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 with propanedinitrile affording the 5-pyrimidinecarbonitriles. The reaction of 1 with methyl cyanoacetate led to the methyl 3-[(aminocarbonyl)amino]propenoates and the 2,4-dioxo-5-pyrimidinecarbonitrile. An analogous cyclization of 1 with cyanamide yielded the 1,3,5-triazines.

The cyclization of dicarbonitriles under acidic conditions is well documented. 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. However, the addition of oxygen nucleophiles to dicarbonitriles followed by cyclization has received scant attention. Recently we reported 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 (1), 1,2,3,4-tetrahydro-2,4-dioxo-5-pyrimidinecarbonitrile (8),

Scheme 1

-463-
and 6-substituted 2-amino-4-methoxy-1,3,5-triazines \((\text{10a-c})\) by the cyclization of the readily accessible\(^5,6\) N-cyanoimidates \((\text{1a-c})\).

The reaction of \(\text{1a-c}\) with an equimolar amount of propanedinitrile and two molar equivalents of sodium methoxide in methanol gave \(\text{2a-c}\) as sole products. The isomeric 4-amino-5-pyrimidinecarbonitriles \(\text{3a-c}\) were prepared independently\(^7,4\) and showed higher melting points than their position isomers \(\text{2a-c}\). 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 \(\text{2c}\) was performed by methylation with methyl cyanocacetate, and sodium methoxide in a small amount of methanol at room temperature, the salts \(\text{6a-c} (\text{M=Na})\) precipitated after few minutes and could be obtained in high yields upon dilution of the mother liquid with diethyl ether. Methyl 3-cyanamino-2-cyan0-3-phenylpropenoate tetraphenylarsonium salt \(\text{6b, M=(C_6H_5)_4As}\), 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 \(\text{6a-c} (\text{M=Na})\) or the reaction mixture from which these salts are isolated was acidified with diluted hydrochloric acid at room temperature, the methyl \([(\text{aminocarbonyl})\text{amino}]\text{propenoates} \(\text{2a-c}\) precipitated and were collected by filtration. Only one geometric isomer of the propenoates \(\text{2a-c}\) was proved according to their \(^1\)H-nmr spectrum and tlc. The products probably possess the \((\text{E})\)-configuration depicted in Scheme 2. By dissolving the compound \(\text{2b}\) in aqueous sodium

<table>
<thead>
<tr>
<th>(\text{C-2})</th>
<th>(\text{C-4})</th>
<th>(\text{C-5})</th>
<th>(\text{C-6})</th>
<th>(\text{CH}_3\text{O})</th>
<th>(\text{CN})</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{2a}) obs.</td>
<td>163.9</td>
<td>163.2(^a)</td>
<td>82.3</td>
<td>169.3</td>
<td>54.2</td>
<td>115.7</td>
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<tr>
<td>calc.</td>
<td>163.9</td>
<td>163.7</td>
<td>83.7</td>
<td>169.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{2b}) obs.</td>
<td>164.8(^b)</td>
<td>163.8(^a)</td>
<td>84.1</td>
<td>166.3(^b)</td>
<td>55.0</td>
<td>116.1</td>
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<tr>
<td>calc.</td>
<td>168.1</td>
<td>161.0</td>
<td>85.3</td>
<td>168.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\text{2c}) obs.</td>
<td>163.3</td>
<td>171.2</td>
<td>80.0</td>
<td>170.4</td>
<td>54.4</td>
<td>116.1</td>
</tr>
<tr>
<td>calc.</td>
<td>163.6</td>
<td>171.3</td>
<td>83.4</td>
<td>169.5</td>
<td>((\text{C-4'})), 136.3 ((\text{C-1'}))</td>
<td></td>
</tr>
<tr>
<td>(\text{3a}) obs.</td>
<td>165.6(^b)</td>
<td>170.5(^b)</td>
<td>81.2</td>
<td>166.5(^b)</td>
<td>54.7</td>
<td>116.5</td>
</tr>
<tr>
<td>calc.</td>
<td>167.8</td>
<td>168.6</td>
<td>85.0</td>
<td>168.3</td>
<td>((\text{C-4'})), 136.3 ((\text{C-1'}))</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) A doublet in off resonance.
\(^b\) The assignment of these signals may be reversed.

By treating equimolar amounts of the alkyl N-cyanoimidates \(\text{1a-c}\), methyl cyanoacetate, and sodium methoxide in a small amount of methanol at room temperature, the salts \(\text{6a-c} (\text{M=Na})\) 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 \(\text{6b, M=(C_6H_5)_4As}\), 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 \(\text{6a-c} (\text{M=Na})\) or the reaction mixture from which these salts are isolated was acidified with diluted hydrochloric acid at room temperature, the methyl \([(\text{aminocarbonyl})\text{amino}]\text{propenoates} \(\text{2a-c}\) precipitated and were collected by filtration. Only one geometric isomer of the propenoates \(\text{2a-c}\) was proved according to their \(^1\)H-nmr spectrum and tlc. The products probably possess the \((\text{E})\)-configuration depicted in Scheme 2. By dissolving the compound \(\text{2b}\) in aqueous sodium
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 \(\mathbf{2}\), which cyclized slowly to the 1,3,5-triazines \(\mathbf{3}\) upon refluxing. A related ring closure under acidic conditions has been reported\(^{5,15}\). The 1,3,5-triazine \(1\) was prepared independently from ethyl N-cyanoacetimidate (\(1b\)) and methyl carbamimidate.

Work in progress indicates that the alkyl N-cyanoimidates are useful starting materials for the preparation of other heterocyclic systems.
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 Böhlen metal block (>260°) and are uncorrected.

2-Amino-4-methoxy-6-phenyl(or alkyl)-5-pyrimidinecarbonitriles \(\mathcal{Z}_1\). (General procedure). A solution of propanedinitrile (10 mmol), alkyl \(N\)-cyanoimidate \(\mathcal{Z}_2\) (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 \(\mathcal{Z}_1\):

2-Amino-4-methoxy-6-methyl-5-pyrimidinecarbonitrile \(\mathcal{Z}_2\); yield: 17%; mp 207-208°C (lit. \(^4\) mp 207-208°C).

2-Amino-4-methoxy-6-phenyl-5-pyrimidinecarbonitrile \(\mathcal{Z}_2\); yield: 21%; mp 255°C (lit. \(^4\) mp 254-255°C).

2-Amino-4-methoxy-6-phenyl-5-pyrimidinecarbonitrile \(\mathcal{Z}_3\); yield: 40%; mp 183°C (lit. \(^4\) mp 183°C).

4-Amino-1,2-dihydro-2-oxo-6-phenyl-5-pyrimidinecarbonitrile \(\mathcal{Z}_3\). To a suspension of pyrimidine \(\mathcal{Z}_4\) (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 cm\(^{-1}\) (NH\(_\text{OH}\)), 2220 cm\(^{-1}\) (cN), 1670 cm\(^{-1}\) (co), 1635 cm\(^{-1}\) (cn); ms: 212 (M'+, 97).


Methyl 3-Cyanamino-2-cyano-3-phenylpropenoate, Tetraphenylarsionium Salt \(\mathcal{Z}_6\). A solution of sodium methoxide (20 mmol), methyl cyanoacetate (1.98 g, 20 mmol), and methyl \(N\)-cyanobenzenecarboximidate \(\mathcal{Z}_6\) (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 \(\mathcal{Z}_6\) (M=Na): yield: 3.85 g (77%); mp 277°C (dec.).

A mixture of the sodium salt \(\mathcal{Z}_6\) (M=Na; 0.99 g, 4 mmol) and tetraphenylarsionium 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 \(\mathcal{Z}_6\); M=Na): \(\delta\) 7.2-6.8 (m, 5H, C\(_6\)H\(_5\)); 3.30 ppm (s, 3H, CH\(_3\)); \(^{13}\)C-nmr (CD\(_3\)OD) (measured as the crude \(\mathcal{Z}_6\); M=Na): \(\delta\) 183.23 (C-3), 167.91 (C0), 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\(_3\)).

Anal. Calcd. for C\(_{36}\)H\(_{28}\)AsN\(_3\)O\(_2\): C, 70.94; H, 4.63; N, 6.98. Found: C, 71.05; H, 4.65; N, 6.93.

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Methyl 3-[(Aminocarbonyl)amino]-2-cyano-3-phenyl(or alkyl)propenoates \( \mathcal{Z} \). (General procedure). A solution of alkyl N-cyanoiminate \( \mathcal{Z} \) (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 \( \mathcal{Z} \):

Methyl 3-[(Aminocarbonyl)amino]-2-cyano-3-methylpropenoate \( \mathcal{Z}_b \); yield: 43%; mp 193-195°C; \( \text{ir (KBr)}: 3400, 3280, 3190 \) (NH), 1730, 1680 (C=O), 1635 cm\(^{-1}\); \( ^1\text{H-nmr (DMSO-d}_6\text{)}: \delta 11.16 \) (s, 1H, NH), 7.45 (s, 2H, NH\(_2\)), 3.78 (s, 3H, CH\(_3\)), 2.65 ppm (s, 3H, CH\(_3\)). \( \text{Anal. Calcld. for C}_7\text{H}_5\text{N}_3\text{O}: C, 45.90; H, 4.95; N, 22.98. \) Found: C, 45.89; H, 4.78; N, 22.66.

Methyl 3-[(Aminocarbonyl)amino]-2-cyano-3-phenylpropenoate \( \mathcal{Z}_c \); yield: 70%; mp 169°C (lit.\(^{13}\) mp 168-169°C).

2,4-Dioxo-6-methyl-1,2,3,4-tetrahydro-5-pyrimidinecarbonitrile \( \mathcal{Z}_b \). Methyl propenoate \( \mathcal{Z}_b \) (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 of colorless crystals; mp 258-260°C; \( \text{ir (KBr)}: 3360, 3280, 3210 \) (CO), 1635 cm\(^{-1}\); \( ^1\text{H-nmr (DMSO-d}_6\text{)}: \delta 11.77 \) (s, exchangeable, 2H, NH+OH), 2.30 ppm (s, 3H, CH\(_3\)). \( \text{Anal. Calcld. for C}_5\text{H}_7\text{N}_3\text{O}: C, 47.68; H, 3.34; N, 27.84. \) Found: C, 47.78; H, 3.50; N, 27.57.

2-Amino-4-methoxy-6-phenyl(or alkyl)-1,3,5-triazines \( \mathcal{\Sigma}_\theta \). (General procedure). A solution of sodium methoxide (20 mmol), cyanamide (11 mmol), and alkyl N-cyanoiminate \( \mathcal{\Sigma}_\theta \) (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 \( \mathcal{\Sigma}_\theta \). (When the initial reaction mixture was stirred for 30 min at room temperature prior to heating, the complete disappearance of the imidates \( \mathcal{\Sigma}_\theta \) and the formation of the intermediate salts \( \mathcal{\Sigma}_\phi \) with Rf-values similar to the ones of the salts \( \mathcal{\Sigma}_\phi \) (M=Na) was observed on tlc.)

2-Amino-4-methoxy-1,3,5-triazine \( \mathcal{\Sigma}_\phi \); yield: 32%; mp 186-187°C (from methanol); \( \text{ir (KBr)}: 3280, 3140 \) (NH), 1660 cm\(^{-1}\); \( ^1\text{H-nmr (CDCl}_3\text{)}: \delta 8.23 \) (s, 1H, H-6), 7.43 (br s, 2H, NH\(_2\)), 3.83 ppm (s, 3H, CH\(_3\)). \( \text{Anal. Calcld. for C}_7\text{H}_6\text{N}_4\text{O}: C, 38.09; H, 4.80; N, 4.43. \) Found: C, 37.82; H, 4.66; N, 44.74.

2-Amino-4-methoxy-6-methyl-1,3,5-triazine \( \mathcal{\Sigma}_\phi \); yield: 41%; mp 255-256°C (from methanol); \( \text{ir (KBr)}: 3320, 3140 \) (NH), 1660 cm\(^{-1}\). \( \text{Anal. Calcld. for C}_7\text{H}_6\text{N}_4\text{O}: C, 42.85; H, 5.75; N, 39.98. \) Found: C, 42.57; H, 5.87; N, 40.08.

2-Amino-4-methoxy-6-phenyl-1,3,5-triazine \( \mathcal{\Sigma}_\phi \); yield: 54%; mp 154-155°C (from a 1:1-mixture of methanol:water); \( \text{ir (KBr)}: 3400, 3320, 3150 \) (NH), 1660 cm\(^{-1}\); \( ^1\text{H-nmr (DMSO-d}_6\text{)}: \delta 11.77 \) (s, exchangeable, 2H, NH+OH), 2.30 ppm (s, 3H, CH\(_3\)).
(CDCl₃): δ 8.2-8.0 (m, 2H, ß-Harom), 7.3-7.1 (m, 3H, α-Harom), 5.67 (br s, 2H, NH₂), 3.93 ppm (s, 3H, CH₃O). Anal. Calcd. for C₁₀H₁₀N₄O: C, 59.39; H, 4.98; N, 27.71. Found: C, 59.19; H, 4.89; N, 27.42.

REFERENCES AND FOOTNOTES

11. The monosubstitution parameters of 4-methoxypyrimidine were extrapolated from the trend of the parameters of methoxybenzene and 2-methoxypyridine.

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