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Decarboxylation and ring fragmentation reactions of sydnone N-oxides

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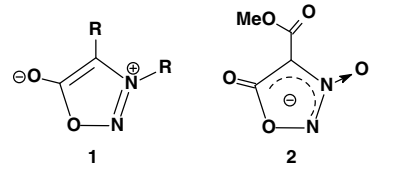
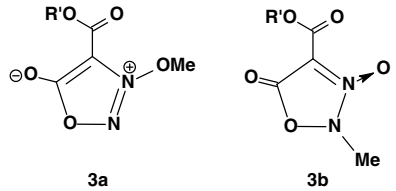
ABSTRACT

4-Carboxylated sydnone N-oxides are readily decarboxylated by benzylation to give 2,4-dibenzylsydnone-N-oxides. Ring cleaveage results from their oxidation with bromine which leads to a nitrile N-oxide which is isolated as its furazan dimer.

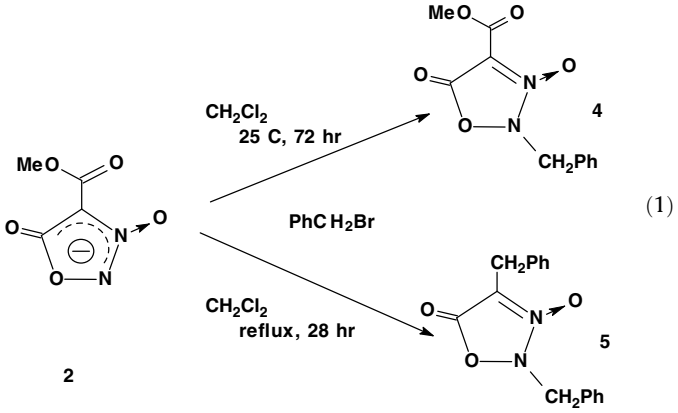
The mesoionic, 1,2,3-oxadiazoles, found in the N-substituted sydnones, **1**, remain of considerable interest as new materials[1,2] and for their biological properties.[3,4] Unfortunately, their singular synthetic access has limited the number of available derivatives as well as an understanding of their associated reactivity patterns.[5] Recently, a new class of remarkably stable sydnones, the N-oxide, **2**, was recognized and are readily prepared by the base-mediated diazeniumdiolation of either dimethylmalonate[6] or terminal alkynes.[7] Unlike other sydnones, the sydnone N-oxides are stable toward strong acids[8] to the extent that, for example, sulfuric acid catalyzed *trans*-esterification[9] of the 4-carboxylate derivatives opens a wide range of accessible derivatives. The sydnone N-oxides thus offer a range of potential new chemistry for this heterocycle, and in this Letter, we describe a facile electrophile-promoted decarboxylation of the 4-carboxylate upon benzylation, and the oxidative cleavage of the sydnone ring with bromine which results in the dimer of the nitrile N-oxide intermediate to give the furazan **6**.



1 **2**



3a **3b**



(1)

We have recently found that the methylation of **2** gives either N–O methylation as the kinetic product **3a** or N-methylation as the thermodynamic product **3b**.[9] Now we find that with benzyl bromide at room temperature only an N-benzyl monobenzylation analog **4** of **3b** product is isolated, Eq. 1. The N-benzylated structure **4** is assigned based on the similarity of the spectroscopic properties of **3b** and **4**,[†] as well as a single crystal X-ray diffraction analysis, not

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† *Characteristic data for new compounds*: Compound **4** mp 103–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 3H,CH_3–O), 4.99 (s, 2H, Ph–CH_2–N), 7.28–7.39 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm): δ 53.5, 61.9, 109.2, 127.3, 129.3, 130.4, 130.9, 155.6, 159.4. IR (KBr, cm^{-1}): 3089w, 3063w, 3040w, 2962w, 1820s, 1804s, 1725s, 1578s, 1497w, 1449s, 1408m, 1364m, 1248s, 1092m, 1067m, 1044w, 1005m, 937w, 861w, 828w, 790w, 778s, 744m, 727m, 710m, 696w, 676w, 645w, 478w. UV (CH_3OH λ_{max}, nm (ε, M^{-1} cm^{-1})): 263 (8900), 300 (sh), 320 (sh). MS (ESI), *m*/*z*: calcd for $C_{11}H_{10}N_2O_5$ [M] 250; found [(M–NO)+Na]$^+$ 243 (17%), [M+Na]$^+$ 273 (100%). Anal. Calcd for $C_{11}H_{10}N_2O_5$ (250 g/mol), %: C, 52.8; H, 4.03; N, 11.19. Found: C, 52.9; H, 3.88; N, 10.81. Compound **5** mp 108.5–110.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.67 (s, 2H, Ph–CH_2–C), 4.86 (s, 2H, Ph–CH_2–N), 6.97–7.00 (m, 5H), 7.17–7.30 (m, 5H). ^{13}C NMR (300 MHz, $CDCl_3$, ppm): δ 27.9, 61.5, 117.8, 127.3, 127.6, 128.8, 128.87, 128.96, 129.85, 131.05, 133.5, 163.9. IR (KBr, cm^{-1}): 3084w, 3062w, 3036w, 3012w, 1809w, 1788s, 1590s, 1494m, 1455m, 1426m, 1394m, 1304w, 1286w, 1286w, 1206w, 1167w, 1085w, 1065w, 1029w, 985w, 956w, 927w, 882w, 842w, 766m, 749m, 725m, 693m, 640m, 488w. UV (CH_3OH λ_{max}, nm (ε, M^{-1} cm^{-1})): 259 (12400). MS (EI), *m*/*z*: calcd for $C_{16}H_{14}N_2O_3$ [M] 282; found [M–NO] 252 (20.3%), [M] 282 (4.0%). Anal. Calcd for $C_{16}H_{14}N_2O_3$ (282 g/mol), %: C, 68.1; H, 4.99; N, 9.92. Found: C, 67.9; H, 4.97; N, 9.91.

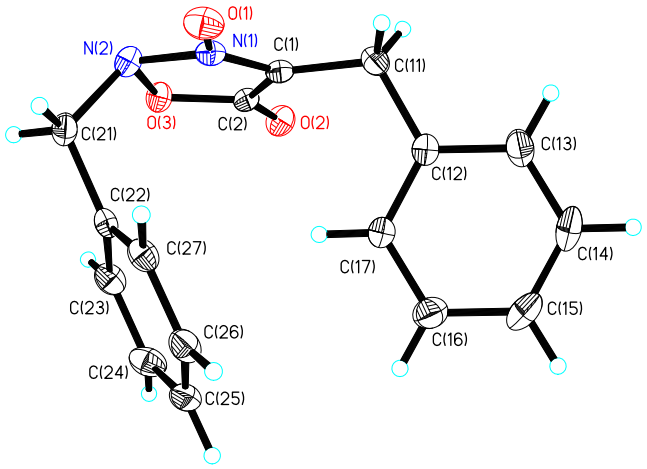
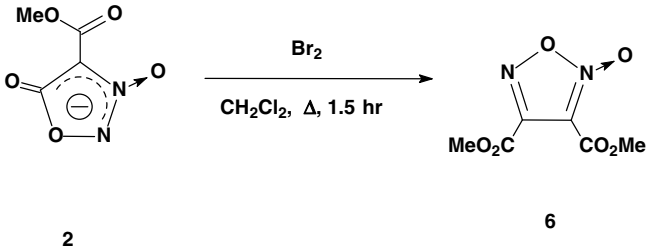


Figure 1. X-ray single crystal diffraction structure of **5** showing H atoms in calculated positions and 40% thermal ellipsoids. Key metric parameters include: N(1)–O(1) = 1.2527(17), N(1)–N(2) = 1.4401(16), N(2)–O(3) = 1.4326(15), C(1)–N(1) = 1.3099(18), C(1)–C(2) = 1.443(2), C(2)–O(3) = 1.3797(17), and C(2)–O(2) = 1.1987(17) Å.

shown. There is no evidence for the formation of a benzyl analog to **3a** or the kinetic product of the methylation of **2** under these conditions. Furthermore, benzylation of **2** at slightly elevated temperatures, methylene chloride at reflux, gives a bis-benzyl product, **5**, in 25% yield, in addition to a minor, 3% yield of **4**. The remarkably facile uncatalyzed decarboxylation of **2** suggests that other electrophiles, and perhaps oxidants, might return a range of new 4-substituted 1,2,3-oxadiazoles related to **5**. We speculate that bromomethane is a side product of this reaction. The structure of **5** has been confirmed by X-ray diffraction,[‡] Figure 1, and corresponds to benzylation/decarboxylation of **2**. The contrast of the structure of **5** with that of **3b**,[9] Figure 2, illustrates the effect of the π-conjugated methylcarboxylate group in **3b** upon the core sydnone structure in that the framework bond lengths for N(1)–C(1), C(1)–C(2), and C(2)–O(3) are all shorter in **5**, while those bond lengths for N(1)–N(2) and N(2)–O(3) frameworks are all slightly longer in **5**. In addition, both N(1)–O(1) and C(2)–O(2) bonds are longer for the bisbenzyl derivative **5**, all of which suggests that in the absence of conjugation with the CO_2Me in **3b** there is a build up of electron density in non-bonding or antibonding orbitals localized in these parts of the ring. Finally, there is substantial pyramidilization of N(2) in **5** with the angles at the nitrogen summing to 321.9°, with the smallest intraring angle being N(1)–N(2)–O(3), 103.4° at this nitrogen.



2 **6**

(2)

[‡] *Crystal data for* **5**: Crystallizes in the orthorhombic space group Pbca. Key crystallographic parameters: $a = 10.868(2)$ Å $b = 8.8483(18)$ Å; $c = 28.561(6)$ Å; $\alpha = \beta = \gamma = 90°$; $V = 2746.5(10)$ Å^3; $Z = 4$; $\rho_c = 1.365$ Mg m^{-3}; crystal size = 0.11×0.06×0.05 mm^3 Data: 2773 independent data and 190 parameters, $S_{gof} = 1.045$; $R_1 = 3.82\%$, $wR_2 = 9.57\%$. Further details are available on the CCDC, # 646992.

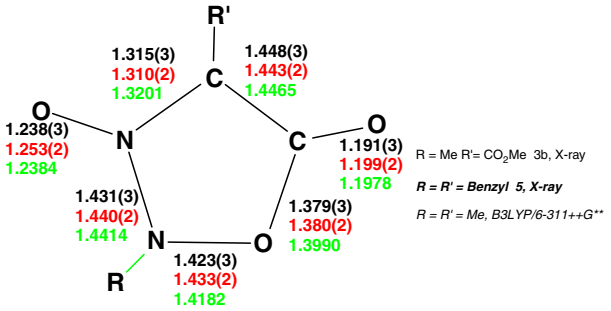
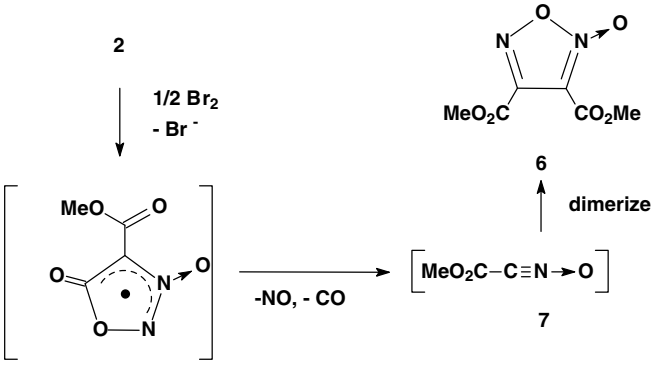


Figure 2. Crystallographic and calculated dimensions. Crystallographic data for **3b** shown on top in black bold, for **5** in the middle in red in bold italics, and the calculated values for the 1,4-dimethyl oxadiazole shown in bottom red italics.

The electrophile-mediated decarboxylation of **2** suggests that the one electron oxidation of the ring might lead to enhanced reaction and/or ring cleavage. This has been borne out experimentally by the facile reaction of **2** with bromine Eq. 2, which gives bis(methylcarboxy)furazan, **6**, in 37% yield. Prior electrochemical studies demonstrated that **2** undergoes an irreversible oxidation at +1.09 V in acetonitrile even with moderately fast CV scan rates of 1000 mV s^{-1}.[6] The formation of a furazan suggests that the oxidation of **2** gives a product which readily looses the nitrile N-oxide, MeO_2CCNO, **7**, which then dimerizes to give **6**, Eq. 3. Although the dimerization of nitrile N-oxides is known, and the spectroscopic features of **6** match those in the literature,[10,11] the oxidation of a sydnone N-oxide represents a new access to nitrile N-oxides,[12] and one which compliments the recently reported manganese dioxide oxidation of aldoximes.[13]Alternatively, the sydnone N-oxides could be viewed as being a formal 1–3 dipolar addition product of a nitrile N-oxide to the fragment [NOCO]$^-$, the one electron oxidation of which leads to a facile retro reaction. Finally, the gaseous side products from reaction 3, in this case proposed to be NO and CO, are likely to be physiologically active, and thus these derivatives have potential biomedical applications.



(3)

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.05.025.

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