2-yl)-2,3,4,5-tetrahydro-1*H*-1,4-diazepine-6-carbonitrile **14**. The IR spectrum has no absorption band characteristic to an ester group and it revealed the presence of C≡N stretching band at 2205 cm^{-1} and two amidic C=O stretching bands at 1672 and 1665 cm^{-1}. Its mass spectrum showed the molecular ion at *m/z* = 310. Two peaks at *m/z* = 151 (37.5 %) and 150 (100%, base peak) identify the 1,4-diazepine unit. The ^{1}H-NMR spectrum of **14** supported its structure, as it revealed the 1,4-diazepine ring protons as two doublet signals at δ 3.45 and 8.63 ppm assignable to 2-CH_2 and 7-H protons, respectively, and a broad singlet signal at 8.31 ppm exchangeable with D_2O characteristic of NH proton, beside the other expected signals. Its ^{13}C-NMR spectrum revealed 13 carbon types, the construction of diazepine ring system **14** makes its two amidic carbonyl carbons resonate downfield at 164.9 and 160.9, the other significant signals being displayed at 115.6 and 48.2 corresponding to nitrile carbon and methylene carbon, respectively. The formation of **14** rather than **13** may be attributed to the intermediacy of the non-isolable transamination adduct **12**, which underwent cyclization *via* loss of ethanol and dimethylamine molecules.

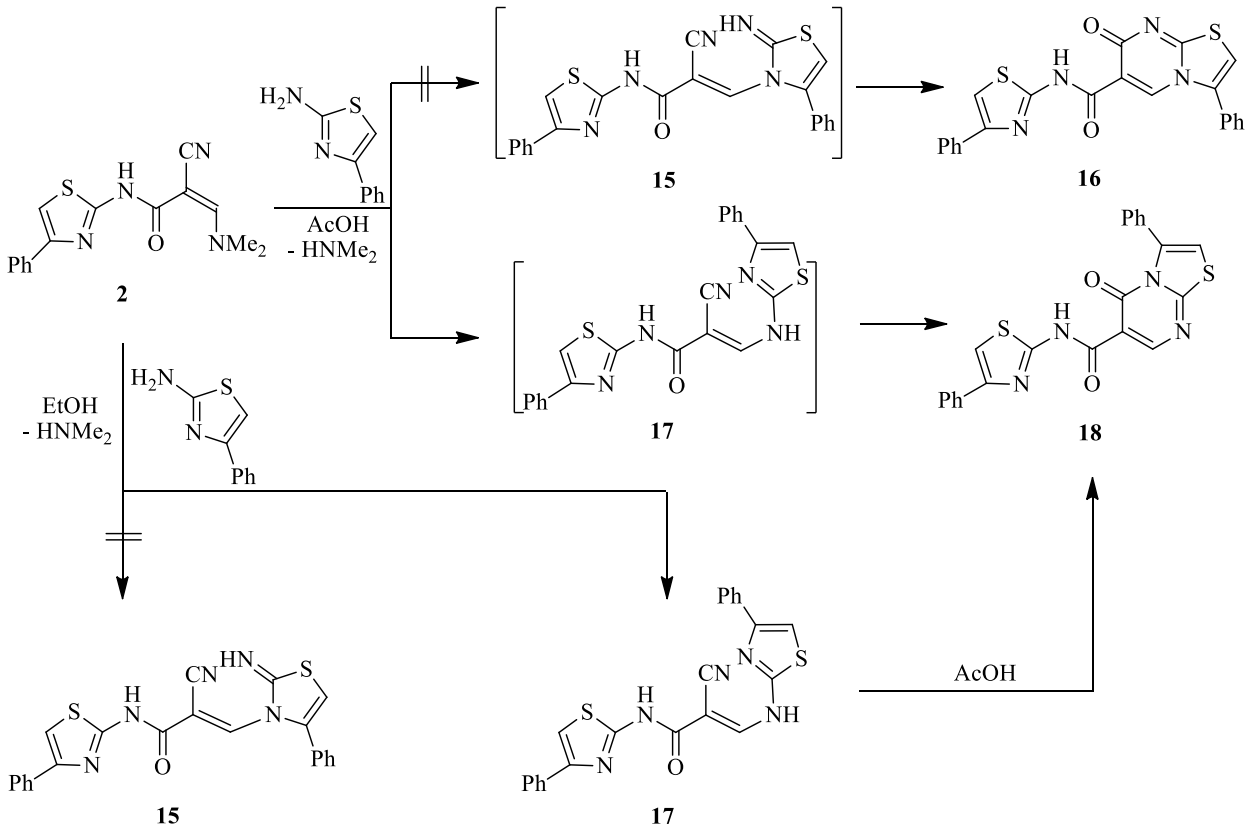
In view of the growing biological importance of fused thiazoles, particularly thiazolo[3,2-*a*]pyrimidines,[32,33] it was of interest to synthesize 5-oxo-3-phenyl-*N*-(4-phenylthiazol-2-yl)-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide. This bicyclic system is considered as a thia-analogue of the natural purine bases, adenine and guanine. Thus, treatment of **2** with 2-amino-4-phenylthiazole in boiling glacial acetic acid furnished a single product for which two possible isomeric structures **16** and **18** were considered (Scheme 3). Unfortunately, both elemental analysis and spectral data of the isolated product were in assignment with the two theoretically possible structures **16** and **18**. The IR spectrum showed the lack of absorption bands corresponding to conjugated C≡N and NH_2 functions and presence of bands at 3385 cm^{-1} due to NH function, 1680 and 1652 cm^{-1} due to two amidic C=O functions. Its ^{1}H-NMR spectrum exhibited two singlet signals at δ 6.13 and 7.52 ppm specific for fused thiazole-H5 proton and thiazole-H5 proton, respectively, a singlet signal at δ 8.38 due to pyrimidine-H6 in addition to an aromatic multiplet at δ 7.29–7.97 ppm region and a broad singlet signal at δ 12.74 ppm exchangeable with D_2O due to NH proton. The mass spectrum showed a molecular ion peak at *m/z* = 340 corresponding to a molecular formula $C_{22}H_{14}N_4O_2S$.

The differentiation between structures **16** and **18** has been achieved by their alternate synthesis through the isolation of the intermediacy **17** rather than **15** *via* conducting the reaction in boiling ethanol followed by cyclization to **18** by boiling in glacial acetic acid. The intermediacy of **17** was confirmed by both elemental analysis and spectral data. The ^{1}H-NMR spectrum displayed no singlet signal for the imino proton and revealed a doublet signal at δ 8.22 ppm due to =CH-NH proton, and two broad singlet signals at δ 11.16 and 12.80 assignable to two NH protons. The mass spectrum showed a molecular ion peak at *m/z* = 429, corresponding to a molecular formula $C_{22}H_{15}N_5OS_2$.

The direct formation of **18** from **2** and 2-amino-4-phenylthiazole indicates that the initially formed substitution product namely 2-cyano-*N*-(4-phenylthiazol-2-yl)-3-[(4-phenylthiazol-2-yl)amino]acrylamide **16** underwent *in situ* deaminative cyclization under the employed reaction

conditions to give 5-oxo-3-phenyl-*N*-(4-phenylthiazol-2-yl)-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide **18** as the end product.

The foregoing results prompted us to investigate the applicability and synthetic potency of **2** to develop a facile and convenient route to bridgehead nitrogen heterocyclic systems namely tetrazolo[1,5-*a*]pyrimidine, pyrido[1,2-*a*]pyrimidine, pyrimido[1,2-*a*]benzimidazole and pyrimido[2,1-*b*]benzothiazole of an expected pharmaceutical interest.

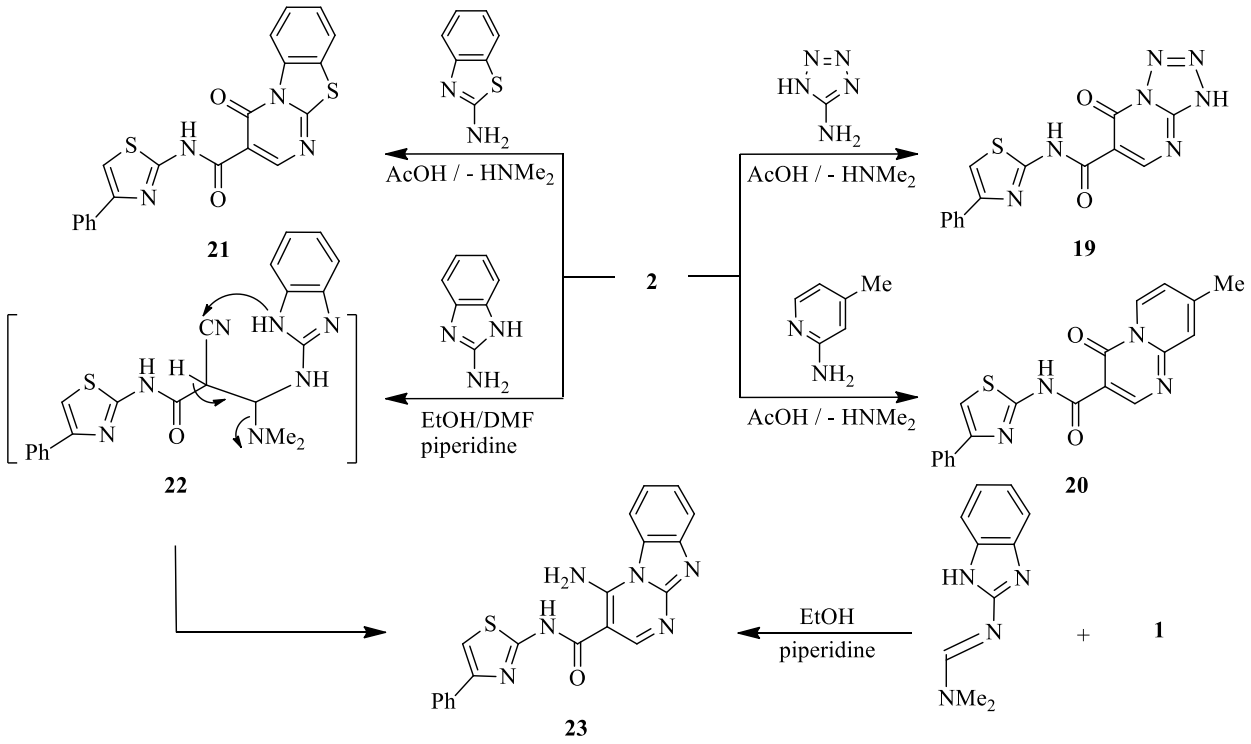


Scheme 3. Synthetic route to thiazolo[3,2-*a*]pyrimidine derivative **18**.

Thus, reaction of **2** with 2-hetarylamines namely, 5-aminotetrazole and 2-amino-4-methylpyridine in refluxing glacial acetic acid afforded solely 7-oxo-*N*-(4-phenylthiazol-2-yl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide **19** and 8-methyl-4-oxo-*N*-(4-phenylthiazol-2-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide **20**, respectively. The IR spectrum of **20** showed two strong absorption bands at 1690 and 1650 cm^{-1} attributed to two amidic C=O functions. The ^{1}H-NMR spectrum revealed a singlet signal at δ 2.30 ppm characteristic of methyl protons, a singlet signal at δ 7.28 ppm assignable to aromatic protons (H_9), two doublets at δ 6.22 and 6.89 ppm assignable to aromatic protons (H_6 and H_7), a singlet signal at δ 8.18 ppm owing to pyrimidine-H2 proton and an aromatic multiplet at δ 7.31–7.92 ppm region. The mass spectrum showed a molecular ion peak at *m/z* = 362, corresponding to a molecular formula $C_{19}H_{14}N_4O_2S$.

In a similar manner, refluxing of **2** with 2-aminobenzothiazole in acetic acid afforded 4-oxo-*N*-(4-phenylthiazol-2-yl)-4*H*-pyrimido[2,1-*b*]benzothiazole-3-carboxamide **21** in quantitative yield.

The reaction of **2** with 2-aminobenzimidazole as potential precursor for pyrimido[1,2-*a*] benzimidazole was also investigated. Thus, the enaminonitrile **2** was refluxed with 2-aminobenzimidazole in ethanol containing a catalytic amount of piperidine to afford the corresponding pyrimido[1,2-*a*]benzimidazole derivative **23**. The structure of **23** was established on the basis of its elemental analyses and spectral data, besides its independent synthesis *via* the reaction of *N*-1*H*-benzimidazol-2-yl-*N*,*N*-dimethylformamidine[34] with 2-cyano-*N*-(4-phenylthiazol-2-yl)acetamide **1** which afforded a product identical in all respects (mp., mixed mp., and IR spectra) with those obtained previously from the reaction of the enaminonitrile **2** with 2-aminobenzimidazole. The presence of an amino group in **23** was evidenced by the presence of two absorption bands at 3445 and 3300 cm^{-1} in its IR spectrum and as a broad D_2O-exchangeable signal at δ 6.35 ppm in its ^{1}H-NMR spectrum. The formation of **23** is therefore assumed to take place *via* the addition of the exocyclic amino group of 2-aminobenzimidazole to the activated double in **2** to give the acyclic non-isolable intermediate **22**, which undergoes cyclization and aromatization *via* loss of dimethylamine molecule affording the final isolated product.



Scheme 4. Synthesis of bridgehead heterocyclic nitrogen compounds **19-23**.

Conclusions

The results of the present study indicate that the enaminonitrile and *N*-nucleophiles are useful precursors for the synthesis of different functionalized 2-hetarylthiazoles. In addition, they indicate that reactions of studied *N*-nucleophiles with enaminonitrile are regiospecific as they yielded, in each case, one product in good yield. The compounds prepared are expected to be of pharmacological interest.

Experimental Section

General. All melting points were determined on an electrothermal Gallenkamp apparatus. The IR spectra were measured on a Mattson 5000 FTIR Spectrometer in potassium bromide discs. The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 or $CDCl_3$ on a Bruker WP spectrometer (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR) and the chemical shifts δ downfield from TMS as an internal standard. The mass spectra were recorded on Finnegan MAT 212 instrument, the ionizing voltage was 70 ev, at Faculty of Science, Cairo University. Elemental analyses were carried out by the Microanalytical unit of Faculty of Science, Mansoura University, Masoura, Egypt. All reactions were followed by TLC (Silica gel, aluminum sheets 60 F_{254}, Merck). 2-Cyano-*N*-(4-phenylthiazol-2-yl)acetamide **1** was prepared according to previously reported procedure.[29]

2-Cyano-3-(dimethylamino)-*N*-(4-phenylthiazol-2-yl)acrylamide (**2**)**.** A mixture of 2-cyano-*N*-(4-phenylthiazol-2-yl)acetamide **1** (3.65 g, 0.015 mole) and dimethylformamide-dimethylacetal (2 ml, 0.015 mole) in dry toluene (30 ml) was heated under reflux for 4 h, then left to cool at room temperature. The orange precipitate product was filtered off, washed with petroleum ether, dried well, and recrystallized from toluene to give compound **2**. Orange crystals; Yield 82%; mp 248ºC; IR (KBr): $\nu_{max.}$/cm^{-1} = 3230 (NH), 2196 (C≡N), 1668 (amidic C=O). ^{1}H NMR (DMSO-d_6): δ_{ppm} = 3.27 (s, 3H, NCH_3), 3.33 (s, 3H, NCH_3), 7.20 – 7.95 (m, 5H, Ar-H), 7.57 (s, 1H, thiazole H-5), 8.07 (s, 1H, CH=), 11.44 (s, br, 1H, NH). MS *m/z* (%): 298 (M^+, 21.8), 124 (7.6), 123 (100), 104 (1.2), 95 (5.2), 80 (9.6), 51 (3.7). Anal. For $C_{15}H_{14}N_4OS$ (298.36) Calcd.: C 60.38; H 4.73; N 18.78. Found: C 60.24; H 4.65; N 18.62 %.

5-Amino-*N*-(-4-phenylthiazol-2-yl)-isoxazole-4-carboxamide (**4**)**.** A mixture of enaminonitrile **2** (0.298 g, 0.001 mole) and hydroxylamine hydrochloride (0.07 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) containing anhydrous potassium carbonate (0.28 g, 0.002 mole) was heated under refluxed for 6 h, then allowed to cool at room temperature and diluted with ice cold water (30 ml). The solid product so formed was filtered off, washed with water, dried well, and recrystallized from ethanol to afford compound **4**. Yellow crystals; Yield 73 %; mp 265ºC; IR (KBr): $\nu_{max.}$/cm^{-1} = 3405, 3345 (NH_2), 3234 (NH), 1666, (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 5.79 (s, br, 2H, NH_2), 7.28 – 8.01 (m, 5H, Ar-H), 7.56 (s, 1H, thiazole

H-5), 8.88 (s, 1H, isoxazole H-3), 11.44 (s, br, 1H, NH). MS *m/z* (%): 286 (M^+, 48.6), 202 (75.2), 176 (53.9), 160 (100), 111 (35.6), 77 (27.5). Anal. For $C_{13}H_{10}N_4O_2S$ (286.31) Calcd. C 54.54; H 3.52; N 19.57. Found: C 54.63; H 3.60; N 19.42 %.

5-Amino-N-(-4-phenylthiazol-2-yl)-1H-pyrazole-4-carboxamide (6). To a solution of enaminonitrile 2 (0.298 g, 0.001 mole) in ethanol (20 ml), hydrazine hydrate (80% 0.1 ml, 0.002 mole) was added. The reaction mixture was refluxed for 4 h, and then left overnight at room temperature. The solid product so formed was filtered off, washed with ethanol dried well, and recrystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound 6.

Yellow crystals; Yield 76 %; mp 122ºC; IR (KBr): vmax./cm-1 = 3454, 3350 (NH2), 3178, 3106 (2NH) 1660 (amidic C=O). 1H NMR (DMSO – d_6): δppm = 6.08 (s, br, 2H, NH2), 7.32 – 7.96 (m, 5H, Ar-H), 7.56 (s, 1H, thiazole H-5), 8.23 (s, 1H, pyrazole H-3), 8.75 (s, br, 1H, pyrazole NH), 11.52 (s, br, 1H, NH). MS *m/z* (%): 285 (M+, 40.5), 203 (49.8), 175 (64.2), 160 (57.2), 127 (32.6), 110 (100), 77 (52.2), 51 (48.9). Anal. For C13H11N5OS (285.32) Calcd.: C 54.72; H 3.89; N 24.55. Found: C 54.60; H 3.95; N 24.42 %.

2,4-Diamino-*N*-(4-phenylthiazole-2-yl)pyrimidine-5-carboxamide (**8**)**.** A mixture of enaminonitrile **2** (0.298 g, 0.001 mole) and guanidine nitrate (0.12 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) containing anhydrous potassium carbonate (0.28 g, 0.002 mole) was heated under refluxed for 8 h, then allowed to cool at room temperature. The reaction mixture was then triturated with cold water (50 ml), and few drops of dilute HCl were added (till *pH* = 7). The resultant solid product, so precipitated was collected by filtration, dried well, and crystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound **8**. Yellow crystals; Yield 71 %; mp 274ºC; IR (KBr): $\nu_{max.}/cm^{-1}$ = 3382 – 3122 ($2NH_2$, NH), 1664 (amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 6.53 (s, br, 2H, NH_2), 7.31 – 7.96 (m, 5H, Ar-H), 7.68 (s, 1H, thiazole H-5), 8.67 (s, br, 2H, NH_2), 8.79 (s, H, pyrimidine H-6), 11.51 (s, br, 1H, NH). MS *m/z* (%): 312 (M^+, 15.8), 279 (4.3), 176 (3.1), 136 (7.6), 137 (100), 134 (5.6), 95 (33.6), 68 (10.2), 53 (5.8). Anal. For $C_{14}H_{12}N_6OS$ (312.35) Calcd.: C 53.83; H 3.87; N 26.91. Found: C 53.94; H 3.73; N 26.99 %.

4-Oxo-*N*-(4-phenylthiazole-2-yl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**9**)**.** A mixture of enaminonitrile **2** (0.298 g, 0.001 mole) and thiourea (0.076 g, 0.001mole) in a mixture of ethanol and dimethylformamide (1:1) (20 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 8 h and then left overnight at room temperature. The solid product so formed was filtered off, washed with ethanol, dried well, and recrystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound **9**. Pale yellow powder; Yield 63%; mp 278ºC; IR (KBr): $\nu_{max.}/cm^{-1}$ = 3395 – 3162 (3NH), 1670, 1635 (2 amidic C=O), 1279 (C=S). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 7.21–7.96 (m, 5H, Ar-H), 7.49 (s, 1H, thiazole H-5), 8.22 (d, *J* = 6.8 Hz, 1H, pyrimidine H-6), 8.98 (s, br, 1H, NH), 11.02 (s, br, 1H, NH), 11.74 (s, br, 1H, NH). ^{13}C NMR (DMSO-d_6): δ_{ppm} = 105.6, 108.4, 125.8, 127.7, 129.2, 131.4, 151.5, 155.6, 163.2, 165.5, 166.7, 175.7. MS *m/z* (%): 330 (M^+, 30), 302 (26.8), 286 (22.5), 252 (31), 203 (32.8), 175 (50.4), 170 (62.2), 160 (60), 155 (100), 127 (41.5), 99 (28.7), 77 (50). Anal. For $C_{14}H_{10}N_4O_2S_2$ (330.38) Calcd.: C 50.90; H 3.05; N 16.96. Found: C 50.74; H 3.13; N 16.84 %.

3,5-Dioxo-4-(4-phenylthiazol-2-yl)-2,3,4,5-tetrahydro-1*H*-1,4-diazepine-6-carbonitrile (**14**)**.** A mixture of enaminonitrile **2** (0.298 g, 0.001 mole) and ethyl glycinate hydrochloride (0.139 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) containing a catalytic amount of triethylamine (3 drops) was refluxed for 12 h. The solid product so formed was filtered off, washed with ethanol, dried well, and recrystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound **14**. White crystals; Yield 57 %; mp 286ºC; IR (KBr): $\nu_{max.}$/cm^{-1} = 2205 (C≡N), 1672, 1665 (2 amidic C=O). ^{1}H NMR (DMSO – *d*$_6$): δ_{ppm} = 3.45 (d, *J* = 8.6 Hz, 2H, diazepine 2-CH$_2$), 7.28 – 7.92 (m, 5H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.31 (s, br, 1H, NH), 8.63 (d, *J* = 8.6 Hz, 1H, diazepine 7-CH). ^{13}C NMR (DMSO-*d*$_6$): δ_{ppm} = 48.2, 83.5, 105.2, 115.6, 125.8, 127.7, 129.2, 131.4, 151.4, 152.3, 155.6, 160.9, 164.9. MS *m/z* (%): 310 (M$^+$, 13.7), 285 (25.9), 254 (18.9), 233 (17.2), 202 (26.9), 174 (74.8), 151 (37.5), 150 (100), 122 (39.6), 110 (20.5), 84 (48.5), 77 (75.6). Anal. For $C_{15}H_{10}N_4O_2S$ (310.33) Calcd.: C 58.05; H 3.25; N 18.05. Found: C 58.24; H 3.43; N 18.16 %.

2-Cyano-*N*-(4-phenylthiazol-2-yl)-3-(4-phenylthiazol-2-ylamino)-acrylamide (**17**)**.** A mixture of enaminonitrile **2** (0.298 g, 0.001 mole) and 2-amino-4-phenylthiazole (0.176 g, 0.01 mole) in a mixture of ethanol and dimethylformamide (1:1) (30 ml) was refluxed for 8 h and then evaporated in *vacuo*. The residue was triturated with ethanol and the resulting solid product was collected by filtration, washed with ethanol, dried well, and crystallized from ethanol-dimethylformamide to give compound **17**. Pale yellow crystals; Yield 52%; mp 267ºC; ^{1}H NMR (DMSO–*d*$_6$): δ_{ppm} = 7.52 (s, 1H, thiazole H'-5), 7.56 (s, 1H, thiazole H-5), 7.27–7.82 (m, 10H, Ar-H), 8.22 (d, *J* = 3.6 Hz, 1H, =CH-NH), 11.16 (s, br, 1H, NH), 12.80 (s, br, 1H, NH). MS *m/z* (%): 429 (M$^+$, 2.5), 376 (12.4), 227 (50.4), 203 (100), 175 (27.5), 77 (50). Anal. For $C_{22}H_{15}N_5OS_2$ (429.52) Calcd.: C 61.52; H 3.52; N 16.31. Found: C 61.44; H 3.43; N 16.22 %.

General procedure for the reaction of enaminonitrile (2) with heterocyclic amines

To a solution of enaminonitrile **2** (0.298 g, 0.001 mole) in glacial acetic acid (3-5 ml), an equimolar amount of the appropriate heterocyclic amines was added and the mixture was heated in oil bath under reflux for 10-16 h, then evaporated in *vacuo*. The residue was triturated with ethanol and the resulting solid product was collected by filtration, dried well, and recrystallized from the appropriate solvent to give compounds **18, 19, 20** and **21**.

5-Oxo-3-phenyl-*N*-(4-phenylthiazol-2-yl)-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxamide (**18**)**.** Prepared from 2-amino-4-phenylthiazole (0.176 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1). Yellow crystals; Yield 53 %; mp 286ºC; IR (KBr): $\nu_{max.}$/cm^{-1} = 3385 (NH), 1680, 1652 (2 amidic C=O). ^{1}H-NMR (DMSO–*d*$_6$): δ_{ppm} = 6.13 (s, 1H, thiazolopyrimidine H-2), 7.29–7.97 (m, 10H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.38 (s, 1H, thiazolopyrimidine H-7), 12.74 (s, br, 1H, NH). MS *m/z* (%): 430 (M$^+$, 25.4), 418 (27.6), 376 (28), 255 (100), 227 (64.3), 203 (48.2), 175 (26.9), 77 (30), 51 (21.6). Anal. For $C_{22}H_{14}N_4O_2S_2$ (430.50) Calcd.: C 61.38; H 3.28; N 13.01. Found: C 61.24; H 3.43; N 13.13 %.

7-Oxo-*N*-(4-phenylthiazol-2-yl)-3,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxamide (**19**)**.** Prepared from 5-aminotetrazole (0.085 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1). Greenish brown powder; Yield 61%; mp 276ºC; IR (KBr): $\nu_{max.}$/cm^{-1} = 3361, 3226 (2NH), 1690, 1655 (2 amidic C=O). ^{1}H NMR (DMSO – d_6): δ_{ppm} = 7.20 – 7.95 (m, 5H, Ar-H), 7.57 (s, 1H, thiazole H-5), 8.56 (s, 1H, tetrazolopyrimidine H-5), 9.46 (s, br, 1H, NH), 11.62 (s, br, 1H, NH). MS *m/z* (%): 339 (M$^+$, 31.7), 311 (19.8), 263 (32.8), 256 (20.9), 228 (36.6), 203 (65), 175 (52.6), 160 (100), 136 (40), 122 (20), 109 (60.2), 77 (45.6). Anal. For $C_{14}H_9N_7O_2S$ (339.33) Calcd.: C 49.55; H 2.67; N 28.89. Found: C 49.74; H 2.78; N 28.76 %.

8-Methyl-4-oxo-*N*-(4-phenylthiazol-2-yl)-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**20**)**.** Prepared from 2-amino-3-methylpyridine (0.108 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1). Yellowish green powder; Yield 62 %; mp 277ºC; IR (KBr): $\nu_{max.}$/cm^{-1} = 3385 (NH), 1690, 1650 (2 amidic C=O). ^{1}H-NMR (DMSO–d_6): δ_{ppm} = 2.30 (s, 3H, CH_3), 6.22 (d, *J* = 2.8 Hz, 1H, pyridopyrimidine H-7), 6.89 (d, *J* = 5.6 Hz, 1H, pyridopyrimidine H-6), 7.28 (s, 1H, pyridopyrimidine H-9), 7.31 –7.92 (m, 5H, Ar-H), 7.52 (s, 1H, thiazole H-5), 8.18 (s, 1H, pyridopyrimidine H-2), 12.74 (s, br, 1H, NH). MS *m/z* (%): 362 (M$^+$, 31.5), 347 (20.1), 320 (29.8), 296 (41.5), 268 (39.8), 243 (29.2), 203 (68.5), 187 (100), 175 (62.5), 160 (68.2), 145 (44.7), 132 (62.6), 118 (40.2), 107 (39.7), 91 (61.5), 58 (55.6). Anal. For $C_{19}H_{14}N_4O_2S$ (362.41) Calcd.: C 62.97; H 3.89; N 15.46. Found: C 62.78; H 3.83; N 15.28 %.

4-Oxo-*N*-(4-phenyl-1,3-thiazol-2-yl)-4*H*-pyrimido[2,1-][1,3]benzothiazole-3-carboxamide (**21**)**.** Prepared from 2-aminobenzothiazole (0.15 g) by heating for 10 h under reflux and recrystallized from a mixture of ethanol and dimethylformamide (1:1). Brown powder; Yield 51 %; mp 281ºC; IR (KBr): $\nu_{max.}$/cm^{-1} = 3364 (NH), 1686, 1648 (2 amidic C=O). ^{1}H NMR (DMSO–d_6): δ_{ppm} = 6.69–8.01 (m, 9H, Ar-H), 7.49 (s, 1H, thiazole H-5), 8.51 (s, 1H, pyrimidobenzothiazole H-2), 12.52 (s, br, 1H, NH). MS *m/z* (%): 404 (M$^+$, 39.4), 376 (22.7), 352 (41.5), 327 (20.2), 300 (25.4), 251 (15.2), 229 (37.4), 201 (100), 194 (38.6), 175 (31.2), 160 (50), 153 (31.5), 134 (44.8), 127 (21.4), 77 (68.5). Anal. For $C_{20}H_{12}N_4O_2S_2$ (404.46) Calcd.: C 59.39; H 2.99; N 13.85. Found: C 59.27; H 3.06; N 13.97 %.

Synthesis of 4-amino-*N*-(4-phenyl-1,3-thiazol-2-yl)pyrimido[1,2-*a*]benzimidazole-3-carboxamide (**23**)

Method A. A mixture of enaminonitrile **2** (0.298 g, 0.001 mole) and 2-aminobenzimidazole (0.133 g, 0.001 mole) in a mixture of ethanol and dimethylformamide (1:1) (20 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 12 h. The precipitated product was filtered off, washed with ethanol, dried well, and crystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound **23**.

Method B. A mixture of 2-cyano-*N*-(4-phenylthiazol-2-yl)acetamide **1** (0.243 g, 0.001 mole) and *N*-1*H*-benzimidazol-2-yl-*N*,*N*-dimethylformamidine (0.188 g, 0.001 mole) in refluxing ethanol (20 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 8 h. The

precipitated product was filtered off, washed with ethanol, dried well, and crystallized from a mixture of ethanol and dimethylformamide (1:1) to give compound **23**. Brown powder; Yield 57%; mp 266 ºC; IR (KBr): $\nu_{max.}$/cm^{-1} = 3445, 3300 (NH_2), 3215 (NH), 1648 (C=O). ^{1}H-NMR (DMSO–d_6): δ_{ppm} = 6.35 (s, br, 2H, NH_2), 7.29 – 8.02 (m, 9H, Ar-H), 7.58 (s, 1H, thiazole H-5), 8.6 (s, 1H, pyrimidobenzimidazole H-2), 12.01 (s, br, 1H, NH). MS *m/z* (%): 386 (M^+, 25.6), 255 (15.2), 229 (37.4), 201 (65.2), 194 (38.6), 175 (100), 160 (54.6), 153 (32.3), 127 (29.9), 77 (70). Anal. For $C_{20}H_{14}N_6OS$ (386.43) Calcd.: C 62.16; H 3.65; N 21.75. Found: C 62.24; H 3.58; N 21.82 %.

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