JOC Notes

Complications from Dual Roles of Sodium Hydride as a Base and as a Reducing Agent

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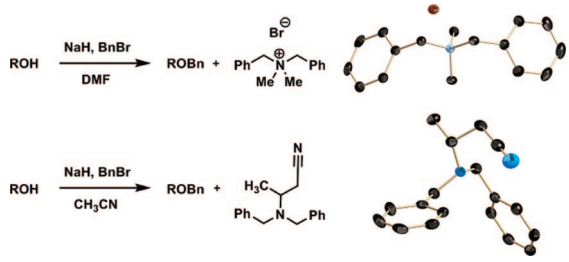
Received July 15, 2008



Sodium hydride is a common reagent for substrate activation in nucleophilic substitution reactions. Sodium hydride can behave both as a base and as a source of hydride. This dual ability in the presence of an electrophile such as benzyl bromide results in the formation of byproducts when dimethylformamide or acetonitrile are used as solvents for these reactions. The structural nature of these byproducts is revealed in this report.

Sodium hydride is a commonly used base for deprotonation of alcohols, phenols, amides, ketones, esters, and other functional groups for the promotion of their nucleophilic substitution.[1] Typically, sodium hydride and the reagents are mixed in polar aprotic solvents such as DMSO, DMF, or acetonitrile for these S_N2-type reactions. Whereas the literature is replete with examples of the use of these solvents in such reactions, our chance discovery of reactivity of sodium hydride with two of these commonly used solvents, DMF and acetonitrile, indicates that certain undesired side reactions involving these two solvents might be common, but unrecognized. As is disclosed in this report, the root cause of these complicating side reactions is the dual role that sodium hydride exhibits as a base and as a source of hydride.

The type of byproducts that will be disclosed in this report are generally difficult to detect with common visualization methods and are easy to overlook. Using benzyl bromide as the electrophile helped us to isolate the byproducts by UV detection and the structures were ultimately assigned by X-ray analysis of single crystals.

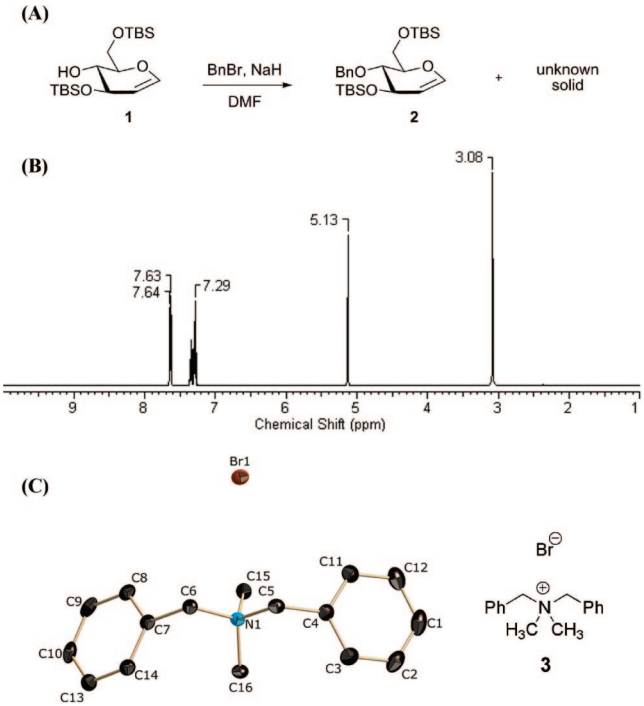


FIGURE 1. (A) Benzylation of compound **1**. (B) The ^{1}H NMR spectrum of the unknown solid in $CDCl_3$. (C) The ORTEP diagram of the X-ray structure of compound **3** is shown at the 50% probability level. Hydrogen atoms are omitted for clarity.

During benzylation of compound **1** in the presence of NaH and benzyl bromide in DMF, we identified an unusual solid byproduct (Figure 1A). The ^{1}H NMR spectrum of this byproduct was simple (Figure 1B), and was without resonances originating from the glucal substrate. Assignment of structure was done by X-ray analysis. This compound crystallized in the monoclinic space group $P2_1/c$. Once in hand, the X-ray structure surprised us, as it showed that the solid, compound **3**, was a derivative of dimethylamine (Figure 1C). The origin of the dimethylamine moiety was clearly DMF, which served as the solvent for the reaction. We note that DMF was freshly distilled prior to use in the reaction and that there was no trace of dimethylamine in DMF as discerned by a negative ninhydrin assay.

A search of the literature revealed that when DMF was treated with BnBr in the presence of K_2CO_3 as the base at 80 °C for 2 days, compound **3** was obtained as a major product.[2] The process is presumably slow, because it is a hydrolytic event. In the observation from our laboratory, hydride reduction of DMF

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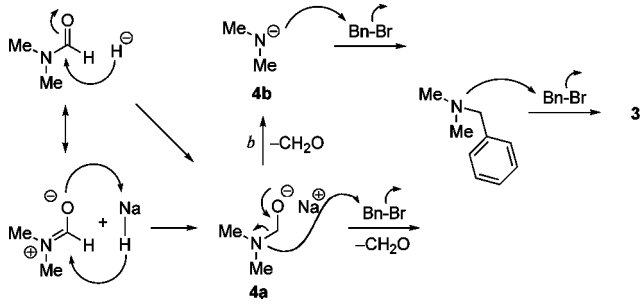
10.1021/jo802706d CCC: $40.75 © 2009 American Chemical Society
Published on Web 02/12/2009

SCHEME 1. Possible Mechanisms for the Formation of Compound 3



could result in the formation of sodium (dimethylamino)methanolate (**4a**), followed by dimethylamine (**4b**; Scheme 1). Subsequent benzylation, either stepwise on **4b** or concerted on **4a**, yields **3** as a stable bromide salt. Compound **3** was obtained in 5−12% yield during benzylation of **1**. Consumption of benzyl bromide by the side reaction lowered the yield of the desired product and gave a complex reaction mixture, which made purification more difficult.

A disproportionation reaction with DMF, resulting in dimethylamine and carbon monoxide, has also been reported.[3] In this reaction, when a mixture of DMF and methyl bromide (in the absence of base) was heated at 80 °C for 6 days in a sealed tube, the formation of tetramethylammonium bromide and carbon monoxide was noted. To explore whether this disproportionation reaction, and not the involvement of NaH, was responsible for the formation of **3**, we carried out two additional experiments. In one, DMF-d_6 and benzyl bromide (and no NaH) were allowed to react. In the second, the mixture of DMF-d_6, benzyl bromide, and NaH was allowed to incubate. These reactions were monitored by ^{1}H NMR at room temperature over a period of 16 h. We did not detect any change in ^{1}H NMR of the first reaction. The ^{1}H NMR spectrum of the second reaction showed the disappearance of the methylene resonance (4.7 ppm) of benzyl bromide and the appearance of a new signal (5.2 ppm) from the resultant deuterated variant of compound **3**. We hasten to add that there was no evidence of carbon monoxide formation in either reaction, as judged by a negative phosphomolybdic acid−palladium chloride test.

We identified another example of a side reaction caused by entry of solvent into reaction with NaH. The *O*-benzylation of glucosamine derivative **5** (Figure 2A), using NaH as base and acetonitrile as solvent, gave a low yield of the product. Moreover, the isolated product (**6**) was contaminated by an impurity of unknown structure. The ^{1}H NMR spectrum of the isolated impurity is shown as Figure 2B. Further analysis by NMR spectroscopy (H−H COSY, Dept, and H−C HETCOR) revealed that the 3H doublet at δ 1.2 was a methyl coupled to the 1H multiplet at δ 3.2. The methylene resonance at δ 2.5 was diastereotopic based on the splitting pattern, while the two methylenes at δ 3.6 originated from two benzyl groups. The structure of this unknown again was solved by X-ray analysis. Crystals were grown by overnight diffusion of Et_2O into a CH_2Cl_2 solution of the compound at room temperature. The structure revealed the overall reaction of two molecules of acetonitrile with two molecules of BnBr (Figure 2C). Compound **7** crystallized in the centrosymmetric space group $P\bar{1}$.We note that the bond lengths between N1 and C7, N1 and C9, and N1 and C12 are 1.467 ± 0.001, 1.471 ± 0.002, and 1.465 ± 0.002 Å, respectively. These bond lengths confirm that these are all single bonds.

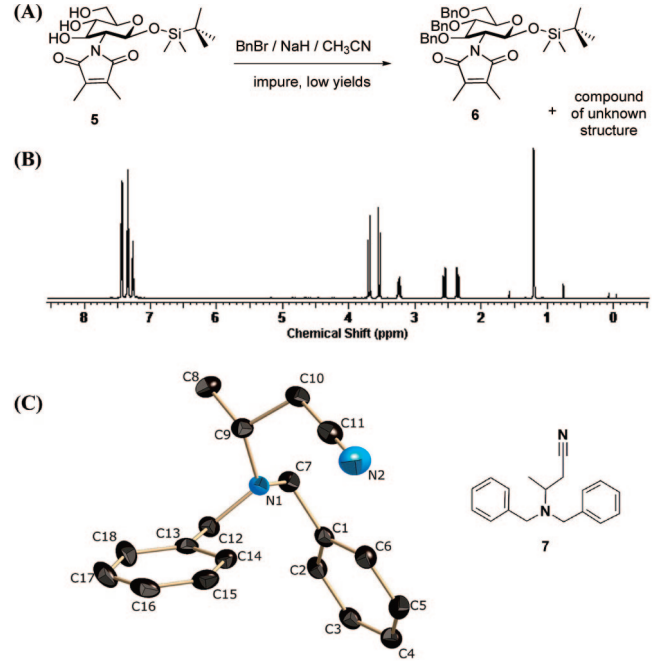


FIGURE 2. (A) Attempt at NaH-mediated benzylation of compound **5** in acetonitrile. (B) The ^{1}H NMR spectrum of the compound of unknown structure in $CDCl_3$. (C) The ORTEP diagram of the X-ray structure of the compound of unknown structure (compound **7**) is shown at the 50% probability level. Hydrogen atoms are omitted for clarity.

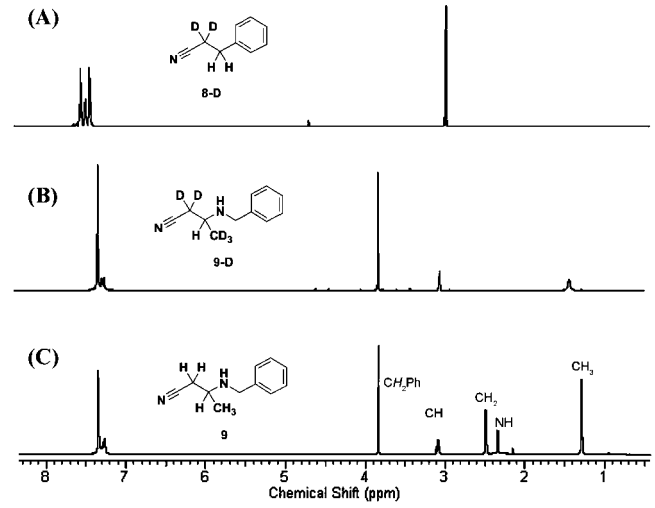
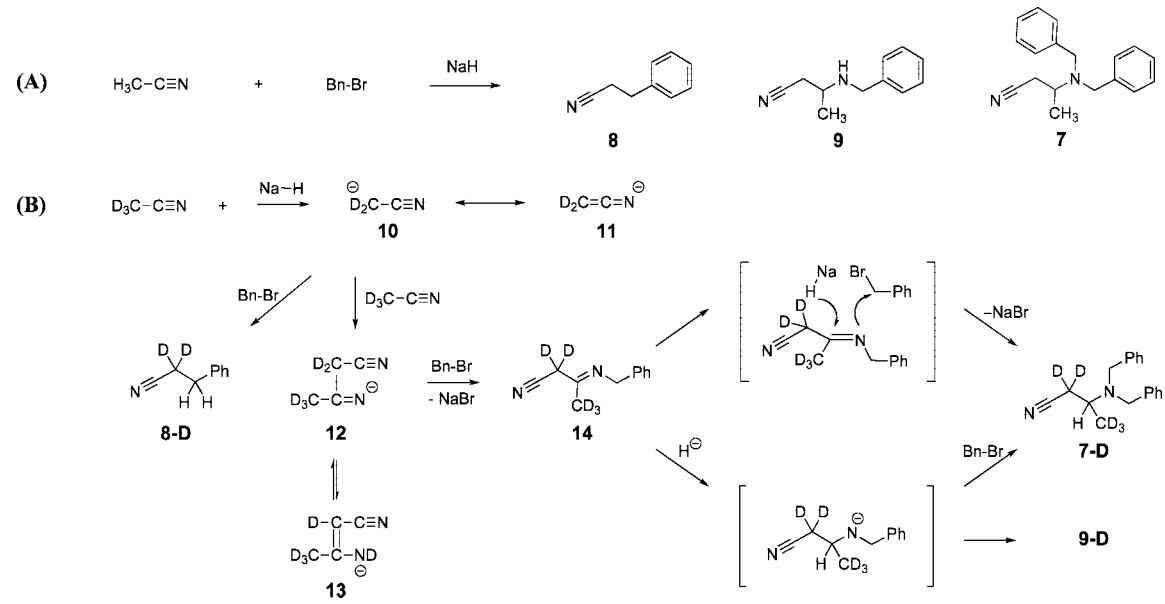


FIGURE 3. Comparison of ^{1}H NMR spectra of (A) deuterated compound **8**, of (B) deuterated compound **9**, and of (C) compound **9** in $CDCl_3$.

The structure for **7** implicates the existence of a sequential benzylation and reduction event. Since the pK_a of alcohols (16−18) is substantially lower than the pK_a of acetonitrile (25), in principle selective deprotonation of the alcohol by NaH (rather than reaction with acetonitrile) should prevail. However, when acetonitrile is used as solvent, the opportunity exists for competitive deprotonation of acetonitrile. It is this opportunity, along with a favorable entropic consideration (high concentration) for the solvent, that initiates the events leading to the formation of **7**.

We set out to confirm the presumptive intermediates for **7** by examination of a reaction mixture of acetonitrile, benzyl bromide, and sodium hydride (Scheme 2A). Two sets of reaction

SCHEME 2. The Proposed Mechanism of NaH-Mediated Benzylation of Acetonitrile



conditions were examined. In one, NaH was added in several portions to an acetonitrile solution of benzyl bromide.

In the second, benzyl bromide was added in several portions to a suspension of NaH in acetonitrile. The first reaction gave 3-phenylpropanenitrile (**8**) as the major product (55%), assigned by comparison of its ^{1}H NMR spectrum with authentic material. The second reaction afforded a mixture of several compounds, including **8**, which was removed from the mixture by vacuum distillation. Crystallization of the remaining mixture (from an EtOAc/hexanes cosolvent system) produced crystals of compound **7**. The mother liquor was concentrated, and the crude material was purified by preparative TLC to give yet another new compound. Its ^{1}H NMR spectrum was similar to that of **7** and suggested the presence of structure arising from overall reaction of two molecules of acetonitrile with benzyl bromide. High-resolution MS confirmed the structure as that of **9**. Compound **9** previously was synthesized by reaction of crotonitrile and benzylamine under reflux in ethanol.[4]

Yields for compounds **7**, **8**, and **9** were 4%, 40%, and 6%, respectively. Yields were calculated from the ^{1}H NMR spectrum of the crude mixture for the second set of reaction conditions.

To further evaluate the mechanism, the products of the reaction of MeCN-d_3 were examined. The ^{1}H NMR spectra for **8-D** and **9-D** isolated from this reaction are shown in Figure 3. The formation of **8-D** is readily explained by base-promoted benzylation of acetonitrile (Scheme 2B). The reaction of the acetonitrile carbanion (**10**) with a second acetonitrile molecule, and subsequent reaction with benzyl bromide, gives intermediate **14**. Acetonitrile anion has two resonance structures (**10** and **11**). The conversion of **14** to **9-D** or to **7-D** requires reduction of the imine. The two-electron reduction presumably is by the hydride anion of NaH. The precedent for such chemistry by NaH is exemplified by carbonyl, halide, disulfide, disilane, silyl ether, azides, and isoquinoline reductions in the literature.[5−11]

Addition of hydride to imine **14** was confirmed by the presence of a singlet at δ 2.99 in the ^{1}H NMR spectrum of **9-D** (Figure 3B). The X-ray structure of compound **7** also confirmed an N1−C9 single bond (bond length of 1.471 ± 0.002 Å, Figure 2C). The conversion of **14** to **7-D** might proceed in a stepwise or in a concerted manner. It is conceivable that the tautomer **13** would exist. The potential intermediate **13** could also serve as the recipient of the hydride, whereby it too will lead to the formation of **7-D** and **9-D**.

DMF and acetonitrile are commonly used solvents in alkylation reactions mediated by NaH. As reported herein, the use of these solvents with NaH entails complications, stemming from competing processes involving NaH both as a base and as a source of two electrons in competing reactions with the intended substrate or with the solvent. While many reactions in the literature have used these conditions with high product yields, there is no doubt that with a problematic substrate, the erosion of reagent stoichiometry as a result of these competing reactions with solvent could account for unacceptably low yields. Reactions of NaH are also performed in DMSO. Since explosions have been reported for the mixture of DMSO and NaH, we did not perform similar reactions in this solvent.[12,13]

Recognition that these reactions do take place, as we have now documented, should influence how these reactions are carried out in the future. The presently unrecognized existence of these types of undesired side reactions is likely to be quite common.

Experimental Section

Compound 3: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.08 (s, 6H, 2 × CH_3), 5.13 (s, 4H, 2 × CH_2Ph), 7.24 −7.39 (m, 6H, Ar−H), 7.59

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− 7.67 (m, 4H, Ar−H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 47.8, 67.1, 127.3, 128.8, 130.3, 133.2; HRMS (FAB, calcd for $C_{16}H_{20}N$ (M^+) 226.1596, found 226.1599.

Syntheses of Deuterated Compound 3. NaH (60% dispersion in oil, 20 mg, 0.5 mmol) was added to a vigorously stirred solution of benzyl bromide (70 μL, 0.6 mmol) in DMF-d_6 (0.7 mL) in an ice−water bath and was stirred for 16 h. The solution was mixed with hexanes and the top hexanes layer was removed. The DMF layer was analyzed by NMR. The sample was purified by recrystallization from chloroform. **Compound 3-D**: ^{1}H NMR (500 MHz, DMF-d_6) δ 5.24 (s, 4H), 7.43−7.52 (m, 6H), 7.73−7.80 (m, 4H); ^{13}C NMR (126 M Hz, DMF-d_6) δ 46.5 (m), 65.8, 128.9, 130.3, 133.5, 139.5; HRMS (FAB) calcd for $C_{16}H_{14}D_6N$ (M^+) 232.1972, found 232.1980.

Syntheses of Compounds 7−9. Two methods were used.

Method A: NaH (60% dispersion on oil, 0.2 g, 5 mmol) was added to a vigorously stirred solution of benzyl bromide (0.7 mL, 6 mmol) in anhydrous acetonitrile (7 mL) in three portions over a period of 5 h in an ice−water bath under a nitrogen atmosphere. The mixture was stirred overnight, then it was filtered through layers of silica gel and Celite and washed with acetonitrile. The combined filtrate was mixed with hexanes and the top hexanes layer was removed. The acetonitrile layer was evaporated to an oil, which was distilled (130 °C/20 mmHg) to yield compound **8** as a major product (55%). The ^{1}H NMR spectrum of this sample matched that of the authentic 3-phenylpropanenitrile purchased from Sigma-Aldrich.

Method B: Benzyl bromide (0.7 mL, 6 mmol) was added to a vigorously stirred suspension of NaH (60% dispersion on oil, 0.2 g, 5 mmol) in anhydrous acetonitrile (7 mL) in three portions over a period of 5 h in an ice−water bath under a nitrogen atmosphere. The mixture was stirred overnight and the resulting suspension was filtered through layers of silica gel and Celite and washed with acetonitrile. The combined filtrate was mixed with hexanes and the top hexanes layer was removed. The bottom acetonitrile layer was evaporated under reduced pressure and the resulting oil was subjected to vacuum distillation to remove compound **8** from the crude reaction mixture. The remaining oil was dissolved in a mixture of ethyl acetate and hexanes (5 mL). Slow evaporation of solvent overnight gave colorless crystals of compound **7**. ^{1}H NMR (500 M Hz, $CDCl_3$) δ 1.20 (d, J = 6.8 Hz, 3H), 2.36 (dd, J = 16.7, 6.8 Hz, 1H), 2.56 (dd, J = 16.7, 7.8 Hz, 1H), 3.24 (sxt, J = 6.9 Hz, 1H), 3.54 (d, J = 13.8 Hz, 2H), 3.69 (d, J = 13.8 Hz, 2H), 7.06−7.58 (m, 10H); ^{13}C NMR (126 M Hz, $CDCl_3$) δ 13.9, 21.9, 50.3, 53.3, 118.7, 127.1, 128.4, 128.6, 139.1; HRMS (FAB) calcd for $C_{18}H_{21}N_2$ ($M + H^+$) 265.1705, found 265.1703.

The mother liquor was evaporated and subjected to preparative thin-layer column chromatography to furnish compound **9**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (d, J = 6.6 Hz, 3H), 2.34 (s, 1H), 2.48 (d, J = 5.6 Hz, 2H), 3.09 (m, 1H), 3.83 (s, 2H), 7.12−7.48 (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 20.2, 24.8, 49.3, 51.0, 117.8, 127.4, 128.1, 128.6, 139.4; HRMS (FAB) calcd for $C_{11}H_{15}N_2$ ($M + H^+$) 175.1235, found 175.1256.

Syntheses of Deuterated Compounds 8 and 9. CD_3CN was subjected to method B as described above and the title compound was isolated by preparative thin-layer chromatography. **Compound 8-D**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.95 (s, 2H), 7.22−7.43 (m, 5H); ^{13}C NMR (126 M Hz, $CDCl_3$) δ 18.6 (m), 31.1, 119.0, 127.0, 128.1, 128.2, 128.6, 137.9; HRMS (FAB) calcd for $C_9H_7D_2N$ (M^+) 133.0861, found 133.0879.

Compound 9-D: ^{1}H NMR (300 M Hz, $CDCl_3$) δ 1.36 (br s, 1H), 2.99 (s, 1H), 3.76 (s, 2H), 7.13−7.34 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.6 (m), 24.4 (m), 48.9, 51.1, 118.0, 127.2, 127.9, 128.5, 139.6; HRMS (FAB) calcd for $C_{11}H_{10}D_5N_2$ ($M + H^+$) 180.1549, found 180.1533.

Crystal Growth and Analysis. Repeated recrystallization from chloroform afforded colorless crystals of compound **3** suitable for X-ray diffraction analysis. For compound **7**, crystals of suitable size for single-crystal X-ray diffraction analysis were obtained by diffusion of diethyl ether into the CH_2Cl_2 solution at room temperature overnight.

Crystals were examined under Infineum V8512 oil and placed on a MiTeGen mount, then transferred to the 100 K N_2 stream of a Bruker SMART Apex CCD diffractometer. Unit cell parameters were determined from reflections with $I > 10\sigma(I)$ harvested from three orthogonal sets of 30 0.5° ω scans. Data collection strategy was calculated with use of COSMO, included in the Apex2 suite of programs[14] to maximize coverage of reciprocal space in a minimum amount of time. Average 4-fold redundancy of measurements was sought. Data were corrected for Lorentz and polarization effects, as well as for absorption.

Structure solution and refinement utilized the programs of the SHELXTL software package.[15] Full details of the X-ray structure determinations are in the CIF files included as Supporting Information.

Previously, the structure of compound **3** was determined by X-ray powder diffraction[2] and later by X-ray single crystal diffraction with an R value of 0.0637.[16] Our data reported herein are of higher quality, with an R value of 0.0215.

Acknowledgment. This work was supported by the National Institutes of Health.

Supporting Information Available: Compound characterization data, including copies of 1D NMR spectra (^{1}H, ^{13}C NMR, and Dept) and 2D NMR spectra (H−H COSY and H−C Hetcor) of compounds **3**, **3-D**, **7**, **9**, **8-D**, and **9-D** and crystallographic information files (CIFs) of compounds **3** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802706D

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