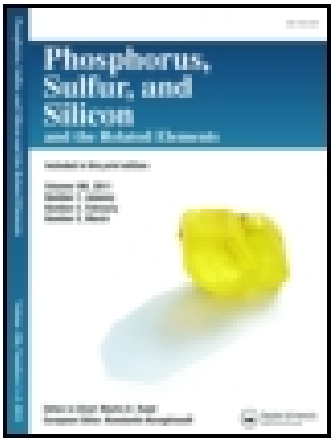


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Synthesis and Reactions of Some New Thiazolylpyrazole Derivatives and Related Compounds

Amer Anwar Amer [a]

[a] Department of Chemistry, Faculty of Science , Sohag University , Sohag, Egypt

Published online: 12 Aug 2008.

To cite this article: Amer Anwar Amer (2008) Synthesis and Reactions of Some New Thiazolylpyrazole Derivatives and Related Compounds, Phosphorus, Sulfur, and Silicon and the Related Elements, 183:9, 2330-2343, DOI: 10.1080/10426500801963608

To link to this article: http://dx.doi.org/10.1080/10426500801963608

Phosphorus, Sulfur, and Silicon, 183:2330–2343, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500801963608

Taylor & Francis
Taylor & Francis Group

Synthesis and Reactions of Some New Thiazolylpyrazole Derivatives and Related Compounds

Amer Anwar Amer
Department of Chemistry, Faculty of Science, Sohag University, Sohag, Egypt

Thiazolylpyrazoles **2-7** *were prepared from the reaction of 2-hydrazino-4-phenylthiazole (***1***) with yielidenenitriles; S,S- or N, S-acetals or ethoxymethylene-malononitrile. 5-Amino-1-(4-phenyl-thiazol-2-yl)-1H-pyrazole-4-carbonitrile (***7***) reacted with phenyl isothiocyanate, carbon disulphide, formic acid, and formamide to furnish the pyrazolopyrimidines* **8**, **9**, **16,** *and* **17**, *respectively. Reaction of compound* **7** *with malononitrile afforded pyrazolopyridine* **10**, *while its reaction with acetic anhydride, acetyl chloride, sulfuric acid, and triethylorthoformate gave thiazolylpyrazoles* **12**, **13**, **15,** *and* **18**, *respectively.*

Keywords 2-hydrazino-4-phenylthiazole; pyrazolopyridine; pyrazolopyrimidines; thiazolylpyrazoles

INTRODUCTION

The thiazole ring has been identified as a central structure element in a number of biological natural products[1–4] and has broad application in drug development for the treatment of allergies,[5] hypertension,[6] inflammation,[7] bacterial infection,[8] and HIV.[9] In this work, we found a good chance to introduce a pyrazole moiety in thiazole ring which has wide applications in different industrial, biological, and medicinal fields beside their application in synthetic organic chemistry.[10–13] Moreover, the biological activity of fused azoles has led to intensive research on their synthesis.[14–17]

RESULTS AND DISCUSSION

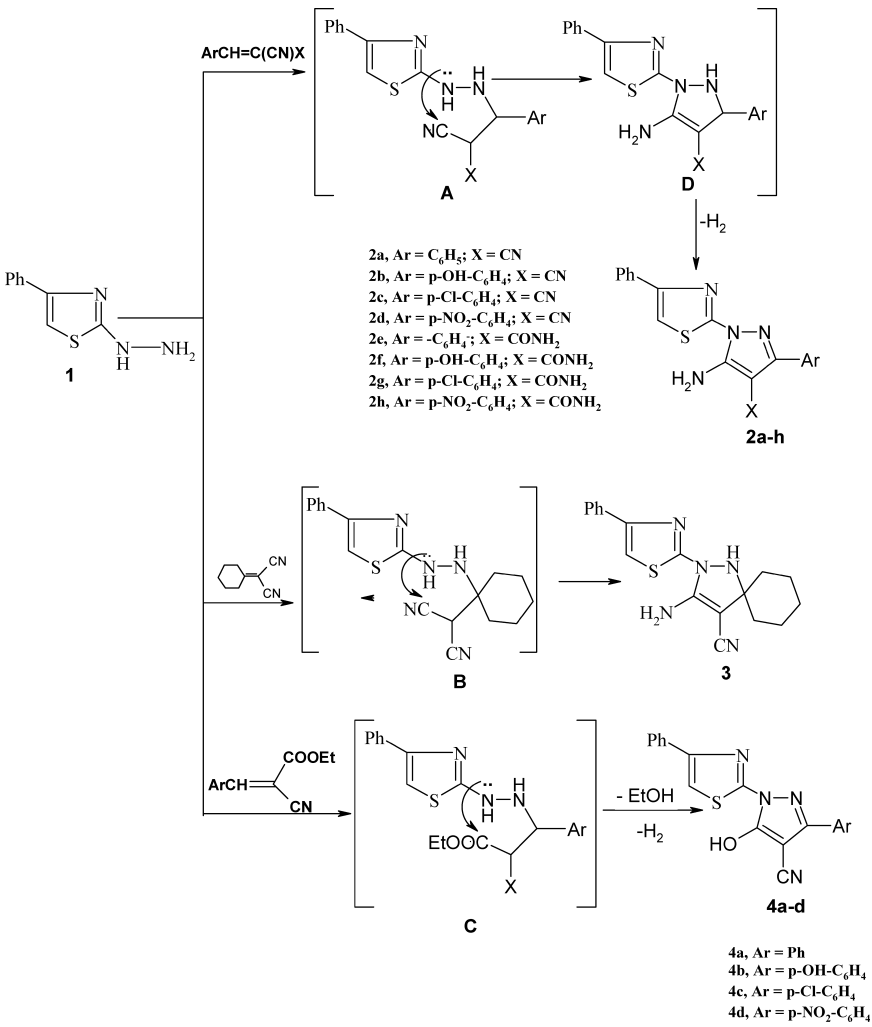
We report here the synthesis of some new thiazolylpyrazoles, pyrazolopyridines and pyrazolopyrimidines. 2-Hydrazino-4-phenylthiazole

Received 24 October 2007; 2 accepted January 2008.
Address correspondence to Amer Anwar Amer, Department of Chemistry, Faculty of Science, Sohag University, Sohag, Egypt. E-mail: amer_chem@Yahoo.com.

(**1**) was prepared via the reaction of phenacylbromide with thiosemicarbazide under reflux in dry ethanol.[18] Compound **1** was allowed to react with arylidenemalononitriles, namely; benzylidenemalononitrile, *p*-hydroxy-, *p*-chloro- and *p*-nitro-benzylidenemalononitrile in 1:2 molar ratio in presence of a catalytic amount of triethylamine to afford the corresponding 5-amino-3-aryl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carbonitriles (**2$_{a-d}$**), respectively. The reaction of compound **1** with benzylidenecyanoacetamide, *p*-hydroxy-, *p*-chloro- and *p*-nitrobenzylidenecyanoacetamide were carried out, where 5-amino-3-phenyl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide (**2$_e$**), 5-amino-3-(*p*-hydroxyphenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide (**2$_f$**), 5-amino-3-(*p*-chlorophenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide (**2$_g$**) and 5-amino-3-(*p*-nitrophenyl)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carb-oxamide (**2$_h$**) were obtained, respectively. By analogy, compound **1** was reacted with cyclohexylidenemalononitrile in the presence of TEA as a basic catalyst to give 3-amino-2-(4-phenylthiazol-2-yl)-1,2-diazaspiro[4.5]dec-3-ene-4-carbonitrile (**3**). Also, treatment of compound **1** with ethyl benzyldenecyanoacetate, ethyl *p*-hydroxy-, *p*-chloro- and *p*-nitrobenzyldenecyanoacetate where 5-hydroxy-3-aryl-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carbonitriles (**4$_{a-d}$**) were obtained, respectively (c. f. Scheme 1).

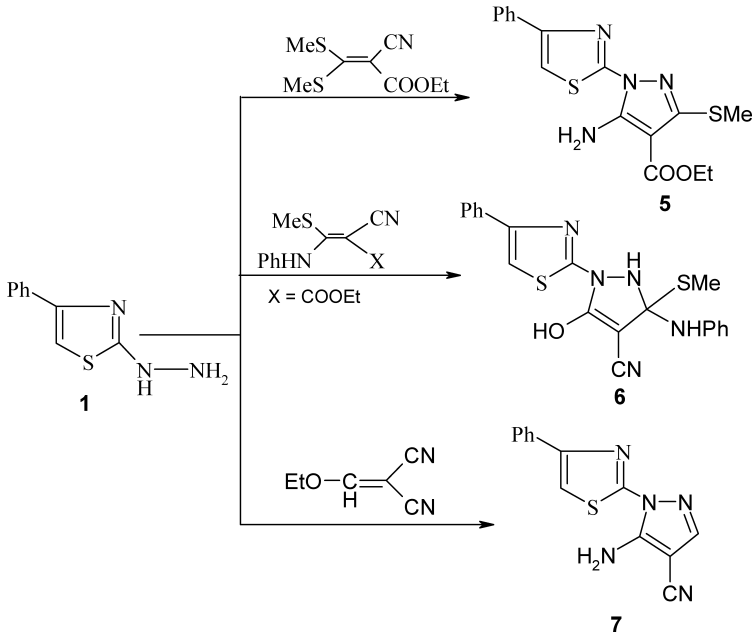
The formation of compounds **2-4** was assumed to proceed *via* the addition of the NH_2 group of compound **1** to the activated double bond of the ylidenenitriles to yield Michael adducts **A-C**, which in turn cyclized through the addition of the NH group to the cyano group or at the C=O group with elimination of ethanol molecule. Aromatization was gained by elimination of hydrogen molecule, which absorbed by another molecule of the ylidenenitrile (c. f. Scheme 2).[19–21] The acyclic adduct **A** and the cyclic product **D** were ruled out based on elemental analysis and ^{1}H NMR spectrum which revealed the absence of any protons attached to SP^3 carbons. Structures **2**, **3,** and **4** were confirmed by elemental as well as spectroscopic data (c. f. Scheme 1, Table I).

Treatment of compound **1** with ethyl dimethylthiomethylenecyanoacetate in presence of TEA, yielded ethyl 5-hydroxy-3-methylthio-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4(2*H*)-carbonitrile (**5**). The formation of compound **5** proceeded through the nucleophilic attack of the NH_2 group of compound **1** to the ethylenic bond with the elimination of MeSH molecule, followed by a nucleophilic attack of the NH group to the cyano group. While the reaction of compound **1** with ethyl anilinomethylthiomethylenemalononitrile yielded 3-anilino-3-methylthio-5-hydroxy-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4(1*H*)-carbonitrile (**6**). The reaction path way was proceed via a nucleophilic attack of the NH_2 group of compound **1** to the



SCHEME 1

ethylenic bond without elimination of MeSH molecule, followed by a nucleophilic attack of the NH group to the carbonyl group with elimination of ethanol. It has been reported[22,23] that some substituted hydrazines react with ethoxymethylenemalononitrile giving the corresponding amino cyanopyrazoles, which are potential prune antagonists. In light of these results, it was of interest to use the hydrazino compound **1** for the preparation of 5-amino-1-(4-phenylthiazol-2-yl)-1 *H*-pyrazole-4-carbonitrile (**7**), by the reaction of compound **1** with



SCHEME 2

ethoxymethylenemalononitrile in presence of TEA as a basic catalyst. The chemical structures of compounds **5**, **6,** and **7** were confirmed by elemental analysis as well as by spectroscopic methods (Scheme 2; Table I).

The o-aminonitrile function in compound **7** was exploited to synthesize some new pyrazolopyrimidines and pyrazolopyridine. The reaction of compound **7** with phenylisothiocyanate and carbon disulphide in ethanolic KOH solution provided 4-anilino-1-(4-phenylthiazol-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine-6(1*H*)-thione (**8**) and 1-(4-phenylthiazol-2 -yl)-1*H*-pyrazolo[3,4-d]pyrimidine-4,6(1*H*,3*H*)-dithione (**9**), respectively. Compound **7** was allowed to react with malononitrile in glacial acetic acid to yield 1:1 adduct. Such a product could be formulated as the 4,6-diamino-1-(4-phenylthiazol-2-yl)-1*H*-pyrazolo[3,4-b]pyridine-5-carbonit-rile (**10**) or 4-amino-1-(4-phenylthiazol-2-yl)-1*H*-pyrazolo-[3,4-*d*]-pyrimidin-6-ylmethylcyanide (**11**). The structure **10** assigned for this product on the basis of its ^{1}H NMR spectrum revealed (beside the aromatic multiplet) two types of D_2O-exchangeable protons and the absence of any protons attached to sp^3 carbon.[24] Treatment of compound **7** with acetic anhydride provided two products, which were identified as 5-diacetylamino-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carbonitrile (**12**)

TABLE I Analytical and Spectral Data of the New Compounds

Product no.	M.p. (°C)[a] cryst. solvent	Yield (%)	Mole. form. (Mol. wt.)	Analytical data calcd./found[b] C	H	N	S	IR (Cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
2_a	239 DMF	77	$C_{19}H_{13}N_5S$ (343.41)	66.45 66.38	3.82 3.65	20.39 19.99	9.34 9.11	3352, 3234 (NH_2), 2200 (CN).	8.4–7.2 (m, 11H, arom. + 1H thiazole), 5.1–4.9 (br, 2H,NH_2).
2_b	134 Ethanol	81	$C_{19}H_{13}N_5OS$ (359.40)	63.50 63.48	3.65 3.51	19.49 19.40	8.92 8.68	3455 (OH), 3372, 3290 (NH_2), 2188 (CN).	10.5 (s, 1H, OH), 8.2–7.2 (m, 10H, arom. + 1H thiazole), 4.9–4.7 (br, 2H, NH_2).
2_c	223 Toluene	68	$C_{19}H_{12}ClN_5S$ (377.85)	60.40 60.10	3.20 2.94	18.53 18.24	8.48 8.30	3330, 3220 (NH_2), 2195 (CN)	7.8–7.0 (m, 10H, arom. + 1H thiazole); 5–4.7 (br, 2H, NH_2)
2_d	285 Acetone	57	$C_{19}H_{12}N_6O_2S$ (388.40)	58.76 59.01	3.11 3.00	21.64 21.49	8.25 8.18	3380, 3230 (NH_2), 2179 (CN), 1540, 1335 (NO_2).	7.6–6.9 (m, 10H, arom. + 1H thiazole); 4.9–4.6 (br, 2H, NH_2).
2_e	73 Ethanol	62	$C_{19}H_{15}N_5OS$ (361.420)	63.14 62.91	4.18 4.10	19.38 19.00	8.87 8.51	3430–3200 ($2NH_2$), 1688 (C═O).	8.1–6.9 (m, 13H, arom. + 1H thiazole + 2H, NH_2); 4.7–4.5 (br, 2H, NH_2).
2_f	222 Ethanol	71	$C_{19}H_{15}N_5O_2S$ (377.42)	60.47 60.31	4.01 3.83	18.56 18.24	8.49 8.33	3460 (OH), 3400–3230 ($2NH_2$), 1649 (C═O).	11.8 (s, 1H, OH), 7.8–6.8 (m, 12H, arom. + 1H thiazole + 2H, NH_2); 5.1–4.8 (br, 2H, NH_2).
2_g	261 Ethanol	83	$C_{19}H_{14}ClN_5OS$ (395.87)	57.65 57.31	3.56 3.20	17.69 17.57	8.10 7.93	3425–3200 ($2NH_2$), 1688 (C═O).	8.2–7.1 (m, 12H, arom. + 1H thiazole + 2H, NH_2), 5.3–5.0 (br, 2H, NH_2).
2_h	303 Acetone	84	$C_{19}H_{14}N_6O_3S$ (406.42)	56.15 56.00	3.47 3.41	20.68 20.38	7.89 7.74	3500–3200 (br., OH + $2NH_2$), 1652 (C═O), 1538, 1344 (NO_2)	7.7–6.8 (m, 12H, arom. + 1H thiazole + 2H, NH_2), 4.6–4.3 (br., 2H, NH_2).

(*Continued on next page*)

TABLE I Analytical and Spectral Data of the New Compounds (*Continued*)

Product no.	M.p. (°C)[a] cryst. solvent	Yield (%)	Mole. form. (Mol. wt.)	Analytical data calcd./found[b] C	H	N	S	IR (Cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
3	87 Ethanol	91	$C_{18}H_{19}N_5S$ (337.44)	64.07 64.09	5.68 5.66	20.75 20.34	9.50 9.39	3418, 3300, 3211 ($NH + NH_2$), 2185 (CN).	10.7–10.5 (br, 1H, NH); 7.4–6.8 (m, 6H, arom. + 1H thiazole), 3.7–3.5 (br, 2H, NH_2), 2.0–1.2 (m, 10 H, cyclic CH_2).
7a	102 Ethanol	64	$C_{19}H_{12}N_4OS$ (344.39)	66.26 66.31	3.51 3.47	16.27 16.25	9.31 9.22	3443 (OH), 2216 (CN).	10.2 (s,1H, OH); 7.8–6.9 (m, 11H, arom. + 1H thiazole).
4b	159 Ethanol	73	$C_{19}H_{12}N_4O_2S$ (360.39)	63.32 63.34	3.36 3.29	15.55 15.21	8.90 8.67	3460–3400 (br., 2 OH), 2210 CN).	8.5 (s,1H, OH); 7.7–7.0 (m, 10H, arom. + 1H thiazole), 5.2 (s,1H, OH)
4c	220 Ethanol	69	$C_{19}H_{11}ClN_4OS$ (378.84)	60.24 60.36	2.93 2.84	14.79 14.63	8.46 8.40	3442 (OH), 2187 (CN).	9.1 (s,1H, OH); 7.7–7.0 m, 10H, 9H arom. + 1H thiazole).
4d	174 Ethanol	71	$C_{19}H_{11}N_5O_3S$ (389.39)	58.61 58.50	2.85 2.71	17.99 17.68	8.23 8.17	3427 (OH), 2187 (CN), 1529, 1330 (NO_2).	7.6–7.0 (m, 10H, arom. + 1H thiazole), 5.5 (s, H, OH).
5	192 DMF	59	$C_{16}H_{16}N_4O_2S_2$ (360.45)	53.32 53.00	4.47 4.33	15.54 15.51	17.79 17.68	3425, 3312 (NH_2), 1680 (C═O).	8.3–8.0 (br, 2H, NH_2), 7.8 (s, 1H, thiazole), 7.5–7.3 (m, 5H, arom.) 4.2 (q, J = 4; 3 Hz, 2H, CH_2), 2.4 (s, 3H, SMe), 1.3–1 (t, J = 4 Hz, 3H, CH_3).

(*Continued on next page*)

TABLE I Analytical and Spectral Data of the New Compounds (*Continued*)

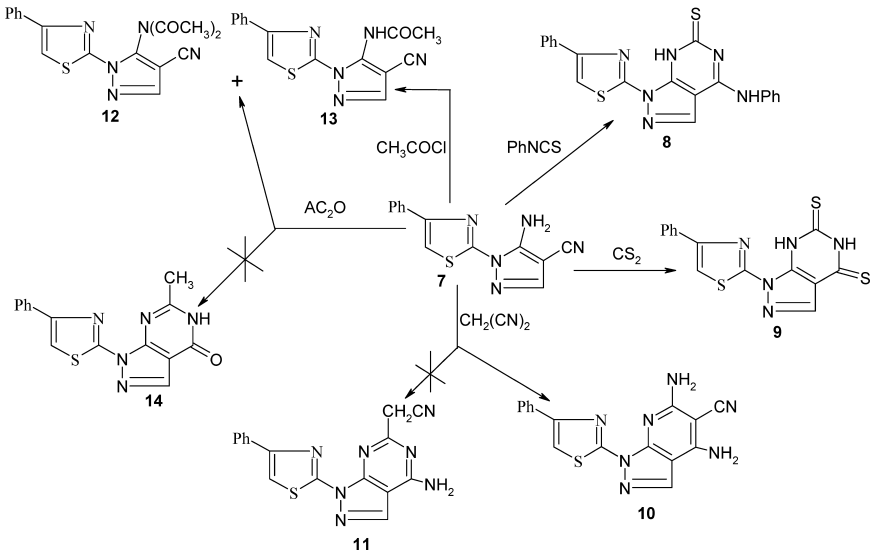
Product no.	M.p. (°C)[a] cryst. solvent	Yield (%)	Mole. form. (Mol. wt.)	Analytical data calcd./found[b] C	H	N	S	IR (Cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
6	144 Ethanol	86	$C_{20}H_{17}N_5OS_2$ (407.51)	58.95 58.64	4.20 4.08	17.19 17.02	15.73 15.64	3460 (OH), 3400, 3323 (2NH), 2190 (CN).	12.6 (s, 1H, OH), 7.4–7.2 (m, 11H, arom. +1H thiazole) 2.72.5 (br, 1H, NH), 2.4 (s, 1 H, NH), 2.2 (s, 3H, SMe).
7	262 DMF	76	$C_{13}H_9N_5S$ (267.31)	58.41 58.49	3.39 3.27	26.20 25.84	11.99 11.84	3396, 3298 (NH_2); 2222 (CN).	7.6 (s, 1H, pyrazole-H), 7.4–7.2 (m, 6 H, arom. + 1H thiazole), 4.6–4.4 (br, 2H, NH_2).
8	240 Ethanol	61	$C_{20}H_{14}N_6S_2$ (402.49)	59.68 59.70	3.51 3.23	20.88 20.74	15.93 15.75	3340, 3299 (2 NH), 1130 C═S).	8.3 (s, 1H, NH); 7.4–6.7 (m, 12 H, arom. 1H-thiazole + 1H pyrazole); 4.5 (s, 1H, NH).
9	221 Ethanol	78	$C_{14}H_9N_5S3$ (343.44)	48.96 48.71	2.64 2.42	20.39 20.17	28.01 27.88	3400, 3279 (2 NH);1140 (C═S).	8.3(s, 1H, NH); 7.3–6.7 (m,8H, arom. + 1H-thiazole + 1H pyrazole + NH).
10	237 Ethanol	63	$C_{16}H_{11}N_7S$ (333.37)	57.65 57.71	3.33 3.24	29.41 28.97	9.62 9.42	3388–3248 (br., 2 NH_2), 2214 (CN).	8.2–8.0 (br., 2H, NH_2); 7.5–7.0 (m,7H, 5H-arom. + 1H-thiaz + 1H pyrazole), 5.4 (s, 2 H, NH_2).
12	310 Benzene	55	$C_{17}H_{13}N_5O_2S$ (351.38)	58.11 57.96	3.73 3.55	19.93 19.71	9.12 8.79	2217 (CN), 1719 (C═O).	7.5–7.0 (m,7H, 5H-arom. + 1H thiazole + 1H pyrazole), 2.4 (s, 6 H, $2CH_3$).

(*Continued on next page*)

TABLE I Analytical and Spectral Data of the New Compounds (*Continued*)

Product no.	M.p. (°C)[a] cryst. solvent	Yield (%)	Mole. form. (Mol. wt.)	Analytical data calcd./found[b] C	H	N	S	IR (Cm^{-1})[c]	^{1}H-NMR ∂ (ppm)[d]
13	240 Benzene	58	$C_{15}H_{11}N_5OS$ (309.34)	58.24 58.31	3.58 3.44	22.64 22.38	10.36 10.21	3293 (NH); 2215 (CN); 1700 (C═O).	7.5–7.0 (m,7H, arom. + 1H-thiazole + 1H pyrazole), 3.4 (s, 1H, NH), 2.4 (s, 3 H, CH_3).
15	220 Toluene	77	$C_{13}H_{11}N_5OS$ (285.32)	54.73 55.10	3.89 3.47	24.55 24.13	11.24 11.04	3428–3300 (2 NH_2), 1652 (C═O).	8.3–8.0 (br, 2H, NH_2); 7.6–7.0 (m, 7H, arom. + 1H thiazole + 1H pyrazole); 4.6–4.4 (br. 2H, NH_2).
16	304 DMF	53	$C_{14}H_9N_5OS$ (295.32)	56.94 56.58	3.07 2.81	23.71 23.47	10.86 10.76	3286 (NH), 1690 C═O).	7.7–7.1 (m, 9H, arom. + NH + 1H thiazole + 1H pyrazole + 1H pyrimidine).
17	287 Ethanol	59	$C_{14}H_{10}N_6S$ (294.33)	57.13 56.81	3.42 3.19	28.55 28.40	10.89 10.71	3420, 3310 (NH_2).	8.4 (s, 1H, H-2, pyrimidine); 7.5–6.8 (m, 7H, arom. + 1H-pyra. + 1H-thiaz.); 5.3–5.0 (br., 2 H, NH_2).
18	215 Benzene	68	$C_{16}H_{13}N_5OS$ (323.37)	59.43 59.11	4.05 3.84	21.66 21.57	9.91 9.82	2215 (CN).	8.6 (s, 1H, N═CH-); 7.5–6.8 (m, 7H, arom. + 1H pyrazole + 1H thiazzole); 4.5–4.2 (q, J = 3; 3 Hz, 2H, CH_2); 1.4–1.1 (t, J = 4; 3 Hz, 3H, CH_3).

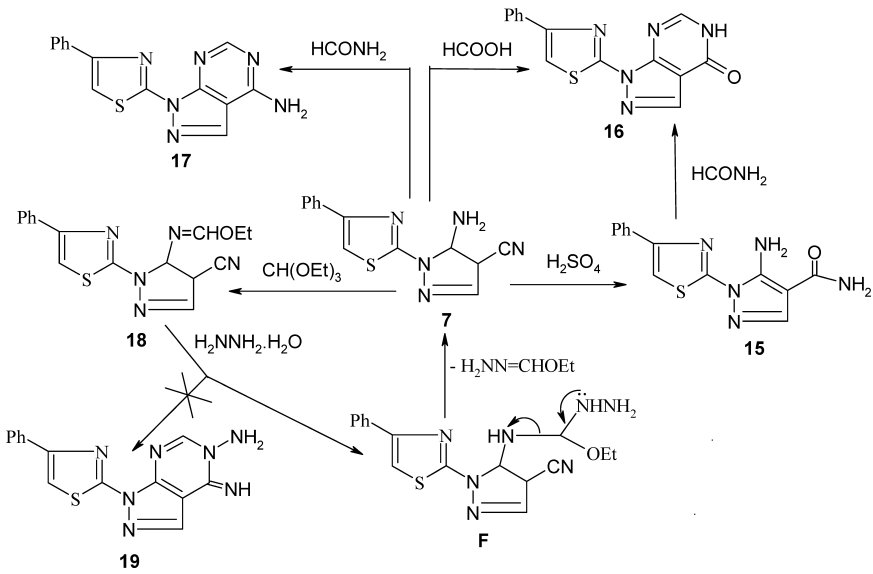
[a]Uncorrected; [b]satisfactory microanalysis obtained C; – 0.47, H; – 0.25, N; – 0.39, S; – 0. 35; [c]measured by Nicolet FT-IR 710 Spectrophotometer; and [d]measured by ^{1}H NMR LA 400 MHz (Jeol) Assiut University.



SCHEME 3

and 5-acetylamino-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carbonitrile (**13**), however the cyclized compound **14** was not obtained.[13] Compound **13** was also prepared by an alternative route *via* the reaction of compound **7** with acetyl chloride in the presence of TEA as a catalyst (Scheme 3).

Hydrolysis of compound **7** with sulfuric acid gave 5-amino-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carboxamide (**15**), which was reacted with formamide to give 1-(4-phenylthiazol-2-yl)-4,5-dihydro-1*H*-pyrazolo[3,4-d]pyrimidin-4-one (**16**). Compound **16** was also obtained by an alternative route by refluxing compound **7** with an excess formic acid. Treatment of compound **7** with an excess formamide afforded 4-amino-1-(4-phenylthiazol-2-yl)-1*H*-pyrazolo[3,4-d]pyrimidine (**17**). The condensation of compound **7** with triethyl orthoformate in boiling acetic anhydride afforded the corresponding 5-(ethyoxymethyleneamino)-1-(4-phenylthiazol-2-yl)-1*H*-pyrazole-4-carbonitrile (**18**). The IR spectrum of compound **18** showed bands at 2940 (CH aliph.) and 2215 (CN), the ^{1}H NMR spectrum of (**18** in DMSO-d_6) revealed signals at 8.6 (s, 1H, N=CH–); 7.5–6.8 (m, 7H, arom. + 1H pyrazole + 1H thiazole); 4.5–4.2 (q, J = 3; 3Hz; 2H, CH_2); 1.4–1.1 (t; J = 4; 3 Hz, 3H, CH_3). When compound **18** was treated with hydrazine hydrate in benzene, the start compound **7** was recovered (m.p., m.m.p., and TLC) instead of the expected pyrimidine **19**. The formation of **7** from the reaction of **18** with hydrazine hydrate was assumed to proceed via the



SCHEME 4

addition of hydrazine at the imino function group to form the intermediate **F**, followed by the elimination of ethyl formate hydrazone[25,26] (Scheme 4).

The structures of new compounds were confirmed based on elemental analyses as well as spectral data (Table I).

CONCLUSION

This study illustrates that 2-Hydrazino-4-phenylthiazole (**1**) is a convenient starting material for the synthesis of thiazolylpyrazole, pyrazolopyrimidine and pyrazolopyridine derivatives. Due to the availability of the starting materials, the simplicity of the procedures, and the comparatively reasonable yields of the products, this synthetic approach might be valuable for the synthesis of such ring systems.

EXPERIMENTAL

All melting points were determined on a Koffler melting points apparatus and are uncorrected. IR spectra were obtained on a Nicolet 710 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian EM 360 at 60 MHz using TMS as an internal reference and DMSO-d_6 as a

solvent. Elemental analyses were performed on a Perkin-Elmer CHN-2400C analyzer model.

Synthesis of 5-Amino-3-aryl-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbonitriles (2a-d), 5-Amino-3-aryl-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carboxamide (2e-2h), and 5-Hydroxy-3-aryl-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbonitriles (4a-d)—General Procedure

A mixture of compound **1** (0.01 mol, 1.91 g), the appropriate arylidenemalononitril, arylidenecyanoacetamide or ethyl arylidenecyanoacetate (0.02 mol), and few drops of TEA (0.02 mL) was refluxed in ethanol (50 mL) for 4 h. The solid thus precipitated was collected and washed several times with ethanol and recrystallized from an appropriate solvent to give compounds $\mathbf{2_{a\text{-}h}}$ and $\mathbf{4_{a\text{-}d}}$, respectively (Scheme 1, Table I).

Synthesis of 3-Amino-2-(4-phenylthiazol-2-yl)-1,2-diazaspiro[4.5]dec-3-ene-4-carbonitrile (3), Ethyl 5-Hydroxy-3-methylthio-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4(2H)-carbonitrile (5), 3-Anilino-3-methylthio-5-hydroxy-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4(1H)-carbonitrile (6), and 5-Amino-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbonitrile (7)—General Procedure

0.01 Mol of compound **1** (1.91 g), cyclohexylidenemalononitrile (1.46 g), ethyl dimethylthiomethylenecyanoacetate (2.17 g), ethyl anilinomethylthiomethylenecyanoacetate (2.62 g), or ethoxymethylenemalononitrile (1.22 g) and triethylamine (0.5 mL) was refluxed in ethanol (30 mL) for 3 h. The solid thus precipitated on hot or after cooling was collected and washed several times with ethanol and crystallized from an appropriate solvent to give compounds **3, 5, 6, and 7**, respectively (Schemes 1 and 2, Table I).

Synthesis of 4-Anilino-1-(4-phenylthiazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidine-6(1H)-thione (8) and 1-(4-Phenylthiazol-2-yl)-1H-pyrazolo[3,4-d]pyrimidine-4,6(1H,3H)-dithione (9)

A mixture of compound **7** (2.67 g, 0.01 mol), phenylisothiocyanate (1.19 mL, 0.01 mol) or carbon disulphide (0.5 mL) and potassium hydroxide (1.12 g, 0.02 mol in 2 mL water) in ethanol (30 mL) was refluxed for 14 h. On cooling, the reaction mixture was poured into ice-cold water containing drops of HCl. The precipitated solid was filtered, dried

and recrystallized to give compounds **8** and **9**, respectively (Scheme 3, Table I).

Synthesis of 4,6-Diamino-1-(4-phenylthiazol-2-yl)-1H-pyrazolo[3,4-b]pyridine-5-carbonit-rile (10)

To a solution of compound **7** (2.67 g, 0.01 mol) in glacial acetic acid (20 mL), malononitrile (0.66 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 5 h, cooled to room temperature, and poured onto an ice/H_2O mixture. The solid product precipitated was filtered off, washed several times with water, dried, and recrystallized to give **10** (Scheme 3, Table I).

Synthesis of 5-Diacetylamino-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbonitrile (12) and 5-Acetylamino-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbonitrile (13)

Method A

Compound **7** (2.67 g, 0.01 mol) was refluxed in acetic anhydride (9 mL) for three hours. The reaction mixture was cooled to room temperature, poured into ice-cold water and the solid product precipitated was filtered off, washed several times with water, dried, and recrystallized from benzene to give **13**. Benzene filtrate was evaporated and the remaining residua was washed several times with petroleum ether (40—60), then the solid obtained was filtered off, dried and recrystallized to give **12** (Scheme 3, Table I).

Method B for the Preparation of Compound 13

A mixture of compound **7** (1.33 g, 0.005 mol), acetyl chloride (2.5 mL) was refluxed in pyridine for 5 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid product precipitated was filtered off, washed several times with water, dried, and recrystallized to give **13** (Scheme 3, Table I).

Synthesis of 5-Amino-1-(4-phenylthiazol-2-yl)-1 H-pyrazole-4-carboxamide (15)

Concentrated sulfuric acid (30 mL) was cooled to 0°C and compound **7** (2.67 g, 0.01 mol) was added and left at room temperature overnight. The reaction mixture was poured onto ice/H_2O mixture and the solid product precipitated was filtered off, washed several times with water, dried, and recrystallized to give **15** (Scheme 3, Table I)

Synthesis of 1-(4-Phenylthiazol-2-yl)-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4-one (16)

Method A

A mixture of compound **15** (1.43 g, 0.005 mol) and formamide (10 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature and the precipitated product was filtered, washed several times with water, dried, and crystallized to give **16** (Scheme 3, Table I).

Method B

Compound **7** (1.33 g, 0.005 mol) was heated under reflux with formic acid (85%, 15 mL) for 15 h. The reaction mixture was cooling at room temperature and the formed solid product was filtered off, washed several times with water, dried, and crystallized to give **16** (Scheme 3, Table I).

Synthesis of 4-Amino- 1-(4-phenylthiazol-2-yl)-1H-pyrazolo [3,4-d]pyrimidine (17)

A mixture of compound **7** (1.33 g, 0.005 mol) and formamide (10 mL) was refluxed for 3 h. The reaction mixture was concentrated and cooled at room temperature, ethanol was added and the precipitated product was filtered, washed several times with water, dried, and crystallized to give **17** (Scheme 3, Table I).

Synthesis of 5-(Ethyoxymethyleneamino)-1-(4-phenylthiazol-2-yl)-1H-pyrazole-4-carbonitrile (18)

A mixture of compound **7** (2.67g, 0.01 mol), triethyl orthoformate (15 mL) and acetic anhydride (15 mL) was refluxed for 8 h. The reaction mixture was concentrated to half volume, cooled and triturated with cold ethanol. The separated product was filtered, washed with petroleum ether (40–60°C) and recrystallized to give **18** (Scheme 3, Table I).

REFERENCES

[1] T. M. Zabriski, C. M. L Mayne, and C. M. Ireland, *J. Am. Chem. Soc.,* **110,** 7919–7920 (1988).
[2] M. Hara, K. Asano, I. Kawamoto, I. Takiguchi, S. Katsumata, K. Takahashi, and H. J. Nakano, *J. Antibiot*., **42,** 1768–1774 (1988).
[3] P. Crews, Y. Kakou, and E. Quinoa, *J. Am. Chem. Soc*., **110,** 4365–4368 (1988).
[4] M. Thierry and O. Daniel, *Tetrahedron*, **57,** 153–156 (2001).
[5] K. D. Hargrave, F. K. Hess, and J. T. Oliver, *J. Med. Chem.,* **26,** 1158 (1983).

[6] W. C. Patt, H. W. Hamilton, M. D. Taylor, M. J. Ryan, D. J. J. Taylor,, C. J. C. Connoly, A. M. Doherty, S. R. Klutchko, I. Sircar, B. A. Steinbaugh, B. L. Batly, C. A. Painchaud, S. T. Rapundalo, B. M. Michniewicz, and S. C. J. Olson, *J. Med. Chem.,* **35,** 2562 (1992).
[7] F. Haviv, J. D. Ratajczyk, R. W. DeNet, F. A. Kerdesky, R. L. Walters, S. P. Schmidt, J. H. Holms, P. R. Young, and G. W. Carter, *J. Med. Chem.,* **31,** 1719 (1988).
[8] K. Tsuji, and H. Ishikawa, *Bioorg. Med. Chem. Lett.,* **4,** 1601 (1994).
[9] F. W. Bell, A. S. Cantrell, M. Hoberg, S. R. Jaskunas, N. G. Johansson, C. L. Jordon, M. D. Kinnick, P. Lind, J. M. Morin, Jr., R. Noreen, B. Oberg, J. A. Palkowitz, C. A. Parrish, J. Pranc, H. Zhang, and X. -X. Zhou, *J. Med. Chem.,* **38,** 4929 (1995).
[10] A. M. Osman, M. S. K. Youssef, and Kh. M. Hassan, *J. Prakt. Chem.,* **320,** 857 (1978).
[11] S. Devi, P. Mitra, S. B. Mishra, and A. S. Mittra, *J. Indian Chem. Soc.,* **60,** 679 (1983).
[12] J. -M. -Z. Gladych, and J. -H. Hunt, *South African Pat.,* **68,** 04, 428 (1968); *Chem. Abstr.*, **71,** 81436^{m} (1979).
[13] R. A. Ahmed, M. S. Kandeel, M. S. Abbady, and M. S. K. Youssef, *J. Heterocycl. Chem.,* **39,** 309 (2002).
[14] M. E. A. Zaki,, *Molecules,* **3,** 71–79 (1998).
[15] H. Hori, E. Ito, T. Jakta, G. Koyama, and H. Umezawa, *J. Antibiot.,* **17A,** 96 (1964).
[16] G. Koyama, and H. Umezawa, *J. Antibiot.,* **18A,** 175 (1965).
[17] R. K. Robins and A. G. Beaman, *J. Heterocycl. Chem.,* **3,** 110 (1965).
[18] A. P. Novikova, N., M. Perova, L. G.; Egorova, and E. I. Bragina, (USSR), *Khim. Getrotsikl. Soedin.* **6,** 846 (1991); *Chem. Abstr.*, **116,** 174115v (1992).
[19] J. L. Soto, C. Seoane, and F. Javier, *Synthesis*, 529 (1981).
[20] A. K. El-Shafei, A. M. El-Sayed, and A. Soliman, *Gazz. Chem. Ital.*, **117,** 385 (1987).
[21] N. Mathur, P. Awani, and K. Ojha, *Pharmazie*, **47,** 944 (1992).
[22] Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Wahab, and S. A. Ahmed, *Syn. Comm.*, **26** (20), 3733 (1996).
[23] I. Y. Mansour and H. A. Hessan, *J. Chin. Chem. Soc.,* **37,** 611 (1990).
[24] S. M. Sherif, *Monatsh. Chem.*, **127,** 955 (1996).
[25] S. M. Hassan, H. E. Emam, and M. M. Abdelall, *J. Chem. Research (S),* 533 (2000); *J. Chem. Res. (M)*, 1301 (2000).
[26] M. S. A. El-Gaby, S. M. Abdel-Gawad, M. M. Ghorab, H. I. Heiba, and H. M. Aly, *Phosphorus, Sulfur, and Silicon*, **181,** 279–297 (2006).