Articles

2,6-Bis(*N*-pyrazolyl)pyridines: The Convenient Synthesis of a Family of Planar Tridentate N_3 Ligands That Are Terpyridine Analogues

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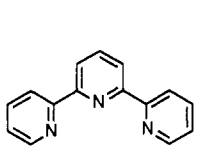
Received March 15, 1990

A series of four symmetric 2,6-bis(*N*-pyrazolyl)pyridines were prepared in good yields by the reaction of an excess of potassium pyrazolate with 2,6-dihalopyridines in the solvent diglyme. Pyrazoles bearing bulky substituents react at the less sterically hindered nitrogen to give only a single regioisomer. The second bromide of 2,6-dibromopyridine is displaced rather sluggishly; thus, the monosubstituted 2-bromo-6-(*N*-pyrazolyl)pyridine can be readily isolated. Treatment of this intermediate with the potassium salt of a substituted pyrazole gives rise to three unsymmetrically substituted bis(*N*-pyrazolyl)pyridines.

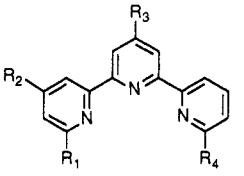
Introduction

Investigations of transition-metal complexes of the planar tridentate ligand 2,2′:6′,2″-terpyridine (**1**) and its substituted derivatives (**2a–d**) are severely limited by the tedious synthesis of this class of compounds.[1,2] At present, the shortest synthesis of terpyridine involves a two-pot reaction sequence that achieves an overall yield of about 45%.[3] Somewhat larger quantities of terpyridine are available via an alternative four-step process.[4] The few substituted terpyridines which have been prepared are generally made either by short, low yield routes from terpyridine itself, or by lengthy routes in which substituted terpyridines are constructed and elaborated. Thus, 6,6″-diphenylterpyridine (**2a**) was prepared in 21% yield from phenyllithium and terpyridine.[5] A series of vinylterpyridine ligands (**2b–d**) have been prepared in four or five steps via transformations of methylterpyridines.[1,6]

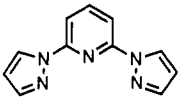
Interest in terpyridine ligands is based in part on their ruthenium complexes, which are potential catalysts for photochemical[7,8] and redox[1,7,9,10] reactions. In order to exploit this reaction chemistry more fully, it would be desirable to be able to vary substituents on the ligand in order to study their effect on the redox and photochemical properties of the metal complexes. Toward this end, we sought a planar tridentate ligand framework which contained three imine donor atoms and whose synthesis would allow for the convenient variation of ligand substituents. In this paper we report a method for the synthesis of a class of terpyridine analogues based on 2,6-bis(*N*-pyrazolyl)pyridine (**3a**).[11] The method is general and it allows for the convenient synthesis of a series of ligands in which the substituents on the pyrazole rings can be varied. We have recently reported that this family of ligands binds ruthenium(II), that the resulting complexes are good structural and redox mimics for the analogous terpyridine complexes, and that varying the number of methyl groups on the ligand allows for systematic variation of the redox and spectroscopic properties of the complexes.[12]



1 2, 2′: 6′, 2″-terpyridine



2a: $R_1 = R_4 =$ Ph, $R_2 = R_3 = H$
2b: $R_1 =$ CH=CH$_2$, $R_2 = R_3 = R_4 = H$
2c: $R_2 =$ CH=CH$_2$, $R_1 = R_3 = R_4 = H$
2d: $R_3 =$ CH=CH$_2$, $R_1 = R_2 = R_4 = H$



3a 2,6-bis(N-pyrazolyl)pyridine

(1) Potts, K. T.; Usifer, D. A.; Guadelupe, A.; Abruna, H. D. *J. Am. Chem. Soc.* **1987**, *109*, 3961.
(2) Hadda, T. B.; Bozec, H. L. *Polyhedron* **1988**, *7*, 575.
(3) Potts, K. T.; Cipullo, M. J.; Ralli, P.; Theodoridis, G.; Winslow, P. *Org. Synth.* **1985**, *66*, 189. Reference 1 gives an improvement over the procedure cited here.
(4) Constable, E. C.; Ward, M. D.; Corr, S. *Inorg. Chim. Acta* **1988**, *141*, 201.
(5) Dietrich-Buchecker, C. O.; Marnot, P. A.; Sauvage, J. P. *Tetrahedron Lett.* **1983**, 5291.
(6) Two groups have prepared an interesting series of annelated terpyridines: (a) Thummel, R. P.; Jahng, Y. *J. Org. Chem.* **1985**, *50*, 2407. (b) Hegde, V.; Jahng, Y.; Thummel, R. P. *Tetrahedron Lett.* **1987**, 4023. (c) Bell, T. W.; Firestone, A. *J. Org. Chem.* **1986**, *51*, 764.
(7) (a) Skorbogaty, A.; Smith, T. D. *Coord. Chem. Rev.* **1984**, *53*, 55. (b) Constable, E. C. *Adv. Inorg. Chem. Radiochem.* **1986**, *30*, 69.
(8) (a) Young, R. C.; Nagle, J. K.; Meyer, T. J.; Whitten, D. G. *J. Am. Chem. Soc.* **1978**, *100*, 4773. (b) Kirchnoff, J. R.; McMillin, D. R.; Marnot, P. A.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1985**, *107*, 1138. (c) Collin, J.-P.; Guillerez, S.; Sauvage, J.-P. *J. Chem. Soc., Chem. Commun.* **1989**, 776.
(9) Llobet, A.; Doppelt, P.; Meyer, T. J. *Inorg. Chem.* **1988**, *27*, 514.
(10) (a) Thompson, M. S.; Meyer, T. J. *J. Am. Chem. Soc.* **1982**, *104*, 5070. (b) Leising, R. A.; Takeuchi, K. J. *J. Am. Chem. Soc.* **1988**, *110*, 4079.
(11) Several mono-pyrazole analogues of bipyridine have been reported. The condensation of 2-hydrazinopyridine with either malonaldehyde bis(diethyl acetal) or 2,4-pentanedione gives 2-(*N*-pyrazolyl)-pyridine and 2-(3,5-dimethyl-*N*-pyrazolyl)pyridine, respectively: Steel, P. J.; Lahousse, F.; Lerner, D.; Marzin, C. *Inorg. Chem.* **1983**, *22*, 1488.
(12) Jameson, D. L.; Blaho, J. K.; Kruger, K. T.; Goldsby, K. A. *Inorg. Chem.* **1989**, *28*, 4312.

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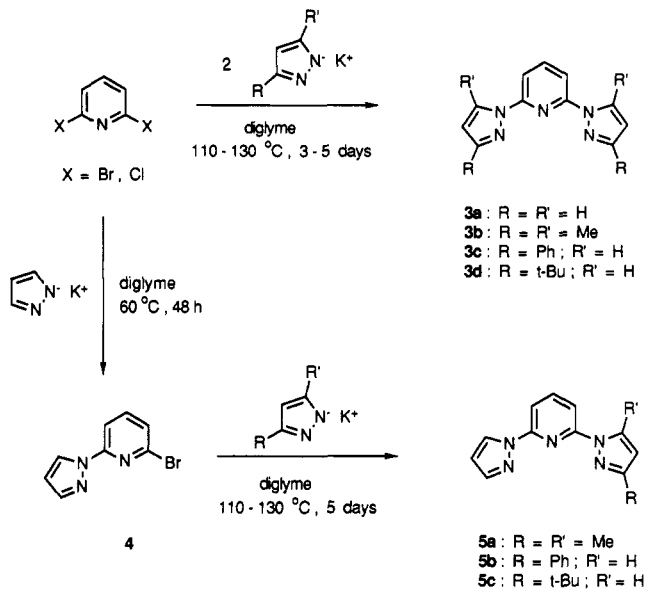
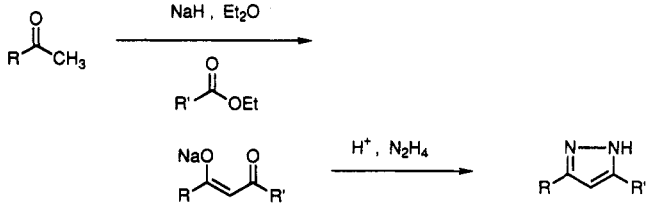
Scheme I



Scheme II



Pyrazole was chosen as the imine donor to replace pyridine in terpyridine for several reasons. First, pyrazole is an effective donor atom for a wide variety of transition metals. The weaker basicity of pyrazole (pK_a = 2.47) compared with pyridine (pK_a = 5.23)[13] and the tendency for pyrazole to bind metals somewhat more weakly than pyridine[14] should be overcome in this system by the chelate effect. Second, a variety of pyrazole-based ligands are available via the nucleophilic displacement of aliphatic halides by the readily formed pyrazolate anion.[15] Pyridyl halides are similarly activated toward nucleophilic displacement, and so we based our synthetic strategy for this class of ligands on the route shown in Scheme I. Third, the pyrazole ring is conveniently elaborated via a Claisen condensation to form a 1,3-dicarbonyl followed by condensation with hydrazine to form the substituted pyrazole (Scheme II).[16,17] The pyrazoles used in this paper are all compounds which have been reported previously. It is possible by combining Schemes I and II to further vary the steric and electronic features of the ligand.[18,19]

Results and Discussion

A solution of pyrazole (or a substituted derivative) was treated with potassium, thereby forming the nucleophilic salt, which was used to displace the halides in either 2,6-dibromopyridine or 2,6-dichloropyridine (Scheme I). The solvent 2-methoxyethyl ether was chosen for its high boiling point, its stability at high temperatures, and its ability to chelate the potassium ion of the nucleophile. Although we made no attempt to systematically optimize reaction conditions, displacement of both halides on the pyridine ring required fairly lengthy reaction times (3–5 days) and fairly high temperatures (110–125 °C).

The preparation of ligands in which both halides are displaced by pyrazole can be achieved by using the forcing conditions noted above. Displacement of one halide significantly decreases the reactivity of the second halide toward displacement so that less than forcing conditions will result in the isolation of a considerable amount of 2-halo-6-(*N*-pyrazolyl)pyridine even in the presence of excess pyrazolate anion. In the preparation of the symmetric ligands, we have used a 50% excess of pyrazolate anion in addition to high temperatures and longer reaction times in order to drive the sluggish substitution of the second halide. The excess pyrazole can be conveniently removed from the product by recrystallization (or a Soxhlet extraction for the case of the removal of 3(5)-phenylpyrazole from **3c**).

Both 2,6-dibromo- and 2,6-dichloropyridine have been used as substrates with the less sterically hindered pyrazole and 3,5-dimethylpyrazole. In spite of the fact that bromopyridines should be more activated toward displacement,[20] there was little difference in the yields of disubstituted pyridines. The yields of **3a** and **3b** differed by less than 5% regardless of whether 2,6-dibromo- or 2,6-dichloropyridine were used. The monosubstituted pyrazoles bearing bulky substituents reacted more sluggishly than the less hindered pyrazoles. Thus, we used the more reactive 2,6-dibromopyridine and longer reaction times to facilitate the synthesis of **3c** and **3d**. The reaction of 2,6-dibromopyridine with 3(5)-phenylpyrazole or 3(5)-*tert*-butylpyrazole gives the single disubstituted regioisomer arising from reaction of the nitrogen farther from the bulky group.[17,21,22] Attempts to prepare the ligand using 3(5)-methylpyrazole resulted in an intractable mixture of products. Apparently the methyl group is too small to control the regiochemistry of the substitution reaction, and both nitrogen atoms of the pyrazole ring are capable of being alkylated.

Unsymmetrically substituted ligands were prepared in two steps as shown in Scheme I. The monosubstituted product, 2-bromo-6-(*N*-pyrazolyl)pyridine, was prepared in 79% yield by reacting equimolar amounts of 2,6-dibromopyridine and potassium pyrazolate under milder reaction conditions (60 °C, 48 h). Reaction of **4** with an excess of pyrazolate salt under forcing conditions cleanly gives the desired unsymmetric ligands **5a–c**.

Experimental Section

General. Anhydrous 2-methoxyethyl ether was either purchased from Aldrich in Sure-Seal bottles and used as received or distilled from molten sodium at atmospheric pressure. Literature procedures were used to prepare 3,5-dimethylpyrazole,[23] 3(5)-phenylpyrazole,[17,22] and 3(5)-*tert*-butylpyrazole.[17,22] All other reagents were purchased from Aldrich and used as received.

(13) Alberty, A. *Physical Methods in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1963; Vol. I, p 44.
(14) Sillen, L. G.; Martell, A. E. *Spec. Publ.-Chem. Soc.* **1971**, *No. 25*, 280, 369.
(15) Sorrell, T. N.; Jameson, D. L. *Inorg. Chem.* **1982**, *21*, 1014.
(16) Sorrell, T. N. *Tetrahedron* **1989**, *45*, 3.
(17) The use of substituted pyrazoles to elaborate the structure of the hydridotris(*N*-pyrazolyl)borate ligands has been demonstrated: Trofimenko, S.; Calabrese, J. C.; Thompson, J. S. *Inorg. Chem.* **1987**, *26*, 1507.
(18) Bessel, C.; Takeuchi, K. J.; Jameson, D. L., manuscript submitted to *J. Chem. Soc., Chem. Comm.*
(19) Jameson, D. L.; Shearer, E. A.; Regitz, C. R., unpublished results.
(20) Katritzky, A. R.; Lagowski, J. M. *Heterocyclic Chemistry*; John Wiley and Sons: New York, 1960.
(21) Sorrell, T. N.; Shen, C.-C.; O'Connor, J. C. *Inorg. Chem.* **1987**, *26*, 1755.
(22) Sorrell, T. N.; Garrity, M. L.; Ellis, D. J. *Inorg. Chim. Acta* **1989**, *166*, 71.
(23) *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 351.

Thin-layer chromatography (TLC) was performed on alumina-coated plastic sheets (J. T. Baker) impregnated with a fluorescent indicator. Column chromatography was performed using neutral alumina. Melting points are uncorrected. ^1H NMR (80 MHz) and ^{13}C NMR (20 MHz) spectra were recorded on an IBM NR-80 spectrometer. Spectra were run in $CDCl_3$ or CD_3SOCD_3 and chemical shifts are reported in parts per million (ppm) versus a TMS internal standard. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

2,6-Bis(*N*-pyrazolyl)pyridine (3a). A solution of 11.0 g of pyrazole (0.162 mol) in 200 mL of anhydrous 2-methoxyethyl ether was stirred with 6.0 g of potassium (0.153 mol) at 70 °C until the metal dissolved. To this solution was added 11.8 g (0.0496 mol) of 2,6-dibromopyridine in one portion. The resulting mixture was stirred at 110 °C for 4 days. The solvent was removed on a rotary evaporator using an efficient water aspirator. Final traces of solvent were removed by adding water to the resulting oil and reducing the volume on a rotary evaporator. Water was added, and the resulting white solid was collected by suction filtration. The compound was purified by dissolving it in methylene chloride, adding methanol, and slowly removing the methylene chloride on a rotary evaporator. The yield of collected crystals was 8.3 g (79%). An additional 0.7 g of product could be isolated by removing the solvent from the filtrate, chromatographing the residue on alumina (chloroform eluent), and recrystallizing as above. The total yield was 9.0 g (85%): mp 136–138 °C; ^1H NMR ($CDCl_3$) δ 6.48 (dd, 2 H, J = 2.6, 1.7 Hz), 7.75 (dd, 2 H, J = 1.6, 0.6 Hz), 7.75–7.95 (m, 3 H), 8.55 (dd, 2 H, 2.6, 0.6 Hz); ^{13}C NMR ($CDCl_3$) δ 108.1, 109.5, 127.2, 141.6, 142.5, 150.2. Anal. Calcd for $C_{11}H_9N_5$: C, 62.56; H, 4.29; N, 33.15. Found: C, 62.59; H, 4.25; N, 33.26.

2,6-Bis(3,5-dimethyl-*N*-pyrazolyl)pyridine (3b). Via a procedure identical with the one used for the preparation of **3a**, the potassium salt of 3,5-dimethylpyrazole (15.5 g, 0.161 mol) and 11.8 g (0.0496 mol) of 2,6-dibromopyridine yielded 10.1 g (77%) of **3b**. Recrystallization once from methanol/water and once from methylene chloride/hexanes yielded white crystals: mp 107–108 °C; ^1H NMR ($CDCl_3$) δ 2.30 (s, 6 H), 2.58 (s, 6 H), 5.99 (s, 2 H), 7.55–7.95 (m, 3 H). ^{13}C NMR ($CDCl_3$) δ 13.6, 14.1, 109.0, 113.7, 140.4, 141.0, 150.1, 151.6. Anal. Calcd for $C_{15}H_{17}N_5$: C, 67.40; H, 6.41; N, 26.19. Found: C, 67.04; H, 6.55; N, 25.98.

2,6-Bis(3-phenyl-*N*-pyrazolyl)pyridine (3c). The potassium salt (0.166 mol) of 3(5)-phenylpyrazole was allowed to react with 2,6-dibromopyridine (11.8 g, 0.0496 mol) for 5 days at 130 °C. The usual workup resulted in a tan powder, which was sparingly soluble in common organic solvents. The product was purified by Soxhlet extraction using methanol as the solvent. The white crystals were collected and washed with methanol to yield 5.58 g (31%) of the desired product: mp 253–255 °C; ^1H NMR (CD_3SOCD_3) δ 7.16 (d, 2 H, J = 2.8 Hz), 7.35–7.70 (m, 6 H), 7.85–8.35 (m, 7 H), 9.04 (d, 2 H, J = 2.8 Hz). Anal. Calcd for $C_{23}H_{17}N_5$: C, 76.04; H, 4.68; N, 19.28. Found: C, 76.00; H, 4.53; N, 19.32.

2,6-Bis(3-*tert*-butyl-*N*-pyrazolyl)pyridine (3d). Via a procedure identical with the one used for the preparation of **3a**, the potassium salt of 3(5)-*tert*-butylpyrazole (20.5 g, 0.165 mol) and 11.8 g (0.0496 mol) of 2,6-dibromopyridine yielded 14.0 g (87%) of **3d**. Recrystallization from methylene chloride/methanol gave a white crystalline solid: mp 83–85 °C; ^1H NMR ($CDCl_3$) δ 1.37 (s, 18 H), 6.32 (d, 2 H, J = 2.6 Hz), 7.77 (s, 3 H), 8.40 (d, 2 H, J = 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 30.3, 32.4, 104.7, 108.6, 127.1, 140.8, 150.2, 164.8. Anal. Calcd for $C_{19}H_{25}N_5$: C, 70.56; H, 7.79; N, 21.65. Found: C, 70.60; H, 7.87; N, 21.79.

2-Bromo-6-(*N*-pyrazolyl)pyridine (4). Potassium pyrazolate (0.499 mol, made from 34.0 g of pyrazole) was treated with 119 g (0.502 mol) of 2,6-dibromopyridine dissolved in 1 L of 2-methoxyethyl ether, and the mixture was heated at 60 °C for 48 h. The solvent was removed, and water was added to precipitate a tan/brown solid. This solid was recrystallized by dissolving it in methanol, filtering, and reprecipitating by adding water and removing the methanol on a rotary evaporator. This tan solid appeared to be better than 90% 2-bromo-6-(*N*-pyrazolyl)pyridine and less than 10% 2,6-bis(*N*-pyrazolyl)pyridine by TLC (1:1, toluene/hexane). The crude solid was dried, dissolved in 1.5 L of hot 1:1 methanol/water, filtered, and allowed to crystallize. The white solid, 66 g (59%), was collected by suction filtration, washed with cold 1:1 methanol/water followed by water, and allowed to air dry. Product purified in this manner appeared to contain less than 2% (**3a**) by TLC and was used in subsequent steps without further purification. The mother liquor contained a considerable amount of the desired product, which could be obtained by column chromatography using 9:1 hexanes/toluene as the eluent. In this manner an additional 22 g of analytically pure sample was obtained: mp 66–68 °C. The total yield of product was 88 g (79%): ^1H NMR ($CDCl_3$) δ 6.45 (dd, 1 H, J = 2.6, 1.7 Hz), 7.25–8.00 (m, 4 H), 8.52 (dd, 1 H, J = 2.7, 0.7 Hz); ^{13}C NMR ($CDCl_3$) δ 108.2, 110.7, 125.2, 127.5, 139.9, 140.6, 142.7, 151.5. Anal. Calcd for $C_8H_6N_3Br$: C, 42.89; H, 2.70; N, 18.75. Found: C, 42.94; H, 2.64; N, 18.70.

2-(3,5-Dimethyl-*N*-pyrazolyl)-6-(*N*-pyrazolyl)pyridine (5a). The potassium salt of 3,5-dimethylpyrazole (3.0 g, 36 mmol) in 100 mL of 2-methoxyethyl ether was treated with 6.7 g (30 mmol) of 2-bromo-6-(*N*-pyrazolyl)pyridine, and the mixture was heated at 130 °C for 5 days. The solvent was removed under reduced pressure, and water was added to precipitate an off-white solid. The product was recrystallized from 1:1 methanol/water to yield 6.2 g (86%) of **5a**: mp 86–88 °C; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3 H), 2.73 (d, 3 H, J = 0.7 Hz), 6.02 (s, 1 H), 6.45 (dd, 1 H, J = 1.7, 2.6 Hz), 7.73 (dd, 1 H, J = 0.7, 1.7 Hz), 7.76–7.88 (m, 3 H), 8.42 (dd, 1 H, J = 0.7, 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.62, 15.1, 107.8, 108.3, 109.6, 112.3, 127.0, 140.9, 141.3, 142.1, 149.4, 150.2, 152.1. Anal. Calcd for $C_{13}H_{13}N_5$: C, 65.26; H, 5.48; N, 29.26. Found: C, 65.48; H, 5.39; N, 29.15.

2-(3-Phenyl-*N*-pyrazolyl)-6-(*N*-pyrazolyl)pyridine (5b). Via a procedure identical with that used for **5a**, the potassium salt of 3(5)-phenylpyrazole (5.2 g, 36 mmol) was treated with 6.7 g (30 mmol) of 2-bromo-6-(*N*-pyrazolyl)pyridine to yield 6.0 g (70%) of white crystals. Recrystallization from methylene chloride/methanol afforded analytically pure **5b**: mp 129–131 °C; ^1H NMR ($CDCl_3$) δ 6.47 (dd, 1 H, J = 2.6, 1.7 Hz), 6.78 (d, 1 H, J = 2.7 Hz), 7.2–7.6 (m, 3 H), 7.7–8.1 (m, 6 H), 8.54 (d, 2 H, J = 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 105.5, 107.9, 109.2, 109.4, 126.0, 127.0, 128.2, 128.4, 128.7, 132.8, 141.3, 142.3, 150.0, 154.0. Anal. Calcd for $C_{17}H_{13}N_5$: C, 71.07; H, 4.56; N, 24.37. Found: C, 71.39; H, 4.62; N, 24.12.

2-(3-*tert*-Butyl-*N*-pyrazolyl)-6-(*N*-pyrazolyl)pyridine (5c). Via a procedure identical with that used for **5a**, the potassium salt of 3(5)-*tert*-butylpyrazole (4.5 g, 36 mmol) and 6.7 g (30 mmol) of 2-bromo-6-(*N*-pyrazolyl)pyridine yielded 6.5 g (81%) of solid **5c**. Recrystallization from methylene chloride/methanol afforded analytically pure product: mp 94–95 °C; ^1H NMR ($CDCl_3$) δ 1.37 (s, 9 H), 6.34 (d, 1 H, J = 2.6 Hz), 6.45 (dd, 1 H, J = 1.7, 2.6 Hz), 7.73 (dd, 1 H, J = 0.7, 1.6 Hz), 7.76–7.86 (m, 3 H), 8.41 (d, 1 H, J = 2.5 Hz), 8.54 (dd, 1 H, J = 0.7, 2.6 Hz); ^{13}C NMR ($CDCl_3$) δ 30.3, 32.5, 104.9, 107.8, 108.6, 109.4, 127.0, 127.2, 141.1, 142.2, 150.0, 150.4, 165.0. Anal. Calcd for $C_{15}H_{17}N_5$: C, 67.40; H, 6.41; N, 26.19. Found: C, 66.90; H, 6.34; N, 25.98.

Acknowledgment. This work was supported by a grant (D.L.J.) from the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Whitaker Foundation Grant of Research Corporation (D.L.J.), and an Institutional Self Renewal Grant from Gettysburg College. The purchase of the FT-NMR was made possible through a grant from the Pew Foundation. Many insightful conversations with Professor K. Takeuchi are gratefully acknowledged. We thank Ms. Sandra McCammon for the preparation of compound **3b**.