Synthesis of 2-Alkoxy-6-aryl-5-cyano-4(3*H*)-pyrimidinones

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The reaction of methyl 3-aryl-2-cyano-3-methoxypropenoates **1** with cyanamide and sodium methoxide in methanol afforded after acid hydrolysis the methyl 3-[(aminocarbonyl)amino]-3-aryl-2-cyanopropenoates **4**. By performing the reaction in higher boiling alcohols the 2-alkoxy-6-aryl-5-cyano-4(3*H*)-pyrimidinones **2** were obtained in good yields.

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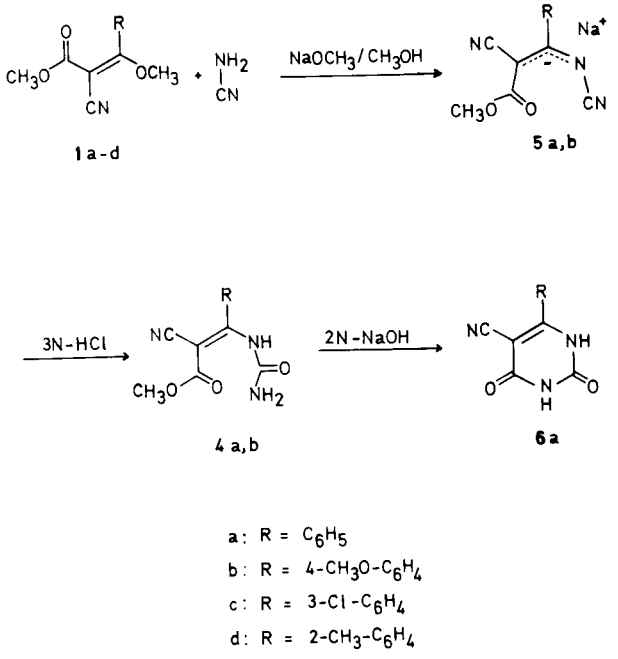
The Michael addition of the sodium salt of propanedinitrile to 2-cyanopropenenitriles and the subsequent sodium alkoxide induced cyclization of the intermediate 1,3-dicarbonitriles followed by aromatization afforded 2-alkoxy-6-amino-3,5-dicyanopyridines (1). The use of alkyl 2-cyanopropenoates led to the formation of 6-alkoxy-3,5-dicyano-2(1*H*)-pyridinones (2). Recently (3) we achieved the formation of 4-alkoxy-2-amino-5-cyanopyrimidines from 3-alkoxy-2-cyanopropenenitriles and the sodium salt of cyanamide through a Michael addition and a regiospecific ring closure. Now we wish to report the reaction of alkyl 2-cyano-3-methoxypropenoates **1** with the sodium salt of cyanamide, where the formation of 2-alkoxy-6-aryl-5-cyano-4(3*H*)-pyrimidinones (**2**) was expected.

The methyl 2-cyano-3-methoxypropenoates **1a-d** needed for this study were prepared with yields of between 55% and 75% by methylation with diazomethane (4) of the methyl 3-aryl-2-cyano-3-oxopropanoates **3a-d**. These in turn were prepared from aroyl chlorides, methyl cyanoacetate and finely divided sodium (5) with 46-90% yield.

Scheme I

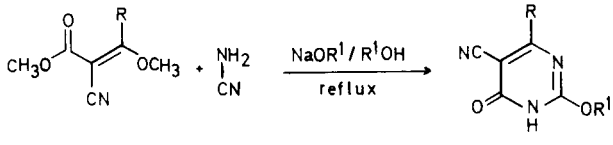


a: R = C_6H_5
b: R = 4-CH_3O-C_6H_4
c: R = 3-Cl-C_6H_4
d: R = 2-CH_3-C_6H_4

Compound **1a** (6) and **3a** (4,5) are reported. The methyl 2-cyano-3-methoxy-3-phenylpropenoate (**1a**) was obtained as an approximate 1:1 mixture of its *E* and *Z* isomers, out of which we were able to isolate pure *E*-**1a** by recrystallization. In pmr the methoxycarbonyl signal of the *E*-**1a** is shielded by the phenyl ring on the same side of the double bond and appears over 0.2 ppm upfield (6) of the corresponding signal of the *Z*-isomer. In cmr significant differences are observed between almost every carbon atom of *E,Z*-**1a**. On analytical tlc both *E* and *Z* forms of **1a** separated neatly, *E* possessing a higher Rf-value. A similar behaviour on tlc and pmr was found for the other compounds **1**, which recrystallized as an *E,Z*-mixture. From the mother liquors of **1c** almost pure *E*-**1c** was recuperated. *E,Z*-Isomerization of compounds **1** takes place upon either Michael addition (7) or sodium alkoxide catalysis (6).

By refluxing equimolar amounts of compounds **1a,b** and cyanamide with sodium methoxide in methanol and acidifying the reaction mixture the methyl 3-[(aminocarbonyl)amino]-2-cyanopropenoates **4a,b** precipitated in 72% and 81% yields, respectively. Prior to acidification the reaction mixture of **1b** contained according to tlc only the intermediate salt **5b**. An aliquot of the reacting solution was column-chromatographed to isolate crude methyl 3-cyanamino-2-cyano-3-(4-methoxyphenyl)propenoate, sodium salt (**5b**), mp *ca.* 250° dec. The ir spectrum of this salt showed the presence of two cyano groups (2200 and 2170 cm^{-1}) and a carbonyl group (1670 cm^{-1}) at frequencies similar to those reported (8,3) for related salts. On dissolution in methanol and dilution with 3*N* hydrochloric acid at room temperature the crude salt **5b** yielded quantitatively the compound **4b**. Only one geometric isomer of the methyl 3-[(aminocarbonyl)amino]-2-cyanopropenoates **4a,b** was obtained as indicated by the pmr spectra. The methoxycarbonyl protons of the products **4** are in the range of 3.80-3.83 ppm, well inside the range found for the *Z*-isomers of the compounds **1** and other methyl propenoates (9). Hence compounds **4a,b** were most probably obtained as the *Z*-isomers depicted in Scheme I. However, no certainty was achieved on the lack of the *E*-isomer for comparison. Several 3-alkyl(or hetero)-substituted analogues of **4** are reported (10).

Scheme II



1b,d 2a-c

		R	R^1
1b: R = 4-CH_3O-C_6H_4	2a	4-CH_3O-C_6H_4	1-C_3H_7
1d: R = 2-CH_3-C_6H_4	2b	"	C_2H_5
	2c	2-CH_3-C_6H_4	1-C_3H_7

The methyl 3-[(aminocarbonyl)amino]-2-cyano-3-phenylpropenoate (**4a**) cyclized to the 5-cyano-6-phenyl-2,4-(1*H*,3*H*)-pyrimidinedione (**6a**) (11) on dissolving in 2*N* aqueous sodium hydroxide or by heating it at temperatures around its melting point. In view of the imprecise melting point reported (11) for the pyrimidinedione **6a**, its structure was confirmed with spectroscopic data and microanalysis. The fragmentation pattern observed in the ms of **6a** is similar to those determined for 6-phenyl-2,4-(1*H*,3*H*)-pyrimidinediones **1** (12).

Alcohols of higher boiling points and longer reflux times were used to achieve the formation of 2-alkoxy-5-cyano-6-aryl-4(3*H*-pyrimidinones **2** from educts **1a,b** and cyanamide. The progress of the reaction was monitored by means of analytical tlc. When the reaction was conducted in dry propanol or ethanol the aliquots diluted with acetone showed the transesterified analogues of intermediate salts **5a,b** and the new pyrimidinones **2a,b**. The aliquots acidified and extracted with chloroform showed the transesterified analogues of compounds **4a,b** and the pyrimidinones **2a,b**. The reaction conducted in propanol was complete after eight days at reflux. The reaction carried out in ethanol was also elaborated after eight days but it did not attain completion in this period. The pyrimidinones **2a-c** were obtained with 54-88% yield and its structure was established on spectroscopic evidence. The competitive formation of aminopyrimidines by cyclization of two carbonitriles could not be detected.

EXPERIMENTAL

The ir spectra were obtained on a Perkin Elmer 257 spectrophotometer. The pmr spectra were recorded on a Varian T-60A spectrometer and the cmr 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 Buchi melting point apparatus or a Bühler metal block (>260°) and are uncorrected. Analytical tlc was performed on silica gel using toluene/ethyl acetate (4:1) as the eluent. Preparative column chromatography was performed on silica gel using toluene/ethyl acetate (1:3) as the eluent.

Methyl 2-Cyano-3-oxo-3-phenylpropanoate (**3a**).

A suspension of 9.2 g of finely divided sodium, prepared by melting under xylene with stirring, and 36.9 g (0.4 mole) of methyl cyanoacetate in 300 ml of diethyl ether and 2 ml of dry methanol was mechanically stirred at room temperature until complete consumption of the sodium (about one day). Benzoyl chloride (28.1 g, 0.2 mole) diluted with 50 ml of diethyl ether was allowed to drop into the reaction mixture with stirring, which was then refluxed for 3 hours. Forty ml of methanol was then added and the mixture was extracted with 10% aqueous sodium carbonate. The aqueous layer was acidified with hydrochloric acid and extracted twice with each 150 ml of toluene. The combined organic phase was washed and dried over magnesium sulfate. Evaporation of the solvent and recrystallization of the residue from methanol yielded 24.8 g (61%) of colorless crystals, mp 74-75° (lit (4) mp 74°); ir (potassium bromide): 2220 (CN), 1650 cm^{-1} (C=O); pmr (deuteriochloroform): δ 3.82 (s, CH_3O, 3H), 7.20-7.40 (m, 3',4'-aromatic, 3H), 7.65-7.88 ppm (m, 2'-aromatic, 2H); cmr (deuteriochloroform): δ 53.31 (CH_3O), 78.83 (C-2), 115.64 (CN), 131.29 (C-1'), 128.62, 133.37 (C-2', C-3', C-4'), 171.60 (CO_2), 182.77 ppm (CO).

E,Z-Methyl 2-Cyano-3-methoxy-3-phenylpropenoate (**1a**).

To a solution of 56.85 g (0.280 mole) of **3a** in 350 ml of diethyl ether kept in the ice bath, a solution of 0.28 mole of diazomethane (prepared from 85.68 g of *N*,4-dimethyl-*N*-nitrosobenzenesulfonamide) in diethyl ether was added dropwise and stirring was continued for 1 hour. Evaporation of the solvent and recrystallization of the residue from methanol yielded 45.93 g (75%) of colorless crystals, mp 113-125°; ir (potassium bromide): 2220 (CN), 1730 cm^{-1} (C=O); pmr (deuteriochloroform): δ 3.61, 3.67 (2 singlets; *E*-CH_3OCO, *E*-CH_3O, respectively, 3H), 3.76, 3.83 (2 singlets, *Z*-CH_3O, *Z*-CH_3OCO, respectively, 3H), 7.1-7.5 ppm (m, aromatic, 5H); cmr (deuteriochloroform): δ 52.14 (*E* + *Z*-CH_3OCO), 58.96 (*E*-CH_3O), 60.58 (*Z*-CH_3O), 87.01 (*E*-C-2), 114.73 (*E*-CN), 116.68 (*Z*-CN), 127.65-133.37 (C-aromatic), 161.81 (*Z*-CO_2), 162.59 (*E*-CO_2), 181.09 (*Z*-C-3), 182.59 (*E*-C-3).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.1; N, 6.5. Found: C, 66.2; H, 5.3; N, 6.5.

E-Methyl 2-Cyano-3-methoxy-3-phenylpropenoate (*E*-**1a**).

Compound *E,Z*-**1a** (20.23 g) yielded after three recrystallizations from methanol 10.52 g (52%) of pure *E*-**1a**, mp 125-126°; pmr (deuteriochloroform): δ 3.61 (s, CH_3OCO, 3H), 3.67 (s, CH_3O, 3H), 7.16-7.56 (m, aromatic, 5H); cmr (deuteriochloroform): δ 52.07 (CH_3OCO), 58.96 (CH_3O), 87.01 (C-2), 114.73 (CN), 127.72, 128.76, 131.03, 131.81 (C-aromatic), 162.59 (CO_2), 182.59 ppm (C-3).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.4; H, 5.1; N, 6.5. Found: C, 66.3; H, 5.2; N, 6.5.

Methyl 2-Cyano-3-(4-methoxyphenyl)-3-oxopropanoate (**3b**).

Following the same procedure used for the preparation of **3a**, compound **3b** was obtained in 90% yield as colorless crystals after recrystallization from methanol, mp 89-90°.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.8; H, 4.8; N, 6.0. Found: C, 61.9; H, 4.9; N, 6.2.

E,Z-Methyl 2-Cyano-3-methoxy-3-(4-methoxyphenyl)propenoate (*E,Z*-**1b**).

Compound **1b** was synthesized from **3b** in a manner similar to the preparation of **1a**, and was obtained in 74% yield as an *E,Z*-mixture (*ca.* 1:1) after recrystallization from methanol, mp 107-108°; pmr (deuteriochloroform): δ 3.53, 3.63 (2 singlets; *E*-CH_3-OCO, *E*-CH_3O, respectively; 3H), 3.72, 3.77 (2 singlets, relative intensity 1:3; *Z*-CH_3O, *Z*-CH_3OCO + 4'-CH_3O, respectively; 6H), 6.7-7.3 ppm (m, aromatic, 4H).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.2; H, 5.3; N, 5.7. Found: C, 63.4; H, 5.0, N, 5.7.

Methyl 2-Cyano-3-(3-chlorophenyl)-3-oxopropanoate (**3c**).

Following the same procedure used for the preparation of **3a**, com-

pound **3c** was obtained in 65% yield as colorless crystals after recrystallization from methanol, mp 108-109°; ir (potassium bromide): 2220 (CN), 1670 cm^{-1} (C=O); pmr (deuteriochloroform): δ 3.85 (s, CH_3O, 3H), 7.0-7.7 ppm (m, aromatic, 4H).

Anal. Clacd. for $C_{11}H_8ClNO_3$: C, 55.6; H, 3.4; Cl, 14.9; N, 5.9. Found: C, 55.4; H, 3.2; Cl, 15.0; N, 5.7.

E,Z-Methyl 2-Cyano-3-(3-chlorophenyl)-3-methoxypropenoate (*E,Z*-**1c**).

Compound **1c** was synthesized from **3c** in a manner similar to the preparation of **1a**, and was obtained in 56% yield as an *E,Z*-mixture (*ca.* 1:1, tlc) after recrystallization from methanol, mp 89-90°; ir (potassium bromide): 2210 (CN), 1720 cm^{-1} (C=O); pmr (of *E*-**1c**, recovered from the mother liquors of the recrystallization) (deuteriochloroform): δ 3.55 (s, *E*-CH_3OCO, 3H), 3.62 (s, *E*-CH_3O, 3H), 7.0-7.3 ppm (m, aromatic, 4H).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.3; H, 3.9; Cl, 14.1; N, 5.6. Found: C, 57.1; H, 3.9; Cl, 14.4; N, 5.3.

E,Z-Methyl 2-Cyano-3-methoxy-3-(2-methylphenyl)propenoate (*E,Z*-**1d**).

Crude **3d** was prepared following the procedure used for **3a** omitting the purification by recrystallization. Compound **1d** was synthesized from crude **3d** in a manner similar to the preparation of **1a**, and was obtained in 55% overall yield as an *E,Z*-mixture (2:3) after recrystallization from ethanol, mp 81-82°; pmr (deuteriochloroform): δ 2.20, 2.30 (2 singlets, relative intensities 2:3; *E*-CH_3, *Z*-CH_3, respectively; 3H), 3.52, 3.57, 3.72 (3 singlets, relative intensities 4:3:3; *E*-CH_3OCO + *E*-CH_3O, *Z*-CH_3O, *Z*-CH_3OCO, respectively; 6H), 7.1-7.2 ppm (m, aromatic, 4H).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.0. Found: C, 67.5; H, 5.7; N, 5.9.

Methyl 3-[(Aminocarbonyl)amino]-2-cyano-3-phenylpropenoate (**4a**).

A solution of 40 mmoles of sodium methoxide and 0.84 g (20 mmoles) of **1a** in 100 ml of dry methanol was refluxed for 8 hours, diluted with water and acidified with 3*N* hydrochloric acid. The precipitate thus formed was collected and recrystallized from methanol giving 3.55 g (72%) of colorless crystals, mp 168-169°; ir (potassium bromide): 3390, 3280, 3220 (N-H), 2230 (CN), 1730, 1690 cm^{-1} (C=O); pmr (deuteriochloroform): δ 3.83 (s, CH_3O, 3H), 7.30 (s, exchangeable, NH_2, 2H), 7.50 (s, C_6H_5, 5H), 10.91 ppm (s, exchangeable, NH, 1H); ms: 245 (M^+, 23), 222 (100).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.8; H, 4.5; N, 17.1. Found: C, 58.7; H, 4.5; N, 17.0.

Methyl 3-[(Aminocarbonyl)amino]-2-cyano-3-(4-methoxyphenyl)propenoate (**4b**).

Compound **4b** was synthesized from **1b** in a manner similar to the preparation of **4a**, and was obtained in 82% yield as colorless crystals after recrystallization from ethanol, mp 179-181°; ir (potassium bromide): 3450, 3300, 3200 (N-H), 2210 (CN), 1730, 1690 cm^{-1} (C=O); pmr (deuteriochloroform): δ 3.80 (s, CH_3O, 3H), 3.83 (s, CH_3O, 3H), 7.25 (s, exchangeable, NH_2, 2H), 6.9-7.5 (m, aromatic, 4H), 10.70 ppm (s, exchangeable, NH, 1H); ms: 275 (M^+, 35), 232 (100).

Anal. Calcd. for $C_{13}H_{13}N_3O_4$: C, 56.7; H, 4.8; N, 15.3. Found: C, 56.7; H, 4.7; N, 15.1.

5-Cyano-6-phenyl-2,4(1*H*,3*H*)-pyrimidinedione (**6a**).

A solution of 0.49 g (2.0 mmoles) of **4a** in 20 ml of 2*N* aqueous sodium hydroxide was kept for 3 hours at room temperature. Upon acidification with 3*N* hydrochloric acid a precipitate separated. This was collected and recrystallized from methanol to yield 0.35 g (80%) of colorless crystals, mp 296-298° (lit (11) mp > 250°); ir (potassium bromide): 3100-2800 (NH + OH), 2230 (CN), 1720, 1670 cm^{-1} (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 7.70 (s, aromatic, 5H), 11.90 ppm (s, exchangeable, NH + OH, 2H); ms: 213 (M^+, 100), 185 (30), 170 (26), 104 (84).

Anal. Clacd. for $C_{11}H_7N_3O_2$: C, 62.0; H, 3.3; N, 19.7. Found: C, 61.8; H, 3.5; N, 19.7.

5-Cyano-6-(4-methoxyphenyl)-2-(1-propoxy)-4(3*H*)-pyrimidinone (**2a**).

A solution of 20 mmoles of sodium propoxide (prepared from 0.46 g sodium) and 2.47 g (10 mmoles) of **1b** in 50 ml of dry 1-propanol was heated under reflux for 8 days. On cooling the sodium salt of **2a** crystallized out of the reaction mixture and was collected. This salt was dissolved in water and acidified with 3*N* hydrochloric acid. The precipitate thus formed was collected and recrystallized from methanol. Acidification of the mother liquors of the reaction mixture and recrystallization of the precipitate afforded a further crop of the same product. Total yield 2.51 g (88%) of colorless crystals, mp 229-230°; ir (potassium bromide): 3150-2400 (NH + OH), 2220 (CN), 1660 cm^{-1} (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 0.97 (t, CH_3-C, 3H), 1.77 (m, C-CH_2-C, 2H), 3.77 (s, CH_3O, 3H), 4.33 (t, CH_2O, 2H), 7.35 ppm (m, aromatic, 4H); ms: 285 (M^+, 56), 243 (100).

Anal. Calcd. for $C_{15}H_{15}N_3O_3$: C, 63.1; H, 5.3; N, 14.7. Found: C, 63.0; H, 5.1; N, 15.0.

5-Cyano-2-ethyl-6-(4-methoxyphenyl)-4(3*H*)-pyrimidinone (**2b**).

Compound **2b** was synthesized from **1b** in a manner similar to the preparation of **2a**, except that sodium ethoxide in refluxing ethanol was used. The product was obtained in 54% yield as colorless crystals after recrystallization from methanol, mp 231-232°; ir (potassium bromide): 3150-2400 (NH + OH), 2220 (CN), 1660 cm^{-1} (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 1.33 (t, CH_3, 3H), 3.77 (s, CH_3O, 3H), 4.43 (q, CH_2O, 2H), 7.35 ppm (m, aromatic, 4H); ms: 271 (M^+, 100), 243 (64).

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 62.0; H, 4.8; N, 15.5. Found: C, 61.9; H, 4.8; N, 15.8.

5-Cyano-6-(2-methylphenyl)-2-(1-propoxy)-4(3*H*)-pyrimidinone (**2c**).

Compound **2c** was synthesized from **1d** in a manner similar to the preparation of **2a**, and was obtained as colorless crystals after recrystallization from benzene, mp 179-180°; ir (potassium bromide): 3200-2400 (NH + OH), 2230 (CN), 1670 cm^{-1} (C=O); pmr (hexadeuteriodimethyl sulfoxide): δ 0.87 (t, CH_3, 3H), 1.68 (m, C-CH_2-C, 2H), 2.32 (s, 2'-CH_3, 3H), 4.27 (t, CH_2O, 2H), 7.0 (m, aromatic, 4H), 10.77 ppm (s, exchangeable, NH + OH, 1H); ms: 269 (M^+, 71), 227 (100).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.9; H, 5.6; N, 15.6. Found: C, 66.6; H, 5.7; N, 15.7.

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