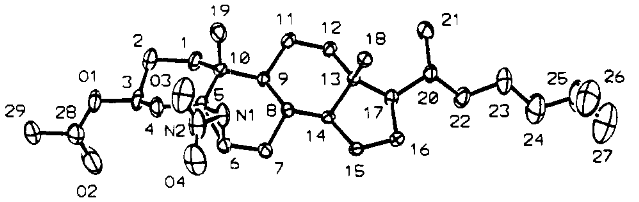

Figure 1. ORTEP drawing of 3β-acetoxy-5β,6β-*N*-nitroaziridinylcholestene.

mentary Material). The aziridine ring is asymmetric with one C–N bond being significantly longer than the other. The longer C–N bond is associated with the more sterically hindered C(5) atom. The two *N*-nitroaziridines reported earlier[2] were found to undergo different thermal rearrangements; the steroid-fused compound gave an epoxide on heating while the decalin-fused *N*-nitroaziridine gave an olefinic nitramine. This difference was thought to be due to steric interactions encountered by the aziridine ring. This study, however, shows no steric interactions either between the aziridine and acetoxy moieties or between the aziridine and the steroidal C ring. The reason for the divergent thermal reactivities remains obscure.

Experimental Section

Crystal Data: monoclinic, space group $P2_1$; at −98 °C a = 19.290 (3), b = 6.037 (2), c = 12.145 (2) Å, β = 92.33 (1)°, V = 1413 Å, Z = 2.

Intensity Data: Syntex P3 diffractometer, graphite monochromator, Mo Kα radiation, λ = 0.71069 Å, omega scans of 1.0°, $4° < 2\theta < 55°$, 3547 reflections.

Structure Solution and Refinement. The structure was solved by direct methods (QTAN). Hydrogen-atom positions were calculated but not refined. The structure was refined by full-matrix, least-squares techniques, 2983 reflections with $I > 2\sigma(I)$, 315 variables, R = 0.061, R_w = 0.058. The largest peak in the final difference Fourier had a magnitude of 0.36 e Å^{-3} and was located near O(2). The mathematical and computational details may be found elsewhere.[5]

Registry No. 2, 63866-33-1.

Supplementary Material Available: Bond distances and angles and positional and thermal parameters of **2** (7 pages). Ordering information is given on any current masthead page.

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Reactions of α-Azido Sulfones with Bases

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In a previous series of publications,[1] we reported our investigations of the reactions of α-halo sulfones with nucleophiles. On the basis of this chemistry, we anticipated that sulfones possessing a pseudohalogen atom in the α-position would exhibit useful and interesting properties. Herein, we report the reactions of α-azido sulfones with bases, reactions which take a course much different from that observed with α-halo sulfones.

The α-azido sulfones were prepared as shown in eq 1. The intermediate α-azido sulfides could be isolated, but

$$\underset{\mathbf{1}}{\mathrm{PhSCH_2R}} \xrightarrow[\text{2. NaN}_3/\text{Me}_2\text{SO-DMF}]{\text{1. SO}_2\text{Cl}_2/\text{CCl}_4} \underset{\mathbf{2}}{\mathrm{PhSCH(N_3)R}} \xrightarrow{\text{MCPBA}} \underset{\mathbf{3}}{\mathrm{PhSO_2CH(N_3)R}} \quad (1)$$

it was often more convenient to oxidize the crude sulfides with *m*-chloroperoxybenzoic acid (MCPBA) to the more crystalline sulfones.

The syntheses of α-azidobenzyl phenyl sulfones (**3**, R = Ar) failed in those cases where the ring of the benzyl group possessed either a strong electron-donating group (e.g., *p*-methoxy) or a very strong electron-withdrawing group (e.g., *p*-nitro). Treatment of *p*-methoxybenzyl phenyl sulfide with sulfuryl chloride under a variety of conditions gave *p*-methoxybenzyl chloride, the result of carbon–sulfur bond cleavage. This type of halogenolysis reaction has been observed previously[2] with benzyl sulfides which contain electron-donating groups. *p*-Nitrobenzyl phenyl sulfide appeared to undergo α-chlorination with sulfuryl chloride smoothly to give α-chloro-*p*-nitrobenzyl phenyl sulfide (monitored by NMR spectroscopy). However, treatment of this α-chloro sulfide in the same manner as the other α-chlorobenzyl sulfides (sodium azide in Me_2SO–DMF) resulted in the formation of *p*-nitrobenzonitrile (eq 2). It was, in fact, this reaction which suggested

$$p\text{-}\mathrm{NO_2C_6H_4CH_2SPh} \xrightarrow[\text{2. NaN}_3]{\text{1. SO}_2\text{Cl}_2} [p\text{-}\mathrm{NO_2C_6H_4CH(N_3)SPh}] \xrightarrow{\mathrm{N_3^-}} p\text{-}\mathrm{NO_2C_6H_4CN} + \mathrm{PhSO_2^-} + \mathrm{N_2} \quad (2)$$

to us that α-azido sulfones would react with bases to give nitriles (infra vide).[3]

The α-azidobenzyl phenyl sulfones (**3**, R = Ar) reacted with 0.25 M piperidine in 95% ethanol (reaction time 3–5 h at 55 °C) to give benzonitriles in 85–100% yield (by GLC analysis). Nitrogen gas also was evolved and liberated benzene sulfinate was trapped with methyl iodide to give methyl phenyl sulfone. Equation 3 outlines a likely

$$\mathrm{PhSO_2CH(N_3)Ar} + \mathrm{B^-} \rightarrow \mathrm{PhSO_2\bar{C}(N_3)Ar} \xrightarrow{-\mathrm{N_2}} \mathrm{PhSO_2C(Ar){=}N^-} \rightarrow \mathrm{ArCN} + \mathrm{PhSO_2^-} \quad (3)$$

mechanism for these reactions. Precedent for this reaction can be found in several isolated examples of the reactions of α-azido ketones with bases which yield α-imino ketones (or α-diketones after hydrolysis).[4]

Extention of this reaction to the synthesis of alkyl nitriles was generally unsuccessful. Since the α-azidoalkyl phenyl sulfones are significantly weaker carbon acids than the α-azidobenzyl phenyl sulfones, it was necessary to use stronger base systems. Both α-azidoisobutyl phenyl sulfone [**3**, R = $CH(CH_3)_2$] and α-azidoneopentyl phenyl sulfone [**3**, R = $C(CH_3)_3$] reacted with potassium *tert*-butoxide in THF at 25 °C and with sodium methoxide in methanol at 60 °C but gave no isolable nitriles. Control experiments showed that both isobutyronitrile and pivalonitrile do not survive under these reaction conditions. However, α-azido-β-phenethyl phenyl sulfone (**3**, R = CH_2Ph) reacted with sodium methoxide in methonol at 60 °C to give phenylacetonitrile, and α-azido-1-

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adamantylmethyl phenyl sulfone (**3**, R = 1-adamantyl) reacted with potassium *tert*-butoxide in THF at 25 °C to give 1-adamantanecarbonitrile. Both these nitriles were formed in ca. 85% yield, but control experiments indicated that these nitriles also slowly disappeared under the reaction conditions.

The benzonitriles can be synthesized directly from the azido sulfides **2** although a stronger base must be employed.[5] Treatment of the crude α-azido sulfides **2** in Me_2SO with potassium *tert*-butoxide gave benzonitriles in varying yields: R = C_6H_5 (64%), R = *p*-ClC_6H_4 (52%), R = *m*-ClC_6H_4 (51%), R = *p*-C_6H_4CN (44%), R = *p*-$CH_3C_6H_4$ (17%), R = *p*-AcC_6H_4 (5%). Since these yields are based on the starting benzyl phenyl sulfide, some are quite respectable considering that none of the intermediates need be isolated.

Treatment of the α-azido sulfides with weaker but more nucleophilic amines generally leads to substitution. Thus, treatment of **2** (R = Ph) with cyclohexylamine gave imine **4** and the hydrazoic acid salt of cyclohexylamine (eq 4).

$$PhCH(N_3)SPh + C_6H_{11}NH_2 \rightarrow PhCH{=}NC_6H_{11} + C_6H_{11}NH_3^+N_3^- \quad (4)$$

The fact that substitutions occur with α-azido sulfides but that the corresponding α-azido sulfones adopt a different reaction pathway resembles in some respects the contrasting chemistry observed with α-halo sulfides vs. α-halo sulfones.[1]

In conclusion, we note that the conversion of α-azido sulfones to nitriles under basic conditions is not a reaction unique to α-azido sulfur-containing compounds. Phenylacetonitrile is converted in a simple reaction sequence to benzonitrile in good yield (eq 5). Thus, it appears that

$$PhCH_2CN \xrightarrow[\text{2. } NaN_3/Me_2SO]{\text{1. } NBS/CCl_4} PhCN + N_2 + NaBr + NaCN \quad (5)$$

azides in which the azido group is on a benzylic carbon bearing an electron-withdrawing group which can function as a leaving group (e.g., SPh, OSPh, O_2SPh, CN, etc.) upon treatment with bases can yield benzonitriles in good yield. These syntheses join a host of new nitrile syntheses introduced in the past decade.[6]

Experimental Section

General Procedures. Melting points were taken on a Mel-Temp or Fisher-Johns apparatus and are uncorrected. Proton NMR spectra were recorded on a 60-MHz instrument in $CDCl_3$ (Me_4Si). Elemental analyses were performed by Dr. Franz Kasler of the University of Maryland. Gas–liquid chromatography (GLC) was performed on a Hewlett-Packard 7610A instrument equipped with a flame-ionization detector. Solutions were dried over anhydrous $MgSO_4$ (and evaporated with a rotary evaporator). GLC analyses were performed on 6 ft × 2 mm (i.d.) glass columns packed with 3% OV-17 on 100/120 Supelcoport at oven temperatures ranging from 80 to 135 °C. Preparation of the substituted benzyl phenyl sulfides has been reported earlier.[7,8]

Preparation of α-Azidobenzyl Phenyl Sulfide (2, R = Ph) and Related Compounds. In a 200-mL round-bottom flask, equipped with an addition funnel and drying tube, was placed 6 g (0.03 mol) of benzyl phenyl sulfide dissolved in 50 mL of reagent-grade CCl_4; 4.2 g (0.03 mol) of sulfuryl chloride in 25 mL of CCl_4 was added dropwise over a period of 15 min. After the solution was stirred for 1 h the solvent was removed and the resulting liquid was added to a cooled (0–10 °C) solution of 3.0 g (0.05 mol) of sodium azide in 75 mL of Me_2SO and 20 mL of DMF at a temperature below 25 °C. After being stirred for 1 h, the mixture was poured into 500 mL of water containing Na_2CO_3 and extracted with pentane. The extracts were dried and evaporated. The resulting crude product crystallized from aqueous ethanol to yield 4.9 g (68%) of the title compound: mp 30.5–32.0 °C; NMR δ 5.77 (s, 1 H), 7.2–7.7 (m, 10 H); IR (CCl_4) 2115 (N_3) cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3S$: C, 64.70; H, 4.59; N, 17.42. Found: C, 64.57; H, 4.67; N, 17.67.

In a like manner were prepared the following α-azido sulfides (solvent of crystallization, % yield):

α-Azido-*p*-chlorobenzyl sulfide (H_2O–EtOH, 51%): mp 42–43 °C; NMR δ 5.78 (s, 1 H), 7.2–7.6 (m, 9 H); IR (CCl_4) 2100 (N_3) cm^{-1}. Anal. Calcd for $C_{13}H_{10}ClN_3S$: C, 56.22; H, 3.66. Found: C, 56.35; H, 3.60.

α-Azido-*p*-cyanobenzyl phenyl sulfide (H_2O–EtOH, 25%): mp 65–66 °C; NMR δ 5.92 (s, 1 H), 7.2–7.8 (m, 9 H); IR (KBr) 2234 (CN) and 2102 (N_3) cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_4S$: C, 63.13; H, 3.78; N, 21.04. Found: C, 62.85; H, 3.82; N, 21.43.

α-Azido-1-adamantylmethyl phenyl sulfide (pentane, 70%): mp 33–34 °C; NMR δ 1.7–2.1 (m, 15 H), 4.2 (s, 1 H), 7.2–7.7 (m, 5 H); IR ($CHCl_3$) 2100 (N_3) cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_3S$: C, 68.19; H, 708; N, 14.04. Found: C, 7.82; H, 7.25; N, 14.41.

None of the other α-azido sulfides were isolated and characterized but were oxidized in situ as described below to give the corresponding sulfones.

Preparation of α-Azidobenzyl Phenyl Sulfone (3, R = Ph). To a cooled (0–10 °C) mixture of 4 g (19.8 mmol) of *m*-chloroperoxybenzoic acid (MCPBA) in 50 mL of CH_2Cl_2 and 3 g of $NaHCO_3$ in 25 mL of water was added dropwise with stirring a solution of 2 g (8.3 mmol) of α-azidobenzyl phenyl sulfide in 10 mL of CH_2Cl_2. After 1 h, the reaction mixture was poured into 100 mL of 5% $NaHCO_3$ solution. The organic layer was washed successively with 100 mL of 5% sodium thiosulfate and 100 mL of 5% sodium carbonate. The organic layer was dried, the solvent was removed by rotary evaporation, and the resulting crude solid was recrystallized from methylene chloride–pentane to yield 1.53 g (65%) of the title compound: mp 91.5–93.0 °C; NMR δ 5.55 (s, 1 H), 6.9–7.8 (m, 10 H); IR (CCl_4) 2110 (N_3), 1130 and 1330 (SO_2) cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06. Found: C, 57.06; H, 4.16.

In a like manner the following sulfones were made from the respective sulfides (solvent of crystallization, % yield):

α-Azido-*p*-chlorobenzyl phenyl sulfone (CH_2Cl_2–pentane, 77%): mp 122–124 °C; NMR δ 5.55 (s, 1 H), 7.0–7.9 (m, 9 H); IR (KBr) 2105 (N_3), 1130 and 1300 (SO_2) cm^{-1}. Anal. Calcd for $C_{13}H_{10}ClN_3O_2S$: C, 50.73; H, 3.28. Found: C, 50.89; H, 3.35.

α-Azido-*p*-cyanobenzyl phenyl sulfone (CH_2Cl_2–pentane, 75%): mp 138–140 °C; NMR δ 5.68 (s, 1 H), 7.2–7.9 (m, 9 H); IR (KBr) 2220 (CN), 2110 (N_3), 1150 and 1325 (SO_2) cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_4O_2S$: C, 56.36; H, 3.38. Found: C, 56.33; H, 3.39.

α-Azido-1-adamantylmethyl phenyl sulfone (Et_2O–pentane, 75%): mp 120–121 °C; NMR δ 1.4–2.3 (m, 15 H), 3.89 (s, 1 H), 7.15–8.05 (m, 5 H); IR (KBr) 2100 (N_3), 1150 and 1310 (SO_2) cm^{-1}. Anal. Calcd for $C_{17}H_{21}N_3O_2S$: C, 61.60; H, 6.39; N, 12.68. Found: C, 61.68; H, 6.60; N, 12.60.

The following α-azido sulfones (solvent of crystallization, % yield) were synthesized from the crude α-azido sulfides by oxidation with MCPA:

α-Azido-*m*-chlorobenzyl phenyl sulfone (H_2O–EtOH, 31%): mp 105–106 °C; NMR δ 5.52 (s, 1 H), 7.0–7.9 (m, 9 H); IR (CCl_4) 2120 (N_3), 1138 and 1335 (SO_2) cm^{-1}. Anal. Calcd for $C_{13}H_{10}ClN_3O_2S$: C, 50.73; H, 3.28. Found: C, 50.58; H, 3.27.

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(5) As one might expect based on electron-withdrawing power, the order of reactivity toward base is α-azido sulfones > α-azido sulfoxides > α-azido sulfides. The α-azido sulfoxides can be prepared from the α-azido sulfides (1 equiv of MCPBA), but they offer no particular advantage in this nitrile synthesis. However, they do exhibit interesting thermal chemistry which will be described elsewhere.

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α-Azido-*p*-methylbenzyl phenyl sulfone (Et_2O–pentane, 22%): mp 97–98 °C; NMR δ 2.33 (s, 3 H), 5.50 (s, 1 H), 7.0–7.75 (m, 9 H); IR (KBr) 2110 (N_3), 1140 and 1320 (SO_2) cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56. Found: C, 58.81; H, 4.47.

α-Azido-*p*-acetylbenzyl phenyl sulfone (Et_2O–pentane, 16%): mp 105–106 °C; NMR δ 2.58 (s, 3 H), 5.63 (s, 1 H), 7.2–8.0 (m, 9 H); IR (CCl_4) 2120 (N_3), 1690 (C=O), 1133 and 1325 (SO_2) cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.15. Found: C, 57.19; H, 4.31.

α-Azidoisobutyl phenyl sulfone (H_2O–EtOH, 70%): mp 72–73 °C; NMR δ 1.00 (d, *J* = 6 Hz, 3 H), 1.19 (d, *J* = 6 Hz, 3 H), 2.40 (m, 1 H), 4.10 (d, *J* = 5 Hz, 1 H), 7.6–8.2 (m, 5 H); IR (CCl_4) 2105 (N_3), 1150 and 1328 (SO_2) cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_3O_2S$: C, 50.19; H, 5.47. Found: C, 50.58; H, 5.57.

α-Azidoneopentyl phenyl sulfone (H_2O–EtOH, 73%): mp 71.5–72.5 °C; NMR δ 1.27 (s, 9 H), 4.08 (s, 1 H), 7.55–8.13 (m, 5 H); IR (CCl_4) 2102 (N_3), 1150 and 1330 (SO_2) cm^{-1}. Anal. Calcd for $C_{11}H_{15}N_3O_2S$: C, 52.15; H, 5.97; N, 16.59. Found: C, 52.21; H, 6.19; N, 16.90.

α-Azidophenethyl phenyl sulfone (CH_2Cl_2–pentane, 70%): mp 86–87 °C; NMR δ 2.68, (dd, *J* = 11.5 and 14 Hz, 1 H), 3.49 (dd, *J* = 2.5 and 14 Hz, 1 H), 4.41 (dd, *J* = 2.5 and 11 Hz, 1 H), 7.0–8.25 (m, 10 H); IR (KBr) 2122 (N_3), 1140 and 1310 (SO_2) cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3O_3S$: C, 58.52; H, 4.56; N, 14.62. Found: C, 58.42; H, 4.58; N, 14.87.

Preparation of 1-Adamantylmethyl Phenyl Sulfide. In a 25-mL round-bottom flask was dissolved 3.2 g (10 mmol) of 1-adamantylmethyl tosylate[9] in 10 mL of Me_2SO. To this solution was added 1.3 g (12 mmol) of thiophenol. Dry nitrogen was bubbled through the solution for 5 min, and then 0.8 g (12 mmol) of potassium hydroxide in 2 mL of water was added. A precipitate which formed quickly redissolved with the addition of 5 mL of Me_2SO. After being heated at 65–70 °C for 20 h, the mixture was diluted in 100 mL of diethyl ether and washed with water and 5% sodium hydroxide. The ether layer was dried and concentrated. The resulting solid was recrystallized from 95% ethanol to yield 2.1 g (81.4%) of the title compound: mp 69–70 °C; NMR δ 1.24–2.09 (m, 15 H), 2.76 (s, 2 H), 6.9–7.44 (m, 5 H). Anal. Calcd. for $C_{17}H_{22}S$: C, 79.00; H, 8.58. Found: C, 78.54; H, 8.76.

Reaction of $XC_6H_4CH(N_3)SO_2Ph$ with Piperidine to Yield Substituted Benzonitriles. Approximately 0.03 mmol of the α-azido sulfone **3** (R = Ph, *p*-ClC_6H_4, *m*-ClC_6H_4, *p*-CNC_6H_4, *p*-$CH_3COC_6H_4$) was weighed accurately to the nearest 0.1 mg and placed in a thick-walled Carius tube. A stock solution (2 mL) containing 10.70 mg of piperidine and 1.514 mg of *n*-tetradecane per milliliter of 95% ethanol was added. A Teflon O-ring-equipped top was added and secured tightly with a thumb-screw pinch clamp. The tube was heated in a 55 (±1) °C oil bath. After a period of heating ranging from 3.75 to 5.75 h, the tube was removed from the bath and allowed to cool. The reaction mixture was analyzed directly by GLC to determine the yield of nitrile, using *n*-tetradecane as the internal standard, for X–$C_6H_4CH(N_3)SO_2Ph$, X (% yield): H (86%), *p*-Cl (85%), *p*-CN (98%), *p*-CH_3CO (93%), and *m*-Cl (94%).

Reaction of $XC_6H_4CH(N_3)SO_2Ph$ with Sodium Methoxide to Yield Substituted Benzonitriles. Approximately 0.1 mmol of the above α-azido sulfones and 0.05 mmol of naphthalene were accurately weighed and placed in a thick-walled Carius tube. A 0.23 M solution (1 mL) of sodium methoxide in methanol was added and the tube was sealed and heated in a 50 °C oil bath for 2 h. The reaction mixture was analyzed directly by GLC to determine the yield of nitrile for X–$C_6H_4CH(N_3)SO_2Ph$, X (% yield): H (72%), *p*-Cl (90%), *p*-CH_3CO (56%), and *m*-Cl (78%).

Conversion of $XC_6H_4CH_2SPh$ to Substituted Benzonitriles. The benzyl phenyl sulfides were converted to the corresponding α-azidobenzyl phenyl sulfides by chlorination with sulfuryl chloride followed by treatment with sodium azide in dimethyl sulfoxide. The α-azido compounds were not isolated; instead, an equivalent amount of potassium *tert*-butoxide was added to the Me_2SO solutions. After an initial brisk evolution of gas, the reactions moderated quickly; after 15 min, the reaction mixtures were poured into water and extracted with CH_2Cl_2. The dried extracts were concentrated to 1–2 mL. A weighed amount of *n*-tetradecane was introduced into each sample, and GLC analysis was performed. The yields of benzonitriles obtained by this method from X–$C_6H_4CH_2SPh$ are for X (% yield): H (64%), *p*-Cl (52%), *m*-Cl (51%), *p*-CH_3 (17%), *p*-CH_3CO (5%), *p*-CN (44%).

Reaction of α-Azidobenzyl Phenyl Sulfide with Cyclohexylamine. α-Azidobenzyl phenyl sulfide (1 g, 4.2 mmol) was dissolved in 10 mL of benzene. Cyclohexylamine (1 mL, 0.87 g, 8.8 mmol) was added; the resulting mixture was allowed to stand at ambient temperature. Crystals were evident after approximately 30 min; after 2 h, the solution, which smelled strongly of thiophenol, was filtered to yield, after washing with cold CCl_4, 286 mg of white crystals. Sublimination at 60 °C (1.5 mm) yielded 245 mg (41%) of cyclohexylammonium azide, mp (sealed tube) 111–113 °C (lit.[10] mp 112–113 °C). The benzene filtrate was shown by comparative thin-layer chromatography to contain *N*-benzylidene cyclohexylamine[11] and diphenyl disulfide.

Reaction of α-Azidobenzyl Phenyl Sulfone with Cyclohexylamine. A 273-mg (1 mmol) sample of α-azidobenzyl phenyl sulfone was dissolved in 5 mL of diethyl ether. Cyclohexylamine (1 mL, 0.87 g, 8.8 mmol) was added with swirling. The mixture was allowed to stand overnight; filtration followed by a wash with cold diethyl ether yielded 237 mg (98%) of cyclohexylammonium benzenesulfinate, mp (sealed tube) 196–198 °C (lit.[12] mp 204–206 °C). Elemental analysis of this material proved satisfactory.

A gas-chromatographic examination of the ether filtrate revealed the presence of benzonitrile.

Reaction of α-Azido-1-adamantylmethyl Phenyl Sulfone with Potassium *tert*-Butoxide. In a 25-mL three-neck flask equipped with a stopper, drying tube, nitrogen inlet, and magnetic stirrer was placed 33.3 mg (0.1 mmol) of α-azido-1-adamantylmethyl phenyl sulfone in 5 mL of dry tetrahydrofuran (THF). While a nitrogen atmosphere was maintained in the reaction flask, 112.1 mg (1.0 mmol) of potassium *tert*-butoxide was added in three portions; the evolution of gas, presumably nitrogen, was brisk initially but quickly subsided.

After 15 min, a check by thin-layer chromatography showed the complete absence of starting material. GLC analysis of the mixture revealed the presence of 13.6 mg (84.5%) of 1-adamantanecarbonitrile.

Reaction of α-Azidophenethyl Phenyl Sulfone with Sodium Methoxide in Methanol To Yield Phenylacetonitrile. An accurately weighed sample (ca. 0.25 mmol) of **3** (R = $PhCH_2$) was placed in each of three thick-walled Carius tubes. A stock solution (1 mL) containing 0.5 mmol/mL of sodium methoxide in absolute methanol was added to each tube. The sealed tubes were heated at 60 °C for 10 min. Samples were analyzed by GLC for phenylacetonitrile ($C_{20}H_{42}$ internal standard) whose yields ranged from 79 to 86%.

Reaction of α-Azidoisobutyl Phenyl Sulfone with Potassium *tert*-Butoxide in THF. A solution of 239 mg (1 mmol) of **3** (R = *i*-Pr) in 5 mL of THF under a nitrogen atmosphere and at ambient temperature was treated with 170 mg (1.6 mmol) of potassium *tert*-butoxide. An immediate brisk evolution of gas was observed; after several minutes, the gas evolution ceased and the reaction mixture acquired a light yellow color. After a total of 20 min, the reaction was diluted with pentane and the resulting insolubles were removed by filtration; the solid material was dissolved in a minimum amount of 95% ethanol and treated with excess methyl iodide. After 12 h, the alcoholic solution was diluted with water and extracted with CH_2Cl_2 to yield 130 mg (83%) of methyl phenyl sulfone which was identified by comparison with an authentic sample.

The organic layer was diluted with ether, washed with water, dried, and concentrated. An infrared spectrum of the very small amount of residue showed no absorption corresponding to the starting azido compound or the expected isobutyronitrile.

Reactions of the Nitriles with Bases. Control Experiments. Treatment of 1-adamantanecarbonitrile (Aldrich) and phenylacetonitrile under the reaction conditions KO*t*-Bu/THF and NaOMe/MeOH, respectively, gave results by GLC analysis

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(hydrocarbon internal standards) which showed that ca. 10% of the former nitrile and ca. 15-20% of the latter nitrile were lost. The weight losses which occurred as a result of these reactions suggested that the products of these reactions were water soluble. Similar treatment of isobutyronitrile and pivalonitrile gave principally water soluble products, and IR and GLC analyses of the small amounts of organic products from these nitriles showed the absence of starting materials.

Conversion of Phenylacetonitrile to Benzonitrile. To a solution of 1.76 g (15 mmol) of phenylacetonitrile in 30 mL of CCl_4 was added 2.7 g of *N*-bromosuccinimide (NBS) and 25 mg of benzoyl peroxide. This solution was heated at reflux in the presence of a sunlamp for 30 min, the succinimide was removed, and the solution was concentrated to a yellow oil. This oil was added dropwise over a period of ca. 5 min to a solution of 3 g of sodium azide in 50 mL of Me_2SO at room temperature. The solution was stirred for 15 min, poured into 1% NaOH solution, and extracted with pentane. The organic layer was dried, concentrated, and distilled to give 1.28 g (80%) of benzonitrile which was identified by comparison with an authentic sample.

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New Hydrogenation Catalyst: Palladium-Poly(ethylenimine) "Ghosts". Applications in Peptide Synthesis

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Polymer "ghosts" are made in a three-step process: (1) The polymer is adsorbed to a porous inorganic bead. (2) The polymer layer is then cross-linked. (3) The inorganic core is leached out to yield a macroporous spheroid with very high surface area and functional group density.[1] Poly(ethylenimine) (PEI) "ghosts" have good mechanical and chemical stability which led us to investigate their use as a support for metal catalysts. Pd-PEI "ghosts" were made with $Pd(Ac)_2$, $NaBH_4$, and PEI "ghosts". They exhibit high catalytic activity and stability in the hydrogenolysis of the carbobenzoxy (Cbz) group. Formic acid was used as the hydrogen donor.[2] The Merrifield peptide (H-Leu-Ala-Gly-Val-OH) was synthesized in high purity by using the active ester method.

Results and Discussion

The catalytic efficiency of Pd-PEI "ghosts" is quite good when compared to that of Pd-carbon and Pd-black which are commonly used in catalytic hydrogenation in peptide synthesis and reduction of functional groups. Cbz-alanine was deblocked with formic acid as shown in Figure 1.

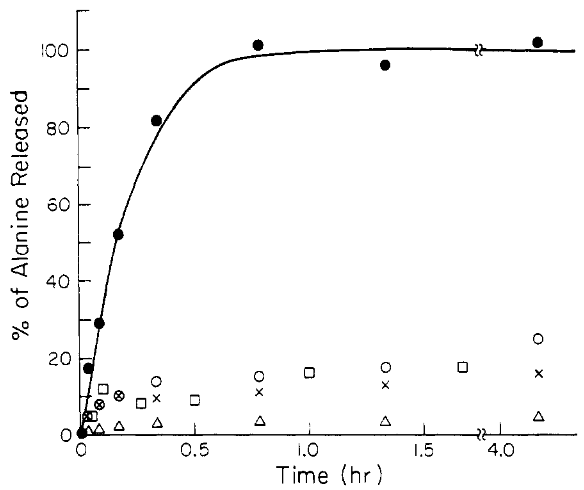

Figure 1. Rate of Pd-catalyzed hydrogenolysis of Cbz-alanine using formic acid as the hydrogen donor. Pd-PEI "ghosts", 100 mg (●); Aldrich 10% Pd on charcoal, lot no. 031597, 10 mg (□); Research Inorganic/Organic Chemical 10% Pd on charcoal, two different samples, 10 mg (X and O); Pd-black, 1 mg (Δ).

To demonstrate the utility of our catalytic system in sequential synthesis of peptides, we prepared H-Leu-Ala-Gly-Val-OH. As judged by TLC, the deblocking reactions at room temperature were complete in 20 min or less. Cbz-Leu-Ala-Gly-Val-OMe was treated with immobilized carboxypeptidase Y to hydrolyze the ester.[3] The final deblocking of the amino terminus was done by the usual procedure. The respective yields following removal of the Cbz groups were 99, 100, and 97%. Coupling yields using the formate salt of the amine component and the *N*-hydroxysuccinimide ester of the Cbz amino acids were 78, 71, and 58%. The product was judged pure by TLC: R_f 0.46 (1-BuOH-AcOH-H_2O 4:1:5), R_f 0.05 ($CHCl_3$-MeOH-AcOH 16:3:1), R_f 0.62 (2-BuOH-88% HCOOH-H_2O 15:3:2), and R_f 0.34 (2-BuOH-3% NH_3 71:29). Amino acid analysis of the acid hydrolysate resulted in the following: Leu 1.02, Ala 0.99, Gly 0.96, Val 1.00. Digestion by leucine aminopeptidase[4] demonstrated the optical purity of leucine and alanine: Leu 1.00, Ala 1.03, Gly 0.99, Val 0.98. Also, C-terminal valine was released by immobilized carboxypeptidase Y (pH 6) to the extent of 95%. The optical rotation of our product was similar to that reported previously: $[\alpha]^{25}_D$ +17.8 (product, 2% in EtOH) and $[\alpha]^{25}_D$ +17.5 (lit.,[5] 2% in EtOH).

Catalytic hydrogenolysis of the Cbz group with the use of Pd-PEI "ghosts" and formic acid is convenient, rapid, and mild. The catalyst beads are mechanically stable and rapidly settle out when agitation is stopped. The storage and operational stability of the catalyst are excellent. One batch of catalyst has been used 10 times with no apparent loss of activity. Pd-PEI "ghosts" do not appear to be pyrophoric. The high activity of our catalyst compared to Pd-carbon and Pd-black may be explained by the attraction of the formic acid to the PEI matrix and/or by the distribution of palladium over a large surface area. Since the PEI matrix is easily modified, we hope to build in chiral and structural substrate specificity for other hydrogenation reactions.

Experimental Section

PEI "ghosts" were made as previously described[1] by using porous silica beads (Corning 5011-S, average pore diameter 350 Å, 40 mesh) rather than alumina. The silica core was leached by treatment with 5 N NaOH. $PdCl_2$ (1.7 g) was dissolved in 20 mL of 1 N HCl by heating to boiling. This solution was mixed with 100 mL of a sodium acetate solution (15 g $NaAc{\cdot}3H_2O$/100 mL). Dry PEI "ghosts" (100 g) were added with gentle agitation and a vacuum was applied to remove trapped air from the particles. The damp "ghosts" were then added to a 1% solution of sodium borohydride in ethanol. The blackened beads were washed with 18% formic acid solution, methanol, and ether and then dried in vacuo.

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