An Efficient Synthesis of 6-Formyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid and some Carbonyl Derivatives of it and its 6-Acetyl Homologue

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Starting with 1,1-dimethoxy-2-propanone (**1**), 6-formyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acid (**5a**) has been prepared in large quantities by a highly efficient, 4-step synthesis. This compound, along with its one carbon homologue, 6-acetyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acid (**5b**) has been reacted with several carbonyl derivative forming reagents to provide a series of side chains for β-lactams. Among these carbonyl derivatives are styrylamides which were prepared from Wittig and Horner-Emmons reagents. The preparation of the phosphonium salts and phosphonate esters is also described.

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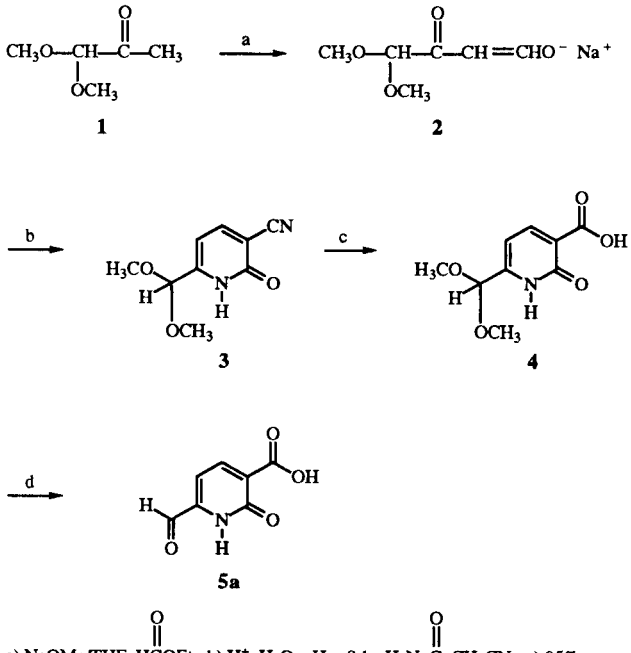
As part of our continuing interest in preparing various 6-acyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acids as side chains for β-lactams [1], we investigated routes which would be capable of preparing 6-formyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acid (**5a**) efficiently and in large quantities. We have already described a useful synthesis of **5a** by the oximation of 6-methyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acid [2]. However, this procedure is not amenable to scale-up to produce the large amounts of material that we required; because of the 4-equivalents of potassium amide and the large volumes of ammonia necessary to produce the anion intermediate. Our previously reported synthesis of the 6-acetylpyridone acid (**5b**) [3] provided that compound in large quantities using a direct route and we felt that we could employ similar methodology to produce **5a** as well.

Scheme 1. Preparation of Pyridone Aldehyde *via* Acetal



a) NaOMe/THF; HCOEt. b) H^+, H_2O, $pH = 9.1$; $H_2N-C-CH_2CN$. c) 85% aq. KOH, reflux; H^+. d) conc. HCl, gl. HOAc, H_2O, 60°C.

Starting with commercially available 1,1-dimethoxy-2-propanone (**1**), the anion was prepared using sodium methoxide in tetrahydrofuran (Scheme 1) and reacted with ethyl formate to produce the formyl salt **2**. This material was reacted with α-cyanoacetamide under the usual conditions for pyridone formation [4] to afford the pyridone nitrile **3**. Vigorous basic hydrolysis followed by acidification provided the pyridone acetal, **4**. This compound was the key synthetic intermediate since carbonyl derivatives could be prepared directly from it, or the acid portion of the molecule could be reacted without affecting the protected aldehyde. Mild hydrolysis of the acetal using an aqueous solution of acetic and hydrochloric acids, at room temperature, provided the desired pyridone aldehyde, **5a**.

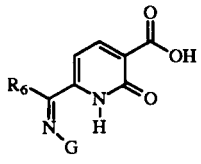
We had previously prepared a series of 6-vinyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic acids utilizing Hauser's conditions [5] to functionalize the C_6-methyl of the *t*-butyl ester of 1,2-dihydro-6-methyl-2-oxo-3-pyridinecarboxylic acid [6]. We wished to expand this series by synthesizing compounds which could not be prepared using the pyridone dianion methodology. The carbonyl derivatives prepared from the acetal **4**, the aldehyde **5a** and the ketone **5b** ranged from simple compounds such as semicarbazones, oximes and thiosemicarbazones to the more complex cyanomethylene, carbethoxymethylene and styrylamides produced from the reaction with Wittig [7] and Horner-Emmons [8] reagents.

The simple carbonyl derivatives prepared from the aldehyde, could be obtained by dissolving the compound in methanol, adding the derivativizing reagent, heating and then removing the crystalline product from the reaction mixture (Table 1). However, in the case of the less reactive ketone, it was necessary to dissolve the compound in water using sodium hydroxide, add the reagent and then main-

tain the *p*H near neutrality. When the reaction was complete, the solution was acidified and the solid product could then be isolated (Table 1).

Table 1

Simple Carbonyl Derivatives of the Pyridone Acetal **4**, The Pyridone Aldehyde **5a** and the Pyridone Ketone **5b**



Starting Pyridone	Reagent	Product	R_6	G	Yield (%)	Mp (°C)
5a	$NH_2OH \cdot HCl$	**6a**	H	-OH	92	250-252
5b	$NH_2OH \cdot HCl$	**6b**	CH_3	-OH	92	246-248
4	$H_2N\text{-}C(=O)\text{-}NHNH_2 \cdot HCl$	**7a**	H	$-NH\text{-}C(=O)\text{-}NH_2$	96	274-275
5b	$H_2N\text{-}C(=O)\text{-}NHNH_2 \cdot HCl$	**7b**	CH_3	$-NH\text{-}C(=O)\text{-}NH_2$	95	277-279
4	$H_2N\text{-}C(=S)\text{-}NHNH_2 \cdot HCl$	**8a**	H	$-NH\text{-}C(=S)\text{-}NH_2$	98	269-270
5b	$MeONH_2 \cdot HCl$	**9b**	CH_3	$-OCH_3$	94	269-271
5a	$EtNH\text{-}C(=S)\text{-}NHNH_2 \cdot HCl$	**10a**	H	$-NH\text{-}C(=S)\text{-}NH_2$	87	275-276

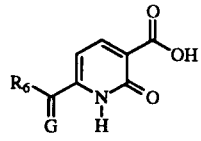
In preparing the more complex carbonyl derivatives, the aldehyde readily reacted with the Wittig reagents. However, once again it was necessary to use more reactive conditions with the ketone and Horner-Emmons reagents had to be employed to prepare the desired derivatives (Table 2).

Some Wittig and Horner-Emmons reagents are commercially available, but the styryl-amide forming reagents were prepared by acetylating the requisite amine with chloroacetyl chloride in toluene using excess amine as the base. The chloromethyl amides were then reacted with either triphenyl phosphine or triethylphosphite to produce the corresponding Wittig or Horner-Emmons reagents. Dehydrohalogenation using sodium hydride or 1,5-diazabicyclo[4.3.0]non-5-ene in a polar solvent (dimethyl sulfoxide, *N,N*-dimethylformamide or *N,N*-dimethylacetamide) for the Wittig reagents and sodium hydride in *N,N*-dimethylacetamide or tetrahydrofuran for the Horner-Emmons reagents followed by addition of the carbonyl compound produced the final pyridone styryl-amides (Table 2).

The products isolated from the Wittig and Horner-Emmons reactions had the expected *E*-stereochemistry [9]. However, in the preparation of the styryl ethylaminoamide **11**, it was possible to isolate a small amount (5%) of

Table 2

Wittig and Horner-Emmons Reactions of the Aldehyde **5a** and Ketone **5b**



Starting Pyridone	Reagent	Product	R_6	G	Yield (%)
5a	$Ph_3\overset{+}{P}CH_2CONHEt\ Cl^-$	**11a**	H	CHCONHEt (*trans*)	62
5b	$(EtO)_2POCH_2CONHEt$	**11a'**	H	CHCONHEt (*cis*)	5
5a	$Ph_3\overset{+}{P}CH_2CO_2Me\ Cl^-$	**11b**	Me	CHCONHEt (*trans*)	93
5a	$Ph_3\overset{+}{P}CH_2CONHCH_2CH_2NMe_2 \cdot HCl\ Cl^-$	**12a**	H	$CHCO_2Me$ (*trans*)	74
		13a	H	$CHCONHCH_2CH_2NMe_2$ (*trans*)	64
5a	$Ph_3\overset{+}{P}CH_2CON$(ring)$\ Cl^-$	**14a**	H	CH–CON(ring) (*trans*)	53
5b	$(EtO)_2POCH_2CN$	**15b**	CH_3	CHCN (*trans*)	79
15a	$con \cdot H_2SO_4$	**16b**	CH_3	$CHCONH_2$ (*trans*)	90
5b	$(EtO)_2POCH_2CON$(ring)	**17b**	CH_3	CH–CON(ring) (*trans*)	66
5a	$Ph_3\overset{+}{P}CH_2CON$(N-Me ring)$\ Cl^-$	**18a**	H	CH–CON(N-Me ring)	85
5a	$Ph_3\overset{+}{P}CH_2CONH$–(ring)$\ Cl^-$	**19a**	H	CHCON(H)–(ring)	48

the *Z*-isomer **11a**. The isolated yields of the *E*-isomer in the other reactions ranged from 48% to 93% and the *Z*-isomer may have been present in theses cases also. However, thin layer chromatography of the reaction failed to indicate the presence of significant amounts of any other product, so no attempts were made to isolate the *Z*-isomer in these cases.

EXPERIMENTAL

Melting points were taken on a Hoover melting point apparatus and are uncorrected. Infrared (ir) spectra were determined on a Digilab FTS-14 or Nicolet FT IR SX-20 with 2 cm^{-1} resolution. Proton magnetic resonance (nmr) spectra were recorded on a Varian EM-390 or an IBM 100 WP100SY spectrometer. Chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were recorded on either a Finnigan 4500 GCMS or a VG Analytical 7070/HF with 11/250 Data System. Solutions were dried over magnesium sulfate and concentrated on a rotary evaporator at 30-45° and at pressures of 10-20 mm. All moisture sensitive reactions were carried out under a dry nitrogen atmosphere. Elemental Analyses were performed on a Perkin-Elmer 240 elemental analyzer.

6-(Dimethoxymethyl)-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**3**).

A suspension of 270 g (5.0 moles) of sodium methoxide in 2.5 liters of tetrahydrofuran was heated to 45° and treated dropwise with a solution of 297.5 g (2.5 moles) of 1,1-dimethoxy-2-propanone and 370 g (5.0 moles) of ethyl formate over 2 hours. The reaction was stirred at 45° for 3.5 hours and then at room temperature overnight. The reaction was then added to one liter of water and the volatiles were removed *in vacuo*. The resulting aqueous solution was washed with ether (2 x 1 liter), acidified to *p*H 9.1 and treated with 210 g (2.5 moles) of α-cyanoacetamide. The reaction was stirred at 60° for 16 hours and the solid was removed by filtration. The filtrate was acidified to *p*H 5.5 and the resulting precipitate was removed by filtration, washed with water and dried *in vacuo* to give 109.6 g (23%) of **3**, mp 185-187°; ^{1}H nmr (DMSO-d_6): δ 3.26 (s, 6H), 5.08 (s, 1H), 6.30 (d, 1H, J = 7 Hz, C_5H), 7.90 (d, 1H, J = 7 Hz, C_4H), 9.28 (bs, 1H).

Anal. Calcd. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.42; H, 5.02; N, 14.18.

6-(Dimethoxymethyl)-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**4**).

A solution of 139.1 g (0.71 mole) of **3**, 184.0 g (2.8 moles) of 85% potassium hydroxide and 1400 ml of water was heated at reflux for 25 hours. The reaction was cooled to 5° and acidified to *p*H 6.5 with 2.5 *M* hydrochloric acid. The precipitate was removed by filtration and the filtrate was acidified to *p*H 2.5 with 2.5 *M* hydrochloric acid. The precipitate was removed by filtration, washed with water and redissolved in water (400 ml) with 1.0 *N* sodium hydroxide (60 ml). The solution was clarified by filtration through a fiber glass pad and the filtrate was acidified to *p*H 2.5 with hydrochloric acid. The precipitate was removed by filtration, washed with water, ether and dried *in vacuo* to give 126.1 g (82%) of **4**, mp 173-175°. ^{1}H nmr (DMSO-d_6): δ 3.32 (s, 6H), 5.30 (s, 1H), 6.69 (d, 1H, J = 8 Hz, C_5H), 8.32 (d, 1H, J = 8 Hz, C_4H), 12.65 (bs, 1H).

Anal. Calcd. for $C_9H_{11}NO_5$: C, 50.70; H, 5.20; N, 6.57. Found: C, 50.52; H, 5.25; N, 6.53.

6-Formyl-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**5a**).

A solution of 2.5 liters of glacial acetic acid, 200 ml of concentrated hydrochloric acid and 1.0 liter of water was stirred at 60° and 220.6 g (1.03 moles) of solid **4** was added. The reaction was stirred at 60° for 15 minutes and filtered to remove a trace of insoluble material. The filtrate was concentrated *in vacuo* to 1.0 liter and cooled in an ice bath to 5°. The solid that formed was removed by filtration, washed with ice water, ether and dried *in vacuo* to give 167.4 g (97%) of **5a**, mp 248-250°; ^{1}H nmr (DMSO-d_6): δ 5.66 (s, 1H), 6.74 (d, 1H, J = 8 Hz, C_5H), 8.36 (d, 1H, J = 8 Hz, C_4H), 9.72 (s, 1H).

Anal. Calcd. for $C_7H_5NO_4$: C, 50.31; H, 3.02; N, 8.38. Found: C, 50.08; H, 2.89; N, 8.14.

General Preparations for the Simple Carbonyl Derivatives of the Pyridone Acetal (**4**), the Pyridone Aldehyde (**5a**) and the Pyridone Ketone (**5b**).

Compounds **6a**, **6b**, **7b**, and **9b** were prepared by reaction of the requisite starting materials (Table 1) in water at *p*H 6.5 (1.0 *N* sodium hydroxide) at room temperature. When the reaction was complete (tlc), the solution was acidified and the product isolated by filtration (Table 1).

Compounds **7a**, **8a** and **10a** were obtained by refluxing the starting materials in methanol-water (1:2), 0.5 *M* hydrochloric acid-methanol (1:2) and methanol (respectively), cooling to room temperature and isolating the product by filtration (Table 1).

1,2-Dihydro-6-[(hydroxyimino)methyl]-2-oxo-3-pyridinecarboxylic Acid (**6a**).

This compound had ^{1}H nmr (DMSO-d_6): δ 6.98 (d, 1H, J = 8 Hz, C_5H), 8.08 (s, 1H), 8.38 (d, 1H, J = 8 Hz, C_4H), 12.62 (s, 1H, NO*H*), 13.38 (bs, 1H), 14.61 (bs, 1H).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.01; H, 3.39; N, 15.22.

1,2-Dihydro-6-[1-(hydroxyimino)ethyl]-2-oxo-3-pyridinecarboxylic Acid (**6b**).

This compound had ^{1}H nmr (DMSO-d_6): δ 2.15 (s, 3H), 3.57 (bs, 2H), 6.97 (d, 1H, J = 7.5 Hz, C_5H), 8.42 (d, 1H, J = 7.5 Hz, C_4H), 12.63 (bs, 1H).

Anal. Calcd. for $C_8H_8N_2O_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.83; H, 3.97; N, 14.42.

6-[2-[(Aminocarbonyl)hydrazino]ethenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**7a**).

This compound had ^{1}H nmr (DMSO-d_6): δ 6.73 (bs, 1H), 6.85 (d, 1H, J = 8 Hz, C_5H), 7.52 (bs, 1H), 7.64 (s, 1H), 8.34 (d, 1H, J = 8 Hz, C_4H), 11.01 (s, 1H).

Anal. Calcd. for $C_8H_8N_4O_4$: C, 42.86; H, 3.60; N, 24.99. Found: C, 42.55; H, 3.66; N, 24.64.

6-[2-[(Aminocarbonyl)hydrazino]-1-methylethenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**7b**).

This compound had ^{1}H nmr (DMSO-d_6): δ 2.12 (s, 3H), 3.56 (bs, 2H), 6.68 (bs, 1H), 6.92 (d, 1H, J = 9 Hz, C_5H), 7.86 (bs, 1H), 8.30 (d, 1H, J = 9 Hz, C_4H), 9.86 (s, 1H).

Anal. Calcd. for $C_9H_{10}N_4O_4$: C, 45.38; H, 4.23; N, 23.52. Found: C, 45.37; H, 4.32; N, 23.27.

6-[2-[(Aminothioxomethyl)hydrazino]ethenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**8a**).

This compound had ^{1}H nmr (DMSO-d_6): δ 6.91 (d, 1H, J = 7.5

Hz, C_5H), 7.80 (s, 1H), 8.35 (d, 1H, J = 7.5 Hz, C_4H), 8.60 (bs, 1H), 8.92 (bs, 1H), 12.02 (s, 1H).

Anal. Calcd. for $C_8H_8N_4O_3S$: C, 40.00; H, 3.36; N, 23.32; S, 13.35. Found: C, 39.71; H, 3.61; N, 23.13; S, 13.30.

1,2-Dihydro-6-[1-(methoxyimino)ethyl]-2-oxo-3-pyridinecarboxylic Acid (**9b**).

This compound had ^{1}H nmr (DMSO-d_6): δ 2.20 (s, 3H), 4.05 (s, 3H), 6.93 (d, 1H, J = 9 Hz, C_5H), 8.33 (d, 1H, J = 9 Hz, C_4H).

Anal. Calcd. for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.23; H, 4.78; N, 13.36.

6-[2-[[(Ethylamino)thioxomethyl]hydrazino]ethenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**10a**).

This compound had ^{1}H nmr (DMSO-d_6): δ 1.22 (t, 3H), 3.61 (q, 2H), 6.88 (d, 1H, J = 8 Hz, C_5H), 7.74 (s, 1H), 6.31 (d, 1H, J = 8 Hz, C_4H); 9.29 (bt, 1H), 10.23 (s, 1H), 11.10 (bs, 1H), 12.70 (bs, 1H).

Anal. Calcd. for $C_{10}H_{12}N_4O_3S$: C, 44.77; H, 4.51; N, 20.88; S, 11.95. Found: C, 44.60; H, 4.53; N, 20.81; S, 11.86.

(*E*)-6-[3-(Ethylamino)-3-oxo-1-propenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**11a**).

To a suspension of 416.0 g (1.08 moles) of phosphonium salt **20** in 220 ml of dimethyl sulfoxide was added 234.1 g (1.08 moles) of 1,5-diazabicyclo[4.3.0]non-5-ene and the reaction mixture was stirred at room temperature for 20 minutes. The reaction was then treated portionwise with 90.5 g (0.54 mole) of solid **5a** and the mixture was stirred at room temperature for 3 hours after the addition was complete. The reaction was then poured onto a solution of 100 ml of 1.0 *N* sodium hydroxide in 1.5 liters of water. The solid triphenylphosphine oxide was removed by filtration and the filtrate was acidified to *p*H 3.0 with 6.0 *M* hydrochloric acid. The resulting precipitate was removed by filtration, washed with water and dried *in vacuo* to give 99.2 g of solids. The solid was stirred in 200 ml of boiling methanol and the insoluble material was removed by filtration, washed with methanol and dried *in vacuo* affording 79.4 g (62%) of **11a**, mp 300-305°; ^{1}H nmr (DMSO-d_6): δ 1.05 (t, 3H), 3.19 (q, 2H), 6.93 (d, 1H, J = 16 Hz, vinyl), 6.96 (d, 1H, J = 8 Hz, C_5H), 7.38 (d, 1H, J = 16 Hz, vinyl), 8.38 (d, 1H, J = 8 Hz, C_4H), 9.30 (bt, 1H).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.86. Found: C, 55.69; H, 4.99; N, 11.75.

(*Z*)-6-[3-(Ethylamino)-3-oxo-1-propenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**11a'**).

The filtrate from the isolation of **11a** was concentrated *in vacuo* and the residue was recrystallized from a minimum of methanol to give 6.9 g (5%) of **11a'**, mp 253-255°; ^{1}H nmr (DMSO-d_6): δ 1.08 (t, 3H), 3.25 (q, 2H), 6.33 (d, 1H, J = 13 Hz, vinyl), 6.81 (d, 1H, J = 13 Hz, vinyl), 6.88 (d, 1H, J = 8 Hz, C_5H), 8.37 (d, 1H, J = 8 Hz, C_4H), 9.24 (bt, 1H).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.92; H, 5.12; N, 11.86. Found: C, 55.80; H, 5.01; N, 11.69.

(*E*)-6-[3-(Ethylamino)-1-methyl-3-oxo-1-propenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**11b**).

To suspension of 0.15 g (3.1 mmoles) of 50% sodium hydride-mineral oil in 25 ml of *N,N*-dimethylacetamide was added dropwise, at room temperature, a solution of 7.0 g (3.1 mmoles) of phosphonate **21** in 10 ml of *N,N*-dimethylacetamide. When the addition was complete, the reaction was stirred at room temperature for 1 hour and treated with a solution of the disodium salt of **5b** prepared by the addition of 0.54 g (3 mmoles) of **5b** to 0.29 g (6 mmoles) of 50% sodium hydride-mineral oil in 25 ml of *N,N*-dimethylacetamide. The reaction was stirred at room temperature for 18 hours and the solvent was removed in high *vacuo* at 50°. The residue was dissolved in water, washed with ether (3 x 100 ml) and acidified to *p*H 2.2 with 6.0 *M* hydrochloric acid. The resulting precipitate was removed by filtration, washed with water and dried *in vacuo* affording 0.7 g (93%) of **11b**, mp 229-230°; ^{1}H nmr (DMSO-d_6): δ 1.03 (t, 3H), 2.37 (s, 3H), 3.12 (q, 2H), 6.33 (s, 1H, vinyl), 6.74 (d, 1H, J = 8 Hz, C_5H), 8.15 (bt, 1H), 8.32 (d, 1H, J = 8 Hz, C_4H).

Anal. Calcd. for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.42; H, 5.68; N, 11.21.

(*E*)-1,2-Dihydro-6-(3-methoxy-3-oxo-1-propenyl)-2-oxo-3-pyridinecarboxylic Acid (**12a**).

A suspension of 2.9 g (60 mmoles) of 50% sodium hydride-mineral oil in 180 ml of tetrahydrofuran was treated portionwise at room temperature with 22.1 g (59.6 mmoles) of **22**. The reaction was stirred at room temperature for 3 hours, filtered to remove inorganics and evaporated *in vacuo*. The residue was triturated with pentane and the solid was removed by filtration, washed with pentane and dried *in vacuo*. The solid was dissolved in 180 ml of dichloromethane, treated with 5.0 g (30 mmoles) of **5a** and the reaction was stirred at room temperature for 18 hours. The precipitate was removed by filtration, washed with dichloromethane and dried *in vacuo* affording 4.95 g (74%) of **12a**, mp >265°; ^{1}H nmr (DMSO-d_6): δ 3.80 (s, 3H), 7.09 (d, 1H, J = 18 Hz, vinyl), 7.22 (d, 1H, J = 8 Hz, C_5H), 7.52 (d, 1H, J = 18 Hz, vinyl), 8.39 (d, 1H, J = 8 Hz, C_4H).

Anal. Calcd. for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.68; H, 4.14; N, 6.02.

(*E*)-6-[3-[[2-(Dimethylamino)ethyl]amino]-3-oxo-1-propenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**13a**).

A suspension of 11.6 g (0.27 mole) of 56% sodium hydride-mineral oil in 140 ml of dimethylsulfoxide was cautiously heated to 60-75° over 1 hour. The solution was cooled to room temperature and treated portionwise with 63.0 g (0.14 mole) of phosphonium salt **24** maintaining the temperature below 40°. The reaction mixture was stirred at room temperature for 1 hour and 11.4 g (68 mmoles) of **5a** was added and the mixture was stirred at 50° for 1 hour. The reaction was cooled to room temperature and poured into an ice cold solution of 70 ml of 2.0 *N* sodium hydroxide in 1.4 liters of water. The solid was removed by filtration and the filtrate was washed with ethyl acetate (3 x 400 ml). The aqueous layer was partially evaporated to remove dissolved ethyl acetate, the *p*H was adjusted to 6.4 with 2.0 *M* hydrochloric acid and stored at 4° for 18 hours. The solid was removed by filtration, washed with cold water and dried *in vacuo* to give 12.1 g (64%) of **13a**, mp 275-276°; ^{1}H nmr (deuteriosodium hydroxide + deuterium oxide): δ 2.19 (s, 6H), 2.50 (t, J = 4 Hz, 2H), 3.36 (t, J = 4 Hz, 2H), 6.61 (d, 1H, J = 16 Hz, vinyl), 6.74 (d, 1H, J = 8 Hz, C_5H), 7.12 (d, 1H, J = 16 Hz, vinyl), 7.78 (d, 1H, J = 8 Hz, C_4H).

Anal. Calcd. for $C_{13}H_{17}N_3O_4 \cdot 1.0H_2O$: C, 52.51; H, 6.44; N, 14.13. Found: C, 52.39; H, 6.65; N, 14.01.

(*E*)-1,2-Dihydro-6-[3-oxo-3-(1-piperidinyl)-1-propenyl]-2-oxo-3-pyridinecarboxylic Acid (**14a**).

A solution of 105.7 g (0.25 mole) of phosphonium salt **25** in 60 ml of dimethyl sulfoxide was treated dropwise with 31.1 g (0.25

mole) of 1,5-diazabicyclo[4.3.0]non-5-ene and the reaction was stirred at room temperature for 20 minutes. The reaction was heated to 50° and 21.0 g (0.125 mole) of **5a** was added and the reaction was exothermic to 80°. The reaction temperature dropped to 60° where stirring was continued for 1 hour with external heating, then 3 hours at room temperature. The reaction mixture was then poured onto 120 ml of 1.0 *N* sodium hydroxide, cooled to 5° and the solid triphenylphosphine oxide was removed by filtration. The filtrate was acidified to *p*H 2.0 with 6.0 *M* hydrochloric acid and the resulting precipitate was removed by filtration, washed with water and dried *in vacuo* affording 18.2 g (53%) of **14a**, mp 275-277°; ^{1}H nmr (DMSO-d_6): δ 1.57 (m, 6H), 3.41 (m, 4H), 7.09 (d, 1H, J = 8 Hz, C_5H), 7.22 (d, 1H, J = 16 Hz, vinyl), 7.70 (d, 1H, J = 8 Hz, C_4H), 8.29 (d, 1H, J = 16 Hz, vinyl).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.87; H, 5.84; N, 10.14. Found: C, 60.51; H, 5.80; N, 10.11.

(*E*)-6-(2-Cyano-1-methylethenyl)-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**15b**).

To a stirred suspension of 4.8 g (0.1 mole) of 50% sodium hydride-mineral oil in 500 ml of tetrahydrofuran was added dropwise with stirring, a solution of 17.7 g (0.1 mole) of diethylcyanomethylphosphonate in 25 ml of tetrahydrofuran. The reaction was stirred at room temperature for 1 hour and treated with 5.4 g (30 mmoles) of **5b**. The reaction was stirred at room temperature for 18 hours and the solvent was removed *in vacuo*. The residue was dissolved in 500 ml of water, washed with ether (2 x 300 ml), clarified with Norit, filtered and the filtrate was acidified to *p*H 2.0 with 6.0 *M* hydrochloric acid. The resulting precipitate was removed by filtration, washed with water and dried *in vacuo* to give 4.8 g (79%) of **15b**, mp 239-241°; ^{1}H nmr (DMSO-d_6): δ 2.44 (s, 3H), 6.46 (s, 1H, vinyl), 7.01 (d, 1H, J = 9 Hz, C_5H), 8.37 (d, 1H, J = 9 Hz, C_4H), 12.50 (bs, 2H).

Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.59; H, 4.02; N, 13.43.

(*E*)-6-(3-Amino-1-methyl-3-oxo-1-propenyl)-1,2-dihydro-2-oxo-3 - pyridinecarboxylic Acid (**16b**).

To 50 ml of 5° sulfuric acid was added portionwise, with stirring, 3.7 g (18 mmoles) of solid **15b**. When the addition was complete, the reaction mixture was stirred at 5° for 4 hours and allowed to come to room temperature over 18 hours. The reaction solution was poured onto 200 g of ice with stirring and the mixture was allowed to stand until the ice melted. A light yellow solid formed and was removed by filtration, washed with water, ethanol, ether and dried *in vacuo* affording 3.6 g (90%) of **16b**, mp 282-283°; ^{1}H nmr (DMSO-d_6): δ 2.31 (s, 3H), 6.32 (s, 1H, vinyl), 6.67 (d, 1H, J = 8 Hz, C_5H), 7.13 (bs, 1H), 7.42 (bs, 1H), 8.73 (d, 1H, J = 8 Hz, C_4H).

Anal. Calcd. for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.79; H, 4.62; N, 12.63.

(*E*)-1,2-Dihydro-6-[1-methyl-3-oxo-3-(1-pyrrolidinyl)-1-propenyl]-2-oxo-3-pyridinecarboxylic Acid (**17b**).

To a suspension of 3.9 g (81 mmoles) of 50% sodium hydride-mineral oil in 500 ml of tetrahydrofuran was added dropwise with stirring, a solution of 19.4 g (81 mmoles) of phosphonate **26** in 25 ml of tetrahydrofuran. When the addition was complete, the reaction was stirred at room temperature for 1 hour and treated portionwise with 3.6 g (20 mmoles) of solid **5b**. The reaction mixture was stirred at room temperature for 18 hours and the solvent was removed *in vacuo*. The residue was dissolved in water, washed with ether and acidified to *p*H 2.2 with 6.0 *M* hydrochloric acid. The resulting precipitate was removed by filtration, washed with water, ethanol, ether and dried *in vacuo* to give 3.6 g (66%) of **17b**, mp 250-251°; ^{1}H nmr (DMSO-d_6): δ 1.81 (m, 4H), 2.20 (s, 3H), 3.48 (m, 4H), 6.60 (s, 1H, vinyl), 6.73 (d, 1H, J = 9 Hz, C_5H), 8.23 (d, 1H, J = 9 Hz, C_4H), 13.2 (bs, 2H).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.90; H, 5.96; N, 10.47.

(*E*)-1,2-Dihydro-6-[3-(4-methyl-1-piperazinyl)-3-oxo-1-propenyl]-2-oxo-3-pyridinecarboxylic Acid (**18a**).

A suspension of 3.6 g (75 mmoles) of 50% sodium hydride-mineral oil in 50 ml of *N,N*-dimethylformamide was cooled to 0° and treated dropwise with a solution of 17.6 g (37 mmoles) of phosphonium salt **28** in 75 ml of *N,N*-dimethylformamide maintaining the temperature at 0-5°. When the addition was complete, the reaction was allowed to come to room temperature over 1 hour and 3.2 g (19 mmoles) of solid **5a** was added. The reaction was exothermic to 31° and was heated to 50° for 2 hours and allowed to come to room temperature where it was stirred for 18 hours. The solvent was removed in high *vacuo* at 50° and the residue was dissolved in 100 ml of water. The solid triphenylphosphine oxide was removed by filtration and the filtrate was acidified to *p*H 4.3 with 6.0 *M* hydrochloric acid. The solid was removed by filtration washed with ether (Note: solid has water solubility) and dried *in vacuo* affording 4.7 g (85%) of **18a**, mp 267-269°; ^{1}H nmr (deuteriosodium hydroxide + deuterium oxide): δ 2.25 (s, 3H), 2.50 (m, 4H), 3.65 (m, 4H), 6.78 (d, 1H, J = 8 Hz, C_5H), 7.20 (s, 2H, vinyl), 7.78 (d, 1H, J = 8 Hz, C_4H).

Anal. Calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.43. Found: C, 57.58; H, 5.79; N, 14.24.

(*E*)-6-[3-(Cyclopropylamino)-3-oxo-1-propenyl]-1,2-dihydro-2-oxo-3-pyridinecarboxylic Acid (**19a**).

To a room temperature suspension of 39.5 g (0.1 mole) of phosphonium salt **29** in 50 ml of dimethylsulfoxide was added 12.4 g (0.1 mole) of 1,5-diazabicyclo[4.3.0]non-5-ene and the reaction was stirred for 20 minutes. The resulting thick suspension was treated with a solution of 8.4 g (50 mmoles) of **5a** in 50 ml of dimethyl sulfoxide. The addition was exothermic and the resulting solution was stirred for 2 hours to room temperature. The reaction mixture was poured onto 400 ml of ice and water, adjusted to *p*H 9.0 with 6.0 *M* hydrochloric acid and stirred to give a fine precipitate of triphenylphosphine oxide. The precipitate was removed by filtration, washed with water and the filtrate was acidified to *p*H 2.5 with 6.0 *M* hydrochloric acid. The resulting precipitate was removed by filtration, washed with water and dried *in vacuo* affording 5.9 g (48%) of **19a**, mp >250°; ^{1}H nmr (DMSO-d_6): δ 0.60 (m, 4H), 2.79 (m, 1H), 6.82 (d, 1H, J = 14 Hz, vinyl), 6.90 (d, 1H, J = 8 Hz, C_5H), 7.29 (d, 1H, J = 14 Hz, vinyl), 8.35 (d, 1H, J = 8 Hz, C_4H), 8.45 (bd, 1H, J = 4 Hz, NH), 13.45 (bs, 1H), 14.53 (bs, 1H).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 57.97; H, 4.58; N, 11.15.

Preparation of Wittig and Horner-Emmons Intermediates **20-29**.

2-[(Ethylamino)-2-oxoethyl]triphenylphosphonium Chloride (**20**).

A solution of 216 g (4.8 moles) of monoethylamine in 2 liters of tetrahydrofuran (THF) was cooled to 5° and treated with a solution of 271.1 g (2.4 moles) of chloroacetyl chloride in 500 ml of tetrahydrofuran maintaining the temperature at 5° during the

addition. After the addition was complete, the reaction was stirred at 5° for 1 hour, the ethylamine hydrochloride was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in 2.4 liters of toluene, filtered to remove a trace of ethylamine hydrochloride and 608.8 g (2.4 moles) of triphenylphosphine was added to the filtrate. The resulting solution was heated at reflux for 6 hours and allowed to stand at room temperature for 10 hours. The solid was removed by filtration, washed with ethyl acetate and dried *in vacuo* to give 673 g (73%) of **20**, mp 247-250°; ^{1}H nmr (DMSO-d_6): δ 0.84 (t, 3H), 2.89 (q, 2H), 5.01 (d, 2H, J = 15 Hz, P-CH_2), 7.72 (m, 15H), 9.05 (bt, 1H, N-H).

Anal. Calcd. for $C_{22}H_{23}ClNOP$: C, 68.84; H, 6.04; N, 3.65. Found: C, 68.58; H, 5.87; N, 3.57.

Diethyl [2-(Ethylamino-2-oxoethyl]phosphonate (**21**).

A solution of 35.5 g (0.29 mole) of *N*-chloroacetamide and 48.5 g (0.29 mole) of triethylphosphite was gradually heated to 170° over 7 hours with moderate gas evolution (ethyl chloride). The reaction was recooled to room temperature and distilled *in vacuo* to give 22.5 g (35%) of **21**, bp 157-160°/1.0 mm; ^{1}H nmr (deuteriochloroform): δ 1.12 (t, 3H), 1.32 (t, 6H), 2.79 (d, 2H, J = 18 Hz, P-CH_2), 3.24 (q, 2H), 3.05 (q, 4H), 6.81 (bs, 1H).

Anal. Calcd. for $C_8H_{18}NO_4P$: C, 43.05; H, 8.13; N, 6.28. Found: C, 42.98; H, 8.01; N, 5.99.

(2-Methoxy-2-oxoethyl)triphenylphosphonium Chloride (**22**).

This compound was prepared according to the procedure of Wittig and Haag [10].

2-Chloro-*N*-[2-(dimethylamino)ethyl]acetamide Hydrochloride (**23**).

A solution of 22.6 g (0.2 mole) of chloroacetyl chloride in 40 ml of dichloromethane was added to a solution of 17.6 g (0.2 mole) of *N,N*-dimethylaminoethylamine in 200 ml of dichloromethane maintaining the temperature at −45 ±5° during the addition and for 45 minutes thereafter. The reaction was then allowed to come to room temperature where it was diluted with 150 ml of ether. The precipitate was removed by filtration, washed with ether and dried *in vacuo* affording 39.3 g (98%) of **23**, mp 103-105°, resolidifies and then remelts 124-125°; ^{1}H nmr (DMSO-d_6): δ 2.73 (s, 6H), 3.01 (dd, 2H), 3.41 (dd, 2H), 4.00 (s, 2H), 8.62 (bt, 1H), 10.21 (bs, 1H).

Anal. Calcd. for $C_6H_{14}Cl_2N_2O$: C, 35.83; H, 7.02; N, 13.93. Found: C, 35.67; H, 6.87; N, 13.78.

[[2-[[2-(Dimethylamino)ethyl]amino]-2-oxoethyl]triphenylphosphonium Chloride Hydrochloride (**24**).

A solution of 29.2 g (145 mmoles) of **23**, 38.3 g (146 mmoles) of triphenylphosphine and 180 ml of nitromethane was heated at reflux for 7 hours. The solvent was removed *in vacuo* and the residue was triturated with 200 ml of ethyl acetate to give a fine granular precipitate. After filtration, the solid was washed with ethyl acetate, ether and dried *in vacuo* to give 63.2 g (94%) of **24**; ^{1}H nmr (DMSO-d_6): δ 2.63 (s, 6H), 2.93 (dd, 2H), 3.32 (dd, 2H), 5.20 (d, 2H, J = 16 Hz, P-CH_2), 7.77 (m, 15H), 9.42 (bs, 1H, N-H).

Anal. Calcd. for $C_{24}H_{29}Cl_2N_2OP$: C, 62.21; H, 6.31; N, 6.05. Found: C, 62.01; H, 6.08; N, 6.01.

[2-Oxo-2-(1-piperidinyl)ethyl]triphenylphosphonium Chloride (**25**).

A solution of 85.2 g (1.0 moles) of piperidine in 1 liter of toluene was cooled to 0° and treated with a solution of 56.5 g (0.5 mole) of chloroacetyl chloride in 500 ml of toluene over 2 hours maintaining the temperature at 0-5°. When the addition was complete, the reaction was allowed to come to room temperature where it was stirred an additional 2 hours. The piperidine hydrochloride was removed by filtration, the organic layer was washed with water (3 x 300 ml), dried, filtered and evaporated to a volume of 500 ml *in vacuo*. The solution was treated with 131.2 g (0.5 mole) of triphenylphosphine, heated at reflux for 6 hours and cooled to room temperature. The initially gummy precipitate crystallized with stirring to give a fine precipitate which was removed by filtration, washed with toluene, ethyl acetate and dried *in vacuo* affording 151.5 g (72%) of **25**; ^{1}H nmr (DMSO-d_6): δ 1.50 (m, 6H), 3.31 (m, 2H), 3.52 (m, 2H), 5.57 (d, 2H, J = 14 Hz, P-CH_2), 7.73 (m, 15H).

Anal. Calcd. for $C_{25}H_{27}ClNOP$: C, 70.83; H, 6.42; N, 3.31. Found: C, 70.87; H, 6.35; N, 3.27.

Diethyl [2-Oxo-2-(1-pyrrolidinyl)ethyl]phosphonate (**26**).

A solution of 35.9 g (0.5 mole) of pyrrolidine in 250 ml of toluene was cooled to −20° and treated dropwise with a solution of 28.8 g (0.25 mole) of chloroacetyl chloride in 25 ml of toluene at a rate to maintain a temperature of −20° to −10°. When the addition was complete, the reaction mixture was allowed to come to room temperature where it was stirred for 18 hours. The reaction was filtered to remove pyrrolidine hydrochloride, which was a tacky solid, and the toluene filtrate was decanted away from a layer of red oil. The organic layer was washed with 0.5 m hydrochloric acid (75 ml), water (2 x 100 ml), dried, filtered and evaporated *in vacuo* to give 15.6 g (0.11 moles) of 1-(chloroacetyl)pyrrolidine. This material was heated at reflux in 18.3 g (0.11 moles) of triethylphosphine for three hours, then distilled at reduced pressure to give 19.6 g (32%) of **26**, bp 129-131°/0.15 mm; ^{1}H nmr (deuteriochloroform): δ 1.32 (t, 6H), 1.89 (m, 4H), 2.90 (d, 2H, J = 21 Hz, P-CH_2), 3.49 (m, 4H), 4.12 (q, 4H).

Anal. Calcd. for $C_{10}H_{20}NO_4P$: C, 48.19; H, 8.09; N, 5.62. Found: C, 48.01; H, 7.80; N, 5.98.

1-(Chloroacetyl)-4-methylpiperazine (**27**).

A solution of 51.1 g (0.5 mole) of 1-methylpiperazine in 1 liter of ether was cooled to −5° and treated dropwise with a solution of 28.8 g (0.25 mole) of chloroacetyl chloride in 50 ml of ether. When the addition was complete, the reaction was allowed to come to room temperature where it was stirred for 3 hours. The methylpiperazine hydrochloride was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was triturated with petroleum ether with cooling and the resulting precipitate was removed by filtration, washed with petroleum ether and dried *in vacuo* affording 37.1 g (84%) of **27**, mp 198-200°; ^{1}H nmr (DMSO-d_6): δ 2.21 (s, 3H), 2.30 (m, 4H), 3.42 (m, 4H), 4.32 (s, 2H).

Anal. Calcd. for $C_7H_{13}ClN_2O$: C, 47.59; H, 7.42; H, 15.86. Found: C, 47.32; H, 7.15; N, 15.58.

[2-(4-Methyl-1-piperazinyl)-2-oxoethyl]triphenylphosphonium Chloride (**28**).

A suspension of 8.8 g (50 mmoles) of **27**, 13.1 g (50 mmoles) of triphenylphosphine and 200 ml of dichloromethane was stirred at room temperature for 48 hours. The solvent was removed *in vacuo* and the residue was successively triturated with 200 ml of benzene and 100 ml of ethyl acetate whereupon, it crystallized. The solid was removed by filtration, washed with ethyl acetate, ether and dried *in vacuo* to give 13.1 g (60%) of **28**, mp 225-227°;

^{1}H nmr (DMSO-d_6): δ 2.28 (s, 3H), 3.58 (m, 8H), 5.62 (d, 2H, J = 14 Hz, P-CH_2), 7.88 (m, 15H).

Anal. Calcd. for $C_{25}H_{28}ClN_2OP$: C, 68.41; H, 6.43; N, 6.38. Found: C, 68.25; H, 6.24; N, 6.15.

[2-(Cyclopropylamino)-2-oxoethyl]triphenylphosphonium Chloride (**29**).

A solution of 57.1 g (1.0 mole) of cyclopropylamine in 300 ml of toluene was cooled to 5° and treated with a solution of 56.5 g (0.5 mole) of chloroacetyl chloride in 500 ml of toluene maintaining the temperature during the addition. When the addition was complete, the reaction was stirred at 5 ° for 1 hour allowed to come to room temperature and the cyclopropylamine hydrochloride was removed by filtration. The precipitate was triturated with ethyl acetate, filtered and the filtrate was combined with the original toluene filtrate. The combined filtrate was concentrated *in vacuo* and the residue was dissolved in 300 ml of nitromethane. The solution was treated with 131.0 g (0.5 mole) of triphenylphosphine and heated at reflux for 5 hours. After cooling to room temperature the mixture was diluted with 200 ml of ethyl acetate and the precipitate was removed by filtration, washed with ethyl acetate, ether and dried *in vacuo* affording 148.7 g (75%) of **29**, mp 248-250°; ^{1}H nmr (DMSO-d_6): δ 0.19 (m, 2H), 0.51 (m, 2H), 4.45 (m, 1H), 4.98 (d, 2H, J = 15 Hz, P-CH_2), 7.71 (m, 15H), 9.22 (bd, 1H).

Anal. Calcd. for $C_{23}H_{23}ClNOP$: C, 69.78; H, 5.86; N, 3.54. Found: C, 69.57; H, 5.67; N, 3.34.

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