ORGANIC LETTERS

2004
Vol. 6, No. 12
1887−1890

Synthesis of Multitopic Verdazyl Radical Ligands. Paramagnetic Supramolecular Synthons

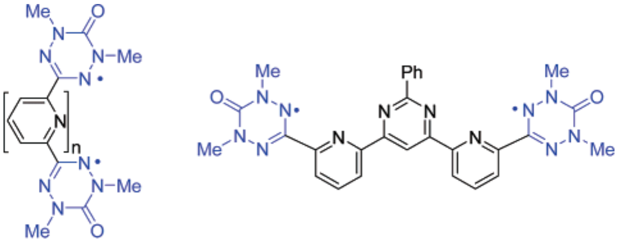
Robin G. Hicks,* Bryan D. Koivisto, and Martin T. Lemaire

*Department of Chemistry, University of Victoria, P.O. Box 3065, STN CSC,
Victoria, B.C. V8W 3V6, Canada*

rhicks@uvic.ca

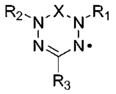
Received February 12, 2004

ABSTRACT

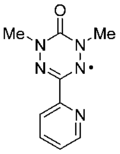


The syntheses of several verdazyl radical and diradicals containing pyridine-based multitopic coordination sites are described. These compounds were designed to be paramagnetic analogues of oligopyridine metallosupramolecular building blocks.

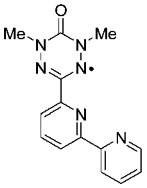
Verdazyls **1** are one of the few families of organic radicals stable enough to be prepared, handled, and isolated using conventional techniques.[1] In recent years, derivatives of **1** have attracted interest as open-shell ligands in coordination chemistry, as alternatives to the established complex chemistry of nitroxide radicals[2] and semiquinone radical anions.[3] The chelating capabilities of multidentate verdazyls such as **2**,[4] **3**,[5] and **4**[6] (among others[7]) render them excellent ligands for transition metals, and the magnetic interactions between verdazyl- and metal-based spins can be exceptionally strong and ferromagnetic.[4a,5a] As such, verdazyl radicals are outstanding candidates for the construction of metal-radical-based molecular magnetic materials.



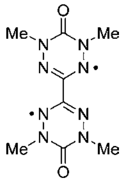
1a X = CHR
1b X = C(O)



2



3



4

The chelating environments offered by verdazyls **2**−**4** are structurally analogous to those found in 2,2′-bipyridine, 2,2′:6′,2″-terpyridine, and 2,2′-bipyrimidine, respectively. The parent oligopyridines are, of course, part of one of the benchmark families of ligands in coordination chemistry. Nitrogen-containing aromatics have also been tremendously important in the burgeoning field of *supramolecular* coor-

---

[1] (a) Neugebauer, F. A. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 455. (b) Neugebauer, F. A.; Fischer, H.; Siegel, R. *Chem. Ber.* **1988**, *121*, 815.

[2] Caneshi, A.; Gatteschi, D.; Rey, P. *Prog. Inorg. Chem.* **1991**, *39*, 331.

[3] Pierpont, C. G.; Lange, C. W. *Prog. Inorg. Chem.* **1994**, *41*, 331.

[4] (a) Hicks, R. G.; Lemaire, M. T.; Thompson, L. K.; Barclay, T. M. *J. Am. Chem. Soc.* **2000**, *122*, 8077. (b) Brook, D. J. R.; Fornell, S.; Noll, B.; Yee, G. T.; Koch, T. H. *J. Chem. Soc., Dalton Trans.* **2000**, 2019. (c) Brook, D. J. R.; Abeyta, V. *J. Chem. Soc., Dalton Trans.* **2002**, 4219.

[5] (a) Barclay, T. M.; Hicks, R. G.; Lemaire, M. T.; Thompson, L. K. *Chem. Commun.* **2000**, 2141. (b) Barclay, T. M.; Hicks, R. G.; Lemaire, M. T.; Thompson, L. K. *Inorg. Chem.* **2003**, *42*, 2261.

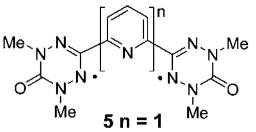
[6] Brook, D. J. R.; Lynch, V.; Conklin, B.; Fox, M. A. *J. Am. Chem. Soc.* **1997**, *119*, 5155.

[7] (a) Barclay, T. M.; Hicks, R. G.; Lemaire, M. T.; Thompson, L. K. *Inorg. Chem.* **2001**, *40*, 5581. (b) Barclay, T. M.; Hicks, R. G.; Lemaire, M. T.; Thompson, L. K. *Inorg. Chem.* **2001**, *40*, 6521. (c) Barclay, T. M.; Hicks, R. G.; Lemaire, M. T.; Thompson, L. K. *Chem. Commun.* **2002**, 1688.

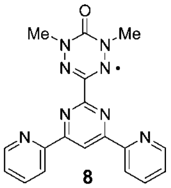
10.1021/ol049746i CCC: $27.50

dination chemistry. A huge array of metallosupramolecular architectures have been realized,[8] including discrete 2D and 3D objects (grids, racks, ladders, polygons, cages, polyhedra),[9] intertwined or interlocked structures (helices, knots, catenanes, rotaxanes),[10] dendrimers,[11] and extended coordination networks.[12] This has been facilitated by the development of efficient synthetic routes to oligopyridine-based ligands with well-defined coordination topologies.[13]

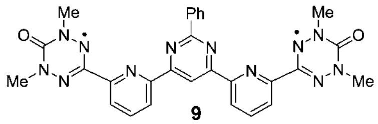
Nearly all of the azaheterocyclic ligands employed in metallosupramolecular chemistry play either a passive role or are inactive (beyond their structure-dictating purpose) in determining the possible *functions* of the structures which they comprise. It occurred to us that judicious design of ligands combining verdazyl and pyridine moieties could facilitate the construction of metal−ligand architectures in which the magnetic, redox, etc. properties of the assembled structure are derived from the *ligands* as well as (or in place of) the metal ions. Herein we describe the synthesis of verdazyl-containing multitopic ligands **5**−**9** which will be of broad interest to the supramolecular and magnetism communities.



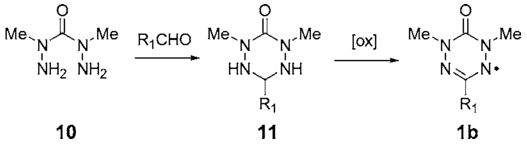
5 n = 1
6 n = 2
7 n = 3



8



9

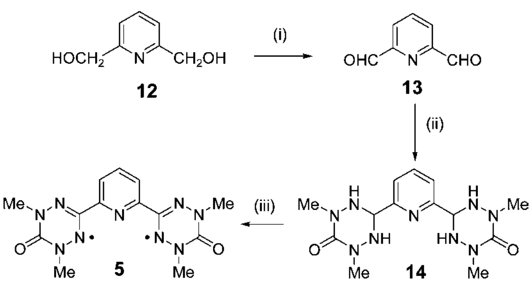


Scheme 1. Generic Verdazyl Synthesis

All of the verdazyl coordination chemistry reported to date is based on derivatives of the carbonyl-containing verdazyl **1b**. The general synthetic route to so-called "6-oxoverdazyls" is shown in Scheme 1. Condensations of aldehydes with the reagent 2,4-dimethylcarbohydrazide **10** yield tetrazanes **11**. The bis(hydrazide) reagent **10** can made by the reaction of methylhydrazine with either phosgene[14] or triphosgene.[15] The tetrazanes **11** can subsequently be oxidized to the radical using a number of different oxidants (Scheme 1). These reactions are general and were employed in the synthesis of the target molecules shown above.

The synthesis of pyridine-bridged diradical **5**, a structural analogue of terpyridine, is shown in Scheme 2. Swern oxidation of 2,6-pyridinedimethanol **12** (in a modification of literature procedures[16]) gives the corresponding dicarboxaldehyde **13** in excellent yield. Dialdehyde **13** is then condensed with **10** to give bis-tetrazane **14**. Oxidation to the diradical **5** was carried out in water using sodium periodate, and the product was isolated as a red precipitate from water.

Scheme 2. Synthesis of **5**[a]



[a] Key: (i) oxalyl chloride/DMSO, CH_2Cl_2, NEt_3, −78 °C, 86%; (ii) 10, MeOH, reflux 16 h, 89%; (iii) $NaIO_4$, H_2O, 83%.

The quaterpyridine mimic bis(verdazyl) **6** is prepared as shown in Scheme 3. Monolithiation of 2,6-dibromopyridine **15** followed by oxidative coupling yields 6,6′-dibromo-2′2-bipyridine **16**, which is then converted to the dialdehyde **17** via double lithium−halogen exchange followed by quenching with DMF.[17] Condensation of **17** with **10** yields bis-tetrazane **18**, which was subsequently oxidized using ferricyanide in DMF/water owing to the insolubility of **18** in pure water. The diradical **6** precipitates on formation as a red solid.

The synthesis of bis(verdazyl) **7**, a diradical analogue of quinquepyridine, is shown in Scheme 4. Dibromopyridine

---

(8) (a) Constable, E. C. *Prog. Inorg. Chem.* **1994**, *42*. 67. (b) Holliday, B. J.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2022. (c) Fujita, M.; Ogura, K. *Coord. Chem. Rev.* **1996**, *148*, 249.

(9) (a) Fujita, M. *Chem. Soc. Rev.* **1998**, *27*, 417. (b) Swiegers, G. F.; Malefetse, T. J. *Chem. Rev.* **2000**, *100*, 3483. (c) Leininger, S.; Olenyuk, B.; Stang, P. J. *Chem. Rev.* **2000**, *100*, 853.

(10) (a) Piguet, C.; Bernardinelli, G.; Hopfgartner, G. *Chem. Rev.* **1997**, *97*, 2005. (b) Albrecht, M. *Chem. Rev.* **2001**, *101*, 3457. (c) Collin, J. P.; Dietrich-Bucheker, C.; Gavina, P.; Jimenez-Molero, M. C.; Sauvage, J. P. *Acc. Chem. Res.* **2001**, *34*, 477. (d) Carlucci, L.; Ciani, G.; Proserpio, D. M. *Coord. Chem. Rev.* **2003**, *246*, 247.

(11) (a) Stoddart, F. J.; Welton, T. *Polyhedron* **1999**, *18*, 3575. (b) van Manen, H. J.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Top. Curr. Chem.* **2001**, *217*, 121. (c) Balzani, V.; Ceroni, P.; Juris, A.; Venturi, M.; Campagna, S.; Puntoriero, F.; Serroni, S.; *Coord. Chem. Rev.* **2001**, *219*, 545.

(12) (a) Blake, A. J.; Champness, N. R.; Hubberstey, P.; Li, W. S.; Withersby, M. A.; Schroëder, M. *Coord. Chem. Rev.* **1999**, *183*, 117. (b) Robson, R. *J. Chem. Soc., Dalton Trans.* **2000**, 3735. (c) Janiak, C. *Dalton Trans.* **2003**, 2781. (d) James, S. L. *Chem. Soc. Rev.* **2003**, 276.

(13) (a) Potts, K. T.; Raiford, K. A. G.; Keshavarz-K., M. *J. Am. Chem. Soc.* **1993**, *115*, 2893. (b) Hanan, G. S.; Schubert, U. S.; Volkmer, D.; Riviere, E.; Lehn, J. M.; Kyritsakas, N.; Fischer, J. *Can. J. Chem.* **1997**, *75*, 169. (c) Schubert, U. S.; Eschbaumer, C. *Org. Lett.* **1999**, *1*, 1027. (d) Benaglia, M.; Ponzini, F.; Woods, C. R.; Siegel, J. S. *Org. Lett.* **2001**, *3*, 967. (e) Heller, M.; Schubert, U. S. *Eur. J. Org. Chem.* **2003**, 947. (f) Newkome, G. R.; Patri, A. K.; Holder, E.; Schubert, U. S. *Eur. J. Org. Chem.* **2004**, *235*.

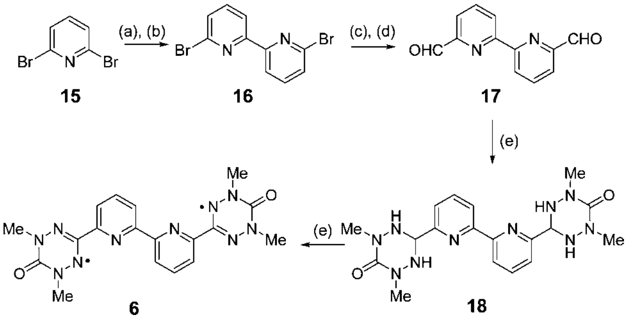
(14) Neugebauer, F. A.; Fischer, A.; Siegel, R.; Krieger, C. *Chem. Ber.* **1983**, *111*, 3461.

(15) Barr, C. L.; Chase, P. A.; Hicks, R. G.; Lemaire, M. T.; Stevens, C. L. *J. Org. Chem.* **1999**, *64*, 8893.

(16) Lüning, U.; Baumstark, R.; Peters, K.; von Schnering, H. G. *Liebigs Ann. Chem.* **1990**, 129.

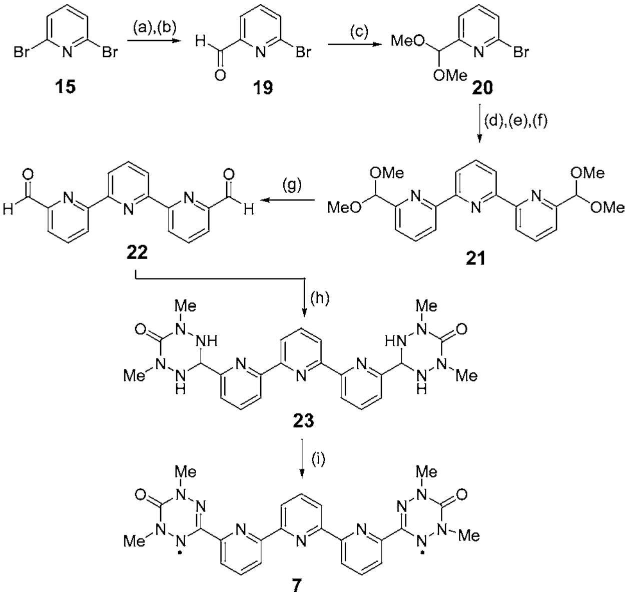
(17) Parks, J. E.; Wagner, B. E.; Holm, R. H. *J. Organomet. Chem.* **1973**, *56*, 53.

Scheme 3. Synthesis of **6**^{a}



^{a} Key: (a) BuLi, −78 °C; (b) $CuCl_2$, O_2; (c) BuLi, −78 °C; (d) DMF; (e) (i) **10**, MeOH, reflux 16 h, 90%, (ii) $K_3Fe(CN)_6$, Na_2CO_3, H_2O/DMF, 91%.

Scheme 4. Synthesis of **7**^{a}



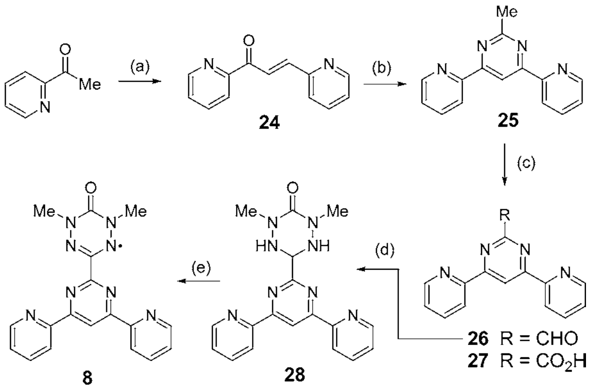
^{a} Key: (a) *n*-BuLi, −78 °C, THF; (b) DMF, −78 °C, THF, 89% (two steps); (c) $HC(OMe)_3$, cat. TsOH, MeOH, 96%; (d) *n*-BuLi, −78 °C, THF; (e) $ZnCl_2$, −78 °C to rt, THF; (f) **15**, $Pd(PPh_3)_4$, THF, 70 °C, 24 h, 74% (three steps); (g) HOAc, H_2O, 100 °C, 93%; (h) **10**, MeOH/$CHCl_3$, 65 °C, 16 h, 87%; (i) $K_3Fe(CN)_6$, Na_2CO_3, water/DMF, 96%.

15 was converted to aldehyde **19** via a lithium−halogen exchange/DMF sequence, based on modification of literature procedures.[18] The aldehyde is protected as its dimethyl acetal **20**[19] and subsequently cross-coupled with **15** under Negishi conditions[20] to yield terpyridine derivative **21**. An excess of **20** is required to minimize the formation of 6-bromo-6′-carboxaldehyde dimethyl acetal-2,2′-bipyridine. The terpyridine product precipitates from the reaction as a zinc complex; extraction with EDTA yields the **21** in very high purity and good yield. The acetal groups are deprotected to give dialdehyde **22** which is then converted to bis(tetrazane) **23** by condensation with **10** in methanol/chloroform, the latter solvent being required to improve the solubility of **22**. The bis(tetrazane) was then oxidized using $K_3Fe(CN)_6$ to afford diradical **7** as a red solid.

Two other verdazyl ligands were prepared containing pyrimidine as well as pyridine rings. The first of these is verdazyl *mono*radical **8** carrying a 3,5-di(2-pyridyl)-2,6-pyrimidin-1-yl substituent at C3. We are not aware of any nonradical analogue with the binding topology inherent in **8**; the most closely related bis-tridentate ligand appears to be tetrakis(2-pyridyl)pyrazine.[21] The synthesis of **8** is shown in Scheme 5. 2-Acetylpyridine is condensed with 2-pyridinecarboxaldehyde under basic conditions[22] to give chalcone **24**, which could not be isolated because of its decomposition on attempted purification by chromatography.[23] The reaction of the in situ generated enone with acetamidine gave methyl substituted pyrimidine **25.** Oxidation of the methyl group with SeO_2 gave the corresponding aldehyde **26** as well as the carboxylic acid **27** as a side product. Reaction with bishydrazide **10** gave tetrazane **28**. Finally, oxidation using periodate in water was facilitated by protonation (HCl/H_2O) to solubilize the tetrazane; the resulting radical **8** precipitated as a dark orange solid.

The structure of diradical **9** was inspired by oligo-tridentate ligands designed to form grid/rack structures upon self-assembly with metal ions.[13b−d] Its synthesis is shown in Scheme 6. Protected aldehyde **20** (Scheme 4) was converted separately to monoprotected bis-aldehyde **29** and acetyl

Scheme 5. Synthesis of **9**^{a}



^{a} Key: (a) 2-pyrdinecarboxaldehyde, NaOH, H_2O, 0.5 h, 62%; (b) acetamidine hydrochloride, EtOH, reflux, 4 h, 40%; (c) SeO_2, dioxane, reflux 72 h, 28%; (d) **10**, MeOH, reflux, 8 h, 79%; (e) $NaIO_4$, HCl/H_2O, 95%.

---

(18) (a) Cai, D. W.; Hughes, D. L.; Verhoeven, T. R. *Tetrahedron Lett.* **1996**, *37*, 2537. (b) Parks, J. E.; Wagner, B. E.; Holm, R. H. *Inorg. Chem.* **1971**, *10*, 2472.

(19) Mukkala, V. M.; Sun, C.; Kwiatkowski, M.; Pasanen, P.; Högberg, M.; Kankare, J.; Takalo, H. *Helv. Chim. Acta* **1992**, *75*,1621.

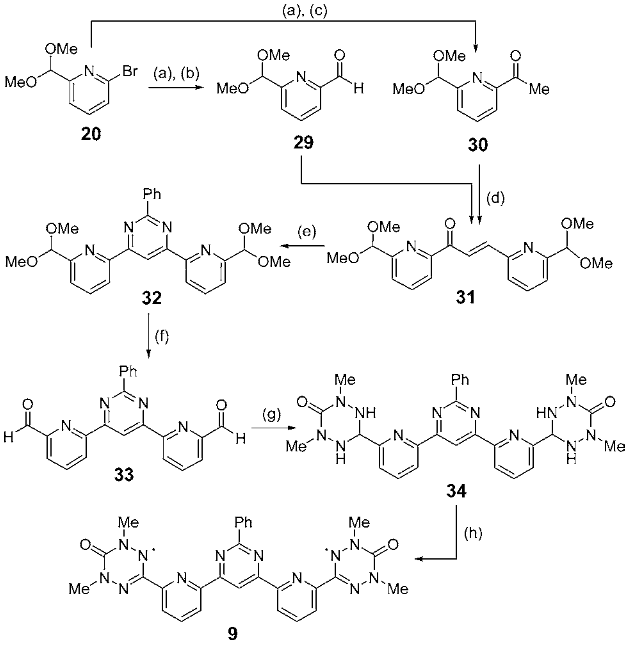
(20) Fang, Y. Q.; Hanan, G. S. *Synlett* **2003**, 852.

(21) (a) Brewer, R. G.; Jensen, G. E.; Brewer, K. J. *Inorg. Chem.* **1994**, *33*, 124. (b) Constable, E. C.; Edwards, A. J.; Phillips, D.; Raithby, P. R. *Supramol. Chem.* **1995**, *5*, 93. (c) Burkholder, E.; Zubieta, J. *Chem. Commun.* **2001**, 2056. (d) Bera, J. K.; Campos-Fernandez, C. S.; Clerac, R.; Dunbar, K. R. *Chem, Commun.* **2002**, 2536.

(22) Jones, P. D.; Glass, T. E. *Tetrahedron Lett.* **2001**, *42*, 2265.

(23) A practical route to **24** in pure form has recently been reported: Zhang, Z.; Dong, Y. W.; Wang, G. W. *Chem. Lett.* **2003**, *32*, 966.

Scheme 6. Synthesis of **9**[a]



[a] Key: (a) *n*-BuLi, −78 °C, THF; (b) DMF, −78 °C, THF, 86% two steps; (c) DMA, −78 °C, THF, 76% (two steps); (d) KOH, H_2O/MeOH; (e) KOH, benzamidine−HCl, air, MeOH, 42% (two steps; (f) HOAc, H_2O, 100 °C, 2 h, 95%; (g) **10**, $CHCl_3$, 65 °C, 16 h, 85%; (h) *p*-benzoquinone, $CHCl_3$, 40 °C, 0.5 h, 65%.

derivative **30**. These two products were then reacted with each other in a Claisen−Schmidt reaction to give chalcone **31** which, like its counterpart **24**, was used without purification. Crude **31** was condensed with benzamidine to give pyrimidine **32**; deprotection of the acetal groups of **32** gave dialdehyde **33**, which was then condensed with **10** to yield bis(tetrazane) **34**. The tetrazane has limited solubility in polar solvents; its oxidation to diradical **9** was carried out in chloroform with *p*-benzoquinone.

The characterization of verdazyl radicals can be hindered by their lack of long term stability, particularly in solution; half-lives in solution range from hours to months.[24] Acceptable elemental analyses were obtained for **7** and **9**; the other three target radicals were identified by high-resolution mass spectra. EPR spectra,[25] though informative with respect to the electronic structure of the radicals, are *not* good indicators of product purity or yield. Other spectroscopic methods are more effective for radical characterization (Supporting Information). The IR carbonyl stretching frequency shifts from ~1620 cm^{-1} in tetrazanes to ~1690 cm^{-1} in the radicals. The radicals are also characterized by the absence of NH stretches above 3000 cm^{-1} in comparison to the tetrazanes, which have multiple bands in this region. The UV−vis spectra of the radicals are also diagnostic as they exhibit two absorption bands with maxima near 410 and 450 nm. The less than optimal stability of verdazyls is not anticipated to be a serious problem for the preparation of supramolecular complexes: There is ample evidence that verdazyl stability improves upon coordination, and it is also possible to prepare metal-verdazyl complexes via in situ tetrazane oxidation in the presence of metal ions.[4b,7c]

In summary, we have synthesized a series of oligopyridine-based verdazyl radicals that can be used as functionalized building blocks in metallosupramolecular chemistry. Although oligopyridine-derivatized nitroxide radicals have been reported,[26] the binding sites offered by these radicals are quite different from the parent bipyridine binding pocket. The close structural relationship between verdazyls and aza-aromatics renders the family of compounds described herein promising building blocks for functional self-assembled coordination complexes. Work to this end, as well as studies on the intramolecular spin exchange interactions in the diradicals, will be reported in due course.

Acknowledgment. We thank the University of Victoria and the Natural Sciences and Engineering Research Council of Canada for their support.

Supporting Information Available: Synthetic procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049746I

---

(24) (a) Brook, D. J. R.; Fox, H. H.; Lynch, V.; Fox, M. A. *J. Phys. Chem.* **1996**, *100*, 2066. (b) Fico, R. M., Jr.; Hay, M. F.; Reese, S.; Hammond, S.; Lambert, E.; Fox, M. A. *J. Org. Chem.* **1999**, *64*, 9386.

(25) The solution EPR spectrum of **8** is typical of verdazyl monoradicals (ref 15), and the EPR of diradicals **9** and **7** show no evidence of exchange coupling (see the Supporting Information). The EPR of **5** and **6** are more complex and will be reported in more detail in a forthcoming publication.

(26) (a) Stroh, C.; Ziessel, R. *Tetrahedron Lett.* **1999**, *40*, 4543. (b) Ziessel, R.; Ulrich, G.; Lawson, R. C.; Echegoyen, L. *J. Mater. Chem.* **1999**, *9*, 1435. (c) Ziessel, R.; Stroh, C. *Org. Lett.* **2003**, *5*, 2397.