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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: SYNTHESIS OF SEVERAL NEW THIAZOLES, PYRAZOLO[5,1-c]TRIAZINES AND OF POLYFUNCTIONALLY SUBSTITUTED PYRIDINES AND PYRIMIDINES.

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Key Words

Thiazolin-4-one; 1,2,4-Triazinethione; Pyrazolo[1,5-c]-1,2,4-triazine; Pyridine and Pyrimidine.

ABSTRACT:

Several thiazolin-4-one **(3)**, 1,2,4-triazinethione **(13)**, pyrazolo[1,5-c]-1,2,4-triazine **(16)** and pyridine **(23)** derivatives could be obtained via the reaction of iminoether **(1)** derivative with thioglycolic acid, aryldiazonium chloride, 3-arylpyrazol-5-yl diazonium chloride and alkylidenemalononitrile derivatives, respectively. The reaction mechanism for each one was discussed. All structures were suggested on the basis of elemental analyses and spectral data.

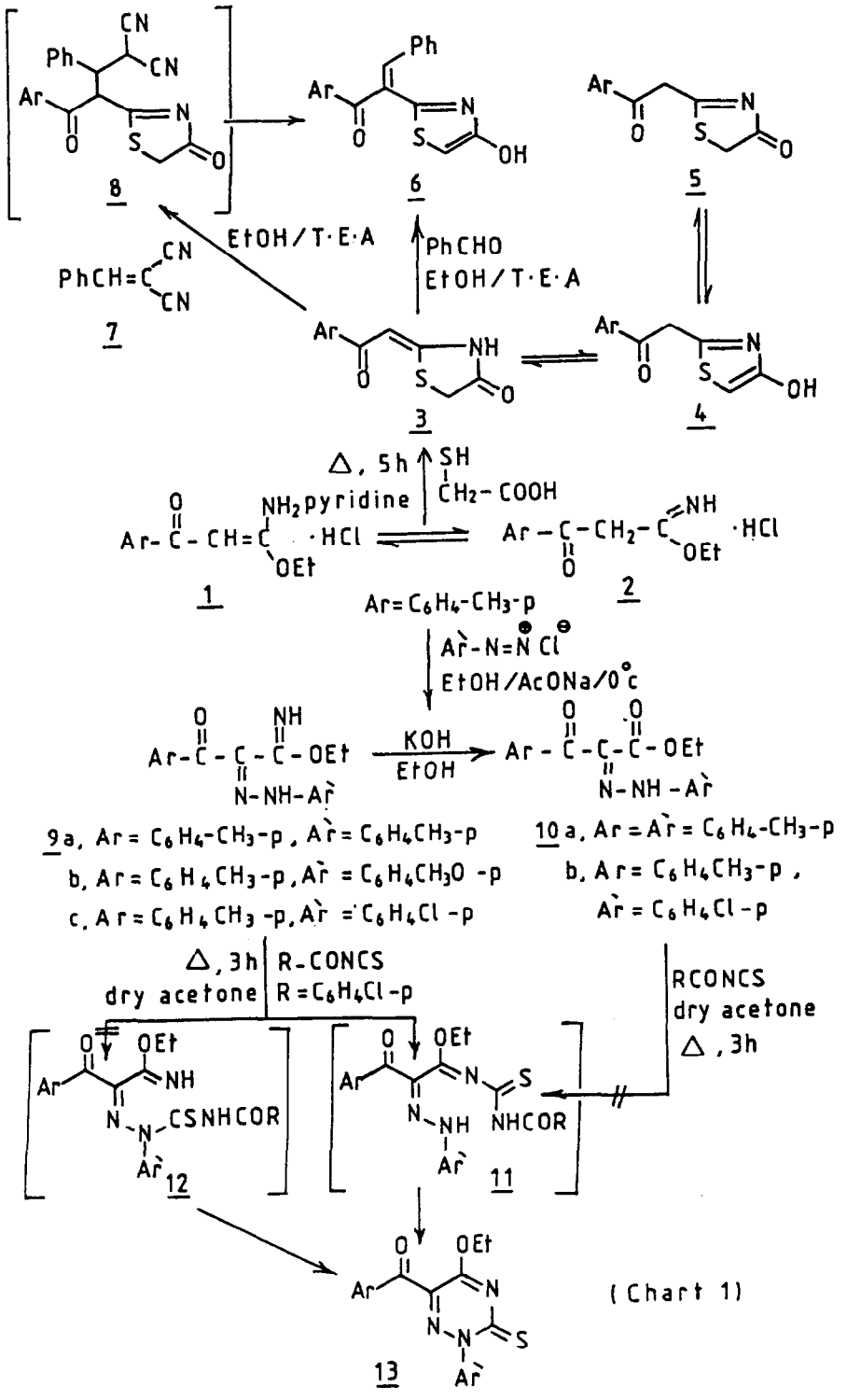
Polyfunctionally substituted heteroaromatics are biologically interesting molecules and their chemistry has recently received considerable attention[1]. Our group has been, in the last few years, involved in program directed at developing approaches for synthesis of polyfunctionally substituted heteroaromatics from simple and laboratory available starting materials[2-4]. These polyfunctional heteroaromatics seemed interesting as potential biodegradable agrochemicals. Now as a part of a biological chemistry program in our

laboratories, samples of certain polyfunctionally substituted heteroaromatics were needed as potential antischistozomal agents.

Classical synthetic approaches to polyfunctionally substituted heteroaromatics were investigated as a possible route to the required compounds. However, these proved either highly inefficient or failed to afford the required compounds. We have thus investigated alternate routes. In the present study, we report the synthesis of several new thiazoles, pyrazolotriazines, pyridines and pyrimidines utilizing the imino ether **2** as starting material. Although active methylene nitriles have long been reported to afford readily imino ethers on treatment with alcohols in presence of dry hydrogen chloride gas, the utility of these imino ethers has received limited attention. Recently, however our group has reported several novel syntheses of functionally substituted heterocycles utilizing **2** as a starting material.

It has been found that **2** reacts with thioglycollic acid in refluxing pyridine to yield thiazole **3** in 90 % yield. Although **3** can be represented also in tautomeric structures **4** and **5**, spectral data reveals that structure **3** is the predominant one, both in solid state and in DMSO solution, which revealed a singlet at δ 11.8 ppm for the NH proton. It is of value to report that, attempt preparation of **3** directly from p-toluoyl-acetonitrile has only afforded very low yield of the required compound and after long reflux. Compound **3** readily condenses with benzaldehyde to yield the benzylidene derivative **6**. Although functionally substituted methyl-2-thiazolin-4-ones have been reported to yield thiazolopyridines on reaction with arylidene-malononitrile **7**[5,6], in this case the reaction of **3** with **7** afforded only the arylidene derivative **6**. The formation of **6** is assumed to proceed via the addition of **7** to the active methylene in **4** to yield the Michael adduct **8**. This readily loses malononitrile to yield the final isolable product **6**. Although similar reaction with thiazolin-4-one has been previously reported to yield the arylidene derivative, we believe that structure **6** is the correct one since the ^{1}H NMR revealed thiazole ring proton at δ 6.9 ppm.

Compound **2** coupled with aromatic diazonium salts to yield the corresponding arylhydrazones **9a-c**. These, in turn, react readily with aqueous KOH to yield the esters **10a,b**, which were also obtained by coupling ethyl benzoylacetate with aromatic diazonium salts. The reaction of **9c** with p-chlorobenzoylisothio-cyanate afforded **13**, most likely via the intermediacy of acyclic **11**. However, this possibility looks very slim as **9a,b** did not react with isothiocyanates under a variety of conditions, indicating that the hydrazone moiety **9a,b** is very inert.


EtOH/T·E·A
PhCHO
EtOH/T·E·A
△, 5h
pyridine
·HCl
Ar=C6H4-CH3-p
Ar-N=N Cl
EtOH/AcONa/0°c
KOH
EtOH
9a, Ar = C6H4-CH3-p, Ar = C6H4CH3-p
b, Ar = C6H4CH3-p, Ar = C6H4CH3O -p
c, Ar = C6H4CH3 -p, Ar = C6H4Cl -p
10a, Ar = Ar = C6H4-CH3-p
b, Ar = C6H4CH3-p,
Ar = C6H4Cl -p
△, 3h
dry acetone
R-CONCS
R = C6H4Cl-p
RCONCS
dry acetone
△, 3h

(Chart 1)

Compound 2 coupled with the diazotized 5-amino-3-(p-methyl-phenyl)-pyrazole to afford 16. Formation of compound 16 is believed to proceed via the usual coupling reaction with the active methylene group to yield intermediate 15 which spontaneously loses ethanol to yield the final isolable product 16. Attempted preparation of 16 by reacting diazotized aminopyrazole with activated nitriles such p-toluoyl-acetonitrile has resulted in the formation of 17[7], most likely via the non-isolable intermediate 18.

The reaction of 2 with cinnamonitriles 7a-c, has also been investigated. The reaction afforded products of addition and ethanol elimination. These were formulated as pyridine 23a-c. Formation of 23a-c is assumed to proceed via a sequence demonstrated in Chart 3. This final parallelism to the previously reported formation of pyridine from the reaction of 7a-c with 2. Thus, this reaction may be looked at as a general route to the synthesis of benzoylpyridine derivatives.

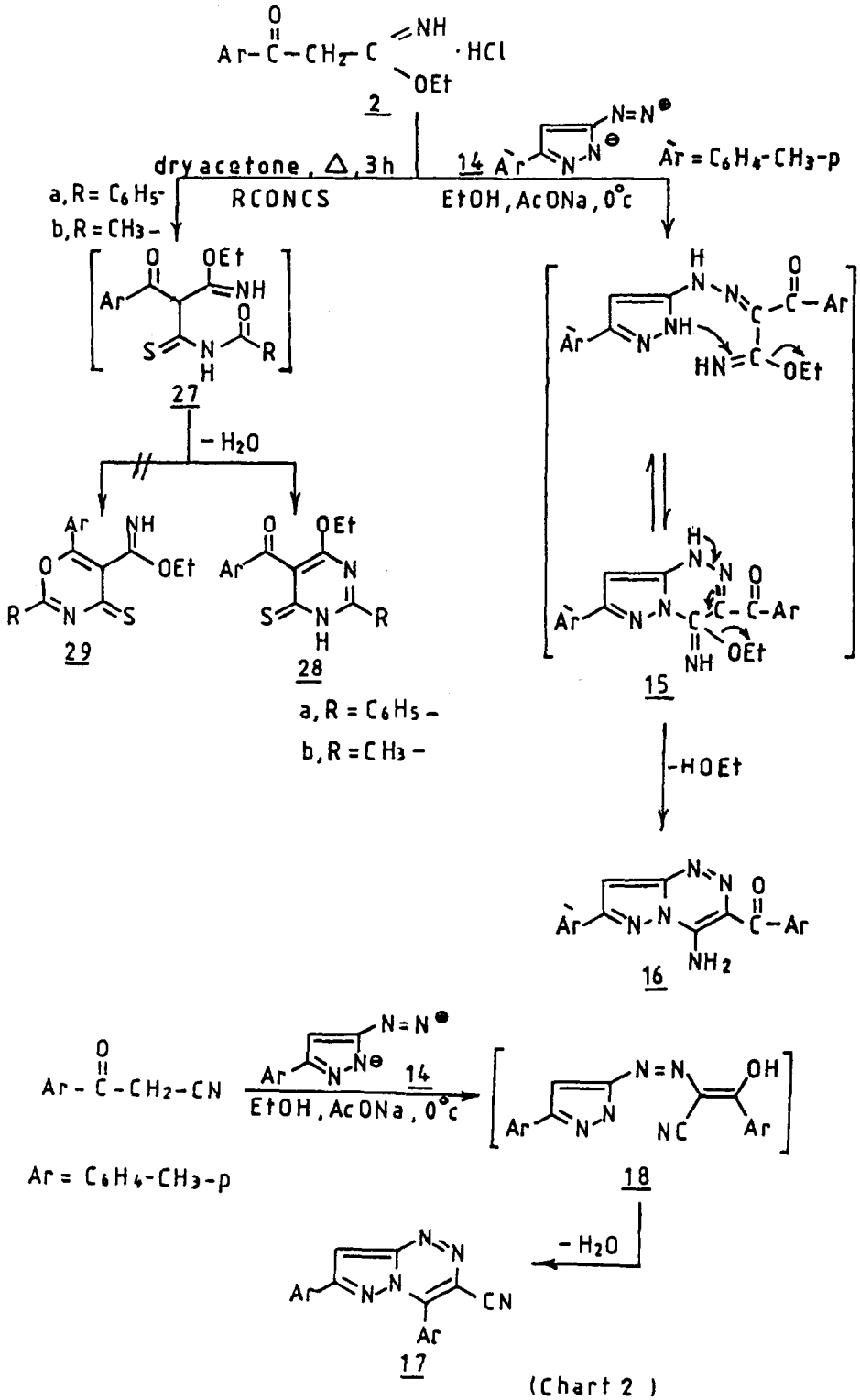
Compound 2 reacted with aroyl and acyl isothiocyanate to yield products of addition and water elimination. These were formulated as the pyrimidines 28a,b. Formation of 28 is assumed to proceed via intermediacy of 27. These, then lose water to yield 28 or 29. Structure 29 was eliminated based on the stability of the reaction product toward mild acid treatment. The imino-function is hydrolyzed under such condition.

EXPERIMENTAL

All melting points are uncorrected, IR spectra were recorded on Beckman and PYE-Unicam Spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian EM-390 90 MHz, Chemical shifts are expressed in δ units ppm down field from TMS as the internal standard. Analytical data were obtained from the Microanalytical Center and Faculty of Pharmacy at Cairo University and Al-Azhar University, respectively.

4-Oxo-4,5-dihydrothiazol-2-yl-p-methylacetophenone (3).

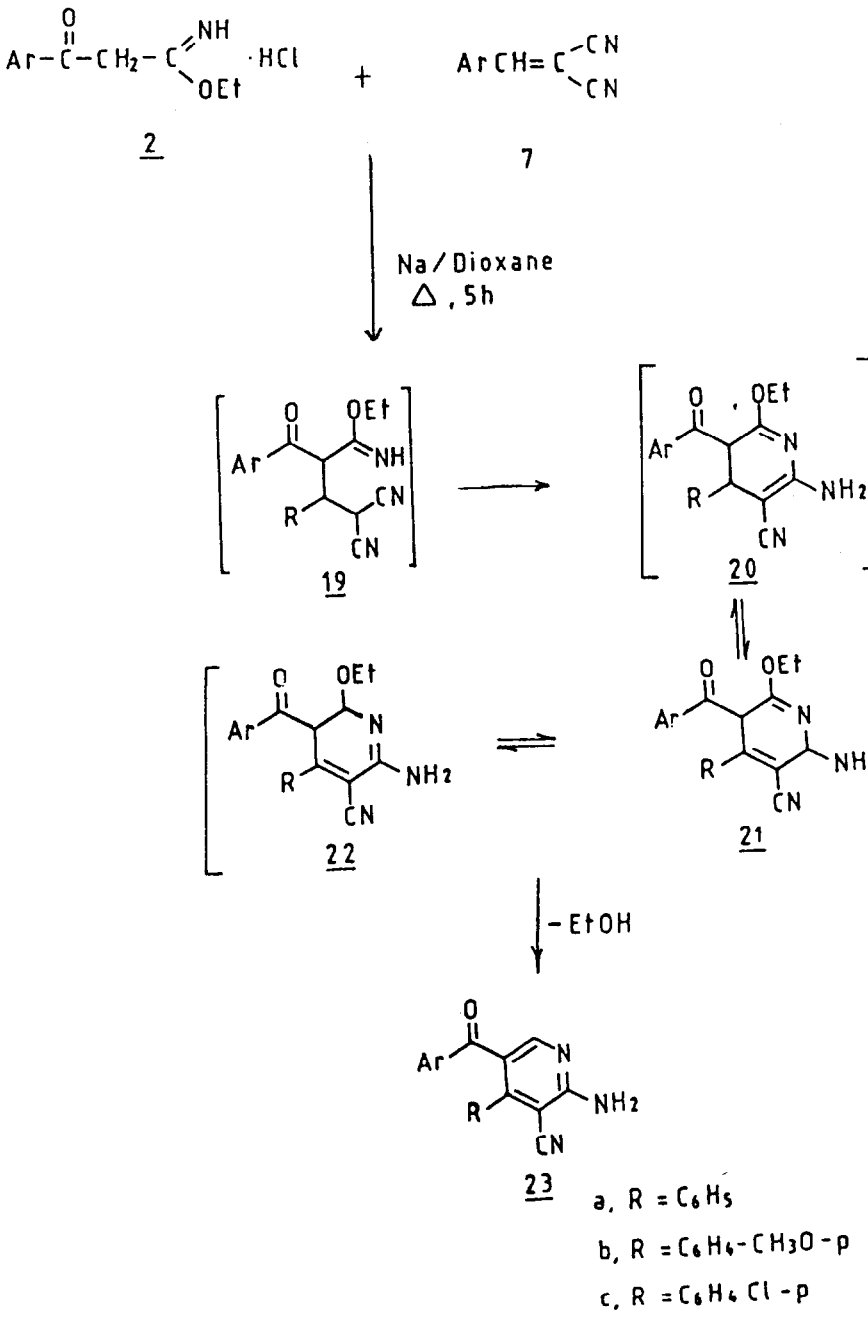
A mixture of imino ether hydrochloride 2 (2.39 g, 0.01 mol) [prepared from an ice-cold solution of p-toluoylacetonitrile (1.57 g, 0.01 mol) and absolute ethanol (0.58 ml, 0.01 mol) in dry dioxane (30 ml). Then, dry hydrogen chloride is passed for four hours. The solid product, so formed is collected by filtration and crystallized from ethanol as white crystals, m.p. 135 C] and thioglycollic acid (1.2 ml, 0.01 mol) was refluxed in pyridine for 3 hours. The reaction mixture poured in cold water and neutralized with



2 27 29 28 14 15 16

18 17

(Chart 2)


Ar-C(=O)-CH2-C(=NH)(OEt)·HCl
2
+
ArCH=C(CN)CN
7
Na/Dioxane
△, 5h
19
20
22
21
-EtOH
23
a, R = C6H5
b, R = C6H4-CH3O-p
c, R = C6H4Cl-p

(Chart 3)

Table 1. Characterization Data for the Newly Synthesized Compounds.

Compd.	m.p. C	Solvent Yield %	Mol.Formula (Mol. Wt.)	Calc. / required % C	H	N	S	Cl
3	220	EtOH	$C_{12}H_{11}NSO_2$	61.8	4.7	6.0	13.7	
		70	(233.16)	62.0	4.6	6.3	14.0	
6	185	EtOH	$C_{19}H_{15}NSO_2$	71.0	4.7	4.4	10.0	
		80	(321.17)	71.1	4.9	4.2	9.9	
9a	85	EtOH	$C_{19}H_{21}N_3O_2$	70.6	6.5	13.0		
		70	(323.17)	70.8	6.4	12.8		
9b	98	EtOH	$C_{19}H_{21}N_3O_3$	67.3	6.2	12.4		
		75	(339.16)	67.2	6.4	12.7		
9c	110	EtOH	$C_{18}H_{18}N_3O_2Cl$	62.9	5.2	12.2		10.3
		75	(343.61)	63.1	5.0	12.4		10.2
10a	110	EtOH	$C_{19}H_{20}N_2O_3$	70.4	6.2	8.6		
		75	(324.16)	70.2	6.1	8.5		
10b	165	EtOH	$C_{18}H_{17}N_2O_3Cl$	62.7	4.9	8.1		10.3
		75	(344.60)	62.9	5.2	8.3		10.1
13	225	EtOH	$C_{19}H_{16}N_3O_2SCl$	59.2	4.1	10.9	8.3	9.2
		75	(385.68)	59.5	4.3	10.7	8.7	9.0
16	>300	EtOH/DMF	$C_{20}H_{17}N_5O$	70.0	5.0	20.4		
		80	(343.19)	69.9	4.7	20.6		
23a	140	EtOH	$C_{20}H_{15}N_3O$	76.7	4.8	13.7		
		60	(313.19)	76.5	4.6	13.2		
23b	225	EtOH	$C_{21}H_{17}N_3O_2$	73.5	5.0	12.2		
		65	(343.19)	73.6	4.8	12.3		
23c	220	EtOH	$C_{20}H_{14}N_3OCl$	69.1	4.0	12.1		10.2
		75	(347.64)	69.3	4.2	12.0		10.4
28a	185	EtOH	$C_{20}H_{18}N_2SO_2$	68.6	5.1	8.0	9.2	
		70	(350.24)	68.7	5.4	7.9	9.3	
28b	240	EtOH	$C_{15}H_{16}N_2SO_2$	62.5	5.6	9.7	11.1	
		60	(288.19)	62.8	5.4	9.5	11.4	

Table 2. Spectroscopic Data for the Newly Synthesized Compounds.

Compd.	IR (cm^{-1})	^{1}H-NMR (δ ppm)
3	3300 (NH); 1720, 1620 (two C=O).	2.5(s, 3H, CH_3); 3.75(s, 2H, CH_2); 6.75(s, 1H,CH); 7.2-7.8(q, 4H, aromatic protons); 11.7(s,br, 1H,NH).
6	3250 (OH); 1690 (C=O).	2.5(s, 3H, CH_3); 6.9(s, 1H, CH); 7.25-7.4(d, 2H, CH, OH); 7.45-8.05(m, 9H, aromatic protons).
9a	3480-3290 (NH); 1660 (C=O); 1600 (C=N).	1.3(t, 3H, CH_3); 2.25(d, 6H, two CH_3); 4.2(q, 2H, CH_2); 7.0-7.8(m, 9H, aromatic and NH protons); 12.0(s, 1H, NH).
9b	3270 (NH); 1660 (C=O); 1600 (C=N).	1.4(t, 3H, CH_3); 2.2(s, 3H, CH_3); 3.7(s, 3H,CH_3O); 4.3(q, 2H, CH_2); 6.8-7.8(m, 9H, aromatic and NH protons); 11.7(s, 1H, NH).
9c	3450-3300 (NH); 1700 (C=O); 1600 (C=N).	1.5(t, 3H, CH_3); 2.3(s, 3H, CH_3); 4.3(q, 2H, CH_2); 7.0-7.9(m, 9H, aromatic and NH protons); 12.6(s, 1H, NH).
10a	3250 (NH); 1720 (C=O);	1.4(t, 3H, CH_3); 2.4(d, 6H, two CH_3); 4.4(q, 2H, CH_2); 6.9-8.0(m, 8H, aromatic protons); 11.3(s, 1H, NH).
10b	3300 (NH); 1730 (C=O); 1590 (C=N).	1.8(t, 3H, CH_3); 2.5(s, 3H, CH_3); 4.5(q, 2H, CH_2); 7.2-7.3(d, 4H, aromatic protons); 7.7-8.1(q, 4H, aromatic protons), 11.4(s, 1H, NH).
13	1670 (C=O); 1590 (C=N).	1.65(t, 3H, CH_3); 2.5(s, 3H, CH_3); 4.3(q, 2H, H_2);7.2-7.9(m,8H, aromatic protons)
16	3360-3200 (NH_2); 1640 (C=O).	2.3(s, 6H, two CH_3); 5.4(s, 2H, NH_2); 7.1-7.9(m, 9H, aromatic protons and pyrazole 4-H).
23a	3300-3050 (NH_2); 2220 (CN); 1640 (C=O).	2.4(s, 3H, CH_3); 5.4(s, 2H, NH_2), 7.3-7.75(m, 10H, aromatic protons and pyridine 6-H).
23b	3450-3300 (NH_2); 2220 (CN); 1600 (C=O).	2.5(s, 3H, CH_3); 3.6(s, 3H, CH_3O); 5.6(s,2H, NH_2); 7.0-7.8(m,9H, aromatic protons and pyridine 6-H).
23c	3400-3250 (NH_2), 2220 (CN); 1730 (C=O)	2.4(s, 3H, CH_3); 5.5(s, 2H, NH_2); 7.1-7.9(m, 9H, aromatic protons and pyridine 6-H).
28a	3250 (NH); 1670 (C=O); 1600 (C=N).	1.5(t, 3H, CH_3); 2.5(s, 3H, CH_3); 4.7(q, 2H, CH_2); 7.2-8.3(m,br,9H, aromatic protons); 11.7(s,1H,NH)
28b	3400-3100 (NH); 1670 (C=O); 1600 (C=N).	1.5(t, 3H, CH_3); 2.2(s, 3H, CH_3); 2.5(s, 3H, CH_3); 4.6(q, 2H, CH_2); 7.0-8.0(m,br, 4H, aromatic protons); 11.1(s, 1H, NH).

hydrochloric acid. The solid product, so formed is collected by filtration and crystallized from the proper solvent.

3-Phenyl-X-(p-methylphenyl)-2-(5-hydroxythiazol-2-yl)-prop-2-ene-1-one (6).

A mixture of thiazolone 3 (2.33 g, 0.01 mol) and benzylidenemalononitrile or benzaldehyde (0.01 mol) in ethanol (50 ml) and triethylamine (0.01 mol) was refluxed for 3 hours. The solvent was removed in vacuo. The remaining product was triturated with water and neutralized with hydrochloric acid. The solid product, so formed, was collected by filtration and crystallized from the proper solvent.

Ethyl 3-(p-methylphenyl)-3-oxo-2-arylhydrazono-1-iminopropanoate derivatives (9a-c); and pyrazolotriazine (16).

General procedure:

A solution of aryl-substituted diazonium chloride (0.01 mol) was gradually added to an ice-cold solution of **2a-c** (2.39 g, 0.01 mol) in 50 ml ethanol containing sodium acetate (2.0 g). The reaction mixture was kept at 0 C in a refrigerator overnight. The solid product, so formed, was collected by filtration, washed with water and crystallized from the proper solvent.

Ethyl 3-(p-methylphenyl)-3-oxo-2-arylhydrazono-1-iminopropanoate (10a,b).

General procedure:

A solution of **9a,c** (0.01 mol) in ethanol (30 ml) was treated with sodium hydroxide (20 ml, 10%). The reaction mixture was refluxed for 3 hours and the solvent was removed in vacuo. The remaining semisolid was triturated with water and neutralized with hydrochloric acid. The solid product, so formed, was collected by filtration and crystallized from the proper solvent. Compounds **10a,b** can also be obtained from coupling of ethyl benzoylacetate derivatives with aromatic diazonium salts.

3-(p-Chlorophenyl)-6-ethoxy-5-(p-toluoyl)-1,3,4-triazine-2-thione (13).

A suspension od **9c** (0.01 mol) in 50 ml dry acetone was treated with the corresponding isothiocyanate solution [prepared from 0.01 mol of ammonium thiocyanate and an equivalent quantity of the corresponding acid chloride in 40 ml acetone for 15 minutes]. The reaction mixture was refluxed for three hours, then evaporated in vacuo. The remaining product was triturated with water. The solid product, so formed, was collected by filtration and crystallized from the proper solvent.

4-Substituted-2-amino-5-(p-toluoyl)pyridine-3-carbonitrile(23a-c)

To a solution of **2** (2.39 g, 0.01 mol) in 50 ml dioxane, the appropriate **7** (0.01 mol) was added. The reaction mixture was refluxed for five hours, and

then evaporated in vacuo. The remaining product was then collected and recrystallized from the proper solvent.

2-Substituted-4-ethoxy-5-toluoyl-1,6-dihydropyrimidin-6-thione (28a,b).

A suspension of 2 (2.39 g, 0.01 mol) in 40 ml acetone, was treated with the appropriate quantity of isothiocyanate solution (prepared as described above). The reaction mixture was refluxed for 3 hours, then evaporated in vacuo. The remaining product is triturated with water, filtered and crystallized from the proper solvent.

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REFERENCES:

1. Elnagdi, M.H.; Negm, A.H. and Erian, A.W. *Liebigs Ann. Chem.*, 1989, 1255
2. Sofan, M.A.;El-Taweel, F.M.; Elagamey A.G.A. and Elnagdi, M.H. *Liebigs Ann. Chem.*, 1989, 935.
3. Harb, A.A.; Hesien, A.M.; Metwally, S.A. and Elnagdi, M.H. *Liebigs Ann. Chem.*, 1989, 985.
4. Elghandour, A.H.H.; Ramiz, M.M.M; and Elnagdi, M.H. *Synthesis*, 1989, *10*, 775.
5. Elmoghayar, M.R.H.; Ibrahim, M.K.A.; Elghandour, A.H.H. and Elnagdi, M.H. *Synthesis*, 1981, *8*, 635.
6. Elnagdi, M.H.; Elmoghayar, M.R.H.; Elghandour, A.H.H. and Sadek, K.U. *Coll. Czech. Chem. Commun.*, 1990, *55*, 745.
7 Elnagdi, M.H.; Elmoghayer, M.R.H.; Fahmy, S.M.; Ibrahim, M.K.A. and Alnima, H.H. *Z. Naturforsch*, 1978, *33*b, 216.