A Three Component Cyclisation of 2-Cyanamido-4,6-dimethylpyrimidine with Aldehydes and Amines

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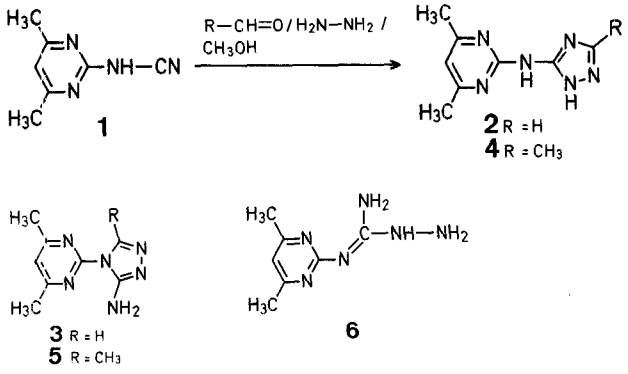
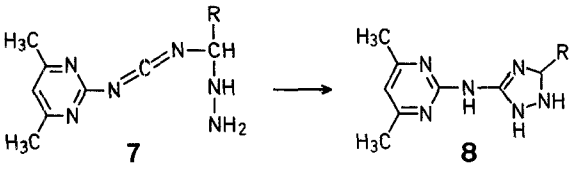
When 2-cyanamido-4,6-dimethylpyrimidine **(1)** was treated with hydrazine hydrate and formaldehyde in aqueous methanol at room temperature a white crystalline solid was deposited over a period of 2 days. Elemental analysis indicated an empirical formula of $C_8H_{10}N_4$ and the ^{1}H-N.M.R. spectrum showed that two aromatic proton signals were present at $\delta = 7.4$ and $\delta = 9.1$ ppm. In the I.R. spectrum a band corresponding to NH-stretching was seen at 3300 cm^{-1}. Thus, the product was proposed to be either the triazolylaminopyrimidine **2** or the aminotriazolylpyrimidine **3**. A similar product, **4** or **5** was prepared using acetaldehyde as the carbonyl component. No other products could be detected in the reaction mixture by T.L.C. (5% methanol in chloroform on silica gel GF_{254}). The structures of the two compounds were shown to be **2** and **4**. Thus, on treatment with benzoyl chloride in pyridine at room temperature the triazole **2** gave an adduct which hydrolysed readily in water to give the starting material. The aminotriazole **3** would be expected to give a stable benzamide. The triazole **4** has an acid pK_a of 10.9 and a basic pK_a of 3.6. The aminotriazole **5** would not be so acidic.

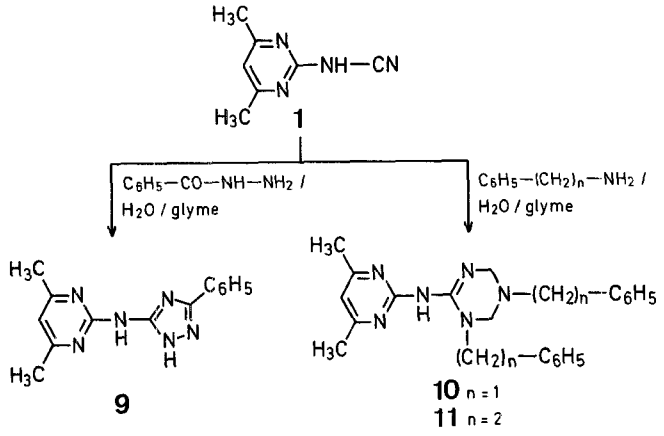


We thought initially that the triazoles were formed as a result of the formation of the aminoguanidine **6**. Cyclization with formaldehyde followed by aerial oxidation then leads to the observed product. However, in the absence of formaldehyde, no reaction of the cyanamide **1** with hydrazine in aqueous glyme or methanol could be observed at room temperature. The cyanamide is reported[1] to react with hydrazine at 140 °C to give 2-amino-4,6-dimethylpyrimidine and 2-hydrazino-4,6-dimethylpyrimidine. At elevated temperatures in acidic solution hydrolysis of the cyanamide also occurs to give the urea[2]. Similarly, no reaction between the cyanamide **1** and formaldehyde could be detected at room temperature in aqueous methanol at neutral pH or on addition of triethylamine as base.

The reaction evidently proceeds in a manner analogous to the Mannich reaction. The cyanamide **1** has an acid pK_a of 6.95 and, at neutral or basic pH, can behave as a nucleophile more readily than as an electrophile to react directly with a hydrazone to produce an intermediate **7** which cyclizes to the dihydrotriazole **8**. Reaction of the cyanamide at its terminus will be favoured because of the extra conjugation achieved in the intermediate and the reduced steric hindrance from the pyrimidine ring. This proposition is supported by the observation that the cyanamide **1** reacts with preformed acetaldehyde hydrazone[3] in anhydrous tetrahydrofuran to give the aminotriazole **4**. This reaction is not as clean as when hydrazine and acetaldehyde are used in aqueous solvents.



The reaction was also examined using benzaldehyde as the carbonyl component. As expected, the major product was the azine but a small yield of the triazole **9** could be isolated using hydrazine and hydrazine acetate. Its identity was confirmed by comparison with a sample prepared by heating the cyanamide **1** with benzoylhydrazine in aqueous glyme. When the amine component of the reaction was benzylamine instead of hydrazine two molecules each of formaldehyde and benzylamine were incorporated to give the tetrahydrotriazine **10** in a 5 component cyclization. A similar tetrahydrotriazine **11** was obtained using phenylethylamine as the amine component.



Melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. ^{1}H-N.M.R. spectra were obtained using Varian A 60 or HA 100 or Perkin-Elmer R 12 instruments. Mass spectra were recorded on an A.E.I. MS 9 or a Hitachi-Perkin-Elmer RMU 6E instrument. I.R. spectra were recorded using Nujol mulls on a Perkin-Elmer 157 instrument.

2-Cyanamido-4,6-dimethylpyrimidine (1):

The compound is prepared according to Ref.[2] and crystallised from ethanol; m.p. 224–225 °C (Ref.[2], m.p. 225 °C).

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 2.4$ (s, 6H, $2CH_3$); 6.5 ppm (s, 1 H_{arom}).

I.R. (Nujol): $\nu = 2200$ cm^{-1}.

M.S.: $m/e = 148$ (M^+).

The acid pK_a is 6.95 (H_2O, potentiometry).

4,6-Dimethyl-2-(1,2,4-triazol-5-ylamino)-pyrimidine (2):
2-Cyanamido-4,6-dimethylpyrimidine (**1**; 6.0 g, 40 mmol) in methanol (250 ml) and water (50 ml) is treated with hydrazine hydrate (2.0 g, 40 mmol) and 40% aqueous formaldehyde (3.0 g, 40 mmol). The mixture is allowed to stand at room temperature for 2 days and the white crystalline solid deposited is collected; yield: 3.0 g (39%); m.p. 323–324 °C (dec., from ethoxyethanol).

$C_8H_{10}N_6$	calc.	C 50.51	H 5.30	N 44.19
(190.2)	found	50.6	5.3	43.9

^{1}H-N.M.R. (CF_3COOH/TMS): $\delta = 2.85$ (s, 6H, $2CH_3$); 7.4 (s, 1 H_{arom}); 9.1 ppm (s, 1H, NH).

I.R. (Nujol): $\nu = 3250$, 1630 cm^{-1}.

U.V. (CH_3OH): $\lambda_{max} = 249$ nm (21400).

M.S.: $m/e = 190$ (M^+).

4,6-Dimethyl-2-(3-methyl-1,2,4-triazol-5-ylamino)-pyrimidine (4):

Method A: 2-Cyanamido-4,6-dimethylpyrimidine (**1**; 1.48 g, 10 mmol) in methanol (100 ml) is treated with hydrazine hydrate (0.5 g, 10 mmol) and acetaldehyde (0.44 g, 10 mmol). The mixture is stirred in air for 4 days at room temperature. The solid separating is collected and crystallised twice from methanol to afford the triazole **4**; yield: 300 mg (15%); m.p. 270–271 °C.

$C_9H_{12}N_6$	calc.	C 52.92	H 5.92	N 41.15
(204.2)	found	52.6	5.8	41.4

^{1}H-N.M.R. (CF_3COOH/TMS): $\delta = 2.84$ (s, 6H, $2CH_3$); 2.86 (s, 3H, CH_3); 7.35 ppm (s, 1 H_{arom}).

I.R. (Nujol): $\nu = 3250$, 1630 cm^{-1}.

U.V. (CH_3OH): $\lambda_{max} = 248$ nm (20100).

The acid pK_a is 10.8 and the basic pK_a 3.4 (4% CH_3OH in H_2O, U.V.).

Method B: 2-Cyanamido-4,6-dimethylpyrimidine (**1**; 0.54 g, 3.6 mmol) in anhydrous tetrahydrofuran (25 ml) is stirred with anhydrous acetaldehyde hydrazone[3] (0.21 g, 3.6 mmol) overnight at room temperature. The solution is evaporated to dryness and the residue crystallised from methanol to afford the triazole **4**; yield: 160 mg (21%).

4,6-Dimethyl-2-(3-phenyl-1,2,4-triazol-5-ylamino)-pyrimidine (9):

Method A: 2-Cyanamido-4,6-dimethylpyrimidine (**1**; 3.0 g, 20 mmol) in glyme (20 ml) is treated with hydrazine hydrate (1.2 g, 24 mmol), glacial acetic acid (0.9 g, 15 mmol), benzaldehyde (2.12 g, 20 mmol) and sufficient water to produce a homogenous solution. The solution is stirred for 3 days at room temperature and the solid deposited is collected and crystallised from chloroform and then from ethyl acetate to give the triazole **9**; yield: 0.7 g (13%); m.p. 307–308 °C.

$C_{14}H_{14}N_6$	calc.	C 63.14	H 5.30	N 31.56
(266.3)	found	63.3	5.4	31.5

^{1}H-N.M.R. (CF_3COOH/TMS): $\delta = 2.92$ (s, 6H, $2CH_3$); 7.42 (s, 1 H_{arom}); 7.7–8.2 ppm (m, 5 H_{arom}).

I.R. (Nujol): $\nu = 3250$, 1630 cm^{-1}.

Method B: 2-Cyanamido-4,6-dimethylpyrimidine (**1**; 2.0 g, 13.3 mmol) in glyme (40 ml) and water (40 ml) is heated under reflux with benzoyl hydrazine (2.0 g, 14.7 mmol) for 48 h. The mixture is cooled and diluted with water to afford the triazole **9**; yield: 0.65 g (18%).

1,3-Dibenzyl-6-(4,6-dimethyl-2-pyrimidinylamino)-1,2,3,4-tetrahydro-1,3,5-triazine (10):
2-Cyanamido-4,6-dimethylpyrimidine (**1**; 2.0 g, 13.3 mmol) and benzylamine (2.9 g, 27 mmol) are treated with 40% aqueous formaldehyde solution (2.0 g, 26.6 mmol) in 50% aqueous glyme. The solution is heated under reflux for 2 h and cooled. The white solid separating is collected and crystallised from cyclohexane to give the triazine **10**; yield: 1.5 g (29%); m.p. 161–162 °C.

$C_{23}H_{26}N_6$	calc.	C 71.47	H 6.78	N 21.75
(386.5)	found	71.4	6.8	21.5

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 2.34$ (s, 6H, $2CH_3$); 3.82 (s, 2H, CH_2); 4.12 (s, 2H, CH_2); 4.38 (s, 2H, CH_2); 4.92 (s, 2H, CH_2); 6.45 (s, 1 H_{arom}); 7.15–7.3 (m, 10 H_{arom}); 13.5 ppm (s, 1H, NH).

I.R. (Nujol): $\nu = 1600$, 1580 cm^{-1}.

M.S.: $m/e = 386.2196$ (M^+), $C_{23}H_{26}N_6$ requires 386.2218.

1,3-Diphenylethyl-6-(4,6-dimethyl-2-pyrimidinylamino)-1,2,3,4-tetrahydro-1,3,5-triazine (11):
2-Cyanamido-4,6-dimethylpyrimidine (**1**; 2.0 g, 13.3 mmol) and phenylethylamine (3.27 g, 27 mmol) are taken up in 50% aqueous glyme and treated with 37% aqueous formaldehyde solution (2.0 g, 26.6 mmol). The mixture is heated under reflux for 2 h and cooled. The products are extracted with chloroform and the chloroform solution washed with water, dried over magnesium sulphate and evaporated to dryness. The residue is chromatographed on neutral alumina and the products eluted with 30% ethyl acetate in petroleum ether (b.p. 60–80 °C) to give the triazine **11**; yield: 1.85 g (33%); oil.

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 2.36$ (s, 6H, $2CH_3$); 2.78 (t, $J = 7.5$ Hz, 2H, CH_2); 2.84 (t, $J = 7.5$ Hz, 2H, CH_2); 3.00 (t, $J = 7.5$ Hz, 2H, CH_2); 3.85 (t, $J = 7.5$ Hz, 2H, CH_2); 3.96 (s, 2H, CH_2); 4.28 (s, 2H, CH_2); 6.40 (s, 1 H_{arom}); 7.25 (m, 10 H_{arom}); 10.58 ppm (s, 1H, NH).

M.S.: $m/e = 414.2513$ (M^+), $C_{25}H_{30}N_6$ requires 414.2531.

The measurement of pKa values and guidance in their interpretation by Mr. P. J. Taylor is gratefully acknowledged.

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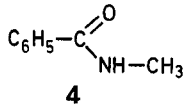
(Revised form: September 13, 1982)

[1] L. Fabbrini, *Gazz. Chim. Ital.* **87**, 1293 (1957).
[2] S. Birtwell, *J. Chem. Soc.* **1953**, 1725.
[3] E. C. Friedrich, S. N. Falling, D. E. Lyons, *Synth. Commun.* **5**, 33 (1975).

Errata and Addenda 1983

E. Haug, W. Kantlehner, P. Speh, H.-J. Bräuner, *Synthesis* **1983** (1), 35–37:

Compound **4** should be *N*-methylbenzamide:



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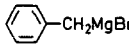
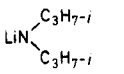
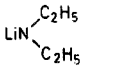
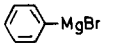
A. I. Meyers, K. A. Lutomski, *Synthesis* **1983** (2), 105–107:
The first seven entries in the Table (p. 106) should be as follows:

Table. Addition of Organometallic Reagents to 2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-methoxynaphthalene **(1)** leading to 1-Substituted 2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-naphthalenes **2**

Product	RM	Yield [%]	m.p. [°C]	I.R. (film) $\nu_{C=N}$ [cm^{-1}]	^{1}H-N.M.R. (solvent) δ [ppm]
2a	H_3CLi	84	oil	1645	(CCl_4): 1.36 (s, 6 H); 2.92 (s, 6 H); 3.97 (s, 2 H); 7.3–8.2 (m, 6 H)
2b	*n*-C_4H_9Li	80	oil	1640	(CCl_4): 0.8–1.85 (m, 13 H); 3.45 (br, t, 2 H); 3.95 (s. 2 H); 7.3–8.2 (m, 6 H)
	n-C_4H_9MgBr	89			
2c		59	oil	1635	(CCl_4): 1.30 (s, 6 H); 3.92 (s, 2 H); 4.97 (s, 2 H); 7.0–8.2 (m, 12 H)
2d		68	oil[a]	1645	($CDCl_3$): 1.00 (d, 6 H); 1.12 (d, 6 H); 1.35 (s, 6 H); 3.45–4.19 (hept, 2 H); 4.0 (s, 2 H); 7.3–7.9 (m, 5 H); 8.65 (m, 1 H)
2e		78	oil[b]	1650	($CDCl_3$): 1.05 (t, 6 H); 1.35 (s, 6 H); 3.30 (d, 4 H); 3.95 (s, 2 H); 7.2–7.8 (m, 5 H); 8.3–8.5 (m, 1 H)
2f		84	oil	1660	(CCl_4): 1.12 (s, 6 H); 3.59 (s, 2 H); 7.2–7.9 (m, 11 H)

S. Takano, K. Seya, E. Goto, M. Hirama, K. Ogasawara, *Synthesis* **1983** (2), 116–117:

The title should read "Synthesis of (*S*)-1-*O*-Benzylglycerol and (*R*)-Benzyl 2,3-Epoxypropyl Ether from (*R*)-1-*O*-Benzylglycerol"; the names of compounds (*R*)-**5**, (*S*)-**5**, and **9** should be (*R*)-1-*O*-benzylglycerol, (*S*)-1-*O*-benzylglycerol, and (*S*)-2,3-Di-*O*-acetyl-1-*O*-benzylglycerol, respectively.

D. Michelot, *Synthesis* **1983** (2), 130–134:

The table under the formula scheme (page 131) should be as follows:

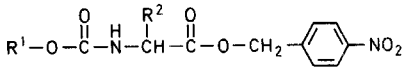
5	m	n	6,7,8,(9)	R
a	4	8	a	*n*-C_4H_9
a	4	8	b	C_2H_5
c		6	c	*n*-C_4H_9
a	4	8	d	H_2C=CH–
b	6	10	e	C_2H_5 

Compounds **6e**, **7e**, **8c**, and **9e** (p. 133) should be named (*Z*, *Z*)-1-(2-tetrahydropyranyloxy)-11,13-hexadecadiene, (*Z*,*Z*)-11,13-hexadecadienol, (*Z*,*Z*)-7,11-hexadecadien-1-yl acetate, and (*Z*,*Z*)-11,13-hexadecadienal, respectively. Compound **8b** is prepared from **5a** and ethylmagnesium bromide.

M. Künstlinger, E. Breitmaier, *Synthesis* **1983** (2), 161–162:

Compounds **5** and **6** should be named pyrimido[1,2-*a*]benzimidazoles.

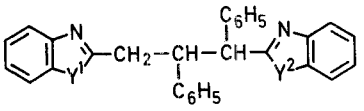
Abstract **6555**, *Synthesis* **1983** (2), 165:

Compound **1** should be: 

1

V. Dryanska, C. Ivanov, *Synthesis* **1983** (2), 143–145:

The formula for compounds **4g, h, 5g, h** (page 144) should be:



4g Y^1 = O, Y^2 = O
4h Y^1 = O, Y^2 = S
5g Y^1 = S, Y^2 = O
5h Y^1 = S, Y^2 = S

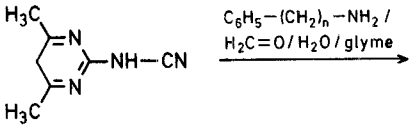
M. A. Brook, T. H. Chan, *Synthesis* **1983** (3), 201–203:

The following addendum should be added:
After publication of our work, our attention was drawn to the fact that the priority for the use of chlorotrimethylsilane for esterification lies with Nakao et al.[24].

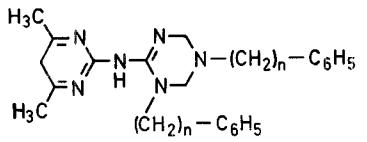
[24] R. Nakao, K. Oka, T. Fukumoto, *Bull. Soc. Chem. Jpn.* **54**, 1267 (1981).

C. W. Thornber, J. M. Farrell, D. S. Clarke, *Synthesis* **1983** (3), 222–223:

The formula scheme **1** ⟶ **10,11** (p. 222) should be:



1



10 n = 1
11 n = 2

H. Takahata, N. Nakajima, Y. Yamazaki, *Synthesis* **1983** (3) 226–228:

Compounds **7** and **8** should be named 3-anilino-6-methyl-1,4,5,6 tetrahydropyrrolo[2,3-*c*]pyrazoles and 3-anilino-7-methyl-4,5,6,7 tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridines, respectively.