Synthesis of Some New 2(1*H*)-Pyridones from 3-Amino-3-(dialkylamino)propenenitriles

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3-Amino-3-(dialkylamino)propenenitriles were reacted with acetylenecarboxylates to give 2(1*H*)-pyridone derivatives. The reaction with ethyl propynate afforded dienamino ester intermediates which cyclized in sodium ethoxide/ethanol to 5-cyano-2(1*H*)-pyridone. The reaction with diethyl acetylenedicarboxylate gave directly the 2(1*H*)-pyridone derivatives.

Recently 2-amino- and 2-hydroxypyridine derivatives have been studied extensively for their biological properties. Previously, we described a useful method for the preparation of these polysubstituted compounds by reaction between 3-amino-3-(dialkylamino)propenenitriles and enol ethers such as diethyl ethoxymethylenemalonate[1] and ethyl ethoxymethylenecyanoacetate.[2] These reactions afford initially a dienamino ester, which under appropriate conditions, easily undergoes intramolecular cyclization to a pyridine derivative.

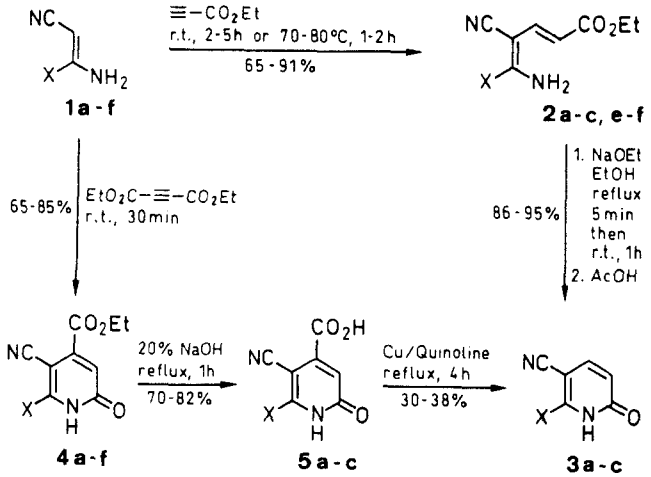
We now report the reaction between 3-amino-3-(dialkylamino)propenenitriles **1** and acetylene derivatives which contain electron-withdrawing groups, since addition of multifunctional nitrogenous nucleophiles to the carbon–carbon triple bond constitutes a route to a wide variety of heterocyclic compounds.[3-6]

When enaminonitriles **1** were treated with an equimolecular quantity of ethyl propynate in ethanol, excellent yields of adducts **2** were reached. The physical characteristics and spectroscopic data of the new dienamino esters **2** are listed in Table 1. For vinyl protons, ^{1}H NMR spectroscopy shows an AB system with doublets at δ = 5.07–5.19 and 7.43–7.54, respectively with J = 14.8 ± 0.2 Hz, typical of a trans configuration and a singlet at δ = 7.07–7.45 for the NH_2 group which disappears after deuteration. IR spectra show a strong absorption band between ν = 1640–1650 cm^{-1}, characteristic of a carbonyl group with an intramolecular hydrogen bond.

The dienamino esters **2** were thermally stable and do not cyclize even after prolonged boiling in ethanol. However, cyclization to 2(1*H*)-pyridone derivatives **3** occured easily within a few minutes by heating with sodium ethoxide in ethanol. The structures of compounds **3** are supported by analytical and spectral data (Table 2).

The ^{1}H NMR spectra of these compounds show a deuterium oxide exchangeable proton between δ = 11.55 and 10.89 due to the NH of the pyridine ring. The H-3 and H-4 protons of the pyridine ring appear as doublets between δ = 6.02 and 5.69 and between δ = 7.69 and 7.45, respectively. These doublets have a coupling constant of about 8 Hz. The reaction between **1** and diethyl acetylenedicarboxylate leads directly to ethyl 2-oxo-4-pyridinecarboxylates **4**. In no case was it possible to isolate the corresponding dienamino ester intermediate.

Subsequently the pyridones **4a–c** were submitted to mild hydrolysis to afford the 2-oxo-4-pyridinecarboxylic acids **5a–c**, which on decarboxylation in quinoline in the presence of copper, gave compounds **3a–c**. It can thus be postulated that the reaction between **1** and the acetylenic compounds initially proceeds via a nucleophilic addition to the triple bond to form Michael-type adducts **2** that subsequently cyclize intramolecularly.



1–5	X	1–5	X
a	1-pyrrolidinyl	d	4-methyl-1-piperazinyl
b	piperidino	e	4-phenyl-1-piperazinyl
c	morpholino	f	4-ethoxycarbonyl-1-piperazinyl

Melting points were determined on Kofler hot stage and are uncorrected. IR spectra were obtained in Nujol with a Perkin-Elmer 398 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Unity 300 spectrometer; the chemical shifts are given in δ downfield from the internal standard hexamethyldisiloxane (HMDSO) and coupling constants are given in Hz. Elemental analyses were carried out with a Carlo Erba Model 1106 Elemental Analyzer. All reagents and solvents were of commercial quality from freshly opened containers.

Compounds **1a–f** were prepared according to the literature procedure.[7]

Ethyl 5-Amino-4-cyano-5-(dialkylamino)-2,4-pentadiene carboxylate 2; General Procedure:

Ethyl propynate (0.5 mL, 5 mmol) was added to a stirred solution of enaminonitrile **1a–f** (5 mmol) in anhydr. EtOH (20 mL). The mixture was stirred at the temperature and for the time reported in Table 1. The resulting precipitate was filtered, washed with *i*-Pr_2O (2 × 10 mL) and recrystallized from a suitable solvent to give dienamino ester **2** (Table 1).

6-Dialkylamino-1,2-dihydro-2-oxo-5-pyridinecarbonitriles 3; General Procedure:

The appropriate dienamino ester **2a–c, e, f** (5 mmol) was added under stirring to a solution of NaOEt (5 mmol), prepared from Na metal (0.112 g) in anhydr. EtOH (10 mL), and the mixture was refluxed for 5 min, then stirred at r.t. for 1 h. After removal of the solvent, the residue was diluted with H_2O (20 mL) and the mixture acidified with glacial AcOH, whereupon a solid precipitate was formed. This was recrystallized from a suitable solvent to give **3** (Table 2).

Table 1. Dienamino Esters **2** Prepared

Product	Reaction Conditions		Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (Nujol) ν (cm^{-1})	^1H NMR (DMSO-d_6/HMDSO) δ, J (Hz)
	Temp. (°C)	Time (h)					
2a	20–25	2	90	165 (EtOH)	$C_{12}H_{17}N_3O_2$ (235.3)	3400, 3220, 2200, 1645, 1585	1.11 (t, 3H, CH_3), 1.82, 3.40 (m, 8H$_{pyrrolidinyl}$), 3.96 (q, 2H, CH_2), 5.07 (d, 1H, $J_{2,3}$ = 15, =CH), 7.07 (s, 2H, NH_2), 7.54 (d, 1H, $J_{2,3}$ = 15, =CH)
2b	20–25	2	85	169 (*i*-PrOH)	$C_{13}H_{19}N_3O_2$ (249.2)	3350, 3280, 2180, 1650, 1620, 1570	1.11 (t, 3H, CH_3), 1.52, 3.32 (m, 10H$_{piperidinyl}$), 3.96 (q, 2H, CH_2), 5.10 (d, 1H, $J_{2,3}$ = 14.7, =CH), 7.28 (s, 2H, NH_2), 7.43 (d, 1H, $J_{2,3}$ = 14.7, =CH)
2c	20–25	5	91	166 (EtOH)	$C_{12}H_{17}N_3O_3$ (251.3)	3370, 3200, 2180, 1640, 1650, 1580	1.11 (t, 3H, CH_3), 3.37, 3.57 (m, 8H$_{morpholinyl}$), 3.97 (q, 2H, CH_2), 5.15 (d, 1H, $J_{2,3}$ = 14.7, =CH), 7.40 (s, 2H, NH_2), 7.44 (d, 1H, $J_{2,3}$ = 14.7, =CH)
2e	70–80	1	86	195 (*i*-PrOH)	$C_{18}H_{22}N_4O_2$ (326.4)	3330, 3180, 2180, 1660, 1590	1.12 (t, 3H, CH_3), 3.15, 3.52 (m, 8H$_{piperazinyl}$), 3.98 (q, 2H, CH_2), 5.19 (d, 1H, $J_{2,3}$ = 14.6, =CH), 6.75, 6.89, 7.17 (m, 5H$_{arom}$), 7.45 (s, 2H, NH_2), 7.49 (d, 1H, $J_{2,3}$ = 14.6, =CH)
2f	70–80	2	65	181 (*i*-PrOH)	$C_{15}H_{22}N_4O_4$ (322.4)	3330, 3210, 2180, 1680, 1640, 1585	1.14 (m, 6H, $2CH_3$), 3.40 (m, 8H$_{piperazinyl}$), 4.02 (m, 4H, $2CH_2$), 5.17 (d, 1H, $J_{2,3}$ = 14.6, =CH), 7.44 (s, 2H, NH_2), 7.46 (d, 1H, $J_{2,3}$ = 14.6, =CH)

[a] Satisfactory microanalyses obtained: C ±0.35.

Table 2. 2(1*H*)-Pyridone Derivatives **3** and **4** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (Nujol) ν (cm^{-1})	^1H NMR (DMSO-d_6/HMDSO) δ, J (Hz)
3a	90	265 (EtOH)	$C_{10}H_{11}N_3O$ (189.2)	3100, 2180, 1650, 1590	1.85, 3.56 (m, 8H$_{pyrrolidinyl}$), 5.69 (d, 1H, $J_{3,4}$ = 7.8, H-3), 7.45 (d, 1H, $J_{3,4}$ = 7.8, H-4), 10.89 (br s, 1H, NH)
3b	90	248 (EtOH)	$C_{11}H_{13}N_3O$ (203.2)	3100, 2190, 1640, 1580	1.54, 3.50 (m, 10H$_{piperidinyl}$), 5.88 (d, 1H, $J_{3,4}$ = 8.8, H-3), 7.57 (d, 1H, $J_{3,4}$ = 8.8, H-4); 11.32 (br s, 1H, NH)
3c	86	268 (EtOH)	$C_{10}H_{11}N_3O_2$ (205.2)	3100, 2200, 1640, 1580	3.53, 3.64 (m, 8H$_{morpholinyl}$), 6.02 (d, 1H, $J_{3,4}$ = 8.5, H-3), 7.68 (d, 1H, $J_{3,4}$ = 8.5, H-4), 11.50 (br s, 1H, NH)
3e	86	256 (*n*-PrOH)	$C_{16}H_{16}N_4O$ (280.3)	3120, 2200, 1640, 1570	3.21, 3.70 (m, 8H$_{piperazinyl}$), 6.02 (d, 1H, $J_{3,4}$ = 8.3, H-3), 6.75, 6.94, 7.18 (m, 5H$_{arom}$), 7.69 (d, 1H, $J_{3,4}$ = 8.3, H-4), 11.55 (br s, 1H, NH)
3f	95	205 (EtOH)	$C_{13}H_{16}N_4O_3$ (276.3)	3140, 2210, 1710, 1650, 1590	1.14 (t, 3H, CH_3), 3.43, 3.52 (m, 8H$_{piperazinyl}$), 4.00 (q, 2H, CH_2), 6.02 (d, 1H, $J_{3,4}$ = 8.3, H-3), 7.69 (d, 1H, $J_{3,4}$ = 8.3, H-4), 11.57 (br s, 1H, NH)
4a	84	229 (*i*-PrOH)	$C_{13}H_{15}N_3O_3$ (261.3)	3150, 2190, 1740, 1710, 1640, 1620	1.17 (t, 3H, CH_3), 1.88, 3.51, 3.82 (m, 8H$_{pyrrolidinyl}$), 4.05 (q, 2H, CH_2), 5.60 (s, 1H, H-3), 11.28 (br s, 1H, NH)
4b	70	180 (MeCN)	$C_{14}H_{17}N_3O_3$ (275.3)	3100, 2190, 1745, 1690, 1600	1.17 (t, 3H, CH_3), 1.59, 3.69 (m, 10H$_{piperidinyl}$), 4.05 (q, 2H, CH_2), 5.65 (s, 1H, H-3), 11.27 (br s, 1H, NH)
4c	65	213 (EtOH)	$C_{13}H_{15}N_3O_4$ (277.3)	3060, 2200, 1750, 1700, 1605	1.17 (t, 3H, CH_3), 3.69, 3.73 (m, 8H$_{morpholinyl}$), 4.06 (q, 2H, CH_2), 5.70 (s, 1H, H-3), 11.30 (br s, 1H, NH)
4d	65	208 (*i*-PrOH)	$C_{14}H_{18}N_4O_3$ (290.3)	3070, 2210, 1745, 1705, 1600	1.15 (t, 3H, CH_3), 2.15 (s, 3H, CH_3), 2.40, 3.71 (m, 8H$_{piperazinyl}$), 4.05 (q, 2H, CH_2), 5.66 (s, 1H, H-3), 11.28 (br s, 1H, NH)
4e	85	238 (EtOH)	$C_{19}H_{20}N_4O_3$ (352.4)	3220, 2190, 1750, 1700, 1675, 1600	1.15 (t, 3H, CH_3), 3.24, 3.86 (m, 8H$_{piperazinyl}$), 4.05 (q, 2H, CH_2), 5.70 (s, 1H, H-3), 6.74, 6.90, 7.15 (m, 5H$_{arom}$), 11.41 (s, 1H, NH)
4f	68	225 (*i*-PrOH)	$C_{16}H_{20}N_4O_5$ (348.3)	3240, 3170, 2190, 1750, 1710, 1600	1.16 (m, 6H, $2CH_3$), 3.51, 3.77 (m, 8H$_{piperazinyl}$), 4.08 (m, 4H, $2CH_2$), 5.72 (s, 1H, H-3), 11.42 (s, 1H, NH)

[a] Satisfactory microanalyses obtained: C ±0.35.

Ethyl 5-Cyano-6-(dialkylamino)-1,2-dihydro-2-oxo-4-pyridinecarboxylates 4; General Procedure:

A solution of diethyl acetylenedicarboxylate (0.85 g, 5 mmol) in anhydrous EtOH (5 mL) was added dropwise to a stirred solution of 2-cyanoacetamidine **1a–f** (5 mmol) in anhydr. EtOH (20 mL) at 25°C during 10 min. The mixture was stirred for 0.5 h and the precipitate formed was filtered, washed with a little EtOH, dried and the crude product **4** recrystallized from a suitable solvent.

Hydrolysis of Ethyl 5-Cyano-1,2-dihydro-2-oxo-6-pyrrolidino-4-pyridinecarboxylate (4a); Typical Procedure:

Compound **4a** (1.30 g, 5 mmol) was suspended in aq 20% NaOH (15 mL) and the suspension refluxed for 1 h. The mixture was cooled and acidified with 6 N HCl. The precipitated product was isolated by suction, washed well with water and recrystallized from DMSO/EtOH (1:1) to give acid **5a**; yield: 1.0 g (82%); mp 330°C (dec).

$C_{11}H_{11}N_3O_3$ (233.2) calc. C 56.65 H 4.75 N 18.02
found 56.59 4.77 17.99

IR (Nujol): ν = 3120, 2190, 1700, 1625 cm^{-1}.

^1H NMR (DMSO-d_6/HMDSO): δ = 1.83, 3.57, 3.64 (3 m, 8H$_{pyrrolidinyl}$), 6.04 (s, 1H, H-3), 10.75 (s, 1H, OH), 11.80 (br s, 1H, NH).

Following the above described procedure, the acids **5b, c** were prepared:

5-Cyano-1,2-dihydro-2-oxo-6-piperidino-4-pyridinecarboxylic Acid (**5b**); yield: 0.60 g (70%); mp 290° (dec), recrystallized from AcOH.

$C_{12}H_{13}N_3O_3$ (247.2) calc. C 58.29 H 5.30 N 17.00 found 58.33 5.28 16.95

IR (Nujol): ν = 3130, 2210, 1700, 1630, 1590 cm^{-1}.

^1H NMR (DMSO-d_6/HMDSO): δ = 1.54, 3.53 (2 m, 10 $H_{piperidinyl}$), 5.96 (s, 1 H, H-3), 10.87 (s, 1 H, OH), 11.20 (br s, 1 H, NH).

5-Cyano-1,2-dihydro-2-oxo-6-morpholino-4-pyridinecarboxylic Acid (**5c**); yield: 0.87 g (70%); mp 270 C (dec); recrystallized from AcOH.

$C_{11}H_{11}N_3O_4$ (249.2) calc. C 53.01 H 4.45 N 16.87 found 53.08 4.40 16.79

IR (Nujol): ν = 3120, 2210, 1690, 1640 cm^{-1}.

^1H NMR (DMSO-d_6/HMDSO): δ = 3.28, 3.62 (2 m, 8 $H_{morpholinyl}$), 6.06 (s, 1 H, H-3), 10.96 (s, 1 H, OH), 11.48 (br s, 1 H, NH).

Decarboxylation of 5-Cyano-6-(dialkylamino)-1,2-dihydro-2-oxo-4-pyridinecarboxylic Acid 5a–c; General Procedure:

A mixture of **5a–c** (3 mmol) and powdered copper (0.08 g) was suspended in quinoline (7.5 mL) and refluxed for 4 h. The hot mixture was filtered and after cooling 6 N HCl was added. The resulting mixture was extracted with $CHCl_3$ (4 × 10 mL), dried (Na_2SO_4), and concentrated at reduced pressure to a solid, which was recrystallized from a suitable solvent to give the pyridones **3a–c**. The physical and spectral data were in agreement with those pyridones **3a–c** obtained by cyclization of **2a–c** (*vide supra*).

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