Scheme I

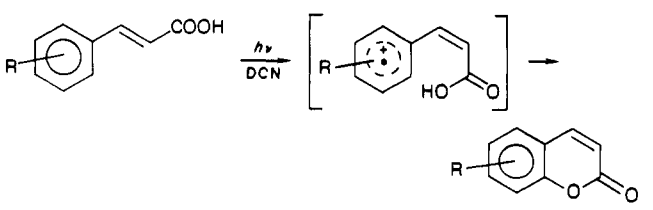
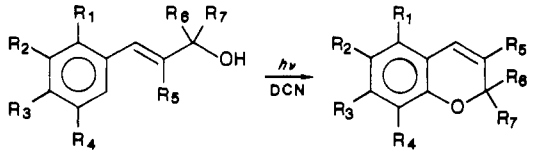


Table I. Photocyclization of 3-Aryl-1,1-dimethylprop-2-en-1-ol



2a-f 3a-f

entry	substituents	time of irradn, h	yield,[a] %	quantum yield[b]
a	$R_1 = R_2 = OMe$, $R_3 = R_4 = R_5 = H$, $R_6 = R_7 = Me$	2	62	2.96×10^{-2}
b	$R_1 = R_4 = OMe$; $R_2 = R_3 = R_5 = H$, $R_6 = R_7 = Me$	2	65	3.20×10^{-2}
c	$R_2 = R_3 = OMe$, $R_1 = R_4 = R_5 = H$, $R_6 = R_7 = Me$	3	60	2.10×10^{-2}
d	R_2–$R_3 = -OCH_2O-$, $R_1 = R_4 = H$, $R_5 = R_6 = R_7 = Me$	3	55	2.61×10^{-2}
e	$R_3 = OMe$, $R_1 = R_2 = R_4 = R_5 = H$, $R_6 = R_7 = H$	2.5	50	2.74×10^{-2}
f	$R_3 = OMe$, $R_1 = R_2 = R_4 = R_5 = H$, $R_6 = R_7 = Me$	2.5	60	2.5×10^{-2}

[a] Isolated yields. [b] Quantum yields were determined by using uranyl oxalate actinometry,[9] and chromenes were estimated by HPLC. [Column C_{18}; MeOH/H_2O (25:75) monitoring at UV λ = 290 nm.]

by comparing with authentic samples made independently by a method similar to that reported earlier.[6] Longer irradiation resulted in the ring cleavage of chromenes.[8] The quantum efficiency of the reaction was estimated to be in the range of ≈0.03 (Table I).

Experimental Section

Melting points were determined in open capillaries with a Mettler FP51 melting point apparatus and are uncorrected. IR data were obtained on a Pye-Unicam SP3-200 spectrophotometer and ^1H NMR data on a Varian FT-80A spectrophotometer using tetramethylsilane as internal standard. HPLC analyses were carried out by utilizing a Shimadzu LC-6A system along with an SPD-6A UV variable-wavelength detector and C-R3A electronic integrator.

The alcohols **2a–f** were prepared by the Grignard reaction of methyl esters of cinnamic acids. A typical example for **2b** is described as follows.

A 100-mL three-necked flask equipped with a condenser, dropping funnel, magnetic stirring bar, and nitrogen inlet was charged with 1.95 g (0.08 g-atom) of magnesium turnings. The apparatus was flame-dried under a vigorous flow of nitrogen. After cooling to 30 °C, a few crystals of iodine and a solution of 4.75 mL (10.83 g, 76.3 mmol) of methyl iodide in dry ether were added over a period of 15 min. After the formation of the Grignard reagent, 8.05 g (36.3 mmol) of 2,5-dimethoxycinnamic acid methyl ester dissolved in dry ether was added and the reaction mixture was stirred for 30–40 min at 25 °C. The reaction mixture was quenched by adding 5% ammonium chloride solution (60 mL). The organic layer was removed, and the aqueous layer was extracted with ether (3 × 60 mL). The combined organic layer was washed with water followed by saturated sodium chloride solution and was dried over anhydrous sodium sulfate. After solvent removal under vacuum, the crude product was purified by column chromatography (silica gel, Merck 230–400 mesh) to give 6.40 g (79.5%) of **2b**: IR (neat, cm^{-1}) 3560–3200, 2960, 2840, 1590, 1480, 1220, 1040; ^1H NMR ($CDCl_3$) δ 1.41 (s, 6 H), 2.36 (s, 1 H), 3.76 (s, 6 H), 6.32 (d, 1 H, J = 16.3 Hz), 6.74–6.99 (m, 4 H).

The ^1H NMR spectral characteristics for **2d** and **2e** are as follows. **2d**: δ 1.42 (s, 6 H), 1.87 (s, 3 H), 1.95 (s, 1 H), 5.93 (s, 2 H), 6.56 (s, 1 H), 6.74 (m, 3 H). **2e**: δ 1.58 (s, 1 H), 3.80 (s, 3 H), 4.29 (d, 2 H, J = 5.3 Hz), 6.30 (m, 1 H), 6.58 (d, 1 H, J = 16 Hz), 6.79–7.37 (m, 4 H).

The spectral pattern for the other alcohols (**2a**, **2c**, and **2f**) remains the same as that for **2b**.

General Irradiation Procedure. All the irradiations were carried out in an immersion-well type photoreactor using a 125-W mercury vapor lamp, surrounded by a Pyrex water jacket. The quantum yield was determined by using a Rayonet reactor equipped with Rayonet RUL 3000-Å lamps. A representative irradiation and workup procedure is given below.

2b (0.55 g, 2.47 mmol) and 0.08 g (0.45 mmol) of DCN were dissolved in 500 mL of an acetonitrile/water (80:20) mixture, and the reaction mixture irradiated for 2 h without removal of air from the solvent system. After the irradiation was stopped, solvent was removed under vacuum and the crude product was chromatographed over basic alumina with hexane/ethyl acetate (8.5:1.5) as eluent, which gave 0.35 g (65%) of **3b**: IR (neat, cm^{-1}) 2980, 2840, 1620, 1580, 1470, 1360, 1260, 930; ^1H NMR ($CDCl_3$) δ 1.30 (s, 6 H), 3.75 (s, 3 H), 3.78 (s, 3 H), 5.80 (d, 1 H, J = 12.6 Hz), 6.32 (d, 1 H, J = 12.6 Hz), 6.78–6.83 (m, 2 H).

The ^1H NMR spectral data for **3d** and **3e** are as follows. **3d**: δ 1.26 (s, 3 H), 1.33 (s, 3 H), 1.87 (s, 3 H), 5.91 (s, 2 H), 6.70 (m, 3 H). **3e**: δ 3.70 (s, 3 H), 4.31 (d, 2 H, J = 6.3 Hz), 5.70 (m, 1 H), 6.38 (d, 1 H, J = 11.7 Hz), 6.71–7.11 (m, 3 H).

The 2*H*-chromenes **3a**, **3c**, and **3f** show the same spectral pattern as **3b**.

Acknowledgment. We are thankful to Dr. A. V. Rama Rao for encouragement. A.K. is grateful to CSIR, New Delhi, for the award of Senior Research Fellowship.

Registry No. **2a**, 113949-25-0; **2b**, 113949-26-1; **2c**, 113949-27-2; **2d**, 113949-28-3; **2e**, 17581-85-0; **2f**, 57918-91-9; **3a**, 67015-34-3; **3b**, 113949-29-4; **3c**, 644-06-4; **3d**, 113949-30-7; **3e**, 18385-89-2; **3f**, 17598-02-6; 2,3-dimethoxycinnamic acid methyl ester, 15854-60-1; 2,5-dimethoxycinnamic acid methyl ester, 28689-10-3; 3,4-dimethoxycinnamic acid methyl ester, 5396-64-5; 2,3-methylenedioxy-α-methylcinnamic acid methyl ester, 7605-45-0; 4-methoxycinnamic acid methyl ester, 832-01-9.

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Synthesis of Spiro Heterocyclic Nitroxides Derived from 4-Piperidone

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Stable nitroxide free radicals[1] that carry substituents capable of further chemical reactions are of considerable interest as spin labels[2] and as possible contrast-enhancing

(1) For a review, see: Keana, J. F. W. In *Spin Labeling in Pharmacology*; Holtzmann, J. L., Ed.; Academic: New York, 1984; Chapter 1.

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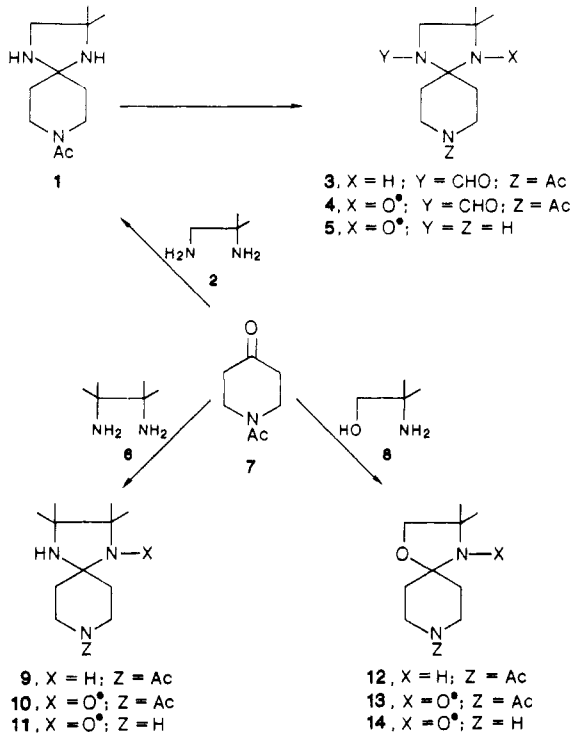
Scheme I



agents for magnetic resonance imaging (MRI) applications.[3,4] Nitroxides substituted with primary and secondary amino groups[5] are particularly versatile owing to the possibility of further modification by way of acylation or alkylation reactions. Amino nitroxides also have potential as indicators of pH using electron spin resonance spectroscopy.[6] For MRI applications, resistance of the nitroxide group toward bioreduction is an important property. We[7] and others[8] had observed previously that certain five-membered ring (pyrrolidine and pyrroline) nitroxides tended to be more resistant toward reduction by ascorbate than six-membered ring (piperidine) nitroxides. We set out to determine the relative resistance of five-membered ring nitroxides containing an additional heteroatom in the ring toward bioreduction. Herein, we report an improved synthesis of nitroxide heterocycle **5**[9] as well as the synthesis of two new heteroatom-containing nitroxides, **11** and **14**, that also incorporate a remote amino group within their structure.

Condensation[6] of 1-acetyl-4-piperidone (**7**) (Scheme I) with 1,2-diamino-2-methylpropane (**2**) gave imidazolidine **1**, which underwent selective formylation to give secondary amine **3**. Oxidation with *m*-chloroperoxybenzoic acid (MCPBA) gave the diacyl nitroxide **4**. The successful hydrolysis of **4** to diamino nitroxide **5**[6] depended critically on the reaction conditions and could be made to proceed in near quantitative yield by using methanolic KOH containing some water at 45 °C. Gentle sublimation gave an analytically pure sample of nitroxide **5**, mp 109–111 °C. Earlier[6] we obtained nitroxide **5** by alkaline hydrolysis of **4** (Z = benzoyl). Nitroxide **5** was obtained directly from the reaction mixture as a crystalline residue, mp 85–87 °C, which could not be recrystallized.

The imidazolidine N-protection–deprotection steps can be avoided by using 2,3-diamino-2,3-dimethylbutane (**6**) as the diamine in the condensation reaction. Thus following an earlier route developed in our laboratory,[10] ketone **7** was condensed with diamine **6**, giving imidazolidine **9**. Direct oxidation of only one of the equivalent imidazolidine nitrogen atoms with MCPBA gave nitroxide **10**. The nitroxide group in **10** serves to lower the basicity and nucleophilicity of the proximal amino group, thus monooxidation of **9** was a feasible reaction. Nitroxide amide **10** was next hydrolyzed to the crystalline diamino nitroxide **11** as described above for the synthesis of **5**.

The series of spiro heterocyclic nitroxides was completed with the synthesis of a doxyl nitroxide[11] analogue of nitroxide **5**. Thus, ketone **7** was condensed with amino alcohol **8** to give oxazolidine **12**. Oxidation of **12** with MCPBA gave nitroxide **13**, hydrolysis (see above) of which gave amino doxyl **14**.

The comparative behavior of several of the nitroxides herein described and 20 other stable nitroxides toward reduction by rat hepatocytes, whole liver homogenate, subcellular fractions, and ascorbate are detailed elsewhere.[12]

Experimental Section[13]

8-Acetyl-2,2-dimethyl-1,4,8-triazaspiro[4.5]decane (1). A 100-mL flask was fitted with a Dean–Stark water separator containing anhydrous K_2CO_3 and then was charged with benzene (80 mL), 1-acetyl-4-piperidone (**7**) (1.90 g, 13.5 mmol), 1,2-diamino-2-methylpropane (1.19 g, 13.5 mmol), and *p*-toluenesulfonic acid monohydrate (20 mg). After a 24-h reflux period with stirring, the volatiles were removed in vacuo, giving a solid, which crystallized upon addition of ether. Filtration gave 2.472 g (87%) of **1** as white flakes, mp 80–82 °C, sufficiently pure for the next reaction. The analytical specimen was obtained as white needles by sublimation at 70–80 °C (0.1 mm): mp 82–83 °C; IR 1630 cm^{-1}; NMR[14] δ 1.21 (s, 6), 1.60–1.72 (br t, 6), 2.10 (s, 3), 2.81 (s, 2), 3.41–3.60 (m, 3), 3.82–3.94 (m, 1); NMR (C_6D_6) δ 0.87 (s, 3), 0.97 (s, 3); 1.10–1.35 (m, 6), 1.75 (s, 3), 2.45 (AB q, 2), 2.95–3.10 (m, 2), 3.40–3.55 (m, 1) 3.85–4.00 (m, 1). Irradiation at δ 1.20 gave rise to an AB quartet centered at δ 3.05 and doublets at δ 3.48 and 3.91. Anal. Calcd for $C_{11}H_{21}N_3O$: C, 62.51; H, 10.02; N, 19.89. Found: C, 62.57; H, 10.09; N, 19.85.

8-Acetyl-2,2-dimethyl-4-formyl-1,4,8-triazaspiro[4.5]decane (3). Formic acetic anhydride was generated[15] by stirring together

(2) For a review, see: *Spin Labeling: Theory and Applications*; Berliner, L. J., Ed.; Academic: New York, 1979.

(3) For a series of papers concerning MRI contrast-enhancing agents, see: *Magn. Reson. Imaging* **1985**, *3*, 1–97. See also: Eriksson, U. G.; Ogan, M. D.; Peng, C-T.; Brasch, R. C.; Tozer, T. N. *Magn. Reson. Med.* **1987**, *5*, 73.

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(9) The use of the *N*-acetyl protecting group here constitutes an improvement upon our earlier method,[6] especially in the hydrolysis step which gives nitroxide **5**.

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(13) Melting points were obtained in a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on a Nicolet QE 300 spectrometer in $CDCl_3$. Chemical shifts are expressed in δ units relative to Me_4Si. IR spectra were recorded on a Nicolet DX-FT IR spectrometer in $CDCl_3$ as the solvent. ESR spectra were measured on a Varian E-3 spectrometer in CH_2Cl_2 as the solvent. Elemental analyses were determined by Mic Anal., Tucson, AZ. All reactions were routinely run under N_2 atmosphere. Flash chromatography used Grade 633, 200–425 mesh 60 Å Aldrich Co. silica gel. Solvents were routinely distilled.

(14) Restricted rotation about the N—C=O single bond in acetyl derivatives **1**, **3**, **9**, and **12** on the NMR time scale causes the sets of piperidine ring protons on one side of the ring to be magnetically nonequivalent to the corresponding proton(s) on the other side of the ring.

acetic anhydride (4.186 g, 41.0 mmol) and 99% formic acid (1.887 g, 41.0 mmol) for 2 h at 55 °C. The solution was cooled to 0 °C and then added slowly to a chilled solution of **1** (7.20 g, 34.1 mmol) in CH_2Cl_2 (40 mL). After 12 h of being stirred at 25 °C the solution was washed with saturated aqueous Na_2CO_3, dried (K_2CO_3), and concentrated to dryness to give an oil (6.83 g), which solidified upon trituration with ethyl acetate. The solid was isolated by filtration and crystallized from 1:1 ethyl acetate–hexanes, giving **3** (4.416 g, 54%) as white needles: mp 140–141 °C; IR 1658, 1638 cm^{-1}; NMR[14] δ 1.27 (s, 3), 1.28 (s, 3), 1.60–2.00 (m, 5), 2.12 (s, 3), 2.65–2.95 (m, 2), 3.25–3.60 (m, 3), 3.70–3.90 (m, 1), 4.60–4.85 (m, 1), 8.27 (s, 1). Anal. Calcd for $C_{12}H_{21}N_3O_2$: C, 60.21; H, 8.85; N, 17.57. Found: C, 60.32; H, 8.96; N, 17.38.

8-Acetyl-2,2-dimethyl-4-formyl-1,4,8-triazaspiro[4.5]decane-1-oxyl (4). To a stirred solution of **3** (2.40 g, 10.0 mmol) in CH_2Cl_2 (60 mL) at −10 °C was added dropwise a solution of 85% MCPBA (2.67 g, 15.0 mmol) in CH_2Cl_2 over 1 h. After 24 h of being stirred at 25 °C, the solution was washed with saturated aqueous $NaHCO_3$, dried (K_2CO_3), and concentrated to dryness to give a red-brown oil (2.209 g). Purification by flash chromatography over silica gel (elution with 1:9 MeOH–ether) gave an orange solid, which was crystallized from 1:1 ethyl acetate–hexanes to give **4** (1.158 g, 45%) as orange-yellow plates: mp 150–151 °C; IR 1667, 1637 cm^{-1}; ESR 3 lines, each showing further splitting, a_N = 14.50 G. Anal. Calcd for $C_{12}H_{20}N_3O_3$: C, 56.66; H, 7.93; N, 16.53. Found: C, 56.78; H, 8.13; N, 16.43.

2,2-Dimethyl-1,4,8-triazaspiro[4.5]decane-1-oxyl (5). Nitroxide **4** (107 mg) was dissolved in a solution of 6 M methanolic KOH (4 mL) and water (1 mL) and stirred at 45 °C for 21 h. The volatiles were removed in vacuo, and the residue was dried (0.05 mm). The residue was triturated with CH_2Cl_2, and the extract was filtered through a column of sand and Celite. The filtrate was dried (K_2CO_3) and then concentrated to dryness, giving 77 mg (100%) of a pale brown solid, mp 95–97 °C. A 20-mg portion was gently sublimed [60 °C (0.05 mm)] to give the analytical sample (12 mg) as a pale yellow powder: mp 109–111 °C (lit.[6] mp 85–87 °C); IR, no C=O; ESR 3 broadened lines, a_N = 14.83 G. Anal. Calcd for $C_9H_{18}N_3O$: C, 58.65; H, 9.85; N, 22.81. Found: C, 58.72; H, 9.96; N, 22.75.

8-Acetyl-2,2,3,3-tetramethyl-1,4,8-triazaspiro[4.5]decane (9). A 250-mL flask was fitted with a Dean–Stark water separator containing anhydrous K_2CO_3 and then was charged with benzene (170 mL), ketone **7** (3.481 g, 24.66 mmol), diamine **6** (2.86 g, 24.7 mmol), and *p*-toluenesulfonic acid monohydrate (20 mg). After a 48-h reflux period with stirring the volatiles were removed in vacuo, giving a thick oil that solidified upon cooling. Trituration with 1:1 ether–hexanes gave a residue, which was collected by filtration giving diamine **9** (5.58 g, 95%) as a white solid, mp 90–95 °C. A 2.00-g portion was sublimed [85 °C (0.2 mm)] to give the analytical sample of **9** (1.84 g) as white needles: mp 100–102 °C; IR 1628 cm^{-1}; NMR[14] δ 1.12 (s, 12), 1.55–1.75 (m, 6), 2.08 (s, 3), 3.45–3.55 (br t, 2), 3.62–3.68 (br t, 2). Anal. Calcd for $C_{13}H_{25}N_3O$: C, 65.22; H, 10.53; N, 17.56. Found: C, 64.92; H, 10.80; N, 17.34.

8-Acetyl-2,2,3,3-tetramethyl-1,4,8-triazaspiro[4.5]decane-1-oxyl (10). To a stirred solution of diamine **9** (1.70 g, 7.11 mmol) in CH_2Cl_2 (75 mL) at −10 °C was added dropwise over 1.5 h a solution of 85% MCPBA (1.90 g, 11.0 mmol) in CH_2Cl_2 (50 mL). The color went from colorless to pale blue to pale green to almost colorless. After the mixture was stirred 24 h at 25 °C, anhydrous K_2CO_3 (5 g) was added. The mixture was stirred for 30 min and then filtered. The filtrate was concentrated to dryness, giving a pale yellow semisolid (3 g). This was dissolved in CH_2Cl_2 and flash chromatographed over silica gel. Elution with 95:5 ether–MeOH gave nitroxide **10** (1.07 g, 59%) as a waxy yellow solid: IR 1632 cm^{-1}; ESR 3 lines, each with further splitting, a_N = 14.75 G.

2,2,3,3-Tetramethyl-1,4,8-triazaspiro[4.5]decane-1-oxyl (11). Nitroxide **10** (150 mg) was dissolved in a solution of 6 M methanolic KOH (6 mL) and water (1.5 mL) and stirred at 48 °C for 24 h. The volatiles were removed in vacuo, and the residue was dried (0.05 mm) and then triturated with CH_2Cl_2. The extract was filtered through sand and Celite, and the filtrate was dried (K_2CO_3). Removal of the solvent gave nitroxide **11** (106 mg, 85%) as a pale yellow-brown powder, mp 164–166 °C (preheated bath). A 15-mg portion was gently sublimed [75 °C (0.01 mm)] to give the analytical specimen (11 mg) as a pale yellow powder: mp 170–171 °C, IR no C=O; ESR 3 lines, a_N = 14.75 G. Anal. Calcd for $C_{11}H_{22}N_3O$: C, 62.21; H, 10.45; N, 19.80. Found: C, 62.21: H, 10.74; N, 19.60.

8-Acetyl-2,2-dimethyl-1,8-diaza-4-oxaspiro[4.5]decane (12). A 250-mL flask fitted with a Dean–Stark water separator containing anhydrous K_2CO_3 was charged with benzene (150 mL), ketone **7** (10.6 g, 75.0 mmol), 2-amino-2-methylpropan-1-ol (**8**) (6.69 g, 75.0 mmol), and *p*-toluenesulfonic acid monohydrate (40 mg). After a 43-h reflux period the volatiles were removed in vacuo, leaving an oil that solidified upon cooling to give **12** (15.35 g, 97%) as a colorless solid, mp 75–78 °C. Distillation [bp 115–120 °C (0.1 mm)] gave 11.38 g (72%) of **12** as a white solid, mp 77–78 °C, sufficiently pure for the next reaction. The analytical specimen was obtained as a white solid by sublimation [75 °C (0.05 mm)]: mp 80–81 °C; IR 1630 cm^{-1}; NMR[14] δ 1.24 (s, 3), 1.25 (s, 3), 1.55–1.95 (m, 5), 2.10 (s, 3), 3.25–3.56 (m, 3), 3.60 (dd, 2), 4.00–4.10 (m, 1). Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.22; H, 9.50; N, 13.20. Found: C, 62.33; H, 9.80; N, 13.50.

8-Acetyl-2,2-dimethyl-1,8-diaza-4-oxaspiro[4.5]decane-1-oxyl (13). To a stirred solution of amine **12** (2.12 g, 10.0 mmol) in CH_2Cl_2 (60 mL) at −10 °C was added dropwise over 1 h a solution of 85% MCPBA (2.67 g, 15.0 mmol) in CH_2Cl_2 (30 mL). After 12 h of being stirred at 25 °C the mixture was washed with 5% aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness, giving 1.59 g of crude **13**. Flash chromatography over silica gel and elution with 95:5 ether–MeOH gave nitroxide **13** (1.38 g, 61%) as an orange-yellow solid, mp 92–93 °C. The analytical specimen was obtained as orange-yellow flakes by sublimation [75 °C (0.05 mm)]: mp 93–94 °C; IR 1636 cm^{-1}; ESR 3 lines, a_N = 14.75 G. Anal. Calcd for $C_{11}H_{19}N_2O_3$: C, 58.11; H, 8.43; N, 12.33. Found: C, 58.03; H, 8.65; N, 12.36.

2,2-Dimethyl-1,8-diaza-4-oxaspiro[4.5]decane-1-oxyl (14). Nitroxide **13** (100 mg) was dissolved in a mixture of 6 M methanolic KOH (4 mL) and water (1 mL) and stirred at 47 °C for 22 h. The volatiles were removed in vacuo, and the residue was triturated with CH_2Cl_2. The extract was filtered through sand and Celite and then dried (K_2CO_3). Removal of the solvent gave nitroxide **14** as a pale yellow powder (77 mg, 95%), mp 88–89 °C. Gentle sublimation [60 °C (0.01 mm)] of **14** (17 mg) gave the analytical specimen (14 mg) as pale yellow cubes: mp 90–91 °C; IR no C=O; ESR 3 lines, a_N = 14.63 G. Anal. Calcd for $C_9H_{17}N_2O_2$: C, 58.34; H, 9.25; N, 15.13. Found: C, 58.34; H, 9.32; N, 15.19.

Acknowledgment. This research was supported by PHS Grant 27137 from the National Institute of General Medical Sciences. The NMR spectra were measured on a 300-MHz spectrometer purchased with funds from PHS Grant RR02336 and NSF Grant CHE 8411177. D.S. thanks the Academia Sinica for a leave of absence.

Registry No. **1**, 113646-66-5; **2**, 811-93-8; **3**, 113646-67-6; **4**, 113646-68-7; **5**, 80028-56-4; **6**, 20485-44-3; **7**, 32161-06-1; **8**, 124-68-5; **9**, 113646-69-8; **10**, 113646-70-1; **11**, 113646-71-2; **12**, 113646-72-3; **13**, 113646-73-4; **14**, 113646-74-5.

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Removal of *N*-Arylsulfonyl Groups from Hydroxy α-Amino Acids

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Arylsulfonyl substituents are highly effective protecting groups for the amino function of α-amino acids. They are stable to most reaction conditions, provide a strong chromophore, and have been especially useful where the car-

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