calcd for 306.1611, found 306.1633.

Reaction of Cepham (1) with Phenyltrimethylstannane (Eq 2). To a mixture of 1 (0.221 g, 0.50 mmol), lithium chloride (0.063 g, 1.50 mmol), and phenyltrimethylstannane (0.144 g, 0.60 mmol) in DMF (1 mL) was added bis(dibenzylidene acetone)-palladium(0) ($Pd(dba)_2$) (0.014 g, 0.025 mmol, 5 mol %). The mixture was heated at 60 °C for 17 h, and then it was partitioned between ether (10 mL) and water (10 mL). The ether layer was washed with a NaCl solution (10 mL), dried over $MgSO_4$, and concentrated. Preparative thin-layer chromatography (silica gel, 20% EtOAc/hexanes) afforded **2** and **3** as mixtures of diastereomers. **2** (mixture of epimers): ^1H NMR (300 MHz) 7.50–7.20 (m, 5 H, Ar H), 6.32 (s, 1 H, C=CHS), 6.17–6.12 (d, 1 H, J = 9 Hz, NH), 5.80–5.67 (dd, 1 H, J = 12 Hz, J = 3 Hz, NCH), 5.23–4.84 (d, 1 H, J = 3 Hz, HCS), 5.00, 4.74, 4.70, 4.50 (d, 2 H, J = 12 Hz, CH_2OAc), 3.61 (s, 2 H, $PhCH_2$), 2.03 (s, 3 H, CH_3CO), 1.49, 1.44 (s, 9 H, $C(CH_3)_3$); mass spectrum (electron impact) m/e 446 (parent). **3** (mixture of epimers): ^1H NMR (300 MHz) δ 7.50–7.20 (m, 5 H, ArH), 6.12 (d, 1 H, J = 9 Hz, NH), 5.85 (s, 1 H, C=CHS), 5.74, 5.63 (dd, 1 H, J = 12 Hz, J = 3 Hz, NCH), 5.21–4.90 (d, 1 H, J = 3 Hz, HCS), 3.62 (d, 2 H, J = 3 Hz, $PhCH_2$), 2.03 (s, 3 H, CH_3), 1.48, 1.44 (s, 9 H, $C(CH_3)_3$); mass spectrum (electron impact) m/e 388 (parent). These compounds were not purified further.

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Competitive Base-Induced α-Elimination and Methanolysis of *N*-Aryl-*O*-pivaloylhydroxylamines

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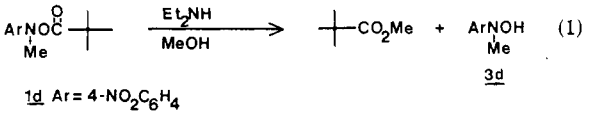
The *N*-aryl-*O*-pivaloylhydroxylamines **1a–c** are quite stable in MeOH under neutral conditions, but under mildly basic conditions (0.05 M Et_2NH or Et_3N) they undergo rapid decomposition ($t_{1/2} \approx$ 3–5 h at 25 °C) by two competitive processes: apparent α-elimination to generate the nitrenes **2a–c** and pivalic acid and basic ester methanolysis to generate the hydroxylamines **3a–c** and methyl pivalate. The nitrenes decompose into the corresponding anilines **5** and azobenzenes **7**, while the hydroxylamines undergo nitrene-mediated oxidation into the corresponding azoxybenzenes **6**. The mechanism of this latter process was probed by addition of excess hydroxylamine, and a mechanism for the oxidation consistent with available data (Scheme II) is proposed. It was also found that the nitrosobenzenes **8** undergo nucleophilic attack by the conjugate bases **4a–c** of the title compounds to produce one of the two possible isomeric nonsymmetrical azoxybenzenes.

In a recent investigation of the hydrolysis under mild conditions of ring-substituted *N*-aryl-*O*-pivaloylhydroxylamines **1**, we obtained products [4-nitroaniline (**5c**) and 4,4′-dinitroazoxybenzene (**6c**)] from the 4-nitro compound **1c**, which may have been formed by way of a nitrene intermediate.[1] Arylnitrenes have been generated via α-elimination of various aniline derivatives, but not under mild conditions in hydroxylic solvents.[2] The potential generation of nitrenes from **1** is also of interest since these species are model compounds for suspected carcinogenic metabolites of polycyclic aromatic amines.[3] The possibility that arylnitrenes may be generated from these species in vivo has not been considered.

Accordingly, we have investigated the decomposition of **1** under mildly basic conditions (0.01–0.10 M Et_2NH) in methanol in an effort to obtain evidence for arylnitrene generation. Methanol was chosen as the solvent for this initial study because the decomposition of **1a** and **1b** by simple pH-independent heterolysis of the N–O bond to generate a nitrenium ion, a facile process in H_2O,[1] will be suppressed in methanol.[4] In methanol it is also possible to easily distinguish α-elimination from base-induced methanolysis of the ester by determination of the yield of methyl pivalate (Scheme I).

Under our reaction conditions α-elimination to generate **2** and methanolysis to form **3** appear to be competitive processes, with the former path predominating for **1a** and **1b** and the latter for **1c**. The nitrenes **2a–c** decompose into the corresponding anilines **5a–c** in moderate to high yields and the azobenzenes **7a–c** in low yields. The hydroxylamines **3a–c** are oxidized under the reaction conditions to the corresponding azoxy compounds **6a–c** in a process that may be nitrene dependent. In contrast to **1a–c**, the ester **1d**, in which deprotonation is not possible, undergoes exclusive methanolysis to generate methyl pivalate and the corresponding hydroxylamine **3d** under our conditions (eq 1).



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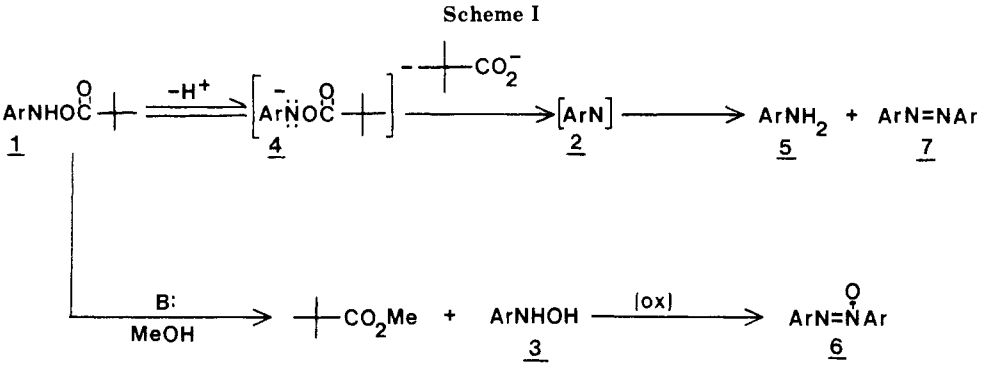
Scheme I



a Ar = 4-ClC_6H_4
b Ar = 3,4-$Cl_2C_6H_3$
c Ar = 4-$NO_2C_6H_4$

Experimental Section

All glassware was soaked in a basic (pH ≈ 11.5) solution of EDTA to remove contaminating metal ions, rinsed with deionized (18.0 MΩ cm) H_2O, and oven-dried. All reactions were initiated in an inert-atmosphere (N_2) box equipped with an evacuable entry port. Reaction mixtures that were removed from the inert-atmosphere box for UV or HPLC analysis were sealed with rubber septa. All reactions were thermostated at 25 ± 1 °C and were run in the dark.

Reagent grade methanol was distilled from $NaBH_4$ and then fractionally distilled from $Mg(OCH_3)_2$. The solvent was degassed with three freeze–thaw cycles under vacuum before being introduced into the inert-atmosphere box. Reagent grade diethylamine and triethylamine were dried over CaH_2, filtered, and fractionally distilled under N_2. They were degassed as indicated above for methanol. Syntheses and purification of **1a–c** and **3a–c** have been previously published.[1,4,5] The preparation of **1d** and **3d** is described below.

***N*-Methyl-*N*-(4-nitrophenyl)-*O*-pivaloylhydroxylamine (1d).** A mixture of **1c** (100 mg, 0.42 mmol), 1,8-bis(dimethylamino)naphthalene (128 mg, 0.60 mmol), and dimethyl sulfate (600 μL, 6.3 mmol) in 25 mL of dry benzene was refluxed under a N_2 atmosphere for 24 h. The cooled mixture was then extracted with 1 N HCl (3 × 10 mL) and 5% aqueous $NaHCO_3$ (2 × 10 mL). After the mixture was dried over Na_2SO_4, the benzene was removed by rotary evaporation and excess dimethyl sulfate was removed under a vacuum of 1 mmHg. The red-orange solid that remained was taken up in ca. 15 mL of hexanes. A reddish precipitate was removed by filtration, and the volume of the resulting solution was reduced to ca. 2 mL. The yellow-orange crystals that formed were recrystallized a second time from hexanes to yield pale yellow flat needles (56 mg, 53%): mp 54–56 °C; IR (KBr) 3091, 2978, 1769, 1592, 1508, 1337, 1081 cm^{-1}; ^1H NMR (90 MHz, $(CD_3)_2CO$) δ 1.36 (9 H, s), 3.39 (3 H, s), 7.11 (2 H, AA'BB' pattern, J = 9.3 Hz), 8.21 (2 H, AA'BB' pattern, J = 9.3 Hz); high-resolution MS, m/e 252.1099, $C_{12}H_{16}N_2O_4$ requires m/e 252.1111.

***N*-Methyl-*N*-(4-nitrophenyl)hydroxylamine (3d).** A solution of **1d** (25.2 mg, 0.1 mmol) in 50 mL of dry, degassed MeOH was prepared in the inert-atmosphere box, and sufficient Et_2NH was added to this solution to bring the amine concentration to 0.05 M. After incubation in the dark for 48 h, the deep red reaction mixture was quenched by addition of 2.5 mL of 1 N HCl. Rotary evaporation of the resulting fluorescent yellow solution led to a yellowish solid mass. This material was taken up in 15 mL of CH_2Cl_2. After being washed with H_2O (3 × 10 mL) and dried over Na_2SO_4, the CH_2Cl_2 solution was concentrated and subjected to preparative-layer chromatography on silica gel (CH_2Cl_2 eluent). The bright yellow hydroxylamine was isolated in 80% yield (13.5 mg): mp 110–112 °C; IR (KBr) 3270, 2921, 1602, 1484, 1292, 1106 cm^{-1}; ^1H NMR (60 MHz, $(CD_3)_2CO$) δ 3.26 (3 H, s), 7.07 (2 H, AA'BB' pattern, J = 9.0 Hz), 8.05 (2 H, AA'BB' pattern, J = 9.0 Hz), 8.90 (1 H, s); high-resolution MS, m/e 168.0540, $C_7H_8N_2O_3$ requires m/e 168.0535.

Kinetic and Product Studies. For product analyses, **1a–d** (0.2–2.0 mM) were incubated in 0.05 M Et_2NH/MeOH or 0.05 M Et_3N/MeOH (10 mL) for 48 h before the reaction was quenched by addition of 1 equiv of 1 N HCl. Product quantification was performed by HPLC for **3a–d**, **5a–d**, **6a–c**, and **7a–c**. Authentic samples of **5a**, **5c**, and **5d** were commercially available, and **5b** was prepared by hydrogenation of the corresponding nitro compound. The authentic azoxy and azo compounds **6a–c** and **7a–c** were obtained by standard methods, and their physical and spectral properties were consistent with their structures and previously published data.[6] All HPLC analyses were performed by injection of 20-μL aliquots onto a μ-Bondapak C_{18} reverse-phase column, MeOH/H_2O (60/40, 70/30, or 80/20) eluent, 1.4 mL/min. Peak areas were determined at 250, 335, or 380 nm. Extinction coefficients were obtained from appropriate solutions of the authentic materials. Products were also isolated by evaporation of the solvent and separated by preparative-layer chromatography as described elsewhere.[4] ^1H NMR spectra of the compounds isolated in this manner were identical with those of the authentic standards. Methyl pivalate yields were determined by GC analysis (10% OV101 on Chromosorb W-HP 80/100, 200 cm × 6.35 mm glass column, 35 °C, He flow rate 50 mL/min, flame ionization detection). Pivalic acid yields were determined by ^1H NMR after removal of solvent by distillation.[1]

The kinetics of the disappearance of **1b** and **1c** were monitored by HPLC (0.2–1.0 mM initial concentration) or UV methods (0.04 mM) that have been described elsewhere.[1,4] Concentrations of Et_2NH were varied from 0.025 to 0.10 M in these studies.

Trapping Studies with Hydroxylamines and Nitroso Compounds. The esters **1a** and **1b** (ca. 2 mM) were decomposed in 0.05 M Et_2NH/MeOH in the presence of 1 or 2 equiv of the hydroxylamines **3a** or **3b** or the corresponding nitroso compounds **8a** or **8b**. The nitroso compounds were made from the appropriate hydroxylamine (**3a** or **3b**) by oxidation with Fe^{3+}.[7] Crude **8a** or

ArNO

8a Ar = 4-ClC_6H_4
8b Ar = 3,4-$Cl_2C_6H_3$

ArN=NAr'

9 Ar = 4-ClC_6H_4, Ar' = 3,4-$Cl_2C_6H_3$
10 Ar = 3,4-$Cl_2C_6H_3$, Ar' = 4-ClC_6H_4
13 Ar = 3,4-$Cl_2C_6H_3$, Ar' = 4-$NO_2C_6H_4$
14 Ar = 4-$NO_2C_6H_4$, Ar' = 3,4-$Cl_2C_6H_3$

$ArNHNEt_2$

15a Ar = 4-ClC_6H_4

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8b was purified by steam distillation followed by recrystallization from MeOH. Reaction products were analyzed as indicated above. Two new azoxy products, **9** and **10**, were produced in these experiments. They were isolated from scaled-up reactions (5-fold) of **1a** in the presence of **8b** (**9**) and **1b** in the presence of **8a** (**10**). They were separated from other reaction products, after rotary evaporation of solvent, by preparative-layer chromatography on silica gel (50/50 CH_2Cl_2/hexanes) and were recrystallized from MeOH to yield pure samples.

3′,4′,4-Trichloroazoxybenzene (9): mp 122–123.5 °C; IR (KBr) 3100, 1584, 1479, 1464, 1403, 1091, 892, 824 cm^{-1}; ^1H NMR (90 MHz, CD_2Cl_2) δ 7.46 (2 H, d, J = 9.2 Hz), 7.62 (1 H, d, J = 8.8 Hz), 8.17 (2 H, d, J = 9.2 Hz), 8.20 (1 H, dd, J = 8.8, 2.6 Hz), 8.45 (1 H, d, J = 2.6 Hz). Anal. Calcd for $C_{12}H_7N_2OCl_3$: C, 47.80; H, 2.34; N, 9.29. Found: C, 47.96; H, 2.31; N, 9.34.

3,4,4′-Trichloroazoxybenzene (10): mp 153–154 °C; IR (KBr) 3104, 1583, 1480, 1450, 1305, 1096, 838, 822 cm^{-1}; ^1H NMR (90 MHz, CD_2Cl_2) δ 7.52 (2 H, d, J = 9.2 Hz), 7.57 (1 H, d, J = 8.8 Hz), 8.01 (1 H, dd, J = 8.8, 2.2 Hz), 8.26 (2 H, d, J = 9.2 Hz), 8.43 (1 H, d, J = 2.2 Hz). Anal. Calcd for $C_{12}H_7N_2OCl_3$: C, 47.80; H, 2.34; N, 9.29. Found: C, 47.67; H, 2.29; N, 9.27.

Independent Synthesis of 9. 3′,4′,4-Trichloroazobenzene-2-carboxylic Acid (11). 3,4-Dichloronitrosobenzene (0.178 g, 1.01 mmol) and 2-amino-5-chlorobenzoic acid (0.172 g, 1.00 mmol) were combined in 5 mL of glacial acetic acid, and the resultant mixture was heated under reflux for 24 h.[8] The reaction mixture was cooled to ca. 10 °C and filtered. The red-orange solid was taken up in CH_2Cl_2 and chromatographed on silica gel (CH_2Cl_2 eluent). Fractions containing **11** were combined and recrystallized from MeOH to yield dull red platelets (185 mg, 56%): mp 210.5–211.5 °C; IR (KBr) 3100–2500 (br), 3086, 1708, 1588, 1306, 1122, 889, 823 cm^{-1}; ^1H NMR (90 MHz, $(CD_3)_2CO$) δ 7.70–7.75 (2 H, m), 7.88–7.96 (3 H, m), 8.07 (1 H, dd, J = 1.8, 0.7 Hz). Anal. Calcd for $C_{13}H_7N_2O_2Cl_3$: C, 47.38; H, 2.14; N, 8.50. Found: C, 47.73; H, 2.11; N, 8.44.

3′,4′,4-Trichloroazoxybenzene-2-carboxylic Acid (12). The oxidation of **11** (100 mg, 0.30 mmol) in H_2O_2/H_2SO_4/AcOH (30 mL) according to the procedure of Berwick and Rondeau[8] required 7 days at room temperature due to the very low solubility of **11**. The reaction mixture was poured into 100 mL of ice water and filtered to isolate the crude product. HPLC and ^1H NMR indicated that one isomer had been formed in >95% yield. Two recrystallizations from MeOH led to slightly yellow platelets (72 mg, 69%): mp 218–220 °C; IR (KBr) 3100–2500 (br), 3092, 1700, 1585, 1479, 1326, 1306, 1267, 895, 840, 822 cm^{-1}; ^1H NMR (90 MHz, $(CD_3)_2CO$) δ 7.55 (1 H, d, J = 8.8 Hz), 7.80 (1 H, dd, J = 8.8, 2.2 Hz), 7.89 (1 H, d, J = 8.8 Hz), 8.02 (1 H, d, J = 2.2 Hz), 8.27 (1 H, dd, J = 8.8, 2.6 Hz), 8.45 (1 H, d, J = 2.6 Hz). Anal. Calcd for $C_{13}H_7N_2O_3Cl_3$: C, 45.18; H, 2.04; N, 8.11. Found: C, 45.36; H, 1.98; N, 8.10.

3′,4′,4-Trichloroazoxybenzene (9). The decarboxylation of **12** (50 mg, 0.14 mmol) was accomplished in refluxing pyridine (10 mL) in the presence of 70 mg of Cu powder and one crystal of $Cu(OAc)_2$.[8] HPLC analysis indicated that the reaction was complete in ca. 9 h. Pyridine was removed by rotary evaporation, and the residue was taken up in CH_2Cl_2 and filtered to remove Cu. After concentration of the CH_2Cl_2 solution, the product was purified by preparative TLC on silica gel (50/50 CH_2Cl_2/hexanes). The slightly yellow material that was obtained (29 mg, 68%) was identical with **9** isolated from the product studies according to HPLC and ^1H NMR. None of its isomer, **10**, was detected; mp 121.5–122.5 °C, melting point not depressed by mixture with **9** isolated from product studies.

***N*-(4-Chlorophenyl)-*N′*,*N′*-diethylhydrazine (15a).** The ester **1a** (64 mg, 0.28 mmol) was dissolved in 50 mL of purified, degassed Et_2NH. After incubation for 24 h, the Et_2NH was removed by rotary evaporation. The residue that remained was taken up in CH_2Cl_2 and subjected to preparative-layer chromatography on silica gel (50/50 CH_2Cl_2/hexanes) to yield a slightly yellow viscous oil (41 mg, 72%): IR (neat) 3306, 2973, 2934, 2816, 1597, 1492, 1242, 1087, 824 cm^{-1}; ^1H NMR (90 MHz, CD_2Cl_2) δ 1.04 (6 H, t, J = 7.0 Hz), 2.67 (4 H, q, J = 7.0 Hz), 4.32 (1 H, s, broad), 6.95 (4 H, AA′BB′ pattern, J = 9.2 Hz). Anal. Calcd for $C_{10}H_{15}N_2Cl$: C, 60.45; H, 7.61; N, 14.10. Found: C, 60.10; H, 7.58; N, 14.41.

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Table I. Yields of Decomposition Products of 1 in 0.05 M Et_2NH/MeOH at 25 °C

ester	initl concen (mM)	yield (%) methyl pivalate[a]	3[b]	5[b]	6[b-d]
1a	1.00 ± 0.02	29 ± 2		44 ± 2	37 ± 2
1a	2.08 ± 0.02	34 ± 2		41 ± 1	46 ± 2
1b	0.21 ± 0.01	35 ± 2		44 ± 3	28 ± 2
1b	0.42 ± 0.01	33 ± 2		39 ± 4	43 ± 1
1b	0.64 ± 0.01	33 ± 2		37 ± 2	48 ± 2
1b	1.06 ± 0.01	35 ± 1		34 ± 1	61 ± 1
1b	1.59 ± 0.02	36 ± 1		32 ± 1	62 ± 1
1b	2.13 ± 0.02	37 ± 1		29 ± 1	60 ± 1
1c	0.48 ± 0.02	72 ± 4	52 ± 3	10 ± 1	26 ± 2
1c	2.04 ± 0.02	79 ± 3	67 ± 2	9 ± 1	21 ± 1
1d	2.00 ± 0.02	94 ± 3	97 ± 3		

[a] Determined by GC on an OV-101 column. These are averages of duplicate runs. [b] Determined by HPLC on a C_{18} reversed-phase column. These are averages of duplicate runs. [c] Since **6** is a dimer, these yields are 2([6]/[1]) × 100%. [d] In all cases low yields (<2%) of the corresponding azobenzenes **7a–c** are detected. In the case of **1b** the yield of **7b** increases from ca. 0.2% to ca. 1.5% as the initial concentration of **1b** increases from 0.2 to 2.1 mM.

Results

In the absence of base the *N*-aryl-*O*-pivaloylhydroxylamines do not undergo significant decomposition in MeOH at 25 °C over a 24-h period.[9] When Et_2NH is added (ca. 0.05 M), they decompose quite rapidly with half-lives of ca. 3–5 h. Immediately after addition of Et_2NH to **1c** in MeOH (0.04 mM) a deep red-orange solution with λ_{max} of 474 nm is produced. This is attributed to the anion **4c**, since addition of Et_2NH to solutions of the N-methylated compound **1d** does not generate any immediate color change. The deprotonation of **1c** is incomplete at Et_2NH concentrations between 0.01 and 0.20 M. A pK_a of 13.2 ± 0.5 can be estimated for **1c** in MeOH on the basis of the [Et_2NH]-dependent ratio [**4c**]/[**1c**], a pK_a of 12.2 for $Et_2NH_2^+$ in MeOH and pK_s of 16.7.[10] The pK_a of **1c** in H_2O at low ionic strength is 8.8 ± 0.1.[11] The ΔpK_a of 4.4 for **1c** (MeOH/H_2O) is comparable to the average ΔpK_a of 4.8 measured for a series of carboxylic acids in the same solvents.[10] No significant spectral changes were observed immediately upon addition of Et_2NH to solutions of **1a** or **1b**. The pK_a values of these species have not yet been measured in H_2O due to their rapid decomposition in base. If the pK_a of **1a–c** correlates with σ^- with a slope ρ^-, similar to that of ArOH in 95% EtOH,[12] then the pK_as of **1a** and **1b** are ca. 16.4 and 15.2, respectively. If this is the case, the anions **4a** and **4b** would not be produced in detectable quantities under our conditions.

Product studies were performed under a N_2 atmosphere to avoid air oxidation of certain reaction products. It was also necessary to remove traces of metal ions from solvents and reaction flasks to obtain reproducible results.[1] Reactions were also run in the dark, but exposure to ambient light does not appear to effect product yield. Product yields determined after incubation for 48 h in 0.05 M

(9) The solvolysis rate constant for **1a** in MeOH at 25 °C is 1.0 × 10^{-6} s^{-1}; neither **1b** nor **1c** undergoes observable solvolysis in MeOH for 48 h at 25 °C. The major solvolysis product of **1a** is 4-chloro-2-hydroxypivalanilide: Novak, M.; Martin, K. A.; Heinrich, J. *J. Org. Chem.* **1989**, *54*, 5430–5431. See ref 1 for a discussion of the mechanism of formation of this product.
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Table II. Decomposition Products of 1a and 1b in the Presence of Hydroxylamine and Nitroso Traps[a]

ester concen (mM)	trap concen (mM)	methyl pivalate[b]	5a[c]	5b[c]	6a[c,d]	6b[c,d]	9[c]	10[c]
1a, 2.04 ± 0.02[e]	**3b**, 2.06 ± 0.03	28 ± 1	62 ± 1		8.3 ± 0.3	(0.79 ± 0.01 mM)[f]	10.9 ± 0.3	5.4 ± 0.2
1a, 2.10 ± 0.04	**8b**, 2.28 ± 0.06	5.7 ± 0.3	5.3 ± 1.0		5.0 ± 0.1		81 ± 2	
1b, 2.03 ± 0.02[g]	**3a**, 2.06 ± 0.04	32 ± 1		55 ± 1	(0.64 ± 0.03 mM)[f]	6.8 ± 0.8	7.7 ± 0.3	10.9 ± 0.3
1b, 2.06 ± 0.02	**8a**, 2.00 ± 0.04	10.8 ± 0.4		7.0 ± 0.3		16.5 ± 0.3		74 ± 2

[a] Conditions: 0.05 M Et_2NH, 25 °C. [b] Determined by GC on an OV-101 column. Yields based on 1 initially present. [c] Determined by HPLC on a C_{18} reversed-phase column. Yields based on 1 initially present. [d] Percent yield = 2([6]/[1]) × 100%. [e] **3a** was also detected in 5.0 ± 0.5% yield. [f] Percent yield not calculated since these azoxy compounds are not derived from 1 but from the trapping agent. [g] **3b** was also detected in 12.3 ± 0.4% yield.

Et_2NH are shown in Table I. The significant yield of methyl pivalate observed for **1a–c** indicates that methanolysis of the esters occurs under these conditions. No *N,N*-diethylpivalamide was detected in any of these reactions. The expected hydroxylamine products of methanolysis (Scheme I), **3a** and **3b**, were not detected, and **3c** was detected in significantly lower yields than methyl pivalate. Control experiments show that **3a–c** are reasonably stable under the reaction conditions in the absence of **1a–c** and O_2. Only ca. 5–10% of **3a–c** is oxidized to the corresponding azoxybenzenes **6a–c** over a 48-h period. HPLC experiments with **1b** (0.2 mM) at early reaction times confirmed that both **3b** and 3,4-dichloroaniline (**5b**) are initial reaction products, but **3b** rapidly decomposes with accompanying formation of **6b**.

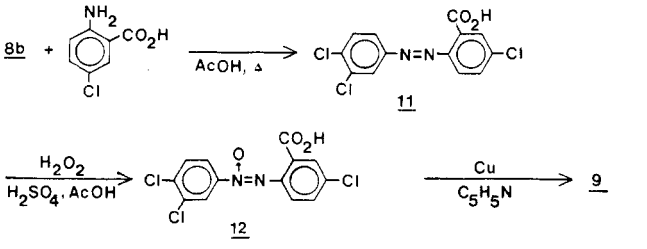
^1H NMR of reaction mixtures showed that pivalic acid accounted for the majority of the pivaloyl moiety of 1 not present as methyl pivalate. For **1a** (2.0 mM) a yield of 55 ± 5% of pivalic acid was observed, and for **1b** (2.0 mM) 49 ± 5% of pivalic acid was detected. The final aromatic products of the decomposition of **1a** and **1b** are the corresponding anilines **5a** and **5b**, the azoxybenzenes **6a** and **6b**, and small amounts of the azobenzenes **7a** and **7b**. Lower yields of **5c** and **6c** are obtained from **1c**, for which the major reaction product is **3c**. Table I shows that the relative yields of **5b** and **6b** vary significantly with initial concentration of **1b** over the range 0.2–2.0 mM, but the yield of methyl pivalate is insensitive to concentration of **1b**. In all three cases small amounts (<2%) of the azobenzenes **7a–c** were detected. HPLC of unreacted **1a–c** confirmed that **7a–c** were not present as impurities in the original esters but were formed under the reaction conditions. The yield of **7b** did increase with increasing concentration of **1b** (Table I, footnote *d*).

The methylated ester **1d** decomposes without formation of **5d**. Methyl pivalate and the hydroxylamine **3d** are generated in essentially quantitative yield (Table I). No other products were detected by HPLC or GC.

The kinetics of the disappearance of **1c** (0.04 mM) were monitored by UV methods in the [Et_2NH] range 0.025–0.10 M. Under these conditions first-order kinetics were observed, and k_{obs} varied with [Et_2NH] from (5.0–8.3) × 10^{-5} s^{-1}. The disappearance of **1c** was also monitored by HPLC at 0.2 mM **1c** and 0.05 M Et_2NH. The value of k_{obs} of (5.7 ± 0.1) × 10^{-5} s^{-1} under these conditions is comparable to k_{obs} obtained in the UV experiments at 0.05 M Et_2NH ((6.3 ± 0.1) × 10^{-5} s^{-1}). The disappearance of **1b** was also monitored by HPLC methods at 0.05 M Et_2NH and initial concentrations of **1b** ranging from 0.2 to 1.0 mM. The reaction follows first-order kinetics to at least 95% completion. The value of k_{obs} is constant at (5.0 ± 0.5) × 10^{-5} s^{-1} under these conditions.

The decomposition of **1b** (2.1 mM) in Et_3N/MeOH (0.05 M) proceeded in much the same way as in Et_2NH/MeOH. The reaction was slower ($t_{1/2} \approx 18$ h), but the product composition was very similar. Yields of **5b** and **6b** determined by NMR were 33 ± 5% and 67 ± 5%, respectively, which are comparable to the HPLC yields of the same two products obtained under similar conditions in Et_2NH/MeOH (Table I). The yield of pivalic acid, also determined by NMR, was 43 ± 5%. The methyl pivalate yield could not be determined by gas chromatography due to interference by Et_3N, and methyl pivalate is too volatile to survive the concentration process necessary for the NMR experiments.

The products of the decomposition of **1a** in the presence of 1 equiv of **3b**, and **1b** in the presence of 1 equiv of **3a**, were determined (Table II) since the data in Table I indicate that the hydroxylamines **3a–c** are oxidized by a species generated during the decomposition of **1**. The data show that the added hydroxylamines are largely converted into the corresponding azoxybenzenes; **6b** accounts for 77 ± 2% of **3b** present during the decomposition of **1a** and **6a** accounts for 62 ± 3% of **3a** added to the reaction mixture containing **1b**. There is also a significant increase in the yield of **5a** or **5b** compared with the decomposition of **1a** or **1b** at the same initial concentration in the absence of added hydroxylamine and a corresponding decrease in the yield of **6a** or **6b** (Table I). In both cases unoxidized hydroxylamine derived from methanolysis of the starting ester can be detected in moderate yields. The two unsymmetrical azoxybenzenes **9** and **10** are also detected in these experiments. The identity of **9** was demonstrated by the synthetic route shown in eq 2. It has previously



(2)

been shown that a 2-carboxylic acid substituent directs oxidation to the nonadjacent nitrogen (typical regioselectivity of 20/1) of an azobenzene when H_2O_2/H_2SO_4/AcOH is used as the oxidizing reagent.[8] In our situation ^1H NMR of the crude reaction product from oxidation of **11** showed that one isomer, **12**, predominated to >95% yield. Decarboxylation of **12** led to **9** in moderate yield (68%) with no detectable formation of its isomer **10**.

Since it has been shown that nitrosobenzenes can trap nitrenes to form azoxybenzenes,[13] we used **8a** and **8b** in trapping experiments summarized in Table II. Methyl pivalate yields were much reduced compared to the decomposition of **1a** or **1b** in the absence of trapping agents (Table I) or in the presence of hydroxylamines (Table II).

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Higher concentrations of **8** reduce the methyl pivalate yield to negligible amounts; when **1b** (2.0 mM) undergoes decomposition in the presence of 2 equiv of **8a**, the yield of methyl pivalate is reduced to 2.3%. A significant increase in the rate of decomposition of **1a** and **1b** was also noted in these experiments. Decomposition rates of **1a** and **1b** are not changed by addition of the hydroxylamines. It is evident that **8** reacts directly with **1** in a process that is competitive with methanolysis and the apparent α-elimination. Control experiments show that Et_2NH is necessary for any reaction to occur. The major reaction products are the unsymmetrical azoxybenzenes **9** and **10**; **9** is detected in high yield when **1a** undergoes decomposition in the presence of **8b**, and **10** is the major product of the decomposition of **1b** in the presence of **8a**. The other isomeric azoxybenzene is not detectable in either case.

Similar results have been obtained in preliminary experiments involving **1c** and **3b** or **8b**. When **1c** (2.0 mM) undergoes decomposition in 0.05 M Et_2NH in the presence of 1 equiv of **3b**, the yield of methyl pivalate is normal at 75 ± 3%, but in the presence of 1 equiv of **8b** the yield is reduced to 8.5 ± 0.4%. Product distributions are changed in the same way as demonstrated for **1a** and **1b** in Table II, and two new products, tentatively identified as the unsymmetrical azoxybenzenes **13** and **14**, are observed. One of these is the major product when **1c** undergoes decomposition in the presence of **8b**.

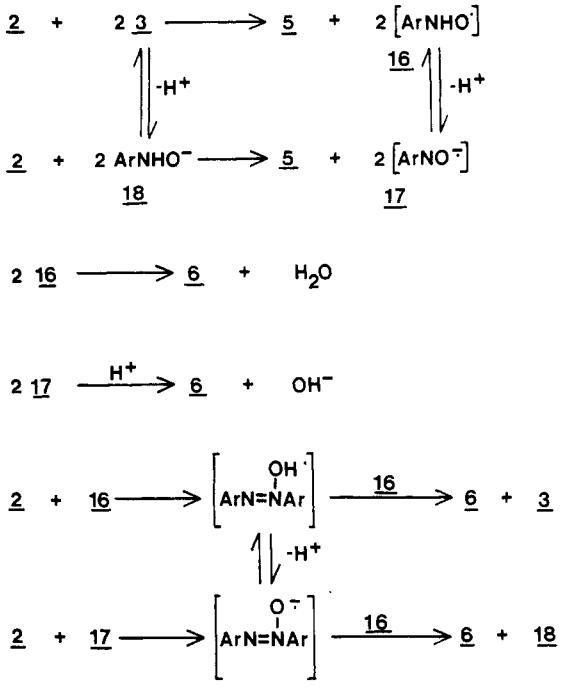
The decomposition of **1a** was also examined at high concentrations of Et_2NH in MeOH (4.8 M, 28 mol %) and in neat Et_2NH. In both cases the only reaction products detected were the hydrazine **15a** and pivalic acid. Similar results have been obtained by others from the reaction of other *N*-aryl-*O*-acylhydroxylamines with neat secondary amines.[14] Examination of HPLC traces from the decomposition of **1a** in 0.05 M Et_2NH/MeOH indicated that small amounts (ca. 1%) of **15a** are produced under these conditions.

Discussion

The base-induced decomposition of **1a–c** in MeOH apparently occurs via two competitive paths (Scheme I). The detection of methyl pivalate, the observation of the hydroxylamine **3b** by HPLC at early reaction times, and the large yields of **3c** indicate that basic methanolysis of **1** is one of these reactions. The other process generates pivalic acid and is apparently responsible for the significant yields of the anilines **5a–c** and lower yields of the azobenzenes **7a–c**. Both of these are typical decomposition products of arylnitrenes,[15] and pivalic acid is the expected byproduct of an α-elimination. The product studies with the *N*-methyl compound **1d** indicate that an ionizable proton on nitrogen is a requirement for this process.

An alternative mechanism for reduction of **1a–c** to the corresponding anilines **5a–c** via single-electron transfer from the amine to produce an intermediate radical anion does not appear to fit the experimental results. Such a mechanism would not require an ionizable proton on nitrogen and would also be expected to be most efficient for **1c** since nitro aromatics are excellent one-electron acceptors.[16] In fact, **1c** is the least prone of the series **1a-c** to undergo this reaction. Et_3N is also a better one-electron donor than Et_2NH,[17] but the product yields from the decomposition of **1b** in Et_3N/MeOH are not significantly different from those in Et_2NH/MeOH.

Scheme II



The available kinetic data cannot distinguish between the stepwise α-elimination of Scheme I or a concerted process, but the observation that **4c** is generated under the reaction conditions favors the stepwise process. Although **4a** and **4b** were not directly observed, they should be stable enough to have a finite lifetime in MeOH. The demonstration that the disappearance of both **1b** and **1c** follow clean first-order kinetics shows that the dimeric products **6** and **7** are not derived from reaction of an intermediate with **1**. A more detailed kinetic study of this reaction is now underway.

Anilines and azobenzenes both appear to be derived from the triplet state of arylnitrenes.[15] Product yields vary considerably with reaction conditions, but yields of azobenzenes are generally larger than observed for **7a–c** in this study (ca. 1%).[15] Since hydroxylamines are excellent hydrogen donors[18] and **3a–c** are produced by the methanolysis reaction, the lower yields of azobenzenes observed in this study can be attributed to efficient reduction of **2** by **3**. The oxidation of **3a–c** to the corresponding azoxybenzenes **6a–c**, under conditions in which **3a–c** are otherwise stable, indicates that this is the case. The yields of **6a** and **6b** in Table I are larger than those of methyl pivalate at all initial concentrations of **1a** or **1b** >0.2 mM. This requires that the nitrene **2** be incorporated into **6**. A mechanism that appears to be consistent with our data is shown in Scheme II. Trapping of **2** by **3** in two one-electron steps yields **5** and 2 equiv of aryl nitroxide **16**, which is the conjugate acid of radical anion **17**. Reaction of **2** with the conjugate base of **3**, **18**, cannot be excluded by the data. Donation of H· to radicals by alkyl- and arylhydroxylamines is a known process.[18] Coupling of 2 equiv of **16** or **17** can yield the azoxybenzene **6**.[19] This

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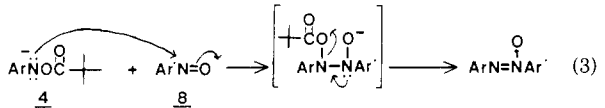
reaction is quite rapid at room temperature in EtOH; the second-order rate constant for disappearance of the ESR signal of **17** (Ar = C_6H_5) is 1.4×10^2 M^{-1} s^{-1} under these conditions.[19a] Labeling experiments indicate that this process occurs by way of a symmetrical intermediate in which both nitrogens and both oxygens become equivalent.[19b]

If these were the only processes occurring, the yield of **6** could never exceed that of methyl pivalate in our system. The fact that it does and that the yield of **5b** decreases at higher concentrations of **1b** (Table I) indicates that **2** can react with **16** or **17** to generate **6**. The mechanism proposed in Scheme II predicts a maximum ratio of 2/1 (percent yield of **6**/percent yield of methyl pivalate) when the reaction of **2** with **16** or **17** is the only source of **6** (percent yield of **6** is 2([**6**]/[**1**]) × 100% since **6** is a dimer). At [**1b**] ≥ 1.0 mM, this ratio is 1.7/1, which indicates that the majority of **6b** is formed by this process under these conditions. The data in Table I indicate that at low concentrations of **1b** significant amounts of **2b** are reduced to **5b** by solvent or an impurity.

Addition of excess hydroxylamine to the reaction mixture (Table II) changed product distributions in accord with Scheme II. When 1 equiv of **3b** was added to the reaction mixture for **1a** (2.0 mM), the yield of **5a** increased from 41% to 62%, near its upper limit according to our mechanisms (100% − methyl pivalate yield). This indicates that excess **3b** traps **2a** effectively as in Scheme II. Since both **16a** and **16b** (or **17a** and **17b**) must be generated under these conditions, a mixture of four different azoxybenzenes should be produced by the coupling reaction.[19] Table II shows that this is the case and **6b** is the predominant product as expected since **3b** will be in excess over **3a** throughout most of the reaction. According to Scheme II, equimolar quantities of **5a** and the sum of the azoxybenzenes **6a**, **6b**, **9**, and **10**, should be produced. The combined concentration of the azoxybenzenes at the end of the reaction is 1.20 ± 0.02 mM and that of **5a** is 1.26 ± 0.01 mM. Since **3b** is in excess, some **3a** should survive the reaction without being oxidized. In fact, a 5.0% yield of **3a** was detected. Finally, the yield of methyl pivalate should be unaffected by the addition of **3b** according to the mechanisms of Schemes I and II. Data in Tables I and II show very little, if any, effect of **3b** on this yield. Very similar results were obtained for the decomposition of **1b** in the presence of **3a**.

Experiments with nitrosobenzenes **8a** and **8b** were intended to provide further evidence for trapping of **2**, but instead revealed an alternative reaction path. The decreased yields of methyl pivalate observed in these experiments (Table II), the increased rate of disappearance of **1a** in the presence of **8b** and **1b** in the presence of **8a**, and the dependence of the process on base shows that a direct reaction occurs between **8** and **4**. The final reaction product can be explained by the mechanism of eq 3. The



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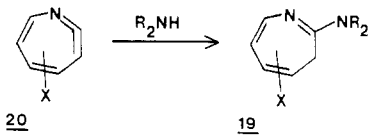
electrophilicity of nitrosobenzenes with respect to carbanions, ylides, and other nucleophiles is well established.[20]

We have also shown that **1c** can react as a nucleophile with both acetyl chloride[5] and dimethyl sulfate. In the latter case it probably acts through its conjugate base **4c** since the addition of the strong base 1,8-bis(dimethylamino)-naphthalene is required for reaction to occur (see Experimental Section). The formation of only one nonsymmetrical azoxybenzene appears to rule out radical processes involving intermediates similar to **16** or **17**.[19] This reaction demonstrates the potential of **1** to behave as a nucleophile via its conjugate base **4**.

No 2-(diethylamino)-3*H*-azepines **19** were detected in this study. Primary and secondary amines often form 3*H*-azepines by trapping 1-azacyclohepta-1,2,4,6-tetraenes **20** that are on the singlet energy surface of arylnitrenes.[21]



20 19

This reaction is very substituent dependent; (4-nitrophenyl)nitrene (**2c**) and a number of other electron-deficient arylnitrenes do not undergo this reaction under conditions in which other arylnitrenes do.[22] This can be attributed, at least in part, to efficient intersystem crossing from the singlet to the ground-state triplet.[21c,22b] The (4-chlorophenyl)nitrene (**2a**), generated by photolysis of the corresponding azide or deoxygenation of 4-chloronitrobenzene, has been reported to yield 3*H*-azepines in good yield with lower yields of **5a**. These experiments were performed in neat secondary amine solvents.[22] The decomposition of **1a** in neat Et_2NH or 28 mol % Et_2NH/MeOH led only to the hydrazine **15a**. At high concentrations of Et_2NH the apparent S_N2 process predominates to such an extent that no other reactions can be detected. The concentration of Et_2NH used in most of this study (0.05 M, 0.2 mol %) is lower than those at which significant yields of 3*H*-azepines are usually detected.[22,23] Low yields of **19** (ca. 1–2%) could have escaped detection in this study.

These results suggest that the previous observation of **5c** and **6c** as decomposition products of **1c** in H_2O[1] can be explained by competitive hydrolysis and α-elimination. A more detailed study of the decomposition of these species in basic aqueous solution is underway and will be reported at a later date. The possible importance of nitrene formation from compounds of this type in vivo cannot be assessed at present, but it is unlikely that nitrene formation can compete with unassisted N–O bond heterolysis for the more reactive members of this series that generate relatively stable nitrenium ions.[1,4]

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