Chemistry of Heterocyclic Compounds, Vol. 40, No. 6, 2004

ACTIVATION OF PYRIDINIUM SALTS FOR ELECTROPHILIC ACYLATION: A METHOD FOR CONVERSION OF PYRIDINES INTO 3-ACYLPYRIDINES

A. Klapars[1] and E. Vedejs[2]

Cyanide adducts of N-MOM pyridinium salts react with strong acylating reagents to provide 3-acyl-4-cyano-1,4-dihydropyridines that can be aromatized to 3-acylpyridines using $ZnCl_2$ in refluxing ethanol.

Keywords: dihydropyridines, pyridine acylation.

Electrophilic aromatic substitution reactions of pyridines are extraordinarily challenging. Instead of C-substitution at the pyridine ring, the electrophile typically forms an adduct with the pyridine nitrogen, which even further deactivates the already electron deficient pyridine ring toward electrophilic substitution. For example, the direct nitration of pyridine may require a reaction temperature of 330°C to provide only a 15% yield of 3-nitropyridine [1]. To the best of our knowledge, no direct, intermolecular C-acylations of pyridines have been reported [2]. This seriously limits the choice of methods for the preparation of the ubiquitous 3-substituted pyridines [3, 4].

In a limited number of cases, the lack of reactivity of pyridines toward electrophiles has been addressed by converting the recalcitrant pyridine into a temporarily activated 1,4-dihydropyridine [5-9]. In contrast to the electron poor parent pyridine, the electron rich 1,4-dihydropyridine features strongly enhanced reactivity toward electrophiles at the 3-position. Several steps are typically required including formation of the dihydropyridine, the subsequent reaction with an electrophile, and rearomatization to the desired 3-substituted pyridine. A similar concept has been ingeniously employed in a one pot nitration of pyridines in the presence of sulfite as the nucleophile that temporarily activates the pyridine, and then acts as a leaving group in an aromatization step [10, 11]. In principle, mechanistically analogous nucleophilic activation-aromatization sequences may also be possible with other combinations of nucleophiles and electrophiles, but other applications of this principle have not been reported.

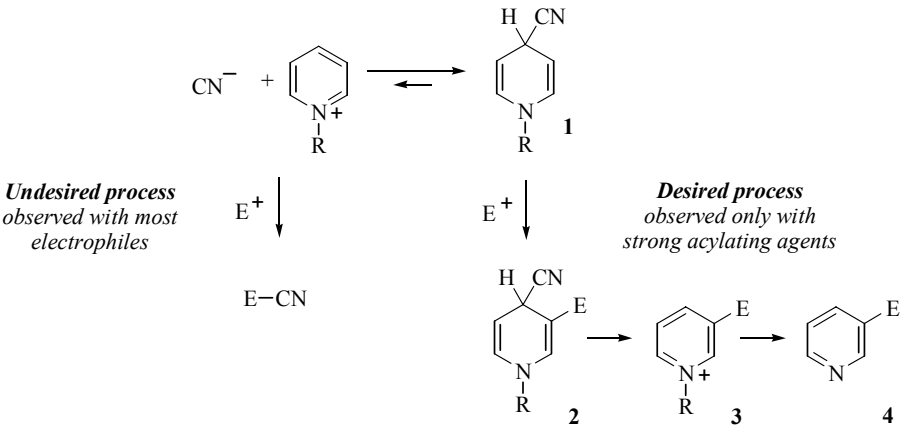
During our studies on indoloquinone synthesis involving the activation of oxazolium salts with cyanide ion [12], we fortuitously encountered the conversion from pyridinium salts to Reissert-type 4-cyano-1,4-dihydropyridines having the general structure **1**. We decided to explore their reactivity with electrophiles in anticipation that this might provide an indirect means for the introduction of a substituent into the 3-position of the pyridine ring. The results of this work are presented here.

---

[1] Department of Process Research, Merck Research Laboratories, NJ 07065, USA; e-mail: artis_klapars@merck.com. [2] Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, USA; e-mail: edved@umich.edu. Published in Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 887-894, June, 2004. Original article submitted June 01, 2004.

The cyanide ion and pyridinium salts form equilibrium mixtures containing labile 1,4-dihydropyridine adducts **1** (Scheme 1) [13, 14]. We found that the treatment of these equilibrium mixtures with strong acylating agents such as trifluoroacetic anhydride, trichloroacetyl chloride, or ethyl oxalyl chloride produces 3-acyl-1,4-dihydropyridines **2**. Due to stabilization by the electron withdrawing substituent in the 3-position, these acylated dihydropyridines **2** are significantly more robust than the parent dihydropyridines **1** and can be purified by aqueous extraction or even flash chromatography on silica gel. The deactivating effect of the 3-acyl group also prevents the introduction of a second acyl group in the 5-position. However, treatment of **1** with weaker acylating agents (AcCl, Ac_2O, Ac_2O–DMAP, EtOCOCl, PhCOCl, PhCOBr) or various other electrophiles (TMSOTf, BnBr, MeOTf, TsCl) did not provide the desired dihydropyridines **2**. Instead, products resulting from the reaction with the cyanide ion, present in the equilibrium mixture, were observed.

Sheme 1

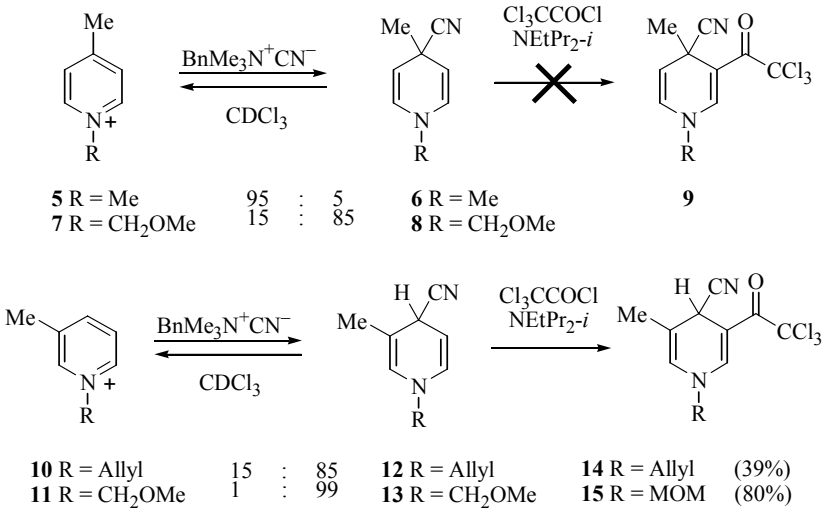


The extent of conversion from pyridinium salts to cyanide adducts is strongly affected by the pyridine ring substituents (Scheme 2). For example, treatment of the 1,4-dimethylpyridinium salt **5** with benzyltrimethylammonium cyanide gave an equilibrium mixture of **5** and the cyanide adduct **6** in a 95:5 ratio according to NMR analysis, favoring the starting pyridinium salt **5**. On the other hand, the presence of a moderately electron withdrawing N-methoxymethyl (MOM) group in **7** reversed the ratio to favor the dihydropyridine **8** over **7** (85:15). Neither of the dihydropyridines **6** nor **8** was reactive enough for acylation by trichloroacetyl chloride.

When the same experiments were repeated with the 3-methylpyridinium salts **10** and **11**, conversion to the cyanide adducts **12** and **13** was strongly favored in both cases. Clearly, the diminished steric effect compared to the 4-methyl analogues is responsible for this difference. More importantly, the reactivity of **12** and **13** with strong electrophiles was also improved. Thus, treatment with trichloroacetyl chloride in the presence of a hindered tertiary amine (Hünig's base) as HCl scavenger resulted in conversion to the acylated dihydropyridines **14** and **15**. Initially, we regarded the N-allyl pyridinium salt **10** as the more desirable starting material compared to the N-MOM analogue **11** in terms of the toxicity and cost issues. However, the N-allyl intermediate **12** consistently gave lower yields of the 3-acylated product **14** compared to the corresponding reaction from **13**. Therefore, the N-MOM pyridinium salts were chosen for further development.

The optimized procedure was applied to the acylation of several pyridine substrates (Scheme 3) using the same sequence of N-alkylation with $MeOCH_2Cl$ (MOMCl), addition of the soluble cyanide source $BnMe_3N^+CN^-$ to generate the activated dihydropyridine, and C-acylation in the presence of Hünig's base. Ethyl oxalyl chloride gave generally good results with several pyridine substrates, so this reagent was used for comparison studies with unsubstituted pyridine as well as with the 3-methyl and 2-methyl derivatives. In the

Sheme 2



case of the 3-methylpyridine, a single regioisomeric dihydropyridine intermediate **16b** was observed, as also seen in the trichloroacetylation experiments to give **12**. However, the 2-methyl pyridine example afforded a 1:7 mixture of two separable regioisomers **18**:**19**.

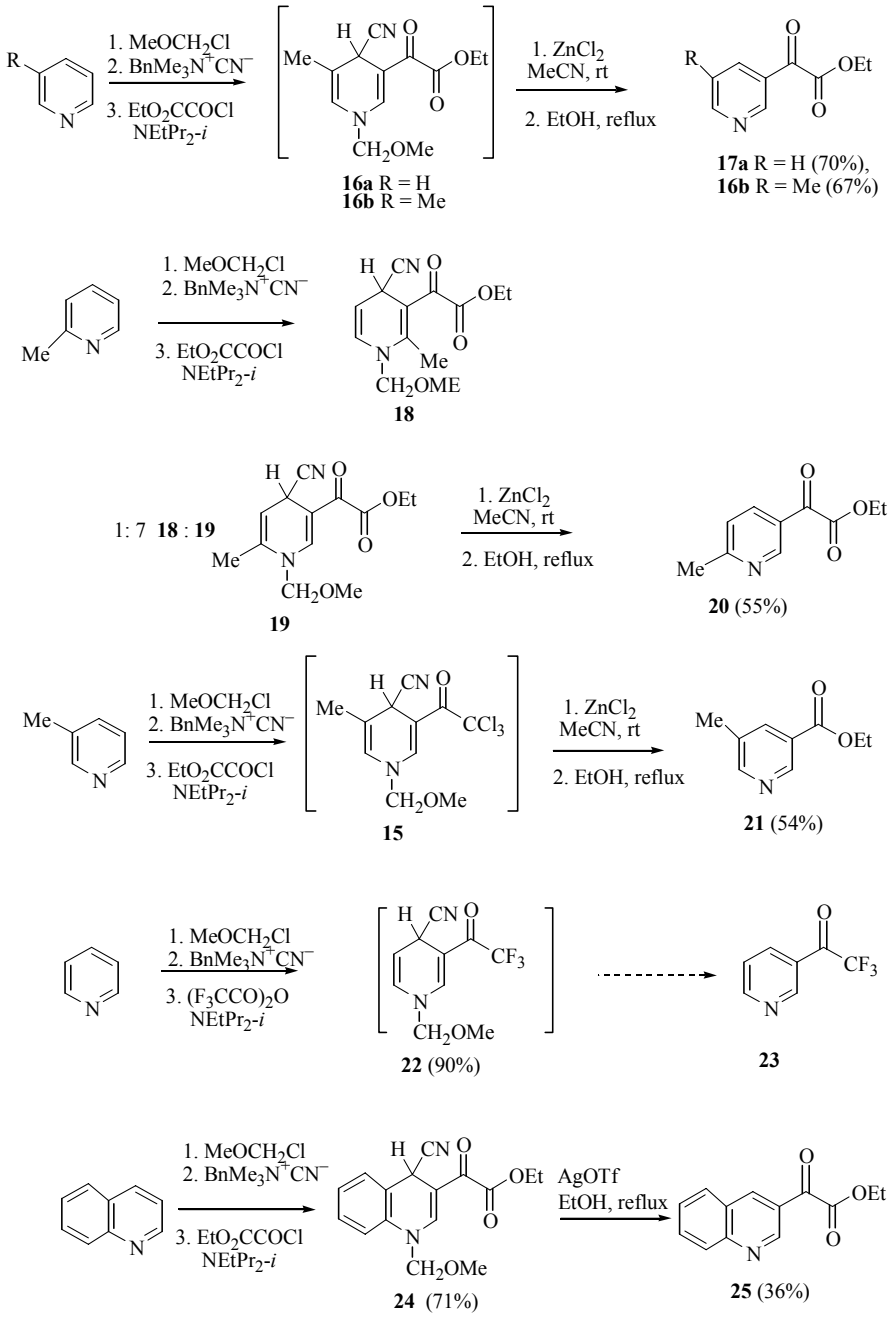
The aromatization of the dihydropyridines **16** and **19** to the desired 3-acyl pyridines **17** and **20** was accomplished with the help of $ZnCl_2$ as a mild cyanophile (Scheme 1). Upon addition of anhydrous $ZnCl_2$ to **16a** or **19**, a rapid decyanation to the pyridinium salt **3** (R = MOM) could be detected by NMR analysis of the reaction mixture. Importantly, the formation of the pyridinium salt activated the MOM group toward deprotection via nucleophilic displacement. This was accomplished by refluxing the crude pyridinium salt mixture in ethanol, resulting in the formation of **17** and **20** in 67-70% overall yield from the starting pyridine.

When the same aromatization procedure was used with the trichloroacetylated dihydropyridine **15**, aromatization occurred as usual, but the refluxing ethanol deprotection step also cleaved the trichloroacetyl group in a haloform-type reaction to give the corresponding picolinate ester **21** (54% overall). This transformation proved quite useful because the alternative of preparing the picolinate via direct carboxylation of the dihydropyridine adduct **13** with chloroformate esters was unsuccessful due to competing cyanide transfer to the relatively unreactive electrophile.

Trifluoroacetylation of pyridine *via* the dihydropyridine **1** (R = MOM) salt was also possible, and gave an isolable dihydropyridine **22**. The aromatization of **22** using the zinc chloride procedure was viable according to NMR assay of the reaction mixture. However, attempts to recover 3-trifluoroacetylpyridine **23** from the crude product were not successful. The product proved to be highly polar, suggesting the formation of hydrates that could not be purified by chromatography. Another unusual example was encountered in the quinoline series. Quinoline activation and C-acylation with oxalyl chloride proceeded normally and gave the dihydroquinoline **24** in a typical 71% yield. However, **24** proved to be relatively stable, and the cyanide group resisted the usual zinc chloride aromatization conditions. Aromatization did take place with the stronger cyanophile AgOTf, but the quinoline product **25** was obtained in low (35%) yield.

In summary, an indirect method for the 3-acylation of pyridines is described *via* the intermediate N-MOM pyridinium salts. This method utilizes the cyanide ion as a temporary nucleophile to form an activated, electron rich dihydropyridine intermediate that is susceptible to acylation at the 3-position, and subsequent aromatization. The cyanide can be permanently introduced in the pyridine ring if a pyridine N-oxide is treated with TMSCN [15, 16]. Although the method is applicable only to highly reactive acylating agents and requires the use of the toxic cyanide and $MeOCH_2Cl$, no better alternatives for the 3-acylation of pyridines in a one-pot procedure are currently available.

Sheme 3



EXPERIMENTAL

General procedures. Solvents and reagents were purified as follows: acetonitrile was distilled from P_2O_5; diisopropylethylamine was distilled from CaH_2; methoxymethyl chloride (Aldrich, technical grade) was distilled and sparged with nitrogen gas to remove the HCl impurity (CAUTION: methoxymethyl chloride and particularly an impurity present in the reagent are strong carcinogens); the purified reagents and solvents were

stored under nitrogen. Chloroform (anhydrous, stabilized with amylenes) was obtained from Aldrich and used immediately after opening of the bottle. Zinc chloride (Mallinckrodt, anhydrous) was used without further purification. All reactions were performed under an atmosphere of nitrogen in glassware dried in an oven (150°C) and cooled with a stream of nitrogen. All reaction mixtures were stirred magnetically. Flash chromatography was performed with 230-400 mesh EM silica gel 60. Analytical TLC was performed on EM glass plates coated with a 250 μm layer of silica gel 60 F_{254}. Melting points were obtained on a Lab Devices MelTemp apparatus and are uncorrected.

Benzyltrimethylammonium Cyanide ($BnMe_3N^+CN^-$) was prepared according to a procedure reported by Vedejs and Monahan [17] with some modifications (CAUTION: cyanide is a strong poison; sodium hypochlorite bleach solution can be used to detoxify the cyanide residues). Benzyltrimethylammonium chloride (Aldrich, 39.8 g, 0.214 mol) was dried at 0.5 mm Hg vacuum and dissolved in 50 ml of anhydrous MeOH. The resulting solution was transferred *via* cannula into a stirred solution of NaCN (15.8 g, 0.322 mol) in 300 ml of anhydrous MeOH. After stirring for 30 min at room temperature, the white suspension was carefully concentrated (rotary evaporation followed by 0.5 mm Hg vacuum) with minimal exposure to the atmospheric moisture. The residue was treated with 200 ml of hot anhydrous acetonitrile, and the resulting suspension was filtered hot through a fritted glass filter under nitrogen. The filtrate was carefully concentrated by rotary evaporation at room temperature to *ca.* 50 ml volume with minimal exposure to atmospheric moisture. The resulting suspension was filtered under nitrogen, and the crystals were dried at 0.5 mm Hg vacuum to give 23.7 g (63%) of the product as white hygroscopic crystals. The product was stable at room temperature for several years if it was stored and handled in a dry box under nitrogen.

Ethyl 4-cyano-1-methoxymethyl-1,4-dihydro-3-pyridineglyoxylate (16a). To a solution of pyridine (0.33 ml, 4.08 mmol) in 10 ml of $CHCl_3$ at room temperature was added methoxymethyl chloride (0.34 ml, 4.48 mmol). After stirring at room temperature for 1 h, the colorless solution was transferred *via* cannula into a 50 ml round bottom flask charged with benzyltrimethylammonium cyanide (660 mg, 3.74 mmol). The resulting clear solution was cooled to 0°C (ice bath), and diisopropylethylamine (0.80 ml, 4.59 mmol) was added followed by ethyl oxalyl chloride (0.48 ml, 4.30 mmol). After stirring at 0°C for 1 h, the orange solution was poured into 50 ml of ether and washed with 2 × 20 ml of water. The bright yellow organic layer was dried (Na_2SO_4) and concentrated by rotary evaporation to give the crude dihydropyridine **16a**, which was used in the next step without further purification. Analytical TLC on silica gel 60 F_{254}, hexane–acetone (1:1), R_f 0.47. Molecular ion calculated for $C_{12}H_{14}N_2O_4$ 250.09530; found *m/e* 250.0943, error = 4 ppm. IR spectrum (neat) ν, cm^{-1}: 2231 (C≡N), 1726 (C=O), 1678 (C=O). NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.97 (1H, d, *J* = 1.4); 6.27 (1H, dt, *J* = 7.9, 1.4); 5.20 (1H, dd, *J* = 7.9, 4.6); 4.65 (2H, s); 4.60 (1H, dd, *J* = 4.6, 1.4); 4.35 (2H, q, *J* = 7.2); 3.36 (3H, s); 1.39 (3H, t, *J* = 7.2). ^{13}C NMR spectrum (76 MHz, $CDCl_3$), δ, ppm: 180.1, 162.2, 146.6, 128.7, 118.4, 103.2, 102.3, 85.4, 62.2, 56.0, 24.0, 13.9.

Ethyl 3-Pyridineglyoxylate (17a). The crude dihydropyridine **16a** prepared above was dissolved in anhydrous acetonitrile (5 ml, including cannula washings), and the solution was transferred *via* cannula into a 25 ml round bottom flask charged with $ZnCl_2$ (1.05 g, 7.70 mmol). After stirring at room temperature for 5 h, the yellow suspension was filtered through Celite eluting with 2 × 2 ml of anhydrous acetonitrile. Anhydrous ethanol (10 ml) was added to the filtrate, the resulting tan solution was refluxed for 15 h, cooled to room temperature, and then poured into 10% aqueous solution of $NaHCO_3$ (20 ml) at 0°C (ice bath). The resulting suspension was filtered through Celite eluting with 2 × 10 ml of ethanol. The tan filtrate was extracted with 3 × 30 ml of CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), concentrated by rotary evaporation, and the residue was purified by flash chromatography on silica gel (2.5 × 20 cm, hexane–acetone (4:1) eluent, 15 ml fractions). Fraction 9-15 gave 467 mg (70%) of the pyridine **17a** as a light yellow liquid [18].

Ethyl 5-Methyl-3-pyridineglyoxylate (16b). To a solution of 3-methylpyridine (0.40 ml, 4.11 mmol) in 10 ml of $CHCl_3$ at room temperature was added methoxymethyl chloride (0.34 ml, 4.48 mmol). After stirring at room temperature for 1 h, the colorless solution was transferred *via* cannula into a 50 ml round bottom flask charged with benzyltrimethylammonium cyanide (670 mg, 3.80 mmol). The resulting clear solution was cooled

to 0°C (ice bath), and diisopropylethylamine (0.80 ml, 4.59 mmol) was added followed by ethyl oxalyl chloride (0.48 ml, 4.30 mmol). After stirring at 0°C for 1 h, the orange solution was poured into 50 ml of ether and washed with 2 × 20 ml of water. The yellow organic layer was dried (Na_2SO_4) and concentrated by rotary evaporation to give the crude dihydropyridine **16b**, which was used in the next step without further purification.

The crude dihydropyridine **16b** prepared above was dissolved in anhydrous acetonitrile (5 ml, including cannula washings), and the solution was transferred *via* cannula into a 25 ml round bottom flask charged with $ZnCl_2$ (1.06 g, 7.78 mmol). After stirring at room temperature for 4 h, the orange suspension was filtered through Celite eluting with 2 × 2 ml of anhydrous acetonitrile. Anhydrous ethanol (10 ml) was added to the filtrate, the resulting tan solution was refluxed for 12 h, cooled to room temperature, and then poured into 10% aqueous solution of $NaHCO_3$ (20 ml) at 0°C (ice bath). The resulting suspension was filtered through Celite eluting with 3 × 5 ml of ethanol. The tan filtrate was extracted with 3 × 30 ml of CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), concentrated by rotary evaporation, and the residue was purified by flash chromatography on silica gel (2.5 × 20 cm, hexane–acetone (4:1) eluent, 15 ml fractions). Fractions 8-12 gave 492 mg (67%) of the pyridine **17b** as a pale yellow liquid. Analytical TLC on silica gel 60 F_{254}, hexane–acetone (2:1), R_f 0.43. Molecular ion calculated for $C_{10}H_{11}NO_3$ 193.07390; found *m/e* 193.0744, error = 3 ppm. IR spectrum (neat), ν, cm^{-1}: 1734 (C=O), 1693 (C=O). NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.05 (1H, d, *J* = 2.0); 8.69 (1H, d, *J* = 2.0); 8.14 (1H, t, *J* = 2.0); 4.48 (2H, q, *J* = 7.1); 2.44 (3H, s); 1.44 (3H, t, *J* = 7.1). ^{13}C NMR spectrum (76 MHz, $CDCl_3$), δ, ppm: 184.8, 162.3, 155.2, 148.6, 136.9, 133.5, 127.9, 62.5, 18.1, 13.9.

Ethyl 2-Methyl-3-pyridineglyoxylate (20). To a solution of 2-methylpyridine (0.42 ml, 4.25 mmol) in 10 ml of $CHCl_3$ at room temperature was added methoxymethyl chloride (0.34 ml, 4.48 mmol). After stirring at room temperature for 1 h, the colorless solution was transferred *via* cannula into a 50 ml round bottom flask charged with benzyltrimethylammonium cyanide (670 mg, 3.80 mmol). The resulting colorless solution was cooled to -40°C (dry ice-acetonitrile bath), and diisopropylethylamine (0.80 ml, 4.59 mmol) was added followed by ethyl oxalyl chloride (0.48 ml, 4.30 mmol). After stirring at -40°C for 3 h, the cooling bath was removed. The reaction mixture was allowed to warm to room temperature for 1 h, poured into 50 ml of ether and washed with 2 × 20 ml of water. The tan organic layer was dried (Na_2SO_4), concentrated by rotary evaporation to give a 7:1 ratio of the dihydropyridine isomers, and the residue was purified by flash chromatography on silica gel (4 × 20 cm, hexane–acetone (3:1) eluent, 15 ml fractions). Fractions 45-70 gave the desired dihydropyridine regioisomer **19**, which was used in the next step without further purification.

The dihydropyridine **19** prepared above was dissolved in anhydrous acetonitrile (5 ml, including cannula washings), and the solution was transferred *via* cannula into a 25 ml round bottom flask charged with $ZnCl_2$ (970 mg, 7.12 mmol). After stirring at room temperature for 4 h, the orange suspension was filtered through Celite eluting with 2 × 1 ml of anhydrous acetonitrile. Anhydrous ethanol (10 ml) was added to the filtrate, the resulting tan solution was refluxed for 12 h, cooled to room temperature, and then poured into 10% aqueous solution of $NaHCO_3$ (20 ml) at 0°C (ice bath). The resulting suspension was filtered through Celite eluting with 3 × 10 ml of ethanol. The tan filtrate was extracted with 3 × 30 ml of CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), concentrated by rotary evaporation, and the residue was purified by flash chromatography on silica gel (2.5 × 20 cm, hexane–acetone (3:1) eluent, 15 ml fractions). Fractions 8-14 gave 406 mg (55%) of the pyridine **20** as a colorless liquid. Analytical TLC on silica gel 60 F_{254}, hexane–acetone (2:1), R_f = 0.40. Molecular ion calculated for $C_{10}H_{11}NO_3$ 193.07390; found *m/e* 193.0742, error = 2 ppm. IR spectrum (neat), ν, cm^{-1}: 1734 (C=O), 1697 (C=O). NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.69 (1H, dd, *J* = 1.8, 4.9); 8.04 (1H, dd, *J* = 1.8, 8.0); 7.30 (1H, dd, *J* = 4.9, 8.0); 4.45 (2H, q, *J* = 7.2); 2.80 (3H, s); 1.42 (3H, t, *J* = 7.2. ^{13}C NMR spectrum (76 MHz, $CDCl_3$), δ, ppm: 187.4, 163.3, 160.1, 152.7, 139.0, 127.3, 120.8, 62.6, 24.4, 13.9.

4-Cyano-1-methoxymethyl-5-methyl-3-trichloroacetyl-1,4-dihydropyridine (15). To a solution of 3-methylpyridine (0.40 ml, 4.11 mmol) in 10 ml of $CHCl_3$ at room temperature was added methoxymethyl chloride (0.34 ml, 4.48 mmol). After stirring at room temperature for 1 h, the colorless solution was transferred

via cannula into a 50 ml round bottom flask charged with benzyltrimethylammonium cyanide (670 mg, 3.80 mmol). The resulting colorless solution was cooled to 0°C (ice bath), and diisopropylethylamine (0.80 ml, 4.59 mmol) was added followed by trichloroacetyl chloride (0.48 ml, 4.30 mmol). The cooling bath was removed, and the reaction mixture was stirred at room temperature for 1 h. The yellow solution was poured into 100 ml of ethyl acetate and washed with 2 × 20 ml of water. The tan organic layer was dried (Na_2SO_4) and concentrated by rotary evaporation to give the crude dihydropyridine **15**, which was used in the next step without further purification. Analytical TLC on silica gel 60 F_{254}, hexane–acetone (2:1), R_f = 0.35. Pure material was obtained by crystallization from chloroform, mp 160-161°C, decomposition, yellow plates. Molecular ion calculated for $C_{11}H_{11}Cl_3N_2O_2$ 307.98861; found *m/e* 307.9857, error = 9 ppm. IR spectrum (KBr), ν, cm^{-1}: 2225 (C≡N), 1695 (C=O). NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.98 (1H, s); 6.08 (1H, s); 4.70 (1H, AB q, *J* = 10.5); 4.63 (1H, AB q, *J* = 10.5); 4.45 (1H, s); 3.34 (3H, s); 1.93 (3H, s); 7.98 (1H, s); 6.08 (1H, s); 4.70 (1H, AB q, *J* = 10.5); 4.63 (1H, AB q, *J* = 10.5); 4.45 (1H, s); 3.34 (3H, s); 1.93 (3H, s). ^{13}C NMR spectrum (76 MHz, DMSO-d_6), δ, ppm: 177.9, 145.9, 124.1, 118.4, 111.5, 95.2, 92.6, 84.6, 55.1, 30.5, 17.9.

Ethyl 5-Methyl-3-pyridinecarboxylate (21). A solution of the crude dihydropyridine **15** prepared above and $ZnCl_2$ (2.04 g, 15.0 mmol) in 10 ml of anhydrous ethanol was refluxed for 24 h. After cooling to room temperature, the reaction mixture was poured into 10% aqueous solution of $NaHCO_3$ (40 ml) at 0°C (ice bath). The resulting suspension was filtered through Celite eluting with 3 × 5 ml of ethanol, and the brown filtrate was extracted with 2 × 60 ml of CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), concentrated by rotary evaporation, and the residue was purified by flash chromatography on silica gel (2.5 × 20 cm, hexane–acetone (4:1) eluent, 7 ml fractions). Fractions 14-22 were concentrated by rotary evaporation and purified by another flash chromatography on silica gel (2.5 × 20 cm, hexane–ethyl acetate (2:1) eluent, 7 ml fractions). Fractions 20-27 gave 340 mg (54%) of the pyridine **21** as a pale tan liquid, identical with the literature report according to NMR assay [19].

4-Cyano-1-methoxymethyl-3-trifluoroacetyl-1,4-dihydropyridine (22). To a solution of pyridine (0.34 ml, 4.20 mmol) in 10 ml of $CHCl_3$ at room temperature was added methoxymethyl chloride (0.34 ml, 4.48 mmol). After stirring at room temperature for 1 h, the colorless solution was transferred *via* cannula into a 50 ml round bottom flask charged with benzyltrimethylammonium cyanide (675 mg, 3.82 mmol). The resulting colorless solution was cooled to 0°C (ice bath), and diisopropylethylamine (0.80 ml, 4.59 mmol) was added followed by trifluoroacetic anhydride (0.60 ml, 4.25 mmol). The yellow solution was stirred at 0°C for 1 h, poured into 50 ml of ether, and washed with 2 × 20 ml of water. The tan organic layer was dried (Na_2SO_4), concentrated by rotary evaporation, and the residue was purified by flash chromatography on silica gel (2.5 × 20 cm, dichloromethane–ether (20:1) eluent, 15 ml fractions). Fractions 9-12 gave 852 mg (90%) of the dihydropyridine **22** as yellow crystals. Analytical TLC on silica gel 60 F_{254}, hexane–acetone (2:1), R_f 0.34. Pure material was obtained by crystallization from ether–hexane, mp 49-50 °C, yellow crystals. Molecular ion calculated for $C_{10}H_9F_3N_2O_2$ 246.06160; found *m/e* 246.0609, error = 3 ppm. IR spectrum (neat), ν, cm^{-1}: 2235 (C≡N), 1662 (C=O). NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.49 (1H, t, *J* = 1.2); 6.31 (1H, dt, *J* = 7.9, 1.2); 5.24 (1H, dd, *J* = 7.9, 4.5); 4.69 (2H, s); 4.58 (1H, dt, *J* = 4.5, 1.2); 3.37 (3H, s). ^{13}C NMR spectrum (76 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 176.5 (q, *J* = 34.8); 145.5 (q, *J* = 4.7); 128.6, 118.1, 116.7 (q, *J* = 290.4); 102.5; 99.6; 85.5; 56.0; 24.2. ^{19}F NMR spectrum (282 MHz, $CDCl_3$), δ, ppm: 69.9.

Ethyl 4-Cyano-1-methoxymethyl-1,4-dihydro-3-quinolineglyoxylate (24). To a solution of quinoline (0.50 ml, 4.23 mmol) in 10 ml of $CHCl_3$ at room temperature was added methoxymethyl chloride (0.34 ml, 4.48 mmol). After stirring at room temperature for 1 h, the light green solution was transferred *via* cannula into a 50 ml round bottom flask charged with benzyltrimethylammonium cyanide (680 mg, 3.86 mmol). After stirring at room temperature for 4 h, the tan solution was cooled to 0°C (ice bath), and diisopropylethylamine (0.80 ml, 4.59 mmol) was added followed by ethyl oxalyl chloride (0.48 ml, 4.30 mmol). The cooling bath was removed, the reaction mixture was stirred at room temperature for 1 h, the resulting brown solution was poured into 50 ml of ether, and washed with 2 × 20 ml of water. The organic layer was dried (Na_2SO_4), concentrated by

rotary evaporation, and the residue was purified by flash chromatography on silica gel (2.5 × 20 cm, hexane–ethyl acetate (1:1) eluent, 15 ml fractions). Fractions 13-21 gave 822 mg (71%) of the dihydroquinoline **24** as a yellow solid. Analytical TLC on silica gel 60 F_{254}, hexane–acetone (1:1), R_f 0.60. Pure material was obtained by crystallization from ethanol, mp 118-119 °C, yellow needles. Molecular ion calculatedd for $C_{16}H_{16}N_2O_4$ 300.1110; found *m/e* 300.1116, error = 2 ppm. IR spectrum (KBr), ν, cm^{-1}: 2233 (C□N), 1736 (C=O), 1722 (C=O). NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.27 (1H, s); 7.46-7.21 (4H, m); 5.24 (1H, s); 5.12 (2H, s); 4.36 (2H, q, *J* = 7.3); 3.41 (3H, s); 1.40 (3H, t, *J* = 7.3). ^{13}C NMR spectrum (76 MHz, $CDCl_3$), δ, ppm: 179.1, 162.3, 148.1, 134.7, 130.3, 129.8, 126.3, 118.9, 117.8, 115.8, 102.6, 84.1, 62.3, 55.9, 27.5, 13.9.

The research reported in this paper was performed at the Department of Chemistry, University of Wisconsin, Madison, WI 53706, USA. Funding was provided by the National Institutes of Health (CA17918).

REFERENCES

1. F. Friedl, *Ber.*, 428 (1912).
2. M. A. Brodney and A. Padwa, *Tetrahedron Lett.*, **38**, 6153 (1997).
3. P. Baumgarten and A. Dornow, *Ber.*, **72**, 563 (1939).
4. Y. Satoh, M. Ichihashi, and K. Okumura, *Chem. Pharm. Bull.*, **40**, 912 (1992).
5. R. M. Acheson, N. D. Wright, and P. A. Tasker, *J. Chem. Soc.*, *Perkin Trans. 1*, 2918 (1972).
6. D. L. Comins and N. B. Mantlo, *Tetrahedron Lett.*, **24**, 3683 (1983).
7. O. Tsuge, T. Kanemasa, T. Naritomi, and T. Tanaka, *J. Chem. Lett.*, 1255 (1984).
8. M. Haase, H. Goerls, and E. Anders, *Synthesis*, 195 (1998).
9. M.-L. Bennasar, C. Juan, and J. Bosch, *Tetrahedron Lett.*, **39**, 9275 (1998).
10. J. M. Bakke and I. Hegbom, *Acta Chem. Scand.*, **48**, 181 (1994).
11. H. Suzuki, M. Iwaya, and T. Mori, *Tetrahedron Lett.*, **38**, 5647 (1997).
12. E. Vedejs, A. Klapars, B. N. Naidu, D. W. Piotrowski, and F. C. Tucci, *J. Am. Chem. Soc.*, **122**, 5401 (2000).
13. R. Foster and C. A. Fyfe, *Tetrahedron*, **25**, 1489 (1969).
14. R. E. Lyle and G. J. Gauthier, *Tetrahedron Lett.*, 4615 (1965).
15. W. K. Fife, *J. Org. Chem.*, **48**, 1375 (1983).
16. H. Vorbrüggen, and K. Krolikiewicz, *Synthesis*, 316 (1983).
17. E. Vedejs and S. D. Monahan, *J. Org. Chem.*, **62**, 4763 (1997).
18. M. K. Nurullaeva, U. M. Azizov, E. E. Mikhlina, K. F. Turchin, V. A. Silin, and L. Yakhontov, *Chem. Abstr.*, **106**, 32790 (1987).
19. D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **38**, 2660 (1973).