Synthesis of New Heterotricyclic Compounds Containing the [1,8]Naphthyridine Group by Thermal Isomerization of 2-Dialkylamino-3-vinylpyridines

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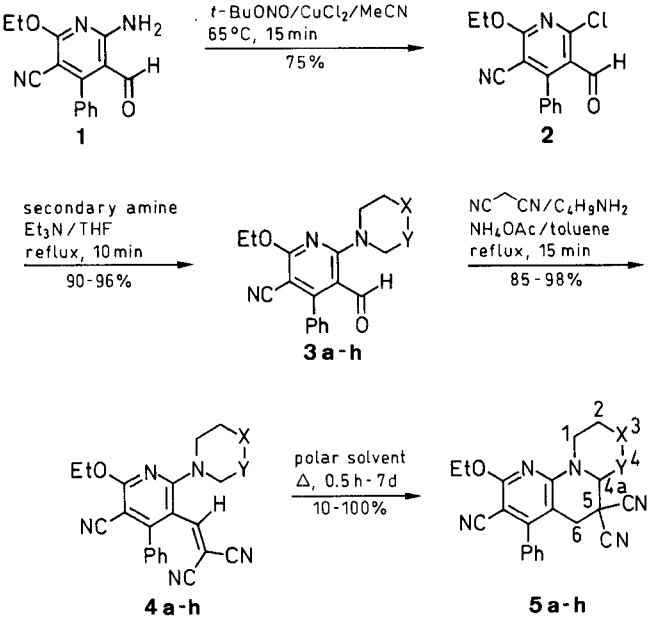
Received 19 June 1991; revised 23 October 1991

2-*N,N*-Dialkylamino-3-(2,2-dicyanovinyl)pyridines react thermally in polar solvents via [1,5] hydrogen transfer followed by carbon–carbon bond formation to yield heterotricyclic compounds containing the [1,8]naphthyridine group. The reaction time is markedly dependent on the solvent used and the stereoelectronic effects of the amino moiety. The presence of thiazolidinyl group results in the thermal isomerization taking place regiospecifically.

We report here the results provided by an extremely simple three-step pathway to fused [1,8]naphthyridines, applying the reaction principle of the "*tert*-amino effect" to a substituted pyridine as the key step. The term "*tert*-amino effect" was coined by Meth-Cohn and Suschizky to generalize cyclization reactions of tertiary anilines that bear an unsaturated *ortho*-substituent including at least one heteroatom.[1] Verboom and Reinhoudt have extended these reactions to *N,N*-dialkylanilines with an *ortho*-vinyl substituent.[2,3]

However, no mention is made in the literature of any synthesis where this "*ortho*-2π substituent" is part of a heteroaromatic compound, except for the recently reported preparation of heterocycles containing a thiophene group.[4] This paper reports the first example of the formation of a six-membered ring via thermal isomerization of 2-vinyl substituted dialkylaminopyridines. This annulation process provides a convenient approach to the synthesis of various other heterotri- and heterotetracyclic compounds containing the [1,8]naphthyridine group which had not previously been described in the literature. Thus, we succeeded in synthesizing the hitherto unknown heterotryciclic compounds **5a–h** (Scheme 1) with good yields. Compounds **5c, 5e, 5f,** and **5g** are, to the best of our knowledge, the first examples of its heterocyclic ring systems. These *N*-heterocycles are expected to show interesting biological properties,[5–7] so the biological activity of compounds **5** is currently being investigated.

The starting compounds for the thermal isomerization **4a–h** were conveniently prepared from 2-chloro-3-formylpyridine derivative **2**. This compound can be directly and efficiently obtained by substitutive deamination[8] [*tert*-butyl nitrite and anhydrous copper(II) chloride in dry acetonitrile] of 2-amino-3-formylpyridine derivative **1**, the synthesis of which was reported elsewhere.[9] Treatment of compound **2** with a suitable secondary amine and triethylamine in tetrahydrofuran yielded the corresponding 2-dialkylamino-3-formylpyridine derivatives **3a–h** in excellent yields (Table 1). The Knoevenagel condensation of the carbonyl group of **3a–h** with malononitrile (butylamine and ammonium acetate as catalyst[10,11]) in toluene for 15 minutes under reflux gave rise to the 2-dialkylamino-3-(2,2-dicyanovinyl)pyridine derivatives **4a–h** as yellow-orange solids with high yields (Table 2). The PyHCC(CN)$_2$ absorption signal in the ^{1}H NMR spectra between δ = 7.4–7.6 as a singlet and the PyHCC(CN)$_2$ absorptions in the decoupled ^{13}C NMR spectra between δ = 155–158 are typical of compounds **4a–h** (Table 2).



3–5	a	b	c	d*	e	f	g	h
X	–	CH_2	$(CH_2)_2$	$2(CH_2)_2$	NPh	O	S	–
Y	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	S

* For compounds **d** there is a CH group in position 2.

Scheme 1

Heating **4a–g** in butanol, pentanol (at refluxing temperature), dimethylformamide or dimethyl sulfoxide (at 140 °C) resulted in the corresponding heterocyclic compounds **5a–g** (Table 4). The ^{1}H NMR spectra of compounds **5a–g** exhibit characteristic signals of the hydrogen atoms at bridgehead carbons (H-3a, H-4a or H-5a) as double doublets between δ = 3.5–4.5 (Table 4). When the amino moiety is the thiazolidinyl group (X = –, Y = S), the thermal isomerization of **4h** could give rise to two isomers: thiazolo[3,2-*a*]- and thiazolo[3,4-*a*][1,8]naphthyridine. However, heating **4h** in butanol, pentanol, dimethylformamide or dimethyl sulfoxide resulted in only one cyclized product (**5h**, Scheme 1), the reaction being faster than for **4a** or **4g** in the chosen sequence (Table 3). The ^{1}H NMR spectrum of the reaction product includes a characteristic singlet at δ = 4.97 that integrates for one proton and can only be assigned to H-3a in a 2*H*-thiazolo[3,2-*a*][1,8]naphthyridine structure (Table 4).

The thermal isomerization can be assumed to occur in two consecutive reactions[12] (Scheme 2). The first step

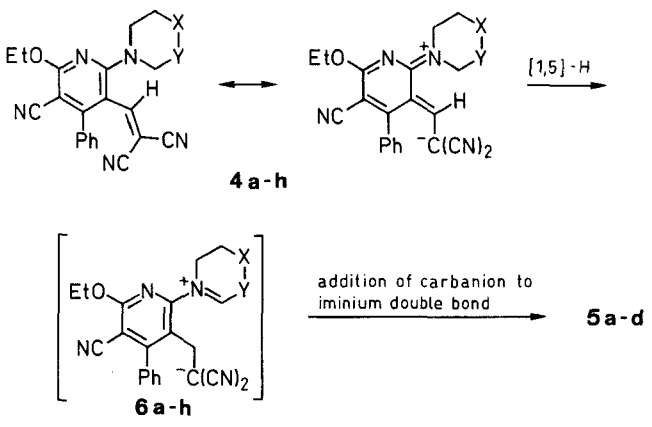
Table 1. 2-Dialkylamino-3-formylpyridines **3** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (%), M^+	^1H NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS)[d,e] δ
3a	95	120–125 (hexane)	$C_{19}H_{19}N_3O_2$ (321.4)	3060–2790, 2220, 1670, 1570–1520	321.1480 (100)	2.01 (br s, 4H, NCH_2CH_2), 3.51 (br s, 4H, NCH_2), 9.33 (s, 1H, CHO)	25.2 (NCH_2CH_2), 51.1 (NCH_2), 186.7 (CHO)
3b	90	145–147 (EtOH)	$C_{20}H_{21}N_3O_2$ (335.4)	2980–2875, 2220, 1660, 1580–1530	335.1614 (91)	1.72 [br s, 6H, $NCH_2(CH_2)_3$], 3.64 (br s, 4H, NCH_2), 9.17 (s, 1H, CHO)	24.1, 26.1 ($NCH_2CH_2CH_2$), 50.7 (NCH_2), 185.7 (CHO)
3c	92	132–135 (EtOH/ hexane)	$C_{21}H_{23}N_3O_2$ (349.4)	2980–2845, 2220, 1660, 1580–1560	349.1780 (100)	1.56 (br s, 4H, $NCH_2CH_2CH_2$), 1.88 (br s, 4H, NCH_2CH_2), 3.59 (br s, 4H, NCH_2), 9.24 (s, 1H, CHO)	27.6, 28.0 ($NCH_2CH_2CH_2$), 51.4 (NCH_2), 186.3 (CHO)
3d	96	192–194 (EtOH)	$C_{23}H_{25}N_3O_2$ (375.5)	3000–2855, 2220, 1660, 1580, 1575–1540, 1535–1495	375.1948 (100)	1.68 (br s, 8H, CH_2CH_2), 2.11 (br s, 2H, CH), 3.82 (d, 4H, J = 3.9, NCH_2), 9.19 (s, 1H, CHO)	24.5 (CH_2CH_2), 30.7 (NCH_2CH), 58.1 (NCH_2), 186.3 (CHO)
3e	90	179–181 (EtOH)	$C_{25}H_{24}N_4O_2$ (412.5)	3040–2800, 2220, 1660, 1595–1560	412.1895 (17)	3.37–3.41 (m, 4H, $PhNCH_2$), 3.86–3.90 (m, 4H, NCH_2), 6.88–6.97 (m, 3H, PhN), 7.25–7.48 (m, 2H, PhN), 9.26 (s, 1H, CHO)	49.2, 49.5 (NCH_2), 116.3, 120.3, 129.3, 150.8 (NC_6H_5), 186.0 (CHO)
3f	94	158–161 (EtOH/ hexane)	$C_{19}H_{19}N_3O_3$ (337.4)	3040–2800, 2215, 1665, 1580–1560, 1530–1480	337.1419 (100)	3.69–3.73 (m, 4H, OCH_2), 3.85–3.88 (m, 4H, NCH_2), 9.21 (s, 1H, CHO)	50.1 (NCH_2), 66.9 (OCH_2), 185.9 (CHO)
3g	96	170–172 (EtOH/ acetone)	$C_{19}H_{19}N_3O_2S$ (353.4)	2980–2925, 2225, 1660, 1585–1550, 1525–1495	353.1195 (100)	2.81–2.85 (m, 4H, SCH_2), 3.93–3.95 (m, 4H, NCH_2), 9.17 (s, 1H, CHO)	27.5 (SCH_2), 52.4 (NCH_2), 185.8 (CHO)
3h	93	140–142 (EtOH/ hexane)	$C_{18}H_{17}N_3O_2S$ (339.4)	2990–2900, 2220, 1660, 1585–1560, 1525–1495	339.1035 (100)	3.11 (t, 2H, J = 6.2, SCH_2), 3.96 (t, 2H, J = 6.2, NCH_2), 4.58 (s, 2H, NCH_2S), 9.35 (s, 1H, CHO)	30.1 (SCH_2), 53.0 (NCH_2), 54.0 (NCH_2S), 185.7 (CHO)

[a] After column chromatography.
[b] Satisfactory microanalyses obtained: C ± 0.20, H ± 0.21, N ± 0.23.
[c] The ^1H NMR spectra of compounds **3a–h** exhibit typical absorption signals for C_6H_5 [7.16–7.52 (m, 5H)], and for OCH_2CH_3 [1.44–1.48 (t, 3H, J = ~7.1 Hz, OCH_2CH_3), and 4.48–4.55 (q, 2H, J = ~7.1 Hz, OCH_2)].
[d] ^{13}C NMR spectra recorded with broad band decoupling.
[e] The ^{13}C NMR spectra of compounds **3a–h** exhibit typical signals for C_6H_5 [128.6–134.3, five absorptions], CN [84.9–86.6], OCH_2CH_3 [14.2–14.3 (OCH_2CH_3), 63.4–63.8 (OCH_2)], and pyridine nucleus [109.0–109.4, 115.2–115.5, 156.7–159.4, and 163.6–165.4 (2 absorptions)].

involves a thermal suprafacial [1,5]-hydrogen shift of one α-methylene proton adjacent to the nitrogen of the amino group in compounds **5a–h** to yield the 1,5-dipolar intermediate **6a–h** (with its "negative end" stabilized by the presence of two electron-withdrawing groups CN). Subsequently, intramolecular addition of the negatively charged carbon to the iminium double bond gives rise to cyclized products **5a–h**.

This mechanism account the differences in reactivity between compounds **4a–h** and the influence of the solvent on the cyclization process (Table 1). The stereoelectronic effects of the **X** group determine the stability of intermediates **6a–h**. First, the presence of an electronegative **X** group destabilizes the "positive end" of the 1,5-dipolar intermediate **6a–g**, so, the reaction time increases in the order piperidine < piperazine < morpholine as amino group in compound **4a–g**. On the other hand, the size of the **X** group seems to determine the



Scheme 2

reactivity of compounds **4a–g**. The 1,5-dipolar intermediate should be more stable at the same time that the

Table 2. 2-Dialkylamino-3-(2,2-dicyanovinyl)pyridines **4** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (%), M^+	^1H NMR ($DCCl_3$/TMS)[c] δ, J (Hz)	^{13}C NMR ($DCCl_3$/TMS)[d] δ
4a	88	184–186 (EtOH)	$C_{22}H_{19}N_5O$ (369.4)	2980, 2880, 2220, 1570–1500	369.1583 (63)	2.10 (br s, 4H, NCH_2CH_2), 3.37 (br s, 4H, NCH_2), 7.51–7.54 (m, 4H, $3H_{arom}$ + =CH)	25.3 (NCH_2CH_2), 52.0 (NCH_2), 114.5, 114.7 [$C(CN)_2$], 155.8 (=CH)
4b	94	182–184 (EtOH)	$C_{23}H_{21}N_5O$ (383.4)	2925–2840, 2220, 1560–1500	383.1742 (100)	1.69–1.73 [m, 6H, $NCH_2(CH_2)_3$], 3.60–3.70 (m, 4H, NCH_2), 7.42 (s, 1H, =CH)	23.6 ($NCH_2CH_2CH_2$), 25.8 (NCH_2CH_2), 49.2 (NCH_2), 75.5 [$C(CN)_2$], 114.6 [$C(CN)_2$], 156.8 (=CH)
4c	90	208–210 (EtOH)	$C_{24}H_{23}N_5O$ (397.5)	2940–2900, 2220, 1565, 1500	397.1910 (34)	1.60 (br s, 4H, $NCH_2CH_2CH_2$), 1.95 (br s, 4H, NCH_2CH_2), 3.44–3.46 (m, 4H, NCH_2), 7.51 (s, 1H, =CH)	27.6 ($NCH_2CH_2CH_2$), 28.2 (NCH_2CH_2); 51.5 (NCH_2), 114.7 [$C(CN)_2$], 156.8 (=CH)
4d	98	173–177 (EtOH)	$C_{26}H_{25}N_5O$ (423.5)	2990–2850, 2220, 1580–1540, 1525–1460	423.2050 (37)	1.68 (br s, 8H, CH_2CH_2), 2.16 (br s, 2H, CH), 3.77 (d, 4H, J = 4.0, NCH_2), 7.46 (s, 1H, =CH)	24.3 (CH_2CH_2), 30.8 (NCH_2CH), 57.2 (NCH_2), 76.7 [$C(CN)_2$], 114.7 [$C(CN)_2$], 157.2 (=CH)
4e	85	220–222 (EtOH/ acetone)	$C_{28}H_{24}N_5O$ (460.5)	3060–2800, 2220, 1580–1550, 1520–1490	460.2014 (60)	3.36–3.40 (m, 4H, $PhNCH_2$), 3.80–3.84 (m, 4H, NCH_2), 6.90–6.95 (m, 3H, C_6H_5N), 7.26–7.34 (m, 2H, C_6H_5N), 7.51 (s, 1H, =CH)	42.8 (CH_2NPh), 48.5 (NCH_2), 114.1, 114.3 [$C(CN)_2$], 115.8, 120.3, 129.3, 150.2 (NC_6H_5), 156.7 (=CH)
4f	94	193–195 (EtOH)	$C_{22}H_{19}N_5O$ (385.4)	3100–2860, 2220, 1580–1550, 1520–1490	385.1531 (100)	3.64–3.68 (m, 4H, OCH_2), 3.77–3.81 (m, 4H, NCH_2), 7.44 (s, 1H, =CH)	48.4 (NCH_2), 66.3 (OCH_2), 79.6 [$C(CN)_2$], 114.0, 114.3 [$C(CN)_2$], 156.6 (=CH)
4g	96	224–228 (EtOH/ acetone)	$C_{22}H_{19}N_5OS$ (401.5)	3020–2855, 2220, 1585, 1565–1520	401.1301 (100)	2.75 (br s, 4H, SCH_2), 3.87–3.91 (m, 4H, NCH_2), 7.44 (s, 1H, =CH)	26.9 (SCH_2), 50.9 (NCH_2), 79.8 [$C(CN)_2$], 113.9, 114.2 [$C(CN)_2$], 156.7 (=CH)
4h	90	168–170 (EtOH/ hexane)	$C_{21}H_{17}N_5OS$ (387.5)	3000–2900, 2220, 1580–1560, 1515–1490	387.1153 (100)	3.17 (t, 2H, J = 6.1, SCH_2), 3.83 (t, 2H, J = 6.1, NCH_2), 4.38 (s, 2H, NCH_2S), 7.55 (s, 1H, =CH)	30.3 (SCH_2), 52.9 (NCH_2), 53.3 (NCH_2S), 80.4 [$C(CN)_2$], 113.7, 114.2 [$C(CN)_2$, 185.7 (=CH)

[a] After column chromatography.
[b] Satisfactory microanalyses obtained: C ± 0.23, H ± 0.25, N ± 0.20.
[c] The ^1H NMR spectra of compounds **4a–h** exhibit typical absorption signals for C_6H_5 [7.25–7.31 (m, 2H), 7.49–7.55 (m, 3H)] and OCH_2CH_3 [1.46–1.49 (t, 3H, J = ~7.1 Hz, OCH_2CH_3), 4.50–4.54 (q, 2H, J = ~7.1 Hz, OCH_2)].
[d] The ^{13}C NMR spectra of compounds **4a–h** exhibit typical absorption signals for C_6H_5 [128.4–128.6, 129.1–129.3, 130.2–130.4, 133.3–133.7], CN [87.8–89.1], OCH_2CH_3 [14.1–14.2 (OCH_2CH_3), 63.4–64.3 (OCH_2)], and pyridine nucleus [102.9–104.2, 111.4–112.3, 156.3–156.6, 161.4–162.9, and 163.7–169.6].

Table 3. Reaction Time and Yields of the Thermal Isomerization

Product	Butanol[a]	Pentanol[a]	DMF[b]	DMSO[b]
5a	7 d (42)	7 d (73)	38 h (65)	20 h (95)
5b	5 d (91)	4 d (90)	6 h (75)	4.5 h (85)
5c	16 h (98)	14 h (95)	2.5 h (90)	1 h (95)
5d	6 h (99)	4 h (94)	1 h (91)	0.5 h (96)
5e	7 d (10)	7 d (45)	30 h (63)	18 h (70)
5f	no reaction[c]	no reaction[c]	40 h (50)	28 h (80)
5g	no reaction[c]	no reaction[c]	40 h (46)	30 h (90)
5h	10 h (96)	8 h (92)	4 h (89)	3 h (93)

[a] Reflux. Yields obtained are given in parenthesis.
[b] Heating at 140 °C. Yields obtained are given in parenthesis.
[c] No reaction was observed even after a reaction time of 15 d.

amino group will develop a conjugated double bond with the heteroaromatic ring more easily. Accordinaly, the reaction time increased in the order 3-azabicyclo-[3.2.2]nonane < perhydroazepine < piperidine < pyrroli dine as amino group. Furthermore, as the reaction proceeds via dipolar intermediates, which are more stable in polar solvents, the cyclization will be faster in dimethyl sulfoxide or dimethylformamide than it is in pentanol or butanol. The unexpected regiospecificity and high rate of reaction in the isomerization of **4h** is consistent with the proposed reaction mechanism. Compound **4h** has two types of α-methylene group liable to undergo the [1,5]-hydrogen shift (C-2′ and C-4′) but the fastest sigmatropic rearrangement takes place over C-2′, because it leads to a more stable 1,5-dipolar intermediate **6h**, with a stabilizing resonance involvemental the sulfur atom (Y) with unshared electrons on the "positive end".

All reagents used were commercial grade chemicals from freshly opened containers. The amines were purchased from Aldrich Chemical Co. Anhydrous $CuCl_2$ was dried in a oven at 110 °C prior to use. Reagent grade solvents were used without further purification, excepts for MeCN, which was distilled from P_2O_5 prior to use

Table 4. [1,8]Naphthyridine-Containing Heterotricyclic Compounds **5** Prepared

Product	Yield[a] (%)	mp (°C) (solvent)	Molecular Formula[b]	IR (KBr) ν (cm^{-1})	MS (70 eV) m/z (%), M^+	^1H NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS)[d] δ
5a	40–95	180–183 (EtOH/ hexane)	$C_{21}H_{19}N_5O$ (369.4)	3000–2850, 2215, 1585, 1575, 1555	369.1594 (100)	2.01–2.30 (m, 2H), 2.55–2.62 (m, 1H), 3.08, 3.23 (AB system, 2H, J = 15.9, H-5), 3.66–3.74 (m, 2H), 3.89–3.99 (m, 2H)	22.5 (C-2), 30.2 (C-3), 33.7 (C-4), 33.5 (C-5), 47.7 (C-1), 62.5 (C-3a), 114.0, 116.0 [$(CN)_2$]
5b	75–90	216–219 (EtOH)	$C_{23}H_{21}N_5O$ (383.4)	3000–2860, 2215, 1590, 1575, 1560–1540	383.1737 (100)	1.55–1.72 (m, 3H, H_{ax}-2, 3, 4), 1.85–1.91, 2.08–2.15, 2.28–2.33 (m, 3H, H_{eq}-2, 3, 4), 2.77–2.88 (m, 1H, H_{ax}-1), 3.05, 3.15 (AB system, 2H, J = 16, H-6), 3.65 (dd, 1H, J = 2.8, 11.8, H-4a), 5.04 (dd, 1H, J = 2.7, 4.5, 13.6, H_{eq}-1)	23.0, 24.1 (C-2, C-3), 29.0 (C-4), 32.7 (C-6), 36.1 (C-5), 45.6 (C-1), 59.2 (C-4a), 113.9, 115.6 [$(CN)_2$]
5c	900100	230–233 (EtOH/ hexane)	$C_{24}H_{23}N_5O$ (397.5)	3000–2850, 2215, 1585, 1575, 1555, 1510	397.1905 (100)	1.49–1.85, 2.14–2.22 (m, 8H, H-2, 3, 4, 5), 3.07 (s, 2H, H-7), 3.11, 3.22 (dd, 1H, J = 5.3, 8.8, 14.2, H_{ax}-1), 4.00–4.06 (dd, 1H, J = 3.5, 6.8, H-5a), 4.65–4.75 (dd, 1H, J = 4.9, 5.9, 14.2, H_{eq}-1)	25.6 (C-3, C-4), 27.0 (C-2), 30.6 (C-5), 31.4 (C-7), 33.0 (C-6), 48.7 (C-1), 65.1 (C-5a), 115.8 [$(CN)_2$]
5d	80–100	188–190 (EtOH)	$C_{26}H_{25}N_5O$ (423.5)	3000–2855, 2215, 1580, 1565, 1545, 1490	423.2058 (100)	1.51–2.05 (m, 8H), 2.25–2.29 (m, 2H, H-2,5), 2.92–3.14 (m, 3H, H_{ax}-1,8, H_{eq}-8), 3.93 (s, 1H, H-6a), 5.25–5.33 (dd, 1H, J = 6.1, 13.8, H_{eq}-1)	21.5, 23.0 (C-3, C-12), 26.2, 27.0 (C-4, C-13), 30.6, 31.2 (C-2, C-5), 34.6 (C-7), 36.1 (C-6), 54.65 (C-1), 64.0 (C-5a), 113.8, 115.3 [$(CN)_2$]
5e	10–70	230–235 (EtOH/ hexane)	$C_{28}H_{24}N_5O$ (460.5)	3000–2860, 2215, 1600, 1580, 1570, 1560	460.2003 (26)	3.04–3.34 (m, 3H, H_{ax}-1, 2, 3), 3.13, 3.24 (AB system, 2H, J = 16, H-6), 3.75 (m, 1H, H_{eq}-2 or 4), 3.92 (dd, 1H, J = 3.2, 10.6, H-4a), 4.09–4.16 (ddd, 1H, J = 2.0, 3.4, 11.8, H_{ax}-2,4, H_{eq}-4) 4.90–4.95 (dd, 1H, J = 2.5, 5.1, 12.8, H_{eq}-1), 6.97–7.03, 7.31–7.38 (m, 5H, NC_6H_5)	34.0 (C-6), 43.7, 49.2 (C-2, C-4), 52.2 (C-1), 57.3 (C-4a), 113.3, 115.3 [$(CN)_2$], 117.3, 121.7, 129.7, 149.8 (NC_6H_5)
5f	50–80	198–200 (EtOH)	$C_{22}H_{19}N_5O$ (385.4)	2980, 2925, 2875, 2215, 1590, 1575–1560, 1555	385.1540 (100)	3.03–3.14 (m, 1H, H_{ax}-1), 3.10, 3.21 (AB system, 2H, J = 16.0, H-6), 3.61–3.81 (m, 3H, H_{ax}-2,4, H_{eq}-4), 4.08–4.14 (dd, 1H, J = 11.8, 3.3, H-4a), 4.35–4.41 (m, 1H, H_{eq}-2), 4.66–4.72 (dd, 1H, J = 13.4, 1.8, H_{eq}-1)	32.4 (C-5), 33.8 (C-6), 43.1 (C-1), 56.2 (C-4a), 66.5 (C-2), 67.6 (C-4), 112.7, 115.2 [$(CN)_2$]
5g	40–90	195–198 (EtOH/ acetone)	$C_{22}H_{19}N_5OS$ (401.5)	3020–2855, 2220, 1585, 1565–1520	401.1304 (100)	2.49–2.55, 2.75–2.97 (m, 4H, H-2, 4), 3.04, 3.12 (AB system, 2H, J = 16.4, H-6), 3.28–3.39 (m, 1H, H_{ax}-1), 4.25–4.39 (dd, 1H, J = 3.0, 10.0, H-4a), 5.32–5.39 (td, 1H, J = 13.7, ~2.6 H_{eq}-1)	25.6 (C-2), 27.8 (C-4), 31.6 (C-6), 34.4 (C-5), 48.7 (C-1), 60.9 (C-4a), 113.3, 115.2 [$(CN)_2$]
5h	70–100	190–193 (EtOH/ hexane)	$C_{21}H_{17}N_5OS$ (387.5)	3000–2900, 2220, 1580–1560, 1515–1490	387.1150 (100)	3.06–3.33 (m, 2H, H_{ax}-1, 2), 3.13, 3.22 (d, 2H, J = ~15, H-5), 3.78–3.89 (dd, 1H, J = 5.8, J = 9.5, 11.5, H_{eq}-2), 4.43–4.92 (dd, 1H, J = 2.6, 6.0, 11.6, H_{eq}-1), 4.97 (s, 1H, H-3a)	28.7 (C-2), 35.0 (C-4), 37.3 (C-5), 51.6 (C-1), 65.5 (C-3a), 113.6, 115.3 [$(CN)_2$]

[a] After column chromatography.

[b] Satisfactory microanalyses obtained: C ± 0.24, H ± 0.26, N ± 0.22.

[c] The ^1H NMR spectra of compounds **5a–h** exhibit typical absorption signals for C_6H_5 [7.15–7.26 (m, 1H), 7.27–7.47 (m, 1H), 7.47–7.58 (m, 3H)] and OCH_2CH_3 [1.43–1.46 (t, 3H, J = ~7.1 Hz, OCH_2CH_3), 4.43–4.48 (q, 2H, J = ~7.1 Hz, OCH_2CH_3)].

[d] The ^{13}C NMR spectra of compounds **5a–h** exhibit typical absorption signals for C_6H_5 [127.7–134.4, six absorptions], CN [85.0–87.0], OCH_2CH_3 [14.2–14.4 (OCH_2CH_3), 62.9–63.3 (OCH_2CH_3)], and pyridine nucleus [99.3–100.2, 112.0–115.9, 152.2–156.1, 155.5–158.5, and 163.7–164.7].

as the reaction solvent. Silica gel 60 $HF_{254+366}$ for TLC and silica gel 60 (230–400 mesh) for medium-pressure chromatography were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of Santiago.

Melting points were measured using a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 383 IR spectrophotometer, ^1H and ^{13}C NMR on a Bruker WM 250 spectrometer and MS on a Kratos MS-50 spectrometer.

2-Chloro-5-cyano-6-ethoxy-3-formyl-4-phenylpyridine (2):
tert-Butyl nitrite (3.53 mL, 30 mmol) was added to a stirred suspension of anhydrous $CuCl_2$ (3.22 g, 24 mmol) in anhydrous MeCN (200 mL). The mixture was heated at 65 °C and then a solution of **1** (5.34 g, 20 mmol) in anhydrous MeCN (100 mL) was added over a period of 5 min to the reaction medium. During the addition, the mixture turned completely black from the initial green colour. After complete gas evolution (~ 15 min) the temperature was allowed to come to r. t. and the mixture was poured into 20% aq HCl (200 mL). EtOAc (300 mL) was added and the organic phase separated, washed with 20% aq HCl (250 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product **2** purified by medium-pressure chromatography on a silica gel column (20 × 4 cm) using CH_2Cl_2/hexane (2:1) as eluent; yield: 4.29 g (75%); mp 119–121 °C (hexane).

$C_{15}H_{11}ClN_2O_2$	calc.	C 62.84	H 3.87	N 9.77
(286.7)	found	62.66	4.08	10.03

IR (KBr): ν = 3050, 2950 (CH), 2230 (CN), 1695 cm^{-1} (C=O).

^1H NMR ($CDCl_3$/TMS): δ = 1.50 (t, 3H, J = 7.1 Hz, $OCH_2\underline{CH_3}$), 4.65 (c, 2H, J = 7.1 Hz, $OC\underline{H_2}CH_3$), 7.28–7.32 (m, $2H_{arom}$), 7.51–7.54 (m, $3H_{arom}$), 9.91 (s, 1H, CHO).

^{13}C NMR ($CDCl_3$/TMS) δ = 14.1 ($OCH_2\underline{C}H_3$), 65.6 ($O\underline{C}H_2CH_3$), 97.5 (CN), 128.5, 128.8, 130.3, 132.4 (C_6H_5), 112.7, 121.8, 154.5, 160.9, 164.2 ($C_{pyridyl}$), 187.2 (CHO).

MS (DEI): m/z (%) = 288 ($M^+ + 2$, 28), 287 ($M^+ + 1$, 31), 286 (M^+, 86), 285 ($M^+ - 1$, 56), 257 (100).

2-Dialkylamino-5-cyano-6-ethoxy-3-formyl-4-phenylpyridines 3a–h; General Procedure:
A solution of **2** (0.5 g, 1.75 mmol), a suitable secondary amine (1.75 mmol) and Et_3N (0.24 mL, 1.75 mmol) in THF (10 mL) was refluxed for 10 min. Upon cooling, precipitated Et_3NHCl was filtered, washed with THF (2 mL), and discarded. The solvent was removed under reduced pressure and the residue purified by recrystallisation (Table 1).

2-Dialkylamino-5-cyano-3-(2,2-dicyanovinyl)-6-ethoxy-4-phenylpyridines 4a–h; General Procedure:
A solution of **3a–h** (1.4 mmol), malononitrile (0.185 g, 2.8 mmol), butylamine (0.14 mL, 1.4 mmol) and NH_4OAc (0.11 g, 1.4 mmol) was refluxed in toluene for 15 min. Upon cooling, the solvent was removed under reduced pressure and the resulting solid was purified by medium-pressure chromatography on a silica gel column (15 × 1.5 cm) using the following eluents: CH_2Cl_2/hexane (1:1) for **4d**; CH_2Cl_2/hexane (3:2) for **4c**; CH_2Cl_2/hexane (2:1) for **4b, 4e, 4g, 4h**; CH_2Cl_2/hexane (3:1) for **4a**; and CH_2Cl_2 for **4f** (Table 2).

2,3,4,4a,5,6-Hexahydro-1*H*-pyrazino[1,2-*a*][1,8]naphthyridine (6e); Typical Procedures:
Method A: A solution of **4e** (0.25 mmol) in butanol or pentanol (5 mL) was refluxed until all the starting material had disappeared as checked by TLC (Table 3). The solvent was removed under reduced pressure and the resulting solid purified by medium-pressure chromatography on a silica gel column (12 × 1 cm) (Table 4).

Method B: A solution of **4e** (0.25 mmol) in DMF or DMSO (5 mL) was heated at 140 °C until all the starting material had disappeared as checked by TLC (Table 3). The mixture was cooled, poured into water (50 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The resulting solid was purified by medium-pressure chromatography on a silica gel column (12 × 1 cm) (Table 4).

Eluents: CH_2Cl_2/hexane (1:1) for **5b, 5c,** and **5e**; CH_2Cl_2/hexane (3:2) for **5d, 5g,** and **5h**; CH_2Cl_2/hexane (2:1) for **5a** and CH_2Cl_2/hexane (3:1) for **5f**.

The authors gratefully acknowledge the Universidad de La Coruña for financial support and the Xunta de Galicia for a grant awarded to one of them. They are also indebted to the General Services of the Universidad de Santiago for recording the NMR and mass spectra.

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