ARTICLE

OBC
www.rsc.org/obc

Synthesis of 1,5-diisopropyl substituted 6-oxoverdazyls†

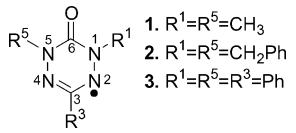
Emily C. Paré, David J. R. Brook,*‡ Aaron Brieger, Mick Badik and Marie Schinke
Department of Chemistry and Biochemistry, University of Detroit Mercy, Detroit, MI, 48221, USA. E-mail: djbrook@scu.edu; Fax: +1 408 554 7811; Tel: +1 408 554 4796

Received 18th July 2005, Accepted 12th October 2005
First published as an Advance Article on the web 2nd November 2005

1,5-Diisopropyl-6-oxo-verdazyl free radicals were synthesized *via* the condensation of BOC protected isopropyl hydrazine with phosgene, deprotection with aqueous HCl, condensation with aldehydes to form tetrazanes and finally oxidation to give the free radicals. The introduction of isopropyl groups results in free radicals that show greater solubility in a variety of solvents and are more stable than their methyl substituted counterparts. ESR shows reduced hyperfine coupling to the isopropyl methine hydrogens consistent with this hydrogen being in the plane of the verdazyl ring.

Introduction

Stable free radicals, in addition to their intrinsic interest, are important in a variety of applications. Recent examples include spin labels to probe polymer structure,[1] catalysts for 'living' free radical polymerizations[2] and components of metallo-organic polymers with unusual magnetic properties.[3–5] Despite their utility, there are a only a limited number of stable free radical families. Nitroxides and the closely related imino nitroxides and nitronyl nitroxides are probably the most extensively studied, however other systems such as semiquinones and verdazyls may also have potential applications.[6] In particular the 1,5-dimethyl-6-oxoverdazyls (**1**) are relatively easily synthesized with a variety of functional groups in the 3 position.[7]



1. $R^1=R^5=CH_3$
2. $R^1=R^5=CH_2Ph$
3. $R^1=R^5=R^3=Ph$

With the nitrogen atoms in the 2 and 4 positions available to coordinate metal ions, these systems have potential for a wide variety of applications. Unfortunately, the stability of these systems is variable depending on the nature of the substituent in the 3 position. While the radicals can frequently be characterized by ESR, this instability can hinder further study. This is particularly frustrating with potential ligands such as the 3-(2′-pyridyl)- (**1a**) and 3-(2′-imidazolyl) (**1c**) substituted species. Several coordination compounds of the former have been reported,[8–10] but the free radical itself must be stored in the long term either as the charge transfer complex with hydroquinone,[11] or under liquid nitrogen.[12] We were interested in the introduction of alternative alkyl groups in the 1 and 5 positions, in particular to increase radical stability and solubility and also to control coordination geometry. Specifically we chose to target the 1,5-diisopropyl system. Calculations suggest that the preferred conformation for these radicals places the two isopropyl methyl groups above and below the plane of the verdazyl ring. Such a conformation provides some steric protection for the free radical, while still allowing the coordination of metal ions to N^2 and N^4.

The synthesis of 1,5-dimethyl-6-oxoverdazyls typically proceeds through the reaction of methyl hydrazine with phosgene to form a bis-hydrazide, followed by condensation with an aldehyde to form a tetrazane and subsequent oxidation to give the verdazyl (Scheme 1).[7,13] Introduction of alternate alkyl groups is limited by the availability of the corresponding hydrazine and the regiochemistry of the condensation with phosgene. We report a synthesis of 1,5-diisopropyl verdazyls utilizing the BOC protecting group to circumvent these problems.

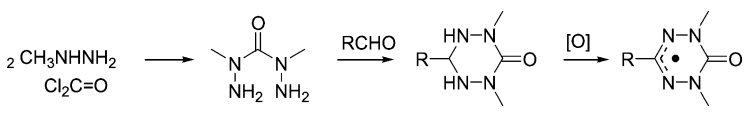
Experimental

General

NMR spectra were recorded on a JEOL Eclipse+ 300 MHz FTNMR spectrometer and referenced to the residual solvent protons in the deuterated solvent. Coupling constants are reported in Hz. IR spectra were recorded as thin films on NaCl plates using a Perkin-Elmer Spectrum 2000 FTIR spectrometer. Mass spectra were recorded on an Agilent 1100 series ion trap spectrometer with electrospray ionization using 0.1 M ammonium acetate in ethanol as solvent or on a Hewlett-Packard 6890 GCMS with electron impact ionization. ESR spectra were recorded on a Bruker ESP300e X band spectrometer or a Varian E-12 X band spectrometer with an HP model 5245L frequency counter. Samples for ESR were dissolved in toluene ($\sim 5 \times 10^{-4}$ mol L^{-1}) and degassed *via* three freeze(77 K)–pump(0.1 Torr)–thaw cycles before measurement. The field was calibrated by placing a dilute sample of MnO in CaO next to the sample. The resonant field positions of the Mn^{2+} lines were computed by 4th order perturbation theory and the appropriate field correction was applied to all spectra. ESR spectra were simulated with the program WINSIM.[14]

Di-*tert*-butyl-2,2′-carbonylbis-(2-isopropylhydrazine-carboxylate) (5)

tert-Butyl 2-isopropylhydrazinecarboxylate (**4**)[15] (20.6 g, 0.118 mol) was dissolved in dry toluene and 1 equivalent (11.9 g, 0.118 mol) dry triethylamine added. To this solution was added a solution of 20% phosgene in toluene (31 mL, 0.06 mol) dropwise



Scheme 1

† Electronic supplementary information (ESI) available: Experimental details of the synthesis and characterization of tetrazanes **7b–g** and verdazyls **8b–g**. See DOI: 10.1039/b510075e

‡ Present Address: Department of Chemistry, Santa Clara University, Santa Clara, CA 95050, USA

DOI:10.1039/b510075e

at a rate of less than one drop per second. During addition a copious precipitate of triethylamine hydrochloride formed. When addition was complete, the solution was stirred at room temperature for 2 h, filtered and the filtrate evaporated to give the crude product. This was purified by recrystallization from heptane to give 9.75 g (0.026 mol, 44%) of the bis hydrazide with mp 148–150 °C (decomp.) (found: C 54.30 H 9.07 N 14.84. calcd for $C_{17}H_{34}N_4O_5$: C 54.52 H 9.15 N 14.96%); ν_{max}(NaCl plate)/cm^{-1} 3255 (N–H), 2978 (C–H), 1712 (C=O), 1659 (C=O); δ_H (300 MHz, $CDCl_3$, 55 °C) 1.12 (12H, d, $J = 6.6$, $(CH_3)_2$-CH), 1.47 (18H, s, $(CH_3)_3C$), 4.15 (2H, septet, $J = 6.6$, $(CH_3)_2$-C*H*), 6.48, (2H, br s, N*H*); δ_C (75 MHz, $CDCl_3$, 55 °C) 19.4, 28.2, 52.3, 81.2, 155.9, 162.3 (motionally broadened); MS (electrospray) 375 (MH$^+$, 46%), 319 (38, MH$^+$ *t*Bu), 263 (100, MH$^+$ 2*t*Bu).

2,4-Diisopropylcarbonohydrazide bis-hydrochloride (6)

Di-*tert*-butyl 2,2′-carbonylbis(2-isopropylhydrazinecarboxylate) (**5**) (0.655 g, 1.75 mmol) was dissolved in 10 mL ethanol and 5 mL concentrated hydrochloric acid and warmed on a hot plate for 0.5 h during which time a mild effervescence occurred. The solution was allowed to cool overnight. Removal of the solvent and excess acid under vacuum left the bis-hydrazide bis hydrochloride as off-white crystals (0.426 g, 99%). The sample for analysis was recrystallized from n-butanol to give white needles with mp 188–190 °C (found: C 32.74 H 8.38 N 21.48. calcd for $C_7H_{20}N_4O{\cdot}2\,HCl{\cdot}0.5\,H_2O$: C 32.82 H 8.26 N 21.87%); ν_{max}(NaCl plate)/cm^{-1} 2974 (C–H), 2880, 2689 (broad, NH), 1712 (C=O); δ_H (300 MHz, D_2O) 1.07 (d, $J = 6.9$) 4.02 (septet, $J = 6.9$); δ_C (75 MHz, D_2O) 18.1, 55.7, 161.1; MS (electrospray) 175 (MH$^+$, 100%).

General procedure for tetrazanes: 2,4-diisopropyl-6-pyridin-2-yl-1,2,4,5-tetrazinan-3-one (7a)

In a typical procedure, 2 mmol of 2,4-diisopropylcarbonohydrazide bis-hydrochloride and 2 mmol of 2-pyridylcarboxaldehyde were dissolved in the minimum amount of ethanol. To this solution was added 4 mmol of sodium acetate in ethanol and the solution allowed to stand at room temperature for 15 h. After this period the mixture was filtered and evaporated and the residue recrystallized from heptane to give the tetrazane (460 mg, 87%) with mp 160–162 °C (found C 59.15 H 8.01 N 26.29. calcd for $C_{13}H_{21}N_5O$ C 59.29 H 8.04 N 26.59); ν_{max}(NaCl plate)/cm^{-1} 3226 (NH), 3187 (C–H), 2966 (C–H), 2930 (C–H), 1594 (C=O) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.09 (6H, d, $J = 6.6$), 1.11 (6H, d, $J = 6.6$), 4.44 (1H, s) 4.70 (2H, septet, $J = 6.6$), 7.35 (1H, ddd, $J = 6.6$, 5.0, 1.0), 7.44 (1H, dt, $J = 6.6$, 1.0), 7.78 (1H, td, $J = 6.6$, 2.0) 8.58 (1H, ddd, $J = 5.0$, 2.0, 1.0); δ_C (75 MHz, $CDCl_3$) 18.5, 19.5, 47.7, 72.3, 123.9, 124.3, 137.7, 149.3, 153.6, 154.4; MS (electrospray) 264 (MH$^+$, 100%).

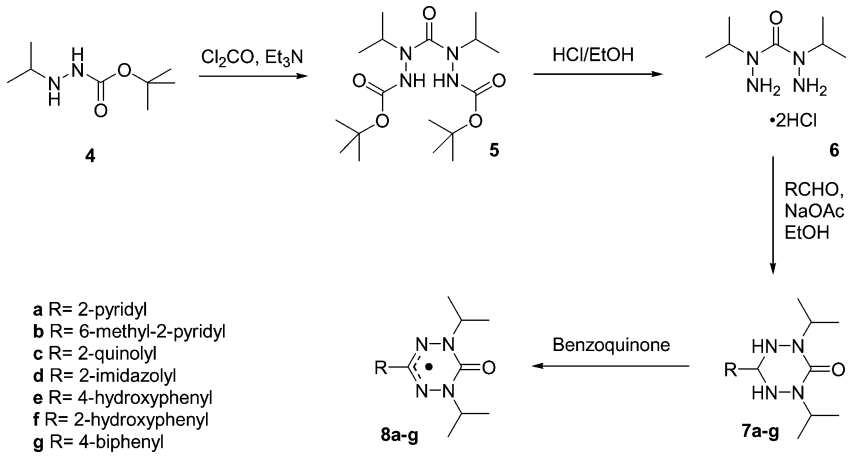
General procedure for verdazyl free radicals: 1,5-diisopropyl-3-pyridin-2-yl-6-oxoverdazyl (8a)

In a typical procedure, 2,4-diisopropyl-6-(pyridin-2-yl)-1,2,4,5-tetrazinan-3-one (164 mg) was refluxed with 1.5 mol eq. benzoquinone in 5 mL toluene for 1 h. When TLC indicated that the starting material had been consumed the resulting solution was cooled, filtered and evaporated. Chromatography of the residue on silica gel eluting with 9:1 CH_2Cl_2–EtOAc gave the verdazyl as an orange crystalline solid (53 mg, 32%) recrystallized from CH_2Cl_2–heptane with mp 122–123 °C; UV-vis (MeCN) 409, 450 nm(sh); ν_{max}(NaCl plate)/cm^{-1} 2973, 2920 (C–H), 1686 (C=O); MS (electrospray) 261 (MH$^+$, 100%). Purity was determined by HPLC on a 150 mm C18 reverse phase column, eluting isocratically for 2 min with 30% acetonitrile–70% 0.1 M aqueous ammonium acetate (pH 6.95) followed by a gradient to 70% acetonitrile over 10 min and isocratic elution thereafter. A UV-vis diode array was used for analyte detection. The product eluted at 9.8 min and was determined to be approximately 98% pure by integration.

Results

The reported syntheses of 1,5-dimethyl and 1,5-dibenzyl verdazyls rely on the more nucleophilic nature of the substituted nitrogen in the alkyl hydrazine. Reaction with phosgene gives the 2,4-dialkyl substituted bis-hydrazide[13] which is taken on to form the verdazyl.[7,16] This regiochemical selectivity is almost certainly an electronic effect, which may be diminished by steric effects; consequently we felt that an analogous reaction with isopropyl hydrazine would give, at best, a mixture of regioisomers. Since the *tert*-butyloxycarbonyl protected form of hydrazine, *tert* butyl carbazate, is commercially available, we elected to use the BOC group to enforce the required regiochemistry. The synthesis is outlined in Scheme 2.

Reduction of acetone *tert*-butyloxycarbonylhydrazone with sodium cyanoborohydride following the procedure of Callabretta and co-workers[15] gave a mixture of the BOC protected isopropyl hydrazine (**4**) and its cyanoborane adduct. Modification of the workup procedure using a 1M aqueous potassium hydroxide instead of aqueous bicarbonate wash gave **4** directly as a white crystalline solid. The reaction of the hydrazine with phosgene gave rather mixed and irreproducible results until we used toluene as solvent and carefully dried the triethylamine by distillation from calcium hydride. The resulting hydrazide (**5**) shows a conformationally restricted structure in NMR with the methyl groups of the isopropyl appearing as a broad singlet. Raising the temperature sharpened the spectrum considerably resolving the doublet resulting from coupling to the methine hydrogen. In the carbon spectrum however, one of



Scheme 2

the carbonyl carbons is observed only as a broad hump even at 55 °C.

Deprotection of **5** was initially attempted with CF_3COOH–Et_3SiH at room temperature, however significant trifluoroacetylation of the product was observed. Excess hydrochloric acid in ethanol gave clean deprotection to give 2,4-diisopropylcarbonohydrazide bis-hydrochloride (**6**) as a white solid. Unlike the protected species, this molecule shows no apparent conformational restriction in solution at room temperature.

Condensation of the hydrazide with aldehydes in 95% ethanol–sodium acetate gave the tetrazanes (**7a–g**) as colorless crystalline solids. In these materials the two isopropyl methyl groups are diastereotopic and give two distinct doublets in the ^{1}H NMR and two signals in the ^{13}C NMR.

A variety of conditions have been reported for the oxidation of 3-oxotetrazanes to verdazyl radicals.[7,8,11,16–23] Though we have found aqueous/alcoholic oxidation conditions useful in the past, the poor solubility of the diisopropyl tetrazanes in aqueous systems makes this method impractical. Oxidation to the verdazyl free radicals (**8a–g**) was accomplished with benzoquinone in toluene.[11] Unlike the previously reported synthesis using this method,[24] hydroquinone adducts were not observed and the hydroquinone precipitated from the reaction mixture as it cooled. Filtration and evaporation gave verdazyls (**8a–g**) which were purified by chromatography on silica gel followed by recrystallization from dichloromethane–heptane or ethanol–water. The free radicals can be identified by their distinct UV-visible spectra with a sharp transition near 410 nm and broad transition showing some vibronic structure between 450 and 500 nm. This gives them a pink to orange color depending upon the substituent in the 3 position. In a previous study of 1,5-dimethyl substituted species these maxima were tentatively identified as π–π* and n–π* transitions based on computational results.[8] Details of spectral maxima are reported in Table 1.

Table 2 Visible maxima and extinction coefficients for **8a–g** in acetonitrile

	λ/nm (ε/L mol^{-1} cm^{-1})
8a	409 (1330), 450 (380)
8b	410 (1300), 450 (390)
8c	410 (1110), 450sh (290)
8d	420 (1030), 495 (350), 555sh, (150)
8e	420 (1230), 502sh (570), 520 (590), 550sh (310)
8f	422 (1040), 500sh (350) 523 (450), 562 (340)
8g	422 (1350), 504 (480)

The ESR spectra of the isopropyl substituted verdazyls are all very similar and can be simulated accounting for coupling to four nitrogens and two hydrogens. Hyperfine parameters for radicals **8a–g** are shown in Table 2 along with data for related verdazyl radicals **1–3**. Experimental and simulated spectra for **8a** are shown in Fig. 1.

Discussion

The above methodology results in the formation of isopropyl substituted verdazyl radicals in a relatively straightforward manner. To demonstrate the versatility of the pathway we have synthesized verdazyls with 3-subtituents that have so far been unreported or have significant problems. In particular the chelating 3-(2′-pyridyl)- (**1** R^3 = 2-pyridyl) and 3-(6′-methylpyrid-2′-yl)- (**1** R^3 = 6-methyl-2-pyridyl) substituted free radicals

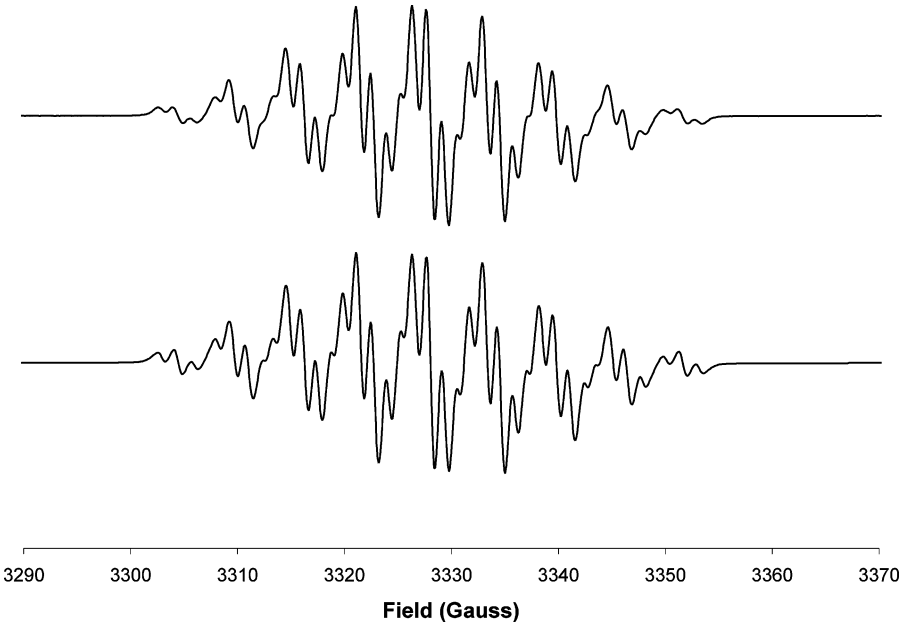


Fig. 1 Experimental (top) and simulated (bottom) ESR spectra of **8a**.

Table 1 ESR hyperfine parameters for **8a–g** and related radicals **1–3**

	a_N2,4/mT	a_N1,5/mT	a_H/mT	Linewidth/mT	g
8a	0.650	0.529	0.150	0.070	2.0043
8b	0.659	0.518	0.121	0.070	2.0044
8c	0.656	0.520	0.122	0.050	2.0044
8d	0.661	0.525	0.115	0.075	2.0047
8e	0.657	0.518	0.130	0.070	2.0044
8f	0.648	0.551	0.157	0.073	2.0044
8g	0.658	0.519	0.123	0.068	2.0044
1 (R = Ph)[7]	0.649	0.513	0.546	—	
2 (R = Ph)[7]	0.663	0.508	0.300	—	
3 (R = Ph)[17]	0.645	0.450	—	—	

have been previously reported but are relatively unstable.[8,12,25] Similarly our previous attempts to study the 3-(2′-imidazolyl)- and the 3-(2′-quinolyl) systems have been hampered by poor stability. For example a solution of 0.3 mM **1**(R^3 = 2-pyridyl) at room temperature lost 20% of the absorbance at 410 nm over a 4 day period. Over the same period the corresponding diisopropyl substituted verdazyls **8a,d** show very little (<1%) signal decay. The other species show similar or greater stability. Crystalline samples appear to be indefinitely stable in air in a standard laboratory refrigerator greatly facilitating the synthesis of coordination compounds.

The phenolic OH in the 2-hydroxy and 4-hydroxyphenyl substituted verdazyls provides a potential site for further derivatization or possibly metal coordination. Synthesis of the 4-hydroxyphenyl verdazyl system has been previously hampered by the very low solubility of the corresponding dimethyl tetrazane precursor. Similarly, attempts to synthesize the corresponding dimethyl tetrazane from salicylaldehyde resulted only in complex, intractable mixtures. Use of the diisopropyl bis(hydrazide) circumvents these problems and allows for the clean synthesis of both tetrazanes and corresponding verdazyls. We note that remarkably, semiquinone formation does not appear to compete with the formation of the verdazyl.

All of the free radicals are soluble in non-polar solvents such as toluene and heptane allowing the measurement of well resolved ESR spectra. Hyperfine coupling to nitrogen is very similar to that observed for other verdazyls, however the coupling to the two isopropyl methine hydrogens is significantly lower than that observed for the corresponding methyl hydrogens. This suggests that in the major conformations of the molecule the methine C–H lies in the plane of the verdazyl ring, minimizing coupling between it and the π system. A similar phenomenon was observed with 1,5-dibenzyl substituted verdazyl free radicals[7] which, with two hydrogens on a methylene group next to the verdazyl, show hyperfine coupling intermediate between the methyl and isopropyl systems (Table 2). No evidence was seen for the contribution of semiquinone type tautomers in the hydroxyphenyl substituted species, though the greater red shift in the electronic spectrum for the 2-hydroxy species (**8f**, λ_{max} = 560 nm) *vs* the 4-hydroxy species (**8e**, λ_{max} = 520 nm) may be a result of intramolecular hydrogen bonding between the hydroxy group and the verdazyl nitrogen lone pair. Such an interaction would hold the two rings in a coplanar arrangement increasing the electronic interaction between them.

Conclusion

Substitution of methyl groups for isopropyl groups in 6-oxoverdazyl radicals results in species with enhanced stability and solubility. The synthetic protocol allows the synthesis of verdazyl free radicals with new substituents in the 3 position, expanding the utility of verdazyl free radicals as spin probes and ligands for metal ions. In addition it should be possible to extend the methodology to groups other than isopropyl in the 1 and 5 positions. These possibilities are being further investigated in our laboratory.

Acknowledgements

This work was supported by the Petroleum Research Fund (Grant 39923-B1 to DJRB) and the National Science Foundation for purchase of ES-MS instrumentation (Award CHE-0116181). We would also like to thank Dr Shulamith Schlick and Dr Andrew Ichimura for help with ESR measurements.

References

1 R. Marchetto, E. M. Cilli, G. N. Jubilut, S. Schreier and C. R. Nakaie, *J. Org. Chem.*, 2005, **70**, 4561.
2 D. A. Shipp, *Journal Macromol. Sci. - Polym. Rev.*, 2005, **C45**, 171.
3 A. Caneschi, D. Gatteschi, N. Lalioti, R. Sessoli, L. Sorace, V. Tangoulis and A. Vindigni, *Chem.-Eur. J.*, 2002, **8**, 286.
4 J. Omata, T. Ishida, D. Hashizume, F. Iwasaki and T. Nogami, *Inorg. Chem.*, 2001, **40**, 3954.
5 M. T. Lemaire, *Pure Appl. Chem.*, 2004, **76**, 277.
6 K. Mukai, T. Yano and K. Ishizu, *Tetrahedron Lett.*, 1981, **22**, 4661.
7 F. A. Neugebauer, H. Fischer and R. Siegel, *Chem. Ber.*, 1988, **121**, 815.
8 D. J. R. Brook, S. Fornell, J. E. Stevens, B. Noll, T. H. Koch and W. Eisfeld, *Inorg. Chem.*, 2000, **39**, 562.
9 D. J. R. Brook, S. Fornell, B. Noll, G. Yee and T. H. Koch, *J. Chem. Soc., Dalton Trans.*, 2000, 2019.
10 R. G. Hicks, M. T. Lemaire, L. K. Thompson and T. M. Barclay, *J. Am. Chem. Soc.*, 2000, **122**, 8077.
11 C. L. Barr, P. A. Chase, R. G. Hicks, M. T. Lemaire and C. L. Stevens, *J. Org. Chem.*, 1999, **64**, 8388.
12 D. J. R. Brook and V. Abeyta, *J. Chem. Soc., Dalton Trans.*, 2002, 4219.
13 F. A. Neugebauer, H. Fischer, R. Siegel and C. Kreiger, *Chem. Ber.*, 1983, **116**, 3461.
14 D. R. Duling, *J. Magn. Reson., Ser. B*, 1994, **104**, 105.
15 R. Callabretta, C. Gallina and C. Giordano, *Synthesis*, 1991, 536.
16 F. A. Neugebauer and H. Fischer, *Angew. Chem. Intl. Ed. Engl.*, 1980, **92**, 761.
17 F. A. Neugebauer, H. Fischer and C. Kreiger, *J. Chem. Soc., Perkin Trans. 2*, 1993, 535.
18 R. G. Hicks and R. Hooper, *Inorg. Chem.*, 1999, **38**, 284.
19 F. A. Neugebauer and R. Siegel, *Angew. Chem. Suppl.*, 1983, 457.
20 F. A. Neugebauer, H. Trischmann and M. Jenne, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 362.
21 T. M. Barclay, R. G. Hicks, M. T. Lemaire and L. K. Thompson, *Chem. Commun.*, 2000, 2141.
22 R. G. Hicks, M. T. Lemaire, L. Öhrström, R. J. F. L. K. Thompson and Z. Xu, *J. Am. Chem. Soc.*, 2001, **123**, 7154.
23 T. M. Barclay, R. G. Hicks, M. T. Lemaire, L. K. Thompson and Z. Q. Xu, *Chem. Commun.*, 2002, 1688.
24 R. G. Hicks, M. T. Lemaire, L. Ohrstrom, J. F. Richardson, L. K. Thompson and Z. Q. Xu, *J. Am. Chem. Soc.*, 2001, **123**, 7154.
25 T. M. Barclay, R. G. Hicks, M. T. Lemaire and L. K. Thompson, *Inorg. Chem.*, 2001, **40**, 6521.