Synthesis and Reactions of 2-Chloro-2-(hydroximino)-1-(4-methyl-2-phenylthiazol-5-yl)ethanone

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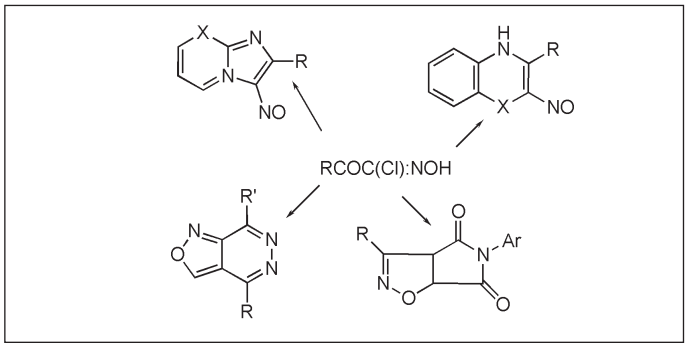

3-Nitrosoimidazo[1,2-*a*]pyridine, 3-nitrosoimidazo[1,2-*a*]pyrimidine, 3-nitrosoquinoxaline, 2-nitroso-4*H*-benzo[*b*]thiazine, 2-nitroso-4*H*-benzo[*b*]oxazine, isoxazoles, isoxazolo[3,4-*d*]pyridazines and pyrrolo[3,4-*d*]isoxazole-4,6-dione were synthesized from 2-chloro-2-(hydroximino)-1-(4-methyl-2-phenylthiazol-5-yl)ethanone and different reagents. Structures of the newly synthesized compounds were confirmed by elemental analysis and spectral data.

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Introduction.

Hydroximoyl halides have been widely used for the synthesis of heterocyclic compounds [1-5]. Isoxazoles are widely investigated for therapentic uses, especially as tranquilizing agents, CNS regulants and are reported to have bacteriostatic, bactericida, antitrypanosomal activity *in vitro* and fungicidal activities [5,6]. In conjunction with our previous work [7-14], we report here the synthesis of several derivatives of imidazo[1,2-*a*]pyridines, imidazo[1,2-*a*]pyrimidines, isoxazoles, isoxazolo[3,4-*d*]pyridazines, and pyrrolo[3,4-*d*]isoxazole-4,6-dione required for biological screening.

Results and Discussion.

Nitrosation of 1-(4-methyl-2-phenylthiazol-5-yl)-2-oxodimethylsulfonium bromide (**1**) [15] in dioxan-water solution in the presence of hydrochloric acid gave 2-chloro-2-(hydroximino)-1-(4-methyl-2-phenylthiazol-5-yl)ethanone (**2**). Structure **2** was confirmed on the basis of elemental analysis, spectral data and chemical transformations. Thus, the ^{1}H NMR spectrum showed signals at δ = 2.47 (s, 3H), 7.19-7.48 (m, 5H) and 13.12 (s, 1H). Its IR spectrum revealed bands at 3400 (OH) and 1645 (CO conjugated).

Treatment of **2** with 2-aminopyridine in ethanol afforded a product that has the molecular formula $C_{17}H_{12}N_4OS$ of which structures **3-5** seemed possible (Figure 1). Structure **5** was eliminated because an absorption band in the region 1650-1800 cm^{-1} corresponding to a CO group in the IR spectrum of the reaction product is not observed. Structure **4** seems unlikely because 2-aminopyridine was reacted with 2-bromo-1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)ethanone to give 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)imidazo[1,2-*a*]pyridine (**6**) which reacted with nitrous acid to afford a product identical in all respects (mp, mixed mp., and spectra) with **3a**. The ^{1}H NMR spectrum of **3a** showed signals at δ = 2.49 (s, 3H), 7.52-7.64 (m, 8H) and 9.75 (d, 1H). Its IR spectrum revealed a band at 1542 cm^{-1} due to the nitroso group. Based on these data 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoimidazo[1,2-*a*]pyridine (**3a**) was taken to be the reaction product.

Similarly, **2** was reacted with each 2-amino-3-methylpyridine, and 2-aminopyrimidine to afford 6-methyl-2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoimidazo[1,2-*a*]pyridine **3b** and 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoimidazo[1,2-*c*]pyrimidine **7**, respectively (Figure 1).

Compound **2** was reacted with *o*-phenylenediamine in ethanol to give a single product (according to tlc). On the basis of their spectral and elemental analyses, the products were assigned as: 1,4-dihydro-2-(4-methyl-2-phenylthiazol-5-yl)-3-nitrosoquinoxaline (**8a**). IR spectra revealed no absorption band between 1650-1800 cm^{-1} due the absence of CO group but showed an absorption band at 1547 for the nitroso group. Compound **8a** was readily oxidized to 2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoquinoxaline (**10**) *via* hydrogen peroxide in acetic solution. Based on the foregoing results the isomeric structure **9** was ruled out.

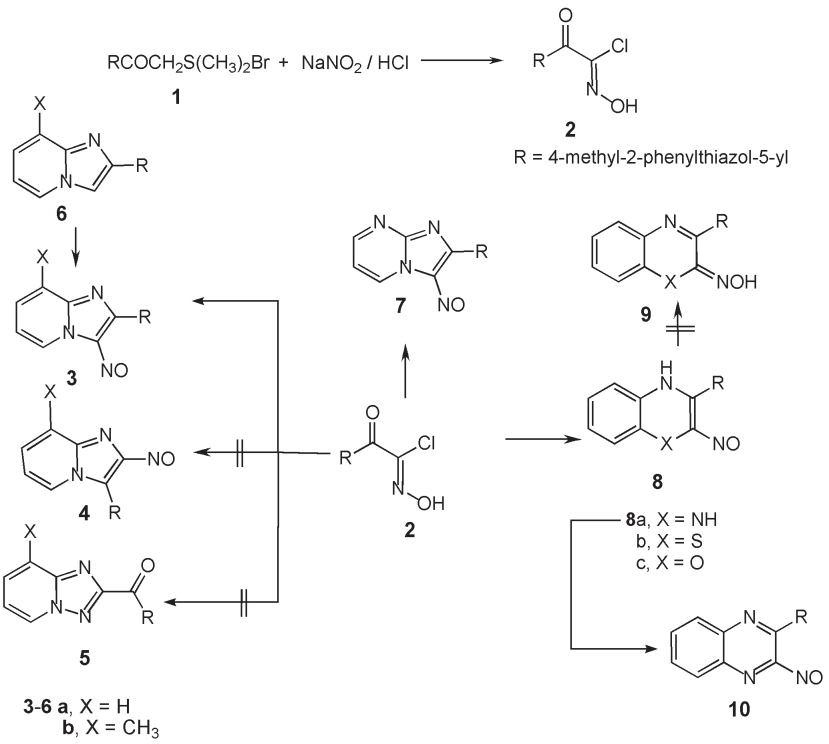

Figure 1

Similarly, treatment of **2** with each of 2-aminothiophenol and 2-aminophenol gave 3-(4-methyl-2-phenylthiazol-5-yl)-2-nitroso-4*H*-benzo[*b*]thiazine (**8b**), 3-(4-methyl-2-phenylthiazol-5-yl)-2-nitroso-4*H*-benzo[*b*]oxazine (**8c**), respectively (Tables 2 and 3).

Treatment of 3-(dimethylamino)-1-(4-methyl-2-phenyl(1,3-thiazol-5-yl))prop-2-ene-1-one (**11**) [16] with hydroximoyl chloride **12a** in toluene containing triethylamine at room temperature afforded one isolable product, according to tlc, whose structure **15a** or isomer **16a** (Figure 2). Formation of **15** can be explained *via* reaction of nitrile oxide, which formed *in situ* from hydroximoyl chloride **12a** and triethylamine, with **11** in the presence of triethylamine to afford cycloadduct intermediate **13a** or **14a**, and spontaneously dimethylamine elimination to give isoxazole **15a** or isoxazole **16a**. Structure of **15** was elucidated by elemental analysis, spectral data and chemical transformations. ^{1}H NMR spectra of **15a** showed signals at

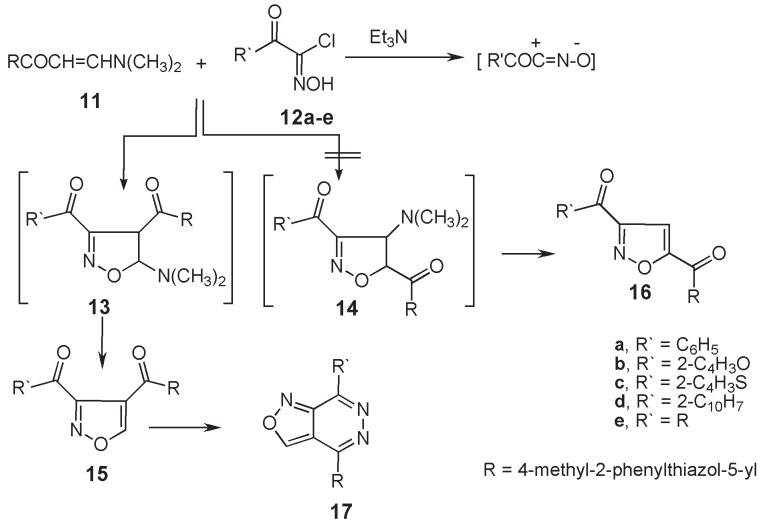

Figure 2

δ = 2.73 (s, 3H), 7.26-7.64 (m, 8H), 7.97-7.98 (d, 1H), 8.08-8.12 (d, 1H) and 9.00 (s, 1H). Its IR spectrum revealed bands at 3047, 2920 (CH), 1674 (CO) and 1594 (C=C). Thus, compound **15a** reacted with hydrazine hydrate in boiling ethanol to give 4-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-7-phenylisoxazolo[3,4-*d*]pyridazine (**17a**) (Figure 2).

Similarly, **11** was reacted with the appropriate hydroximoyl chlorides **12b-e** to afford 4-[(4-methyl-2-phenylthiazol-5-carbonyl)-isoxazol-3-yl]-substituted methanone derivatives **15b-e**, which converted to 4-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-7-substituted isoxazolo[3,4-*d*]-pyridazine derivatives **17b-e**, respectively.

Treatment of acrylonitrile with **2** in boiling toluene afforded one isolable product, according to tlc, which structures **18** and **19** seemed possible (Figure 3). ^{1}H NMR spectrum of the product showed signals at δ = 2.79 (s, 3H), 2.93-2.97 (d, 2H, J = 10 Hz, isoxazoline C-4), 3.75 (t, 1H, J = 10 Hz, isoxazoline C-5), 7.40-7.89 (m, 3H) and 7.89-8.12 (m, 2H). Its IR spectrum revealed bands at 1660 (CO) but no absorption at 2200 cm^{-1} for CN group, which supports the 5-cyano structure (**19**) [17]. Furthermore, the product was readily hydrolysed by sulfuric acid to give the corresponding amide **20** (IR spectral bands at 3330, 3180 (NH_2) and 1690 (CO)). Also, treatment of **2** with acryloamide in boiling toluene afforded product identical with **20**. Hence structure **18** was eliminated and the product was assigned to have the structure formulated as 3-[(4-methyl-2-phenyl-1,3-thiazol-5-yl)carbonyl]-4,5-dihydroisoxazole-5-carbonitrile (**19**).

Finally, treatment of **2** with the appropriate *N*-arylmalemides **21a-c** [18] in boiling toluene gave 3-[(4-methyl-2-phenyl-1,3-thiazol-5-yl)carbonyl]-5-substituted-3a*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione **22a-c**, respectively (Figure 3). Structure **22** was confirmed by elemental analysis and spectral data. The IR spectra of **22a-c** raveled bands near at 1720 and 1635 cm^{-1} due to CO and -CO-NAr-CO- groups [18]. ^{1}H NMR spectrum of **22a** showed signals at δ = 2.86 (s, 3H), 5.13-5.14 (d, 1H), 5.71-5.75 (d, 1H), 6.92-7.27 (m, 6H), 7.43-7.48 (d, 2H) and 8.01-8.05 (d, 2H).

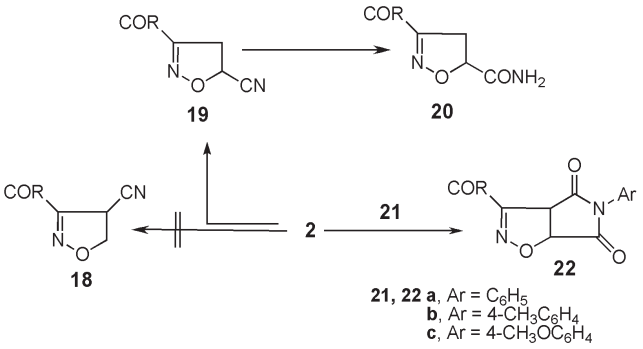

Figure 3

Antimicrobial Activity.

The tested microorganism was gram +ve bacteria, gram -ve bacteria and some Fungal-plant. Sensitivity of the

Table 1

Response of various microorganisms to some synthesized compounds in vitro (culture).

Microorganism/ Compound no	*Staphylococcus albus (G+)*	*Streptococcus faecalis (G+)*	*Bacillus subtilis (G+)*	*Echerichia coli (G-)*	*Aspergills flvus (Fungus)*	*Candida albicans (Fungus)*
Ampicillin / Tetracycline	34R / 27	37 / 31	33 / 30	39 / 34	0.0 / 0.0	20 / 37
2	8	10	0.0	11	0.0	16
3a	5	3	2	0.0	0.0	10
3b	25	10	10	13	0.0	20
8a	11	8	0.0	8	0.0	8
8b	10	12	14	9	0.0	10
8c	0.0	3	2	9	0.0	10
15b	14	15	15	17	0.0	11
15c	13	12	13	13	0.0	10
15d	17	16	22	15	0.0	10
15e	8	10	20	2	0.0	10
17d	17	19	19	21	0.0	14
17e	16	13	17	21	0.0	16
19	23	13	29	30	0.0	13
20	22	12	22	26	0.0	16
22a	23	13	25	28	0.0	23
22b	10	12	8	11	0.0	8
22c	8	14	25	9	0.0	10

St. Reference standerd; Ampicillin and tetracycline were used as standard antibacterial agent and antifungal agents. Values show zone of inhibition in mm. Diameter of the inhibition zones were: high (11-15 mm), moderate (6-10 mm), slight (1-5 mm), negative (0)

Table 2

Characterization Data of the Newly Synthesized Compounds

Compd No.	M.P., °C Solvent	Color Yield %	Mol. Formula mol.wt	% Analyses calcd./found C	H	N	S
2	192-93	Yellow	$C_{12}H_9ClN_2O_2S$	51.34	3.23	9.98	11.42
	EtOH	78	280.73	51.33	3.26	10.00	11.38
3a	233-35	Yellow	$C_{17}H_{12}N_4OS$	63.73	3.78	17.49	10.01
	Dioxan	89	320.37	63.71	3.80	17.52	9.99
3b	228-29	Yellow	$C_{18}H_{14}N_4OS$	64.65	4.22	16.75	9.59
	Dioxan	87	334.39	64.62	4.19	16.77	9.57
6	98-101	Yellow	$C_{17}H_{13}N_3S$	70.08	4.50	14.42	11.01
	Dioxan	80	291.37	70.10	4.52	14.39	10.98
7	240-42	Yellow	$C_{16}H_{11}N_5OS$	59.80	3.45	21.79	9.98
	Dioxan	90	321.35	59.77	3.44	21.83	10.00
8a	226-28	Yellow	$C_{18}H_{14}N_4OS$	64.65	4.22	16.75	9.59
	Dioxan	85	334.39	64.62	4.20	16.74	9.62
8b	263-65	Yellow	$C_{18}H_{13}N_3OS_2$	61.51	3.73	11.96	18.25
	Dioxan	81	351.44	61.49	3.77	12.00	18.22
8c	198-200	Yellow	$C_{18}H_{13}N_3O_2S$	64.46	3.91	12.53	9.56
	Dioxan	88	335.38	64.44	3.90	12.55	9.56
10	> 300	Yellow	$C_{18}H_{12}N_4OS$	65.04	3.64	16.86	9.65
	Dioxan	64	332.38	65.07	3.66	16.85	9.64
15a	155-58	Pale Brown	$C_{21}H_{14}N_2O_3S$	67.37	3.77	7.48	8.56
	EtOH	75	374.41	67.35	3.80	7.44	8.55
15b	159-61	Pale Brown	$C_{19}H_{12}N_2O_4S$	62.63	3.32	7.69	8.80
	EtOH	78	364.37	62.65	3.29	7.71	8.83
15c	168-70	Yellow	$C_{19}H_{12}N_2O_3S_2$	59.98	3.18	7.36	16.86
	EtOH	83	380.44	60.00	3.15	7.35	16.90
15d	173-75	Yellow	$C_{25}H_{16}N_2O_3S$	70.74	3.80	6.60	7.55
	EtOH	80	424.47	70.71	3.82	6.59	7.53
15e	167-69	Yellow	$C_{25}H_{17}N_3O_3S_2$	63.68	3.63	8.91	13.60
	EtOH	81	471.55	63.71	3.66	8.88	13.55
17a	206-208	Yellow	$C_{21}H_{14}N_4OS$	68.09	3.81	15.12	8.66
	Dioxan	77	370.42	68.13	3.85	15.15	8.69
17b	215-17	Yellow	$C_{19}H_{12}N_4O_2S$	63.32	3.36	15.55	8.90
	Dioxan	79	360.39	63.33	3.39	15.51	8.88
17c	222-15	Yellow	$C_{19}H_{12}N_4OS_2$	60.62	3.21	14.88	17.04
	Dioxan	80	376.45	60.59	3.22	14.91	17.00
17d	232-35	Yellow	$C_{25}H_{16}N_4OS$	71.41	3.84	13.32	7.63
	Dioxan	73	420.48	71.44	3.85	13.35	7.66
17e	221-23	Yellow	$C_{25}H_{17}N_5OS_2$	64.22	3.66	14.98	13.72
	Dioxan	76	467.56	64.25	3.63	15.00	13.74
19	109-112	Pale Yellow	$C_{15}H_{11}N_3O_2S$	60.59	3.73	14.13	10.78
	EtOH	71	297.33	60.61	3.74	14.11	10.80
20	200-202	Pale Yellow	$C_{15}H_{13}N_3O_3S$	57.13	4.16	13.33	10.17
	EtOH	66	315.34	57.14	4.19	13.30	10.19
22a	199-201	Yellow	$C_{22}H_{15}N_3O_4S$	63.30	3.62	10.07	7.68
	EtOH	85	417.43	63.28	3.65	10.10	7.65
22b	202-204	Yellow	$C_{23}H_{17}N_3O_4S$	64.03	3.97	9.74	7.43
	EtOH	84	431.46	63.99	3.97	9.72	7.40
22c	195-97	Yellow	$C_{23}H_{17}N_3O_5S$	61.74	3.83	9.39	7.17
	EtOH	82	447.46	61.77	3.81	9.42	7.14

selected microorganisms to some synthesized compounds were determined *in vitro* culture that were dissolved in chloroform, the tests were carried out using the filter paper and hole plate method [19]. Studies on the biological activity of compounds in comparison with Ampicillin and tetracycline are shown in Table 1. In general all tested compounds were capable of inhibiting the growth of gram positive and gram negative.

EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP1000 EX Shimadzu.

Table 3
Spectra of Synthesized Compounds

Comp. No.	Spectral data
2	IR: 3420 (OH), 3074, 2954 (CH)
3a	^{1}H NMR: 2.49 (s, 3H), 7.52-7.64 (m, 8H) and 9.75 (d, 1H). IR: 3062, 2950 (CH), 1624 (C=N) and 1542 (NO).
3b	^{1}H NMR: 2.71 (s, 3H), 3.12 (s, 3H), 7.11-7.64 (m, 7H) and 9.72-9.75 (d, 1H). IR: 3050, 2920 (CH), 1614 (C=N) and 1539 (NO).
7	^{1}H NMR: 2.18 (s, 3H), 7.25-7.54 (m, 4H), 8.18-8.20 (m, 2H), 8.97 (d, 1H), and 9.98 (d, 1H). IR: 3112, 3066 (CH), 1647 (C=N), 1604 (C=C) and 1533 (NO).
8a	^{1}H NMR: 2.74 (s, 3H), 6.85-7.30 (m, 6H), 7.78-7.85 (m, 3H), 9.05 (s, br., 1H), and 10.08 (s, br., 1H). IR: 3398 (NH), 3047, 2920 (CH), 1635 (C=N), 1604 (C=C) and 1477 (NO).
8b	^{1}H NMR: 2.51 (s, 3H), 7.37-7.55 (m, 8H), 7.95-7.99 (m, 1H) and 13.01 (s, br., 1H). IR: 33421 (NH), 3047, 2920 (CH), 1643 (C=N), 1604 (C=C) and 1562 (NO). MS: 351 (8.6%, M^+), 336 (17.9%), 335 (32.9%), 333 (100%), 308 (66.8%), 301 (23.2), 2.05 (67.3%), 160 (23.9%), 104 (11.6%), 71 (28.8%), 70 (17.3%).
8c	^{1}H NMR: 2.98 (s, 3H), 7.34-7.52 (m, 5H), 7.71-7.74 (m, 1H), 7.96-8.01 (dd, 1H), 8.11-8.16 (m, 2H) and 13.01 (s, br., 1H). IR: 3413 (NH), 3047, 2920 (CH), 1635 (C=N), 1616 (C=C) and 1535 (NO). MS: 320 (46.3%, M-CH_3), 292 (25.8%), 202 (80%), 174 (33.7%), 104 (17.9%), 71 (100%).
10	^{1}H NMR: 2.74 (s, 3H), 6.85-7.30 (m, 6H) and 7.78-7.85 (m, 3H) IR: 3047, 2920 (CH), 1635 (C=N), 1604 (C=C) and 1477 (NO).
15a	^{1}H NMR: 2.73 (s, 3H), 7.26-7.64 (m, 8H), 7.97-7.98 (d, 1H), 8.08-8.12 (d, 1H) and 9.00 (s, 1H) IR: 3047, 2920 (CH), 1674 (CO) and 1594 (C=C).
15b	^{1}H NMR: 2.64 (s, 3H), 6.86-6.87 (d, 1H), 7.58-7.70 (m, 4H), 8.02-8.05 (m, 2H), 9.25 (s, 1H) and 9.96 (s, 1H) IR: 3047, 2920 (CH), 1663, 1636 (CO's) and 1594 (C=C).
15c	^{1}H NMR: 2.63 (s, 3H), 7.34-7.38 (t, 1H), 7.55-7.58 (m, 3H), 8.01-8.05 (m, 3H), 8.30-8.32 (d, 1H) and 9.96 (s, 1H) IR: 3047, 2920 (CH), 1636 (CO) and 1561 (C=C).
15d	^{1}H NMR: 2.68 (s, 3H), 7.55-7.93 (m, 5H), 7.96-8.19 (m, 6H), 8.63 (s, 1H), and 10.12 (s, 1H) IR: 3047, 2920 (CH), 1666, 1635 (CO) and 1590 (C=C).
15e	^{1}H NMR: 2.73 (s, 3H), 2.78 (s, 3H), 7.26-9.05 (m, 10H) and 8.94 (s, 1H) IR: 3047, 2920 (CH), 1635 (CO) and 1585 (C=C).
17a	^{1}H NMR: 2.73 (s, 3H), 7.26-7.64 (m, 8H), 7.97-7.98 (d, 1H), 8.08-8.12 (d, 1H) and 9.00 (s, 1H) IR: 3047, 2920 (CH) and 1594 (C=C).
19	^{1}H NMR: 2.79 (s, 3H), 2.93-2.97 (dd, 2H), 3.75 (t, 1H), 7.40-7.89 (m, 3H) and 7.89-8.12 (m, 2H). IR: 2916, 2846 (CH), 1660 (CO).
20	^{1}H NMR: 2.84 (s, 3H), 2.64-3.70 (dd, 2H), 5.16-5.26 (s, br., 1H), 5.92 (s, br., 1H), 6.52 (s, br., 1H), 7.43-7.48 (m, 3H) and 8.03-8.05 (m, 2H). IR: 3330, 3180 (NH_2), 2916, 2846 (CH), 1690 (CO).
22a	^{1}H NMR: 2.86 (s, 3H), 5.13-5.14 (d, 1H), 5.71-5.75 (d, 1H), 6.92-7.27 (m, 6H), 7.43-7.48 (d, 2H) and 8.01-8.05 (d, 2H). IR: 2916, 2846 (CH), 1712, 1635 (CO's), 1635 (C=N)
22b	^{1}H NMR: 2.37 (s, 3H), 2.87 (s, 3H), 5.10-5.15 (d, 1H), 5.71-5.76 (d, 1H), 7.17-7.28 (m, 5H), 7.45-7.48 (d, 2H) and 8.01-8.05 (d, 2H). IR: 2916, 2850 (CH), 1716, 1635 (CO's), 1635 (C=N)
22c	^{1}H NMR: 2.86 (s, 3H), 3.80 (s, 3H), 5.13-5.14 (d, 1H), 5.71-5.75 (d, 1H), 6.92-7.27 (m, 5H), 7.43-7.48 (d, 2H) and 8.01-8.05 (d, 2H). IR: 2916, 2846 (CH), 1712, 1635 (CO's), 1635 (C=N)

Elemental analyses were carried out at the Microanalytical Center of the Cairo University. Hydroximoyl chlorides **11a-d** were prepared using previously described methods [7,9-12].

2-Chloro-2-(hydroximino)-1-(4-methyl-2-phenyl)thiazol-5-yl)ethanone (**2**).

Hydrochloric acid (12 *M*, 100 ml) was added while stirring to a mixture of **1** (11.2 g, 40 mmol), sodium nitrite (3.5 g, 50 mmol) in dioxn (50 ml) and water (50 ml) at 25 °C. Stirring was continued for 3 hours to produce a pale yellow solid, which was separated by filtration and recrystallized from ethanol to give **2** (Tables 2 and 3).

Synthesis of 2-(4-Methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoimidazo[1,2-*a*]pyridine (**3a**), 6-Methyl-2-(4-methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoimidazo[1,2-*a*]pyridine (**3b**) and 2-(4-Methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoimidazo[1,2-*c*]pyrimidine (**7**).

General Procedure.

A mixture of **2** and the appropriate of 2-aminopyridine or 2-amino-3-methylpyridine or 2-amino-pyrimidine (5 mmol for each) in ethanol (20 ml) was stirred for 2 hours. The resulting solid was collected, washed with water and recrystallized from dioxan to give **3a,b** and **7**, respectively (Tables 2 and 3).

Synthesis of 2-(4-Methyl-2-phenyl-1,3-thiazol-5-yl)imidazo-[1,2-a]pyridine (**6**).

Equimolar amounts of 2-bromo-1-(4-methyl-2-phenyl-1,3-thiazol-5-yl)ethanone and 2-aminopyridine (5 mmol for each) in ethanol (20 ml) were heated under reflux for 2 hours. The

resulting solid was collected, washed with water and recrystallized from dioxan to give **6** (Tables 2 and 3).

Synthesis of 1,4-Dihydro-2-(4-methyl-2-phenylthiazol-5-yl)-3-nitrosoquinoxaline (**8a**), 3-(4-Methyl-2-phenylthiazol-5-yl)-2-nitroso-4*H*-benzo[*b*]thiazine (**8b**), 3-(4-Methyl-2-phenylthiazol-5-yl)-2-nitroso-4*H*-benzo[*b*]oxazine (**8c**).

General Procedure.

Equimolar amounts of **2** and the appropriate of *o*-phenylenediamine, *o*-aminothiophenol or 2-aminophenol (5 mmol for each) in ethanol (20 ml) were stirred for 2 hours (or boiled under reflux in case of 2-aminophenol). The resulting solid was collected, washed with water and recrystallized from dioxan to give **8a, 8b** and **8c**, respectively (Tables 2 and 3).

Synthesis of 2-(4-Methyl-2-phenyl-1,3-thiazol-5-yl)-3-nitrosoquinoxaline (**10**).

A solution of **8a** (0.5 g) in acetic acid (15 ml) and hydrogen peroxide (30%, 5 ml) was stirred at room temperature for 24 hours. The reaction was poured onto water (50 ml), the resulting solid was collected and recrystallized from dioxan to give **10** (Tables 2 and 3).

Synthesis of 4-[(4-Methyl-2-phenylthiazol-5-carbonyl)-isoxazol-3-yl]-substituted Methanone (**15a-e**).

General Method.

Triethylamine (0.5 g (0.75 ml), 5 mmol) was added dropwise to an equimolar amount of each **11** and the appropriate hydroximoyl chlorides **12a-e** (5 mmol) in dry toluene (20 ml) while stirring at 0-5 °C. The reaction mixture was stirred for 6 hours. The reaction mixture was filtered, the filtrate was evaporated and the resulting oil was triturated with petroleum ether (40-60 °C). The solid, so formed, was collected and recrystallized to give **15a-e**, respectively (Tables 2 and 3).

Synthesis of 4-(4-Methyl-2-phenyl-1,3-thiazol-5-yl)-7-substitutedisoxazolo[3,4-*d*]pyridazine (**17a-e**).

General Method.

Equimolar amounts of each of the appropriate isoxazoles **15a-e** (5 mmol) and hydrazine hydrate (1 ml, 99%) in ethanol (20 ml) was boiled under reflux for 2 hours. The resulting solid was collected and recrystallized from dioxane to give isoxazolo [3,4-*d*]-pyridazines **17a-e**, respectively (Tables 2 and 3).

Synthesis of 3-[(4-Methyl-2-phenyl-1,3-thiazol-5-yl)carbonyl]-4,5-dihydroisoxazole-5-carbonitrile (**19**), 3-[(4-Methyl-2-phenyl-1,3-thiazol-5-yl)carbonyl]-4,5-dihydroisoxazole-5-carboxamide (**20**) and 3-[(4-Methyl-2-phenyl-1,3-thiazol-5-yl)carbonyl]-5-substituted3a*H*-pyrrolo[3,4-*d*]isoxazole-4,6(5*H*,6a*H*)-dione (**22a-c**).

General Method.

An equimolar amount of the appropriate **2**, acrylonitrile or acryloamide or the appropriate *N*-arylmalemides **22a-c** (5 mmol each) in toluene (30 ml) was heated under reflux for 18 hours. The solvent was evaporated under vacuum and the residual oil was triturated with petroleum ether (40-60 °C). A solid was collected and recrystallized from ethanol to give **19**, **20** and **22a-c**, respectively (Tables 2 and 3).

Alternative Method for Synthesis of 3-[(4-Methyl-2-phenyl-1,3-thiazol-5-yl)carbonyl]-4,5-dihydroisoxazole-5-carboxamide (**20**).

Compound **19** (0.5 g) and sulphuric acid (5 ml) was stirred at room temperature for 1 hour, and then poured onto crushed ice (20 g). The resulting solid was collected and recrystallized from ethanol to give **20** (Tables 2 and 3).

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