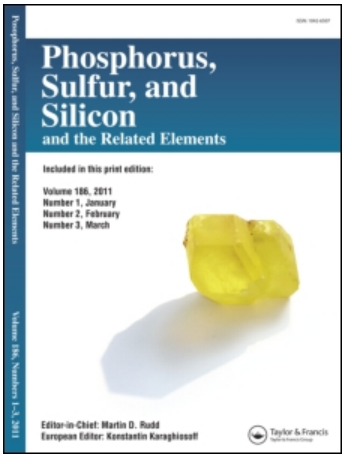

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SYNTHESIS OF SOME THIAZOLO-[3, 2=a]PYRIMIDINES

A. A. Geies[a]; A. M. Kamal El-Dean[a]; A. A. Abd El-Hafez[a]; A. M. Gaber[a]
[a] Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

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SYNTHESIS OF SOME THIAZOLO-[3,2-a]PYRIMIDINES

A. A. GEIES,* A. M. KAMAL-EL-DEAN, A. A. ABD EL-HAFEZ and A. M. GABER

Chemistry Department, Faculty of Science, Assiut University, Assiut, Egypt

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2-Acetyl-6-cyano-7-ethyl-3-methylthiazolo[3,2-a]-pyrimidine-5-one (**3**) prepared by reaction of compound (**1**) with 3-chloropentan-2,4-dione followed by ring closure, was used as starting material to synthesise other heterocyclic compounds. The acetyl compound (**3**) was easily condensed with different amines to produce the imines (**4–8**), or the corresponding chalcone (**9**) when allowed to react with an aromatic aldehyde in presence of zinc chloride. Coupling of compound (**3**) with benzene diazonium chloride gave the phenylazo derivative (**10**). When compound (**4**) was treated with α-haloketones or α-haloesters, the thiazoline or thiazolidine compounds (**11–15**) were produced. Compound (**15**) was condensed with aromatic aldehydes to give the corresponding arylidene-derivatives (**16a-c**). Finally the chalcone (**9**) was reacted with hydrazine hydrate, phenyl hydrazine and hydroxyl amine to give pyrazolo and isoxazole compounds (**17-19**) respectively.

Key words: Synthesis; pyrimidine; thiazolopyrimidine; thiazolylthiazolopyrimidine and pyrazolylthiazolopyrimidine.

INTRODUCTION

Thiazolopyrimidines are of great importance in the field of medicinal chemistry for example as analgesics or due to their cerebral nervous system[1] or their antipurine activity.[2]

The synthesis of thiazolopyrimidines has already been reported in the literature. It can be achieved by two routes: (i) initial formation of the pyrimidine ring followed by building the thiazole ring in the terminal step (azine approach)[3] or (ii) initial formation of the thiazole ring followed by building the pyrimidine ring in the terminal step (azole approach).[4] According to route (i), we used 5-cyano-6-ethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (**1**)[5] as a precursor for the synthesis of thiazolopyrimidine derivatives.

RESULTS AND DISCUSSION

5-Cyano-6-ethyl-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine (**1**) was alkylated with 3-chloroacetylacetone at room temperature in ethanol in the presence of potassium hydroxide in quantitative yield to the intermediate 3-thio(5-cyano-6-ethyl-3,4-dihydro-4-oxo-pyrimidin-2-yl)pentan-2,4-dione (**2**) which was cyclised by boiling in acetic anhydride/pyridine mixture to the thiazolo[3,2-a]pyrimidine derivative (**3**).

Compound (**3**) was easily condensed in acetic acid or ethanol/sodium acetate with thiosemicarbazide, semicarbazide, phenyl hydrazine, hydroxylamine and an-

TABLE I

Physical and spectral data of compounds (**2–10**)

d.	M.P. [C]° (Solvent)	Yield % (Colour)	Molecular[a] formula	I.R. cm^{-1}	NMR δ
	195 (Ethanol)	82 (White)	$C_{12}H_{13}N_3O_3S$	3200(NH), 2200(CN), 1670 (2C=O) β-diketone, 1650(C=O)	($CDCl_3$) 1.2(t, 3H, CH_3), 2.3(s, 6H, $2CH_3$) 2H, CH_2), 4.6(s, 1H, CH).
	144 (Ethanol)	64 (Yellow)	$C_{12}H_{11}N_3O_2S$	2210(CN), 1680, 1660(C=O)	($CDCl_3$) 1.3(t, 3H, CH_3), 2.6(s, 3H, CH_3) 2H, CH_2), 3.2(s, 3H, CH_3).
	273 (Acetic acid)	78 (Yellow)	$C_{13}H_{14}N_6OS_2$	3480, 3360(NH_2), 3180(NH), 2240(C≡N), 1690(C=O)	
	284 (Acetic acid)	76 (Yellow)	$C_{13}H_{14}N_6O_2S$	3480, 3340(NH_2) 3200(NH), 2220(C≡N), 1710–1680(C=O)	
	258 (Ethanol)	80 (Yellow)	$C_{18}H_{17}N_5OS$	3320(NH), 2220(C≡N), 1660(C=O)	
	255 (Ethanol)	66 (White)	$C_{12}H_{12}N_4O_2S$	3280(OH), 2240(C≡N), 1690(C=O)	(DMSO) 1.2(t, 3H, CH_3), 2.2(s, 3H, -CO 2.7(q, 2H, CH_2), 2.8(s, 3H, CH_3), 11.9 OH).
	198 (Ethanol)	63 (Pale yellow)	$C_{18}H_{16}N_4OS$	2220(CN), 1670(C=O)	
	190 (Ethanol)	74 (Yellow)	$C_{19}H_{15}N_3O_2S$	2200(CN), 1680, 1660(C=O)	($CDCl_3$) 1.2(t, 3H, CH_3), 2.8(q, 2H, CH_2), 3H, CH_3), 6.9–7.9(m, 7H, 2CH and aro
	220 (Ethanol)	58 (Red)	$C_{16}H_{13}N_5OS$	2240(C≡N), 1690(C=O)	($CDCl_3$) 1.2(t, 3H, CH_3), 2.9(q, 2H, CH_2), 3H, CH_3), 7.2–7.6(m, 5H, arom.).

l products gave satisfactory micro analysis ($C \pm 0.32$, $H \pm 0.2$, $N \pm 0.34$, $S \pm 0.28$).

TABLE II

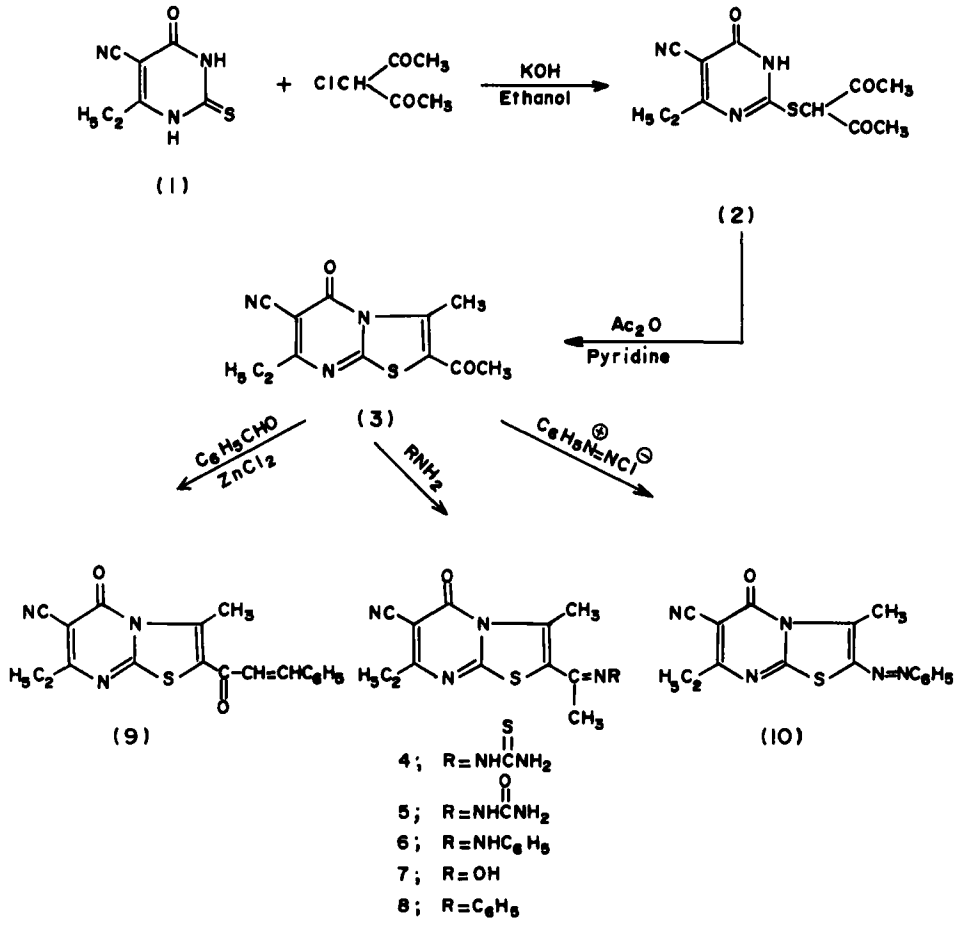
Physical and spectral data of compounds (11–19)

Compd. No.	M.P. [C]° (Solvent)	Yield % (Colour)	Molecular formula	I.R. cm $^{-1}$	^{1}H NMR δ
11	275 (Ethanol)	71 (Orange)	$C_{21}H_{18}N_6OS_2$	2240(C≡N), 1680(C=O)	($CDCl_3$) 1.2(*t*, 3H, CH_3), 2.1(*s*, 2H, CH_2), 2.3(*s*, 3H, CH_3), 2.8(*q*, 2H, CH_2), 3.9(*s*, 3H, CH_3), 7.2–7.6(*m*, 5H, arom.)
12	280 (Ethanol)	57 (Yellow)	$C_{18}H_{18}N_6O_2S_2$	2220(C≡N), 1720, 1680(C=O)	
13	314 (Ethanol)	72 (Yellow)	$C_{16}H_{16}N_6O_2S_2$	3140(NH), 2240(C≡N), 1720, 1680(C=O)	
14	244 (Acetic acid)	68 (Yellow)	$C_{18}H_{18}N_6O_4S_2$	3400(NH), 2220(C≡N), 1730, 1680(C=O)	
15	296 (Ethanol)	74 (Yellow)	$C_{15}H_{14}N_6O_2S_2$	3400(NH), 2240(C≡N), 1710, 1690(C=O)	
16a	282 (Ethanol)	69 (Yellow)	$C_{22}H_{17}N_6O_2S_2$	3400(NH), 2240(C≡N), 1720, 1700(C=O)	($CDCl_3$) 1.2(*t*, 3H, CH_3), 2.3(*s*, 3H, CH_3), 2.[illegible] (*q*, 2H, CH_2), 3.0(*s*, 3H, CH_3), 4.6(*s*, 1H, NH), 7.5(*s*, 5H, arom.), 7.9(*s*, 1H, CH)
16b	245 (Dioxane)	77 (Orange)	$C_{22}H_{16}N_7O_4S_2$	3420(NH), 2220(C≡N), 1740, 1700(C=O)	
16c	286 (Ethanol)	76 (Yellow)	$C_{23}H_{20}N_6O_3S_2$	3340(NH), 2240(C≡N), 1740, 1690(C=O)	
17	223 (Ethanol)	64 (Pale yellow)	$C_{21}H_{19}N_5O_2S$	2220(C≡N), 1720–1690(C=O)	($CDCl_3$) 1.3(*t*, 3H, CH_3), 2.3(*s*, 3H, $COCH_3$) 2.8(*q*, 2H, CH_2), 2.9(*s*, 3H, CH_3), 3.2(*d*, 2H, CH_2), 5.5(*q*, 1H, CH) and 7.4(*m*, 5H, arom.)
18	211 (Ethanol)	74 (Yellow)	$C_{25}H_{21}N_5OS$	2220(C≡N), 1680(C=O)	($CDCl_3$) 1.3(*t*, 3H, CH_3), 2.7(*q*, 2H, CH_2), 2.9(*s*, 3H, CH_2), 3.1(*d*, 2H, CH_2), 5.4(*t*, 1H, CH) 6.8–7.4 (*m*, 10H, arom.).
19	213 (Ethanol)	59 (Pale yellow)	$C_{19}H_{16}N_4O_2S$	2200(C≡N), 1690(C=O)	

iline as amino compounds to the corresponding thiosemicarbazone, semicarbazone, phenylhydrazone, oxime and Schiff base (**4–8**). Furthermore, fusion of (**3**) with benzaldehyde in the presence of catalytic amounts of zinc chloride gave the corresponding chalcone (**9**). On the other hand, compound (**3**) coupled with benzenediazonium chloride in ethanol in the presence of sodium acetate to give 2-phenylazo derivative (**10**) as a result of an electrophilic attack of the diazonium salt on the ring carbon bearing the acetyl group followed by their displacement[6] (Scheme I).

The thiosemicarbazone (**4**) was used as staring material for the synthesis of thiazoline and thiazolidinone derivatives (**11–15**) via reaction with α-haloketones or α-haloesters, namely phenacyl bromide, 3-chloro acetylacetone, ethyl chloroacetate, ethyl-2-bromopropionate and bromodiethyl malonate in refluxing ethanol in the presence of sodium acetate. The reaction proceeds by S-alkylation of thiosemicarbazone (**4**) followed by dehydration or loss of ethanol.

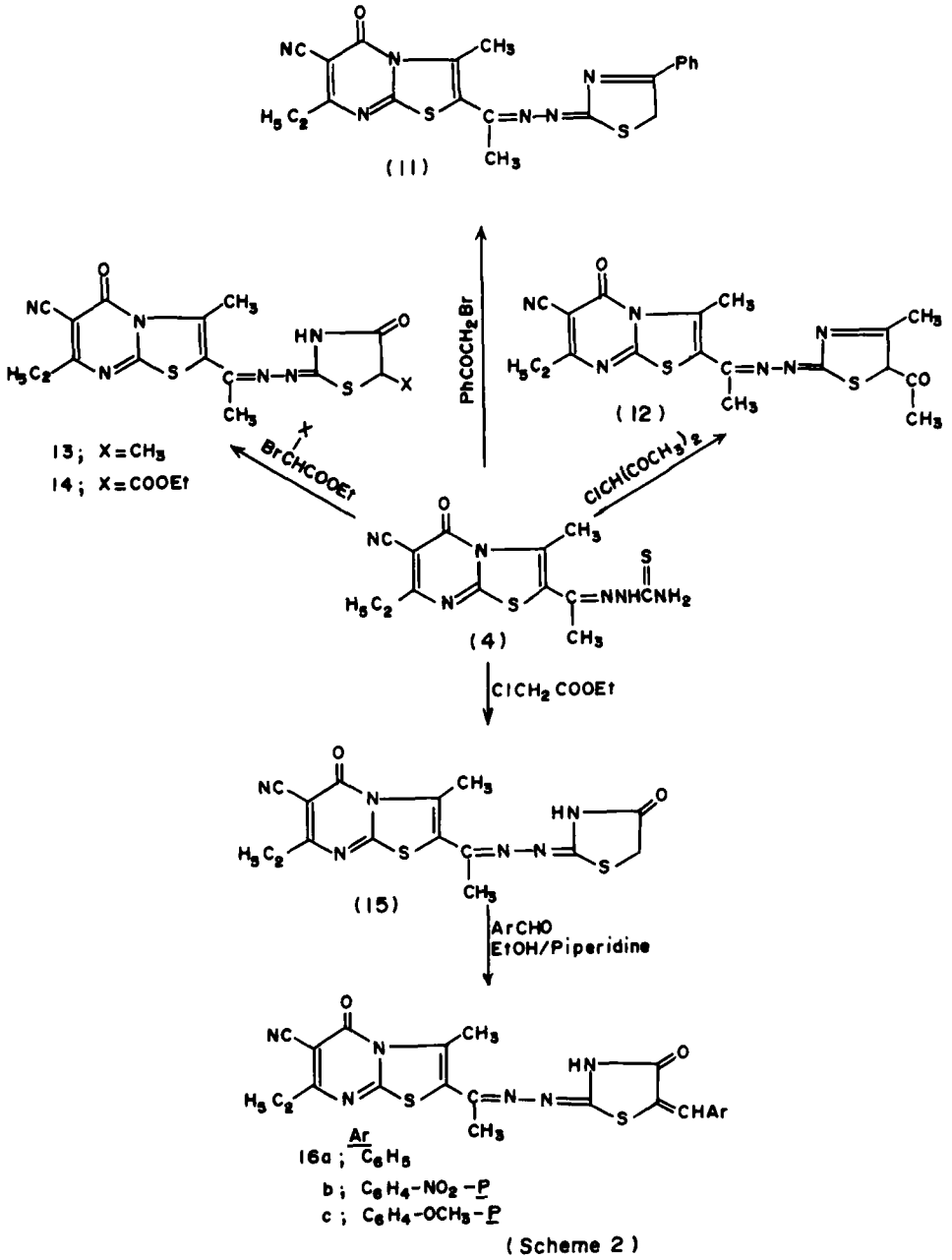
Further condensation of thiazolidinone (**15**) with aromatic aldehydes in ethanol



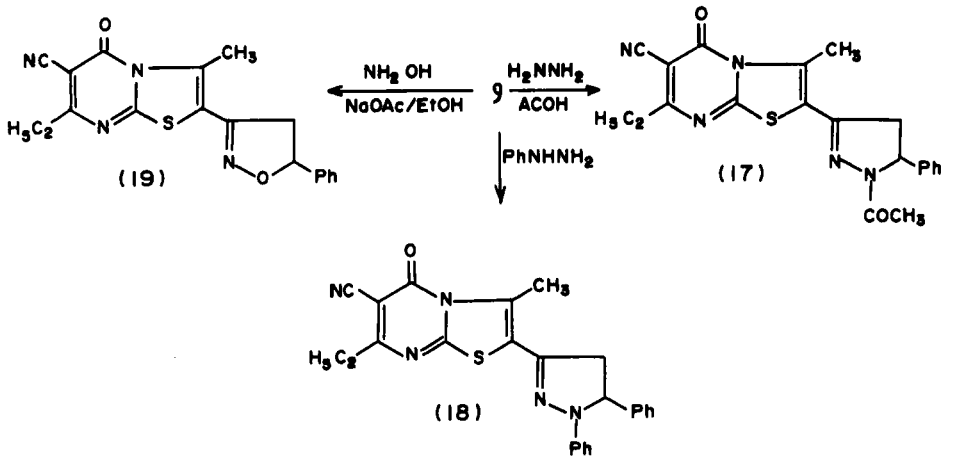
(Scheme I)

in the presence of few drops of piperidine led to the corresponding arylidene derivatives (**16a-c**) (Scheme II).

Finally, reaction of chalcone (**9**) with hydrazine hydrate in acetic acid or with phenyl hydrazine or hydroxyl amine in ethanol gave the corresponding pyrazoline compounds (**17, 18**) or the isoxazoline derivative (**19**) respectively (Scheme III).



(Scheme 2)



(Scheme 3)

EXPERIMENTAL

All melting points are uncorrected and determined on Fisher-Jnones melting point apparatus. I.R. spectra were determined on a Pye-Unicam Spectrometer using KBr Wafer technique, ^1H NMR spectra were obtained on a Varian 90 MHz NMR Spectrometer in suitable deuterated solvent using TMS as internal standard and the chemical shift was expressed as δ. Elemental analysis were determined on a Perkin-Elemer microanalyser.

3-Thio[5-cyano-6-ethyl-3,4-dihydro-4-oxopyrimidin-2-yl]pentan-2,5-dione (**2**): To a solution of compound (**1**) (0.01 mol) and potassium hydroxide (0.012 mol) in ethanol (50 mol), 3-chloroacetylacetone (0.01 mol) was added dropwise while stirring. The reaction mixture was stirred for 1 hour and poured into cold water. The precipitated product was collected by filtration.

2-Acetyl-6-cyano-7-ethyl-3-methylthiazolo[3,2-a]pyrimidin-5-one (**3**): A mixture of 2 (0.01 mol) and acetic anhydride (20 ml) in pyridine (20 ml) was heated on a water bath for 6 hrs., after which the reaction mixture was cooled and poured in ice/water mixture. The precipitated product was collected by filtration.

Condensation of compound **3** *with different amino compounds:*

(a) with thiosemicarbazide and semicarbazide: A mixture of 3 (0.01 mol) and thiosemicarbazide or semicarbazide (0.01 mol) in acetic acid (30 ml) was refluxed for 2 hours. The product which precipitated from the hot mixture was collected by filtration.

(b) with hydroxyl amine: A mixture of 3 (0.01 mol), hydroxyl amine hydrochloride (0.01 mol) and sodium acetate (2 g) was refluxed in ethanol (30 ml) for 2 hrs. The precipitated product thus formed whilst hot was collected by filtration and washed several times with water.

(c) with phenyl hydrazine and aniline: A mixture of 3 (0.01 mol) and phenyl hydrazine or aniline (0.012 mol) in ethanol (30 ml) was refluxed for 2 hrs. The precipitated product was collected by filtration.

Preparation of benzal chalcone (**9**): A mixture of 3 (0.01 mol) and benzaldehyde (0.01 mol) was fused in presence of catalytic amount of zinc chloride for 15 min, then the mixture was triturated with ethanol and the precipitate thus formed was collected by filtration.

6-Cyano-7-ethyl-3-methyl-2-phenylazothiazolo[3,2-a]pyrimidin-5-one (**10**): To a cold mixture of 3 (0.01 mol) and sodium acetate in ethanol (30 ml) a solution of benzene diazonium chloride (0.01 mol) was added drop wise while stirring. Stirring was continued at 0–10°C for 1 hr and the precipitate thus formed was collected by filtration.

Reaction of **4** *with α-haloketones and α-haloesters (compounds* **11–15**):

General procedure: A mixture of 4 (0.01 mol), α-haloketone or α-haloester (0.01 mol) and anhydrous

sodium acetate (3 g) in ethanol (30 ml) was refluxed for 5 hrs, and then allowed to cool. The solid products were collected by filtration.

5'-Arylidene-2' (6-cyano-7-ethyl-3-methyl-5-oxo-thiazolo[3,2-a]-pyrimidine-2-acetylazino)-4'-thiazolidinone (**16a-c**): A mixture of 15 (0.01 mol) and aromatic aldehyde (0.01 mol) in ethanol (30 ml) was refluxed in the presence of few drops of piperidine for 3 hours. The reaction mixture was then allowed to cool and the precipitated products were collected by filtration.

6-Cyano-7-ethyl-3-methyl-2(1'-acetyl-5'-phenyl Δ^2 *pyrazolin-3'-yl)-thiazolo[3,2-a]pyrimidin-5-one* (**17**): A mixture of chalcone (**9**) (0.01 mol) and hydrazine hydrate (0.01 mol) in acetic acid (20 ml) was refluxed for 4 hrs, then cooled and poured into an ice/water mixture. The precipitated product was collected by filtration.

6-Cyano-7-ethyl-3-methyl-2(1',5'-diphenyl Δ^2 *pyrazolin-3'-yl)-thiazolo[3,2-a]pyrimidin-5-one* (**18**): A mixture of chalcone (**9**) (0.01 mol) and phenyl hydrazine (0.015 mol) in ethanol (30 ml) was refluxed for 8 hrs., then allowed to cool, and the solid product collected by filtration.

6-Cyano-7-ethyl-3-methyl-2(5'-phenyl-Δ^2 *isoxazolin-3'-yl)thiazolo-[3,2-a]pyrimidin-5-one* (**19**): A mixture of chalcone (**9**) (0.01 mol), hydroxylamine hydrochloride (0.01 mol) and anhydrous sodium acetate (5 g) was refluxed in ethanol for 8 hrs., then allowed to cools and poured into cold water. The precipitated product thus formed was collected by filtration.

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