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The Application of Vinylogous Iminium Salts and Related Synthons to the Preparation of Trisubstituted Pyridines

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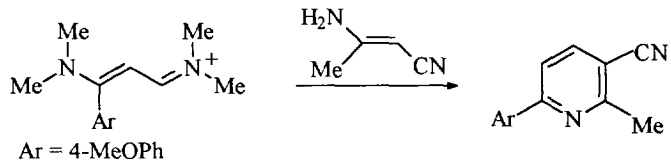
Abstract: The reaction of unsymmetrical vinylogous iminum salts and related analogs with β-aminocrotononitrile to yield 2,3,6-trisubstituted pyridines with regioselective control is described.

In our quest to utilize vinylogous iminium salts as three-carbon synthons in the formation of heterocyclic compounds, we have recently directed our attention to the formation of pyridine derivatives. Recent papers on the synthesis of streptonigrin[1] have shown the need to be able to synthesize highly substituted pyridine rings in a regiocontrolled manner. A recent paper by Robinson et al. has addressed this issue by reacting α,β-unsaturated carbonyl compounds with enamino nitriles.[2] Previous recent work done in our research group using vinylogous iminium salts has concentrated on the formation of five-membered rings such as pyrroles.[3] Amino acid esters provide the other two atoms to form the ring. In synthesizing a six-membered ring, it is necessary for the other starting material to provide a three-atom link. A paper by Jutz et al.[4] has reported the synthesis of 2,3,5-trisubstituted pyridines using the reaction of β-aminocrotononitrile with 2-substituted symmetrical vinamidinium salts under basic conditions.

We have concentrated our efforts in this area by addressing the question of regiochemistry with the unsymmetrical vinamidinium salts. It is possible to form two different pyridines in the reaction between β-aminocrotononitrile and 1-substituted vinamidinium salts (**1**). From previous work, nucleophilic attack on the unsymmetrical vinamidinium salts have been shown to be under steric control.[3] If initial attack by the nitrogen of the enamine occurs at the least sterically hindered carbon of the vinamidinium salt, the result will be a 2,3,4-trisubstituted pyridine. If initial attack by the carbon of the enamine occurs, the result will be a 2,3,6-trisubstituted pyridine. A variety of conditions were used to determine which set of conditions was best to form pyridines (Table 1).

Scheme 1



1a **2a**

Table 1

Solvent	Equiv. of β-ACN[a]	Base (Equiv.)	Conditions	Product (% Yield)[b]
CH_3CN	1.2	Pyridine (1.2)	15 hr rt, 5 hr 50 °C, 8 hr reflux	NR
Pyridine	1.2	None	15 hr rt, 5 hr 50 °C, 8 hr reflux	NR
EtOH	1.2	NaOEt (3.0)	15 hr reflux	No Pyridine[c]
DMF	1.2	None	2 hr rt, 15 hr reflux	NR
DMF	1.5	Na_2CO_3 (1.5)	15 hr reflux	NR
DMF	3.2	NaH (3.2)	4 hr rt, 12 hr reflux	**4** (9)
DMF	3.2	NaH (1.5)	30 min rt, 4 hr reflux	**4** (75)
DMF	3.2	NaH (2.5)	15 hr rt, 4 hr 100 °C	**4** (80)

[a]Equivalents of β-aminocrotononitrile; [b]NR is no reaction; products characterized by tlc and proton NMR; [c]No pyridine was produced.

The reaction proved to be very sensitive to solvent, time, temperature, and stoichiometry. Dimethylformamide was the only solvent which produced a pyridine product using sodium hydride as the base. The best set of conditions used 3.2 equivalents of β-aminocrotonitrile with 2.5 equivalents of sodium hydride in dimethylformamide. This reaction mixture was stirred overnight at room temperature and heated at 100 °C for four hours. A series of vinamidinium salts (**1**) were reacted with β-aminocrotonitrile under these optimized set of conditions with the results shown in Table 2. In all cases, only one pyridine product was observed and in very good isolated yields.

Since there could be two possible pyridine products, the question of regiochemistry needed to be addressed. For pyridine (**2e**), where the aryl group is phenyl, both possible isomers are known. Table 3 shows the comparison of melting points and coupling constants of the pyridine (**2e**), prepared from the vinamidinium salt (**1e**), with the literature values of the known pyridines.[5,6] Pyridine (**2e**) has a melting point of 139-140 °C which is consistent with the 6-substituted pyridine (127-128 °C). The melting point of the 4-substituted pyridine is only 98.5-99.5 °C. The coupling constant between the pyridine hydrogens of pyridine (**2e**) is 8.2 Hz which is also consistent with the 6-substituted pyridine (8.5 Hz). The 4-substituted pyridine has a coupling constant of 5.2 Hz. All of the analogous pyridines (**2**) gave similar proton NMR coupling patterns, so by these comparisons we were able to determine the structure of pyridines (**2**) as 2,3,6-trisubstituted pyridines.

Scheme 2

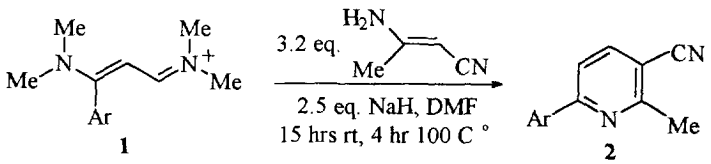
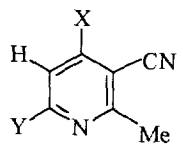


Table 2

Compound	Ar	% Yield (Isolated)
a	4-MeOPh	80
b	4-MePh	74
c	4-ClPh	58
d	4-BrPh	49
e	Ph	67
f	4-NO_2Ph	52
g	4-FPh	67
h	3,4-$(MeO)_2$Ph	65
i	3-NO_2Ph	55

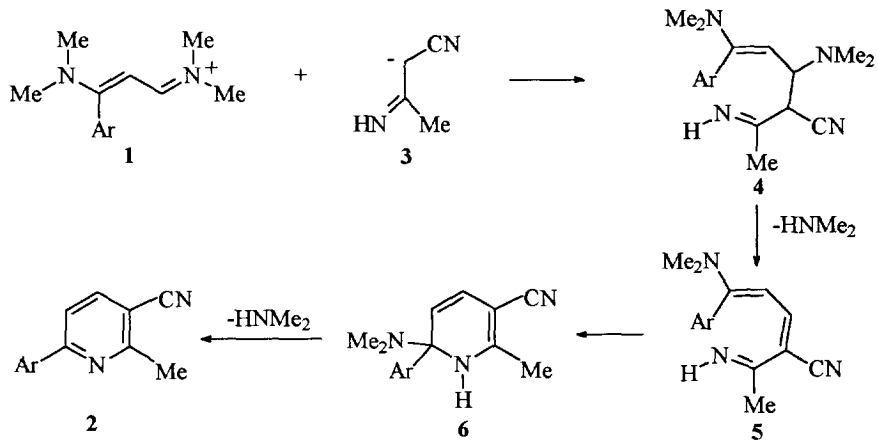
Table 3



Compound	X	Y	MP (°C)	J value (Hz)
Lit. value[5]	H	Ph	127-128	8.5 (H_X-H)
Lit. value[6]	Ph	H	98.5-99.5	5.2 (H_Y-H)
2e	---	---	139-140	8.2

A proposed mechanism for this reaction is shown in Scheme 3. Since the reaction is performed under basic conditions, the aminocrotononitrile should exist as the anion (**3**). Nucleophilic attack by the carbanion should be under steric control and attack would occur at the least sterically hindered carbon of the vinamidinium salt (**1**) to form intermediate (**4**). Loss of dimethylamine can occur by deprotonation of the acidic hydrogen α to the cyano group followed by elimination of dimethylamide to form the azatriene intermediate (**5**). Subsequent ring closure will yield dihydropyridine (**6**) followed by loss of another equivalent of dimethylamine to give pyridine (**2**). Attempts to observe or isolate the proposed intermediates were not successful.

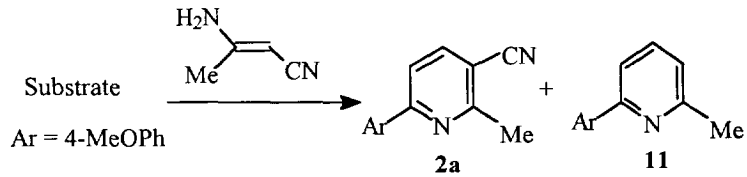
Scheme 3



Since we were able to synthesize 2,3,6-trisubstituted pyridines in very good yields, we extended our investigation to include other related three-carbon synthons in determining if it was possible to synthesize the 2,3,4-trisubstituted pyridine isomer. The synthons that were chosen included vinylogous amide (**7**), chloropropeniminium salt (**8**), vinamidinium salt (**1a**), β-chloroenal (**9**), and vinylogous formamide (**10**). The synthons were allowed to react with aminocrotononitrile under acidic (acetic acid reflux), neutral (DMF reflux), and basic (NaH, DMF reflux) conditions (Scheme 4). The results are shown in Table 4.

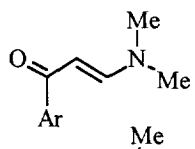
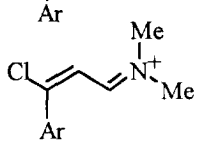
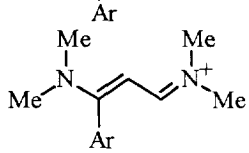
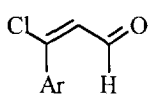
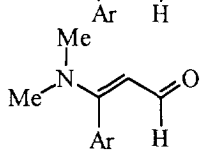
This study brought up several interesting points. Not surprisingly, the best condition for making 2,3,6-trisubstituted pyridines was the reaction under basic conditions with the unsymmetrical vinamidinium salt (**1a**). No other pyridine-like product was detected by proton NMR. However, the reactions under basic conditions only produced pyridines with vinylogous iminium salts. Neutral conditions only produced pyridines with the β-chloroenal (**9**). The reactions with the most interesting results were performed under acidic conditions. Another pyridine product was obtained which, initially, we assumed was the 2,3,4-isomer. However, when the product was isolated, analysis of the proton NMR, MS, and IR indicated that a hydrogen had replaced the cyano group of pyridine (**2**). The coupling constants between the three hydrogens of the pyridine ring were 7.7 Hz indicating that the product was the 2,6-disubstituted pyridine (**11**). If the aryl group was at the 4-position, the coupling constants would not be the same, and they would be much smaller.

Scheme 4



2a **11**

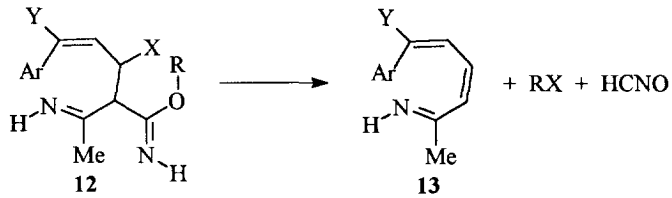
Table 4

Substrate	Compound	Conditions	% Yield (2a:11)
	**7**	Acid	79 (3:1)
		Neutral	---
		Base	---
	**8**	Acid	23 (3:1)
		Neutral	---
		Base	11 (>95:1)
	**1**	Acid	---
		Neutral	---
		Base	47 (>95:1)
	**9**	Acid	29 (2:1)
		Neutral	23 (>95:1)
		Base	---
	**10**	Acid	50 (1:2)
		Neutral	---
		Base	---

crude products were characterized by tlc and proton NMR; ratios were determined by proton NMR.

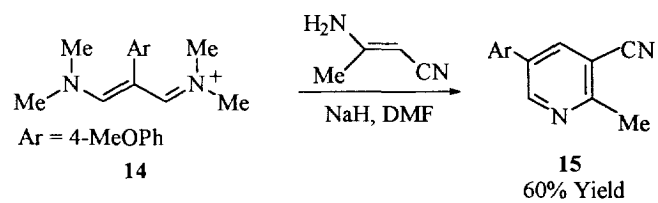
When the trisubstituted pyridine **(2a)** was subjected to the reaction conditions (acetic acid reflux), no disubstituted pyridine **(11)** was observed. This result would be consistent with the cyano group being lost in one of the intermediate steps. The loss of the first equivalent of dimethylamine may be retarded under acidic conditions allowing other reactions to compete. The cyano group can be protonated which would increase the probability of nucleophilic attack by water or acetic acid. Subsequent loss of a proton would give intermediate **(12)** which could eliminate both potential leaving groups, X and the modified cyano group, by a six-centered transition state forming azahexatriene **(13)** and isocyanic acid (Scheme 5). No attempts were made at isolating intermediate **(12)** or the isocyanic acid.

Scheme5



A reaction was performed where the unsymmetrical vinamidinium salt was replaced with the symmetrical vinamidinium salt (**14**) under the best conditions observed (Scheme 6). A 60% isolated yield of pyridine (**15**) was obtained which demonstrated that these conditions can also be used with the symmetrical vinamidinium salts to obtain very good yields of 2,3,5-trisubstituted pyridines.

Scheme 6



In summary, we have synthesized a series of 2,3,6-trisubstituted pyridines in a clean, efficient, and regioselective manner. The best conditions involve the reaction of β-aminocrotononitrile with unsymmetrical vinamidinium salts and sodium hydride in dimethylformamide. These conditions can also be applied to the reactions involving symmetrical vinamidinium salts to form 2,3,5-trisubstituted pyridines. Additional insight has been gained into which three-carbon synthon gave the best results under a variety of reaction conditions. This study further clarifies how vinylogous iminium salts can effectively be used in the construction of various heterocyclic systems. Work is now in progress to synthesize tetrasubstituted pyridines which will be closely related to known biologically active pyridines such as streptonigrin.

Experimental

The following procedures are typical of the experimental conditions used for the preparation of trisubstituted pyridines. The vinylogous iminium salts and related synthons were prepared by standard methods.[7,8] All melting points and boiling points are uncorrected and all purified compounds gave a single spot upon tlc analysis on silica gel 7GF using an ethyl acetate/hexane mixture as eluent.

3-Cyano-6-(4-methoxyphenyl)-2-methylpyridine (2a): A 100 mL three-neck round-bottom flask was equipped with a stir bar, condenser and placed under a nitrogen atmosphere. Into the

flask was placed 0.300 g (7.5 mmoles) of a 60% mineral oil dispersion of sodium hydride. The sodium hydride dispersion was washed twice with dry hexane, and the hexane was removed via cannula. Part of a 40 mL portion of dry DMF was added to the sodium hydride, and 0.79 g (9.6 mmoles) of 3-aminocrotononitrile were subsequently added. This solution was allowed to stir for fifteen minutes. Finally, 1.00 g (2.8 mmoles) of vinamidinium salt **(1a)** and the remaining DMF were added, and the reaction was allowed to proceed at room temperature overnight followed by heating at 100 °C for four hours. The mixture was cooled to room temperature and the solvent was removed in vacuo. The residue was partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated. The crude product was passed through a short pack of silica gel and purified by radial chromatography using a gradient elution of hexane: ethyl acetate. A white solid was obtained in 80% yield (0.54 g) and exhibited the following properties: mp 133-135 °C, (Lit. value[9] 94 °C); ^{1}H NMR (DMSO-d_6) δ 2.73 (s, 3H), 3.85 (s, 3H), 7.10 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.4 Hz, 1H), 8.15 (d, J = 8.8 Hz, 2H) and 8.25 (d, J = 8.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 25.3, 57.1, 107.1, 116.1, 118.3, 119.3, 130.6, 131.1, 143.0, 159.8, 162.3 and 163.0; FTIR (KBr pellet) 2221, 1578, 825 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_2O$ 224.0954 found 224.0952.

3-Cyano-6-(4-methylphenyl)-2-methylpyridine (2b): This compound was prepared in 74% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the following properties: mp 151-153 °C; ^{1}H NMR (DMSO-d_6) δ 2.40 (s, 3H), 2.75 (s, 3H), 7.36 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.3 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H) and 8.29 (d, J = 8.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 22.7, 25.3, 107.8, 118.9, 119.3, 128.9, 131.4, 136.0, 142.2, 143.3, 160.1 and 162.5; FTIR (KBr pellet) 2220, 1583, 818 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_2$ 208.1000 found 208.1000.

3-Cyano-6-(4-chlorophenyl)-2-methylpyridine (2c): This compound was prepared in 58% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the following properties: mp 140-141 °C (Lit. value[10] 121-123°C); ^{1}H NMR (DMSO-d_6) δ 2.76 (s, 3H), 7.62 (d, J = 8.6 Hz, 2H), 8.06 (d, J = 8.1 Hz, 1H), 8.22 (d, J = 8.6 Hz, 2H) and 8.35 (d, J = 8.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 25.3, 108.6, 119.0, 119.3, 130.7, 137.1, 137.5, 143.5, 158.7 and 162.5; FTIR (KBr pellet) 2226, 1586, 822 cm^{-1}; HRMS calcd for $C_{13}H_9N_2Cl$ 228.0454 found 228.0452.

3-Cyano-6-(4-bromophenyl)-2-methylpyridine (2d): This compound was prepared in 49% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the following properties: mp 146-148 °C; ^{1}H NMR (DMSO-d_6) δ 2.75 (s, 3H), 7.75 (d, J = 8.6 Hz, 2H), 8.05 (d, J = 8.3 Hz, 1H), 8.13 (d, J = 8.6 Hz, 2H) and 8.34 (d, J = 8.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 25.3, 108.6, 119.0, 119.3, 126.0, 130.9, 133.7, 137.8, 143.5, 158.8 and 162.6; FTIR (KBr pellet) 2225, 1584, 820 cm^{-1}; HRMS calcd for $C_{13}H_9N_2Br$ 271.9949 found 271.9942.

3-Cyano-6-phenyl-2-methylpyridine (2e): This compound was prepared in 67% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the following properties: mp 139-140 °C; ^{1}H NMR (DMSO-d_6) δ 2.76 (s, 3H), 7.53-7.61 (m, 3H), 8.04 (d, J = 8.2 Hz, 1H), 8.15-8.21 (m, 2H) and 8.32 (d, J = 8.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 25.3, 108.3, 119.2, 119.3, 129.0, 130.7, 132.2, 138.7, 143.4, 160.1 and 162.5; FTIR (KBr pellet) 2223, 1578, 784, 742 cm^{-1}; HRMS calcd for $C_{13}H_{10}N_2$ 194.0842 found 194.0847.

3-Cyano-6-(4-nitrophenyl)-2-methylpyridine (2f): This compound was prepared in 52% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the

following properties: mp 175-176 °C; ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 3H), 8.20 (d, J = 8.1 Hz, 1H), 8.36-8.49 (m, 5H); ^{13}C NMR (DMSO-d_6) δ 25.3, 109.8, 118.8, 120.6, 125.8, 130.2, 143.9, 144.5, 150.1, 157.6 and 162.8; FTIR (KBr pellet) 2224, 1518, 1343 cm^{-1}; HRMS calcd for $C_{13}H_9N_3O_2$ 239.0695 found 239.0698.

3-Cyano-6-(4-fluorophenyl)-2-methylpyridine (2g): This compound was prepared in 67% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the following properties: mp 128-130 °C; ^{1}H NMR (DMSO-d_6) δ 2.76 (s, 3H), 7.39 (t, J = 8.9 Hz, 2H), 8.04 (d, J = 8.3 Hz, 1H), 8.26 (d of d, J = 8.9 Hz, J = 5.5 Hz, 2H) and 8.33 (d, J = 8.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 25.3, 108.2, 117.6 (d, J = 21.8 Hz, 2C), 119.1, 131.4 (d, J = 8.8 Hz, 2C), 135.2, 135.3, 143.5, 159.0, 162.5 and 165.4 (d, J = 247 Hz, 1C); FTIR (KBr pellet) 2222, 1584, 824 cm^{-1}; HRMS calcd for $C_{13}H_9N_2F$ 212.0748 found 212.0743.

3-Cyano-6-(3,4-dimethoxyphenyl)-2-methylpyridine (2h): This compound was prepared in 65% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the following properties: mp 106-107 °C; ^{1}H NMR (DMSO-d_6) δ 2.74 (s, 3H), 3.85 (2, 3H), 3.87 (s, 3H), 7.11 (d, J = 8.3 Hz, 1H), 7.76-7.82 (m, 2H), 8.00 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 25.4, 57.4, 107.2, 112.0, 113.4, 118.6, 119.4, 122.3, 131.2, 143.0, 150.7, 152.8, 159.9 and 162.3; FTIR (KBr pellet) 2219, 1582 cm^{-1}; HRMS calcd for $C_{15}H_{14}N_2O_2$ 254.1052 found 254.1057.

3-Cyano-6-(3-nitrophenyl)-2-methylpyridine (2i): This compound was prepared in 55% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the following properties: mp 145-147 °C; ^{1}H NMR (DMSO-d_6) δ 2.79 (s, 3H), 7.85 (t, J = 8.1 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.42 (d, J = 8.1 Hz, 1H), 8.61 (d, J = 8.1 Hz, 1H), 8.95 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 25.3, 109.5, 118.8, 119.9, 123.3, 126.6, 132.4, 135.1, 140.2, 143.9, 150.1, 157.4 and 162.7; FTIR (KBr pellet) 2225, 1585, 1529, 1348, 731 cm^{-1}; HRMS calcd for $C_{13}H_9N_3O_2$ 239.0693 found 239.0695.

3-Cyano-5-(4-methoxyphenyl)-2-methylpyridine (15): This compound was prepared in 60% yield in a manner similar to the preparation of pyridine **(2a)**. The purified product exhibited the following properties: mp 116-118 °C; ^{1}H NMR (DMSO-d_6) δ 2.70 (s, 3H), 3.82 (s, 3H), 7.07 (d, J = 8.9 Hz, 2H), 7.76 (d, J = 8.9 Hz, 2H), 8.52 (d, J = 2.4 Hz, 1H), 9.02 (d, J = 2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 24.6, 57.1, 110.1, 116.4, 119.0, 129.0, 130.0, 134.5, 139.2, 151.7, 160.3 and 161.6; FTIR (KBr pellet) 2228, 1463, 832 cm^{-1}; HRMS calcd for $C_{14}H_{12}N_2O$ 224.0950 found 224.0956.

Reactions performed under basic conditions: A 100 mL three-neck round-bottom flask was equipped with a stir bar, condenser and placed under a nitrogen atmosphere. Into the flask was placed 0.117 g (2.9 mmoles) of a 60% mineral oil dispersion of sodium hydride. The sodium hydride dispersion was washed twice with dry hexane, and the hexane was removed via cannula. Part of a 30 mL portion of dry DMF was added to the sodium hydride, and 0.185 g (2.3 mmoles) of 3-aminocrotononitrile were subsequently added. This solution was allowed to stir for fifteen minutes. Finally, 0.500 g (1.5 mmoles) of chloropropeniminium salt **(8)** and the remaining DMF were added, and the reaction was allowed to proceed at 100 °C overnight. The mixture was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was partitioned several times between chloroform and water. The combined chloroform extracts were dried and concentrated leaving 0.04 g (11% yield) of **(2a)**. This material was characterized by ^{1}H

NMR and tlc and compared with an authentic sample.

Reactions performed under neutral conditions: Into a 100 mL one-neck round-bottom flask were placed 0.300 g (1.5 mmoles) of β-chloroenal **(9)**, 0.18 g (2.2 mmoles) of 3-aminocrotononitrile, 30 mL of DMF and a stir bar. The flask was equipped with a condenser and the reaction was allowed to proceed overnight at 100 °C. The flask was allowed to cool to room temperature and the solvent was removed in vacuo. The residue was partitioned several times between water and chloroform. The combined chloroform extracts were dried and concentrated leaving 0.08 g (23% yield) of **(2a)**. This material was characterized by ^{1}H NMR and tlc and compared with an authentic sample.

Reactions performed under acidic conditions: Into a 100 mL one-neck round-bottom flask were placed 0.30 g (1.5 mmoles) of vinylogous formamide **(10)**, 0.18 g of 3-aminocrotononitrile, 30 mL of acetic acid and a stir bar. The flask was equipped with a condenser and the reaction was heated at reflux overnight. The reaction mixture was neutralized with saturated sodium bicarbonate and extracted several times with chloroform. The combined chloroform extracts were dried and concentrated. The crude ^{1}H NMR and tlc indicated two products. A 2:1 ratio of the two products were removed together in 50% yield by radial chromatography using 80:20 hexane:ethyl acetate as eluent. The minor product was determined to be trisubstituted pyridine **(2a)** by comparison of ^{1}H NMR and tlc with authentic samples. An analytical pure sample of the major product, disubstituted pyridine **(11)**, was obtained by radial chromatography and exhibited the following properties: mp 51-53 °C; ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 3.86 (s, 3H), 6.99 (d, J = 8.9 Hz, 2H), 7.04 (d, J = 7.7 Hz, 1H), 7.46 (d, J = 7.7 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H) and 7.94 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 26.8, 57.4, 116.0, 118.9, 122.9, 130.2, 134.4, 138.8, 158.6, 160.2 and 162.2; FTIR (KBr pellet) 1456, 1251, 791 cm^{-1}; HRMS calcd for $C_{13}H_{13}NO$ 199.0997 found 199.1002.

Reaction of pyridine (2a) in acetic acid: A dry 100 mL three-neck round-bottom flask was equipped with a condenser and stir bar. Into the flask was placed 0.5 g (2.2 mmol) of pyridine **(2a)** and 20 mL of acetic acid. The solution was heated at reflux for 15 hours. The solvent was removed in vacuo leaving a quantitative amount of recovered starting material. The product was characterized by ^{1}H NMR and tlc and compared with an authentic sample.

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References

1. a) D. Boger and J. Panek, *J. Am. Chem. Soc.*, 1985, **107**, 5745; b) S. Weinreb, F. Basha, S. Hibino, N. Khatri, D. Kim, W. Pye, T. Wu, *J. Am. Chem. Soc.*, 1982, **104**, 536; c) A. Kende, D. Lorah, and R. Boatman, *J. Am. Chem. Soc.*, 1981, **103**, 1271.
2. J. Robinson, L. Brent, C. Chau, K. Floyd, S. Gillham, T. McMahan, D. Magda, T. Motycka, M. Pack, A. Roberts, L. Seally, S. Simpson, R. Smith,and K. Zalesny, *J. Org. Chem.*, 1992, **57**, 7352.
3. a) J. Gupton, D. Krolikowski, R. Yu, S. Riesinger, and J. Sikorski, *J. Org. Chem.*, 1990, **55**, 4735; b) J. Gupton, D. Krolikowski, R. Yu, P. Vu, J. Sikorski, M. Dahl, and C. Jones, *J. Org. Chem.*, 1992, **57**, 5480.
4. C. Jutz, H.-G. Lobering, and K.-H. Trinkl, *Synthesis*, **1977**, 326.
5. A. Padwa and P. Carlsen, *J. Org. Chem.*, 1978, **43**, 3757.
6. K. Shibata, K. Urano, andM. Matsui, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2199.
7. J. Liebscher and H. Hartman, *Synthesis*, **1979**, 241.
8. S. Petrich, Z. Qian, L. Santiago, J. Gupton, and J. Sikorski, *Tetrahedron*, manuscript submitted.
9. A. Gupta, H. Ila, and H. Junjappa, *Tetrahedron*, 1990, **46**, 3703.
10. R. Troschuetz and K.-H. Nietsch, *Chem.-Ztg.*, 1990, **114**, 321.

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