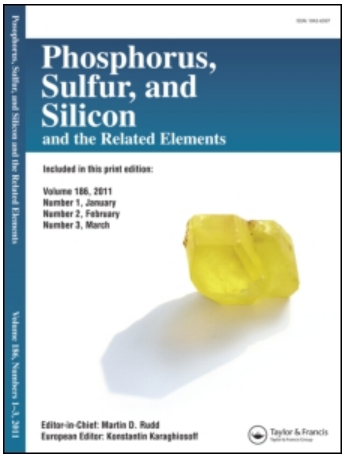

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BEHAVIOR OF TEREPHTHALOYL ISOTHIOCYANATE TOWARDS CARBON AND NITROGEN REAGENTS

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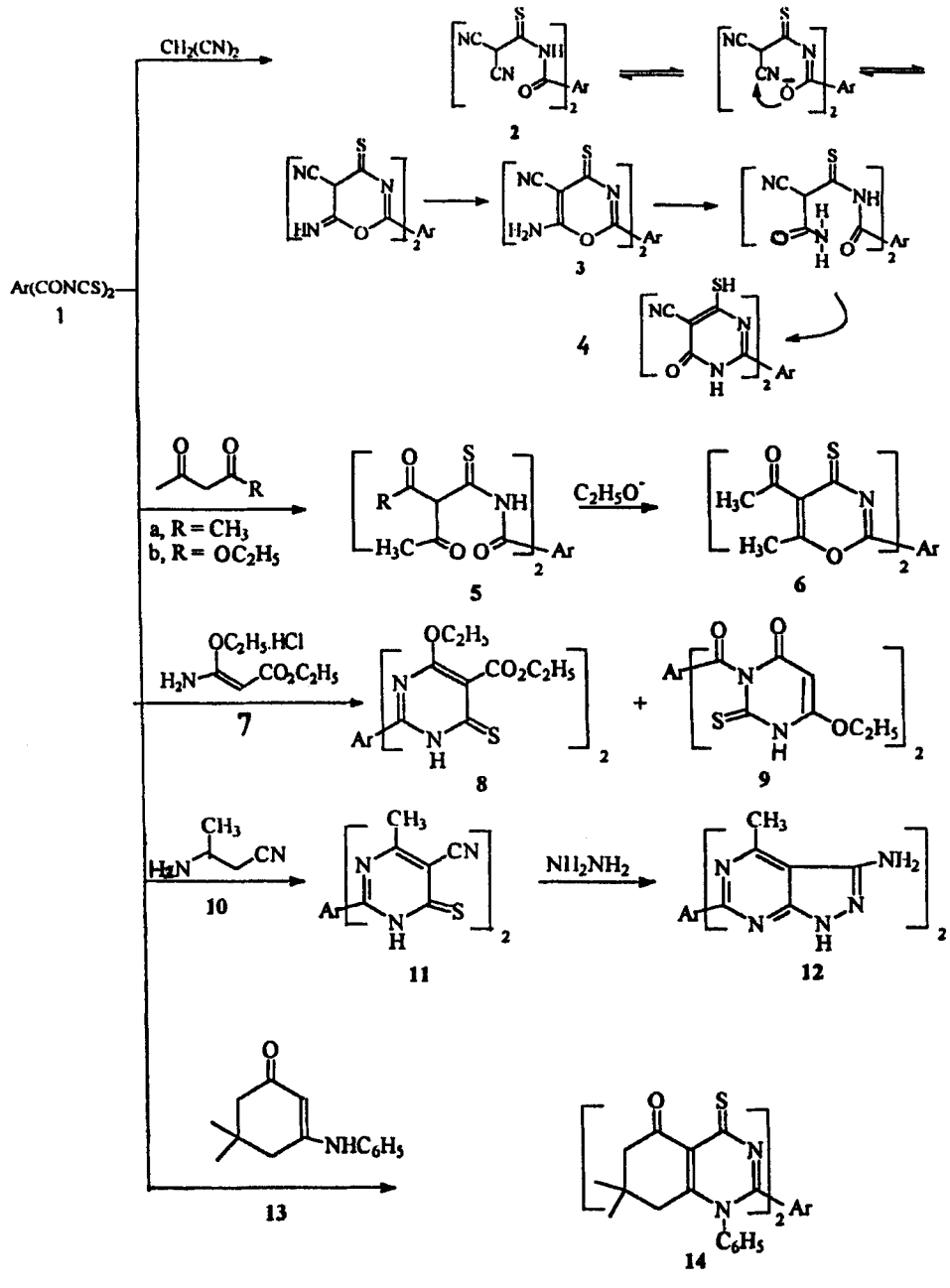
Cyclization of terephthaloyl isothiocyanate with nucleophilic partners either spontaneously, or with added reagents is reported.

Key words: Terephthaloyl isothiocyanate, azoles, azines.

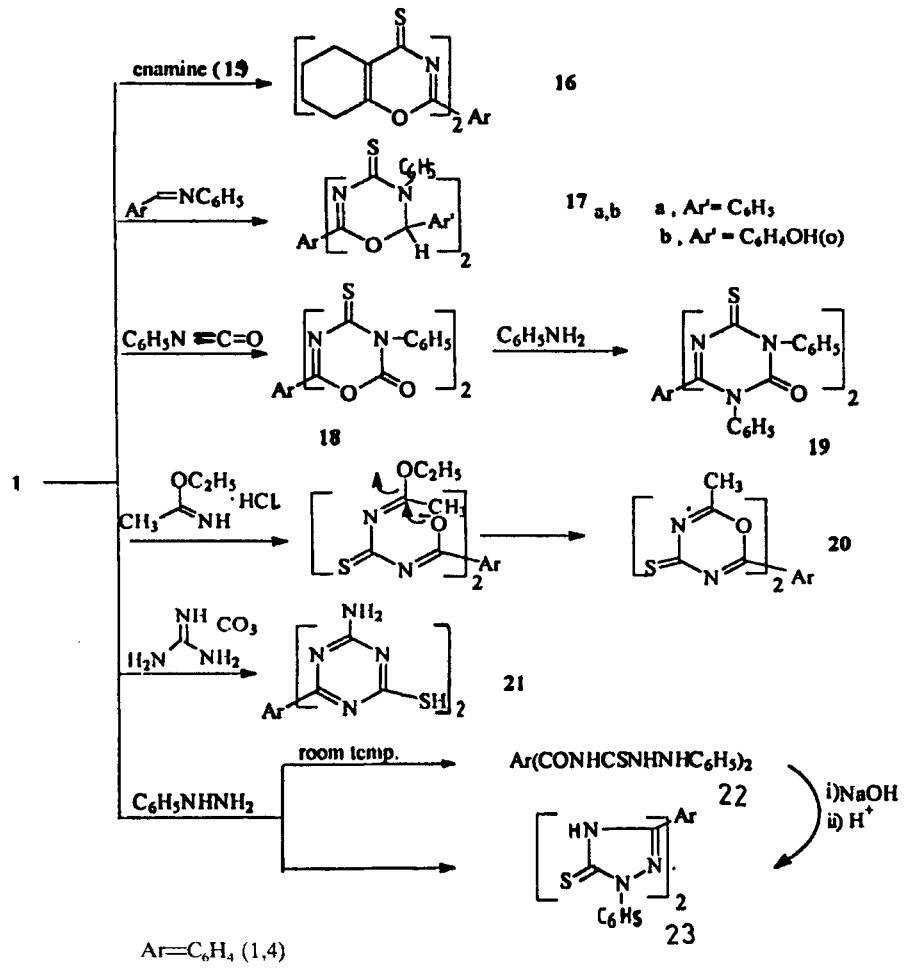
Aroyl isothiocyanates are versatile building units that have been extensively utilized in organic synthesis.[1–3] As a part of a program directed towards the synthesis of heterocyclic systems using of aroyl isothiocyanate.[4,5] The present work describes the cyclization of terephthaloyl isothiocyanate with nucleophilic partners either spontaneously, or with added reagents. Addition of malononitrile to terephthaloyl isothiocyanate in the presence of base yielded 1,3-oxazine **3** presumably via the initial formation of the nonisolable thioamide **2**. Base induced ring transformation of oxazine **3** afforded pyrimidinethione 4.[6] IR spectra of **4** revealed bands at 1670 and 2230 cm^{-1} corresponding to CO and CN respectively. Reaction of compound **1** with acetylacetone or ethyl acetoacetate provided thioamides **5a** or **b**. Keeping 5b in ethanolic sodium ethoxide resulted in cyclization affording oxazinethione **6**. Refluxing of iminoether **7** and isothiocyanate **1** furnished pyrimidinethione **8**[8] and **9**.[9] The formation of compound **8** can be rationalized by assuming the involvement of the electron-rich β-carbon atom of enamine **7**.[7] The pyrimidine derivative **11** was obtained by the interaction of 3-aminobutenenitrile **10** and isothiocyanate **1**.[8] Hydrazinolysis of compound **11** provided pyrazolopyrimidine **12**. Cycloaddition of the cyclic enaminone **13** and isothiocyanate **1** yielded quinazoline **14**. Cyclohexanone was converted into tetrahydro-1,3-benzooxazine **16** via reaction of its enamine **15** with isothiocyanate **1**.[10] Oxazines **17** were formed as a result of cycloaddition of compound **1** and aldimines.[11] The reaction of compound **1** with phenyl isocyanate involved of aroyl group and furnished oxadiazine **18**. The interaction of **18** with aniline resulted in ring transformation affording triazine **19**. Oxadiazine **20** was obtained from the reaction of ethyl acetimidate hydrochloride with isothiocyanate **1**.[12] Cyclocondensation of **1** and guanidinium carbonate afforded triazine **21**.[13] Addition of phenylhydrazine to isothiocyanate **1** at room temperature gave thiosemicarbazide **22**. Triazole **23** was formed by refluxing **1** with phenylhydrazine. Base induced cyclization of **22** gave **23**.

Compounds **4–14** and **19–21** were tested in vitro for biological activity against a variety of bacteria such as Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Bacillus subtilis.[14,15] The activity was compared with that of pen-



SCHEME 1

icillin G procaine (reference) at a concentration of a 0.2 g/L. The most potent compounds against E. coli are **4**, **8** and **14**, against Staph. aureus **11** and **21** against Pseudomonas aeruginosa are **8**, **11**, **20**, and **21**, against Bacillus subtilis are **4**, **12**, **14** and **20** (Table IV).



SCHEME 2

EXPERIMENTAL

All melting points are uncorrected, IR spectra were recorded on a Pye Unicam spectrophotometer. ^{1}H-NMR spectra were measured on a Varian (EM-390) spectrophotometer. Microanalytical data were performed at the Microanalytical Center, Cairo University. Biological activity was carried out at the Department of Botany, Faculty of Science, Zagazig University.

Reaction of **1** *with Carbon Nucleophiles*

A mixture of **1** (0.01 mole) malononitrile, acetylacetone or ethyl acetoacetate (0.02 mole) and triethylamine (TEA) (3 drops) in dioxane (20 mL) was refluxed for one h. The separated solid upon dilution with water (20 mL) was filtered and recrystallized from ethanol to give brown crystals of **3** or yellow crystals of **5a** or **5b**.

Bis 1,4-[5-cyano-6-mercapto-4-oxo(3H)pyrimidine-2-yl]benzene **4** *and bis 1,4-(5-acetyl-6-methyl-4-thioxo-1,3-oxazine-2-yl) benzene* **6**

A mixture of **3** or **5a** (0.01 mole) and sodium ethoxide (0.02 mole) in ethanol (20 mL) was refluxed for one h. The solid obtained upon acidification with HCl (10 mL, 20%), was crystallized from acetic acid to give yellow crystals of **4** or **6**.

TABLE I
Physical properties of the new compounds

Compound	Formula mol. wt.	MP (°C) (Yield %)	Analysis calc./found % C	H	N
3	$C_{16}H_8N_6O_2S_2$	238–50	50.55	2.12	22.10
	380.41	(60)	50.80	2.00	22.3
4	$C_{16}H_8N_6O_2S_2$	>300	50.55	2.12	22.10
	380.41	(65)	50.50	2.00	22.00
5a	$C_{20}H_{20}N_2O_6S_2$	228–30	53.56	4.50	6.25
	448.52	(70)	53.40	4.56	6.30
5b	$C_{22}N_{24}N_2O_8S_2$	210–12	51.96	4.76	5.51
	508.58	(70)	51.80	4.70	5.50
6	$C_{20}H_{16}N_2O_4S_2$	>300	58.24	3.91	6.79
	412.49	(55)	58.30	3.8	6.70
8	$C_{24}H_{26}N_4O_6S_2$	218–20	54.22	5.11	10.53
	530.63	(50)	55.50	5.00	10.70
9	$C_{20}H_{18}N_4O_6S_2$	196–98	50.62	3.82	11.81
	474.52	(30)	50.60	3.80	11.70
11	$C_{18}H_{12}N_6S_2$	238–40	57.43	3.21	22.32
	376.46	(55)	57.40	3.20	22.30
12	$C_{18}H_{16}N_{10}$	250–52	58.06	4.33	37.61
	372.40	(50)	58.00	4.40	37.60
14	$C_{38}H_{34}N_4O_2S_2$	255–56	71.00	5.33	8.72
	642.85	(55)	71.20	5.30	8.80
16	$C_{22}H_{20}N_2O_2S_2$	240–42	64.68	4.94	6.86
	408.54	(65)	64.60	4.80	6.80
17a	$C_{36}H_{26}N_4O_2S_2$	288–90	70.80	4.29	9.17
	610.72	(60)	70.80	4.20	9.00
17b	$C_{36}H_{26}N_4O_4S_2$	>300	67.27	4.08	8.72
	642.72	(55)	67.10	4.00	8.60
18	$C_{24}H_{14}N_4O_4S_2$	280–82	59.25	2.90	11.52
	486.53	(50)	59.30	2.8	11.50
19	$C_{36}H_{24}N_6O_2S_2$	>300	67.91	3.80	13.20
	636.76	(65)	68.00	3.60	13.10
20	$C_{14}H_{10}N_4O_2S_2$	>300	50.90	3.05	16.96
	330.39	(60)	51.10	3.00	16.90
21	$C_{12}H_{10}N_8S_2$	270–73	43.62	3.05	33.92
	330.40	(75)	43.70	3.00	31.10
22	$C_{22}H_{20}N_6O_2S_2$	228–30	56.88	4.34	18.09
	464.57	(75)	56.90	4.30	18.00
23	$C_{22}H_{16}N_6S_2$	240–42	61.66	3.76	19.61
	428.54	(60)	61.50	3.70	19.60

Bis 1,4-(5-carbethoxy-6-ethoxy-4-thioxo-(3H)-pyrimidine-2yl) benzene **8** *or thiouracil* **9**

A mixture of **1** (0.01 mole), iminoether **7** (0.02 mole) and triethylamine (0.02 mole) in dioxane was refluxed for one h. The solid which separates upon dilution with water (20 ml) was filtered, then dissolved in hot ethanol and filtered, the residue was recrystallized from DMF, to give yellow crystals of **8** and the filtrate was cooled, to give yellow crystals of **9**.

Bis 1,4-(5-cyano-6-methyl-4-thioxo (3H) pyrimidine-2-yl) benzene **11**, *Bis 1,4-(7,7-dimethyl-1-phenyl-5-oxo-4-thioxo-5,6,7,8-tetrahydroquinolin-2-yl) benzene* **14** *and/or Bis 1,4-(4-thioxo-5,6,7,8-tetrahydro-1,3-benzoxazin-2-yl) benzene* **16**

A mixture of **1** (0.01 mole), appropriate enamine **10**, **13** or **15** (0.02 mole) and TEA (34 drops) in dioxane (20 mL) was refluxed for one h. The yellow solid that was obtained upon dilution with water (20 mL) was filtered, and recrystallized from acetic acid to give yellow crystals of **11**, **14** or **16** respectively.

TABLE II

^{1}HNMR spectra of some of new compounds

Compound	^{1}H NMR (δ DMSO)
3	6.8 (s, 4H, NH_2), 7.2–8.1 (m, 4H, ArH's)
4	7.0–7.9 (m, 4H, ArH's), 8.7 (s, 2H, 2NH), 9.0 (s, 2H, 2SH)
6	1.5 (s, 6H, $2CH_3$), 2.1 (s, 6H, $2CH_3$), 7.1–8.0 (m, 4H, ArH's)
8	1.3 (t, 6H, $2CH_3$), 1.45 (t, 6H, $2CH_3$), 3.45 (q, 4H, $2CH_2$), 3.6 (q, 4H, $2CH_2$), 7.0–7.8 (m, 4H, ArH's), 9.3 (s, 2H, 2NH).
9	1.3 (t, 3H, CH_3), 3.7 (q, 2H, CH_2), 5.6 (s, H, pyrimidine proton), 7.1–7.5, 7.9–8.2 (m, 4H, ArH's), 9.3 (s, 1H, SH).
11	2.3 (s, 6H, $2CH_3$), 7.0–7.9 (m, 4H, ArH's), 8.5 (s, 2H, 2NH).
12	2.3 (s, 6H, $2CH_3$), 6.4 (s, 4H, $2NH_2$), 7.0–7.9 (m, 4H, ArH's).
14	1.5 (s, 12H, $4CH_3$), 1.8–2.4 (m, 8H, $4CH_2$), 7.0–8.1 (m, 14H, ArH's).
16	1.0, 1.7, 2.6, 2.9 (m, 16H, $8CH_2$), 6.9–8.0 (m, 4H, ArH's).
17a	6.3 (s, 2H, methinyl proton), 6.8–7.9 (m, 24H, ArH's).
17b	6.2 (s, 2H, methinyl proton), 6.9–8.4 (m, 24H, ArH's + 20H).
18	7.0–8.3 (m, 14H, ArH's).
19	6.8–8.2 (m, 24H, ArH's).
20	2.5 (s, 6H, $2CH_3$), 7.0–8.2 (m, 4H, ArH's).
21	6.9–8.2 (m, 8H, ArH's + $2NH_2$), 9.3 (s, 2H, 2SH).
22	7.0–8.2 (m, 14H, ArH's), 8.9–9.3 (m, 6H, 6NH).
23	6.8–7.9 (m, 14H, ArH's), 8.4 (s, 2H, 2SH).

TABLE III

IR spectra of some of the new compounds

Compound	IR KBr (ν cm^{-1})
3	3400–3300 (NH_2), 2230 (CN), 1020(C═S)
5a	3400–3300 (NH), 1690, 1675, 1665 (CO)
5b	3400–3320 (NH), 1700, 1680, 1665 (CO)
6	1690 (CO), 1050 (C═S)
8	3500–3320 (NH), 1690 (CO) 1050 (C═S)
9	3450–3300 (NH), 1680, 1675 (CO), 1100 (C═S)
11	3400–3350 (NH), 2230 (CN), 1090 (C═S)
12	3450–3320 (NH_2, NH)
14	1680 (CO), 1090 (C═S)
16	1080 (C═S)
17a	1080 (C═S)
17b	3420–3200 (OH), 1085 (C═S)
18	1670 (CO), 1090 (C═S)
19	1665 (CO), 1100 (C═S)
20	1085 (C═S)
21	3500–3300 (NH_2)
22	3450–3200 (NH), 1665 (CO), 1090 (CS)
23	3300–3200 (NH), 1090 (C═S)

Bis 1,4-(5-amino-3-methylpyrazolo[3,4-d]pyrimidine-2-yl) benzene **12**

A mixture of **11** (0.01 mole) and hydrazine hydrate (0.025 mole) in DMF (15 ml) was refluxed for one h. The solid obtained upon concentration and cooling was filtered and recrystallized from acetic acid to yield colorless crystals of 12.

Bis 1,4-(6-aryl-4-thioxo-(6H)-1,3,5-oxadiazine-2-yl) benzene **17a,b** *or bis 1,4-(5-phenyl-6-oxo-4-thioxo-1,3,5-oxadiazine-2-yl) benzene* **18**

TABLE IV
Biological activity of some of the new compounds

Compound	Diameter of inhibition zone in mm			
	In vitro activity against			
	E. coli	Staph. aureus	Pseudomonas aeruginosa	B. subtilis
4	+	−	−	+
5	−	−	−	−
6	−	−	−	−
8	+	−	+	−
9	−	−	−	−
11	−	+	+ +	−
12	−	+	−	+ +
14	+	−	−	+ +
19	−	+	−	−
20	−	−	+	+
21	−	−	+	−
Reference	+	+	+	+ +

A mixture of **1** (0.01 mole) and N-phenylbenzaldehyde imine or phenyl isocyanate (0.02 mole) in dioxane (20 mL) was refluxed for one h. The solid obtained upon dilution with water (20 mL) was filtered, and recrystallized from acetic acid to give yellow crystals of **17** or **18**.

Bis 1,4-(1,3-diphenyl-2-oxo-4-thioxotriazine-6-yl) benzene **19**

A mixture of **18** (0.01 mole) and aniline (0.02 mole) in DMF (15 mL) was refluxed for one h. The solid obtained upon concentration and cooling was filtered and recrystallized from ethanol to give colorless crystals of **19**.

Bis 1,4-(6-methyl-4-thioxo-1,3,5-oxadiazin-2-yl) benzene **20** *or bis 1,4-(4-amino-2-thioxotriazine-6-yl) benzene* **21**

A mixture of (0.01 mole) ethylacetimidate hydrochloride or guanidinium carbonate (0.02 mole) and TEA (2 mL) in dioxane (20 mL) was refluxed for two h, the solid obtained upon dilution with water was filtered and recrystallized from acetic acid to give yellow crystals of **20** or **21**.

Bis thiosemicarbazide **22**

A mixture of **1** (0.01 mole) and phenylhydrazine (0.2 mole) in dioxane was left at room temperature for 20 min. The solid obtained upon dilution with water was filtered and recrystallized from ethanol to give colorless crystals of **22** (Table I).

Bis 1,4-(5-mercapto-1-phenyl-1,2,4-triazole-3-yl) benzene **23**

1. A mixture of **1** (0.01 mole) and phenylhydrazine (0.025 mole) in dioxane (15 mL) was refluxed for one h. The solid separated upon cooling was filtered and recrystallized from acetic acid to give yellow crystals of **23** (Table I).
2. A mixture of **22** (0.01 mole) and sodium hydroxide (0.020 mole) in ethanol (20 mL) was left at room temperature for one h, the solid obtained upon addition of HCl (10 mL, 20%) was filtered and recrystallized from acetic acid to give yellow crystals of **23** (Table I).

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