Novel 3-Aza-Grob Fragmentation in Hydride Reduction of Ether-Protected Aromatic Lactams

Jeh-Jeng Wang* and Wan-Ping Hu

School of Chemistry, Kaohsiung Medical College, Kaohsiung City 807, Taiwan, R.O.C.

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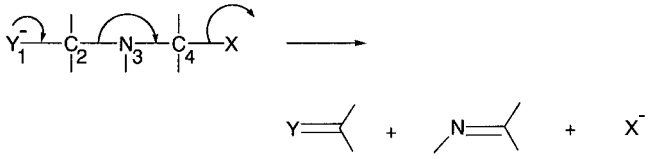
Heterolytic fragmentation reactions occur widely in organic chemistry.[1] According to the definition of Grob fragmentation, molecules containing certain combinations of carbon and heteroatoms undergo a regulated cleavage into three fragments, electrofuge, alkene, and nucleofuge.[2−4]

During the course of developing the synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepines, a family of anticancer DNA alkylating agents,[5,6] we have found an unusual amide bond cleavage of *N*-methoxymethylpyrrolo[2,1-*c*]-[1,4]benzodiazepine-5,11-diones by hydride reduction.[7] Although ring cleavage in systems of this type had been reported,[8] the novelty here is the presence of a leaving group in the correct location to allow a fragmentation instead of simple ring cleavage. Furthermore, stabilization of incipient negative charge on nitrogen would appear not to be a factor since both electron-donating and -withdrawing substituents on the aromatic ring have little influence.[7] On the basis of our observations, we postulated that this reaction proceeds via 3-aza-Grob fragmentation as shown in Scheme 1.[7] This reaction is

Scheme 1



similar to those of Grob[2−4] or Wharton fragmentations;[9−12] nevertheless, such systems bearing a nitrogen in the 3-position with the same electrofuge and nucleofuge are unprecedented.

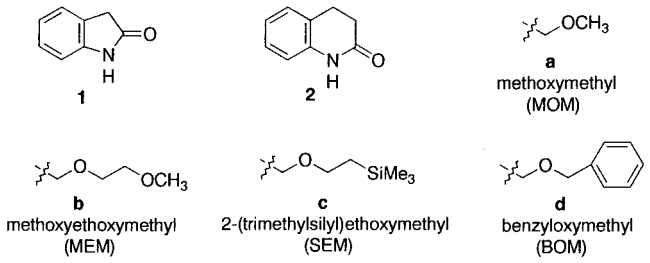


Figure 1. Structures of oxindole analogues **1** and **2** as well as ether protective groups; MOM, MEM, SEM, and BOM.

Herein, we describe our studies to a more general investigation of this phenomenon, with the scrutiny of MOM-protected simple aromatic lactams of five- and six-membered ring size (Figure 1).

The results of hydride reduction of *N*-methoxymethyloxindole **1a** and *N*-methoxymethyl-3,4-dihydro-2(1*H*)-quinolinone **2a** are shown in Scheme 2. The fragmentation reactions were completed to form ring-opening products via the same path as seven-membered ring lactams, *N*-methoxymethylpyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones,[7] with 15 equiv of $NaBH_4$ in excellent yields (Table 1, entries 1 and 2). This indicated that ring size and ring strain appear not to be critical factors in these reactions.

Ethers are among the most widely used protective groups in organic synthesis.[13] In principle, the 3-aza-Grob fragmentation chemistry can be extended to other ether-protecting groups such as MEM (2-methoxyethoxymethyl), SEM (2-(trimethylsilyl)ethoxymethyl), and BOM (benzyloxymethyl) (Figure 1). We thus turned our attention to the ether-protected aromatic lactams. The fragmentation reactions of MEM-protected oxindole analogues (Table 1, entries 3 and 4) were completed with 15 equiv of $NaBH_4$ in excellent yields. Although the SEM- and BOM-protected lactams (Table 1, entries 5−8) were less reactive than the MEM-protected lactams, the yields of fragmentation products were excellent, based upon the recovered starting material.

A plausible mechanistic interpretation of this intriguing reaction is shown in Scheme 2. Ether-protected amides are reduced with hydride to give secondary alcohols (**5** and **6**), followed by 3-aza-Grob fragmentation to form imine aldehydes (**7** and **8**). Excess hydride converts the active intermediates (**7** and **8**) to saturated amino alcohols (**3** and **4**). These results provide evidence that 3-aza-Grob fragmentation can proceed with several different nucleofuges.

In conclusion, we have examined the 3-aza-Grob fragmentation occurring during hydride reduction of oxindole analogues. The results demonstrate that this system is effective for simple aromatic lactams presenting a variety of ether protecting groups. Efforts are now underway to determine the mechanism and synthetic applications of this reaction.

Experimental Section

Melting points are uncorrected. Infrared spectra were run as neat films unless otherwise noted. ^{1}H NMR and

(1) Weyersthal, P.; Marschall, H. Fragmentation Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 6, p 1044.
(2) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.
(3) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.
(4) Becker, K. B.; Grob, C. A. In *The Chemistry of Double-bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1977; Part 2, p 653.
(5) Thurston, D. E. Advances in the Study of Pyrrolo[2,1-c][1,4]-benzodiazepine (PBD) Antitumor Antibiotics. In *Molecular Aspects of Anticancer Drug−DNA Interactions*; Neidle, S., Waring, M. J., Eds.; Macmillan Press: New York, 1993; Vol. 1, pp 54−88.
(6) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433.
(7) Wang, J. J.; Hu, W. P.; Chung, H. W.; Wang, L. F.; Hsu, M. H. *Tetrahedron* **1998**, *54*, 13149−13154.
(8) Thurston, D. E.; Kaumaya, P. T. P.; Hurley, L. H. *Tetrahedron Lett.* **1984**, *25*, 2649 and references therein.
(9) Wharton, P. S. *J. Org. Chem.* **1961**, *26*, 4781.
(10) Wharton, P. S.; Hiegel, G. A.; Coombs, R. V. *J. Org. Chem.* **1963**, *28*, 3217.
(11) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254.
(12) Caine, D. *Org. Prep. Proced. Int.* **1988**, *20*, 1.
(13) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991.

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Scheme 2. Plausible Reaction Pathways for the Conversion of Ether-Protected 1 and 2 into 3 and 4

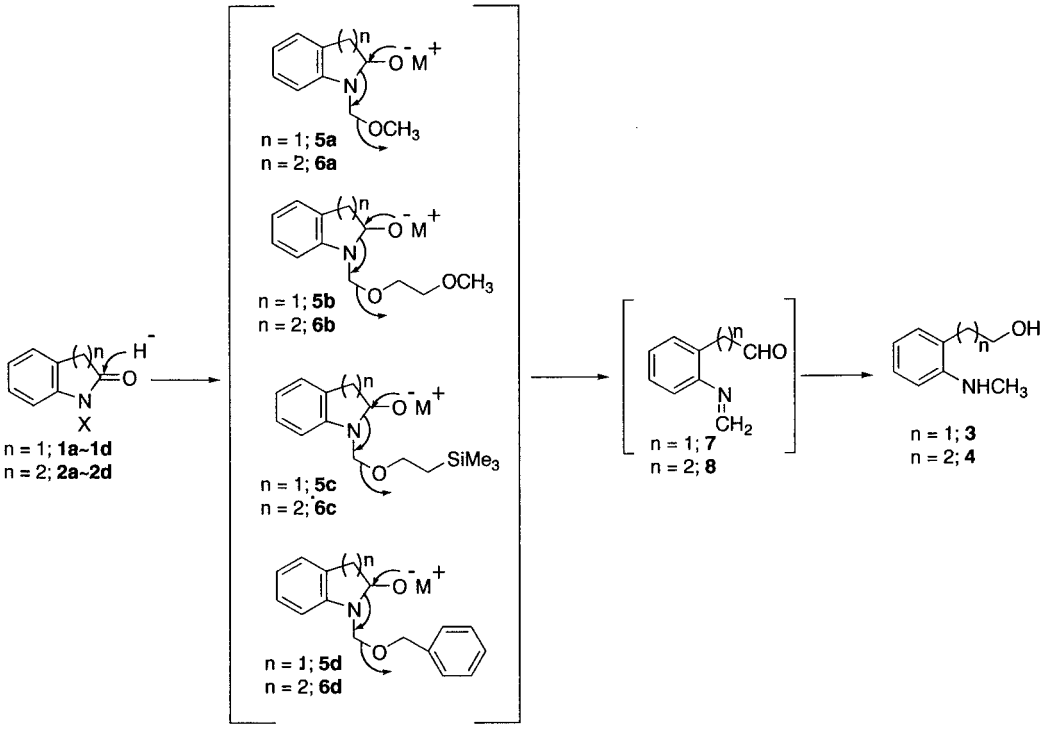

Table 1. Products (3 and 4) of Hydride Reduction of Ether-Protected Aromatic Lactams

entry	substrate	X	product	conversion (%)	yield[a] (%)
1	**1a**	MOM	**3**	100	95
2	**2a**	MOM	**4**	100	93
3	**1b**	MEM	**3**	100	93
4	**2b**	MEM	**4**	100	93
5	**1c**	SEM	**3**	51	85[b]
6	**2c**	SEM	**4**	48	98[b]
7	**1d**	BOM	**3**	66	90[b]
8	**2d**	BOM	**4**	67	98[b]

[a] All reactions were carried out with 15 equiv of $NaBH_4$. All yields are for pure, isolated compounds. [b] The yields of products are based upon the recovered starting material.

^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using $CDCl_3$ as a solvent. ^1H NMR chemical shifts are referenced to TMS or $CDCl_3$ (7.26 ppm). ^{13}C NMR was referenced to $CDCl_3$ (77.0 ppm). Multiplicities were determined by the DEPT sequence and are given as s, d, t, q. Mass spectra and high-resolution mass spectra (HRMS) were measured using the electron-impact (EI, 70 eV) technique. Elemental analyses were performed by the Tainan Regional Instrument Center of NSC at NCKU. Flash chromatography was carried out on silica gel 60 (E. Merck, 230−400 mesh).

Oxindole **1**, 3,4-dihydro-2-(*1H*)-quinolinone **2**, MOMCl, MEMCl, and SEMCl are commercially available. BOMCl was prepared according to the reported procedure.[14] Solvents were distilled and dried before use. All reactions were carried out in predried glassware and under nitrogen atomosphere.

General Procedure for Syntheses of Ether-Protected Oxindole (1a−d) and 3,4-Dihydro-2-(1*H*)-quinolinone (2a−d). To a stirred solution of aromatic lactam **1** or **2** (4 mmol) in THF (10 mL) and DMF (10 mL) was added NaH (4 mmol) under nitrogen at 0 °C, and the reaction mixture was stirred at the same temperature for 30 min. Ether protective agent (**a**−**d**) (5.2 mmol) was added dropwise into the reaction mixture. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was poured into ice−water (100 mL) and extracted four times with ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$, H_2O, and brine and dried over $MgSO_4$. After removal of solvent, the residue was purified by flash chromatography to give the products.

***N*-Methoxymethyloxindole (1a)**. Compound **1a** was prepared by the reaction of **1** with MOMCl (**a**) according to the general procedure. Pure **1a** was obtained as a pink solid by flash chromatography (hexane/AcOEt = 2:1) in 52% yield: mp 76−78 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.24 (m, 2H), 7.06 (td, J = 7.5, 0.9 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 5.12 (s, 2H), 3.59 (s, 2H), 3.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.5 (s), 143.0 (s), 127.9 (d), 124.4 (d), 123.9 (s), 122.8 (d), 109.4 (d), 71.2 (t), 56.2 (q), 35.8 (t); LRMS (EI, *m/z*) 177 (M^+); HRMS (EI, *m/z*) for $C_{10}H_{11}NO_2$ calcd 177.0790, found 177.0799. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.69; H, 6.26; N, 7.84.

***N*-(2-Methoxyethoxymethyl)oxindole (1b)**. Compound **1b** was prepared by the reaction of **1** with MEMCl (**b**) according to the general procedure. Pure **1b** was obtained as a pink oil by flash chromatography (hexane/AcOEt = 3:1) in 47% yield: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27−7.24 (m, 2H), 7.08−7.06 (m, 2H), 5.22 (s, 2H), 3.68−3.66 (m, 2H), 3.58 (s, 2H), 3.52−3.50 (m, 2H), 3.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.4 (s), 143.4 (s), 127.9 (d), 124.3 (d), 123.8 (s), 122.8 (d), 109.6 (d), 71.4 (t), 70.1 (t), 67.9 (t), 58.9 (q), 35.8 (t); LRMS (EI, *m/z*) 221 (M^+); HRMS (EI, *m/z*) for $C_{12}H_{15}NO_3$ calcd 221.1053, found 221.1045.

***N*-[2-(Trimethylsilyl)ethoxymethyl]oxindole (1c)**. Compound **1c** was prepared by the reaction of **1** with

(14) Connor, D. S.; Klein, G. W.; Taylor, G. N.; Boeckman, R. K., Jr.; Medwid, J. B. *Organic Synthesis*; Wiley: New York, 1986; Collect. Vol. VI, p 101.

SEMCl (**c**) according to the general procedure. Pure **1c** was obtained as a yellow oil by flash chromatography (hexane/AcOEt = 4:1) in 48% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29−7.25 (m, 2H), 7.08−7.03 (m, 2H), 5.15 (s, 2H), 3.61−3.57 (m, 4H), 0.95−0.90 (m, 2H), 0.02−0.04 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.4 (s), 143.7 (s), 127.9 (d), 124.3 (d), 124.0 (s), 122.7 (d), 109.6 (d), 69.4 (t), 66.1 (t), 35.9 (t), 17.8 (t), 1.5 (q); LRMS (EI, *m*/*z*) 263 (M^+); HRMS (EI, *m*/*z*) for $C_{14}H_{21}NO_2Si$ calcd 263.1342, found 263.1348.

***N*-Benzyloxymethyloxindole (1d)**. Compound **1d** was prepared by the reaction of **1** with BOMCl (**d**) according to the general procedure. Pure **1d** was obtained as a white solid by flash chromatography (hexane/AcOEt = 3:1) in 55% yield: mp 74−76 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.23 (m, 7H), 7.07−7.05 (m, 2H), 5.26 (s, 2H), 4.57 (s, 2H), 3.54 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.5 (s), 143.4 (s), 137.3 (s), 128.5 (s), 128.3 (d), 128.0 (s), 127.8 (s), 124.4 (d), 124.0 (s), 122.8 (d), 109.6 (d), 70.8 (t), 69.6 (t), 35.8 (t); LRMS (EI, *m*/*z*) 253 (M^+); HRMS (EI, *m*/*z*) for $C_{16}H_{15}NO_2$ calcd 253.1104, found 253.1108. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.59; H, 6.07; N, 5.46.

***N*-Methoxymethyl-3,4-dihydro-2-(1*H*)-quinolinone (2a)**. Compound **2a** was prepared by the reaction of **2** with MOMCl (**a**) according to the general procedure. Pure **2a** was obtained as a white solid by flash chromatography (hexane/AcOEt = 2:1) in 98% yield: mp 55−57 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31−7.00 (m, 4H), 5.31 (s, 2H), 3.40 (s, 3H), 2.93−2.89 (m, 2H), 2.71−2.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (s), 139.4 (s), 127.5 (d), 127.5 (d), 125.9 (s), 123.3 (d), 115.8 (d), 73.8 (t), 56.1 (q), 31.7 (t), 25.2 (t); LRMS (EI, *m*/*z*) 191 (M^+); HRMS (EI, *m*/*z*) for $C_{11}H_{13}NO_2$ calcd 191.0947, found 191.0944. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.94; H, 6.95; N, 7.24.

***N*-(2-Methoxyethoxymethyl)-3,4-dihydro-2-(1*H*)-quinolinone (2b).** Compound **2b** was prepared by the reaction of **2** with MEMCl (**b**) according to the general procedure. Pure **2b** was obtained as a colorless oil by flash chromatography (hexane/AcOEt = 2:1) in 90% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 8.1 Hz, 1H), 7.24−7.03 (m, 3H), 5.41 (s, 2H), 3.76−3.74 (m, 2H), 3.55∼3.53 (m, 2H), 3.37 (s, 3H), 2.93−2.89 (m, 2H), 2.71−2.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2 (s), 139.6 (s), 127.5 (d), 127.4 (d), 125.8 (s), 123.3 (d), 116.1 (d), 72.9 (t), 71.5 (t), 67.8 (t), 58.8 (q), 31.7 (t), 25.2 (t); LRMS (EI, *m*/*z*) 235 (M^+); HRMS (EI, *m*/*z*) for $C_{13}H_{17}NO_3$ calcd 235.1209, found 235.1202.

***N*-[2-(Trimethylsilyl)ethoxymethyl]-3,4-dihydro-2-(1*H*)-quinolinone (2c).** Compound **2c** was prepared by the reaction of **2** with SEMCl (**c**) according to the general procedure. Pure **2c** was obtained as a colorless oil by flash chromatography (hexane/AcOEt = 5:1) in 99% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36 (dd, J = 8.1, 0.7 Hz, 1H), 7.27−7.23 (m, 1H), 7.16−7.15 (m, 1H), 7.04 (td, J = 7.3, 1.1 Hz, 1H), 5.35 (s, 2H), 3.69−3.65 (m, 2H), 2.94−2.90 (m, 2H), 2.71−2.67 (m, 2H), 0.98−0.94 (m, 2H), 0 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1 (s), 139.7 (s), 127.5 (d), 127.5 (d), 126.0 (s), 123.3 (d), 116.2 (d), 72.2 (t), 71.5 (t), 66.0 (t), 31.9 (t), 25.4 (t), 18.1 (t), 1.4 (t); LRMS (EI, *m*/*z*) 277 (M^+); HRMS (EI, *m*/*z*) for $C_{15}H_{23}NO_2Si$ calcd 277.1499, found 277.1496.

***N*-Benzyloxymethyl-3,4-dihydro-2-(1*H*)-quinolinone (2d).** Compound **2d** was prepared by the reaction of **2** with BOMCl (**d**) according to the general procedure. Pure **2d** was obtained as a colorless oil by flash chromatography (hexane/AcOEt = 5:1) in 99% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.01 (m, 9H), 5.45 (s, 2H), 4.65 (s, 2H), 2.89−2.85 (m, 2H), 2.67−2.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3 (s), 139.6 (s), 137.9 (s), 128.2 (d), 127.7 (d), 127.6 (d), 126.0 (s), 123.4 (d), 116.1 (d), 72.6 (t), 71.0 (t), 31.8 (t), 25.3 (t); LRMS (EI, *m*/*z*) 267 (M^+); HRMS (EI, *m*/*z*) for $C_{17}H_{17}NO_2$ calcd 267.1260, found 267.1266.

General Procedure for Hydride Reduction of Ether-Protected Oxindole (1a−d) and 3,4-Dihydro-2-(1*H*)-quinolinone (2a−d). To a solution of ether-protected aromatic lactam **1a**−**d** or **2a**−**d** (0.3 mmol) in dry EtOH (6 mL) was added sodium borohydride (4.5 mmol) in one protion at 0 °C, and then the mixture was stirred at room temperature for 24−48 h. The reaction was diluted with CH_2Cl_2 and washed twice with water. The combined aqueous phases were extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated under vacumn. The crude product was subjected to flash chromatography (CH_2Cl_2/MeOH = 30:1) to give the corresponding compounds **3** or **4**. The reaction yields are shown in Table 1.

2-(2-Methylaminophenyl)ethanol (3): yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (td, J = 7.8, 1.6 Hz, 1H), 7.01 (dd, J = 7.5, 1.6 Hz, 1H), 6.70 (td, J = 7.5, 1.4 Hz, 1H), 6.64 (dd, J = 8.0, 1.2 Hz, 1H), 3.79 (t, J = 6.3 Hz, 2H), 3.14 (br s, −NH and −OH, 2H), 2.81 (s, 3H), 2.71 (t, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 147.6 (s), 130.0 (d), 127.8 (d), 123.7 (s), 117.3 (d), 110.3 (d), 62.8 (t), 34.6 (t), 30.7 (q); IR (neat) 3400, 2839, 1613, 1521 cm^{-1}; LRMS (EI, *m*/*z*) 151 (M^+); HRMS (EI, *m*/*z*) for $C_9H_{13}NO$ calcd 151.0998, found 151.0993.

3-(2-Methylaminophenyl)propan-1-ol (4): yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.16 (td, J = 7.9, 1.3 Hz, 1H), 7.05 (dd, J = 7.3, 1.3 Hz, 1H), 6.71 (td, J = 7.3, 1.1 Hz, 1H), 6.65 (dd, J = 7.9, 1.0 Hz, 1H), 3.67 (t, J = 5.9 Hz, 2H), 2.87 (s, 3H), 2.60 (t, J = 7.4 Hz), 1.90−1.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 147.0 (s), 129.1 (d), 127.3 (d), 125.5 (s), 117.3 (d), 110.1 (d), 61.9 (t), 31.8 (t), 30.9 (q), 26.9 (t); IR (CCl_4) 3418, 2930, 1613, 1507 cm^{-1}; LRMS (EI, *m*/*z*) 165 (M^+); HRMS (EI, *m*/*z*) for $C_{10}H_{15}NO$ calcd 165.1155, found 165.1153.

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Supporting Information Available: Spectral data (Varian Unity Plus 400 MHz ^{1}H NMR and 100 MHz ^{13}C DEPT NMR) for compounds **1a**−**d**, **2a**−**d**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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