Pyridine Syntheses. II. Condensation Routes Toward Streptonigrin Ring C [1]

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Alternative complimentary syntheses of penta-substituted pyridine rings with full regiochemical control of substituents were studied as a method for the synthesis of Streptonigrin (**1**). Various α-substituted acetophenones **2** were reacted with enones **3** in acetic acid/ammonium acetate and air to afford penta-substituted pyridines **4**. α-Substituents that could provide a source of exocyclic nitrogen at position 3 of these Steptonigrin ring-C models proved to be the limiting factor. However, an inverse "3+2+1" cyclocondensation of α-cyanochalcone **5c** with 2-furyl ethyl ketone (**6b**) afforded the desired model 6-(2-furyl)-5-methyl-2,4-diphenyl-3-pyridinecarbonitrile (**4g**) in 75% yield.

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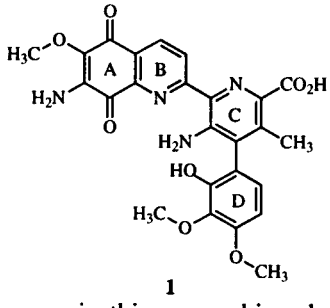
In this series we have sought methods to achieve penta-substituted pyridines with high yields and full regiochemical control of substituents. For example, the synthesis of the multisubstituted pyridine ring-C of Streptonigrin (**1**), [2] with five diverse substituents, has presented quite a synthetic challenge [3,4]. The construction of a pyridine ring-C of **1** with appropriate groups was best accomplished by sequential inverse electron demand aza Diels-Alder reactions [3]. However, these two steps achieved only a 28% yield of the desired pyridine due to lack of regiochemical control.

Structure 1



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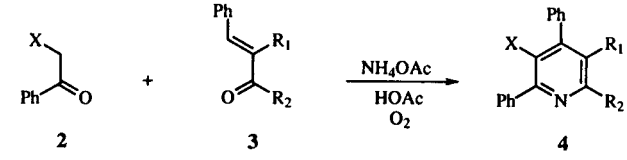
Our initial paper in this area achieved regiocontroled syntheseis of pyridines in good yields by a novel "3+3" pyridine synthesis which condensed enaminonitriles with α,β-unsaturated ketones [5]. However, the method was limited by not allowing a nitro or carboxyl group in an appropriate position for elaboration into an amino group as in **1**. Therefore, we have explored a "3+2+1" condensation route to pyridines which could allow such groups in the product.

Background and Synthetic Strategy.

The "3+2+1" cyclocondensation of α-substituted acetophenones **2** and variously substituted α,β-unsaturated ketones **3** [6] together with ammonium ion as the source of nitrogen affords pyridines **4** as models for Streptonigrin ring C (Equation 1). This classical method of pyridine synthesis has only been used in a few cases for penta-substituted pyridines [7]. However, in the typical reactions with less substituted examples, the dihydropyridines initially formed often underwent further reactions, including disproportionation, to a mixture of products. Subsequent oxidation of the isolated dihydropyridines with any of a variety of reagents, also gave pyridines **4** but with overall poor yield. Several recent reports show the successful use of air [1], oxygen [9a] and cupric acetate/oxygen [9b] to simultaneously oxidize dihydropyridine intermediates

Equation 1



2 **3** **4**

under acid or base conditions as they are formed during the reaction. Indeed, this is in contrast to this ammonium acetate/acetic acid method generally employed herein as reported by Weiss [10] who stated "bubbling air through the reaction mixture was without effect." Immediate conversion of incipient dihydropyridines to the aromatic moieties by either oxidative or eliminative means is a strategy that precludes any further reversibility of these intermediates and ensures higher yields of fewer and more stable products.

Phenyl groups in ketones **2** and enones **3** (Equation 1) are used in these model studies to temporarily avoid the complexity of the appropriate aromatic rings in an actual Streptonigrin synthetic sequence. This study simply seeks

an efficient method to incorporate the amino (X), methyl (R1), and carboxyl (R2) groups as well as the two aromatic moieties regiospecifically as shown in pyridine **4**.

Functional groups X, that either were a direct nitrogen attachment or groups that could function as a progenitor of the amino group ultimately required in **1** were studied. These include both the nitro and protected amino group as well as the acid derivatives, *i.e.*, nitrile and ester. The latter groups could undergo reactions to eventually give the amine.

Results and Discussion.

Reactions of various α-substituted acetophenones **2** with enones **3** according to Equation 1 were conducted as shown in Table 1. α-Nitroacetophenone (**2a**) is very activated which results in the retro Michael addition being favored over the forward Michael addition. Thus, 3-nitro-2,4,6-triphenylpyridine (**4a**) is only formed under dilute conditions using a very long reaction time. In contrast, the nitro group is eliminated and the undesired 2,4,6-triphenylpyridine (**4b**) [10] is formed almost exclusively in the absence of air. Such elimination provides an alternative to air oxidation as a means of gaining the fully aromatic pyridines **4** directly. This elimination of the nitro, like the earlier report with cyano, [5] may find use in syntheses of other pyridines. The lack of success in synthesizing the nitro pyridine **4a** led us to pursue alternative means of attaching a nitrogen.

If the nitro group is first reduced to amino and protected as the α-acetamidoacetophenone (**2b**), then cyclocondensation with chalcone **3a** to pyridine **4c** can be successful. Chalcone **3a** is an excellent Michael addition substrate but does not have the appropriate groups for elaboration as a Streptonigrin ring C model. On the other hand, when the enone substrate does have the appropriate groups as in **3b**, the reaction is more difficult. Consequently, reaction of the acetamido compound **2b** with **3b** fails.

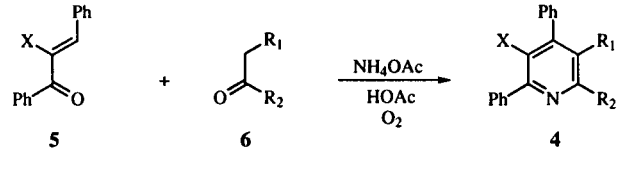
α-Cyanoacetophenone (**2c**) provides an eventual, albeit indirect, source of nitrogen attachment for the X-substituent in **4**. Fortuitously, **2c** reacts with chalcone **3a** affording 3-cyano-2,4,6-triphenylpyridine **4e** [16] in excellent yield. But reactions of **2c** with more appropriately substituted **3b** and **3d**, where R1 = Me and R2 = 2-furyl or methyl, resulted in reduced conversions to the desired products. These reactions were further complicated by two equivalents of α-cyanoacetophenone (**2c**) reacting with **3d** or **3b** to give the undesired 3,5-dicyano- 2,4,6-triphenylpyridine (**4h**) in significant and major yields, respectively. This problem was solved by using a reversed strategy of placing the group X, which will eventually provide the Streptonigrin amino substituent, on the 3-carbon component (enone) rather than on the 2-carbon component (ketone). Such a reversed strategy provides an alternative "3+2+1" cyclocondensation to pyridines **4**. Equation 2 shows this alternate "3+2+1" condensation of X-substituted enone **5** [17] and substituted ethanones **6** to afford pyridines **4**.

Table 1

"3 + 2 + 1" Cyclocondensations to Pyridines 4

2	X	+	3	R1	R2	→	4	X	R1	R2	% Yield
a	NO_2	+	a	H	Ph	→	a [11]	NO_2	H	Ph	45 [12]
a	NO_2	+	a	H	Ph	→	b [13]	H	H	Ph	88 [10]
b	NHAc [14]	+	a	H	Ph	→	c	NHAc	H	Ph	66
b	NHAc	+	b	Me	2-Furyl [15]	→	d	NHAc	Me	2-Furyl	0
c	CN	+	a	H	Ph	→	e	CN	H	Ph	95 [16]
c	CN	+	c	H	2-Furyl	→	f	CN	H	2-Furyl	57
c	CN	+	b	Me	2-Furyl	→	g	CN	Me	2-Furyl	33
							h	CN	CN	Ph	61 [16]
c	CN	+	c	Me	Me [17]	→	i	CN	Me	Me	57
							h	CN	CN	Ph	24
d	CO_2Et	+	a	H	Ph	→	j	CO_2Et	H	Ph	0

Equation 2



The nitro, acetamido, and carboethoxy functional groups, X that proved to be labile in the initial reactions (Equation 1) showed the same poor results in this reversed "3+2+1" condensation (Table 2). α-Acetamidochalcone **5b** and α-cyanochalcone **5c** were prepared by Knoevenagel condensations similar to the method of Pratt and Werble [18] in excellent yield. But again the nitrile group was most successful when reaction of **5c** gave a 75% yield of the desired Streptonigrin model **4g** with all five appropriate groups. This route is facilitated by the use of an excess of the small 2-furyl ethyl ketone (**6b**) [19] to push the equilibrium further toward products.

Table 2

Alternate "3 + 2 + 1" Cyclocondensations to Pyridines 4

5	X	+	6	R1	R2	→	4	X	R1	R2	% Yield
a	NO_2 [20]	+	b	Me	2-Furyl [19]	→	k	NO_2	Me	2-Furyl	0
b	NHAc	+	b	Me	2-Furyl	→	d	NHAc	Me	2-Furyl	0
c	CN [21]	+	a	H	2-Furyl	→	f	CN	H	2-Furyl	64
c	CN	+	b	Me	2-Furyl	→	g	CN	Me	2-Furyl	75
d	CO_2Et [22]	+	b	Me	2-Furyl	→	l	CO_2Et	Me	2-Furyl	5 [23]

Pyridine **4g**, having the desired substituents, X = cyano, R1 = methyl, and R2 = 2-furyl, is made with more than twice the yield given by the method of Equation 1. It is also purified with greater ease as excess **6** is a readily soluble oil and formation of the dicyano compound **4h** is minimized.

Pyridine **4g** serves as an important model for the elaboration of the cyano and furyl groups to amino and carboxyl groups of Streptonigrin ring C. The cyano group can be transformed into an amino group by reaction with hydroxide ion in *t*-butyl alcohol to afford an amide. Subsequent Hoffman degradation should afford the amine. The 2-furyl group serves as a protected carboxyl group. Conversion of the 2-furyl group of **4g** to the methyl ester **4m** was accomplished in 97% yield, demonstrating the effectiveness of this synthon.

Conclusion.

Results in Table 1 show that simultaneous air oxidation and concentrated conditions during these "3+2+1" cyclocondensations usually affords good conversion to aromatic pyridines **4** even though the penta-substituted examples are sterically difficult. The Michael addition of activated methylenes to these enones was found to be more reversible than desired; side reactions were often more prominent than the desired reaction. However, a reversed "3+2+1" condensation of the 2-cyano substituted enone **5c** gave a targeted model **4g** of Streptonigrin's ring C in 75% yield. Application of this synthetic method toward a total synthesis of Streptonigrin (**1**) is in progress.

EXPERIMENTAL

General.

Starting materials **2**, **3**, **5** and **6** were either commercially available, referenced in Table 1 and Table 2, or described in this section. Spectra (FTIR) for solids were obtained by diffuse reflectance in potassium bromide and are reported in cm^{-1}. Analyses by gc/ms (electron impact mode) employed a HP-1 (0.2 mm ID x 12.5 m, 0.33 μm film, β = 150) capillary column connected to a Hewlet Packard 5988A mass spectrometer. The nmr spectra, ^1H (250 MHz) and ^{13}C (65 MHz), were obtained on a Bruker Avance DPX-250 instrument and were run in deuteriochloroform with tetramethylsilane as an internal reference unless otherwise specified. Suitable data and spectra were obtained to match the literature data for all known compounds. When spectral data for known compounds was not available in the literature, it was included herein. Thin layer and preparative plate chromatography were performed with silica gel 60 (F254) plates. Melting points were taken in capillary tubes and are reported uncorrected in degrees C. Combustion analyses were conducted at Galbraith Labs, Inc. Only representative experimental procedures are included.

5,6-Dimethyl-2,4-diphenyl-3-pyridinecarbonitrile (**4i**).

Benzoylacetonitrile (**2c**, 2.90 g, 20.0 mmoles) and (*E*)-3-methyl-4-phenyl-3-buten-2-one (**3d**, 3.20 g, 20.0 mmoles) were dissolved in 12.0 ml of glacial acetic acid containing ammonium acetate (8.0 g, 104 mmoles). The mixture was refluxed under a slow stream of air for 2 hours. The reaction was neutralized using 10% sodium hydroxide and was extracted with methylene chloride. The methylene chloride layer was washed with water and dried with anhydrous sodium sulfate. Evaporation of the solvent gave 5.849 g of product mixture. Analysis by gc/ms showed the residue to contain **4i** (50%) and 2,4,6-triphenyl-3,5-pyridinedicarbonitrile (**4h**) (39%). Recrystallization from 95% ethanol initially gave 1.19 g of crude mixture of **4h** and some of the dihydro-**4h** compound. Concentration of the solution then afforded 1.45 g of **4i**, mp 168-173°. An analytical sample of **4i** was obtained by selective extraction of the crystalline mass with warm cyclohexane. Evaporation of cyclohexane at reduced pressure gave a residue which was recrystallized from 95% ethanol: mp 177.5-178°; ir: ν 2199 (CN); ms: m/z 284 (M^+, 43), 283 (100); ^1H nmr: δ 2.14 (s, 3H), 2.70 (s, 3H), 7.28-7.33 (m, 2H), 7.43-7.59 (m, 6H), 7.85-7.91 (m, 2H); ^{13}C nmr: δ 16.3, 24.2, 105.8, 117.4, 128.4, 128.5, 128.8, 129.0, 129.6, 136.4, 137.8, 153.8, 158.4, 161.5.

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.20; H, 5.85; N, 9.79.

3-Acetamido-2,4,6-triphenylpyridine (**4c**).

This compound had mp 264-265°, ir: ν 3245 (NH), 1651 (C=O); ms: m/z 364 (M^+, 45), 322 (81), 321 (100), 242 (13), 189 (14); ^1H nmr (dimethyl-d_6 sulfoxide): δ 1.65 (s, 3H), 7.35-7.6 (m, 11H), 7.65-7.75 (m, 2H), 7.9 (s, 1H), 8.1-8.2 (m, 2H), 9.6 (s, 1H); ^{13}C nmr (dimethyl-d_6 sulfoxide): δ 30.0, 127.6, 127.9, 134.5, 135.5, 135.6, 135.8, 135.9, 136.1, 136.3, 136.3, 136.8, 145.1, 145.9, 146.8, 157.6, 162.1, 165.0, 176.9.

Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 81.98; H, 5.50; N, 7.58.

2,4,6-Triphenyl-3-pyridinecarbonitrile (**4e**).

This compound had mp 221-222°; ir: ν 2220 (CN); ms: m/z 332 (M^+, 47), 331 (100), 253 (7), 165 (9); ^1H nmr (dimethyl-d_6 sulfoxide): δ 7.45-7.65 (m, 9H), 7.65-7.77 (m, 2H), 7.83-7.88 (d, 1H), 7.99-8.09 (m, 2H), 8.16-8.25 (m, 2H); ^{13}C nmr (dimethyl-d_6

sulfoxide): δ 104.4, 117.7, 118.7, 126.0, 127.6, 128.5, 128.8, 129.0, 129.4, 129.9, 130.1, 130.6, 136.9, 137.6, 138.1, 155.5, 159.2, 162.4.

6-(2-Furyl)-2,4-diphenyl-3-pyridinecarbonitrile (**4f**).

This compound had mp 247-248°; ir: ν 2220 (CN); ms: m/z 322 (M^+, 74), 321 (100), 293 (48), 292 (64); ^1H nmr: δ 6.6 (s, 1H), 7.25-7.35 (m, 1H), 7.45-7.80 (m, 10H), 7.90-8.05 (m, 2H); ^{13}C nmr: δ 103.7, 112.5, 112.7, 116.5, 117.7, 128.5, 128.7, 129.0, 129.3, 129.9, 130.1, 136.6, 137.8, 144.9, 150.8, 152.7, 155.3, 162.7.

Anal. Calcd. for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69. Found: C, 81.62; H, 4.48; N, 8.73.

2-Cyano-1,3-diphenyl-2-propen-1-one (**5c**).

Benzoylacetonitrile (**2c**) (7.261 g, 50 mmoles), benzaldehyde (6.368 g, 60 mmoles), propanoic acid (0.236 g, 3.2 mmoles), piperidine (0.133 g, 1.6 mmoles) and 25 ml benzene were brought to reflux in a flask fitted with a Dean-Stark water separator. After about 2 hours approximately all of the theoretical amount of water (0.9 ml) had been collected. The solvent was removed *in vacuo* and the residue recrystallized from 95% ethanol to afford 10.93 g (94%) of **5c**, mp 83-84°; ir: ν 2231 (C≡N), 1656 (C=O); ms: m/z 233 (M^+, 20), 105 (100), 77 (73); ^1H nmr: δ 7.5-7.8 (m, 6H), 7.9-8.0 (m, 2H), 8.0-8.2 (m, 3H); ^{13}C nmr: δ 110.7, 117.2, 129.1, 129.8, 131.5, 132.2, 133.8, 136.2, 155.9, 189.4.

N-(1-Oxo-1,3-diphenyl-2-propenyl)acetamide (**5b**).

Reaction of α-acetylaminoacetophenone (**2b**) with benzaldehyde in the same manner as used for **5c** above gave **5b** (49%), mp 188-191°; ir: ν 3339 (NH), 1682 and 1667 (C=O); ms: m/z 265 (M^+, 40), 223 (71), 194 (43), 118 (100), 77 (64); ^1H nmr: δ 2.1 (s, 3H), 6.7 (s, 1H), 7.3-7.6 (m, 9H), 7.8-7.9 (m, 2H).

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.76; H, 5.82; N, 5.05.

6-(2-Furyl)-5-methyl-2,4-diphenyl-3-pyridinecarbonitrile (**4g**).

2-Cyano-1,3-diphenyl-2-propen-1-one (**5c**, 1.165 g, 5.0 mmoles), 1-(2-furyl)propanone (**6b**, 0.957 g, 7.72 mmoles), ammonium acetate (2.000 g), and glacial acetic acid (3.0 ml) were refluxed under a slow stream of air for 2.5 hours. After cooling, the solution was extracted with 5% sodium hydroxide and ether. The solvent was dried with anhydrous sodium sulfate and evaporated at reduced pressure. Recrystallization of the residue from 95% ethanol gave 0.335 g (20%) of **4g**, mp 193-195°. The mother liquor, containing 1.427 g, was analyzed by gc/ms to estimate 55% of additional **4g**, for a combined total of 75% yield. The remains were later purified by chromatography on silica gel with benzene. Compound **4h** was the major impurity. An analytical sample of **4g** gave mp 192.5-193°; ir: ν 2220 (CN); ms: m/z 336 (M^+, 69), 335 (86), 261 (100), ^1H nmr: δ 2.400 (s, 3H, CH_3), 6.59-6.61 (q, 1H), 7.32-7.36 (m, 2H), 7.45-7.58 (m, 6H), 7.65-7.66 (q, 1H), 7.94-8.00 (m, 2H); ^{13}C nmr: 17.2, 105.5, 111.9, 114.7, 117.3, 126.1, 128.4, 128.8, 129.0, 129.7, 136.4, 137.5, 144.5, 150.1, 153.4, 156.3, 158.1.

Anal. Calcd. for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.33. Found: C, 82.23; H, 4.81; N, 8.34.

Methyl 3-Methyl-5-cyano-4,6-diphenyl-2-pyridinecarboxylate (**4m**).

Ammonium vanadate (0.37 g, 3.14 mmoles), water (225 ml), and concentrated nitric acid (150 ml) were heated to boiling. Compound **4g** (0.75 g, 2.23 mmoles) was added to the hot solution with vigorous stirring. This mixture was refluxed 15 minutes before the water/nitric acid was removed at reduced pressure. Methyl alcohol (300 ml) was acidified with anhydrous hydrogen chloride gas and added to residue, *i.e.*, 3-methyl-5- cyano-4,6-diphenyl-2-pyridinecarboxylic acid, and refluxed 2.5 days. The methyl alcohol was removed and the product was extracted with 5% sodium hydroxide and ether. The solvent was dried with anhydrous sodium sulfate and removed at reduced pressure. The residue weighed 0.709 g (97%) and on analysis indicated essentially pure **4m**. Recrystallization from 95% ethanol gave colorless needles, mp 164-166°; ir: ν 2226 (CN), 1733 (C=O), 1212 (C-O); ms: m/z 328 (M^+, 57), 327 (93), 269 (34), 268 (50), 267 (100), 240 (25); ^1H nmr: δ 2.25 (s, 3H, CH_3), 4.00 (s, 3H, CO_2CH_3), 7.25-7.30 (m, 2H), 7.45-7.60 (m, 6H), 7.88-8.00 (m, 2H); ^{13}C nmr: δ 16.2, 53.0, 109.7, 116.3, 128.1, 128.6, 129.0, 129.1, 129.5, 130.2, 135.4, 136.8, 151.9, 156.8, 158.7, 166.4.

Anal. Calcd. for $C_{21}H_{16}N_2O_2$: C, 76.77; H, 4.91; N, 8.57. Found: C, 76.52; H, 4.89; N, 8.52.

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REFERENCES AND NOTES

[1] Presented in part at the 50th Southwest Regional Meeting of the American Chemical Society, Fort Worth, TX, November 13-16, 1994, Abstr. ORGN 189 and 190.

[2] K. V. Rao, K. Biemann and R. B. Woodward, *J. Am. Chem. Soc.*, **85**, 2532 (1963).

[3] D. L. Boger and J. S. Panek, *J. Am. Chem. Soc.*, **107**, 5745 (1985).

[4a] S. M. Weinreb, F. Z. Basha, S. Hibino, N. A. Khatri, D. Kim, W. E. Pye and T.-T. Wu, *J. Am. Chem. Soc.*, **104**, 536 (1982); [b] A. S. Kende, D. P. Lorah and R. J. Boatman, *J. Am. Chem. Soc.*, **103**, 1271 (1981).

[5] J. M. Robinson, L. W. Brent, C. Chau, K. A. Floyd, S. L. Gillham, T. L. McMahan, D. J. Magda, T. J. Motycka, M. J. Pack, A. L. Roberts, L. A. Seally, S. L. Simpson, R. R. Smith and K. N. Zalesny, *J. Org. Chem.*, **57**, 7352 (1992).

[6] Unsaturated ketones **3** are easily prepared with a variety of substituents R1 - R2 [7].

[7] The Perkin, Claisen-Schmidt and Knoevenagel condensations have been extensively reviewed: [a] J. R. Johnson, *Org React.*, **1**, 210 (1942); [b] G. Jones, *Org. React.*, **15**, 204 (1967); [c] H. O. House, Modern Synthetic Reactions, 2nd Ed, Benjamin, Menlo Park CA, Chapter 10, 1972; [d] A typical example is the preparation of chalcone **3a**: E. P. Kohler and H. M. Chadwell, Organic Syntheses, Coll. Vol **I**, Wiley, New York 1941, p 78.

[8a] F. Brody and P. R. Rudy, in Pyridine and its Derivatives, Vol **14**, Part One, E. Klingsberg, Ed, Interscience, New York 1960, Chapter 2; [b] N. S. Boodman, J. O. Hawthorne, P. X. Masciantonio and and A. W. Simon, in Pyridine and its Derivatives, Vol **14**, Supplement Part One, R. A. Abramovitch, Ed, Wiley-Interscience, New York 1972, Chapter 2; [c] G. R. Newkome and W. W. Paudler, Contemporary Heterocyclic Chemistry, Wiley: New York 1982; [d] Pyridine and Its Derivatives, Vol **14**, Part **5**, G. R. Newkome, ed, Wiley, New York 1984.

[9a] R. Jain, F. Roschangar and M. A. Ciufolini, *Tetrahedron Letters*, **36**, 3307 (1995); [b] T. W. Bell and S. D. Rothenberger, *Tetrahedron Letters*, **28**, 4817 (1987).

[10] M. Weiss, *J. Am. Chem. Soc.*, **74**, 200 (1952) and references therein.

[11] Dilute conditions for 6 days.

[12] I. Shibuya and M. Kurabayashi, *Bull. Chem. Soc., Japan*, **48**, 73 (1975).

[13] Normal (concentrated) conditions but under nitrogen.

[14] L. M. Long and H. D. Troutman, *J. Am. Chem. Soc.*, **71**, 2469 (1949).

[15] D. D. Weller, G. R. Luellen and D. L. Weller, *J. Org Chem.*, **47**, 4803 (1987).

[16] W. Zecher and F. Kröhnke, *Chem. Ber.*, **94**, 707 (1961) and references therein. These authors obtained only 18% yield of pyridine **4e** apparently without the use of air for oxidation.

[17] G. H. Müller and C. Harries, *Chem. Ber.*, **35**, 966 (1902); J. D. Gettler and L. P. Hammett, *J. Am. Chem. Soc.* **65**, 1824 (1943).

[18] E. F. Pratt and E. Werble, *J. Am. Chem. Soc.*, **72**, 4638 (1950).

[19] J. V. Heid and R. Levine, *J. Org. Chem,*. **13**, 409 (1948).

[20] A. Dornow, A. Müller and S. Lüpfert, *Liebigs Ann. Chem.*, **594**, 191 (1995).

[21] S. Cusmano, *Gazz. Chim. Ital.*, **81**, 380 (1951); *Chem. Abstr.*, **46**, 4001a (1952).

[22] S. Ruhemann, *J. Chem. Soc.*, **83**, 717 (1903).

[23] Identified by gc/ms but not isolated.