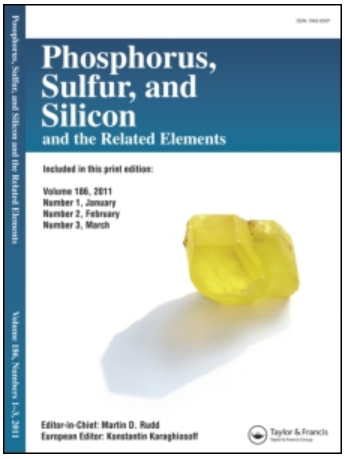

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND TRANSFORMATION OF 2-THIOXOPYRIMIDO [4,5-d]PYRIMIDINES

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To cite this Article Shaker, Rafat M.(2000) 'SYNTHESIS AND TRANSFORMATION OF 2-THIOXOPYRIMIDO [4,5-d]PYRIMIDINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 158: 1, 9 — 16
To link to this Article: DOI: 10.1080/10426500008042069
URL: http://dx.doi.org/10.1080/10426500008042069

Phosphorus, Sulfur, and Silicon, 2000, Vol. 158, pp. 9-16
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SYNTHESIS AND TRANSFORMATION OF 2-THIOXOPYRIMIDO[4,5-d]PYRIMIDINES

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(Received June 02, 1999; In final form July 21, 1999)

Synthesis of bicyclic system pyrimido[4,5-d]pyrimidines and its S-mono- and unsymmetrical S,S′-di-substituted deivatives are described.

Keywords: Synthesis; pyrimido[4; 5-d]pyrimidines; triazolopyrimidopyrimidines

Compounds containing a fused pyrimidine ring represent a broad class of compounds which have received considerable attention over the past years due to their wide range of biological activity[1–3]. However, the pyrimido[4,5-d]pyrimidines have long been used as bronchodilators,[4] antiallergics,[4] vasodilators,[4] antihypertensives,[5] antiinflammatory,[6] and immunosuppressive[6] activity. Also, they displayed rather strong analgesic action,[7] inhibited amphetamine hyperactivity,[7] and abolished apomorphine stereotypy[7]. Prompted by the aforesaid biological and pharmaceutical activities, and in continuation of our previous work aimed at developing new approaches for the synthesis of polyfunctionally substituted heterocyclic compounds of expected biological activity[8–13], we report here the synthesis of the versatile hiltherto unreported, otherwise difficult accessible, bicyclic system 2-thioxo-pyrimido[4,5-d]pyrimidines in order to study their biological activity.

Thus, the starting 2-ethylthio-4-amino-5-carbethoxypyrimidine (**1**) was readily obtained by a previously described procedure[14]. Compound **1** on cyclocondensation with phenyl isothiocyanate (**2**) in boiling pyridine gave 7-ethylthio-4-oxo-3-phenyl-2-thioxo-1,2-dihydro-pyrimido[4,5-d]-pyrimidine (**4**) (Scheme 1). The structural assignments of compound **4** was estab-

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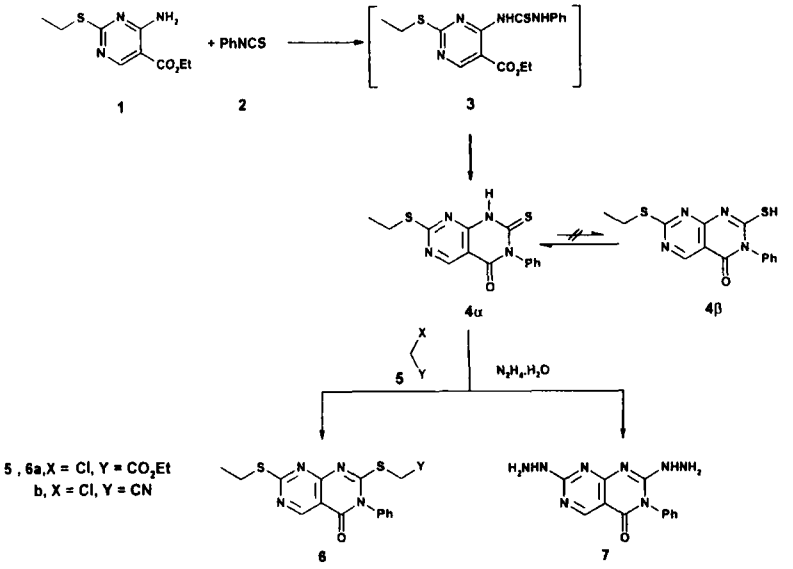
lished by spectroscopic studies and elemental analysis. Thus, the mass spectrum of **4** was compatible with the molecular formula $C_{14}H_{12}N_4OS_2$ (M^+ 316). Its IR spectrum revealed a strong bands at 3390 cm^{-1} (NH), 1700 cm^{-1} (CO), and 1200 cm^{-1} (C=S). The tautomeric equilibrium between thioamide- **4α** and iminethiol-form **4β** seems to be widely shifted towards the thioamide-form as indicated by the ^1H NMR spectrum which revealed a broad singlet at δ 13.50 assigned to the pyrimidine ring NH. The structure **4** was further confirmed by ^{13}C-NMR spectrum (see Experimental).



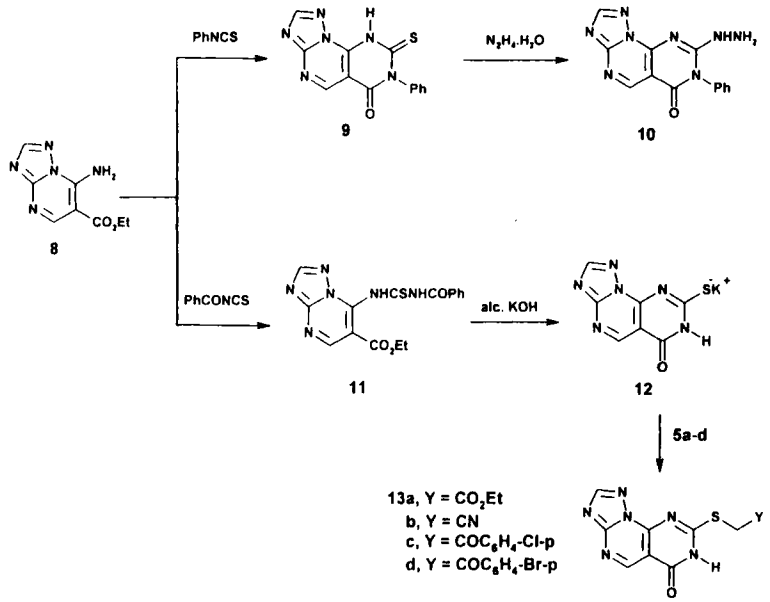
SCHEME 1

The formation of **4** was rationalized in terms of the initial formation of the intermediate thiourea derivative **3** which then cyclized to yield the final product **4** (Scheme 1). During the synthesis of **4**, attempets to isolate **3** under various reaction conditions like refluxing in benzene, toluene, xylene and dioxane, were unsuccessful while direct cyclization was achieved in boiling pyridine.

Compound **4** bearing latent functional substituents were found to be useful for the synthesis of pyrimido[4,5-d]pyrimidine derivatives. It was found that **4** reacted with ethyl chloroacetate (**5a**), and/or chloroace-

tonitrile (**5b**) in sodium ethoxide to afford the corresponding unsymmetrical S,S′-di-substituted pyrimido[4,5-d]pyrimidine-4-one derivatives **6a,b**. Nucleophilic substitution of **4** with hydrazine in ethanol led to 2,7-dihyrazino derivative **7**. The structures of **6** and **7** were also established on the basis of elemental analysis and spectral data which were found to be in good agrecement with the assigned structures (Scheme 1 and see Experimental).

With a view to expand the scope of our investigation, 7-amino-6-carbethoxy-1,2,4-triazolo-[1,5-a]pyrimidine[15] (**8**) was used as a key intermediate to synthesize triheterocyclic derivatives containing the pyrimidopyrimidine moiety. Thus, the reaction of **8** with **2** in boiling pyridine yielded the triazolopyrimidopyrimidine **9**. Compound **9** was transformed into the corresponding 2-hydrazino derivative **10** through the reaction with hydrazine hydrate in ethanol. The structures of **9** and **10** were confirmed on the same line as for **4** (Scheme 2 and see Experimental).



SCHEME 2

In contrast of the previous behaviour, the reaction of **8** with an equimolar amount of benzoyl isothiocyanate in dioxane at reflux for 2 h afforded the acyclic product 7-(N-benzoyl-thioureido)-6-carbethoxy-1,2,4-triazolo-[1,5-a]

pyrimidine (**11**). Intermediate 2-thio-3,4-dihydro-4-oxo-1,2,4-triazolo[1,5-b] pyrimido[4,5-d]pyrimidine potassium salt (**12**) was obtained by alkaline (KOH/EtOH) ring closure reaction of **11**. Compound **12** was alkylated with **5a,b** and/or α-bromoacetophenone derivatives **5c,d** to yield the corresponding sulphides **13a,d**. Structures **11** and **13a,d** were confirmed by the results of elemental analysis and spectral data (Scheme 2 and see Experimental).

EXPERIMENTAL

All mps. were recorded on a Gallen Kamp apparatus and are uncorrected. IR spectra were recorded (as KBr pellets) on a Shimadzu 480 spectrophotometer. The ^1H NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with a Bruker AM 400 (400 MHz) spectrometer using TMS as an internal standard; the ^{13}C NMR spectra were recorded at 100 MHz. The chemical shifts are expressed as δ values (ppm). Mass spectra were determined on a Finnigan MAT 8430 mass spectrometer operating at 70 eV. Microanalysis were performed by the Microanalytical Data Unit at Cairo University.

General Procedure for the synthesis of compounds 4 and 9

To a solution of **1** or **8** (0.01 mol) in pyridine (25 ml), phenyl isothiocyanate (**2**) (0.012 mol) was added and the reaction mixture was refluxed in an oil bath for 35–40 hours (monitored by TLC). After completion of the reaction, it was cooled to room temperature and poured into aqueous methanol (70% v/v). The resulting solid was filtered, washed with cold aqueous methanol, dried, and recrystallized from DMF.

7-Ethylthio-4-oxo-3-phenyl-2-thioxo-1,2-dihydro-pyrimido[4,5-d] pyrimidine (4)

Obtained in 83 % yield; m.p. 221–223 °C; (found : C, 53.30; H, 4.00; N, 17.50; S, 20.10. $C_{14}H_{12}N_4OS_2$ requires C, 53.14; H, 3.82; N, 17.71; S, 20.27%); ν_{max} / cm^{-1} 3390 (NH), 3050 (Ar-CH), 1700 (CO), and 1200 (C=S); δ_H(DMSO-d_6) 1.35 (t, J 7 Hz, 3H, CH_3); 3.20 (q, J 7 Hz, 2H, CH_2), 7.25–7.60 (m, 5 H, Ar-H), 8.90 (s, 1H, H-5), 13.50 (br s, 1H, NH);

δ_C 15.20, 26.60, 107.20, 126.6, 127.2, 128.8, 139.30, 155.20, 157.40, 159.20, 176.70, 179.20; m/z 316 (M^+).

3-Phenyl-4-oxo-2-thioxo-1,2-dihydro-1,2,4-triazolo[1,5-b]pyrimido [4,5-d]pyrimidine (9)

Obtained in 78 % yield; m.p. 364–365 °C; (found : C, 52.50; H, 2.90; N, 28.20; S, 10.70. $C_{13}H_8N_6OS$ requires C, 52.69; H, 2.72; N, 28.37; S, 10.82 %); ν_{max} / cm^{-1}3400 (NH), 3050 (Ar-CH), 1710 (CO), and 1190 (C=S); δ_H (DMSO-d_6) 7.30–7.65 (m, 5 H, Ar-H), 8.50 (s, 1H, CH-triazole), 8.90 (s, 1H, H-5), 13.60 (br s, 1H, NH).

General Procedure for the synthesis of 6a,b

To a solution of sodium ethoxide [prepared by disolving sodium metal (0.01 mol) in anhydrous ethanol (10 ml)], the equivalent amount of 4 dissolved in DMF was added. The reaction mixture was refluxed for 15 min, cooled, and then ethyl chloroacetate (**5a**) and/or chloroacetonitrile (**5b**) (0.012 mol) was added. The mixture was refluxed for 2 hours, cooled and then poured into ice-water (150 ml) and acidified by 1N HCl. The precipitate product so formed was filtered, washed with cold water, dried, and recrystallized from ethanol.

2-Ethoxycarbonylmethylthio-7-ethylthio-4-oxo-3-phenyl-pyrimido [4,5-d]pyrimidine (6a)

Obtained in 71% yield; m.p. 120–122 °C; (found : C, 53.60; H, 4.40; N, 14.10; S, 15.80. $C_{18}H_{18}N_4O_3S_2$requires C, 53.71; H, 4.51; N, 13.92; S, 15.93 %); ν_{max}/ cm^{-1} 3050 (Ar-CH), 1710,1680 (CO); δ_H ($CDCl_3$) 1.25 (t, J 7 Hz, 3H, CH_3); 1.40 (t. J 7 Hz, 3H, CH_3); 3.20 (q, J 7 Hz, 2H CH_2), 4.25 (q, J 7 Hz, 2H, CH_2), 4.60 (s, 2H, CH_2),7.20–7.60 (m, 5 H, Ar-H), 8.90 (s, 1H, H-5).

2-Cyanomethylthio-7-ethylthio-4-oxo-3-phenyl-pyrimido[4,5-d] pyrimidine (6b)

Obtained in 78% yield; m.p. 112–114 °C; (found : C, 54.20; H, 3.50; N, 19.80; S, 18.20. $C_{16}H_{13}N_5OS_2$ requires C, 54.07; H, 3.69; N, 19.71; S. 18.04 %); ν_{max} / cm^{-1} 3050 (Ar-CH), 2200 (CN), 1710 (CO); δ_H ($CDCl_3$)

1.30 (t, J 7 Hz, 3H, CH_3); 3.20 (q, J 7 Hz, 2H, CH_2), 4.50 (s, 2H, CH_2), 7.20–7.60 (m, 5 H, Ar-H), 8.90 (s, 1H, H-5).

General Procedure for the synthesis of compounds 7 and 10

To a suspension of **4** or **9** (0.01 mol) in absolute ethanol (30 ml), hydrazine hydrate 80 % (5 ml) was added. The mixture was refluxed for 5–7 hours. After cooling to room temperature the resulting precipitate was filtered, dried, and recrystallized from the appropriate solvent.

2,7-Dihydrazino-4-oxo-3-phenyl-pyrimido[4,5-d]pyrimidine (7)

Obtained in 67 % yield; m.p >300 °C (from AcOH); (found : C, 50.80; H, 4.40; N, 39.30. $C_{12}H_{12}N_8O$ requires C, 50.70; H, 4.26; N, 39.42 %); ν_{max} / cm^{-1} 3390–3120 (NH_2, NH), 3050 (Ar-CH), 1680 (CO); δ_H (DMSO-d_6) 3.20 (br s, 2H, NH_2), 3.80 (br s, 2H, NH_2), 6.66 (s, 1H, NH),), 6.90 (s, 1H, NH), 7.25–7.60 (m, 5 H, Ar-H), 8.90 (s, 1H, H-5).

2-Hydrazino-4-oxo-3-phenyl-1,2,4-triazolo[1,5-b]pyrimido[4,5-d] pyrimidine (10)

Obtained in 74 % yield; m.p. 243–245 °C (from DMF); (found : C, 53.20; H, 3.60; N, 38.20. $C_{13}H_{10}N_8O$ requires C, 53.06; H, 3.43; N, 38.08 %); ν_{max} / cm^{-1} 3400–3120 (NH_2, NH), 3050 (Ar-CH), 1680 (CO); δ_H (DMSO-d_6) 3.80 (br s, 2H, NH_2), 6.70 (s, 1H, NH), 7.30–7.65 (m, 5 H, Ar-H), 8.50 (s, 1H, CH-triazole), 8.90 (s. 1H, H-5).

Synthesis of 7-(N-benzoyl-thioureido)-6-carbethoxy-1,2,4-triazolo-[1,5-a]pyrimidine (11)

To a stirred solution of benzoyl isothiocyanate [prepared from 0.012 mol of NH_4SCN and the equivalent amount of benzoyl chloride as has been previously described[16]], a solution of **8** (0.01 mol) in dioxane was slowly added drop by dropwise and the mixture was refluxed for 2h. After cooling to roomtemperature the resulting precipitate was collected by filtration, washed with cold water, dried, and recrystallized from ethanol, yield 69 %; m.p. 204–206 °C; (found : C, 52.00; H, 3.60; N, 22.50; S, 8.80. $C_{16}H_{14}N_6O_3S$ requires C, 51.88; H, 3.81; N, 22.69; S, 8.66 %); ν_{max} / cm^{-1} 3250–3100 (NH), 1700,1680 (CO), 1200 (C=S); δ_H (DMSO-d_6)

1.30 (t, J 7 Hz, 3H, CH_3); 4.30 (q, J 7 Hz, 2H, CH_2), 7.40–7.90 (m, 5 H, Ar-H), 8.60 (s, 1H, CH-triazole), 8.80 (s, 1H, H-5), 9.20 (br s, 1H, NH), 9.60 (br s, 1H, NH).

Synthesis of (13a,d)

To a solution of potassium hydroxide (0.02 mol) in absolute ethanol (40 ml), thiourea derivative **11** (0.01 mol) was added. The mixture was refluxed under stirring for 3 hours and after cooling to roomtemperature the resulting precipitate was filtered off to give **12** dried (yield : 95 %, m.p. > 300 °C) which used without purification in the next step.

To a suspension of the collected solid material **12** in ethanol (50 ml), **5a,b** and/or α-bromo-acetophenone derivatives **5c,d** was added and then the mixture was refluxed for 4 hours. After cooling, to roomtemperature the resulting precipitate was collected by filtration, washed with cold aqueous methanol, dried, and recrystallized from DMF to give **13a,d**.

2-Ethoxycarbonylmethylthio-3,4-dihydro-4-oxo-1,2,4-triazolo[1,5-b] pyrimido[4,5-d]-pyrimidine (13a)

Obtained in 68 % yield; m.p. 243–245 °C; (found : C, 43.30; H, 3.10; N, 27.60; S, 10.30. $C_{11}H_{10}N_6O_3S$ requires C, 43.13; H, 3.29; N, 27.44; S, 10.47 %); ν_{max} / cm^{-1} 3150 (NH), 1710,1680 (CO); δ_H (DMSO-d_6) 1.30 (t, J 7 Hz, 3H, CH_3); 4.50 (q, J 7 Hz, 2H, CH_2), 4.50 (s, 2H, CH_2), 8.50 (s, 1H, CH-triazole), 8.80 (s, 1H, H-5), 12.50 (s, 1H, NH).

2-Cyanomethylthio-3,4-dihydro-4-oxo-1,2,4-triazolo[1,5-b]pyrimido [4,5-d]-pyrimidine (13b)

Obtained in 66 % yield; m.p. 210–212 °C; (found : C, 41.50; H, 2.10; N, 37.70; S, 12.50. $C_9H_5N_7OS$ requires C, 41.69; H, 1.94; N, 37.82; S, 12.37 %); ν_{max} / cm^{-1} 3140 (NH), 2200 (CN), 1670 (CO); δ_H (DMSO-d_6) 4.30 (s, 2H, CH_2), 8.50 (s, 1H, CH-triazole), 8.90 (s, 1H, H-5), 12.40 (s, 1H, NH).

2-(*p*-Chlorobenzoyl)methylthio-3,4-dihydro-4-oxo-1,2,4-triazolo [1,5-b]pyrimido[4,5-d]-pyrimidine (13c)

Obtained in 63 % yield; m.p. 240–242 °C; (found : C, 48.50; H, 2.60; N, 22.30; S, 8.50. $C_{15}H_9ClN_6O_2S$ requires C, 48.32; H, 2.43; N, 22.55; S,

8.60 %); ν_{max} / cm^{-1} 3240 (NH), 1700,1675 (2 CO);_δ_H (DMSO-d_6) 4.85 (s, 2H, CH_2), 7.40–7.70 (m, 4H, Ar-H), 8.50 (s, 1H, CH-triazole), 8.90 (s, 1H, H-5), 12.50 (s, 1H, NH).

2-(*p*-Bromobenzoyl)methylthio-3,4-dihydro-4-oxo-1,2,4-triazolo [1,5-b]pyrimido[4,5-d]-pyrimidine (13d)

Obtained in 64 % yield; m.p. 243–245 °C; (found : C, 43.30; H, 2.30; N, 20.20; S, 7.50. $C_{15}H_9BrN_6O_2S$ requires C, 43.18; H, 2.17; N, 20.14; S, 7.68 %); ν_{max} / cm^{-1} 3230 (NH), 1700,1670 (2 CO); δ_H (DMSO-d_6)_4.80 (s, 2H, CH_2), 7.30–7.80 (m, 4H, Ar-H), 8.50 (s, 1H, CH-triazole), 8.90 (s, 1H, H-5), 12.50 (s, 1H, NH).

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