JOC Article

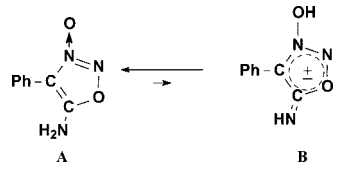
A New Synthetic Route to 3-Oxo-4-amino-1,2,3-oxadiazole from the Diazeniumdiolation of Benzyl Cyanide: Stable Sydnone Iminium *N*-Oxides

D. Scott Bohle* and Inna Perepichka

Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, H3A 2K6, Quebec, Canada

scott.bohle@mcgill.ca

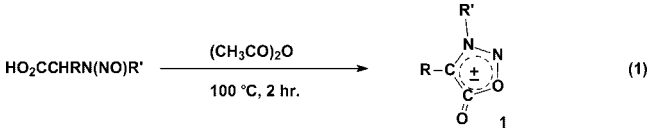
Received October 21, 2008



Treating benzylcyanide with nitric oxide in basic methanol returns 3-oxo-4-phenyl-5-amino-1,2,3-oxadiazole (a 5-iminium-sydnone *N*-oxide), **5**, in addition to the known 2-(hydroxyimino)-2-phenylacetonitrile, **6**, and the bisdiazeniumdiolate imidate salt, **7**. Conditions for the separation and purification of the new 1,2,3-oxadiazole **5** are described along with its theory, structure, spectroscopy, and reactivity which demonstrate the predominance of the amino tautomer over the *N*-hydroxide tautomer. New derivatives of **5** include a Schiff base, from the condensation with salicylaldehyde, **8**, and a dimethylamino analogue of **5**, from its reaction with methyliodide and NaH. As with other related 3-oxo-1,2,3-oxadiazoles **5** has pronounced acid/base stability. Theoretical calculations demonstrate that the only other prior sydnone *N*-oxides prepared were misformulated as the *N*-hydroxide imines and are better described as 3-oxo-5-amino-derivatives of 1,2,3-oxadiazoles.

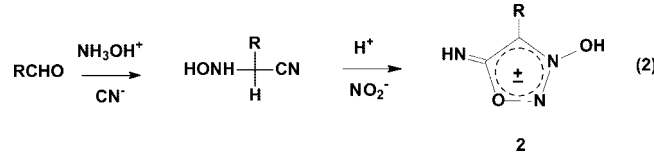
Introduction

The singular synthetic access to 1,2,3-oxadiazoles or sydnones has sharply limited their chemistry and utility. As a consequence, although these dense highly polarizable mesoionic heterocycles have many potential applications as new materials, pharmaceuticals, or as synthons for other heterocycles, this potential has not been realized. The original synthesis of the sydnone core **1**, from the cyclodehydration of *N*-alkyl or aryl *N*-nitroso-α-aminoacids with acetic anhydride, eq 1,[1] has since been



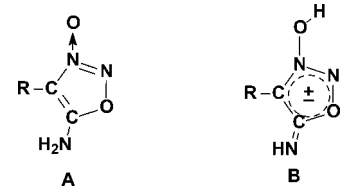
(1)

elaborated[2] but as a rule the chemistry of the *N*-aryl and alkyl derivatives is limited by their facile hydrolysis in strong acids or base. In 1971 Götz and Grozinger[3] discovered an alternative to this synthesis from the nitrosation of the Mannich condensation of aldehydes with hydroxylamine and cyanide to give **2**, eq 2, with overall yields between 2% and 10%.



(2)

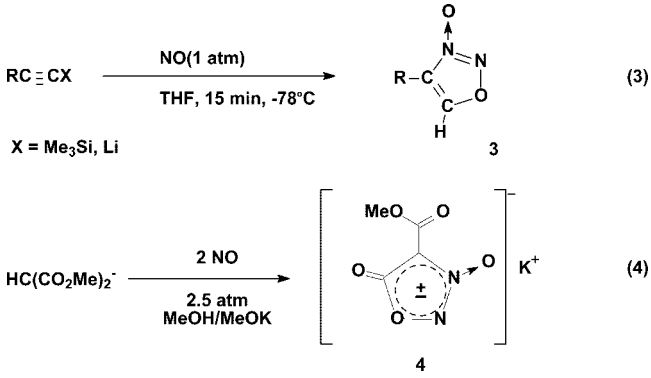
In this unique and remarkable prior report the product was formulated as an *N*-hydroxide **B** and its unusual acid and base stability was noted in passing.



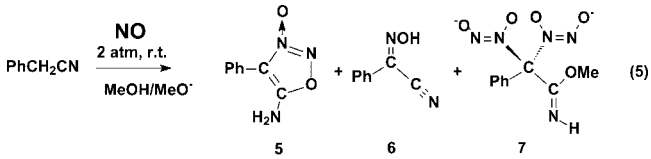
Recently two new syntheses of the 1,2,3-oxadiazoles from the diazeneiumdiolation of acidic carbon precursors were described, eqs 3 and 4. The reaction of NO with alkynes returns **3**, eq 3,[4] while with dimethylmalonate in base the product **4** forms in 31% yield, eq 4.[5] Unlike the *N*-aryl/alkyl sydnones **1**,

(1) Earl, J. C.; Mackney, A. W. *J. Chem. Soc.* **1935**, 899.

10.1021/jo802343k CCC: $40.75 © 2009 American Chemical Society
Published on Web 01/14/2009



the *N*-oxides **2A**, **3**, and **4** are remarkably stable toward acids and bases and have an emerging unique chemistry that includes the facile electrophilic decarboxylation[6] of **4** and the kinetic or thermodynamically controlled *O*- or *N*-methylation.[7] In the course of extending our studies of the diazeniumdiolation of carbanions with nitric oxide[8] we reexamined the reaction[9] of nitric oxide with benzyl cyanide described by Arnold et al. and have found that in addition to the nonheterocyclic products described by these authors a new 1,2,3-oxadiazole, **5**, can be isolated from these reaction mixtures.[9] In this paper we describe (1) a new synthesis of a new 3-oxo-1,2,3-oxadiazole, **5**, (2) the structure and spectroscopy of the species derived from benzylcyanide, (3) theoretical results relating to its ground state tautomeric structure, and (4) its reactions with salicylaldehyde and methyliodide to give a Schiff base and dimethylamino derivatives, respectively. Together these results demonstrate that **5** is an amine derivative **A** of the sydnone *N*-oxide family and not the *N*-hydroxy tautomer **2B**.



Results

The reactions of nitric oxide with organic substrates are often strongly dependent upon the base, pressure, temperature, and salts formed. These factors influence the equilibrium between the NO monomer and the NO dimer, both of which are competent electrophiles for these carbanions.[7] Although the products from this reaction, eq 5 and Table 1, are usually dominated by the bisdiazeniumdiolate imidate salt **7**, conditions for the isolation of **6** in 70% yield and for the 3-oxo-1,2,3-oxadiazole **5** in 22% yield are described. This modest yield of **5** is offset by the ease of isolation that simply requires a filtration from the dipotassium salt **7** and a chromatographic separation from any unreacted starting material and the imidate **6**. The products in eq 5 are all air and thermally stable derivatives which do not require any additional care in handling or storage. Note

TABLE 1. Reaction Conditions for the Diazeniumdiolation of Benzyl Cyanide in the Presence of Base[a]

conditions		yield, %			
	T, °C	BnCN	**5**	**6**	**7**
BnCN/THF	(0−3) °C to rt	+	no reaction occurred		
BnCN/CH_3OH	(0−3) °C to rt	+	no reaction occurred		
BnCN/CH_3ONa/CH_3OH[b]	rt	trace	10.5	3	51
BnCN/CH_3OK/CH_3OH					
1:1	−20 °C	+	trace	<5	10
1:1	(0−3) °C to rt	trace	6	11	30
1:0.1	(0−3) °C to rt	+	trace	+	trace
1:1.5	(0−3) °C (48 h)	trace	22	5	32
1:2	(0−3) °C to rt	−	4	9	32
1:2	60 °C, 24 h	trace	−	70	−
BnCN/KOH/CH_3OH					
1:1	rt	+	10	+	trace
1:2.5	rt		11.1	+	20
1:5	rt	+	5	46	25
1:1	0−3 °C	+	8	+	30
BnCN/K_2CO_3/CH_3OH					
3:1	rt	+	trace	trace	−

[a] Yields for the dipotassium salt **7** were determined from the dried precipitate isolated from the reaction mixture. The yields for **5** and **6** were determined after chromatographic separation of the reaction mixture. [b] Conditions were the same as used in ref 9 with **7** in this case being isolated as a disodium salt.

that although methanol reacts with nitric oxide to give formate,[10] this is a slow reaction under these conditions and no potassium formate is observed in the precipitate.

The identity of the new product in this reaction, 3-oxo-4-amino-5-phenyl-1,2,3-oxadiazole, **5**, was clearly established by X-ray diffraction, spectroscopy, and elemental analysis. The X-ray crystallography for **5**, Figure 1, was particularly informative due to the high-quality crystals grown for **5** from acetone/ether and which allow for data collection in the Ewald sphere out to 56° in 2θ. As a consequence, all protons were located in the penultimate electron density maps and could be refined independently. At this stage two protons were clearly located on the amino nitrogen in **5**, which also refined as a nonplanar geometry with bond angles at the amino nitrogen summing to 347.2°. For a disordered structure with an imine tautomer **B** the geometry at the nitrogen is anticipated to be coplanar with the ring. In the final refinement, the amino hydrogen atoms were refined isotropically while for the phenyl ring a riding model was used for the five carbon bound hydrogens. The resulting metric parameters are listed in Table 2 with the ORTEP depiction shown in Figure 1. Attempts to refine this structure as an *N*-hydroxyimino tautomer **B** with riding models for a proton on O(1) and N(3) consistently gave poorer models for the electron density as evidenced by the higher *R* values (>0.5%), larger S_{gof} values, and larger metric parameter esd values. The phenyl and sydnone rings are not coplanar and form a dihedral angle of 32.3(1)°. Crystal packing in **5** juxtaposes the amine hydrogens and the *N*-oxide at the 3 position to form a centrosymmetric eight-member hydrogen-bonded ring, Figure 2. The heavy atoms in this ring are coplanar and minor deviations of the hydrogens H1A and H1B are 0.12 and 0.19 Å

(2) Gilchrist, T. L.; O'Neill, P. M. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: London, UK, 1996; Vol. 5, pp 165−178.
(3) Gotz, M.; Grozinger, K. *Tetrahedon.* **1971**, *27*, 4449–4456.
(4) Sugihara, T.; Kuwahara, K.; Wakabayashi, A.; Takao, H.; Imagawa, H.; Nishizawa, M. *Chem. Commun.* **2004**, 216–217.
(5) Arulsamy, N.; Bohle, D. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2089–2091.
(6) Bohle, D. S.; Ishihara, Y.; Perepichka, I.; Zhang, L. *Tetrahedron Lett.* **2008**, *48*, 4550–4552.
(7) Bohle, D. S.; McQuade, L. E.; Perepichka, I.; Zhang, L. *J. Org. Chem.* **2007**, *72*, 3625–3631.
(8) Arulsamy, N.; Bohle, D. S. *J. Org. Chem.* **2006**, *71*, 572–581.
(9) Arnold, E. V.; Keefer, L. K.; Hrabie, J. A. *Tetrahedron Lett.* **2000**, *41*, 8421–8424.
(10) DeRosa, F.; Keefer, L. K.; Hrabie, J. A. *J. Org. Chem.* **2008**, *73*, 1139–1142.

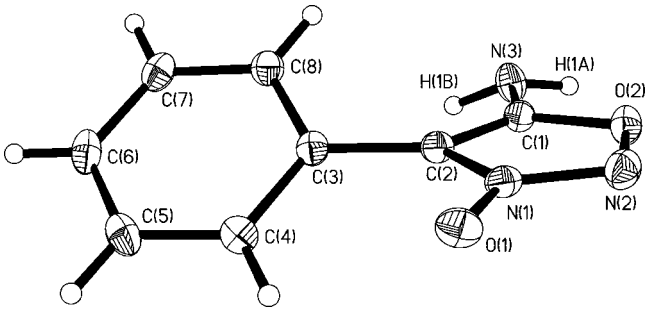


FIGURE 1. ORTEP representation of **5** with 50% thermal ellipsoids shown for non-hydrogen atoms and the amine hydrogen atoms shown as isotropic spheres.

TABLE 2. Experimental and Theoretical Dimensions for Aminosydnones

metric parameter	exptl[a,b]	DFT, amino **A**[c]	DFT, hydroxoimide **B**[c]
C(1)−N(3), Å	1.3440(15)	1.36173	1.26885
C(1)−C(2), Å	1.3739(16)	1.36689	1.45302
C(2)−N(1), Å	1.3817(19)	1.41389	1.34163
N(1)−O(1), Å	1.2893(13)	1.24665	1.36263
N(1)−N(2), Å	1.3100(14)	1.31470	1.30710
N(2)−O(2), Å	1.4014(13)	1.40844	1.38721
O(2)−C(1), Å	1.3458(15)	1.33927	1.40599
C(2)−C(3), Å	1.4601(16)	1.46133	1.45302
C(2)−C(1)−N(3), deg	132.11(11)	133.04745	124.01
C(1)−C(2)−C(3), deg	130.78(11)	131.60755	129.356
N(1)−C(2)−C(3), deg	126.32(10)	125.09716	128.38627
N(1)−C(2)−C(3)−C(4), deg	147.39(12)	147.35407	175.565

[a] Value from X-ray diffraction. [b] Metrics for the phenyl ring carbons are not included here. [c] Calculated by density functional theory with a triple-ζ basis set: B3LYP/6-311++G**.

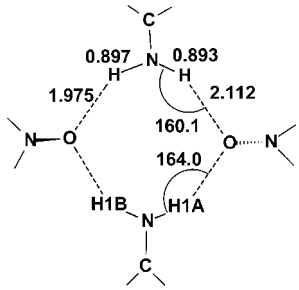


FIGURE 2. Hydrogen bonding between the amine and *N*-oxide groups in **5**. The center of inversion located at the midpoint relates two halves of a ring.

out of this plane. ORTEP plots for this ring are depicted in Figures S1 of the Supporting Information.

To assist with the structural assignment of **5**, **2**, and **9** (discussed below), ab initio density functional calculations were used to determine the relative energies and vibrational frequencies for the possible ground states. For **5** the two key tautomers **A** and **B** both correspond to theoretical stationary points which are local ground states with the geometries shown in the figures in the Supporting Information. Their Cartesian coordinates and normal vibrational modes are listed in Tables S2−S4 of the Supporting Information. In general density function theory with triple-ζ basis sets, B3LYP/6-311++G** gives very good representations for the geometries, energies, and vibrations of these types of heterocycles.[7]

In the gas phase the isomer **5A** is 21.11 kcal·mol^{-1} more stable than **5B.** The gas phase optimized ab initio ground state structures (B3LYP/6-311++G**) for **A** and **B** predict relatively

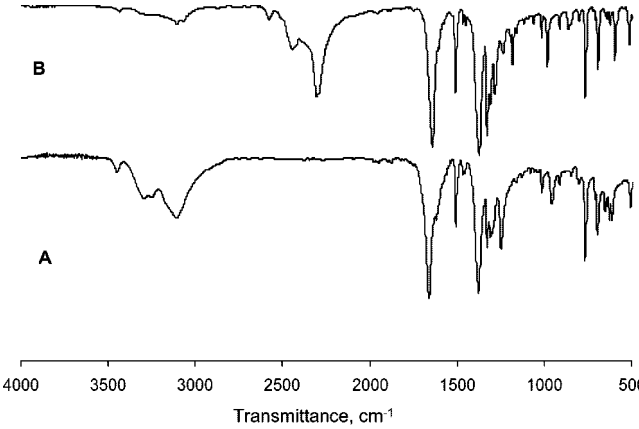
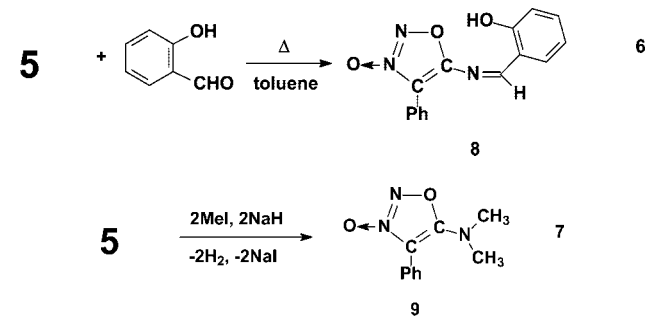


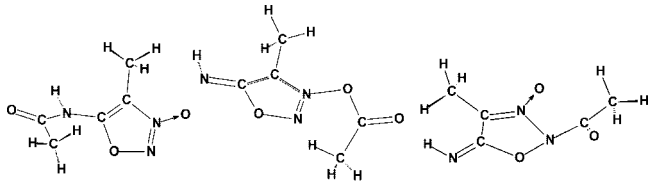
FIGURE 3. Infrared spectra (KBr) for **5** shown in the bottom panel (A) with N−H, O−H, and C−H stretching bands at 3447, 3298, 3249, and 3113 cm^{-1} and for the deuterium exchanged sample shown in the top panel (B) with new peaks at 2578, 2443, and 2304 cm^{-1}.

short or long exocyclic N−C and N−O bond lengths. The contrast of the solid state dimensions of C(1)−N(1) and N(1)−O(1) with the calculated values for **A** and **B** shows them to be much closer to the $-NH_2$ tautomer **A**. A likely consequence of the solid state H-bonds shown in Figure 2 is a slight decrease in the C(1)−N(1) bond length and an increase in N(1)−O(1) from those predicted in the gas phase. To aid in the assignment of **A** and **B** we contrast the IR of the normal NH_2 and deuterated ND_2 derivatives in Figure 3. Here three N−H···O bands are observed in addition to the characteristic fingerprint bands for the 3-oxo-1,2,3-oxadiazole ring. The number and relative intensities of the bands correspond well to those predicted for a gas phase tetramer calculated at the B3LYP/3-21+G* level, as well as those found for simple aromatic amines such as aniline. Significantly, the band at 1660 cm^{-1} shifts to 1639 cm^{-1} on deuteration, and corresponds to an antisymmetric combination of a ring stretch with exocyclic C=N and N−O modes.

The vibrational spectroscopy is consistent with the presence of the *N*-oxo amino tautomer **A** versus the *N*-hydroxoimino form **B** and the bond lengths, particularly the N−O and C−N exocyclic bonds, correspond to those expected theoretically for the *N*-oxo amino tautomer.



In its reactions **5** also behaves like a nucleophilic amine as well as a weak Bronsted acid. For example, with salicylaldehyde **5** adds slowly in toluene at reflux to give the yellow Schiff base adduct **8**, eq 6. This condensation is slower than that of typical aromatic amines and reflects the weak nucleophilicity and basicity of the amine in **5**. This amine can also be dimethylated with methyl iodide and sodium hydride, eq 7. The dimethylamino product, **9**, has similar UV and fingerprint-IR properties



C D E

Isomer	N_{imine}acetylated	$O_{N\text{-}oxide}$ acetylated	2-N-acetylated
Rel. Energy Kcal mol^{-1}	0.0	29.73	21.61
Rel. Energy Kcal mol^{-1} **(F)**	0.0	26.4	26.36
ν(CO) cm^{-1}	1783.8	1906.0	1829.1
Asym stretch cm^{-1}	1728.6	1711.5	1647.9
Sym stretch cm^{-1}	1515.0, 1237.4	1580.1, 1287.3	1300.6, 1225.9

FIGURE 4. Optimized ground states and relative B3LYP/6-311++G** energies (kcal mol^{-1}) for 3-oxo-4-methyl-5-amino-1,2,3-oxadiazole acetylation isomers. Corresponding isomers for 3-oxo-5-amino-1,2,3-oxadiazole, **F**, are listed but not shown. Strong vibrational acetyl and ring modes are listed below each isomer. DFT also predicts a strong amide like stretch at 1281 cm^{-1} found for **C**.

as **5** with its ^{1}H and ^{13}C NMR spectra indicating that the methyl resonances are equivalent on the NMR time scale.

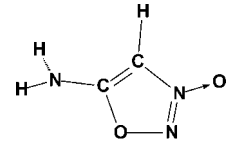
There are three prominent absorption bands in the ultraviolet spectrum of **5** and these shift to lower energies when treated with base and are then restored when treated with acid, Figure S4 in the Supporting Information. There is no change in this spectrum upon treatment with acid or dissolution in 1 M HCl. The relative acidity of these protons is demonstrated by their downfield shift in the ^{1}H NMR spectrum to 8.05 ppm in contrast with many aromatic amines which have a typical shift range of 3−5 ppm. A spectrophotometric titration in 50:50 water−methanol with 1 M sodium hydroxide solution gives an isosbestic point at 314 nm, and a pK_a = 11.4 for these protons.

Discussion

The diazeniumdiolation of carbanions is a general reaction that requires careful control of the reaction conditions to achieve product yield and specificity. The utility of the reaction is exemplified here in that a stable heterocyclic *N*-oxide derivative is readily prepared in a single step from the condensation of readily available precursors. Thus while at first glance there is an array of complex products formed during the reaction in eq 5, by varying the condition yields can be maximized to select from the different products. The ease of product separation and their inherent stability are important practical features in these preparations as well.

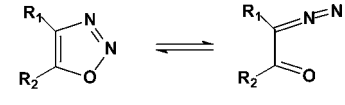
The role of the *N*-oxide in stabilizing these heterocycles was perhaps not appreciated by Götz and Gronzinger in their initial ground-breaking studies of **2**. In their paper they are designated variously as tautomer **A** seven times and as tautomer **B** seven times and designated as imines in the title. Given that at the point of time of their discoveries only 3-alkyl, aryl, and aminated sydnones were known it is perhaps logical to formulate **2** as derivatives with N−O single bonds rather than as *N*-oxides. We now know the *N*-oxide is an important stabilizing factor in these heterocycles and that it is responsible for their unusual stability.

These distinctions in tautomers are important if we are to understand the reactivity of **2** and **5**. Thus the Mannich condensation products **2**, which readily add electrophiles such as methyliodide or acetic anhydride to give products, originally formulated as a bis(*N*-methyl) derivatives of **2** or as *O*-acetylated mesoionic analogues.[3] Although the spectroscopic data presented for the bis-*N*-methylation of **2** is unequivocal, their remains considerable uncertainty in the acetylation site. We have found that theory and X-ray crystallography is often required to predict and to rigorously determine the site of electrophilic addition[7] and the proposed structures of these acetylated products must be considered tentative. There are potentially three acetylation sites in **2** and to evaluate which is most likely to be the thermodynamically preferred we have calculated the ground-state geometries and energies with DFT for all three acetylated isomers for acetylated 1,2,3-oxadiazine, Figure 4. Acetylation of the amine nitrogen to give **C** gives a more stable isomer by over 21.6 kcal·mol^{-1} over the exocyclic O addition product **D** and the ring acetylated product **E**. While substitution at the 4 position to give the derivatives prepared by Götz and Grozinger might affect the stabilities of **C**−**E** slightly, the most likely product in his preparation is that related to **C** and this fits well with the cursory IR data given in his paper, 1730 and 1660, which most closely matches the strong bands associated with this isomer. Götz formulated his product as that shown in **D**.



F

The X-ray diffraction structure and DFT results also suggest that **A** best describes the tautomeric structure. For example, the exocyclic nitrogen−carbon bond length in **5**, 1.3440(15) Å, is well within the range of aromatic amine C−N bond lengths, over 2100 entries, found in the Cambridge Crystallographic database, 1.38(3) Å. Although there is some pyramidalization of the geometry of the nitrogen in **5**, where the three bond angles at the nitrogen sum to 347°, this value should not be overinterpreted given the general problems of refining hydrogen atom positions from X-ray data. However, DFT predicts *N*-pyramidalization and in the gas phase these angles sum to 346.51°, in remarkable agreement with experiment. Consistent with the formation of the amine tautomer **A** for **5** is that it readily forms a Schiff base **8** with salicylaldehyde, eq 6, and a dimethylamino derivative, **9**, eq 6.



G 8

Finally, although *N*-oxides are often written with the designation N$^+$−O$^-$, for many Lewis representations the valence bond formulation does not really express the remarkable strength, shortness, and inertness of these bonds and this functionality. These bond lengths are typically much shorter than N−O single bonds and even those found in many formally N=O double bonding nitroso species. In terms of reactivity, heterocyclic *N*-oxides are often poor ligands, and their weak Lewis basicity correlates with poor O-atom nucleophilicity. One way to think of the *N*-oxide substituent in these and many heterocycles is as a lone pair place holder that blocks any reaction in which the lone pair contributes substantially. In the case of the 1,2,3-oxadiazoles the reaction which is blocked is the ring open diazo-

tautomer **G** in eq 8.[11] With this localization and ring opening reaction blocked these compounds are more stable to acids, bases, and heat.

The 1,2,3-oxadiazole heterocycle is readily stabilized by the presence of an *N*-oxide substitution at the 3-position. Thus with this substituent in place it is possible to isolate 2-*N*-alkylated heterocycles, to decarboxylate the ring for 4-carboxylate-substituted derivatives, and it is possible to isolate 5-amino derivatives such as **5**, **8**, and **9**. Clearly there is now considerable scope for chemistry of the 3-oxides of the 1,2,3-oxadiazoles, and there are likely to be a wide range of new heterocycles that can be prepared from these simple rings.

Conclusion

In basic methanol benzyl cyanide reacts rapidly with nitric oxide to give product distributions which are dependent upon the base, stoichiometry, temperature, and pressure. Among the products is the unusual heterocycle 3-oxo-4-phenyl-5-amino-1,2,3-oxadiazole, **5**, which correponds to an *N*-oxide resulting from the cyclic addition of the NO dimer to the benzyl cyanide. As with the other 3-oxo-1,2,3-oxadiazoles **5** is stable toward acids and bases and is best represented as an aromatic amine.

Experimental Section

General. All reagents and solvents were used as supplied commercially, except for methanol, which was distilled from sodium. Nitric oxide was passed over potassium hydroxide pellets and was used in an evacuated and purged Schlenck line before introduction into the medium pressure reaction vessel. The apparatus for the diazeniumdiolation reactions has been described in detail in prior publications[8] with a key detail being the use of a thick-walled glass pressure bottle for the reactions.

Reaction of Benzyl Cyanide with Nitric Oxide. In a typical procedure, benzyl cyanide was added to a solution of potassium methoxide in methanol in a pressure bottle. After 4 cycles of nitrogen:vacuum degassing, the solution was exposed to 250 kPa nitric oxide for 4 h with stirring at the listed temperature. During this period, as the nitric oxide is consumed, the pressure is topped up with fresh gas until no further gas is consumed. The reaction mixture is allowed to warm to room temperature and kept under an atmosphere of nitric oxide overnight. During this reaction copious amounts of a light cream colored precipitate form. After venting the excess nitric oxide, the precipitate is filtered and washed with methanol/dichloromethane (1:1). The resulting snow white material is bis-diazeniumdiolated imidate, **7**. The filtrate is reduced in volume and the crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (1:1, v/v) as an eluent to give unreacted starting benzyl cyanide, compound **5** (R_f 0.4) and **6** (R_f 0.8).

3-Oxo-4phenyl-5-amino-1,2,3-oxadiazole, 5: mp 145−147 °C; ^{1}H NMR (DMSO, 400 MHz, ppm) δ 7.37 (t, J = 7 Hz, 1H), 7.46 (t, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 2H), 8.05 (s, NH_2); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) δ 105.8, 124.1, 127.5, 128.4, 128.5, 163.6; IR (KBr, cm^{-1}):3447 m, 3298 m, 3249 m, 3113 m, 1660 s, 1507 s, 1468 w, 1450 w, 1375 s, 1322 m, 1310 m, 1282 m, 1247 s, 1160 w, 1064 w, 1013 m, 957 s, 911 w, 844 w, 801 w, 765 s, 709 w, 693 s, 65 m, 643 w, 625 w, 613 w, 506 m; UV/vis (CH_3OH) λ_{max}, nm (ε (mol/L cm)$^{-1}$) 233 (12750), 256 (10100), 290 (9646); (NaOH 2M) λ_{max}, nm (ε (mol/L cm)$^{-1}$) 279 (8300), 334 (11400). Anal. Calcd for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.71. Found: C, 54.14, H, 3.74, N 23.50. **Deuterium derivative of 5:** Protio **5** dissolved in a 1:1 mixture of d_6-acetone/D_2O stirred for an hour and the solvents were evaporated. IR (KBr, cm^{-1}) 3109 w, 3068 w, 2578 m, 2443 m, 2303 m, 1639 s, 1509 s, 1465 w, 1449 w, 1371 s, 1327 s, 1309 m, 1284 m, 1237 w, 1192 w, 1181 m, 1060 w, 1013 m, 982 s, 910 m, 859 m, 799 w, 764 s, 691 s, 637 w, 620 w, 594 s, 511 m, 484 w.

2-(Hydroxyimino)-2-phenylacetonitrile, 6: mp 102−104 °C (lit.[12] mp 100 °C); ^{1}H NMR (DMSO, 300 MHz, ppm) δ 7.49 − 7.55 (m), 7.69−7.72 (m), 7.92−7.95 (m), 13.8 (s); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) δ 109.3, 126.5, 129.1, 129.3, 131.7, 149.9; IR (KBr, cm^{-1}) 3360 s, 2975 w, 2815 w, 2236 m, 1569 w, 1498 m, 1450 m, 1417 m, 1318 w, 1282 s, 1060 s, 1030 m, 1001 m, 967 s, 920 w, 765 s, 689 s, 675 s, 661 m, 607 m, 480 m; UV/vis (CH_3OH, λ_{max}, nm) 260. Anal. Calcd for $C_8H_6N_2O$: C, 65.74; H, 4.13; N 19.16. Found: C, 65.47; H 3.81; N, 19.07.

Preparative Conditions for the Selective Synthesis of 6. Under nitrogen in a glass pressure reaction bottle 0.50 g (4.27mmol) of benzyl cyanide was added to a solution of potassium hydroxide in absolute methanol (30 mL). The reaction flask was repeatedly flushed with nitrogen, pressurized with nitric oxide (250 kPa), and warmed to 60 °C (oil bath) for 24 h. After completion of the reaction, the yellow reaction mixture was flushed with nitrogen and the solvent was evaporated. Recrystallization of the crude product from acetone/hexane gave pure compound **6**, yield 0.42 g (70%).

Synthesis of Schiff Base 8. Under nitrogen, a mixture of **5** (0.022 g, 0.18mmol) and salicylaldehyde (0.031 g, 1.75 mmol) in 10 mL of toluene was refluxed for 24 h. After evaporation, the crude yellow product was purified by column chromatography on silica gel with hexane/ethyl acetate (1:2, v/v) as an eluent, R_f 0.5, to give 0.02 g (42.5%) of compound **8** as a bright yellow solid: mp 162 °C (DSC); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.06 (t, J = 8 Hz, 2H), 7.54 (m, 5H), 7.94 (d, J = 8 Hz, 2H), 9.14 (s, CH), 11.63 (s, OH); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) δ 118.4, 120.8, 122.4, 127.6, 128.3, 129.3, 129.5, 130.8, 134.9, 137.6, 158.9, 162.4, 168.2; IR (KBr, cm^{-1}) 3048 w, 2923 w, 2851 w, 1658 m, 1618 s, 1594 s, 1561 s, 1502 w, 1485 w, 1451 m, 1430 s, 1379 s, 1350 m, 1327 m, 1281 m, 1249 m, 1233 m, 1213 m, 1233 s, 1117 w, 1007 w, 997 w, 977 w, 904 m, 810 w, 757 s, 747 s, 684 s, 648 m, 585 s, 505 m, 478 w, 462 m; Raman 1662 s, 1622 s, 1607 m, 1599 m, 1566 s, 1506 w, 1465 m, 1450 m, 1434 w, 1395 m, 1354 w, 1330 m, 1292 w, 1251 m, 1234 s, 1217 m, 1178 s, 1155 m, 1031 m, 999 s, 979 w, 813 m, 793 s, 761 w, 712 w, 646 w, 616 w, 558 w, 475 w, 442 w, 396 w, 350 w, 291 w, 246 w, 225 w; UV/vis (CH_3OH, λ_{max}, nm) 339, 394; MS (ESI), m/z calcd for $C_{15}H_{11}N_3O_3$ [M] 281, found [M + H]$^+$ 282 (100%), [M + Na]$^+$ 304 (10%), exact mass calcd for $C_{15}H_{11}N_3O_2$ [M − H]$^-$ 280.07280, found 280.07277.

3-Oxo-4-phenyl-5-dimethylamino-1,2,3-oxadiazole, 9. To a solution of **5** (0.1 g, 0.565 mmol) in anhydrous DMF (1 mL) under nitrogen at room temperature was portion-wise added 0.06 g (2.5 mmol) NaH, 60% dispersion in mineral oil in DMF (2−3 mL) via a syringe. In addition, the mixture was stirred 30 min then cooled to 5 °C. Methyl iodide (0.21 g, 1.5 mmol) in DMF was slowly introduced and the reaction mixture was left overnight at ambient temperature. The solution was poured into cold water and repeatedly extracted with chloroform, washed with brine, and dried over magnesium sulfate. After removal of the solvent the crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (1:1, v/v, R_f 0.6) as an eluent; yield 0.076 g (66%, from DCM/hexane) of **9**; mp 105−107 °C; ^{1}H NMR ($CDCl_3$, 400

(11) Blocher, A.; Zeller, K. P. *Angew. Chem.* **1991**, *103*, 1489–1490. See also *Angew. Chem., Int. Ed. Engl.* **1991**, 1430, 1476−1487.

(12) Wieland, H. *Ann. Chem.* **1903**, *328*, 154–156.

(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, J. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Kamaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian98*; Gaussian Inc.: Pittsburgh, PA, 1998.

MHz, ppm) δ 2.94 (s, 6H), 7.44 (s, br, 5H); ^{13}C NMR ($CDCl_3$, 300 MHz, ppm) δ 38.6, 107.9, 124.4, 128.8, 129.8, 131.5, 161.9; IR (KBr, cm^{-1}) 3072 w, 3032 w, 2932 w, 2821 w, 1665 s, 1604 m, 1524 m, 1480 w, 1446 w, 1379 s, 1289 m, 1270 m, 1156 w, 1070 m, 1015 m, 944 m, 912 m, 789 w, 760 m, 729 m, 701 m, 692 m, 649 m, 580 w, 496 w, 467 w. UV/vis (DCM) λ_{max}, nm (ε (mol/L cm)$^{-1}$) 240 (9800), 287 (11100); MS (electron impact), *m*/*z* exact mass calcd for $C_{10}H_{11}N_3O_2$ [M] 205.0851, found 205.0855.

Computational Details. All of the calculations described above were performed with Gaussian 98.[13] We have studied the neutral amine **5** as both **A** and **B** tautomers as well the possible acetylation isomers of Götz **C**−**E**. Computations were carried out at the restricted Hartree−Fock (RHF),[14] and Density Functional Theory (DFT). DFT calculations used the hybrid B3LYP functional and triple-ζ 6-311++G** basis sets.[14−16] Vibrational frequencies were calculated for all stationary points to define them as either minima or transition states.

X-ray Crystallography: Single-crystal X-ray diffraction experiments were carried out with a BRUKER SMART CCD diffractometer using graphite-monochromated Mo-K_α radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods and refined by full-matrix least-squares on F^2 of all data, using SHELXTL software.[17] Key crystallographic data is summarized in Table S1in the Supporting Information.

Acknowledgment. We gratefully acknowledge the CRC, CFI, and NSERC for support in the forms of a CRC, CFI, and discovery grant to DSB, and the CIHR for a Chemical Biology Fellowship to Dr. Inna Perepichka.

Supporting Information Available: General experimental instrumentation, crystallographic data (CIF files, Tables S1−S5), and density functional results for **5** and its tautomers. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802343K

(14) Roothaan, C. C. *J. Rev. Mod. Phys.* **1951**, *23*, 69–89.
(15) Lee, C. Y. W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
(16) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
(17) *SHELXTL*, SHELXTL 5.10 ed.; Bruker AXS, Inc.: Madison, WI., 1997.