

# Reactions of *N*-Heteroarylformamide Oximes and *N*-Heteroarylacetamide Oximes with *N,N*-Dimethylformamide Dimethyl Acetal. Synthesis of 2-Methyl-*s*-triazolo[1,5-*x*]azines and *N*-Methylcyanoaminoazines

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*N*-Heteroarylformamide oximes **3** (R = H) were converted with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) into *N*-heteroaryl-*N*-methylcyanoamino compounds **5**, as the main products. In some instances *N*-heteroarylcyanoamino compounds **4**, cyanoimino compounds **7**, and some other products, such as **9** and **10** were also formed. On the other hand, *N*-heteroarylacetamide oximes **3** (R = CH<sub>3</sub>) were cyclized under the same reaction conditions into 2-methyl-*s*-triazolo[1,5-*x*]azines (**6**). *N*-Heteroarylacetamide *O*-methyl oximes **11** and **12** were prepared from the corresponding acetamidines **2** (R = CH<sub>3</sub>) and *O*-methylhydroxylamine.

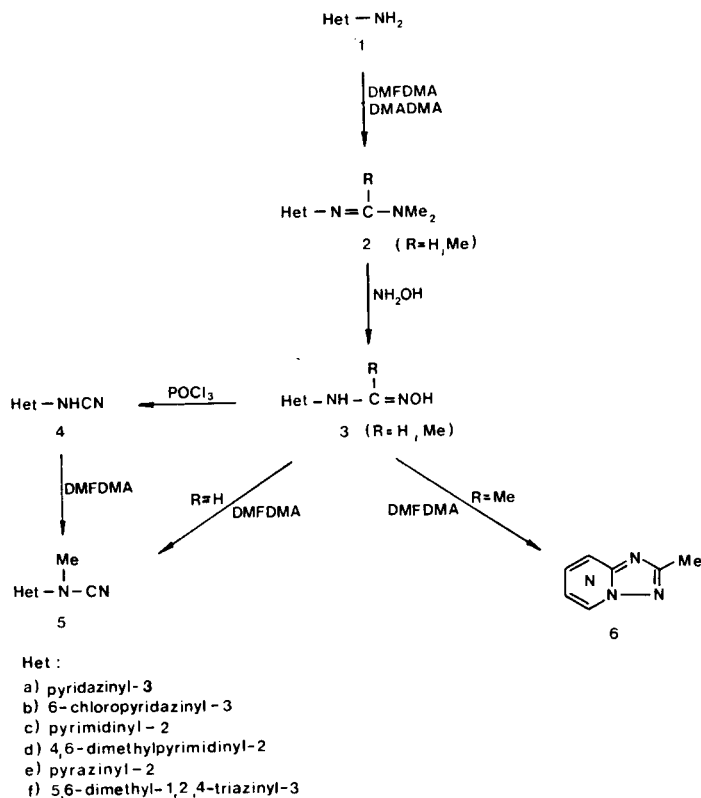
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Recently, *N,N*-dimethylformamide dimethyl acetal (DMFDMA) has been used for methylation of NH, SH and OH or potential NH, SH and OH groups giving the corresponding methylated products in high yields (1,2). On the other hand, this reagent has been also used for transformation of primary amines into *N,N*-dimethylaminomethylene amino derivatives, which could be transformed into *N*-heteroarylformamide oximes, the class of compounds, which turned out to be extremely versatile in the synthesis of various heterocyclic systems. On this basis, new methods for the synthesis of *s*-triazolo[1,5-*x*]azines (3-6), *s*-triazino[1,5-*x*]azine 3-oxides (7,8), pyrido[2,3-*d*]pyrimidine 3-oxides (9,10), pteridines and pteridine 3-oxides (11) have been elaborated. The first example of the synthesis of *N*-heteroarylformamide oxime was reported to result from the reaction of hydroxylamine on 4-hydroxy-6-methylpteridine (12). The best synthetic procedure is the reaction of heterocyclic amines with DMFDMA followed by treatment with hydroxylamine or its hydrochloride to give under mild conditions the corresponding formamide oximes (3). A new method for the preparation of 2-pyrimidinyl and *s*-triazinylformamide oximes from the corresponding formylated heterocycles has been developed recently (13).

In this communication we would like to report on the reaction between *N*-heteroarylformamide oximes and DMFDMA. In this connection the following oximes were selected: *N*-(pyridazin-3-yl)formamide oxime (**3a**, R = H), *N*-(6-chloropyridazin-3-yl)formamide oxime (**3b**, R = H), *N*-(pyrimid-2-yl)formamide oxime (**3c**, R = H), *N*-(4,6-dimethylpyrimid-2-yl)formamide oxime (**3d**, R = H), *N*-pyrazinylformamide oxime (**3e**, R = H), *N*-(5,6-dimethyl-1,2,4-triazin-3-yl)formamide oxime (**3f**, R = H).

Reaction between *N*-heteroarylformamide oximes and DMFDMA gave mainly *N*-methylcyanoaminoazines **5**. In this manner, pyridazine derivatives **3a,b** (R = H) gave only 3-(*N*-methylcyanoamino)pyridazines **5a** and **5b**.

*N*-(Pyrimid-2-yl)formamide oxime (**3c**, R = H) gave a mixture of two products 2-(*N*-methylcyanoamino)pyrimidine (**5c**) and 1-methyl-2(1*H*)-cyanoiminopyrimidine (**7c**, R = H) in the ratio 1:1, while *N*-(4,6-dimethylpyrimid-2-yl)formamide oxime (**3d**) afforded a mixture of three products 2-(*N*-methylcyanoamino)-4,6-dimethylpyrimidine (**5d**) (58%), 2(1*H*)-cyanoimino-1,4,6-trimethylpyrimidine (**7d**, R = CH<sub>3</sub>) (3.5%) and *N*-cyanoamino-4,6-dimethylpyrimidine (**4d**) (6.4%).



Scheme 1

Instead of DMFDMA *N,N*-dimethylformamide diethyl acetal (DMFDEA) was used and *N*-ethylcyanoamino compounds could be obtained. In this way, *N*-(6-chloropyridazin-3-yl) formamide oxime (**3b**, R = H) was converted into 3-(*N*-ethylcyanoamino)-6-chloropyridazine (**8**).

When *N*-(5,6-dimethyl-1,2,4-triazin-3-yl)formamide oxime (**3f**, R = H) was treated with DMFDMA the formamide oxime group was converted into *N*-methyl-*N*-cyano group. At the same time, the more reactive methyl group, most probably that at position 5, was transformed into enamine group to give 5-[2-(*N,N*-dimethylamino)-1-ethenyl]-3-(*N*-methylcyanoamino)-6-methyl-1,2,4-triazine (**9**). The enamine group of compound **9** reacted with hydroxylamine affording 5-(*cis*-2-hydroxyamino-1-ethenyl)-3-(*N*-methylcyanoamino)-6-methyl-1,2,4-triazine (**10**), for which *cis* orientation around the double bond was established on the basis of the coupling constant between olefinic protons ( $J_{H_A, H_B} = 7.0$  Hz), most probably due to the intramolecular hydrogen bond formation.

The method has been extended to the preparation of *N*-heteroaryl acetamide oximes **3** (R = CH<sub>3</sub>). In this respect, *N,N*-dimethyl-*N'*-heteroarylacetimidines were prepared by treatment of heterocyclic amines **1** with dimethylacetamide dimethylacetal (DMADMA). These gave with hydroxylamine the corresponding acetamide oximes **3** (R = CH<sub>3</sub>): *N*-(6-chloropyridazin-3-yl)acetamide oxime (**3b**, R = CH<sub>3</sub>), *N*-(pyrimid-2-yl)acetamide oxime (**3c**, R = CH<sub>3</sub>), *N*-(4,6-pyrimid-2-yl)acetamide oxime (**3d**, R = CH<sub>3</sub>), *N*-(pyrazin-2-yl)acetamide oxime (**3e**, R = CH<sub>3</sub>) and *N*-(5,6-dimethyl-1,2,4-triazin-3-yl)acetamide oxime (**3f**, R = CH<sub>3</sub>), in high yields. Since dehydration of these derivatives giving cyanoamino derivatives **4** and/or **5** is not possible, cyclodehydration occurred by treatment with DMFDMA affording 2-methyl-*s*-triazolo[1,5-*x*]azines (**6**).

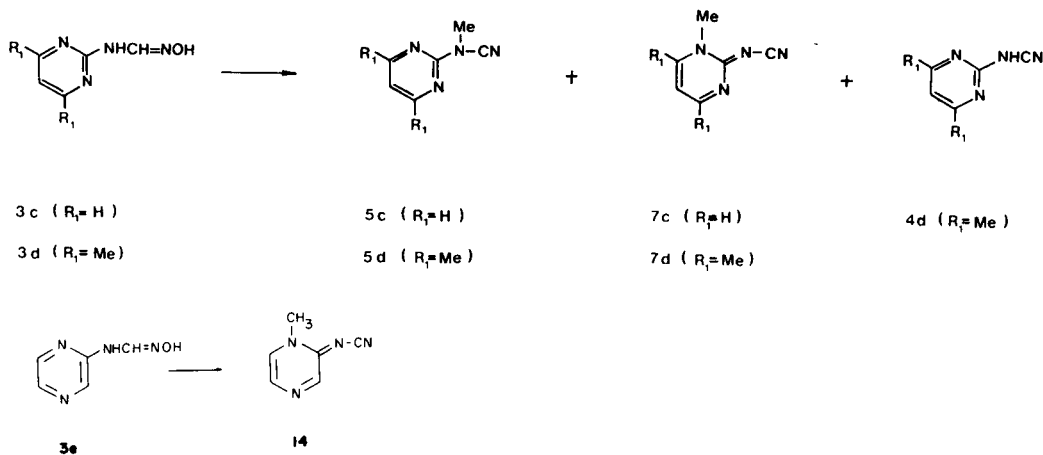
Similar results were obtained also by heating oximes **3** (R = CH<sub>3</sub>) in polyphosphoric acid at 145°, or by heating in phosphorus oxychloride in chloroform or mixture of chloroform and pyridine.

This method represents an alternative to the previously described syntheses of *s*-triazolo[1,5-*x*]azines, such as Dimroth rearrangement of *s*-triazolo[4,3-*x*]azines (**14**), oxidative cyclization of *N*-heteroarylamidines (**15,16**) and cyclization of *N*-aminoazinium salts (**17,18**), and an extension of the "oxime method" (**3**), by which only *s*-triazolo[1,5-*x*]azines, unsubstituted at position 2, could be prepared.

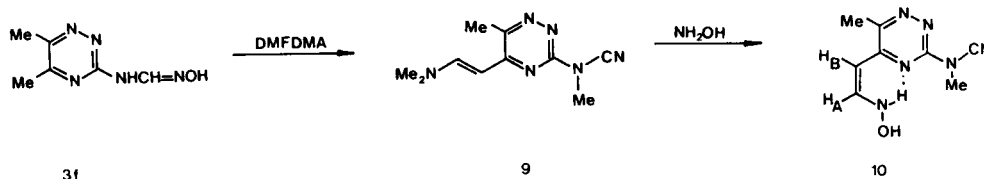
*O*-Methylacetamide oximes could be prepared in a different way. Thus, from *N,N*-dimethyl-*N'*-(6-chloropyridazin-3-yl)acetamide (**2b**, R = CH<sub>3</sub>) and *O*-methylhydroxylamine (hydrochloride) *N*-(6-chloropyridazin-3-yl)acetamide *O*-methyl oxime (**11**) was obtained, which could be further methylated with DMFDMA to give *N*-(6-chloropyridazin-3-yl)-*N*-methylacetamide *O*-methyl oxime (**12**).

We studied the reaction course in more detail in the case of *N*-(6-chloropyridazin-3-yl)formamide oxime (**3b**, R = H). The molar ratio 1:2 between oxime and DMFDMA is required in order to complete the reaction. Since the reaction at room temperature is too slow, it was carried out in toluene under reflux. On the other hand, 3-cyanoamino-6-chloropyridazine was prepared by dehydration of *N*-(6-chloropyridazin-3-yl)formamide oxime (**3b**, R = H) with phosphorus oxychloride, followed by treatment with DMFDMA in 1:1 molar ratio. This conversion was followed also by nmr technique at 90-100°. Besides the *N*-methylcyanoamino compound **5b** *N,N*-dimethylformamide and methanol were formed as the reaction products. Most probably, first dehydration affording *N*-cyanoamino compound occurred followed by *N*-methylation.

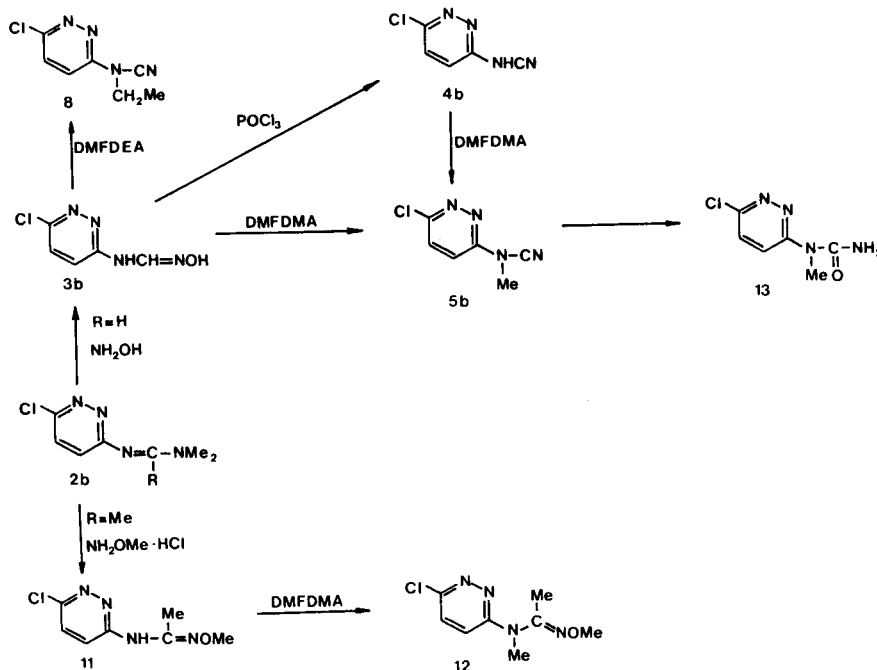
It was shown on the basis of <sup>1</sup>H nmr spectra, that some



Scheme 2



Scheme 3



Scheme 4

N-heteroarylacetamide oximes, such as *N*-(6-chloropyridazin-3-yl)acetamide oxime (**3b**, R = CH<sub>3</sub>) and *N*-(pyrazin-2-yl)acetamide oxime (**3e**, R = CH<sub>3</sub>) exist in solution as equilibrium of two isomers in the ratio of 2:1 and 3:1, respectively. The nmr spectrum of *N*-(6-chloropyridin-3-yl)-*N*-methylacetamide *O*-methyl oxime (**12**) shows at room temperature four signals for C-CH<sub>3</sub> groups at  $\tau = 7.86$ -8.06 and eight signals for N-CH<sub>3</sub> and O-CH<sub>3</sub> groups at  $\tau = 6.15$ -6.70, indicating that there is an equilibrium of at least four different isomers (rotamers) existing in solution.

## EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. All nmr spectra were obtained on a JEOL JNM C60-HL spectrometer and mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6L instrument.

General Procedures for the Preparation of *N*-Heteroarylformamide Oximes (**3**, R = H) (19).

A mixture of a heterocyclic amino compound **1** (10 mmoles), DMFDMA (1.5 ml) and toluene (10 ml) was heated under reflux for two hours. The solvent was evaporated *in vacuo*, the crude *N,N*-dimethyl-*N'*-heteroarylformamidinium salt (**2** (R = H) dissolved in methanol (50 ml) and hydroxylamine hydrochloride (0.834 g, 12 mmoles) added and the solution left at room temperature for one hour. The precipitated product **3** (R = H) was collected by filtration and washed with water.

The following compounds were prepared according to this procedure:

*N*-Pyridazin-3-yl)formamide Oxime (**3a**, R = H).

This compound was obtained in 89% yield, mp 185°, lit (3) mp 194-195°.

*N*-(6-Chloropyridazin-3-yl)formamide Oxime (**3b**, R = H).

This compound was obtained in 89% yield, mp 195-199°, lit (3) 190-194°.

*N*-(Pyrimid-2-yl)formamide Oxime (**3c**, R = H).

This compound was obtained in 81% yield, mp 192-196° (from ethanol/water), lit (3) mp 198-200°.

*N*-(4,6-Dimethylpyrimid-2-yl)formamide Oxime (**3d**, R = H).

This compound was obtained in 80% yield, mp 269-270° (from DMF/ethanol), lit (3) mp 269-270°.

*N*-(Pyrazinyl)formamide Oxime (**3e** R = H).

This compound was obtained in 80% yield, mp 195-200° (from ethanol), lit (3) mp 202-204°.

*N*-(5,6-Dimethyl-1,2,4-triazin-3-yl)formamide Oxime (**3f**, R = H).

This compound was obtained in 88% yield, mp 236-238° (from ethanol/water), lit (20) mp 226-227°.

*N,N*-Dimethyl-*N'*-(4,6-dimethylpyrimid-2-yl)acetamidinium salt (**2d**, R = CH<sub>3</sub>).

A mixture of 2-amino-4,6-dimethylpyrimidine (**1d**) (0.62 g, 5 mmoles),

Table I

*N*-Heteroarylacetamide Oximes (**3**, R = CH<sub>3</sub>)

Compound	mp (°C)	Crystallized from	Yield (%)	Molecular formula	Analysis			MS M*	'H-Nmr data: solvent chemical shifts (τ) and coupling constants J   Hz	
					C	H	N			
<b>3b</b>	149-150	methanol	98	C <sub>6</sub> H <sub>7</sub> ClN <sub>4</sub> O	Calcd.	38.62	3.78	30.03	186	DMSO-d <sub>6</sub> : isomer I: 7.77 (s, CH <sub>3</sub> ), 2.60 (d) and 2.42 (d) (H <sub>5</sub> , H <sub>6</sub> ), 1.0 (br, NH), -0.15 (br, OH); J <sub>H<sub>4</sub>, H<sub>5</sub></sub> = 9.5 Hz. Isomer II: 7.96 (s, CH <sub>3</sub> ), 2.42 (d) and 1.98 (d) (H <sub>4</sub> , H <sub>5</sub> ), 0.57 (br, NH), 0.33 (br, OH), J <sub>H<sub>4</sub>, H<sub>5</sub></sub> = 9.5 Hz. Ratio: isomer I: isomer II 2:1.
					Found	38.79	4.30	30.16		
<b>3c</b>	164-167	methanol	83	C <sub>6</sub> H <sub>8</sub> N <sub>4</sub> O	Calcd.	47.36	5.30	36.82	152	DMSO-d <sub>6</sub> : 7.72 (s, CH <sub>3</sub> ), 1.55 (d, H <sub>4</sub> , H <sub>6</sub> ), 3.09 (t, H <sub>5</sub> ), 2.75 (br, HN), -0.77 (s, OH), J <sub>H<sub>4</sub>, H<sub>5</sub></sub> = J <sub>H<sub>5</sub>, H<sub>6</sub></sub> = 4.6 Hz.
					Found	47.64	5.43	36.53		
<b>3d</b>	182-183	methanol	74	C <sub>8</sub> H <sub>12</sub> N <sub>4</sub> O	Calcd.	53.32	6.71	31.09	180	DMSO-d <sub>6</sub> : 7.7 (s, C-CH <sub>3</sub> , 4-CH <sub>3</sub> , 6-CH <sub>3</sub> ), 3.35 (s, H <sub>5</sub> ), 2.0 (br, NH), -0.9 (s, OH).
					Found	53.43	6.75	31.15		
<b>3e</b>	180-182	water	77	C <sub>6</sub> H <sub>8</sub> N <sub>4</sub> O	Calcd.	47.36	5.30	36.82	152	DMSO-d <sub>6</sub> : isomer I: 7.78 (s, CH <sub>3</sub> ), 1.54 (d, H <sub>3</sub> ), ~1.9 (H <sub>5</sub> , H <sub>6</sub> ), 1.05 (br, NH), -0.5 (s, OH), J <sub>H<sub>4</sub>, H<sub>6</sub></sub> = 1.2 Hz; isomer II: 7.95 (s, CH <sub>3</sub> ), 0.9 (d, H <sub>3</sub> ), ~1.9 (H <sub>5</sub> , H <sub>6</sub> ), 1.05 (br, NH), 0.37 (s, OH), J <sub>H<sub>3</sub>, H<sub>6</sub></sub> = 1.2 Hz. Ratio: isomer I: isomer II 3:1.
					Found	47.36	5.41	37.13		
<b>3f</b>	205-208(a)	methanol	87	C <sub>7</sub> H <sub>11</sub> N <sub>5</sub> O	Calcd.	46.40	6.12	38.65	181	DMSO-d <sub>6</sub> : 7.72 (s, C-CH <sub>3</sub> ), 7.60 (s) and 7.52 (s) (5-CH <sub>3</sub> and 6-CH <sub>3</sub> ), 1.8 (br, NH), -0.2 (br, OH)
					Found	46.44	6.30	38.98		

(a) Lit (20) mp 208-209°.

DMFDMA (0.8 ml) in toluene (5 ml) was heated under reflux for five hours. The solvent was evaporated *in vacuo* and crude residue purified by column chromatography (Kieselgel 60, Merck, 70-230 mesh ASTM, 25-30 g). First, by products were eluted with ether followed by the elution of the main product with methanol to give after evaporation of methanol **2d** in 90% yield; ms: M\* = 192; nmr (deuteriochloroform): τ = 7.94 (s, C-CH<sub>3</sub>), 7.62 (s, 4-CH<sub>3</sub>, 6-CH<sub>3</sub>), 6.92 (s, N(CH<sub>3</sub>)<sub>2</sub>), 3.5 (br. s, H<sub>5</sub>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>16</sub>N<sub>4</sub>: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.10; H, 8.19; N, 29.23.

In an analogous manner the following compounds were prepared:

*N,N*-Dimethyl-*N'*-(5,6-dimethyl-1,2,4-triazin-3-yl)acetamidine (**2f**, R = CH<sub>3</sub>).

This compound was prepared from 3-amino-5,6-dimethyl-1,2,4-triazine (**1f**) in 68% yield, mp 84-86° (from petroleum ether/carbon tetrachloride), lit (20) mp 84-86°; ms: M\* = 193; nmr (deuteriochloroform): τ = 7.85 (s, C-CH<sub>3</sub>), 7.55 (s) and 7.43 (s) (5-CH<sub>3</sub> and 6-CH<sub>3</sub>), 6.87 (s, N(CH<sub>3</sub>)<sub>2</sub>).

*Anal.* Calcd. for C<sub>9</sub>H<sub>15</sub>N<sub>5</sub>: C, 55.94; H, 7.82; N, 36.24. Found: C, 56.06; H, 7.91; N, 36.03.

*N,N*-Dimethyl-*N'*-(6-chloropyridazin-3-yl)acetamidine (**2b**, R = CH<sub>3</sub>).

This compound was prepared from 3-amino-6-chloropyridazine (**1b**) according to the procedure described in literature (21).

General Procedure for the Preparation of *N*-Heteroarylacetamide Oximes (**3**, R = CH<sub>3</sub>).

A mixture of heterocyclic amino compound **1** (5 mmoles) and DMFDMA (0.8 ml) in toluene (5 ml) was refluxed for 5 hours. The solvent was removed *in vacuo*, water (2-3 ml) was added to the residue, followed by addition of methanol in order to obtain a clear solution. Hydroxylamine hydrochloride (417 mg, 6 mmoles) was added and the mixture left one hour at room temperature. The precipitated *N*-heteroarylacetamide oxime (**3**, R = CH<sub>3</sub>) was collected by filtration and recrystallized from appropriate solvent. The experimental details are listed in Table I.

3-(*N*-Methylcyanoamino)pyridazine (**5a**).

A mixture of *N*-(pyridazin-3-yl)formamide oxime (**3a**, R = H) (1.381 g, 10 mmoles), DMFDMA (3.3 ml) in toluene (25 ml) was heated under reflux for two hours. Evaporation of solvent gave the compound **5a** in 36% yield, mp 151-154° (from ethanol); ms: M\* = 134; nmr (deuteriochloroform): τ = 6.40 (s, CH<sub>3</sub>), 2.87 (dd, H<sub>4</sub>), 3.22 (dd, H<sub>5</sub>), 2.65 (dd, H<sub>6</sub>), J<sub>H<sub>4</sub>, H<sub>5</sub></sub> = 8.5 Hz, J<sub>H<sub>4</sub>, H<sub>6</sub></sub> = 1.8 Hz, J<sub>H<sub>5</sub>, H<sub>6</sub></sub> = 3.9 Hz.

Table 2

## 2-Methyl-s-triazolo[1,5-x]azines (6)

Compound	mp	Crystallized from	Method of preparation yield	Molecular formula ms: M <sup>+</sup>
6-Chloro-2-methyl-s-triazolo[1,5-b]pyridazine (6b)	121-123.5 (a)	petroleum ether	A 84 B 95	C <sub>6</sub> H <sub>5</sub> ClN <sub>4</sub> 168
2-Methyl-s-triazolo[1,5-a]pyrimidine (6c)	134-135 (b)	subl 130° (1 torr)	A 81 B 100	C <sub>6</sub> H <sub>6</sub> N <sub>4</sub> 134
2,5,7-Trimethyl-s-triazolo[1,5-a]pyrimidine (6d)	142-145 (c)	subl 180° (1 torr)	A 96 B 89	C <sub>8</sub> H <sub>10</sub> N <sub>4</sub> 162
2-Methyl-s-triazolo[1,5-a]pyrazine (6e)	134.5 (d)	subl 140° (1 torr)	A 88 C 75	C <sub>6</sub> H <sub>6</sub> N <sub>4</sub> 134
2,6,7-Trimethyl-s-triazolo[1,5-b]-1,2,4-triazine (6f)	88-89 (e)	distill 160° (1 torr)	C 49	C <sub>7</sub> H <sub>9</sub> N <sub>5</sub> 163

(a) lit (17) mp 123°. (b) lit (17) mp 132-132.5°. (c) lit (16) mp 144-146°. (d) lit (17) mp 130-132°. (e) lit (20) mp 86-87°.

*Anal.* Calcd. for C<sub>6</sub>H<sub>5</sub>N<sub>4</sub>: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.94; H, 4.52; N, 41.71.

In the same way the following compound was obtained.

## 3-(N-Methylcyanoamino)-6-chloropyridazine (5b).

This compound was obtained from N-(6-chloropyridazin-3-yl)formamide oxime (3b, R = H) in 63% yield, mp 160-161.5° (from 1-propanol); ms: M<sup>+</sup> = 168, nmr (DMSO-d<sub>6</sub>): τ = 6.52 (s, CH<sub>3</sub>), 2.87 (s, H<sub>a</sub>, H<sub>b</sub>).

*Anal.* Calcd. for C<sub>6</sub>H<sub>5</sub>ClN<sub>4</sub>: C, 42.75; H, 2.99; N, 33.23. Found: C, 42.87; H, 3.31; N, 33.47.

## 1-Methyl-2(1H)-cyanoiminopyrazine (14).

N-Pyrazinylformamide oxime (3e, R = H) (1.381 g, 10 mmoles), DMFDMA (3.3 ml) in toluene (25 ml) were heated under reflux for 30 minutes. After cooling undissolved material was filtered off, the filtrate evaporated *in vacuo* and the solid residue extracted with chloroform. The combined extracts, dried over anhydrous sodium sulphate, were evaporated *in vacuo* to give 14 in 3.8% yield, mp 154-163°; ms: M<sup>+</sup> = 134; nmr (deuteriochloroform): τ = 6.39 (s, CH<sub>3</sub>), 1.27 (d, H<sub>3</sub>), 2.40 (d, H<sub>5</sub>), 2.75 (dd, H<sub>6</sub>), J<sub>H<sub>3</sub>, H<sub>6</sub></sub> = 4.2 Hz, J<sub>H<sub>3</sub>, H<sub>5</sub></sub> = 1.0 Hz.

*Anal.* Calcd. for C<sub>6</sub>H<sub>6</sub>N<sub>4</sub>: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.73; H, 4.49; N, 41.87.

## 6-Chloro-3-cyanoaminopyridazine (4b).

N-(6-Chloropyridazin-3-yl)formamide oxime (3b, R = H) (172 mg, 1 mmole) was suspended in dimethoxyethane (4.5 ml) and pyridine (0.3 ml). During cooling in an ice-water bath a solution of phosphorus oxychloride (0.75 ml) in dimethoxyethane (1 ml) was added dropwise. The solvent was evaporated *in vacuo* after one hour, water (3 ml) added to the residue and the solution adjusted by addition of sodium hydrogen carbonate to pH = 5. The precipitated product 4b was collected by filtration and washed with water, yield 32%, mp 180-181° (from ethanol); ms: M<sup>+</sup> = 154, nmr (DMSO-d<sub>6</sub>): τ = 2.87 (d) and 3.10 (d) H<sub>a</sub> and H<sub>b</sub>, J<sub>H<sub>a</sub>, H<sub>b</sub></sub> = 9.0 Hz.

## 3-(N-Methylcyanoamino)-6-chloropyridazine (5b).

3-Cyanoamino-6-chloropyridazine (4b) (77 mg, 0.5 mmole), DMFDMA (0.1 ml) in toluene (1 ml) were heated under reflux for one hour. The reaction mixture was evaporated *in vacuo*, and the dry residue purified, yield 92%, mp 160-161° (from ethanol). The ir spectrum was identical with the compound 5b obtained from 3b (R = H), as described above.

2-(N-Methylcyanoaminopyrimidine (5c) and 1-Methyl-2(1H)-cyanoiminopyrimidine (7, R = H).

A mixture of N-(pyrimid-2-yl)formamide oxime (3c, R = H) (1.381 g, 10 mmoles), DMFDMA (3.3 ml) and toluene (25 ml) was heated under reflux

for two hours. After cooling the crude 1-methyl-2(1H)-cyanoiminopyrimidine (7, R = H) was collected by filtration, yield 27%, mp 246-248° (from ethanol); ms: M<sup>+</sup> = 134; nmr (DMSO-d<sub>6</sub>): τ = 6.45 (s, 1-CH<sub>3</sub>), 1.30 (dd, H<sub>4</sub>), 3.25 (dd, H<sub>5</sub>), 1.60 (dd, H<sub>6</sub>), J<sub>H<sub>4</sub>, H<sub>5</sub></sub> = 3.8 Hz, J<sub>H<sub>4</sub>, H<sub>6</sub></sub> = 2.0 Hz, J<sub>H<sub>5</sub>, H<sub>6</sub></sub> = 6.0 Hz.

*Anal.* Calcd. for C<sub>6</sub>H<sub>6</sub>N<sub>4</sub>: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.89; H, 4.62; N, 41.80.

Evaporation of the filtrate gave crude 2-(N-methylcyanoamino)-pyrimidine (5c) in 23% yield, mp 132-133.5° (from 1-propanol); ms: M<sup>+</sup> = 134; nmr (deuteriochloroform): τ = 6.58 (s, CH<sub>3</sub>); 1.52 (d, H<sub>a</sub>, H<sub>b</sub>), 3.07 (t, H<sub>3</sub>), J<sub>H<sub>a</sub>, H<sub>b</sub></sub> = 4.6 Hz.

*Anal.* Calcd. for C<sub>6</sub>H<sub>6</sub>N<sub>4</sub>: C, 53.72; H, 4.51; N, 41.77. Found: C, 53.72; H, 4.41; N, 41.75.

Reaction of N-(4,6-Dimethylpyrimid-2-yl)formamide Oxime (3d, R = CH<sub>3</sub>) with DMFDMA.

2-(N-Methylcyanoamino)-4,6-dimethylpyrimidine (5d) 2-Cyanoamino-4,6-dimethylpyrimidine (4d) and 2-Cyanoimino-1,4,6-(1H)-trimethylpyrimidine (7, R = CH<sub>3</sub>).

A mixture of N-(4,6-dimethylpyrimid-2-yl)formamide oxime (3d, R = H) (1.66 g, 10 mmoles), DMFDMA (3.3 ml) and toluene (20 ml) was heated under reflux for two hours. After cooling a small amount of solid material was filtered off. Evaporation of the filtrate gave 1.25 g of dry residue, a mixture of products 5d, 7 (R = CH<sub>3</sub>) and 4d, which were separated by column chromatography (E. Merck Kieselgel 60, 70-230 mesh ASTM, 200 g). Elution with ether afforded 2-(N-methylcyanoamino)-4,6-dimethylpyrimidine (5d) in 58% yield, mp 107-108° (from ethanol); ms: M<sup>+</sup> = 162; nmr (DMSO-d<sub>6</sub>): τ = 6.65 (s, N-CH<sub>3</sub>), 7.65 (s, 4-CH<sub>3</sub>, 6-CH<sub>3</sub>), 3.11 (s, H<sub>5</sub>).

*Anal.* Calcd. for C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>: C, 59.24; H, 6.22; N, 34.54. Found: C, 59.11; H, 5.95; N, 34.42.

Further elution with ethyl acetate gave 2-cyanoamino-4,6-dimethylpyrimidine (4d) in 6.3% yield, mp 228-234° (from ethyl acetate), lit (22) mp 233-234°; ms: Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>4</sub>: 148.074892. Found: 148.0755; nmr (DMSO-d<sub>6</sub>): τ = 7.57 (s, 4-CH<sub>3</sub>, 6-CH<sub>3</sub>), 3.10 (s, H<sub>5</sub>), 6.5 (br, NH). The ir and nmr spectra were identical with those reported (23,24).

Further elution with acetone produced 2-cyanoimino-1,4,6-(1H)-trimethylpyrimidine (7, R = CH<sub>3</sub>) in 3.5% yield, mp 259°; ms: Calcd. for C<sub>9</sub>H<sub>10</sub>N<sub>4</sub>: 162.090542. Found: 162.0910; nmr (DMSO-d<sub>6</sub>): τ = 6.50 (s, N-CH<sub>3</sub>), 7.70 (s, 4-CH<sub>3</sub>), 7.57 (s, 6-CH<sub>3</sub>), 3.42 (s, H<sub>5</sub>).

## 3-(N-Ethylcyanoamino)-6-chloropyridazine (8).

A mixture of N-(6-chloropyridazin-3-yl)formamide oxime (3b, R = H) (172 mg, 1 mmole), N,N-dimethylformamide diethylacetal (0.5 ml) and

toluene (5 ml) was heated under reflux one hour. The solvent was evaporated *in vacuo* and dry residue recrystallized from 1-propanol, yield 34%; mp 103-112°; ms:  $M^+ = 182$ ; nmr (deuteriochloroform):  $\tau = 8.59$  (t,  $\text{CH}_2\text{CH}_3$ ), 5.75 (q,  $\text{CH}_2\text{CH}_3$ ), 2.36 (d), 2.77 (d)  $\text{H}_4, \text{H}_5$ ,  $J_{\text{CH}_2\text{CH}_3} = 6.5$  Hz,  $J_{\text{H}_4, \text{H}_5} = 9.0$  Hz.

*Anal.* Calcd. for  $\text{C}_7\text{H}_9\text{ClN}_4$ : C, 46.04; H, 3.86; N, 30.68. Found: C, 46.15; H, 3.82; N, 30.54.

*N*-(6-Chloropyridazin-3-yl)acetamide Oxime (**3b**, R =  $\text{CH}_3$ ).

To a solution of *N,N*-dimethyl-*N'*-(6-chloropyridazin-3-yl)acetamide (**2b**, R =  $\text{CH}_3$ ) (198 mg, 1 mmole) in anhydrous ethanol a solution of hydroxylamine (equivalent to ~ 100 mg of hydroxylamine) was added and the mixture left 24 hours at room temperature. The precipitate was collected by filtration to give 59% of **3b** (R =  $\text{CH}_3$ ). Evaporation of the filtrate produced further 39% of **3b** (R =  $\text{CH}_3$ ). Experimental details are given in Table I.

Reaction of *N*-(6-Chloropyridazin-3-yl)acetamide Oxime (**3b**, R =  $\text{CH}_3$ ) with *N,N*-Dimethylformamide Dimethylacetal. (6-Chloro-2-methyl-*s*-triazolo[1,5-*b*]pyridazine **6b**).

A mixture of *N*-(6-chloropyridazin-3-yl)acetamide oxime (**3b**, R =  $\text{CH}_3$ ) (186 mg, 1 mmole) and DMFDMA (1.65 ml) was stirred at room temperature for 24 hours. The product was separated from unreacted starting material by tlc. (E. Merck PSC-Fertigplatten Kieselgel 60 F 254 and chloroform/methanol 5:1 were used). The band with  $R_f = 0.66$  was eluted with methanol, to give after evaporation of solvent the product **6b** in 30% yield, mp 121-123°, lit (17) mp 123°. The ir and nmr spectra were identical with those obtained from the compound prepared according to method A or B.

General Procedure for the Preparation of 2-Methyl-*s*-triazolo[1,5-*x*]azines (**6**).

Method A.

*N*-Heteroarylacetamide oxime (**3**, R =  $\text{CH}_3$ ) (1 mmole) and polyphosphoric acid (~ 1g) were heated at 120° one to two hours. After cooling water (20 ml) was added and the mixture neutralized with sodium hydrogen carbonate. The aqueous layer was extracted 3-4 times with chloroform (30 ml each time), combined extracts dried over anhydrous sodium sulphate, the solvent evaporated *in vacuo* and the crude product **6** recrystallized from appropriate solvent or sublimed *in vacuo*. The experimental details are summarized in Table II.

Method B.

To a refluxing suspension of *N*-heteroarylacetamide oxime (**3**, R =  $\text{CH}_3$ ) (1 mmole) in chloroform (10 ml) a solution of phosphorus oxychloride (0.7 ml) in chloroform (1.2 ml) was slowly added, and the mixture heated under reflux for 30 minutes. The solvent was evaporated *in vacuo*, and after addition of water (20 ml) precipitate collected by filtration and purified as described above.

Method C.

To a suspension or solution of *N*-heteroarylacetamide oxime (**3**, R =  $\text{CH}_3$ ) (1 mmole) in chloroform (10 ml) and pyridine (1.25 ml) phosphorus oxychloride (0.45 ml) was added and left at room temperature for 30 minutes. The solvent was evaporated, water added to dry residue and product **6** purified as described by method A.

5-[2-(*N,N*-Dimethylamino)-1-ethenyl]-3-(*N*-methylcyanoamino)-6-methyl-1,2,4-triazine (**9**).

*N*-(5,6-Dimethyl-1,2,4-triazin-3-yl)formamide oxime (**3f**, R = H) (1.672 g, 10 mmoles) and DMFDMA (3.3 ml) in toluene (25 ml) were heated under reflux for two hours. The solvent was evaporated *in vacuo* to give **9** in 26% yield, mp 190-192°; ms:  $M^+ = 218$ ; nmr (deuteriochloroform):  $\tau = 7.82$  (s, 6- $\text{CH}_3$ ), 6.40 (s, N- $\text{CH}_3$ ), 6.70 (s), 6.92 (s) ( $\text{N}(\text{CH}_3)_2$ ), 5.0 (d,  $\text{H}_B$ ), 1.60 (d,  $\text{H}_A$ ),  $J_{\text{H}_A, \text{H}_B} = 12$  Hz.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{14}\text{N}_6$ : N, 38.50. Found: N, 38.73.

5-(*cis*-2-Hydroxyamino-1-ethenyl)-3-(*N*-methylcyanoamino)-6-methyl-1,2,4-triazine (**10**).

To a solution of 5-[2-(*N,N*-dimethylamino-1-ethenyl)-3-(*N*-methylcyanoamino)-6-methyl-1,2,4-triazine (**9**) (109 mg, 0.5 mmole) in methanol (1.2 ml) a large excess of hydroxylamine (~ 400 mg) in methanol (20 ml) was added and left at room temperature for 30 minutes. The precipitated product **10** (60%) was collected by filtration. Evaporation of the filtrate gave further 39% of **10**, mp 185-188° (from methanol); ms:  $M^+ = 206$ , nmr (DMSO- $d_6$ ):  $\tau = 7.95$  (s, 6- $\text{CH}_3$ ), 6.70 (s, N- $\text{CH}_3$ ), 4.68 (d,  $\text{H}_B$ ), 2.15 (d,  $\text{H}_A$ ), ~ 0.5 (br,  $\text{NHOH}$ ),  $J_{\text{H}_A, \text{H}_B} = 7.0$  Hz.

*Anal.* Calcd. for  $\text{C}_8\text{H}_{10}\text{N}_6\text{O}$ : C, 46.60; H, 4.89; N, 40.75. Found: C, 46.75; H, 5.00; N, 40.67.

*N*-(6-Chloropyridazin-3-yl)acetamide *O*-Methyl Oxime (**11**).

To a solution of *N,N*-dimethyl-*N'*-(6-chloropyridazin-3-yl)acetamide (**2b**, R =  $\text{CH}_3$ ) (198 mg, 1 mmole) in methanol (1 ml) a solution of *O*-methylhydroxylamine hydrochloride (92 mg, 1.1 mmoles) in methanol (1 ml) was added. The reaction mixture was left at room temperature for one hour and precipitate collected by filtration, yield 82%, mp 153-155° (from methanol); ms:  $M^+ = 200$ ; nmr (deuteriochloroform): isomer I:  $\tau = 7.63$  (s, C- $\text{CH}_3$ ), 6.17 (s,  $\text{OCH}_3$ ), 3.12 (d), 2.70 (d)  $\text{H}_4, \text{H}_5$ ,  $J_{\text{H}_4, \text{H}_5} = 9.0$  Hz; isomer II:  $\tau = 7.80$  (s, C- $\text{CH}_3$ ), 6.22 (s,  $\text{OCH}_3$ ), 2.70 (d), 1.63 (d)  $\text{H}_4, \text{H}_5$ ,  $J_{\text{H}_4, \text{H}_5} = 9.0$  Hz.

*Anal.* Calcd. for  $\text{C}_7\text{H}_9\text{ClN}_4\text{O}$ : C, 41.91; H, 4.52; N, 27.93. Found: C, 41.93; H, 4.73; N, 28.01.

*N*-(6-Chloropyridazin-3-yl)-*N*-methylacetamide *O*-Methyl Oxime (**12**).

A mixture of *N*-(6-chloropyridazin-3-yl)acetamide *O*-methyloxime (**11**) (200 mg, 1 mmole) and DMFDMA (2.2 ml) in toluene (7 ml) was heated under reflux for six hours. The solvent was evaporated *in vacuo* and the oily residue extracted with hot petroleum/ether. Evaporation of the solvent gave **12**, yield 85%; ms:  $M^+ = 214$ ; nmr (deuteriochloroform): (an equilibrium of at least 4 isomers):  $\tau = 7.86$ -8.06 (at least four different signals for C- $\text{CH}_3$ ), 6.15-6.70 (at least eight signals for N- $\text{CH}_3$  and  $\text{OCH}_3$ ), 2.35-3.60 (more overlapping dd for  $\text{H}_4$  and  $\text{H}_5$  in different isomers).

*Anal.* Calcd. for  $\text{C}_8\text{H}_{11}\text{ClN}_4\text{O}$ : C, 44.76; H, 5.17; N, 26.10. Found: C, 45.09; H, 5.25; N, 25.89.

*N*-(6-Chloropyridazin-3-yl)-*N*-methylurea (**13**).

3-(*N*-Methylcyanoamino)-6-chloropyridazine (**5b**) (168 mg, 1 mmole) dissolved in aqueous sulphuric acid (50%, 2 ml) was left at room temperature for two hours. The mixture was diluted with water (20 ml), neutralized with sodium hydrogen carbonate and extracted with chloroform (4 times with 20 ml). Evaporation of the combined extracts dried over anhydrous sodium sulphate gave *N*-(6-chloropyridazin-3-yl)-*N*-methylurea (**13**) in 88% yield, mp 137-141° (from 1,2-dimethoxyethane); ms:  $M^+ = 186$ ; nmr (deuteriochloroform):  $\tau = 6.5$  (s,  $\text{CH}_3$ ), 3.30 (d,  $\text{H}_4$ ), 2.13 (d,  $\text{H}_5$ ), 8.1 (br,  $\text{NH}_2$ ),  $J_{\text{H}_4, \text{H}_5} = 9.0$  Hz.

*Anal.* Calcd. for  $\text{C}_6\text{H}_7\text{ClN}_4\text{O}$ : C, 38.62; H, 3.78; N, 30.03. Found: C, 38.53; H, 4.02; N, 30.06.

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