Synthesis of (Pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridines

Daniel B. Moran, George O. Morton and J. Donald Albright*

American Cyanamid Company, Medical Research Division, Lederle Laboratories,
Pearl River, New York 10965

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Methods for the synthesis of (pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridines were developed. The principal route to the required intermediate 2-chloropyridines was based on rearrangements of mono *N*-oxides of 2,2'-bipyridine, 2,3'-bipyridine, 3,3'-bipyridine, 2,4'-bipyridine and 4,4'-bipyridine with phosphorus oxychloride. Reaction of 3,3'-bipyridine 1-oxide or 2,2'-bipyridine 1-oxide with phosphorus oxychloride gave mixtures of chloro isomers. Reaction with acetic anhydride, 3,3'-bipyridine 1-oxide and 2,2'-bipyridine 1-oxide gave exclusively [3,3'-bipyridine]-2(1*H*)-one and [2,2'-bipyridine]-6(1*H*)-one, respectively.

1,2,4-Triazolo[4,3-*a*]pyridines with pyridinyl groups at the 5,6,7 and 8 positions were synthesized.

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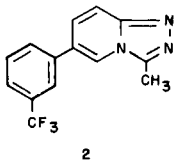
Since the initial discovery of a series of 6-substituted-phenyl-1,2,4-triazolo[4,3-*b*]pyridazines with interesting anxiolytic properties [1] we have been interested in 6,5-fused nitrogen heterocycles with a bridgehead nitrogen [2]. A number of such systems have exhibited potent anxiolytic activity [3-10].

The triazolo[4,3-*a*]pyridine **2** [7] exhibited interesting anxiolytic properties and this report describes our synthetic efforts to prepare the 3-pyridinyl analogue **5** as well as related compounds **6** which contain a pyridinyl group at either the 5,6,7 or 8 positions.



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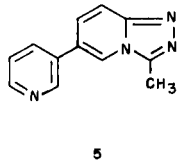

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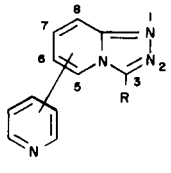
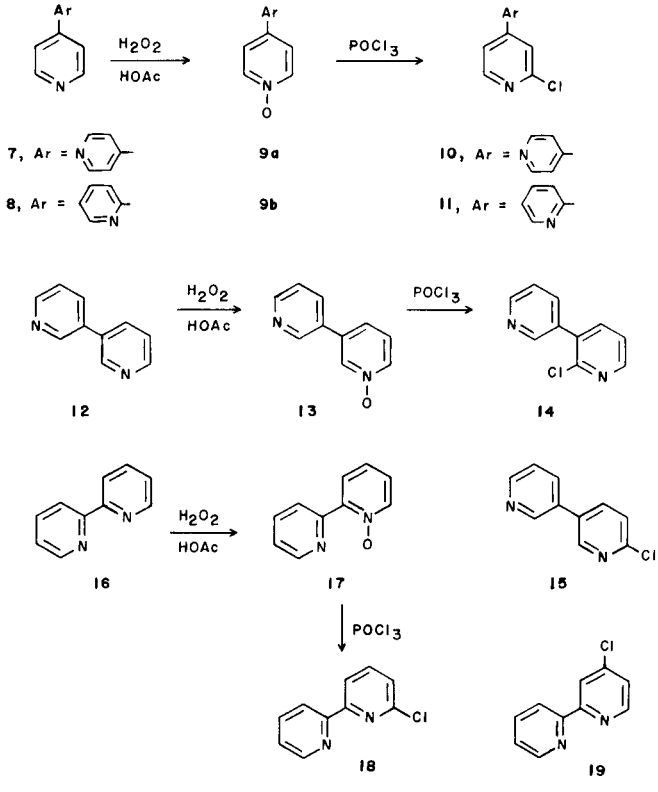


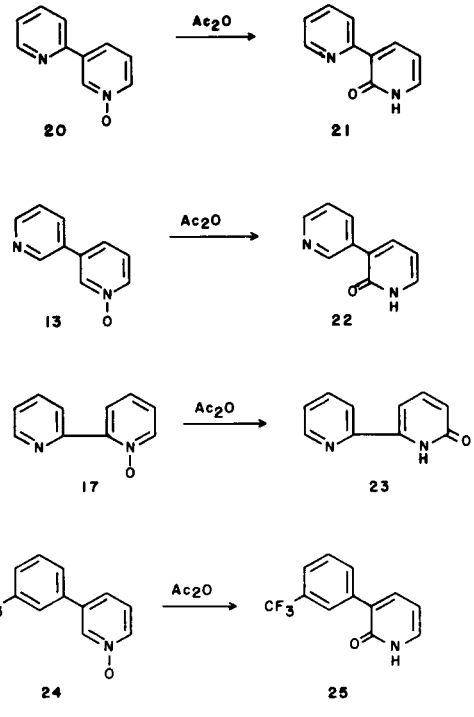
6 R = H, CH_3

Our initial objective was an expeditious synthesis of 2-chloropyridines, since 2-chloropyridines react with hydrazine to yield hydrazino derivatives which undergo ring closure with orthoformates and orthoacetates to afford 1,2,4-triazolo[4,3-*a*]pyridines. A potential route to pyridinyl-2-chloropyridines is the rearrangement of mono *N*-oxides of bipyridines. The mono *N*-oxides of 2,2'-bipyridine [11], 3,3'-bipyridine [12], 4,4'-bipyridine [13] and 2,3'-bipyridine [14] have been reported. However, when we initiated this work, only the preparation of 4,4'-bipyridine 1-oxide (60% yield) was described with experimental details. Similar conditions [13] (hydrogen peroxide-acetic acid, 70%) were used to prepare mono *N*-oxides of 2,2'-bipyridine, 3,3'-bipyridine 4,4'-bipyridines 2,3'-bipyridine and 2,4'-bipyridine in 50-60% yields. Under these conditions, the crude reaction mixtures consisted of unreacted bipyridine, mono *N*-oxide and di-*N*-oxide. The utility of this reaction depends on removal of the insoluble di-*N*-oxide and purification of the mono *N*-oxide.

Rearrangements of 4,4'-bipyridine 1-oxide (**9**, Ar = 4-pyridinyl) and 2,4-bipyridine 1-oxide (**9**, Ar = 2-pyridinyl) with phosphorus oxychloride gave exclusively the 4-(pyridinyl)-2-chloropyridines **10** and **11**. Mixtures of chloro isomers were obtained on reaction of 3,3'-bipyridine 1-oxide **13** or 2,2'-bipyridine 1-oxide **17** with phosphorus oxychloride. The proportion and identity of each chloro isomer in the product mixture were determined by ^{13}C-nmr spectroscopy. Reaction of 3,3'-bipyridine 1-oxide (**13**) with phosphorus oxychloride (reflux) gave a mixture of 2-chloro-3,3'-bipyridine (**14**) (50%) and 6-chloro-3,3'-bipyridine (**15**) (50%). With 2,2'-bipyridine 1-oxide (**17**) a 1:1 mixture of 6-chloro-2,2'-bipyridine (**18**) and 4-chloro-2,2'-bipyridine (**19**) was obtained.

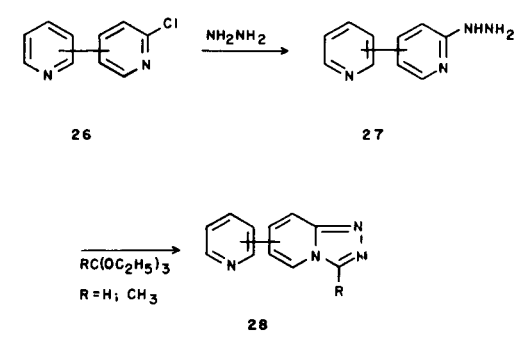


The formation of mixtures from the reaction of substituted pyridine *N*-oxides with trimethylsilyl cyanide [15], phosphorus oxychloride [16], or acetic anhydride has been reported [16]. The position of substitution on reaction of mono *N*-oxides of substituted pyrazines with phosphorus oxychloride or acetic anhydride (chlorination or acetylation) is reported to occur mainly at those positions with the lowest π-electron density [17]. Reaction of 2,3'-bipyridine 1'-oxide (**20**) or 3,3'-bipyridine 1-oxide (**13**) with acetic anhydride gave pyridin-2(1*H*)-ones **21** and **22** respectively, with the rearrangement occurring exclusively toward the proximate pyridinyl group. Similarly, rearrangement of 3-[3-trifluoromethyl)phenyl]pyridine *N*-oxide (**24**) with acetic anhydride gave exclusively 3-[3-(trifluoromethyl)-phenyl]pyridin-2(1*H*)-one (**25**) while 2,2'-bipyridine 1-oxide (**17**) afforded only 6-(2-pyridinyl)pyridin-2(1*H*)-one (**23**). The selectivity in reactions of these *N*-oxides with acetic anhydride compared to the non-selectivity with phosphorus oxychloride is not readily rationalized.



Nucleophilic displacement by hydrazine of the 2-chloro group in these pyridines substituted with an aryl or heteroaryl group is accomplished less readily than in related 3-chloropyridazines [1]. This unreactivity required the reaction of 2-chloropyridines **26** with hydrazine to be carried out in refluxing pyridine for 1 to 2 days.

Ring closure of the 2-hydrazinopyridines **27** with triethyl orthoformate or triethyl orthoacetate gave the desired (pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridines **28** in good yields.

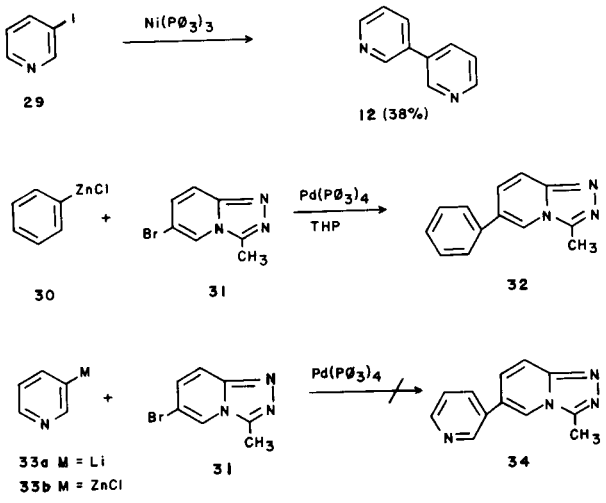


In an attempt to prepare the mono *N*-oxide of 4,7-phenanthrolin-5,6-dione [18], we discovered a convenient method for the preparation of 3,3'-bipyridine-2,2'-dicarboxylic acid [19]. Reaction of 4,7-phenanthraline-5,6-dione with 30% hydrogen peroxide in glacial acetic gave directly (by filtration of the mixture) the di-acid in 88% yield. The desired 3,3'-bipyridine [19a,20] (**12**) was then obtained by thermal decarboxylation of the diacid [19b].

The synthesis of 3,3'-bipyridine through symmetric coupling of iodopyridine (**29**) catalyzed by metal complexes [21] was briefly investigated. Tris-(triphenylphosphine) nickel (0) was prepared *in situ* by zinc reduction of bis(triphenylphosphine) nickel (II) dichloride [21a] and used to mediate the symmetric coupling of 3-iodopyridine (**29**) to give 3,3'-bipyridine (**12**) in 38% yield. A modified procedure has been recently reported [22] to give bipyridines in high yields from bromopyridines.

A potential alternative method for the preparation of (pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridines is cross-coupling *via* transition metal catalysis [23]. As a model reaction, the coupling of phenyllithium and phenylzinc chloride with 6-bromo-3-methyl-1,2,4-triazolo[4,3-*a*]pyridine (**31**) catalyzed by tetrakis (triphenylphosphine) palladium (0) [24] was investigated. The reaction failed with phenyllithium but with phenylzinc chloride (**30**) gave 3-methyl-6-(phenyl)-1,2,4-triazolo[4,3-*a*]pyridine (**32**) in 38% yield. Higher yields with organic zinc chloride as the organometallic reagent have been reported in couplings catalyzed with tetrakis (triphenylphosphine) palladium (0) [25]. Despite this preliminary success, the unsymmetrical coupling of 3-pyridinyllithium (**33a**) or 3-pyridinyl zinc chloride (**33b**) with 6-bromo-3-methyl-1,2,4-triazolo[4,3-*a*]pyridine (**31**) failed to give a recognizable product. The failure in couplings with the 3-pyridinyl organometallic may be due to difficulties in preparation of the 3-pyridinyllithium from butyllithium and 3-bromopyridine. Organolithium reagents are known to add readily at the 2-position of the pyridine ring [26]. Experiments to establish that 3-pyridinyllithium or 3-pyridinyl zinc chloride had been prepared (*in situ*) in high yield were not carried out. The $Pd(PPh_3)_4$ catalysed coupling of 3-bromopyridines with phenylboronic acids to give 3-arylpyridines was reported

recently [27], as well as the coupling of diethyl-(3-pyridyl)borane with arylhalides to give 3-heteroarylpyridines [28].



EXPERIMENTAL

All melting points were taken on a Mel-Temp® apparatus and are not corrected. Samples for analysis were dried *in vacuo* over Drierite® at 70° for 16-25 hours. Infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Pmr spectra were determined in $CDCl_3$ with a Varian A-100 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Solvents were removed under reduced pressure by the use of a rotary evaporator. Magnesol® is the trade name for hydrous magnesium silicate.

3,3'-Bipyridine 1-Oxide (**13**).

A mixture of 15.6 g (0.10 mole) of 3,3'-bipyridine, 13.6 ml (0.12 mole) of 30% hydrogen peroxide and 100 ml of glacial acetic acid was stirred and heated for 18 hours with the internal temperature kept at 70° with an I²R Therm-O-Watch automatic control. The solvent was removed under vacuum and ice added to the residue. The mixture was made alkaline with 10*N* sodium hydroxide and extracted with chloroform in a liquid-liquid extractor. The extract was concentrated under vacuum and the residual solid heated with 600 ml of acetone. Filtration gave 4.3 g of off-white crystals, mp >305° of 3,3'-bipyridine 1,1'-dioxide. The filtrate was concentrated to 150 ml, chilled and filtered to give 6.5 g (35%) of off-white crystals, mp 151-153°.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.8; H, 4.7; N, 16.3. Found: C, 69.4; H, 4.9; N, 16.3.

[3,3'-Bipyridin]-2(1*H*)-one (**22**).

A mixture of 3.0 g (0.0175 mole) of 3,3'-bipyridine 1-oxide and 100 ml of acetic anhydride was refluxed for 5 hours and the solvent removed under vacuum. Toluene was added and the solvent removed. The residue was dissolved in chloroform and passed through a short pad of hydrous magnesium silicate. The filtrate was concentrated and hexane added while boiling off the solvent. Chilling and filtering gave 2 g (66%) of off-white crystals, mp, 187-195°. From a similar run, a sample was twice recrystallized from isopropyl alcohol to give off-white crystals, mp 189-192°; R_f 0.5, tlc on silica gel with solvent chloroform-methanol (9:1).

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.8; H, 4.7; N, 16.3. Found: C, 69.3; H, 4.9; N, 16.1.

2-Bromo-3,3'-bipyridine.

A mixture of 1.5 g (8.7 mmoles) of [3,3'-bipyridin]-2(1*H*)-one and 25 ml of phosphorus oxybromide was heated on a steam bath for 18 hours, poured onto crushed ice and made alkaline with 10*N* sodium hydroxide. The resulting solid was filtered, washed with water and dissolved in dichloromethane. The solution was dried (sodium sulfate), passed through a short pad of hydrous magnesium silicate and concentrated while diluting with hexane. Chilling gave 1.4 g (63%) of white crystals, mp 95-98°. A sample from a similar run on recrystallization from hexane gave white crystals, mp 97-98°; one spot tlc (silica gel) 10% methanol/-chloroform: R_f 0.8.

Anal. Calcd. for $C_{10}H_7BrN_2$: C, 51.1; H, 3.0; N, 11.9; Br, 34.0. Found: C, 50.9; H, 2.8; N, 12.0; Br, 33.9.

3-Methyl-6-(3-pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine and 8-(3-Pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture (2.0 g) of 3,3'-bipyridine 1-oxide and 50 ml of phosphorus oxychloride was refluxed for 18 hours and then concentrated under vacuum. To the residue was added crushed ice and solid potassium carbonate until the solution was strongly alkaline. The mixture was extracted with chloroform, the extract dried (sodium sulfate) and passed through a short pad of hydrous magnesium silicate. The eluant was concentrated to give 2.3 g of yellow oil which was dissolved in hexane, treated with activated carbon, concentrated and chilled. Filtration gave 0.7 g (31%) of white crystals, mp 68-73°, tlc, silica gel with solvent ethyl acetate (R_f 0.7); mixture (1:1) of 2-chloro-3,3'-bipyridine and 6-chloro-3,3'-bipyridine by ^{13}C-nmr. Similar runs where the mixture was isolated in 50-60% yield (sufficiently pure for analysis) consistantly showed a 1:1 mixture of isomers.

The preceding mixture (0.5 g) and 5 ml of anhydrous hydrazine in 50 ml of dry pyridine was refluxed for 3 days. Tlc (silica gel-ethyl acetate) showed only a trace of starting material remaining. The mixture was concentrated under vacuum to give a gum. To the gum was added 40 ml of triethyl orthoacetate and the mixture was heated on a steam bath for 18 hours. Concentration under vacuum and chromatography on silica gel with methanol-chloroform (1:4) as solvent gave 0.5 g of solid. Analysis by ^{13}C-nmr showed the product to be a mixture of 3-methyl-6-(3-pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine (40%) and 3-methyl-8-(3-pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine (60%).

2,2'-Bipyridine 1-Oxide (**17**).

A mixture of 51.55 g (0.33 mole) of 2,2'-bipyridine, 40 ml of 30% hydrogen peroxide (0.35 mole) and 250 ml of glacial acetic acid was heated for 18 hours, with the internal temperature kept at 70° by an I²R Therm-O-Watch automatic control. The solvent was removed under vacuum and the residue diluted with 100 ml of water. Solid potassium carbonate was added until the mixture was strongly alkaline. The mixture was extracted with chloroform in a liquid-liquid extractor for 18 hours. The organic extract was concentrated under vacuum. The semi-solid was heated with ether and the mixture filtered. The filtrate was concentrated to give 35.7 g of an oily solid. Tlc [ethyl acetate-hexane (1:4) on silica gel] showed two spots; product near the origin. This product was chromatographed on a Waters Prep 500 column (silica gel) with ethyl acetate-hexane (1:3). After impurities were eluted, the column was washed with ethyl acetate to give 16.0 g (35%) of oil which crystallized to give white crystals, mp 59-61°. From a similar run (104 g, 0.66 mole) followed by chromatography on a Waters Prep 500 column [product elution monitored by tlc of fractions (silica gel-3% methanol in chloroform)] with chloroform as solvent gave 57 g (49%) of white crystals, mp 58-60°.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.8; H, 4.7; N, 16.3. Found: C, 69.6; H, 4.7; N, 16.3.

[2,2'-Bipyridin]-6(1*H*)-one (**23**).

A mixture of 20.0 g (0.116 mole) of 2,2'-bipyridine 1-oxide and 200 ml of acetate anhydride was refluxed for 18 hours. The volatiles were removed under vacuum and the residue heated on a steam bath with 200 ml of 5*N* sodium hydroxide for 5 hours. After treatment with activated carbon and filtration while hot, the mixture was allowed to cool and dichloromethane was added. Filtration gave 17.0 g of tan solid. The solid was stirred in water and the *p*H adjusted to *ca* 7.0 with dilute

hydrochloric acid. Extraction with dichloromethane and concentration of the organic extracts gave 6.2 g (31%) of product. Recrystallization of a 7.5 g sample from dichloromethane-hexane (99:1) gave 6.0 g of off-white crystals, mp 124-127°; ^{1}H nmr: δ 6.61 (d, 1, C_3 or C_5H, J = 8 Hz), 6.79 (d, 1, C_3 or C_5H, J = 6 Hz), 7.20-7.65 (m, 2H), 7.80, 7.85 (2), 7.64 (d, 1, C_6H, J = 5 Hz), 10.69 (s, 1, NH), 1.40 (CH_3 of hexane solvate).

Anal. Calcd. for $C_{10}H_8N_2O$. 0.15% hexane; C, 70.7; H, 5.5; N, 15.1. Found: C, 70.3; H, 5.3; N, 15.0.

4'-Chloro-2,2'-bipyridine (**19**) and 6'-Chloro-2,2'-bipyridine (**18**).

To 19.0 g (0.11 mole) of 2,2'-bipyridine 1-oxide was added slowly (exotherm) 125 ml of phosphorus oxychloride and the mixture was refluxed for 18 hours. After concentrating under vacuum the residue was treated with ice and ice-water and made alkaline with 5*N* sodium hydroxide. The mixture was extracted with dichloromethane and the solution passed through a short pad of hydrous magnesium silicate. The filtrate was concentrated to give 16.6 g of yellow oil which was crystallized from pentane to afford 9.0 g (44%) of white crystals, mp 46-48°.

Anal. Calcd. for $C_{10}H_7ClN_2$: C, 63.0; H, 3.7; N, 14.7; Cl, 18.6. Found: C, 62.8; H, 3.8; N, 14.9; Cl, 18.2.

The ^{13}C-nmr showed the product to be a mixture (1:1) of **18** and **19**. Similar runs, where the mixture (as an oil) was isolated in 50-55% yield (sufficiently pure for analyses), consistently showed a 1:1 mixture of isomers.

6'-Chloro-2,2'-bipyridine (**18**).

A mixture of 5.3 g (0.031 mole) of [2,2'-bipyridin]-6(1*H*)-one and 100 ml of phosphorus oxychloride was heated on a steam bath for 18 hours and then concentrated to dryness under vacuum. Crushed ice was added to the oily residue and the mixture made basic with solid potassium carbonate. The mixture was extracted with dichloromethane, the extracts treated with activated carbon, filtered and concentrated to give 4.5 g (76%) of yellow crystals, mp 57-59°, tlc on silica gel (ethyl acetate) showed a major spot at R_f 0.8 and minor spot at R_f 0.1. The product was purified by chromatography on silica gel with ethyl acetate as solvent to give 4.12 g (70%) of white crystals, mp 60-62°; ^{1}H nmr: 7.15-7.45 (m, 2), 7.62-8.0 (m, 2), 8.35 (d, 1, J = 4 Hz), 8.44 (d, 1, J = 4 Hz), 8.67 (d, 1, J = 4 Hz).

Anal. Calcd. for $C_{10}H_7ClN_2$: C, 63.0; H, 3.7; N, 14.7; Cl, 18.6. Found: C, 63.1; H, 3.7; N, 14.9; Cl, 18.6.

6'-Hydrazino-2,2'-bipyridine.

A mixture of 4.0 g (0.021 mole) 6'-chloro-2,2'-bipyridine and 10 ml of anhydrous hydrazine in 50 ml of dry pyridine was refluxed for 48 hours. Additional hydrazine (10 ml) was added and the solution refluxed for an additional 72 hours while 5 ml portions of hydrazine were added at 18 hour intervals. The volatiles were removed under vacuum, the residue dissolved in ether, dried over sodium sulfate and concentrated to give 4.0 g of off-white crystals. Recrystallization from ether-heptane gave 3.0 g (76%) of crystals, mp, 69-70°.

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.3; H, 5.5; N, 30.3.

3-Methyl-5-(2-pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture of 1.0 g (5.38 mmoles) of 6'-hydrazino-2,2'-bipyridine, 50 ml of triethyl orthoacetate and 5 drops of acetic acid was heated on a steam bath for 2.5 days. The volatiles were removed under vacuum and the residue crystallized from ether-hexane to give 0.69 g (61%) of gold colored crystals. The solid was dissolved in dichloromethane and the solution passed through a short pad of hydrous magnesium silicate. Concentration of the filtrate gave 0.46 g (39%) of crystals, mp, 168-170°; ^{1}H nmr: (deuteriochloroform): δ 2.15 (s, 3, CH_3), 6.75 (d, 1, aromatic, J = 7 Hz), 7.07-8.1 (m, 5, aromatic), 8.79 (d, 1, aromatic, J = 6 Hz).

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.6; H, 4.8; N, 26.6. Found: C, 68.1; H, 4.8; N, 26.3.

5-(2-Pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture of 1.2 g (6.4 mmoles) of 6'-hydrazino-2,2'-bipyridine and 7 ml of diethoxymethyl acetate was stirred at 23° for 24 hours (crystals separated). The mixture was diluted with hexane and filtered to give 1.3 g of yellow crystals. Recrystallization from ethyl acetate-hexane with the aid of activated carbon gave 1.0 g (79%) of white crystals, mp 120-123°.

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.3; H, 4.1; N, 28.6. Found: C, 67.3; H, 4.1; N, 28.7.

2,3'-Bipyridine 1'-Oxide (**20**).

A mixture of 25.78 g (0.17 mole) of 2,3'-bipyridine, 20 g of 30% hydrogen peroxide and 125 ml of acetic acid was stirred at 70° for 18 hours. The mixture was concentrated under vacuum and the residue dissolved in 50 ml of water. Solid potassium carbonate was added until the solution was strongly alkaline and the solution was extracted with chloroform (liquid-liquid extractor) for 19 hours. The extract was treated with activated carbon and passed through a short pad of hydrous magnesium silicate. The filtrate was concentrated to give 28.5 g of a yellow oil which crystallized on addition of pentane to give 22.5 (97%) of off-white crystals. The crystals were heated with acetone and the mixture filtered to remove insoluble solid (1.7 g). The filtrate was concentrated to 75 ml and allowed to stand. Filtration gave 8.0 g of crystals which were chromatographed on silica gel with chloroform-ethanol (1:1) as solvent to give 7.5 g of crystals. Recrystallization from acetone-hexane afforded 6.0 g (21%) of white crystals, mp 78°; one spot by tlc on silica gel with solvent chloroform-ethanol (1:1).

Anal. Calcd. for $C_{10}H_8N_2O{\cdot}H_2O$: C, 63.1; H, 5.3; N, 14.7. Found: C, 63.0; H, 5.4; N, 14.8.

2,3'-Bipyridine 1,1'-Dioxide.

A mixture of 49.0 g (0.31 mole) of 2,3'-bipyridine, 40 ml of hydrogen peroxide (0.35 mole) (8.8 mmoles/ml) and 200 ml of glacial acetic acid was heated on a steam bath 2 hours. An additional 20 ml of hydrogen peroxide (8.8 mmoles/ml) was added, the solution heated on a steam bath 4 hours, 10 ml of hydrogen peroxide (8.8 mmoles/ml) added again, and the solution heated (steam bath) for 4 hours. The volatiles were removed under vacuum and the residual yellow oil dissolved in 100 ml of water, the solution made alkaline with solid potassium carbonate and extracted with chloroform in a liquid-liquid extractor for 18 hours. The organic layer (containing solid) was cooled and filtered to give 30.0 g (52%) of white crystals, mp 240-243°. Recrystallization of a sample from methanol with the aid of activated carbon gave white crystals, mp 240-243°.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9. Found: C, 63.8; H, 4.3; N, 14.8.

Concentration of filtrate from which di-*N*-oxide was obtained, gave 20 g of yellow oil which crystallized. Recrystallization from acetone-hexane gave 14.9 g (2%) of 2,3'-bipyridine 1'-oxide as white crystals, mp 78°.

[2,3'-Bipyridine]-2'(1*H*)-one (**21**).

A mixture of 3.0 g of 2,3'-bipyridine 1'-oxide and 150 ml of acetic anhydride was refluxed for 18 hours and solvent removed under vaucuum. The residue was dissolved in methanol and treated with activated carbon. The mixture was filtered and the solvent removed. The residue was crystallized from dichloromethane-hexane to give 2.2 g (73%) of yellow crystals, mp 149-150°, tlc (silica gel), 10% chloroform-methanol (9:1); R_f 0.4.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.8; H, 4.7; N, 16.3. Found: 69.4; H, 5.0; N, 16.4.

2'-Chloro-2,3'-bipyridine.

A 5.9 g (0.034 mole) sample of [2,3'-bipyridine]-2'(1*H*)-one in 100 ml of phosphorus oxychloride was heated on a steam bath for 18 hours and concentrated under vacuum. The residue was stirred with crushed ice and chloroform and the mixture adjusted to *p*H 7 with 10*N* sodium hydroxide. The organic layer was separated, dried (sodium sulfate) and passed through a short pad of hydrous magnesium silicate, which was washed with chloroform. The combined filtrates were concentrated under vacuum to an oil which was heated with hexane and the hot mixture filtered. The filtrate was cooled to room temperature to give 3.5 g

(54%) of white needles, mp 50°.

Anal. Calcd. for $C_{10}H_7ClN_2$: C, 63.0; H, 3.7; N, 14.7; Cl, 18.6. Found: C, 63.3; H, 3.7; N, 14.6; Cl, 18.5.

A similar run with 6.0 g of **21** gave 3.7 g (55%) of white crystals, mp 57-60°.

2'-Hydrazino-2,3'-bipyridine.

A mixture of 2.5 g (0.013 mole) of 2'-chloro-2,3'-bipyridine, 12.6 ml (0.39 mole) of anhydrous hydrazine and 50 ml of pyridine was refluxed for 36 hours and concentrated to a gum. A solution of the gum in dichloromethane was treated with activated carbon, dried (sodium sulfate) and concentrated. The residue was crystallized from ether-hexane to give 2.1 g (91%) of yellow crystals, mp 64-65°, one spot by tlc (silica gel) (ethyl acetate).

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.6; H, 5.4; N, 30.2.

8-(2-Pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture of 1.7 g (9.14 mmoles) of 2'-hydrazino-2,3'-bipyridine and 50 ml of triethyl orthoformate was heated on a steam bath 3 hours. On standing, crystals separated and the mixture was chilled, filtered and the crystals washed with hexane to give 1.5 g (84%) of cream crystals, mp 212-214°.

Anal. Calcd. for $C_{11}H_7N_4$: C, 67.7; H, 3.6; N, 28.7. Found: C, 67.5; H, 4.0; N, 28.8.

3-Methyl-8-(2-pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture of 0.5 g of 2'-chloro-2,3'-bipyridine, 5 ml of anhydrous hydrazine and 50 ml of pyridine (dried over 3-A sieves) was refluxed for 24 hours, concentrated under vacuum and the residue dissolved in dichloromethane. The solution was dried (sodium sulfate), passed through a short pad of hydrous magnesium silicate and concentrated under vacuum to a gum. To the gum was added 50 ml of triethyl orthoacetate and the mixture was heated on a steam bath for 2.5 hours. After concentrating under vacuum, the residue was dissolved in dichloromethane and while boiling, hexane was added gradually. Cooling gave 0.3 g (55%) of tan crystals, mp 142-143°, which when recrystallized from dichloromethane-hexane gave tan crystals, mp 143-145°.

Anal. Calcd. for $C_{10}H_{12}N_4$: C, 68.6; H, 4.8; N, 26.6. Found: C, 68.1; H, 4.6; N, 26.6.

2,4'-Bipyridine 1-Oxide (**9b**).

A mixture of 23.0 (0.15 mole) of 2,4'-bipyridine, 17.0 ml (0.15 mole) of 30% hydrogen peroxide and 100 ml of glacial acetic acid was stirred and heated for 48 hours with the internal temperature kept at 70°C with an I²R Therm-O-Watch automatic control. The solvent was removed under vacuum, the residue diluted with water and made alkaline with solid potassium carbonate. The mixture was extracted with chloroform in a liquid-liquid extractor and the extract concentrated to give 25 g of solid. Acetone was added and the insoluble crystals filtered to give 4.3 g of di-*N*-oxide, mp 240-242°.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9. Found: C, 64.2; H, 4.4; N, 14.9.

The acetone solution was placed on a Waters-Prep 500 column and the column eluted with acetone followed by elution with methanol-acetone (1:9). Fraction showing one spot by tlc (silica gel) with solvent methanol-acetone (3:22) were combined and concentrated to give 12.2 g (48%) of off-white crystals, mp 114-117°. A sample was recrystallized twice from acetone-hexane to give white crystals, mp 119-121°.

Anal. Calcd. for $C_{10}H_8N_2O$: C, 69.8; H, 4.7; N, 16.3. Found: C, 69.8; H, 4.7; N, 16.2.

2'-Chloro-2,4'-bipyridine (**11**).

A mixture of 2.0 g (0.012 mole) of 2,4'-bipyridine 1'-oxide and 50 ml of phosphorus oxychloride was heated on a steam bath for 18 hours and concentrated under vacuum. Crushed ice was added to the residue and the mixture made alkaline by addition of solid potassium carbonate. The solution was extracted with ethyl acetate and the extract dried (sodium sulfate), treated with activated carbon and passed through a short pad of hydrous magnesium silicate. The pad was washed with ethyl acetate and the filtrate concentrated to give 2.0 g (87%) of off-white crystals, mp 77-80°. Recrystallization from dichloromethane-hexane gave 1.3 g (56%) of off-white crystals, mp 80-81°.

Anal. Calcd. for $C_{10}H_7ClN_2$: C, 63.0; H, 3.7; N, 14.7; Cl, 18.6. Found: C, 63.0; H, 3.7; N, 14.9; Cl, 18.6.

2'-Hydrazino-2,4'-bipyridine.

A mixture of 5.0 g (26 mmoles) of 2'-chloro-2,4'-bipyridine, 5 ml (0.16 mole) of anhydrous hydrazine and 100 ml of pyridine was refluxed. Additional 5 ml portions of anhydrous hydrazine were added after 18 hours, 36 hours and 54 hours of refluxing. The solution was then refluxed for an additional 48 hours and the solvent removed under vacuum. The residual yellow solid was dissolved in dichloromethane, treated with activated carbon, filtered and the filtrate concentrated to dryness. The residue was triturated with hexane to give 4.8 g (98%) of yellow crystals, mp 119-121°. Recrystallization of a sample from dichloromethane-hexane gave yellow crystals, mp 120-121°.

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.5; H, 5.3; N, 30.4.

7-(2-Pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture of 2.0 g (0.011 mole) of 2'-hydrazino-2,4'-bipyridine and 50 ml of triethyl orthoformate was heated on a steam bath for 18 hours, chilled and filtered to give 1.8 g (78%) of tan crystals, mp 141-143°. The crystals were dissolved in dichloromethane, treated with activated carbon, filtered and the filtrate concentrated. Chilling and filtering afforded 1.5 g (69%) of cream colored crystals, mp 144-145°.

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.3; H, 4.1; N, 28.6. Found: C, 67.1; H, 4.2; N, 29.0.

3-Methyl-7-(2-pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture of 2.0 g (0.011 mole) of 2'-hydrazino-2,4'-bipyridine and 50 ml of triethyl orthoacetate was heated on a steam bath for 18 hours. Chilling, filtering and washing crystals with hexane gave 2.0 g (86%) of tan crystals, mp 238-240°. Recrystallization from dichloromethane (with addition of small amounts of hexane) gave 1.8 g (78%) of white crystals, mp 239-241°; ^1H nmr: δ 2.80 (s, 1, CH_3), 7.20-7.75 (m, 1), 7.60-8.22 (m, 4), 8.30 (s, 1, C_8H), 8.73 (d, 1, -N=CH-, J = 5 Hz).

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.6; H, 4.8; N, 26.7. Found: C, 68.9; H, 4.8; N, 27.0.

4,4'-Bipyridine 1-Oxide (**9a**).

A mixture of 37.68 g (0.196 mole) of 4,4'-bipyridine, dihydrate, 25 g of 30% hydrogen peroxide and 150 ml of glacial acetic acid was stirred and heated for 18 hours with the internal temperature kept at 70° with an I²R Therm-O-Watch automatic control. The solution was concentrated to dryness under vacuum, diluted with 100 ml of water, made alkaline with solid sodium carbonate and extracted with chloroform in a liquid-liquid extractor for 18 hours. The chloroform layer was concentrated under vacuum to give a solid (25 g). The solid was placed in a Soxhlet thimble and extracted with hexane for 36 hours. The hexane extract was concentrated to give 10 g of crystals (mainly starting material). The solid (14 g) from the Soxhlet thimble was suspended in 300 ml of cyclohexane and heated on a steam bath for 0.5 hour. The mixture was cooled to 23° and filtered to give 13.5 g (40%) of cream colored crystals, mp 174-176°, one spot on tlc (silica gel) with acetone as solvent, R_f 0.2.

2-Chloro-4,4'-bipyridine (**10**).

To 100 ml of phosphorus oxychloride cooled in an ice bath was added 10.0 g of 4,4'-bipyridine 4'-oxide. The mixture was stirred 1 hour, heated on a steam bath for 18 hours, and concentrated under vacuum. To the residue was added crushed ice and solid potassium carbonate. The alkaline solution was extracted with chloroform, and the extract dried (sodium sulfate), treated with activated carbon and passed through a pad

of hydrous magnesium silicate. The filtrate was concentrated to give 5.0 g (45%) of white crystals, mp 193-196°. Recrystallization of a sample from dichloromethane-hexane gave white crystals, mp 203-205°, R_f 0.9 (silica gel with solvent acetone).

Anal. Calcd. for $C_{10}H_7ClN_2$: C, 63.0; H, 3.7; N, 14.7; Cl, 18.6. Found: C, 63.1; H, 3.8; N, 14.8; Cl, 18.8.

2-Hydrazino-4,4'-bipyridine.

A mixture of 4.6 g (24.1 mmoles) of 2-chloro-4,4'-bipyridine and 5 ml of anhydrous hydrazine in 50 ml of pyridine was refluxed 18 hours. After the addition of 5 ml of anhydrous hydrazine the mixture was refluxed for 3 more days, with 2 ml of anhydrous hydrazine added after the first day and an additional 2 ml of hydrazine added after the second day. Tlc on silica gel [dichloromethane-methanol (9:1)] showed only small amounts of starting material and the solvent was removed under vacuum. The residue was triturated with hexane to give 6.0 g of solid. The solid was dissolved in hot chloroform, treated with activated carbon and the mixture filtered. The filtrate was concentrated to near dryness and hexane added to give 2.9 g of crystals, mp 108-110°. An additional 1.0 g was recovered from the mother liquors (total yield, 87%). A sample was recrystallized (5x) from dichloromethane to give yellow crystals, mp 109-110°.

Anal. Calcd. for $C_{10}H_{10}N_4$: C, 64.5; H, 5.4; N, 30.1. Found: C, 64.4; H, 5.4; N, 30.1.

7-(4-Pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A 1.0 g sample of 2-hydrazino-4,4'-bipyridine and 50 ml of triethyl orthoformate was refluxed for 18 hours. The mixture was chilled and filtered to give 1.0 g (89%) of tan crystals, mp 180-186°. The product was dissolved in acetone-ethyl acetate, treated with activated carbon, filtered and the filtrate concentrated while hexane was added. Cooling gave white crystals, mp 194-196°.

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.3; H, 4.1; N, 28.6. Found: C, 67.5; H, 4.2; N, 28.6.

3-Methyl-7-(4-pyridinyl)-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture of 1.0 g (5.2 mmoles) of 2-chloro-4,4'-bipyridine, 7 ml of hydrazine and 30 ml of pyridine was refluxed for 48 hours and the solvent removed. The crude 2-hydrazino-4,4'-bipyridine and 100 ml of triethyl orthoacetate was refluxed 18 hours. Chilling the mixture gave 1.0 g (91%) of tan crystals, mp 223-224°. Recrystallization from methanol-ethyl acetate with the aid of activated carbon gave 0.5 g (46%) of off-white crystals, mp 225-227°, one spot by tlc (silica gel) with ethyl acetate-methanol (17.3); ^1H nmr (deuteriochloroform): δ 2.82 (s, 1, CH_3), 7.17 (d, 1, J = 9 Hz), 7.57 (d, 2, J = 7 Hz), 8.0 (s, 1) overlapping doublet), 8.06 (d, 1, J = 9 Hz), 8.51 (d, 2, J = 7 Hz).

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.6; H, 4.8; N, 26.6. Found: C, 68.2; H, 4.8; N, 26.5.

3,3'-Bipyridine-2,2'-dicarboxylic Acid.

A. 4,7-Phenanthroline was oxidized with potassium permanganate by literature procedure [19c,20] to give product, mp 214-215°.

B. A mixture of 42.0 g (0.20 mole) of 4,7-phenanthroline-5,6-dione (generously donated by Ciba-Geigy Corp., Basel, Switzerland), 28.0 ml of 30% hydrogen peroxide (0.25 mole) and 500 ml of glacial acetic acid was stirred at 23° for 1 hour, at 40° for 1 hour, at 60° for 1 hour and then at 70° for 18 hours (internal temperature kept constant with I^2R Therm-O-Watch control). The hot mixture was filtered and the solid dried to give 43 g (88%) of white crystals, mp 210-211°. Multiple runs (6) consistantly gave 42 to 44 g of product which was sufficiently pure for decarbosylation to 3,3'-bipyridine (**12**).

3,3'-Bipyridine (**12**).

To a three neck flask with overhead stirrer was added 39.18 g (0.060 mole) of bis(triphenylphosphine) nickel (II) dichloride, 31.44 g (1.2 mole) of triphenylphosphine and 3.96 g (0.060 mole) of zinc powder. The flask was evacuated and filled with argon three times and 300 ml of dry *N,N*-dimethylformamide added. The mixture was heated at 50° (internal temperature) controlled by I^2R Therm-O-Watch) for 2 hours. To the flask was added dropwise over 15 minutes 12.3 g (0.060 mole) of 3-iodopyridine in 120 ml of *N,N*-dimethylformamide and the mixture stirred at 50° under argon for 18 hours. The volatiles were removed under vacuum, chloroform added and the mixture made alkaline with 5*N* sodium hydroxide. Extraction with chloroform in a liquid-liquid extractor, followed by concentration of the chloroform extract gave a solid which was washed with 10% hydrochloric acid. The washings were concentrated under vacuum, made alkaline with 10*N* sodium hydroxide and extracted with chloroform in a liquid-liquid extractor for 18 hours. The extract was concentrated and the residue distilled (bulb-bulb) to give 3.63 g (39%) of 3,3'-bipyridine as an oil.

3-Methyl-6-phenyl-1,2,4-triazolo[4,3-*a*]pyridine (**33**).

A 2.58 g (15.0 mmoles) sample of zinc dichloride dihydrate was fused under argon in a three necked flask to remove the water. Dry tetrahydrofuran (30 ml) was added *via* syringe and needle to the cooled flask followed by stirring and the addition of 8.3 ml of a 1.8 molar solution of phenyl lithium in tetrahydrofuran. After stirring for 1.5 hours this solution was added *via* a double tipped needle to a stirred solution of tetrakis (triphenylphosphine) palladium (0) and 2.12 g (10.0 mmoles) of 6-bromo-3-methyl-1,2,4-triazolo[4,3-*a*]pyridine in 70 ml of dry tetrahydrofuran. The mixture was stirred at 22° for 18 hours, diluted with 100 ml of 6*N* hydrochloric acid and extracted with dichloromethane. The aqueous layer on standing gave a white solid which was partitioned between 1*N* sodium hydroxide and dichloromethane. The organic layer was concentrated to give 0.8 g (38%) of off-white crystals. Recrystallization from dichloromethane-hexane gave 0.5 g (24%) of white crystals, mp 181-183° (lit [7] mp 182-184°) (identical with an authentic sample by ir and pmr spectral analysis).

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.6; H, 5.3; N, 20.1. Found: C, 74.1; H, 5.3; N, 20.5.

6-Bromo-3-methyl-1,2,4-triazolo[4,3-*a*]pyridine (**31**).

A mixture of 5.0 g (0.021 mole) of 2,5-dibromopyridine, 3 ml of hydrazine hydrate and 100 ml of pyridine was refluxed for 18 hours and concentrated to dryness under vacuum. The residue was partitioned between 1*N* sodium hydroxide and dichloromethane, the organic layer separated, dried (sodium sulfate) concentrated and diluted with hexane to give 2.8 g (71%) off-white crystals, mp 134-136°C. The 5-bromo-2-hydrazinopyridine (2.8 g) and 150 ml of triethyl orthoacetate was refluxed for 18 hours. the volatiles were removed under vacuum and the residue in dichloromethane passed through hydrous magnesium silicate. While heating and concentrating, the filtrate was diluted with hexane to give 1.8 g of crystals, mp 142-144°. Recrystallization from dichloromethane-hexane gave 1.6 g (51%) of cream crystals, mp 147-149°.

Anal. Calcd. for $C_7H_6BrN_3$: C, 39.6; H, 2.9;N, 19.8; Br, 37.7. Found: C, 39.6; H, 2.9; N, 20.0; Br, 37.6.

6-Bromo-1,2,4-triazolo[4,3-*a*]pyridine.

A mixture of 0.5 g (2.7 mmoles) of 5-bromo-2-hydrazinopyridine and 5 ml of diethoxymethyl acetate was stirred at room temperature for 3 hours, diluted with hexane and filtered. The solid in dichloromethane was passed through a short pad of hydrous magnesium silicate and the filtrate concentrated while diluting with hexane. Cooling and filtering gave 0.3 g (57%) of white crystals mp 153-155°; ^1H nmr: δ 7.18-7.85 (m, 2H), 8.40 (s, 1H), 8.87 (s, 1H).

Anal. Calcd. for $C_6H_4BrN_3$: C, 36.4; H, 2.0; N, 21.2; Br, 40.4. Found: C, 36.2; H, 1.9; N, 21.2; Br, 40.9.

3-[3-(Trifluoromethyl)phenyl]pyridine.

A mixture of 3.0 g (11.6 mmoles) of 2-chloro-5-[3-trifluoromethyl)-phenyl]pyridine, 1.18 g (11.6 mmoles) of triethylamine, 50 ml of dry *N,N*-dimethylformamide and 10% palladium on carbon was shaken in a Paar hydrogenator (10 lb. H_2 pressure) for 1 hour. The mixture was filtered, concentrated and the residual oil partitioned between water and dichloromethane. The organic layer was separated, dried (sodium sulfate)

and passed through a short pad of hydrous magnesium silicate. The filtrate was concentrated to give 2.6 g (100%) of product as a yellow oil, one spot by tlc on silica gel (5% methanol-chloroform).

3-[3-(Trifluoromethyl)phenyl]pyridine 1-Oxide (**24**).

A mixture of 2.7 g (11.6 mmoles) of 3-[3-trifluoromethyl)phenyl]pyridine, 1.5 ml of 30% hydrogen peroxide (13.2 mmoles) and 30 ml of glacial acetic acid was heated at 70° (internal temperature) for 18 hours. Additional 30% hydrogen peroxide was added and heating continued until no starting material remained (tlc). The volatiles were removed under vacuum and the residue was partitioned between dichloromethane and dilute sodium hydroxide. The organic layer was separated, dried (sodium sulfate) and passed through a short pad of hydrous magnesium silicate. The filtrate was concentrated to a solid which was triturated with hexane to give 2.1 g (73%) of off-white crystals, mp 62-65°, one spot by tlc on silica gel (5% methanol-chloroform).

3-[3-(Trifluoromethyl)phenyl]pyridin-2(1*H*)-one (**25**).

A mixture of 2.0 g (8.36 mmoles) of 3-[3-(trifluoromethyl)phenyl]pyridine 1-oxide and 50 ml of acetic anhydride was refluxed for 18 hours and the volatiles removed under vacuum. The residue in methanol was treated with activated carbon, filtered and the filtrate concentrated to an oil. Tlc on silica gel (5% methanol-chloroform) and comparison with authentic 5-[3-trifluoromethyl)phenyl]pyridin-2(1*H*)-one [7] showed the absence of this isomer. The oil was crystallized from dichloromethane-hexane and gave 0.5 g (25%) of off-white crystals, mp 134-136°. A solution in dichloromethane was passed through a short pad of hydrous magnesium silicate and the filtrate concentrated and diluted with hexane to give off-white crystals, mp 138-139°.

Anal. Calcd. for $C_{12}H_7F_3NO$: C, 60.5; H, 3.0; N, 5.9; F, 23.9. Found: C, 60.3; H, 3.3; N, 5.8; F, 23.7.

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