Synthesis of 6-Substituted 2-(*N*-Acetylamino)pyridines and 2-Aminopyridines by Cyclization of 5-Oximinoalkanenitriles

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Oxime derivatives of 5-oxoalkanenitriles (C_6 chain or longer) were cyclized in most cases with a combination of AcCl and Ac_2O, or Ac_2O and HCl to 6-substituted 2-(*N*-acetylamino)pyridines. Alkaline hydrolysis gave the corresponding 2-aminopyridines in overall yields of 40–65%, with the exception of pyridine **3e**. Oxime derivatives of 5-oxopentanenitriles did not cyclize but gave glutaronitriles instead. In some experiments with 5-oximinohexanenitrile (**1a**), 2,4-dimethyl-5-(2-cyanoethyl)oxazole (**9**) was detected in addition to the main product, 2-(*N*-acetylamino)-6-methylpyridine (**2a**). Formation of these compounds can be explained on the basis of a common intermediate **7** formed through rearrangement of the O-acetylated 5-oximinohexanenitrile (**4**).

Introduction

During attempts to obtain oxazole derivatives from 5-oximinoalkanenitriles in analogy with a literature procedure using oximes with no extra functionality,[1-3] we discovered a new and practical synthesis of 6-substituted 2-(*N*-acetylamino)pyridines[4] (Scheme I). The corresponding 2-aminopyridines were readily obtained by hydrolysis and constitute an important class of nitrogen heterocycles used in the agrochemical and pharmaceutical industries.

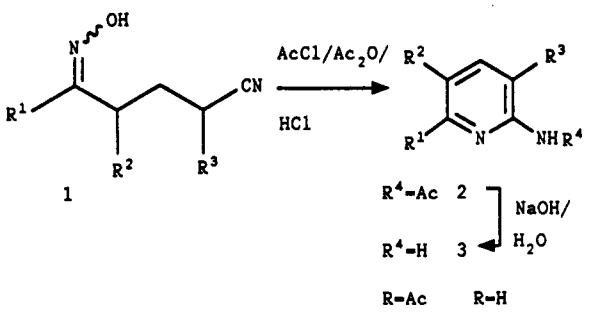
The "classical" preparation of 2-aminopyridines is the amination of pyridines (Chichibabin reaction).[5] Other syntheses use 2-pyridinecarboxylic acid *N*-oxides,[6] glutaronitriles,[7] 2-chloropyridines,[8] or 2-pyridones[9] as starting materials. Other approaches toward 2-aminopyridines are cyclization of acyclic precursors such as 5-aminoalkanenitriles,[10] or trimerization of malonitriles.[11]

The formation of 2-aminopyridine *N*-oxides by base-catalyzed rearrangement of 5-(cyanomethyl)-2-isoxazolines followed by cyclization[12] may have some features in common (type of hypothetical intermediate) with the preparation of 2-aminopyridines from 5-oximinoalkanenitriles reported here.

Results and Discussion

The necessary 5-oximinoalkanenitriles **1a–h** were prepared in good to excellent isolated yields from the corresponding 5-oxoalkanenitriles by reaction with aqueous alkaline hydroxylamine (1–1.5 equiv) at 10–20 °C. Refluxing oximino nitrile **1a** with a combination of AcCl and Ac_2O (130 °C, 4 h) afforded 2-(*N*-acetylamino)-6-methylpyridine (**2a**) in 69% yield (Table I, entry 5) which was hydrolyzed with aqueous NaOH to give the known 2-amino-6-methylpyridine (**3a**) in 58% overall yield from **1a** (Scheme I; Table II, entry 1).

Scheme I. The Synthesis of Pyridines 2 and 3 from Oximino Nitriles 1



	R=Ac	R=H
R^1=Me; R^2,R^3=H :1a	2a	3a
R^1=Et; R^2=H, R^3=Me :1b	2b	3b
R^1,R^2,R^3=Me :1c	2c	3c
R^1,R^2=$(CH_2)_4$; R^3=H :1d	2d	3d
R^1,R^2=$(CH_2)_3$; R^3=H :1e	2e	3e
R^1,R^2,R^3= H :1f	-	-
R^1,R^3=H; R^2=Me :1g	-	-
R^1=Me; R^2=Ac; R^3=H :1h	-	-

The influence of several parameters on the yield of reaction of oximino nitrile **1a** to pyridine **2a** was investigated to find the optimum conditions and to gain insight into the mechanism of formation of **2a**. The presence of 1 equiv of pyridine to neutralize the HCl formed resulted in a drastic decrease in the yield of **2a** (compare entries 2 and 4, Table I). Bubbling a small excess of HCl (1.2 equiv) through the solution partly overcame this effect and resulted in a moderate yield (43%) of **2a** (compare entries 1 and 2, Table I). It followed that a similar result was obtained in the absence of pyridine and using HCl gas (45% yield, entry 3, Table I). A method of in situ formation of AcCl from Ac_2O and HCl was also found to give similar yields to the experiments in which AcCl was added (compare entries 4 and 6, Table I). However, an increase from 2.3 to 5.4 equiv of Ac_2O gave a much lower yield (30% versus 55%, compare entries 6 and 7, Table I). Treatment of **1a** with excess HCl at 100–130 °C did not afford 2-aminopyridine **3a** or oxazole **9** (Scheme II) (entry 8, Table I).

A product, which based on proton NMR data is probably the intermediate *O*-acetyl derivative of **1a** (**4**; Scheme II),

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Table I. The Synthesis of Pyridines 2a and 3a and Oxazole 9 from Oximino Nitriles 1a and 1j (Influence of Parameters)

entry	oxime	AcCl, equiv	Ac_2O, equiv	HCl, equiv	pyridine, equiv	temp, °C	time, h	yields,[a] % 2a	3a	9
1	1a	1.3	1.0	1.2[b]	1.0	100–130	10	43		15
2	1a	1.3	1.0		1.0	100–130	7	12		6
3	1a	1.3	1.0	1.2[b]		100–130	7	45		0.5
4	1a	1.3	1.0			100–130	6	61		1
5	1a[c]	1.3	1.0			100–130	4	69		
6	1a		2.3	excess[d]		100–130	4	55		0.5
7	1a		5.4	excess[d]		100–130	4	30		
8	1a			1.6[e,f]		100–130	3		0	0
9	1a	1.0			1.1	20	1	<5[g]		
10	1j			excess[d,h]		100–130	4		2	

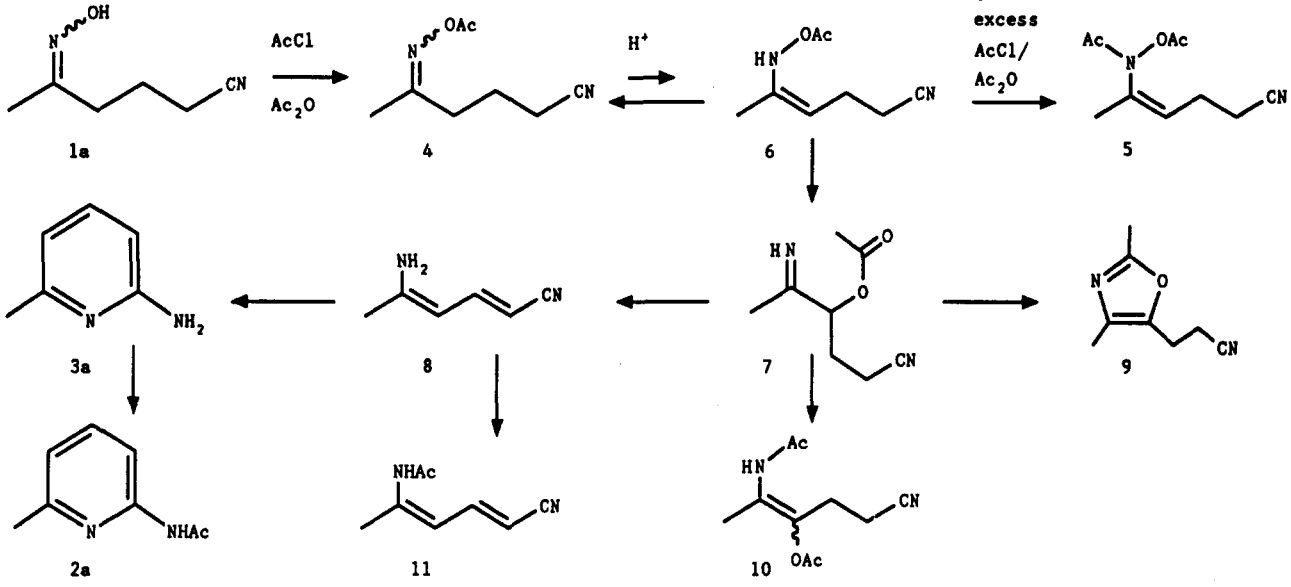
[a] Yields (determined by GC) in mol % based on 1. [b] HCl passed through during 3 h, 4 h after start of the reaction. [c] Distilled 1a, fresh AcCl. [d] HCl passed through during 4 h. [e] HCl passed through 3 h. [f] 2 equiv of HOAc present. [g] *O*-Acetyl oxime 4 isolated in crude state (67% yield). [h] 2.3 equiv of HOAc present.

Table II. The Synthesis of 2-(*N*-Acetylamino)pyridines 2 and 2-Aminopyridines 3 from Oximino Nitriles 1

entry	oxime 1	AcCl, equiv	Ac_2O, equiv	HCl	temp, °C	time, h	yields[a] 2	%	3[b]	%
1	1a	1.3	1.0		100–130	4	2a	69	3a	58
2	1b	1.4	1.1		100–130	4	2b		3b	43
3	1c	1.6	1.4		100–130	4	2c		3c	63[c]
4	1d	2.1	1.6		100–130	4	2d	36		
5	1d	2.0	1.5		100–130	4.5	2d		3d	43[d]
6	1e		5.0	+[e]	18–22	21	2e	5	3e	4
7	1f	1.4	1.1		100–130	3.5	–[f]			
8	1g	1.6	1.3		18–110[g]		–[h]			
9	1h	1.8	1.3		100–130	4	–[i]			

[a] Yields (determined by GC) in mol % based on 1. [b] Obtained by alkaline hydrolysis of 2. [c] 44% after distillation. [d] Crude product also contained 2d (7% yield). [e] Excess HCl gas passed through during first 5 h. [f] Glutaronitrile formed. [g] Rapid exothermic reaction. [h] 2-Methylglutaronitrile formed. [i] 4-(2-Cyanoethyl)-3,5-dimethylisoxazole (14) formed.

Scheme II. Postulated Mechanism for the Formation of Oxazole 9 and Pyridine 2a from 1a

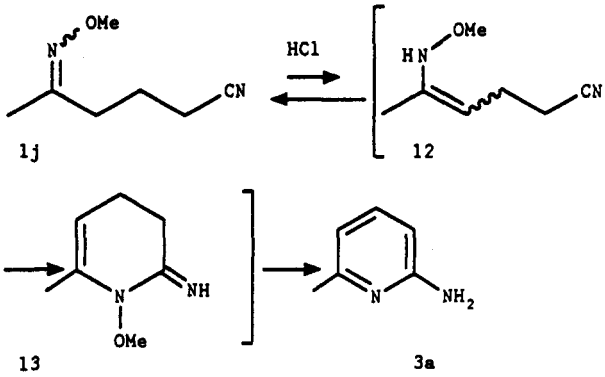


could be isolated in an impure state (67% yield) from the reaction of 1a with 1 equiv of AcCl in the presence of 1.1 equiv of pyridine at rt (entry 9, Table I). It was interesting to investigate the effect of O-substitution at the oxime group (no O-acetylation possible) on the yield of 2a/3a. Treatment of the *O*-methyl ether of 1a (1j) with excess HCl gave 2-aminopyridine 3a in very low yield (entry 10, Table I; Scheme III). In all experiments conversion of the 5-oximinonitriles 1a and 1j was more than 95%.

In several experiments involving pyridine (ca. 0.5 equiv to HCl present and formed) (entries 1 and 2, Table I), oxazole 9 (Scheme II) was formed as a minor component compared to 2a. The highest yield was 15% (entry 1, Table I). In the absence of pyridine the yield of oxazole 9 is lower than 2% (entries 3, 4, and 6, Table I). Chromatography afforded pure oxazole 9.

The formation of pyridine 2a and oxazole 9 from 1a can be explained on the basis of the following postulated mechanism (Scheme II). In the first step oximino nitrile 1a (mixture of *E*/*Z* isomers) is acetylated with AcCl and/or Ac_2O to give *O*-acetyl oximino nitrile 4 (detected by GC in the reaction mixture and identified by GC–MS and ^1H NMR) which is in tautomeric equilibrium with *N*-acetoxy enamine 6. Enamine 6 rearranges sigmatropically to α-acetoxy imine 7. This type of rearrangement has been observed previously[3,13,14] and has been put forward to explain the Semmler–Wolff aromatization of 2-cyclohexenone oximes to anilines.[15,16] From 7 two pathways are

Scheme III. Synthesis of 3a from 1j



followed. In the first pathway imine 7 and/or its enamine tautomer cyclizes, with elimination of water, to oxazole 9, in accordance with the formation of alkyl-substituted oxazoles via O-acetylated oximes as described by Bhatt et al.[1-3] In the second pathway 7 eliminates HOAc, followed by isomarization to give amino nitrile 8 which cyclizes via the *Z,Z*-diene geometry (*E* to *Z* isomerization possible under the acidic reaction conditions) and probably an imidyl chloride (HCl salt) intermediate[17-19] (HCl present) to 2-amino-6-methylpyridine (3a). Similar cyclizations of the 5-amino-2,4-pentadienenitrile system are reported in the literature.[10,12,20,21] Pyridine 3a reacts with AcCl and/or Ac_2O present to the *N*-acetyl derivative 2a.

Intermediates 5–8, 10, and 11 were never observed by GC–MS or proton NMR.

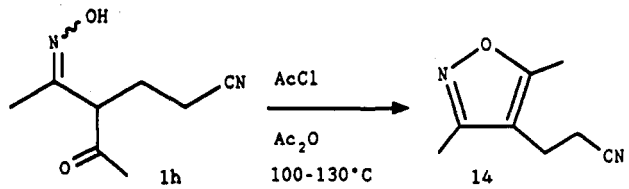
The fact that imine 7 gives predominantly pyridine 2a instead of oxazole 9 in contrast to ketoximes without additional functionality which give oxazoles in rather high yields[1-3] can be explained by assuming that firstly fast HOAc elimination in 7 occurs resulting in 8, a system stabilized by conjugation, and secondly that activation by HCl of the cyano group toward nucleophilic addition of the NH(2) group takes place.

The presence of a HCl scavenger is essential to obtain oxazole 9 in more than minimal yields, probably by inhibiting the activation of the cyano group (entries 1 and 2, Table I). However, the intermediacy of an imidyl chloride (HCl salt) derivative of the CN group is not a "condition sine qua non" for the cyclization of 8 to 3a.[10,12]

The presence of a too large excess of AcCl and Ac_2O (entry 7, Table I) probably leads to more N-acetylation of 4 (to 5), 6 (to 5), 7 (to 10), and 8 (to 11) which can explain the lower yields of 2a obtained. Hypothetical intermediates 5, 10, and 11 are assumed not to cyclize to 2-aminopyridine derivatives since the enamide nitrogen is much less nucleophilic[22] than an enamine nitrogen.

The formation of 2-aminopyridine 3a from *O*-methyl oxime 1j is assumed to proceed via (hypothetical) intermediates 12 and 13 (Scheme III).

Scheme IV. Formation of Isoxazole 14



By pyrolyzing 2,3,5-triphenyl-5-oximinopentanenitrile, 2-amino-3,4,6-triphenylpyridine has been obtained,[23] indicating that under drastic conditions 5-oximinoalkanenitriles can be cyclized and dehydrogenated to 2-aminopyridines.

To investigate the scope and limitations of this type of reaction, 5-oximino nitriles 1b–h were reacted with AcCl/Ac_2O or Ac_2O/HCl followed by alkaline hydrolysis of the 2-(*N*-acetylamino)pyridines formed (Table II). 2-Aminopyridines 3b–d were obtained in overall moderate yields of 43, 63, and 43%, respectively (entries 2, 3, and 5, Table II). In another experiment 1d afforded 2-(*N*-acetylamino)-pyridine 2d in 36% yield (entry 4, Table II). Oximino nirile 1e afforded pyridine 2e in low yield (5% according to GC; entry 6, Table II). Hydrolysis with aqueous NaOH gave 2-aminocyclopenteno[*e*]pyridine (3e) in 4% yield. Passing HCl gas for 4 h at 100 °C through a solution of oxime 1e and 2.3 equiv of Ac_2O did not afford 2e, nor did refluxing 1e with a combination of AcCl and Ac_2O. It should be noted that these reactions, with the exception of 2a, were not optimized.

The reason why 1e gave a much lower yield of 2e compared to the yield of cyclization of 1d to 2d, although unclear, could be due to the fact that the transition-state conformation of the cyclization of 1e, starting from the cyclopentane analogue of 8 (Scheme II), is more difficult to reach than in the case of 1d (as can be seen in framework molecular models).

Oximino nitriles 1f and 1g, derived from aldehydonitriles, did not afford the corresponding 2-(*N*-acetylamino)-pyridines, but glutaronitrile and 2-methylglutaronitrile, respectively, as a result of the well-documented,[24] rapid elimination of HOAc from the *O*-acetyl oxime derivatives (entries 7 and 8, Table II; yields not determined). Oximino nitrile 1h yielded 4-(2-cyanoethyl)-3,5-dimethylisoxazole (14) and no 2-(*N*-acetylamino)pyridine derivative, apparently due to a preferred cyclization of the oxime/*O*-acetyl oxime functionality onto the keto group (Scheme IV; entry 9, Table II).

2-Aminopyridines 3a–e were isolated in crude form and further purified by distillation or flash chromatography. 2-Aminopyridines 3b, 3d, and 3e are new. The *N*-acetyl precursors 2a (known), 2d (unknown), and 2e (new) were also isolated, and the structure of 2e was fully characterized.

Experimental Section

Unless otherwise stated, materials ($H_2NOH{\cdot}H_2SO_4$, Ac_2O, AcCl, HCl gas, pyridine, solvents) were obtained from commercial suppliers and used without further purification. H_2NOMe, 24.4 wt % solution in water, was supplied by DSM. The 5-oxoalkanenitriles, precursors for the 5-oximinoalkanenitriles 1a–h, were prepared according to literature procedures. Mp's and bp's are uncorrected. R_f values were obtained via TLC on silica gel (Merck silica 60 F_{254}) coated glass or aluminum sheets. Chro-

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matographic purification refers to flash chromatography[25] with Merck silica gel 60 (230–400 mesh). GC purity is in weight %. ^{1}H NMR spectra were recorded in $CDCl_3$. Chemical shifts are given in ppm downfield from tetramethylsilane. J values are given in hertz. ^{13}C NMR spectra were recorded at 50 MHz in $CDCl_3$. Electron impact mass spectra were obtained at 70 eV ionization energy. Compounds for which exact masses are reported exhibited no significant peaks at m/e greater than that for the parent. Yields of (*N*-acetyl)-2-aminopyridines before further purification by chromatography or distillation were determined by GC.

General Procedure for the Synthesis of Oximino Nitriles 1a–h. Method A. The oxo nitrile is added to a solution of hydroxylammonium sulfate in water, and the resulting mixture was cooled to ca. 10 °C and stirred. Aqueous NaOH solution is added portionwise at such a rate that the temperature remains below 20 °C. After addition of NaOH, the mixture is stirred for 2 h at rt, followed by extraction with diethyl ether (3×). Drying over $MgSO_4$, filtration, and concentration in vacuo gives crude oximinonitrile.

Method B. A solution of the oxo nitrile in diethyl ether or CH_2Cl_2 is added to a solution of hydroxylammonium sulfate in water. The mixture is cooled to ca. 10 °C and stirred. Aqueous NaOH solution is added portionwise at such a rate that the temperature remains below 20 °C. After addition of NaOH, the mixture is stirred for 16 h. The organic phase is separated and the water phase extracted with diethyl ether (3×). Drying over $MgSO_4$, filtration, and concentration in vacuo gives crude oximino nitrile.

5-Oximinohexanenitrile (1a).[26] **Method A.** Prepared from 50.2 g (0.45 mol) of 5-oxohexanenitrile,[27] 37.0 g (0.45 mol) of $H_2NOH{\cdot}H_2SO_4$ in 75 mL of water, 18.0 g (0.45 mol) of NaOH in 35 mL of water. Yield 48.1 g (84%) of **1a** as an oil. GC purity 99%. ^{1}H NMR (200 MHz): 9.5 (br s, 1 H, OH), 2.42 (t, J = 6, 2 H), and 2.35 (t, J = 6, 2 H) (CH_2CN, N=CCH_2), 1.90 (quin, J = 6, 2 H, CH_2CCN), 1.90 (s, 3 H, Me).

2-Methyl-5-oximinoheptanenitrile (1b). Method A. Prepared from 41.8 g (0.3 mol) of 2-methyl-5-oxoheptanenitrile,[28] 36.9 g (0.45 mol) of $H_2NOH{\cdot}H_2SO_4$ in 100 mL of water, 17.0 g (0.43 mol) of NaOH in 50 mL of water. Yield 47.9 g (94%) of **1b** as an oil. GC purity 97%. ^{1}H NMR (60 MHz): 10–9 (br s, 1 H, OH), 2.8–1.5 (m, 7 H), 1.3 (d, J = 7, 3 H, MeCCN), 1.05 (t, J = 6 , 3 H, CH_3).

2,4-Dimethyl-5-oximinohexanenitrile (1c). Method A. Prepared from 45.9 g (0.33 mol) of 2,4-dimethyl-5-oxohexanenitrile,[28] 30.3 g (0.37 mol) of $H_2NOH{\cdot}H_2SO_4$ in 50 mL of water, 14.7 g (0.37 mol) of NaOH in 40 mL of water. Yield 49.6 g (93%) of **1c** as an oil. GC purity 95%. ^{1}H NMR (60 MHz) 8.5–6.8 (br s, 1 H, OH), 3.0–1.5 (m, 4 H, 2 CH, CH_2CCN), 1.85 and 1.80 (2 s, 3 H, MeC=N), 1.3 (d, J = 7) and 1.25 (d, J = 7) (3 H, MeCC=N), 1.1 (d, J = 7, 3 H, MeCCN).

2-(2-Cyanoethyl)cyclohexanone Oxime (1d). Method B. Prepared from 15.2 g (0.1 mol) of 2-(2-cyanoethyl)cyclohexanone[29] in 40 mL of diethyl ether, 9.0 g (0.11 mol) of $H_2NOH{\cdot}H_2SO_4$ in 40 mL of water, 5.0 g (0.13 mol) of NaOH in 25 mL of water. Yield 13.8 g (59%) of **1d** as an oil. GC purity 71%. (The other 29% is unconverted keto nitrile. It is assumed that this impurity does not interfere with the pyridine formation.) ^{1}H NMR (60 MHz): 8.4–6.7 (br s, 1 H, OH), 2.7–2.1 (m, 5 H, CH_2CN, CH_2C=N, CHC=N), 2.1–1.5 (m, 8 H, CH_2CCN, rest ring protons).

2-(2-Cyanoethyl)cyclopentanone Oxime (1e). Method B. Prepared from 27.3 g (0.2 mol) of 2-(2-cyanoethyl)cyclopentanone[29] in 50 mL of diethyl ether, 25.8 g (0.31 mol) of $H_2NOH{\cdot}H_2SO_4$ in 50 mL of water, 12.0 g (0.3 mol) of NaOH in 40 mL of water. Yield 26.2 g (85%) of **1e** as an oil. GC purity 99%. ^{1}H NMR (60 MHz): 9.5–8 (br s, 1 H, OH), 2.7–2.1 (m, 5 H, CH_2CN, H_2CC=N, CHC=N), 2.1–1.2 (m, 6 H, CH_2CCN, rest ring protons).

5-Oximinopentanenitrile (1f). Method A. Prepared from 48.4 g (0.5 mol) of 5-oxopentanenitrile,[30] 41.0 g (0.5 mol) of $H_2NOH{\cdot}H_2SO_4$ in 125 mL of water, 20 g (0.5 mol) of NaOH in 60 mL of water. Yield 48.9 g (81%) of **1f** as an oil. GC purity 93%. ^{1}H NMR (60 MHz): 7.3 (t, J = 6, 0.55 H, N=CH *E*), 6.65 (t, J = 6, 0.45 H, N=CH *Z*), 4.6 (br s, 1 H, OH), 2.4 (t, J = 6, 2 H) and 2.3 (t, J = 6, 2 H) (CH_2CN, CH_2C=N), 1.85 (quin, J = 6, 2 H, CH_2CCN).

4-Methyl-5-oximinopentanenitrile (1g). Method A. Prepared from 28.1 g (0.25 mol) of 4-methyl-5-oxopentanenitrile,[30] 24.6 (0.3 mol) of $H_2NOH{\cdot}H_2SO_4$ in 100 mL of water, 11.1 g (0.28 mol) of NaOH in 40 mL of water. Yield 27.6 g (69%) of **1g** as an oil. GC purity 80%.

4-Acetyl-5-oximinohexanenitrile (1h). Method B. Prepared from 38.2 g (0.25 mol) of 4-acetyl-5-oxohexanenitrile[31] in 75 mL of CH_2Cl_2, 22.9 g (0.28 mol) of $H_2NOH{\cdot}H_2SO_4$ in 50 mL of water, 10.6 g (0.27 mol) of NaOH in 25 mL of water. Yield 42.7 g (85%) of **1h** as an oil. GC purity 84%.

5-Oximinohexanenitrile *O*-Methyl Ether (1j). A mixture of 14 g (0.30 mol) of H_2NOMe in 43.3 mL of water (24.4 wt % solution in water), and 33.3 g (0.30 mol) of 5-oxohexanenitrile was stirred for 45 h at rt and then heated for 2 h at 50–60 °C. An extra amount of 6.75 g (0.14 mol) of H_2NOMe in 21 mL of water was added, and the mixture was heated 10 h at 50–60 °C. Diethyl ether (50 mL) was added, and the layers separated. The aqueous layer was extracted with diethyl ether (2 × 50 mL), and further workup gave 36.3 g (86%) of almost pure **1j** as a liquid. ^{1}H NMR (60 MHz): 3.75 (s, 3 H, OMe), 2.6–1.6 (m, 6 H), 1.85 (s, 1.5 H, Me *E*), 1.80 (s, 1.5 H, Me *Z*).

General Procedure for the Synthesis of 2-(*N*-Acetylamino)pyridines 2a–e. Ac_2O was added to the 5-oximino nitrile and the solution cooled to 5 °C. AcCl was added portionwise in 15 min (unless stated otherwise) with stirring. The mixture was refluxed (100–130 °C) for 4 h (unless stated otherwise). After cooling to rt the mixture was poured into water (100 mL; unless stated otherwise) and neutralized with NaOH(aq). Workup, which refers to extraction with CH_2Cl_2 (4 × 50 mL; unless stated otherwise), drying over $MgSO_4$, filtering, and concentration in vacuo on a rotary evaporator, afforded crude **2a–e**. The workup procedure was also applied in the synthesis of **3a–d**, **9**, and **14**.

2-(*N*-Acetylamino)-6-methylpyridine (2a).[32] Prepared from 10 g (0.1 mol) of Ac_2O, 12.5 g (0.1 mol) of 5-oximinohexanenitrile (**1a**), and 9.9 g (0.13 mol) of AcCl. A solid was obtained containing 10.3 g (69%) of **2a**. ^{1}H NMR (60 MHz): 8.9 (br s, 1 H, NH), 7.9 (d, J = 7, 1 H, H-3), 7.45 (t, J = 7, 1 H, H-4), 6.8 (d, J = 7, 1 H, H-5), 2.40 (s, 3 H, MeC=O), 2.15 (s, 3 H, Me at C-6).

2-Amino-6-methylpyridine (3a).[33] Preparation identical to procedure for **2a**, except that after reflux the mixture was cooled to 50 °C, 26.4 g (0.66 mol) of NaOH in 75 mL of water was added, and the mixture was heated at 70 °C for 1 h. After cooling to rt workup gave a solid containing 6.3 g (58%) of **3a**. Chromatography (EtOAc) gave pure **3a** as light yellow crystals. Mp: 41–42.5 °C (EtOAc). R_f = 0.28 (EtOAc) UV, I_2 active. ^{1}H NMR (200 MHz): 7.27 (t, J = 7, 1 H, H-4), 6.45 (d, J = 7, 1 H, H-3), 6.25 (d, J = 7, 1 H, H-5), 4.9 (br s, 2 H, NH_2), 2.35 (s, 3 H, Me). ^{13}C NMR: 158.30 and 156.66 (C-2, C-6), 137.98 (C-4), 112.81 (C-5), 105.37 (C-3), 23.97 (Me).

2-Amino-6-ethyl-3-methylpyridine (3b). Prepared from 10 g (0.1 mol) of Ac_2O, 15.1 g (0.09 mol) of 5-oximinoheptanenitrile (**1b**), and 10.0 gave (0.13 mol) of AcCl (30 min). After cooling to rt 20.0 g (0.5 mol) of NaOH in 80 mL of water was added, and the mixture was refluxed 1.5 h. After cooling to rt workup gave a liquid containing 5.3 g (43%) of **3b**. Vacuum distillation (68–70 °C (0.55 mmHg)) followed by chromatography (EtOAc) gave 62 mg of almost pure **3b** as a light yellow liquid. Bp: 250 °C. R_f = 0.23 (EtOAc) UV, I_2 active. ^{1}H NMR (200 MHz): 7.17 (d, J = 7, 1 H, H-4), 6.47 (d, J = 7, 1 H, H-5), 4.55 (br s, 2 H, NH_2), 2.63 (q, J = 7, 2 H, CH_2), 2.07 (s, 3 H, Me at C-3), 1.25 (t, J = 7, 3 H, ethyl CH_3). ^{13}C NMR: 158.55 and 155.55 (C-2, C-6), 137.25 (C-4), 112.40 (C-3), 110.96 (C-5), 29.68 (CH_2), 15.67 (Me),

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13.04 (Me). MS (EI): 136 (96) M^+, 135 (100), 121 (31), 108 (17), 94 (11), 80 (7). Exact mass: found 136.0999, calculated for $C_8H_{12}N_2$ 136.1000.

Comparing the physical properties of **3b** with an aminoethylmethylpyridine of unknown substitution pattern described in ref 34, it is concluded that these compounds are not identical.

2-Amino-3,5,6-trimethylpyridine (3c).[35] Prepared from 10.5 g (0.11 mol) of Ac_2O, 12.8 g (0.079 mol) of 2,4-dimethyl-5-oximinohexanenitrile (**1c**), and 10.0 g (0.13 mol) of AcCl. After alkaline hydrolysis (1 h), the mixture was cooled to rt and worked up (4 × 30 mL). A liquid was obtained containing 6.77 g (63%) of **3c**. Vacuum distillation (110 °C (14.5 mmHg)) gave 4.7 g (44%) of almost pure **3c** as off-white crystals. Mp: 99–102 °C (lit.[35] mp 105–105.5 °C). ^1H NMR (200 MHz): 6.98 (s, 1 H, H-4), 4.45 (s, 2 H, NH_2), 2.30 (s, 3 H, Me at C-6), 2.08 (s, 3 H, Me), 2.04 (s, 3 H, Me). ^{13}C NMR: 154.66 and 151.80 (C-2, C-6), 139.78 (C-4), 120.76 (C-5), 113.54 (C-3), 21.47 (Me), 17.81 (Me), 16.46 (Me). MS (EI): 136 (100) M^+, 135 (42), 121 (21), 108 (15), 94 (16), 80 (6). Exact mass: found 136.0996, calculated for $C_8H_{12}N_2$ 136.1000.

2-(*N*-Acetylamino)-5,6,7,8-tetrahydroquinoline (2d). Prepared from 5.7 g (0.056 mol) of Ac_2O, 7.9 g of 2-(2-cyanoethyl)-cyclohexanone oxime (**1d**) (71 wt % pure; contained 0.034 mol of **1d**), and 5.7 g (0.073 mol) of AcCl (in 8 min at such a rate that the temperature remained below 15 °C); 50 mL of water and 4 × 25 mL of CH_2Cl_2. A black tar was obtained containing 2.3 g (36%) of **2d**. The tar was boiled with *n*-hexane (50 mL) and the *n*-hexane layer decanted. This procedure was repeated three times. The yellow residue, obtained after concentration in vacuo of the combined *n*-hexane layers, was chromatographed (EtOAc) to furnish **2d** as light yellow crystals (GC purity 88%). R_f = 0.36 (EtOAc) UV, I_2 active. ^1H NMR (60 MHz): 8.55 (br s, 1 H, NH), 7.75 (d, J = 7, 1 H, H-4), 7.2 (d, J = 7, 1 H, H-3), 2.8–2.5 (m, 4 H, CH_2 at C-5, C-8), 2.1 (s, 3 H, Me), 2.0–1.6 (m, 4 H, CH_2 at C-6, C-7).

2-Amino-5,6,7,8-tetrahydroquinoline (3d). Prepared from 9.0 g (0.09 mol) of Ac_2O, 13.8 g of 2-(2-cyanoethyl)cyclohexanone oxime (**1d**) (71 wt % pure; contained 0.06 mol of oxime), and 9.5 g (0.12 mol) of AcCl (20 min). Refluxed for 4.5 h and then cooled to rt. NaOH (12.5 g, 0.3 mol) in 25 mL of water was added and the mixture refluxed for 2 h. After cooling to rt workup gave a black tar containing 3.82 g (43%) of **3d** and 0.8 g (7%) of *N*-acetyl derivative **2d**. Chromatography (EtOAc) of 200 mg of crude **3d** furnished 72 mg of pure **3d** as white crystals (needles). R_f = 0.17 (EtOAc) UV, I_2 active. Mp: 87–90 °C (CH_2Cl_2). ^1H NMR (200 MHz) 7.10 (d, J = 7, 1 H, H-4), 6.28 (d, J = 7, 1 H, H-3), 4.5 (br s, 2 H, NH_2), 2.70 (t, J = 4, 2 H, CH_2 at C-5 or C-8), 2.58 (t, J = 4, 2 H, CH_2 at C-5 or C-8), 1.75 (m, 4 H, CH_2's at C-6, C-7). ^{13}C NMR: 156.15 and 154.72 (C-2, C-8a), 138.95 (C-4), 121.66 (C-4a), 106.36 (C-3), 32.12 and 27.82 (C-5, C-8), 23.18 and 23.08 (C-6, C-7). MS (EI): 148 (100) M^+, 147 (48), 132 (6), 120 (55), 119 (12), 105 (4), 93 (5), 80 (6). Exact mass: found 148.0997, calculated for $C_9H_{12}N_2$ 148.1000.

2-(*N*-Acetylamino)cyclopenteno[*e*]pyridine (2e). Ac_2O (25.0 g, 0.25 mol) was added to 8.0 g (0.05 mol) of 2-(2-cyanoethyl)-cyclopentanone oxime (**1e**). HCl gas was passed through the mixture for 5 h at 18–22 °C, followed by stirring for 16 h at rt. After 75 mL of water was added, workup (4 × 35 mL) furnished a black tar containing 0.44 g (5%) of **2e**. This tar was boiled with *n*-hexane (10 mL) and the *n*-hexane layer decanted. This procedure was repeated three times. The yellow residue, obtained after concentration in vacuo of the combined *n*-hexane layers, was chromatographed (EtOAc) to afford pure **2e** as off-white crystals. Mp: 117.5–118 °C. R_f = 0.34 (EtOAc) UV, I_2 active. ^1H NMR (200 MHz): 9.48 (br s, 1 H, NH), 7.96 (d, J = 7, 1 H, H-4), 7.51 (d, J = 7, 1 H, H-3), 2.90 (m, 4 H, 2 CH_2), 2.17 (s, 3 H, Me), 2.12 (quintet, J = 7, 2 H, CH_2). ^{13}C NMR: 168.81 and 163.29 (C-2, C-6), 150.21 (C=O), 134.21 (C-4), 132.72 (C-5), 111.73 (C-3), 33.85 (CH_2), 30.08 (CH_2), 24.34 (MeC=O), 23.13 (CH_2). MS (EI): 176 (29) M^+, 161 (3), 134 (100), 133 (84), 116 (6), 106 (6), 79 (5), 78 (5). Exact mass: found 176.0942, calculated for $C_{10}H_{12}N_2O$ 176.0950.

2-Aminocyclopenteno[*e*]pyridine (3e). Crude **2e**, obtained from an identical experiment as described above, was refluxed for 30 min with 10 mL of 50 wt % aqueous NaOH. The mixture was extracted with CH_2Cl_2 (2 × 10 mL) and $CHCl_3$ (2 × 10 mL). The combined organic layers were washed with 10 mL of saturated aqueous NaCl and dried ($MgSO_4$). Concentration in vacuo afforded a black tar containing 0.27 g (4%) of **3e**. Chromatography (EtOAc) of 218 mg of crude **3e** gave 102 mg of almost pure **3e** as yellow crystals. R_f = 0.15 (EtOAc) UV, I_2 active. ^1H NMR (200 MHz): 7.25 (d, J = 7, 1 H, H-4), 6.27 (d, J = 7, 1 H, H-3), 4.4 (br s, 2 H, NH_2), 2.84 (t, J = 6, 2 H, CH_2), 2.80 (t, J = 6, 2 H, CH_2), 2.06 (quintet, J = 6, 2 H, CH_2). ^{13}C NMR: 163.45 and 157.59 (C-2, C-6), 134.10 (C-4), 126.26 (C-5), 105.77 (C-3), 34.17, 29.93, and 23.15 (3 × CH_2). MS (EI): 134 (82) M^+, 133 (100), 116 (10), 106 (8), 93 (4), 79 (5), 66 (9). Exact mass: found 134.0840, calculated for $C_8H_{10}N_2$ 134.0844.

5-(2-Cyanoethyl)-2,4-dimethyloxazole (9). To a solution of 11.0 g (0.087 mol) of 5-oximinohexanenitrile (**1a**) in 6.6 g (0.083 mol) of pyridine, cooled to 0 °C, was added 27.0 g (0.26 mol) of Ac_2O at such a rate as to maintain the temperature below 25 °C. To the resulting yellow solution, cooled to 0 °C, was added a mixture of 21.6 g (0.21 mol) of Ac_2O and 7.9 g (0.10 mol) of AcCl at a temperature below 5 °C. The orange mixture was heated for 9 h at 110 °C. After cooling to rt 85 mL of water was added, and the whole was heated for 1 h at 110 °C. After cooling to rt, 35 mL of water was added. Workup (2 × 35 mL + 4 × 15 mL) gave 9.5 g of a brown oil (mixture of compounds according to GC and TLC); 4.3 g of this oil was chromatographed (successively 500 mL of EtOAc/*n*-hexane, 1:3, 250 mL, 1:2, 300 mL, 1:1, 500 mL, 2:1) to furnish 0.8 g of **9** as a slightly yellow liquid, corresponding to a total yield of 1.77 g (14%). R_f = 0.14 (EtOAc/*n*-hexane, 1:1) UV, I_2 active. ^1H NMR (200 MHz): 2.94 (t, J = 7, 2 H, CH_2), 2.65 (t, J = 7, 2 H, CH_2), 2.38 (s, 3 H, Me at C-2), 2.10 (s, 3 H, Me at C-4). ^{13}C NMR: 159.98 (C-2), 142.44 (C-5), 132.31 (C-4), 118.59 (CN), 21.09 (CH_3), 16.74 (CH_3), 13.82 (CH_2), 11.07 (CH_2). MS (EI): 150 (18) M^+, 110 (100), 68 (8), 54 (3), 42 (16). Exact mass: found 150.0795, calculated for $C_8H_{10}N_2O$ 150.0793.

4-(2-Cyanoethyl)-3,5-dimethylisoxazole (14). Prepared from 5.5 g (0.054 mol) of Ac_2O, 8.6 g (0.043 mol) of 4-acetyl-5-oximinohexanenitrile (**1h**), and 6.0 g (0.076 mol) of AcCl (10 min at 5 °C). After cooling to rt, 8.0 g (0.2 mol) of NaOH in 20 mL of water was added (temperature rose to 116 °C) and the mixture stirred for 15 min. After cooling to rt, workup (4 × 25 mL) gave crude **14**. Chromatography (EtOAc/*n*-hexane, 2:1) afforded 0.70 g (11%) of pure **14** as off-white crystals. Mp: 51–54 °C (EtOAc). R_f = 0.52 (EtOAc) UV, I_2 active. ^1H NMR (200 MHz): 2.70 (t, J = 6, 2 H, CH_2), 2.52 (t, J = 6, 2 H, CH_2), 2.38 (s, 3 H, Me), 2.25 (s, 3 H, Me). ^{13}C NMR: 166.36 (C-5), 159.03 (C-3), 118.76 (CN), 110.45 (C-4), 18.57 (CH_3), 18.03 (CH_3), 11.04 (CH_2), 10.05 (CH_2). MS (EI): 150 (29) M^+, 110 (98), 68 (100), 66 (7), 53 (5), 43 (46), 42 (14). Exact mass: found 150.0786, calculated for $C_8H_{10}N_2O$ 150.0793.

Supplementary Material Available: ^1H- and ^{13}C-NMR spectra of **2e**, **3b–e**, **9**, and **14** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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