Studies on Pyrimidine Derivatives; XXXVII.[1] Synthesis of Pyrimidinecarbonitriles by Reaction of Pyrimidine *N*-Oxides with Trimethylsilyl Cyanide

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Recently, Vorbrüggen et al.[2] reported that trimethylsilyl cyanide smoothly reacts with pyridine *N*-oxides to give 2-pyridinecarbonitriles in good yields. This conversion enlarges the chemistry of heteroaromatic amine *N*-oxides, since pyridine *N*-oxides except for 4-chloropyridine[3a] and trifluoromethylpyridine 1-oxides[3b] are known not to be reactive towards a deoxy-cyanation with potassium cyanide and benzoyl chloride (Reissert-Henze reaction). Although some pyrimidine *N*-oxides, unlike pyridine *N*-oxides, are susceptable to the Reissert-Henze reaction[4], the reaction of 4-methyl- (**5b**) and 2,4-dimethylpyrimidine 1-oxide (**1b**) produces

Table. Reaction of Pyrimidine *N*-Oxides **1**, **3**, **5**, **8** with Trimethylsilyl Cyanide

Educt	Product	Reaction time [h]	Yield [%]	b.p. [°C]/torr and/or m.p. [°C]	Molecular formula[a] or Lit. m.p. [°C]	^{1}H-N.M.R. (CCl_4/TMS) δ [ppm]
1a	**2a**	2.5	71	100°/20; 27–29°	29–30.5°[7]	2.78 (s, 3H); 7.45 (d, J = 5 Hz, 1H); 8.83 (d, J = 5 Hz, 1H)
1b	**2b**	12	81	110°/21; 51.5–52°	55–57°[4a]	2.55 (s, 3H); 2.72 (s, 3H); 7.23 (s, 1H)
8	**2b**	36	18[b]			
1c	**2c**	3	90	145°/3; 95–96°	96–98°[8]	2.73 (s, 3H); 7.4–7.6 (m, 3H); 7.77 (s, 1H); 8.0–8.2 (m, 2H)
1d	**2d**	24	0[c]			
3a	**4a**	3	71	115°/20; 49.5–50°	49–51°[4a]	2.60 (s, 3H); 7.28 (d, J = 5 Hz, 1H); 8.62 (d, J = 5 Hz, 1H)
3b	**4b**	4	87	135°/20; 81–82°	85°[5]	2.53 (s, 6H); 7.10 (s, 1H)
3c	**4c**	5	90	160°/3; 113–113.5°	110°[6]	2.63 (s, 3H); 7.4–7.7 (m, 3H); 7.75 (s, 1H); 8.0–8.2 (m, 2H)
3d	**4d**	0.5	87	145°/15; 95–96°	97–99°[4a,b]	2.48 (s, 3H); 4.01 (s, 3H); 6.07 (s, 1H)
5a	**6a** + **7a**	0.17	75[d]	105°/20		
5b	**6b** = **4a**	3	74	115°/20; 49.5–50.5°	49–51°[4a]	2.60 (s, 3H); 7.28 (d, J = 5 Hz, 1H); 8.62 (d, J = 5 Hz, 1H)
5c	**6c**	1	21	154–155° (cyclohexane)	$C_{11}H_7N_3$ (181.2)	7.5–7.7 (m, 3H); 7.88 (d, J = 6 Hz, 1H); 8.0–8.3 (m, 2H); 8.33 (d, J = 6 Hz, 1H)[e]
	+ **7c**		55	160–161° (cyclohexane)	$C_{11}H_7N_3$ (181.2)	7.5–7.7 (m, 3H); 8.0–8.3 (m, 3H); 9.37 (s, 1H)[e]
5d	**6d**	4[f]	86	115°/20; 51.5–52.5°	53°[4c]	4.07 (s, 3H); 6.91 (d, J = 6 Hz, 1H); 8.48 (d, J = 6 Hz, 1H)

[a] Satisfactory microanalysis obtained: C ±0.24, H ±0.10, N ±0.38.

[b] 50% recovery of educt **8**.

[c] 74% recovery of educt **1d**.

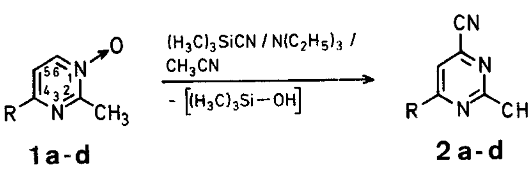
[d] Products **6a** and **7a** have not been separated; as determined by G.L.C. (column: SE 30, 2 m; column temperature: 100 °C) **6a** and **7a** are present in a ratio 2 : 3. Reference compounds have been obtained according to Lit. methods: **6a**[9]; **7a**[10].

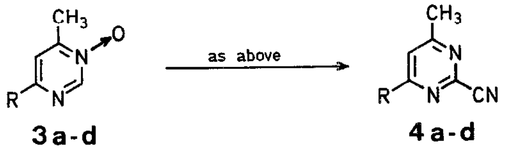
[e] Measured in $CDCl_3$.

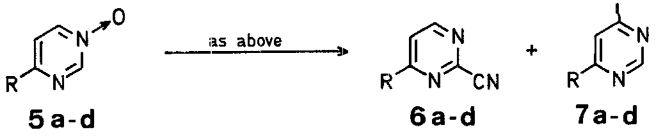
[f] Reaction has been carried out at room temperature.

a considerable amount of resinous products, and the yields of 4-methyl-2-pyrimidinecarbonitrile (**6b** ≡ **4a**) and 2,6-dimethyl-4-pyrimidinecarbonitrile (**2b**) are less than 2%. As anticipated by Vorbrüggen et al.[2], pyrimidine *N*-oxides should behave analogously to pyridine *N*-oxides when reacted with trimethylsilyl cyanide. Therefore, we have focused our interest on the synthesis of pyrimidinecarbonitriles by an adaption of this method.

When 2,4-dimethylpyrimidine 1-oxide (**1b**) is treated with trimethylsilyl cyanide in acetonitrile in the presence of triethylamine, 2,6-dimethyl-4-pyrimidinecarbonitrile (**2b**) is obtained in excellent yield. In the same way, other 2-substituted pyrimidine 1-oxides such as 2-methyl- (**1a**) and 2-methyl-4-phenylpyrimidine 1-oxide (**1c**) are conveniently converted into the corresponding 6-pyrimidinecarbonitriles (**2a**, **c**). Similarly, the reaction of 4,6-disubstituted pyrimidine 1-oxides (**3b–d**) including 6-methylpyrimidine 1-oxide (**3a**) with trimethylsilyl cyanide gives the corresponding 2-pyrimidinecarbonitriles (**4a–d**) in good yields.



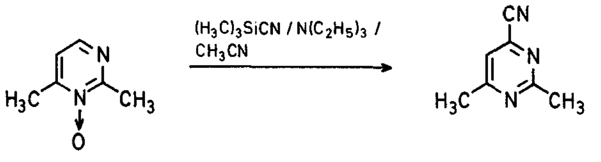




1-7	a	b	c	d
R	H	CH_3	C_6H_5	OCH_3

These results suggest that, in pyrimidine 1-oxides, the 6- and the 2-positions show comparable reactivities. In order to investigate the regioselectivity, pyrimidine *N*-oxides in which both the 2- and the 6-position are unsubstituted (**5a–d**) have been treated with trimethylsilyl cyanide under conditions indicated above. The crude reaction products are analyzed by G.L.C. and ^{1}H-N.M.R. spectroscopy. As shown in the Table, the 2-position is more reactive than the 6-position. In the case of 4-methoxypyrimidine 1-oxide (**5d**), the 2-carbonitrile **6d** is formed exclusively. The enhanced reactivity of the 2-position is also reflected by the results obtained with the educts **1d** and **3d**. Whereas **3d** is converted to **4d** in 90% yield, **1d** does not afford the isomeric **2d** (Table).

2,6-Dimethylpyrimidine 1-oxide (**8**) reacts with trimethylsilyl cyanide to give 2,6-dimethyl-4-pyrimidinecarbonitrile (**2b**). Since 2,6-dimethylpyridine 1-oxide is not reactive under these conditions, the formation of **2b** from **8** demonstrates the superiority of pyrimidine *N*-oxides over pyridine *N*-oxides in this deoxy-cyanation reaction.



8 **2b**

In conclusion, the reaction of pyrimidine *N*-oxides with trimethylsilyl cyanide may be recommended as an experimentally simple method for the preparation of pyrimidinecarbonitriles.

Reaction of Pyrimidine *N*-Oxides (1, 3, 5, 8) with Trimethylsilyl Cyanide; General Procedure:

A solution of the pyrimidine *N*-oxide (10 mmol), trimethylsilyl cyanide (2.97 g, 30 mmol), and triethylamine (2.02 g, 20 mmol) in acetonitrile (10 ml) is refluxed for an appropriate time (see Table). After evaporation of the solvent, the residue is partitioned between aqueous 3 normal sodium carbonate solution (10 ml) and dichloromethane (50 ml). The dichloromethane layer is dried with potassium carbonate and evaporated. The residue is distilled using a Kugelrohr apparatus, giving products **2**, **4**, **6**, or **7**, respectively.

4-Phenyl-2-pyrimidinecarbonitrile (6c) and 4-Phenyl-6-pyrimidinecarbonitrile (7c):

The crude product obtained from **5c**, by the above procedure is separated by silica gel column chromatography using hexane triethylamine (9 : 1/V : V) as eluent. The first fraction gives **7c** as colorless needles, followed by **6c**; colorless needles.

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