PREPARATION OF SUBSTITUTED 5-PYRIMIDINECARBONITRILES AND 1,3,5-TRIAZINES FROM ALKYL N-CYANOIMIDATES

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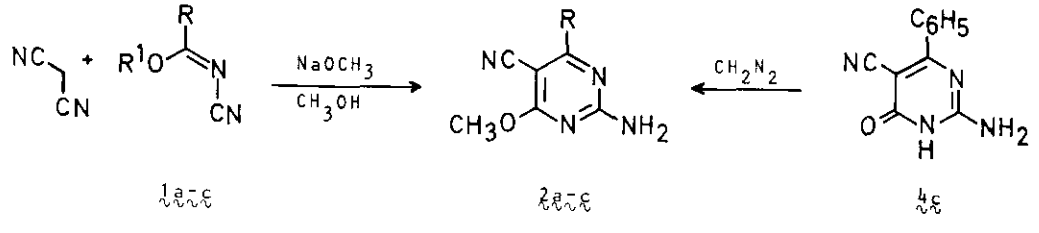
Abstract - Sodium methoxide induced the cyclization of alkyl N-cyanoimidates 1 with propanedinitrile affording the 5-pyrimidinecarbonitriles 2. The reaction of 1 with methyl cyanoacetate led to the methyl 3-[(aminocarbonyl)amino]propenoates 7 and the 2,4-dioxo-5-pyrimidinecarbonitrile 8. An analogous cyclization of 1 with cyanamide yielded the 1,3,5-triazines 10.

The cyclization of dicarbonitriles under acidic conditions is well documented[1]. Thus, hydrogen chloride induced the cyclization of the intermediate salts formed from N-cyanoalkanimidates and the sodium salt of propanedinitrile affording 4-alkyl-6-amino-2-chloro-5-pyrimidinecarbonitriles[2]. However, the addition of oxygen nucleophiles to dicarbonitriles followed by cyclization has received scant attention[3]. Recently we reported [4] the formation of 4-alkoxy-2-amino-5-pyrimidinecarbonitriles from 3-alkoxy-2-cyanopropenenitriles and the sodium salt of cyanamide through a Michael addition and a regioselective ring closure.

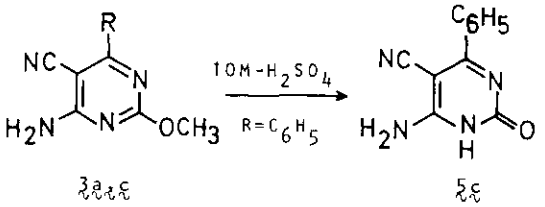
Now we wish to report the synthesis of 6-substituted 2-amino-4-methoxy-5-pyrimidinecarbonitriles (2a-c), 1,2,3,4-tetrahydro-2,4-dioxo-5-pyrimidinecarbonitrile (8b),

Scheme 1



1a-c 2a-c 4c

	R	R^1
a	H	C_2H_5
b	CH_3	C_2H_5
c	C_6H_5	CH_3



3a-c 5c

and 6-substituted 2-amino-4-methoxy-1,3,5-triazines (10a-c) by the cyclization of the readily accesible[5,6] N-cyanoimidates (1a-c).

The reaction of 1a-c with an equimolar amount of propanedinitrile and two molar equivalents of sodium methoxide in methanol gave 2a-c[4] as sole products. The isomeric 4-amino-5-pyrimidinecarbonitriles 3a-c were prepared independently[7,4] and showed higher melting points than their position isomers (2a-c). The ^{13}C-nmr spectra of several representatives of both pyrimidine series in DMSO-d_6 were compared (Table 1). The measured ^{13}C-nmr chemical shifts are in good agreement with the ones calculated by means of the known additivity for pyrimidines[8,9] of recently published monosubstitution parameters[9,10,11]. The chemical shifts of pyrimidine in DMSO-d_6[12] were used as basic values. An independent synthesis of the pyrimidine 2c was performed by methylation with diazomethane of the dihydro-4-oxo-5-pyrimidinecarbonitrile 4c[4]. The isomeric dihydro-2-oxo-5-pyrimidinecarbonitrile 5c was obtained quantitatively on hydrolisis of the pyrimidine 3c.

Table 1. ^{13}C-chemical shifts for pyrimidines 2a-c and 3a-c (in DMSO-d_6, TMS as inner standard)

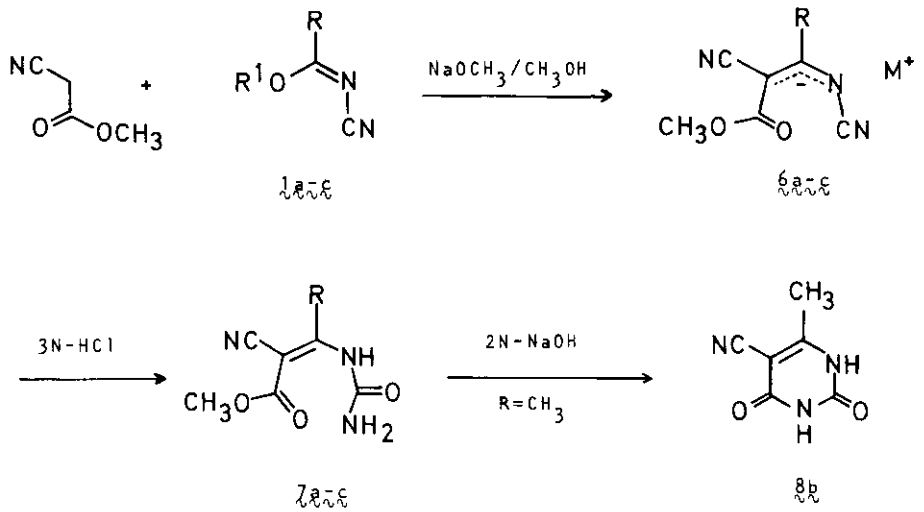
		C-2	C-4	C-5	C-6	CH_3O	CN	Others
2a	obs.	163.9	163.2[a]	82.3	169.3	54.2	115.7	
	calc.	163.9	163.7	83.7	169.8			
3a	obs.	164.8[b]	163.8[a]	84.1	166.3[b]	55.0	116.1	
	calc.	168.1	161.0	85.3	168.6			
2c	obs.	163.3	171.2	80.0	170.4	54.4	116.1	128.3 (C-2',C-3'), 130.8
	calc.	163.6	171.3	83.4	169.5			(C-4'), 136.3 (C-1')
3c	obs.	165.6[b]	170.5[b]	81.2	166.5[b]	54.7	116.5	128.4 (C-2',C-3'), 130.9
	calc.	167.8	168.6	85.0	168.3			(C-4'), 136.3 (C-1')

[a] A doublet in off resonance.

[b] The assignment of these signals may be reversed.

By treating equimolar amounts of the alkyl N-cyanoimidates 1a-c, methyl cyanoacetate, and sodium methoxide in a small amount of methanol at room temperature, the salts 6a-c (M=Na) precipitated after few minutes and could be obtained in high yields upon dilution of the mother liquid with diethyl ether. Methyl 3-cyanamino-2-cyano-3-phenylpropenoate tetraphenylarsonium salt [6c, M=$(C_6H_5)_4As$], prepared from its sodium salt by cation exchange, gave a correct analysis and was further characterized by means of its ^{13}C-nmr spectrum. When a methanolic aqueous solution of the sodium salts 6a-c (M=Na) or the reaction mixture from which these salts are isolated was acidified with diluted hydrochloric acid at room temperature, the methyl [(aminocarbonyl)amino]propenoates 7a-c precipitated and were collected by filtration. Only one geometric isomer of the propenoates 7a-c was proved according to their ^{1}H-nmr spectrum and tlc. The products probably[13] possess the (Z)-configuration depicted in Scheme 2. By dissolving the compound 7b in aqueous sodium

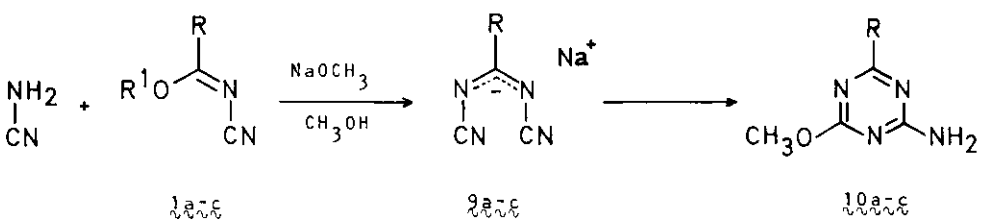
Scheme 2



hydroxide or heating it at temperatures around its melting point, the 1,2,3,4-tetrahydro-6-methyl-2,4-dioxo-5-pyrimidinecarbonitrile (8b)[2,14] was formed.

The reaction of the alkyl N-cyanoimidates 1 with cyanamide and sodium methoxide in methanol afforded at room temperature the sodium salts 9, which cyclized slowly to the 1,3,5-triazines 10a-e upon refluxing. A related ring closure under acidic conditions has been reported[5,15]. The 1,3,5-triazine 10b was prepared independently from ethyl N-cyanoacetimidate (1b) and methyl carbamimidate.

Scheme 3



Work in progress indicates that the alkyl N-cyanoimidates are useful starting materials for the preparation of other heterocyclic systems.

EXPERIMENTAL

The ir spectra were obtained on a Perkin Elmer 257 spectrophotometer. The ^{1}H-nmr spectra were recorded on a Varian T-60A spectrometer and the ^{13}C-nmr spectra on a Varian CFT 20 spectrometer with TMS as an internal standard in the solvents as indicated. Mass spectra were obtained on a Varian MAT 711 mass spectrometer at 70 eV. Melting points were determined on a Büchi melting point apparatus or a Bühler metal block (>260°) and are uncorrected.

2-Amino-4-methoxy-6-phenyl(or alkyl)-5-pyrimidinecarbonitriles 2. (General procedure). A solution of propanedinitrile (10 mmol), alkyl N-cyanoimidate 1 (10 mmol), and sodium methoxide (20 mmol) in dry methanol (50 ml) was heated under reflux for 8 to 48 h and poured into water. The precipitate thus formed was collected and recrystallized from ethanol to yield the following pyrimidines 2:

2-Amino-4-methoxy-5-pyrimidinecarbonitrile (2a); yield:17%; mp 207-208°C (lit.[4] mp 207-208°C).

2-Amino-4-methoxy-6-methyl-5-pyrimidinecarbonitrile (2b); yield:21%; mp 255°C (lit.[4] mp 254-255°C).

2-Amino-4-methoxy-6-phenyl-5-pyrimidinecarbonitrile (2c); yield 40%; mp 183°C (lit.[4] mp 183°C).

4-Amino-1,2-dihydro-2-oxo-6-phenyl-5-pyrimidinecarbonitrile (5c). To a suspension of pyrimidine 3c[4] (1.73 g, 8 mmol) in acetic acid (50 ml), 10M sulfuric acid (50 ml) was added, and the solution was allowed to stand for 5 h and neutralized to pH 5. The precipitate thus formed was collected and recrystallized from acetic acid; yield:1.66 g (98%); mp 345-347°C; ir (KBr): 3500-2500 (NH+OH), 2220 (CN), 1670 (CO), 1635 cm^{-1}; ms: 212 (M^+, 97). Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.26; H, 3.80; N, 26.40. Found: C, 61.97; H, 3.68; N, 26.64.

Methyl 3-Cyanamino-2-cyano-3-phenylpropenoate, Tetraphenylarsonium Salt [6c, M=$(C_6H_5)_4As$]. A solution of sodium methoxide (20 mmol), methyl cyanoacetate (1.98g, 20 mmol), and methyl N-cyanobenzenecarboximidate (1c) (3.2 g, 20 mmol) in dry methanol (20 ml) was stirred at room temperature for 30 min. After dilution with dry diethyl ether (230 ml) the precipitate was collected and dried in vacuo to give crude 6c (M=Na); yield: 3.85 g (77%); mp 277°C (dec.).
A mixture of the sodium salt 6c (M=Na; 0.99 g, 4 mmol) and tetraphenylarsonium chloride (1.67 g, 4 mmol) in dry acetone (50 ml) was stirred at room temperature for 1 h. The precipitated sodium chloride was removed and the filtrate was evaporated. The residue was recrystallized from a mixture of dichloromethane and diethyl ether at -20°C giving 1.93 g (80%) of colorless crystals; mp 152-153°C; ir (KBr): 2220. 2180 (CN), 1665 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6)(measured as the crude 6c, M=Na): δ 7.2-6.8 (m, 5H, C_6H_5), 3.30 ppm (s, 3H, CH_3O); ^{13}C-nmr (CD_3OD)(measured as the crude 6c, M=Na): δ 183.23 (C-3), 167.91 (CO), 139.99 (C-1'), 130.25, 129.08, 127.98 (C-2', C-3', C-4'), 122,26 (CN), 121.35 (CN), 77.20 (C-2), 51.36 ppm (CH_3O). Anal. Calcd. for $C_{36}H_{28}AsN_3O_2$: C, 70.94; H, 4.63; N, 6.98. Found: C, 71.05; H, 4.65; N, 6.93.

Methyl 3-[(Aminocarbonyl)amino]-2-cyano-3-phenyl(or alkyl)propenoates 7. (General procedure). A solution of alkyl N-cyanoimidate 1 (10 mmol), methyl cyanoacetate (10 mmol), and sodium methoxide (10 mmol) in dry methanol (50 ml) was stirred for 1 h at room temperature, diluted with water (300 ml), and acidified with 3N hydrochloric acid. The precipitate thus formed was collected after 2 h and recrystallized from methanol to yield the following propenoates 7:

Methyl 3-[(Aminocarbonyl)amino]-2-cyanopropenoate (7a); yield: 42%; mp 217-219°C; ir (KBr): 3360, 3270, 3190 (NH), 2240 (CN), 1740, 1690 (CO), 1610 cm^{-1}. Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.60; H, 4.17; N, 24.84. Found: C, 42.50; H, 4.21; N, 25.07.

Methyl 3-[(Aminocarbonyl)amino]-2-cyano-3-methylpropenoate (7b); yield: 43%; mp 193-195°C; ir (KBr): 3400, 3280, 3210 (NH), 2220 (CN), 1730, 1680 (CO), 1635 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 11.16 (s, 1H, NH), 7.45 (s, 2H, NH_2), 3.78 (s, 3H, CH_3O), 2.65 ppm (s, 3H, CH_3); ms: 183 (M^+, 33), 140 (89). Anal. Calcd. for $C_7H_9N_3$: C, 45.90; H, 4.95; N, 22.94. Found: C, 45.89; H, 4.78; N, 22.66.

Methyl 3-[(Aminocarbonyl)amino]-2-cyano-3-phenylpropenoate (7c); yield: 70%; mp 169°C (lit.[13] mp 168-169°C).

2,4-Dioxo-6-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile (8b). Methyl propenoate 7b (0.36 g, 2 mmol) was dissolved in 2N aqueous sodium hydroxide (20 ml). The solution was allowed to stand for 3 h at room temperature and acidified with diluted hydrochloric acid. The precipitate thus formed was collected by filtration and recrystallized from methanol giving 0.15 g (41%) of colorless crystals; mp 285°C (dec.) (lit.[14] mp 280°C (dec.); lit.[2] mp 350°C); ir (KBr): 3200-2800 (NH+OH), 2240 (CN), 1740, 1680 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ 11.77 (s, exchangeable, 2H, NH+OH), 2.30 ppm (s, 3H, CH_3). Anal. Calcd. for $C_6H_5N_3O_2$: C, 47.68; H, 3.34; N, 27.84. Found: C, 47.78; H, 3.50; N, 27.57.

2-Amino-4-methoxy-6-phenyl(or alkyl)-1,3,5-triazines 10. (General procedure). A solution of sodium methoxide (20 mmol), cyanamide (11 mmol), and alkyl N-cyanoimidate 1 (10 mmol) in dry methanol (25 ml) was refluxed for 5 d. The reaction mixture was concentrated over silica gel and the product was eluted with a 1:1-mixture of toluene:ethyl acetate through a short silica gel column (10 g). The product was recrystallized to yield the 1,3,5-triazines 10. (When the initial reaction mixture was stirred for 30 min at room temperature prior to heating, the complete disappearance of the imidates 1 and the formation of the intermediate salts 9 with Rf-values similar to the ones of the salts 6 (M=Na) was observed on tlc).

2-Amino-4-methoxy-1,3,5-triazine (10a); yield: 33%; mp 186-187°C (from methanol); ir (KBr): 3280, 3140 (NH), 1680 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 8.23 (s, 1H, H-6), 7.43 (br s, 2H, NH_2), 3.83 ppm (s, 3H, CH_3O). Anal. Calcd. for $C_4H_6N_4O$: C, 38.09; H, 4.80; N, 4.43. Found: C, 37.82; H, 4.66; N, 44.74.

2-Amino-4-methoxy-6-methyl-1,3,5-triazine (10b); yield: 41%; mp 255-256°C (from methanol)(lit.[5] mp 258-260°C); ir (KBr): 3320, 3140 (NH), 1660 cm^{-1}. Anal. Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.57; H, 5.87; N, 40.08.

2-Amino-4-methoxy-6-phenyl-1,3,5-triazine (10c); yield: 54%; mp 154-155°C (from a 1:1-mixture of methanol:water); ir (KBr): 3400, 3320, 3150 (NH), 1660 cm^{-1}; ^{1}H-nmr

($CDCl_3$): δ 8.2-8.0 (m, 2H, o-Harom), 7.3-7.1 (m, 3H, m,p-Harom), 5.67 (br s, 2H, NH_2), 3.93 ppm (s, 3H, CH_3O). Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.39; H, 4.98; N, 27.71. *Found*: C, 59.19; H, 4.89; N, 27.42.

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