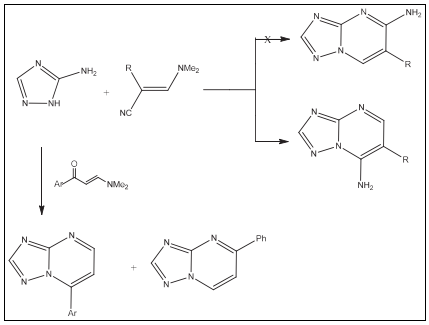
Synthesis of New [1,2,4]Triazolo[1,5-*a*]pyrimidine Derivatives: Reactivity of 3-Amino[1,2,4]triazole towards Enaminonitriles and Enaminones

Abdulaziz Alnajjar,[a] Mervat Mohammed Abdelkhalik,[a] Mohamed Abdelmonem Raslan,[b] Solwan Maher Ibraheem,[b] and Kamal Usef Sadek[c]*

[a]Applied Science Department, College of Technological Studies, Public Authority for Applied Education and Training, P. O. Box 42325, Safat 70654, Kuwait
[b]Chemistry Department, Faculty of Science, Aswan University, Aswan 81528, Egypt
[c]Chemistry Department, Faculty of Science, Minia University, Minia, 61519, Egypt
*E-mail: kusadek@yahoo.com
Received March 27, 2018
DOI 10.1002/jhet.3222
Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com).

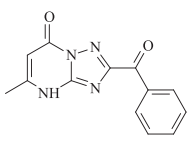


A diversity of new **7**-substituted[1,2,4]triazolo[1,5-*a*]pyrimidine and 6-substituted[1,2,4]triazolo[1,5-*a*]pyrimidine-7-amine derivatives has been synthesized *via* reaction of 3-amino-[1,2,4]triazole with enaminonitriles and enaminones. The regio orientation and the structure of the products were confirmed by spectral and analytical data and synthesis *via* an alternative route. The procedure proved to be simple, efficient, and high yielding, and diversities of [1,2,4]triazolo[1,5-*a*]pyrimidines were obtained.

J. Heterocyclic Chem., **00,** 00 (2018).

INTRODUCTION

Essramycin is the first reported antibiotic with a [1,2,4]triazolo[1,5-*a*]pyrimidines scaffold [1]. The biological importance of [1,2,4]triazolo[1,5-*a*]pyrimidines, as purine analogues, is well documented. Over the years, various substituted derivatives of these scaffolds have shown to act as antifungal [2], antitubercular [3], and antibacterial [4] agents. They have proven as well to be excellent herbicidal and plant growth regulators [5]; polycyclic systems containing [1,2,4]triazolo[1,5-*a*]-pyrimidine moiety are reported as corticotropin-releasing factor 1 receptor antagonists [6] or calcium channel modulators [7]. They were also reported to possess promising anticancer activities, particularly those with C-5, C-6, or C-7 substituents [8].



Essramycin

The synthetic approaches of [1,2,4]triazolo[1,5-*a*]pyrimidines mainly involve two main groups. Either *via* cyclocondensation of 3(5)-amino[1,2,4]triazole with 1,2-dielectrophiles, such as dicarbonyl substituted vinyl ketones, enaminones, and chalcones in refluxing acetic acid, acetonitrile, or pyridine/HCl [9,10], or *via* oxidation of aminopyrimidine Schiff bases utilizing iron chloride [11]. Condensation of diamino-substituted pyrimidines can also be used with ortho-esters or with cyanohydrides [12].

Recently, some [1,2,4]triazolo[1,5-*a*]pyrimidines-7-amines were found to have marked anticancer activity. These scaffolds have been reported to be synthesized *via* a lengthy multistep procedure utilizing 8-butyrolactone as a starting material [13,14] or introducing the isomeric [1,2,4]triazolo[4,3-*a*]pyrimidines into a formal Dimorth rearrangement with diamines under heating in basic medium [15].

3(5)-Amino-1,2,4-triaoles have two nucleophilic reaction centers which can lead to the formation of different cyclic reaction products. Most of the reported literature has confirmed that cyclocondensation of 3(5)-amino-1,2,4-triaoles with electrophiles starts with the interaction of exocyclic amino function with electrophiles, followed by cyclization with N-2 ring nitrogen. However, it has been recently reported [16] that the regioselectivity in such a reaction was controlled by the type of solvent utilized, whether it is a proton or a non-proton donor.

In continuation of our efforts aimed at developing new routes for the synthesis of polyfunctional substituted

heterocycles [17–20], we report, herein, the results of our investigation for the reactivity of 3(5)-amino-[1,2,4] triazole with enaminonitriles and enaminones. A variety of new functionally 5-substituted [1,2,4]triazolo[1,5-*a*] pyrimidines and 6-substituted [1,2,4]triazolo[1,5-*a*] pyrimidines-7-amine was obtained in excellent yields. The structure proposed for the reaction products was established based on analytical and spectral data and alternative synthetic routes.

RESULTS AND DISCUSSION

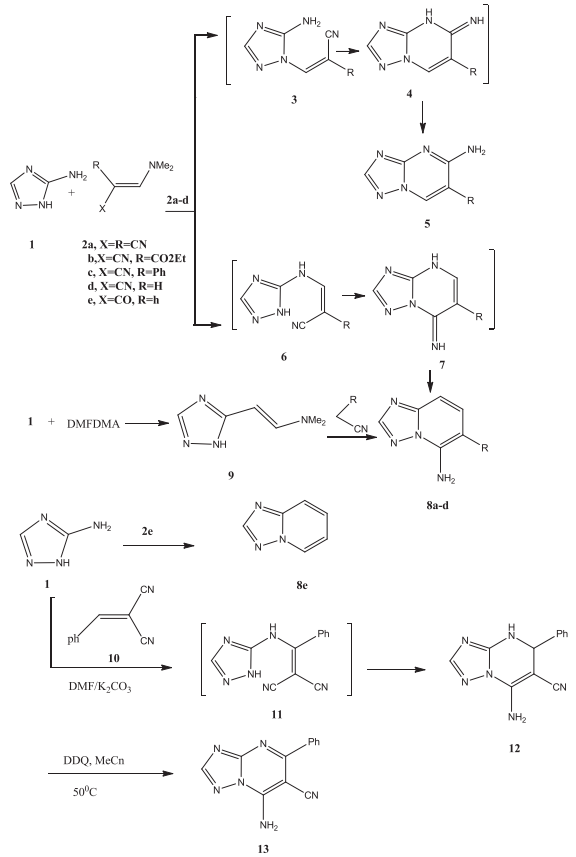
We began this study by reacting 3(5)-amino[1,2,4]triaole **1** and 2-[(dimethylamino)methylene] malononitrile **2a** utilizing several solvents such as ethanol, acetic acid, or methanol/HCl. No significant reaction was observed, even for long reaction period times. However, we were delighted to find that heating under reflux the reaction mixture in dimethylformamide (DMF) with catalytic amount of anhydrous potassium carbonate afforded a solid product in 85% yield. This may be formulated as the 5-amino-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carbonitrile **5a** or isomeric 7-amino derivative **8a**. Product **8a** was established based on analytical and spectral data. The mass spectrum of the reaction product showed a molecular ion peak *m/z* = 160.2 (100%). IR spectrum revealed the presence of an amino and cyano groups at λ_{max} = 3126 and 2225 cm^{-1}, respectively. ^1H NMR spectrum showed two broad singlets at δ = 9.29 and 6.79 ppm assigned for NH_2 protons. The downlow field shift of amino protons could be rationalized for the anisotropic effect of N-**7a**. If the reaction product was **5a**, these protons will appear at a higher field δ ≈ 7.4 ppm. In addition, ^{13}C NMR chemical shift of enamine carbon C-6 appears at a higher field δ = 77.36 ppm, as the cyano substituent shifts the δ value of this carbon to higher field. The structure of **8a** was further confirmed through the reaction of *N*,*N*-dimethyl-*N*′-(4*H*)-([1,2,4]triazol-3-yl)-formamidine **9** with malononitrile under the same reaction conditions, affording an authentic sample of **8a**.

Subsequently, we investigated the scope of this reaction by extending the synthesis to other [1,2,4]triazolo[1,5-*a*] pyrimidine derivatives under the same reaction conditions. Thus, reacting **1** with ethyl 2-cyano-3-(dimethylamino) acrylate **2b** for 2 h afforded the corresponding ethyl 7-amino[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate **8b** in 85% yield. Similarly, the reaction of **1** with 3-(dimethylamino)-2-phenylacrylonitrile **2c** yielded the corresponding 7-amino derivative **8c**. Compound **8c** showed proton shifts at δ =7.96, 8.30, and 8.53 ppm for amino protons, H-2 and H-5, respectively, in addition to aromatic protons. Compounds **8b**,**c** could also be alternatively synthesized *via* reacting **9** with ethyl cyanoacetate and benzyl cyanide. Compound **1** also reacted with 3-(dimethylamino)acrylonitrile **2d** to afford the parent [1,2,4]triazolo[1,5-*a*]pyrimidin-7-amine **8d**. Mass spectrum of the reaction product revealed ion peak at 135.1 (100%) *m/z*. IR spectrum of the reaction product reveals the absence of cyano group and the presence of NH_2 function at λ_{max} = 3336 cm^{-1}. ^1H NMR showed absorption bands at δ = 6.29, 8.10, 8.24, and 8.43 ppm assigned for H-6, NH_2, H-5, and H-2 protons, respectively. ^{13}C NMR revealed absorption bands for C-6 and C-7 carbons at δ = 90.65 and 149.16 ppm, respectively. If the reaction product was **5d**, it will reveal such peaks at downfield shifts (≈105 and 163 ppm). This synthetic approach extended to the synthesis of unsubstituted [1,2,4]triazolo[1,5-*a*]pyrimidine **8e** through the reaction of **1** with **2e**. The structure proposed for **8e** was established based on analytical and spectral data. To the best of our knowledge, the synthesis of **8e** has not been extensively reported, and it was marketed in a very high price.

The reaction of **1** with benzylidene malononitrile **10** in refluxing DMF/K_2CO_3 afforded the corresponding triazolo[1,5-*a*]dihydropyrimine derivative **12** formed *via* initial addition of exocyclic amino group to the activated double bond system of **10** forming the acyclic adduct **11** which was cyclized to final product **12** *via* addition of ring nitrogen to the cyano function. The structure of **12** could be established in bases of analytical and spectral data. Compound **12** showed a molecular ion peak *m/z* = 238.2 (17%). ^1H NMR spectrum showed two proton singlets at δ = 5.32 and 8.61 ppm assigned for NH and H-5 protons in addition to H-2 proton signal at δ = 8.78 as well as aromatic protons. ^{13}C NMR was in agreement of the proposed structure. Heating under reflux **12** in MeCN in the presence of 3 eq. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone afforded the corresponding triazolopyrimidine **13** (Scheme 1).

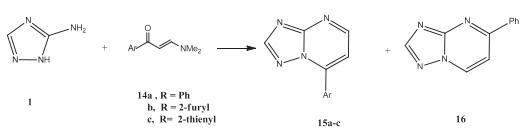
The cyclocondensation of **1** with β-enaminones **14a**–**c** in acetic acid under reflux has been recently reported to afford the corresponding 5-substituted [1,2,4]-triazolo[1,5-*a*] pyrimidines. We examined the cyclocondensation of an equimolecular amount of β-enaminones **14a** with **1** in DMF/K_2CO_3 under reflux for 2 h. Two supposed products **15a** and **16** were isolated in 1:1 ratio. Both products showed a molecular ion peak *m/z* = 196.0 (100%). 7-Phenyl derivatives **15a** mp. 141–143°C (Litmp. 146°C) [21] showed ^1H NMR signals at δ ppm = 7.63–7.58 (m, 3H, Ar–H), 7.98 (d, 1H, J = 4.8 Hz, H-6), 8.28–8.32 (m, 2H, Ar–H), 8.68 (s, 1H, H-2), 9.45 (d, 1H, J = 5.0 Hz H-5). Additionally, ^{13}C NMR spectra established the proposed structure. 5-Phenyl derivative **16** mp. 182–184°C, Lit. mp. 186°C [22], revealed ^1H NMR absorption bands at δ ppm = 7.54–7.60 (m, 3H, Ar–H), 7.95 (d, 1H,

Scheme 1



J = 7.2 Hz, H-6), 8.28 (t, 2H, J = 4.0 Hz, Ar–H), 8.67 (s, 1H, H-2), 8.92 (d, 1H, J = 7.3 Hz H-7). Compounds **15a** and **16** resulted from the initial condensation of both exocyclic amino group and ring nitrogen. Comparison of the coupling constants values of the 7-substituted isomer **15a** and 5-substituted isomer **16** enabled us to differentiate between them. The coupling constant value of compound **15a** is consistent with that of previously reported isomer synthesized from the reaction of vinyl iminium salt with 3-amino-1,2,4-triazole [21]. However, the reaction of **1** with **14b**,**c** resulted in the formation of 7-aryl-substituted derivatives **15b**,**c** as the sole isolable products. We do believe that in going from **14a** to the strong electron donating furyl or thienyl substituents, the reaction became more regioselective and condensation initially proceeds with the less basic exocyclic amino function (cf. Scheme 2).

Scheme 2



CONCLUSION

In conclusion, a simple, efficient, and high yielding process could be developed that provides access to [1,2,4]triazolo[1,5-*a*]pytimidin-7-amine derivatives. Furthermore, this methodology is tolerant to various unsubstituted and 7-aryl substituted [1,2,4]triazolo[1,5-*a*] pyrimidine derivatives. We can reveal that the reaction of 3(5)-1,2,4-triazole with enaminonitriles and enaminones proceeds with an initial attack of exocyclic amino function followed by cyclization. Although the initial ring nitrogen attack can be proposed, here, steric factors hinder such an attack, and the reaction exclusively occurs at the exocycli amino.

EXPERIMENTAL

Melting points were determined on a Shimadzu-Gallenkamp apparatus (Gemini BV Laboratory, DG Apeldoorn, Netherlands) and are uncorrected. Elemental analysis was obtained by means of a LECO CHNS-932 Elemental Analyzer (LECO Corporation, St. Joseph, MI). NMR spectra were measured using a Bruker DPX 400 MHz superconducting spectrometer (Bruker Corporation, Billerica, MA), and FT-IR measurements were obtained from a Perkin Elmer 2000 FT-IR system (MasSpec Consulting Inc., Oakville, ON, Canada). Mass spectrometric analysis was carried out on a VG-Autospec-Q high performance tri-sector GC/MS/MS.

General Procedure for the Synthesis of Polysubstituted[1,2,4]triazolo[1,5-*a*]pyrimidines 8a–e, 12,13, and 14,15. ***Method A.*** To a mixture of 3(5)-aminotriazole (1 mmol), enaminonitriles **2a**–**c**, benzylidene malononitrile **10**, or enaminones **14a**–**c** (1 mmol) in DMF (10 mL) was added catalytic amount of K_2CO_3 (10 mol %), and the reaction mixture was heated under reflux for 2 h. After cooling to room temperature, the solid product formed was collected by filtration and recrystallized from the proper solvent to afford analytically pure sample. The reaction product of **1** with enaminone **14a** was isolated by column chromatography using acetone-*n*-hexane (1:3) as eluent that affords analytically pure samples of **15a** and **16**.

Method B for the Synthesis of 8a–c. To a mixture of *N*,*N*-dimethyl-*N*′-(4*H*-[1,2,4]triazol-1-yl)formamidine **9** (1 mmol), malononitrile, ethyl cyanoacetate, or benzyl cyanide (1 mmol) in DMF (10 mL) was added catalytic amount of K_2CO_3 (10 mol %). The reaction mixture was heated under reflux for 2 h. After cooling to room temperature, the solid product formed was collected by filtration and crystallized from the proper solvent to afford analytically pure samples of **8a**–**c**.

7-Amino-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (8a). Golden yellow crystals from ethanol, mp. 283–285°C. Yield 88% (1.40 g); ESI-Ms: m/z: 160.2 [M^+]. IR λ max/cm^{-1}: 3126 (NH_2), 2225 (CN). ^{1}H NMR (DMSO-d_6) δ ppm: 9.29 (br s, 1H, NH), 8.63 (s, 1H, H-2), 8.59 (s, 1H, H-5), 6.79 (br s, 1H, NH), ^{13}C NMR (DMSO-d_6) δ ppm: 77.36, 115.61, 151.13, 155.91, 157.35 and 162. *Anal.* Calcd. for $C_6H_4N_6$ (160.14): C 45.0, H 2.52, N 52.48. Found: C 45.12, H 2.51, N 52.35.

Ethyl 7-amino-[1,2,4]triazolo[1,5-a]pyrimidine-6-carboxylate (8b). Brown crystals from methanol, mp. 223–224°C. Yield 85% (1.74 g); ESI-MS: *m/z* = 207.0 (M^+); IR λ max/cm^{-1}: 3362(NH_2), 1694 (CO). ^{1}H NMR (DMSO-d_6) δ ppm: 9.18 (s, 1H, hydrogen bonded, NH of NH_2), 8.86 (s, 1H, H-2), 8.62 (br s, 1H, NH), 8.59 (s, 1H, H-5), 4.33–4.38 (q, 2H, J = 7.2 Hz, CH_2), 1.34 (t, 3H, J = 7.2 Hz, CH_3). ^{13}C NMR (DMSO-d_6) δ ppm: 14.63, 61.28, 93.57, 150.17, 156.03, 156.57 and 165.75. *Anal.* Calcd. for $C_8H_9N_5O_2$ (207.19): C 46.38, H 4.38, N 33.80. Found: C 46.26, H 4.49, N 33.79.

6-Phenyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-amine (8c). Brown crystals from dioxane, mp. 291–292°C. Yield 83% (1.75 g); ESI-MS: *m/z* = 211.0 (M^+); IR λ max/cm^{-1}: 3414 (NH_2). ^{1}H NMR (DMSO-d_6) δ ppm: 8.53 (s, 1H, H-2), 8.30 (s, 1H, H-5), 7.96 (s, 2H, NH_2), 7.42–7.54 (m, 5H, Ar–H). ^{13}C NMR (DMSO-d_6) δ ppm: 102.21, 105.32, 128.17, 129.86, 132.07, 133.68, 144.59, 146.96, 154.46, 155.29 and 153.39. *Anal.* Calcd. for $C_{11}H_9N_5$ (211.23): C 62.55, H 4.29, N 33.16. Found: C 62.45, H 4.44, N 33.01.

[1,2,4]Triazolo[1,5-a]pyrimidin-7-amine (8d). Pale yellow crystals from ethanol, mp. 288–290°C. Yield 78% (1.05 g); ESI-MS: *m/z* = 135 (M^+); IR λ max/cm^{-1}: 3336 (NH_2).^{1}H NMR (DMSO-d_6) δ ppm: 8.43 (s, 1H, H-2), 8.24 (d, 1H, J = 2.8 Hz. H-5), 8.10 (brs, 2H, NH_2), 6.29 (d, 1H, J = 3.6 Hz. H-6), ^{13}C NMR (DMSO-d_6) δ ppm: 90.65, 149.16, 153.40, 154.31 and 155.83. *Anal.* Calcd. for $C_5H_5N_5$ (135.13): C 44.44, H 3.73, N 51.83. Found: C 44.42, H 3.73, N 51.72.

[1,2,4]Triazolo[1,5-a]pyrimidine (8e). Colorless crystals from benzene, mp. 144–146°C, Lit. mp Sigma Aldrich 142–145°C. Yield 82% (0.96 g); ESI-MS: *m/z* = 120 (M^+); IR λ max/cm^{-1}: 3083 (C–H), 1661 (C=N). ^{1}H NMR (DMSO-d_6) δ ppm: 9.41–9.43 (m, 1H, H-5), 8.90–8.89 (m, 1H, H-7), 8.62 (s, 1H, H-2), 7.31–7.34 (m, 1H, H-6). ^{13}C NMR (DMSO-d_6) δ ppm: 110.87, 137.36, 154.61, 155.47 and 155.79. *Anal.* Calcd. for $C_5H_4N_4$ (120.11): C 50.00, H 3.36, N 46.64. Found: C 50.23, H 3.49, N 46.71.

7-Amino-5-phenyl-4,5-dihydro-[1,2,4]-triazolo[1,5-a] pyrimidine (12). Colorless crystals from dioxane, mp. 133–135°C. Yield 82% (1.93 g). ESI-MS: *m/z* = 238.2. ^{1}H NMR (DMSO-d_6) δ ppm: 8.791 (s, 1H, H-2), 8.62 (s, 1H, H-5), 7.71–7.28 (m, 5H, Ar–H), 7.22 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ ppm: 155.89, 153.91, 151.82, 146.92, 143.14, 136.94, 130.48, 128.63, 125.97, 118.91, 56.01, and 53.98. *Anal.* Calcd. for $C_{12}H_{10}N_6$ (238.25): C 60.50, H, 4.23, N 35.27. Found: C 60.38, H 4.22, N 35.24.

7-Phenyl-[1,2,4]triazolo[1,5-a]pyrimidine (13a). Yellow crystals, mp. 141–143°C. Yield 44% (0.86 g); ESI-MS: *m/z* = 196.0 (M^+); IR λ max/cm^{-1}: 3100 (C–H) and 1620 (C=N). ^{1}H NMR (DMSO-d_6) δ ppm: 7.63–7.58 (m, 3H, Ar–H), 7.98 (d, 1H, J = 7.2 Hz, H-6), 8.32–8.28 (m, 2H, Ar–H), 8.68 (s, 1H, H-2), 9.45 (d, 1H, J = 8.8 Hz, H-5); ^{13}C NMR (DMSO-d_6) δ ppm: 107.87, 127.67, 129.10, 131.44, 135.85, 137.56, 154.74, 156.44 and 160.87. *Anal.* Calcd. for $C_{11}H_8N_4$ (196.21): C 67.34, H 4.11, N 28.55. Found: C 67.36, H 4.13, N 28.42.

5-Phenyl-[1,2,4]triazolo[1,5-a]pyrimidine (14). Pale yellow crystals, mp. 182–184°C. Yield 40% (0.78 g); ESI-MS: *m/z* = 196.0 (M^+). ^{1}H NMR (DMSO-d_6) δ ppm: 8.92 (d, 1H, J = 7.3 Hz, H-7), 8.67 (s, 1H, H-2), 8.28 (t, 2H, J = 4 Hz, Ar–H), 7.95 (d, 1H, J = 7.2 Hz, H-6), 7.54–7.60(m, 3H, Ar–H). ^{13}C NMR (DMSO-d_6) δ ppm: 107.83, 109.62, 127.62, 129.48, 131.63, 135.80, 137.49, 147.21, 156.41 and 160.82. *Anal.* Calcd. for $C_{11}H_8N_4$ (196.21): C 67.34, H 4.11, N 28.55. Found: C 67.36, H 4.15, N 28.58.

7-(Furan-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine (13b). Brown crystals from ethanol, mp 193–149°C. Yield 75% (1.4 g); ESI.MS: *m/z* = 186.2 (M^+). ^{1}H NMR (DMSO-d_6) δ ppm: 8.88 (d, 1H, J = 4 Hz, H-5), 8.80 (s, 1H, H-2), 8.20 (d, 1H, J = 5 Hz, furan-H), 8.05 (d, 1H, J = 5 Hz, furan-H, 7.62 (d, 1H, J = 4 Hz, H-6), 6.91–7.60 (m, 1H, furan-H). ^{13}C NMR (DMSO-d_6) δ ppm: 104.9, 114.11, 120.78, 136.81, 142.88, 148.54, 154.91, 155.74 and 156.29. *Anal.* Calcd. for $C_9H_6N_4O$ (186.17): C 58.06, H 3.25, N 30.09. Found: C 58.16, H 3.34, N 30.15.

7-(Thien-2-yl)-[1,2,4]triazolo[1,5-a]pyrimidine (13b). Brown crystals from ethanol, mp 172–173°C. Yield 82% (1.65 g); ESI.MS: *m/z* = 202.2 (M+). ^{1}H NMR (DMSO-d_6) δ ppm: 8.87 (d, 1H, J = 5 Hz, H-5), 8.81 (s, 1H, H-2), 8.53 (d, 1H, J = 3 Hz, thienyl-H), 8.16 (d, 1H, J = 5 Hz, thienyl-H), 7.94 (d, 1H, J = 5 Hz, CH-6), 7.37–7.39 (m, 1H, thienyl-H). ^{13}C NMR (DMSO-d_6) δ ppm: 106.45, 128.72, 130.16, 133.51, 135.87, 141.44, 154.64, 155.84 and 155.89.

Anal. Calcd. for $C_9H_6N_4S$ (202.23): C 53.45, H 2.99, N 27.70, S 15.85. Found: C 53.40, H 2.94, N 27.75.

Oxidation of Compound 12. Compound **12** (0.238 g, 0.5 mmol) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (0.27 g) in acetonitrile (5 mL) and heated at 55°C for 4 h. The product was then separated by filtration and washed with ethanol to afford **13**.

7-Amino-5-phenyl-[1,2,4]triazolo[1,5-a]pyrimidine-6-carbonitrile (11). Colorless crystals from dioxane, mp. 235°C. Yield 80% (0.19 g); ESI-MS: *m/z* = 236 (M^+); IR λ max/cm^{-1}: 3345(NH_2), 2226 (CN). ^{1}H NMR (DMSO-d_6) δ ppm: 8.61 (s, 1H, H-2), 7.56–7.96 (m, 5H, Ph–H), 7.38 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6) δ ppm: 81.53, 116.57, 127.8, 128.54, 129.24, 130.39, 134.26, 132.19, 134.26, 150.46, 161.48 and 162.69. *Anal.* Calcd. for $C_{12}H_8N_6$ (236.24): C 61.01, H 3.41, N 35.57. Found: C 60.68, H 3.46, N 35.25.

Acknowledgments. This research was done by the financial support of Public Authority for Applied Education and Training (Transform Grant TS-15-02) of Kuwait. We are grateful to the University of Kuwait, general facility projects in the chemistry department for the analytical and spectral measurements.

REFERENCES AND NOTES

[1] El-Gendy, M. M. A.; Shaaban, M.; Kh, A.; El-Bondkly, A. M.; Laatsh, H. J Antibiot 2008, 61, 149.

[2] (a) Xiong, Q.; Lin, X.; Liu, J.; Bi, L.; Bao, X. Chin J Org Chem 2012, 32; (b) Chen, Q.; Zhu, X.-L.; Jiang, L.-L.; Liu, Z.-M.; Yang, G.-F. Eur J Med Chem 2008, 43, 595.

[3] (a) Bhatt, J. D.; Chudasama, C. J.; Patel, K. D. Bioorg Med Chem 2015, 23, 7711; (b) Abdel-Rahman, H. M.; El-Koussi, N. A.; Hassan, H. Y. Arch Pharm Chem Life Sci 2009, 342, 94.

[4] Wang, H.; Lee, M.; Peng, Z.; Blázquez, B.; Lastochkin, E.; Kumarasiri, M.; Bouley, R.; Chang, M.; Mobashery, S. J Med Chem 2015, 58, 4194.

[5] (a) Tang, W.; Shi, D.-Q. J Heterocyclic Chem 2010, 47, 162; (b) Jiang, L.; Chen, C.; Zhou, Y.; Chen, Q. Chin J Org Chem 2009, 29, 1392.

[6] Saito, T.; Obitsu, T.; Minamoto, C.; Sugiura, T.; Matsumura, N.; Ueno, S.; Kishi, A.; Katsumata, S.; Nakai, H.; Toda, M. Bioorg Med Chem 2011, 19, 5955.

[7] Hougaard, C.; Hammami, S.; Eriksen, B. L.; Sorensen, U. S.; Jensen, M. L.; Strobak, D.; Christophersen, P. Mol Pharmacol 2012, 81, 210.

[8] Wu, L. Q.; Zhang, C.; Li, W. L. Bioorg Med Chem Lett 2013, 2013, 5002.

[9] He, X.; Kassab, S. E.; Heinzl, G.; Xue, F. Tetrahedron Lett 2015, 65, 1034.

[10] Frizzo, C. P.; Scapin, E.; Marzari, M. R. B.; Munchen, M. A. P. UltrasonicsSonochem 2014, 21, 958.

[11] (a) Pattan, S.; Hole, M.; Pattan, J.; Dengale, S.; Shinde, H.; Muluk, R.; Nirmal, S.; Jadhav, R. Indian J Chem Sec B Org Chem Incl Med Chem 2012, 51B, 774; (b) Bartels, B.; Bolas, C. G.; Cueni, P.; Fantasia, S.; Gaeng, N.; Trita, A. S. J Org Chem 2015, 80, 1249.

[12] Kishida, M.; Natsume, F.; Kawaguchi, S. Jpn Kokai Tokyo Koho 2004, 107, 228.

[13] Zhai, X.; Zhao, Y.-F.; Liu, Y.-J.; Zhang, Y.; Xun, F.-Q.; Liu, J.; Gong, P. Chem Pharm Bull 2008, 2008, 941.

[14] Zhao, X.-L.; Zhao, Y.-F.; Guo, S.-C.; Song, H.-S.; Wang, D.; Dong, P. Molecules 2007, 12, 1136.

[15] Salgado, A.; Valera, C.; García Collazo, A. M.; Garcia, F. P. I.; Alkora, P. I.; Elguero, J. J Mol Struct 987, 13.

[16] Britsun, V. N. Russian J Org Chem 2008, 44, 1528.

[17] Sadek, K. U.; Mekheimer, R. A.; Mohamed, T. M.; Moustafa, M. S.; Elnagdi, M. H. Beil J Org Chem 2012, 2012, 18.

[18] Abd El Latif, F. M.; Barsy, F. M.; Aref, A. M.; Sadek, K. U. Green Chem 2002, 4, 196.

[19] Sadek, K. U.; Mekheimer, R. A.; Abdel Hameed, A. M.; Elnahas, F.; Elnagdi, M. H. Molecules 2012, 17, 6011.

[20] Mekheimer, R. A.; Asiri, A. M.; Abdel Hameed, A. M.; Awed, R. R.; Sadek, K. U. Green Process and Synth 2016, 5, 365.

[21] Petrich, S. A.; Lisa, Z. Q.; Santigo, M.; Gupton, J. T.; Sikorski, J. A. Tetrahedron 1994, 50, 12113.

[22] Sirakawa, K. J Pharm Soc Japan 1960, 86, 956.