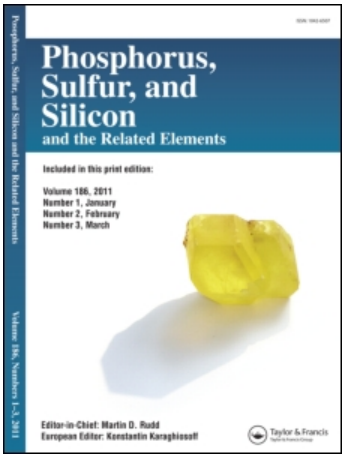

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REACTION OF ACYL ISOTHIOCYANATES WITH NUCLEOPHILES: A CONVENIENT SYNTHESIS OF 1,3-OXAZINE, PYRIMIDINETHIONE AND THIAZOLE DERIVATIVES

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The reaction of acetyl isothiocyanate **1** with ethyl cyanoacetate, malononitrile and/or a cyclic β-diketone afforded the corresponding 1,3-oxazines **3**, **11** and thioamide **12** respectively. The heteroannulation of **3** and the synthesis of thiazole **18** is described.

Key words: Acyl isothiocyanate, 1,3-oxazine, thiazole.

Acyl and aroyl isothiocyanates are versatile building units that have been extensively utilized in organic synthesis.[1–5] Recently we have reported the synthesis of heterocyclic systems utilizing aroyl isothiocyanates and simple available reagents.[6,7] This paper describes a novel synthetic route to oxazines and thiazoles from acyl isothiocyanates. Acetyl isothiocyanate reacted with ethyl cyanoacetate in the presence of triethylamine to yield a 1:1 adduct. The oxazine structure **3** was established for the reaction product based on the absence of the CN absorption in IR; the ^{1}H NMR of **3** revealed a signal for NH_2. The reaction proceeds via the non-isolable thioamide **2** that cyclizes intramolecularly to 1,3-oxazine **3**. Further confirmation of oxazine structure **3** was obtained by studying its reactivity towards various chemical reagents. Thus, refluxing **3** with TEA resulted in ring transformation affording pyrimidine **5** via the initial formation of intermediate **4**.[8,9] The reaction of **3** with guanidine in refluxing DMF furnished oxazinopyrimidine **6**. Cycloaddition of **3** and phenyl isocyanate provided oxazinopyrimidine **8** presumably via the nonisolable urea derivative **7**. Refluxing **3** and ethyl acetimidate hydrochloride in the presence of base provided oxazinopyrimidine **9**. 6-Amino-5-cyanooxazine **11** was also obtained by the reaction of isothiocyanate **1** and malononitrile in presence of base via the formation of thioamide intermediate **10**. Thioamide **12** was obtained via reacting cyclohexanedione with acetyl isothiocyanate **1** in refluxing dioxane. The refluxing of thioamides **12** in xylene in the presence of triethylamine afforded oxazine **13** as the product of cyclodehydration. Thioamide **12** reacted also with aniline to give quinazolinone **14**, which was obtained from enaminone **15** and acetyl isothiocyanate **1**. Compound **16** reacted with diphenylamine to yield thiourea derivative **17**. IR spectra of **17** show bands about 3300 cm^{-1} and 1675 cm^{-1} corresponding to NH and CO respectively. Sodium hydroxide transformed compounds **17** into thiazole **18** as the product of intramolecular nucleophilic substitution reaction. ^{1}H NMR of **18** revealed signals at δ 4.9 and δ 7.2–8.3 for CH_2 and ArH's protons respectively. The synthesis of 2-ethoxythiazole **19** was accomplished by reaction of **1** with sodium ethoxide. Compounds **3–8**, **11–13** and **17–18** were tested in vitro for biological activity against a variety of

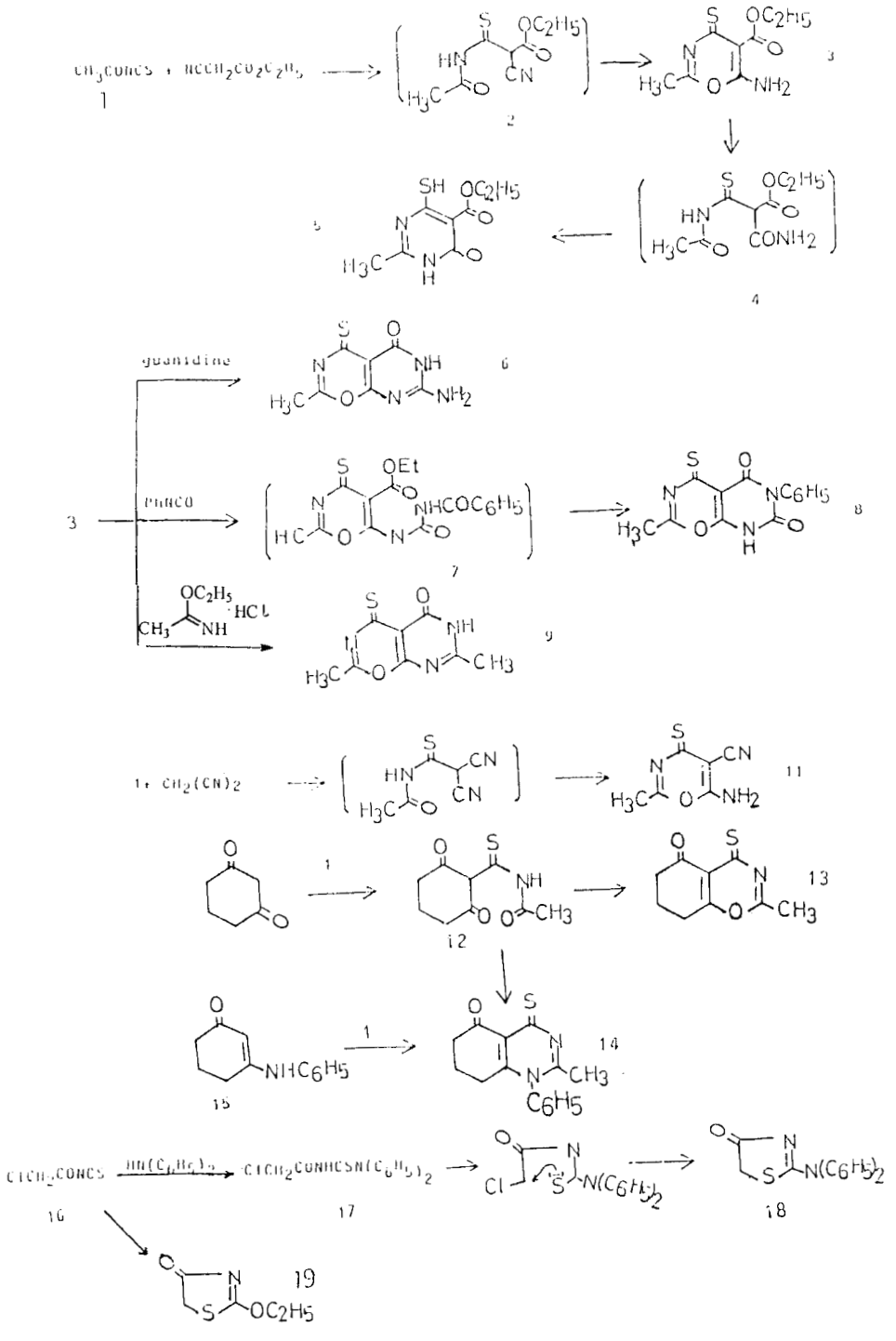

TABLE I

Compound	MP °C (yield%)	Molecular formula (MW)	Analysis Calc / Found %		
			C	H	N
3	>300 (60)	$C_8H_{10}N_2O_3S$ (214.24)	44.85 44.70	4.70 4.80	13.07 13.00
5	>300 (50)	$C_8H_{10}N_2O_3S$ (214.24)	44.85 44.90	4.70 4.80	13.07 12.90
6	>300 (70)	$C_7H_6N_4O_2S$ (210.21)	39.99 39.80	2.88 2.80	26.65 26.70
8	230-32 (65)	$C_{13}H_9N_3O_3S$ (287.29)	54.35 54.30	3.16 3.20	14.63 14.80
9	252-54 (60)	$C_8H_7N_3O_2S$ (209.22)	45.93 45.80	3.37 3.50	20.08 20.00
11	>300 (60)	$C_6H_5N_3OS$ (167.18)	43.11 43.00	3.10 3.20	25.13 25.00
12	289-300 (50)	$C_9H_{11}NO_3S$ (213.25)	50.69 50.60	5.20 5.00	6.57 6.70
13	>300 (50)	$C_9H_9NO_2S$ (195.23)	55.37 55.20	4.65 4.60	7.17 7.00
14	148-50 (65)	$C_{15}H_{14}N_2OS$ (270.35)	66.64 66.70	5.22 5.20	10.36 10.20
17	265-67 (70)	$C_{15}H_{13}ClN_2OS$ (304.79)	59.11 59.00	4.30 4.40	9.19 9.30
18	78-80 (50)	$C_{15}H_{12}N_2OS$ (268.33)	67.14 67.20	4.51 4.60	10.44 10.50
19	>300 (50)	$C_3H_7NO_2S$ (145.18)	41.36 41.20	4.46 4.30	9.65 9.70

TABLE II

Compound	IR (υ_{max} cm^{-1}) Selected bands
3	3570-3500 (NH_2), 1723 (CO), 1131 (CS)
5	3580-3500 (NH), 1720 (CO), 1665 (CO)
6	3590 - 3500 (NH, NH_2), 1670 (CO), 1140 (CS)
8	3580-3500 (NH), 1660 (CO), 1130 (CS)
9	3590-3520 (NH), 1665 (CO), 1130 (CS)
11	3530-3500 (NH_2), 2225 (CN), 1135 (CS)
19	1670 (CO)

TABLE III

Compound	^{1}H NMR (δ ppm)
3	1.2 (t, 3H, $\underline{CH_3}$ CH_2), 2.35 (S, 3H, CH_3), 4.2 (q, 2H, CH_2 CH_3), 8.0 (S, 2H, NH_2).
5	1.3 (t, 3H, $\underline{CH_3}$-CH_2),2.3 (S, 3H, CH_3), 4.2 (q, 2H, CH_2, (CH_2 CH_3), 8.5 (S, 1H, NH), 8.7 (S, 1H, SH)
6	2.3 (s, 3H, CH_3), 6.8 (s, 2H, NH_2), 9.1 (s, 1H, NH)
8	2.35, (S, 3H , CH_3), 7.2 - 7.8 (m, 5H, ArH's), 8.7 (S, 1H, NH)
9	2.2 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 8.2 (s, 1H, NH)
11	2.2 (S, 3H, CH_3), 6.4 (S, 2H, NH_2).
13	1.8, 2.25, 2.35 (m, 9H, $3CH_2$, + CH_3).
14	1.8, 2.2, 2.3 (m, 9H, $3CH_2$ + CH_3), 7.1–7.9 (m, 5H, ArH's)
19	1.5 (t, 3H, CH_3), 4.0 (q, 2H, CH_2), 4.8 (s, 2H, CH_2)

TABLE IV

Compound	Diameter of inhibition zone in mm			
	In vitro activity aganist			
	Salmonella Spp	Proteus Spp	ST ablus	B. subtilis
3	-	10	-	-
5	7	-	8	-
6	6	5	7	5
7	-	-	-	-
8	-	-	6	-
11	-	-	-	-
12	-	6	8	-
13	5	-	-	6
17	6	-	-	5
18	8	6	-	
Reference	9	9	8	10

bacteria such as Salmonella Spp, Proteus Spp. Bacillus Subtilis and Staphylococcus albus.[10,11] The activity was compared with that of penicillin G procaine (reference) at a concentration of a 0.02 g/l. The most potent compounds against Salmonella Spp are **5, 6, 17** and **18**, against proteus Spp., are **3, 6, 12** and **18**, against ST. albus are **5, 6, 8** and **12** and against B-subtilis are **6, 13** and **17** (Table III).

EXPERIMENTAL

All m.p's are uncorrected. IR spectra were recorded in KBr pellets on a Pye Unican spectrophotometer. ^{1}H-NMR spectra were measured in $CDCl_3$ on a varian EM-390 (90 Mz) spectrophotometer using TMS as internal standard. Analytical data were performed by the microanalytical data unit at Cairo University. The biological activity was carried out at the Botany Department, Faculty of Science, Zagazig University.

6-Amino-2-methyl-4-thioxo-4H-1,3-oxazines **3** *and* **11**

A mixture of acetyl isothiocyanate **1** (0.01 mol), ethyl cyanoacetate and/or malononitrile (0.01 mol) and triethylamine (3 drops) in dioxane (15 ml) was stirred for 2 hours, poured into water (20 ml), filtered and crystallized from ethanol to give yellow crystals of **3** and **11** respectively (Table I).

Ethyl 2-methyl-4-mercapto-6-oxopyrimidine 5 carboxylate (**5**)

A mixture of oxazine **3** (0.01 mol) and TEA (2 ml) in ethanol (20 ml) was refluxed for 4 hours and then cooled, the precipitate was collected by filtration and crystallized from ethanol to give orange crystals of **5** (Table I).

Oxazinopyrimidines **6** and **8**

A mixture of **3** (0.01 mol) and guanidine or phenyl isocyanate (0.01 mol) in DMF (15 ml) was refluxed for one hour. The solid obtained upon concentration and cooling, was collected by filtration and crystallized from ethanol to give colourless crystals of **6** or yellow crystals of **8**, respectively (Table I).

Oxazinopyrimidine **9**

A mixture of **3** (0.01 mol), ethyl acetimidate hydrochloride (0.01 mol) and triethylamine (1 ml) in DMF (15 ml) was heated under reflux for one hour. The solid obtained upon pouring into water (20 ml) was filtered off and crystallized from ethanol to give yellow crystals of **9** (Table I).

2-Acetylthiocarboxamido-1,3-cyclohexanedione 12; 2-methyl-1-phenyl-4-thioxo-5,6,7,8-tetrahydro-4H-quinazolin-5-one **14**

a) A mixture of **3** (0.01 mol) and cyclohexanedione **11** and/or enaminone **15** (0.01 mol) in dioxane (20 ml) was refluxed for one hour. After cooling the yellow precipitate was collected and crystallized from aqueous ethanol to give yellow crystals of **12** or **14** respectively (Table I).

b) A mixture of **12** (0.01 mol) and aniline (0.01 mol) in ethanol (10 ml) was heated under reflux for one hour. The mixture was then poured into water (20 ml), filtered and crystallized from aqueous ethanol to give yellow crystals of **14**.

2-Methyl-4-thioxo-5,6,7,8-tetrahydro-4H-1,3-benzoxzin-5-one **13**

A solution of **12** (0.01 mol) in xylene (15 ml) containing triethylamine (3 drops) was refluxed for one hour. The solid obtained upon cooling was collected by filtration and crystallized from xylene to give brown crystals of **13** (Table I).

Chloroacetylthiourea derivative **17**

A mixture of **16** (0.01 mol) and diphenylamine (0.01 mol) in dioxane (10 ml) was stirred at room temperature for 20 minutes. The precipitate obtained upon pouring into water (10 ml) was collected by filtration and crystallized from ethanol to give yellow crystals of **17** (Table I).

2-N,N diphenylamino-2-thiazolin-4-one **18**

A mixture of **17** (0.01 mol) and NaOH (0.01 mol) in ethanol (10 ml) was left at room temperature for one hour. The solid obtained upon addition of HCl (5 ml, 20%) was collected and crystallized from ethanol to give yellow crystals of **18** (Table I).

2-Ethoxy-2-thiazolin-4-one (**19**)

A mixture of **16** (0.01 mol) and sodium ethoxide (0.01 mol) in dioxane (10 ml) was left at room temperature for 2 hours. The solid obtained was collected by filtration and crystallized from methanol to give brown crystals of **19**.

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