SYNTHESIS AND TRANSFORMATIONS OF ALKYL 1,5-BIS-(DIMETHYLAMINO)-3-OXOPENTA-1,4-DIENE-2,4-DICARBOXYLATES. A SIMPLE SYNTHESIS OF DIALKYL 1-SUBSTITUTED 4-OXO-1,4-DIHYDROPYRIDINE-3,5-DICARBOXYLATES

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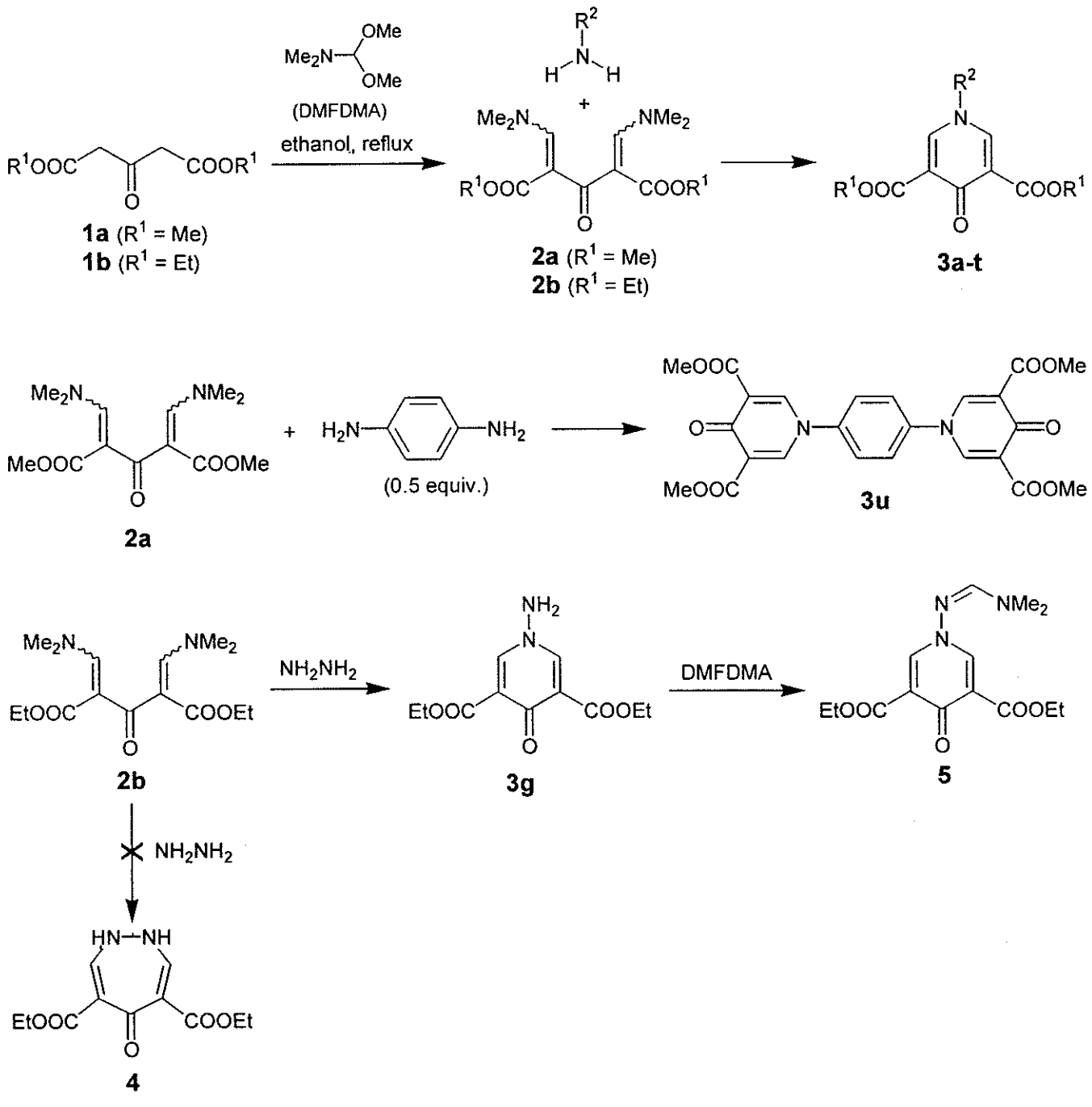
Dedicated to Professor Richard Neidlein, University of Heidelberg, on the occasion of his 70th birthday

Abstract – Dimethyl (**2a**) and diethyl 1,5-bis(dimethylamino)-3-oxo-penta-1,4-diene-2,4-dicarboxylate (**2b**), available in good yields from the corresponding dialkyl acetonedicarboxylates (**1a, b**) and *N,N*-dimethylformamide dimethyl acetal (DMFDMA), were used as reagents for a one-step preparation of 1-substituted 1,4-dihydropyridin-4-ones (**3a–u**). Thus, compounds (**2**) were treated with ammonia, hydrazines, and primary aliphatic, aromatic, or heterocyclic amines to form dialkyl 1-substituted 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates (**3a–u**).

There are several methods for the preparation of 4-oxo-1,4-dihydropyridine derivatives described in the literature.[1–3] 1-Substituted 4-oxo-1,4-dihydropyridinecarboxylic acid moiety is found in several drugs with antibacterial activity, such as nalidixic acid,[4] oxolinic acid,[5] pyridonic acid,[6] and pipemidic acid.[7] The outstanding activity of fluoridone as a terrestrial and aquatic herbicide[8] has stimulated considerable work toward discovering alternative methods for the synthesis of 3,5-disubstituted 4(1*H*)-pyridinones. 1-Substituted 3,5-dinitro-4-oxo-1,4-dihydropyridines react with diethyl sodio 3-oxo-pentanedioate to give 1-substituted 3,5-bis(ethoxycarbonyl)-4-oxo-1,4-dihydropyridines.[9–11] 4-Oxo-1,4-dihydropyridine-3-carboxylate and its 5-substituted derivatives have been prepared by reacting of 1,3,5-triazine with 4-substituted ethyl acetoacetates in ethanol in the presence of sodium ethoxide.[12,13] However, there are only few methods available for the preparation of dialkyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates.

Diethyl acetonedicarboxylate condenses with triethyl orthoformate in hot acetic anhydride, followed by treatment of the product with ammonia to give diethyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylate in poor yield (only 4%).[14] The intermediate, the di(ethoxyvinyl) ketone has not been isolated. 3-Chloroaniline has been used to obtain the corresponding *N*-(3-chlorophenyl) substituted derivative in 17% yield.[15] Recently, the ring transformation of 3-methyl-5-nitropyrimidin-4(3*H*)-one, as an activated diformylamine, produces in the presence of bidentate enolate anions pyridin-4(1*H*)-ones functionalized at the 3- and 5-position.[16]

Scheme 1



In the course of our studies we have prepared 2-acylamino-3-(dimethylamino)propenoates and their analogs, as masked α-formyl-α-amino- and α-formyl-α-hydroxy acids, and their derivatives. They have been applied as reagents for the preparation of a variety of heterocyclic systems with an amino or hydroxy acid structural element incorporated into the newly formed heterocyclic system. Among these systems are: pyridinones, pyrimidinones, pyranones, pyrroles, imidazoles, 1,2,4-oxadiazoles, and others.[17]

In continuation of our research in this area, we report now a simple synthesis of dialkyl 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates. In this manner, dimethyl (**1a**) or diethyl acetonedicarboxylate (**1b**) was transformed with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) by heating in etanol for 1.5 h into dimethyl (**2a**) or diethyl 1,5-bis(dimethylamino)-3-oxo-penta-1,4-diene-2,4-dicarboxylate (**2b**) in good yield. Dialkyl 1,5-bis(dimethylamino)-3-oxo-penta-1,4-diene-2,4-dicarboxylates (**2a,b**) were not isolated in analytically pure form and were used without purification for further transformations. IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectral data for diethyl 1,5-bis(dimethylamino)-3-oxo-penta-1,4-diene-2,4-dicarboxylate (**2b**) are in agreement with the proposed structure. Compounds (**2**) were treated with ammonia, hydrazines, primary aliphatic, aromatic, or heterocyclic amines to form dialkyl 1-substituted 4-oxo-1,4-dihydropyridine-3,5-dicarboxylates (**3a–t**). 1,4-Diaminobenzene reacts with **2** in 1:2 molar ratio to produce 1,4-bis[3,5-bis(methoxycarbonyl)-4-oxo-1,4-dihydropyridinyl-1]benzene (**3u**) in 57% yield. Reaction with hydrazine could theoretically afford either the 1-aminopyridine (**3g**) or the diazepine (**4**). Formation of the pyridone (**3g**) was confirmed by traetment with DMFDMA which gave the amidine (**5**), thus proving the 1-aminopyridine structure (Scheme 1).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H NMR spectra was obtained on a Bruker Avance DPX 300 (300 MHz) spectrometer with DMSO–d_6 as solvent and Me_4Si as internal standard. The microanalyses for C, H, and N were obtained on a Perkin-Elmer CHN *Anal*yser 2400. Mass spectra were obtained on an *Autospeck Q* spectrometer.

Diethyl 1,5-Bis(dimethylamino)-3-oxopenta-1,4-diene-2,4-dicarboxylate (2b). A mixture of diethyl 1,3-acetondicarboxylate (0.95 mL, 5 mmol), *N,N*-dimethylformamide dimethyl acetal (95%, 2.7 ml, 19.3 mmol), and ethanol (4 mL) was refluxed for 1.5 h. Volatile components were evaporated *in vacuo* and the residue was purified by flash chromatography (silica gel, chloroform-methanol, 95:5). Fractions containing the product were combined and evaporated *in vacuo* to give **2b** as a yellow oil in 50%yield. MS (FAB): m/z = 313 (MH^+). IR (film, cm^{-1}): 2981, 1682, 1594. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (6H, t, J = 6.9 Hz, CH_3CH_2); 3.02 (12H, s, NMe_2); 4.10 (4H, q, J = 6.9 Hz, CH_2CH_3); 7.58 (2H, s, 1–H,

5–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.3, 44.4, 59.4, 105.1, 155.0, 168.1, 189.2. HRMS Calcd for $C_{15}H_{24}N_2O_5$: 312.169400. Found: 312.168522 (M^+).

General Procedure for the Preparation of Dialkyl 1-Substituted 1,4-Dihydro-4-oxopyridine-3,5-dicarboxylates (3a–t). A mixture of dialkyl 1,3-acetonedicarboxylate (**1**) (5 mmol); propyl acetate (15 mL); and DMFDMA (95%, 2.7 mL, 19.3 mmol) was refluxed for 1.5 h. Volatile components were evaporated *in vacuo* to give a crude **2** as a brown oil which was dissolved in an alcohol (10 mL, **2a**: in methanol, **2b**: in ethanol). To this solution amine (7.5 mmol) was added and the mixture was refluxed for 1–28 h. The reaction mixture was concentrated to one half of the volume, cooled, and the precipitate was collected by filtration to give **3**.

In this manner, the following compounds were prepared:

Dimethyl 1,4-Dihydro-4-oxopyridine-3,5-dicarboxylate (3a). This compound was prepared from **2a** and ammonia in methanol, reflux for 2 h, yield 34%; mp 258–268° (from DMF). IR (KBr, cm^{-1}): 3422, 3062, 1713, 1280, 815. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.73 (6H, s, OMe); 8.19 (2H, s, 2–H and 6–H); 11.00–12.00 (1H, br s, 1–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 50.9, 120.7, 142.0, 164.4, 169.9. *Anal.* Calcd for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.63. Found: C, 51.21; H, 4.31; N, 6.54.

Diethyl 1,4-Dihydro-4-oxopyridine-3,5-dicarboxylate (3b). This compound was prepared from **2b** and ammonia in ethanol, reflux for 2h, yield 60%; mp 238–240° (from DMF). MS (EI): m/z = 239 (M^+). IR (KBr, cm^{-1}): 3404, 3062, 1694, 1280, 815. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.26 (6H, t, J = 6.9 Hz, CH_3CH$_2$); 4.21 (4H, q, J = 6.9 Hz, CH$_2$CH$_3$); 8.16 (2H, s, 2–H and 6–H); 11.00–12.00 (1H, s, 1–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 13.6, 59.7, 120.8, 141.9, 164.0, 169.8. *Anal.* Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.85. Found: C, 55.30; H, 5.66; N, 5.98.

Dimethyl 1,4-Dihydro-1-(2-propyl)-4-oxopyridine-3,5-dicarboxylate (3c). This compound was prepared from **2a** and isopropylamine in methanol, reflux for 5 h, yield 17%; mp 136–146° (from MeOH). IR (KBr, cm^{-1}): 3445, 2981, 1740, 1598, 1283, 818. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.40 (6H, d, J = 6.6 Hz, Me_2CH); 3.73 (6H, s, Me); 4.45 (1H, m, J = 6.6, CHMe$_2$); 8.35 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.7, 51.7, 58.61, 122.1, 142.6, 164.8, 170.1. *Anal.* Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.62; H, 6.08; N, 5.43.

Diethyl 1,4-Dihydro-1-[(2-hydroxyethyl)amino]-4-oxopyridine-3,5-dicarboxylate (3d). This compound was prepared from **2b** and 2-hydroxyethylhydrazine in ethanol, reflux for 1.5 h, yield 21%; mp

102–105° (from *n*-propanol). IR (KBr, cm^{-1}): 3462, 2977, 1731, 1510, 1265, 1026, 822. ^1H NMR (300 MHz, DMSO-d_6): δ 1.26 (6H, t, *J* = 7.2 Hz, CH_3CH_2); 3.10 (2H, m, *J* = 5.3 Hz, CH_2NH); 3.46 (2H, m, *J* = 5.13 Hz, CH_2OH); 4.20 (4H, q, *J* = 7.2 Hz, CH_2CH_3); 4.78 (1H, t, *J* = 5.1 Hz, OH); 7.03 (1H, t, *J* = 5.3 Hz, 1–H); 8.26 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 54.0, 54.1, 58.1, 58.2, 60.4, 121.3, 145.86, 145.89, 163.7, 169.8. *Anal.* Calcd for $C_{13}H_{18}N_2O_6$: C, 52.35; H, 6.08; N, 9.39. Found: C, 52.38; H, 6.03; N, 9.31.

Diethyl 1,4-Dihydro-1-(1-hydroxybutyl-2)-4-oxopyridine-3,5-dicarboxylate (3e). This compound was prepared from **2b** and 2-amino-1-butanol in ethanol, reflux for 20 h, yield 28%; mp 124–130° (from EtOH). IR (KBr, cm^{-1}): 3367, 2982, 1738, 1689, 1523, 1273, 1172, 810. ^1H NMR (300 MHz, DMSO-d_6): δ 0.83 (3H, t, *J* = 7.5 Hz, CH_3CH_2CH); 1.26 (6H, t, *J* = 7.2 Hz, OCH_2CH_3); 1.74 (2H, q, *J* = 7.5 Hz $CHCH_2CH_3$); 3.65 (2H, t, *J* = 7.0 Hz, CH_2OH); 4.08 (1H, m, $CHCH_2CH_3$); 4.20 (4H, q, *J* = 7.2 Hz, OCH_2CH_3); 5.15 (1H, t, *J* = 7.0 Hz, OH); 8.25 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 10.0, 14.1, 22.6, 60.4, 62.2, 70.1, 122.1, 143.4, 164.4, 170.5. *Anal.* Calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.51; H, 6.80; N, 4.65.

Diethyl 1,4-Dihydro-1-(ethoxycarbonylmethyl)-4-oxopyridine-3,5-dicarboxylate (3f). This compound was prepared from **2b** and ethyl glycinate hydrochloride in ethanol, reflux for 21 h, yield 33%; mp 175–177° (from EtOH). IR (KBr, cm^{-1}): 2995, 1738, 1481, 1171. ^1H NMR (300 MHz, DMSO-d_6): δ 1.21–1.28 (9H, m, OCH_2CH_3); 4.10–4.25 (6H, m, OCH_2CH_3); 4.98 (2H, s, CH_2COOEt); 8.31 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.0, 14.1, 56.1, 60.4, 61.5, 121.6, 146.2, 163.9, 168.1, 170.1. *Anal.* Calcd for $C_{15}H_{19}NO_7$: C, 55.38; H, 5.89; N, 4.31. Found: C, 54.99; H, 5.69; N, 4.21.

Diethyl 1-Amino-1,4-dihydro-4-oxopyridine-3,5-dicarboxylate (3g). This compound was prepared from **2b** and hydrazine hydrate in ethanol, reflux for 3 h, yield 34%; mp 127–130° (from EtOH). MS (EI): m/z = 254 (M^+). IR (KBr, cm^{-1}): 3466, 3283, 3176, 2980, 1731 ,1570, 1262. ^1H NMR (300 MHz, DMSO-d_6): δ 1.25 (6H, t, *J* = 6.9 Hz, CH_2CH_3); 4.19 (4H, q, *J* = 6.9 Hz, CH_2CH_3); 6.66 (2H, s, NH_2); 8.14 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 60.3, 120.7, 146.5, 163.6, 169.6. *Anal.* Calcd for $C_{11}H_{14}N_2O_5$: C, 51.97; H, 5.55; N, 11.02. Found: C, 51.85; H, 5.66; N, 11.13.

Diethyl 1,4-Dihydro-1-phenyl-4-oxopyridine-3,5-dicarboxylate (3h). This compound was prepared from **2b** and aniline in ethanol, reflux for 28 h, yield 62%; mp 151–154° (from EtOH). MS (EI): m/z = 315 (M^+). IR (KBr, cm^{-1}): 2985, 1745, 1264, 712. ^1H NMR (300 MHz, DMSO-d_6): δ 1.26 (6H, t, *J* = 6.9 Hz, CH_2CH_3); 4.21 (4H, q, *J* = 6.9, CH_2CH_3); 7.45–7.70 (5H, m, Ph); 8.41 (2H, s, 2–H and 6–H). ^{13}C

NMR (75 MHz, DMSO-d_6): δ 14.1, 60.5, 122.4, 123.5, 128.9, 129.9, 142.2, 143.5, 163.8, 170.1. *Anal.* Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 65.14; H, 5.42; N, 4.36.

Diethyl 1,4-Dihydro-1-(4-methylphenyl)-4-oxopyridine-3,5-dicarboxylate (3i). This compound was prepared from **2b** and 4-methylaniline in ethanol, reflux for 20 h, yield 92%; mp 137–141° (from EtOH). IR (KBr, cm^{-1}): 1976, 1740, 1694 ,1267. ^1H NMR (300 MHz, DMSO-d_6): δ 1.26 (6H, t, J = 7.2 Hz, CH_2CH_3); 2.38 (3H, s, $ArCH_3$); 4.21 (4H, q, J = 7.2 Hz, CH_2CH_3); 7.37 (2H, dd, J = 2.1, 8.7 Hz, 2H–Ar); 7.55 (2H, dd, J = 2.1, 8.7 Hz, 2H–Ar); 8.36 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 20.5, 60.5, 122.4, 123.3, 130.3, 138.6, 139.9, 143.5, 163.8, 170.0. *Anal.* Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.40; H, 5.76; N, 4.56.

Diethyl 1,4-Dihydro-1-[4-(hydroxymethyl)phenyl]-4-oxopyridine-3,5-dicarboxylate (3j). This compound was prepared from **2b** and 4-(hydroxymethyl)aniline in ethanol, reflux for 2.5 h, yield 86%; mp 226–230° (from EtOH). IR (KBr, cm^{-1}): 3393, 2984, 1737, 1267, 1027. ^1H NMR (300 MHz, DMSO-d_6): δ 1.24 (6H, t, J = 7.2 Hz, CH_2CH_3); 4.19 (4H, q, J = 7.2 Hz, CH_2CH_3); 4.41 (2H, d, J = 5.1 Hz, CH_2OH); 5.37 (1H, d, J = 5.1 Hz, OH); 7.56 (4H, m, Ph); 8.25 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 59.2, 60.4, 121.7, 126.7, 128.7, 129.7, 130.0, 137.3, 140. 7, 145.1, 163.7, 170.1. *Anal.* Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.84; H, 5.50; N, 4.12.

Diethyl 1,4-Dihydro-1-(2-aminophenyl)-4-oxopyridine-3,5-dicarboxylate (3k). This compound was prepared from **2b** and 2-aminoaniline in ethanol, reflux for 20 h, yield 77%; mp 127–130° (from EtOH). IR (KBr, cm^{-1}): 3438, 3323, 3223, 1746, 1651, 1265, 1031. ^1H NMR (300 MHz, DMSO-d_6): δ 1.24 (6H, t, J = 7.2 Hz, CH_2CH_3); 4.19 (4H, q, J = 7.2 Hz, CH_2CH_3); 5.49 (2H, s, NH_2); 6.66 (1H, deg dt, J = 7.9, 1.5 Hz, 1H–Ar); 6.86 (1H, dd, J = 8.2, 1.2 Hz, 1H–Ar); 7.22 (2H, m, 2H–Ar); 8.05 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 60.3, 116.4, 116.6, 122.3, 127.1, 127.4, 130.4, 143.3, 145.6, 163.7, 170.5. *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.92; H, 5.40; N, 8.42.

Dimethyl 1,4-Dihydro-1-(4-hydroxyphenyl)-4-oxopyridine-3,5-dicarboxylate (3l). This compound was prepared from **2a** and 4-hydroxyaniline in methanol, reflux for 2 h, yield 76%; mp 262–270° (from DMF). IR (KBr, cm^{-1}): 3455, 3062, 1742, 1704, 1515, 1279 ,1237. ^1H NMR (300 MHz, DMSO-d_6): δ 3.74 (6H, s, OMe); 6.90 (2H, dd, J = 6.6, 2.4 Hz, 2H–Ph); 7.46 (2H, dd, J = 6.6, 2.4 Hz, 2H–Ph); 8.32 (2H, s, 2–H and 6–H); 10.00 (1H, s, OH). ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.8, 116.1, 121.9, 125.0, 134.1, 144.3, 157.9, 164.3, 169.9. *Anal.* Calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62. Found: C, 59.62; H, 4.37; N, 4.52.

Dimethyl 1,4-Dihydro-1-(3-bromophenyl)-4-oxopyridine-3,5-dicarboxylate (3m). This compound was prepared from **2a** and 3-bromoaniline in methanol, reflux for 1 h, yield 75%; mp 274–276° (from MeOH). IR (KBr, cm^{-1}): 3059, 1752, 1643, 1277, 1145, 814. ^1H NMR (300 MHz, DMSO-d_6): δ 3.75 (6H, s, OMe); 7.53 (1H, deg t, J = 8.1 Hz, 1H–Ar); 7.71 (2H, m, 2H–Ar); 8.01 (1H, deg t, J = 1.8 Hz, 1H–Ar); 8.46 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 51.7, 121.97, 122.02, 122.6, 126.4, 131.5, 131.6, 143.1, 143.6, 164.0, 169.9. *Anal.* Calcd for $C_{15}H_{12}NO_5Br$: C, 49.20; H, 3.30; N, 3.83. Found: C, 49.22; H, 3.28; N, 3.61.

Diethyl 1,4-Dihydro-1-(3,4-methylenedioxyphenyl)-4-oxopyridine-3,5-dicarboxylate (3n). This compound was prepared from **2b** and 3,4-methylenedioxyaniline in ethanol, reflux for 3 h, yield 94%; mp 194–196° (from EtOH). IR (KBr, cm^{-1}): 2986, 1739, 1694, 1263, 1067. ^1H NMR (300 MHz, DMSO-d_6): δ 1.26 (6H, t, J = 7.2 Hz, CH_2CH_3); 4.21 (4H, q, J = 7.2 Hz, CH_2CH_3); 6.15 (2H, s, CH_2); 7.07 (1H, d, J = 7.7 Hz, 1H–Ar); 7.13 (1H, dd, J = 7.7, 2.4 Hz, 1H–Ar); 7.37 (1H, d, J = 2.4 Hz, 1H–Ar); 8.30 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 60.5, 102.3, 105.5, 108.4, 117.6, 122.1, 136.6, 144.0, 147.6, 148.0, 163.8, 170.0. *Anal.* Calcd for $C_{18}H_{17}NO_7$: C, 60.17; H, 4.77; N, 3.90. Found: C, 60.38; H, 4.67; N, 3.64.

Diethyl 1,4-Dihydro-1-(5-methylisoxazolyl-3)-4-oxopyridine-3,5-dicarboxylate (3o). This compound was prepared from **2b** and 3-amino-5-methylisoxazole in ethanol, reflux for 19 h, yield 63%; mp 145–148° (from EtOH). IR (KBr, cm^{-1}): 3131, 1736, 1695, 1471, 1270, 814. ^1H NMR (300 MHz, DMSO-d_6): δ 1.28 (6H, t, J = 7.2 Hz, CH_2CH_3); 2.50 (3H, s, 5'–CH_3); 4.25 (4H, q, J = 7.2 Hz, CH_2CH_3); 7.07 (1H, s, 4'–H); 8.60 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 12.5, 14.1, 60.9, 95.4, 122.7, 140.1, 160.4, 163.3, 170.6, 173.4. *Anal.* Calcd for $C_{15}H_{16}N_2O_6$: C, 56.25; H, 5.03; N, 8.75. Found: C, 56.11; H, 4.88; N, 8.76.

Diethyl 1,4-Dihydro-1-(thiazolyl-2)-4-oxopyridine-3,5-dicarboxylate (3p). This compound was prepared from **2b** and 2-aminothiazole in ethanol, reflux for 21 h, yield 34%; mp 170–173° (from EtOH). IR (KBr, cm^{-1}): 3079, 1734, 1639, 1261, 1030. ^1H NMR (300 MHz, DMSO-d_6): δ 1.28 (6H, t, J = 7.2 Hz, CH_2CH_3); 4.25 (4H, q, J = 7.2 Hz, CH_2CH_3); 7.75 (1H, d, J = 1.5 Hz, 1H–thiazole); 7.78 (1H, d, J = 1.5 Hz, 1H–thiazole); 8.75 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 60.9, 120.2, 122.3, 140.2, 140.4, 160.8, 163.3, 170.6. *Anal.* Calcd for $C_{14}H_{14}N_2O_5S$: C, 52.17; H, 4.38; N, 8.69. Found: C, 52.00; H, 4.33; N, 8.37.

Diethyl 1,4-Dihydro-1-(pyridinyl-2)-4-oxopyridine-3,5-dicarboxylate (3q). This compound was prepared from **2b** and 2-aminopyridine in ethanol, reflux for 17 h, yield 66%; mp 149–151° (from EtOH).

IR (KBr, cm^{-1}): 3391, 2978, 1709, 1659, 1244. ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (6H, t, J = 7.2 Hz, CH_2CH_3); 4.26 (4H, q, J = 7.2 Hz, CH_2CH_3); 7.55 (1H, ddd, J=7.3, 4.9 1.0 Hz, 5'–H); 7.96 (1H, deg dt, J = 8.4, 1.0 Hz, 3'–H); 8.12 (1H, ddd, J = 8.4, 7.3, 2.0 Hz, 4'–H); 8.62 (1H, ddd, J = 4.9, 2.0, 1.0 Hz, 6'–H); 8.93 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 60.7, 114.6, 122.2, 123.7, 140.3, 140.4, 148.7, 150.8, 163.8, 170.7. *Anal.* Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.88; H, 5.05; N, 8.94.

Diethyl 1,4-Dihydro-1-(6-methylpyridinyl-2)-4-oxopyridine-3,5-dicarboxylate (3r). This compound was prepared from **2b** and 2-amino-6-methylpyridine in ethanol, reflux for 21 h, yield 73%; mp 170–171° (from EtOH). IR (KBr, cm^{-1}): 2985, 1745, 1450, 1271. ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (6H, t, J = 7.2 Hz, CH_2CH_3); 2.56 (3H, s, 6'–Me); 4.25 (4H, q, J = 7.2 Hz, CH_2CH_3); 7.40 (1H, d, J = 8.4 Hz, 5'–H); 7.73 (1H, d, J = 7.5 Hz, 3'–H); 7.98 (1H, dd, J = 8.4, 7.5 Hz, 4–H); 8.90 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 23.7, 60.7, 111.4, 122.3, 123.0, 140.3, 140.5, 150.2, 157.9, 163.9, 170.7. *Anal.* Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.67; H, 5.53; N, 8.42.

Diethyl 1,4-Dihydro-1-(6-aminopyridinyl-2)-4-oxopyridine-3,5-dicarboxylate (3s). This compound was prepared from **2b** and 2,6-diaminopyridine in ethanol, reflux for 3 h, yield 53%; mp 213–216° (from EtOH). IR (KBr, cm^{-1}): 3431, 3321, 3217, 1732, 1265. ^1H NMR (300 MHz, DMSO-d_6): δ 1.28 (6H, t, J = 6.9 Hz, CH_2CH_3); 4.24 (4H, q, J = 6.9 Hz, CH_2CH_3); 6.51 (1H, d, J = 8.1 Hz, 5'–H); 6.61 (2H, s, NH_2); 6.90 (1H, d, J = 7.5 Hz, 3'–H); 7.61 (1H, dd, J = 8.1, 7.5 Hz, 4'–H); 8.81 (2H, s, 2–H and 6–H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 60.6, 100.1, 107.7, 122.0, 140.3, 140.3, 149.6, 159.3, 164.0, 170.7. HRMS Calcd for $C_{16}H_{17}N_3O_5$: 331.116821. Found: 331.117500 (M^+).

Diethyl 1,4-Dihydro-1-(pyrimidinyl-2)-4-oxopyridine-3,5-dicarboxylate (3t). This compound was prepared from **2b** and 2-aminopyrimidine in ethanol, reflux for 24 h, yield 28%; mp 158–177° (from EtOH). IR (KBr, cm^{-1}): 3088, 1734, 1698, 1345. ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (6H, t, J = 7.2 Hz, CH_2CH_3); 4.27 (4H, q, J = 7.2 Hz, CH_2CH_3); 7.64 (1H, t, J = 4.8 Hz, 5'–H); 9.00 (2H, d, J = 4.8 Hz, 4'–H and 6'–H); 9.35 (2H, s, 2–H and 6–H);. ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 60.8, 120.4, 121.6, 138.8, 154.2, 159.6, 163.5, 171.2. *Anal.* Calcd for $C_{15}H_{15}N_3O_5$: C, 56.78; H, 4.76; N, 13.24. Found: C, 56.59; H, 4.68; N, 13.60.

1,4-Bis[3,5-bis(methoxycarbonyl)-1,4-dihydro-4-oxopyridinyl-1]benzene (3u). A mixture of dimethyl 1,3-acetonedicarboxylate (**1**) (0.870 g, 5 mmol), propyl acetate (15 mL), and DMFDMA (95%, 2.7 mL,

19.3 mmol) was refluxed for 1.5 h. Volatile components were evaporated *in vacuo* to give a crude **2** as a brown oil which was dissolved in methanol (10 mL). To this solution 4-aminoaniline (0.270 g, 2.5 mmol) was added and the mixture was refluxed for 2.5 h. The reaction mixture was concentrated to one half of the volume, cooled, and the precipitate was collected by filtration to give **3u**. Yield 57% (0.706 g); mp >350° (from AcOH). MS (EI): m/z = 496 (M^+). IR (KBr, cm^{-1}): 3036, 1753, 1639, 1266, 1152, 816. ^1H NMR (300 MHz, DMSO-d_6): δ 3.77 (12H, s, OMe); 7.86 (4H, s, 4H–Ar); 8.39 (4H, s, 2'–H and 6'–H). ^{13}C NMR (75 MHz, CF_3COOH): δ 56.6, 119.3, 129.4, 146.2, 152.1, 166.3, 175.6. *Anal.* Calcd for $C_{24}H_{20}N_2O_{10}$: C, 58.07; H, 4.06; N, 5.64. Found: C, 57.87; H, 4.08; N, 5.59.

Diethyl 1,4-Dihydro-1-[(dimethylamino)methylideneimino]-4-oxopyridine-3,5-dicarboxylate (5). A mixture of diethyl 1-amino-1,4-dihydro-4-oxopyridine-3,5-dicarboxylate(**3g**)(0.912 g, 3.6 mmol); ethanol (15 mL); and DMFDMA (95%, 1 mL, 7.1 mmol) was refluxed for 2.5 h. The reaction mixture was concentrated to one half of the volume, cooled (0°C), and the precipitate was collected by filtration to give **5**. Yield 71% (0.792 g); mp 137–147° (from ethanol). MS (EI): m/z = 309 (M^+). IR (KBr, cm^{-1}): 3445, 2986, 1731, 1592, 1258. ^1H NMR (300 MHz, DMSO-d_6): δ 1.25 (6H, t, J = 7.2 Hz, CH_3CH_2); 2.85 (6H, s, NMe_2); 4.18 (4H, q, J = 7.2 Hz, CH_2CH_3); 8.14 (2H, s, 2–H and 6–H); 8.22 (1H, s, $CHNMe_2$). ^{13}C NMR (75 MHz, DMSO-d_6): δ 14.1, 34.4, 60.3, 121.1, 142.4, 161.6, 163.9, 169.4. *Anal.* Calcd for $C_{14}H_{19}N_3O_5$: C, 54.36; H, 6.19; N, 13.58. Found: C, 54.42; H, 6.32; N, 13.94.

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