Anomalous addition of 2-cyanoprop-2-yl radicals to 2-(4-*t*-butyl-2-nitrosophenyl)-2-methylpropanoic acid

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Abstract

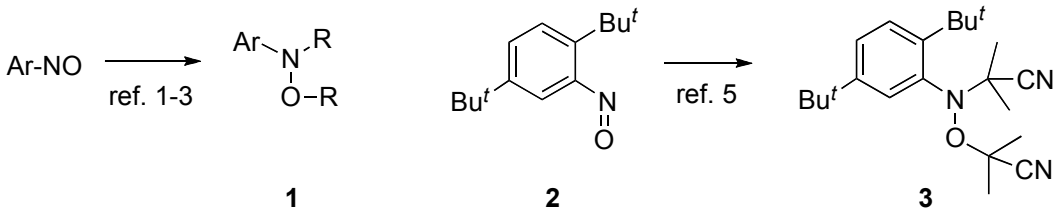
It has been reported that *tertiary* radicals like 2-cyanoprop-2-yl add to 1,4-di-*t*-butyl-2-nitrosobenzene **2** at the N and O atoms of the nitroso group. In contrast, treatment of the the analogous nitrosobenzene, 2-(4-*t*-butyl-2-nitrosophenyl)-2-methylpropanoic acid **12**, with azobisisobutyronitrile in boiling benzene afforded a 1,6-addition product, 2-[5-*t*-butyl-1-(1-cyano-1-methylethoxy)imino-4-(1-cyano-1-methylethyl)cyclohexa-2,5-dien-2-yl]-2-methyl-propanoic acid **16** as the sole isolable product.

Keywords: Aminyl radicals, cyclohexa-1,4-dienes, nitroso-arenes, oxidative ring opening, radical trapping

Introduction

Some fifty years ago, it was reported that *tertiary* C-radicals add pairwise to nitrosobenzenes Ar-NO at the nitroso group to generate *N*-aryl-*N*,*O*-dialkylhydroxylamines **1** (Ar = Phenyl or mono- and disubstituted phenyl group, R = CMe_2COOMe or CMe_2CN).[1-3]

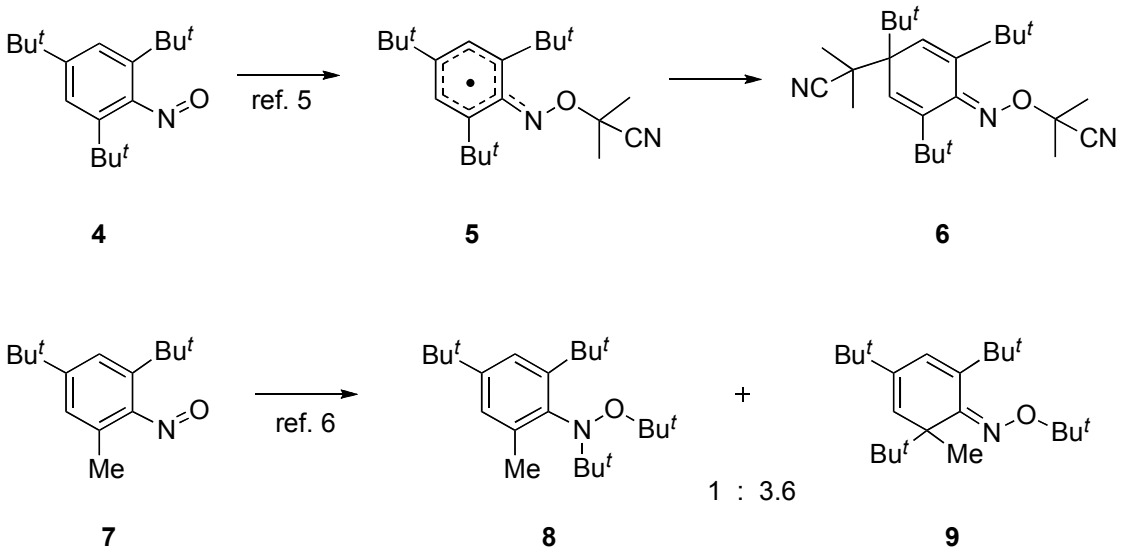
A similar result has also been observed in a radical addition reaction using the moderately encumbered 1,4-di-*t*-butyl-2-nitrosobenzene **2**[4] which is transformed into the N,O-adduct **3** upon treating with a 2.5 molar amount of azobisisobutyronitrile (AIBN) in boiling benzene for three hours[5] (Scheme 1).



1 **2** **3**

Scheme 1

The same authors also investigated the behavior of the highly encumbered 1,3,5-tri-*t*-butyl-2-nitrosobenzene **4**[4] toward 2-cyanoprop-2-yl radicals and found an 'abnormal' reaction leading to the cross-conjugated adduct **6**, the formation of which was rationalized with the intermediacy of the spin-delocalized anilino radical **5** (Scheme 2).[5]



4 **5** **6**

7 **8** **9**

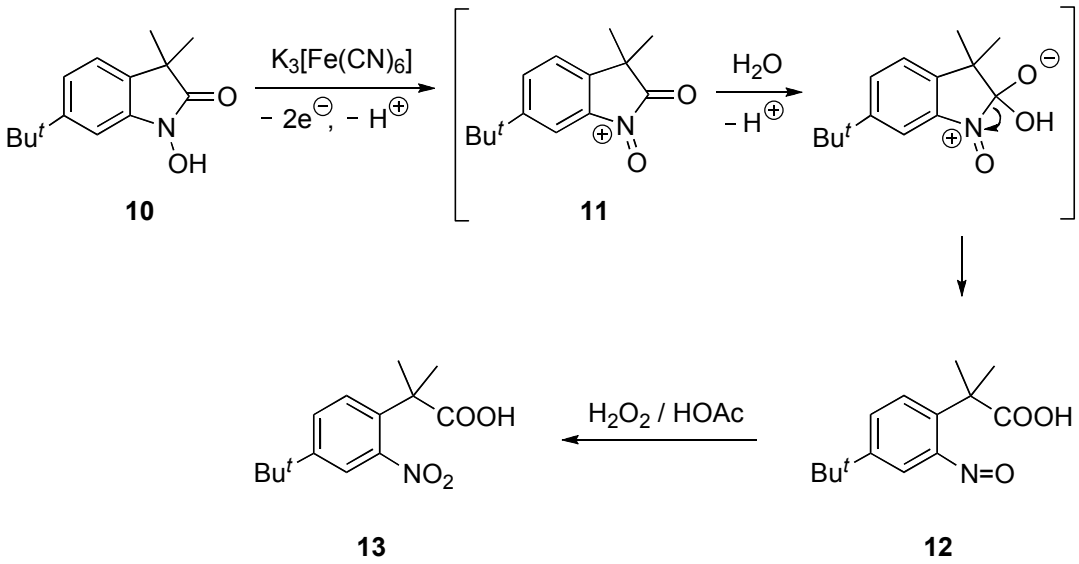
Scheme 2

A slightly less hindered nitrosobenzene, namely 2,4-di-*t*-butyl-6-methylnitrosobenzene **7**,[4] shows a partitioning (1:3.6) between the 'normal' N,O-addition (generating product **8**) and an 'abnormal' addition (generating a 2,4-cyclohexadieneimine **9**) when subjected to *t*-butyl radicals generated by the photolysis of 2,2'-dimethyl-2,2'-azopropane.[6]

Other authors had earlier shown that *tertiary* alkyl radicals attack the nitroso group of **4** exclusively at the oxygen atom, whereas *primary* alkyl radicals attack the N atom giving exclusively nitroxides, and *secondary* radicals followed both options.[7] Thus, both the nitroso compound and the nature of the radicals influence the course of radical additions to nitrosoarenes. The above mentioned findings are of relevance to the use of nitrosoarenes in general[8,9] and especially of **4**[10,11] as spin traps.

Results and Discussion

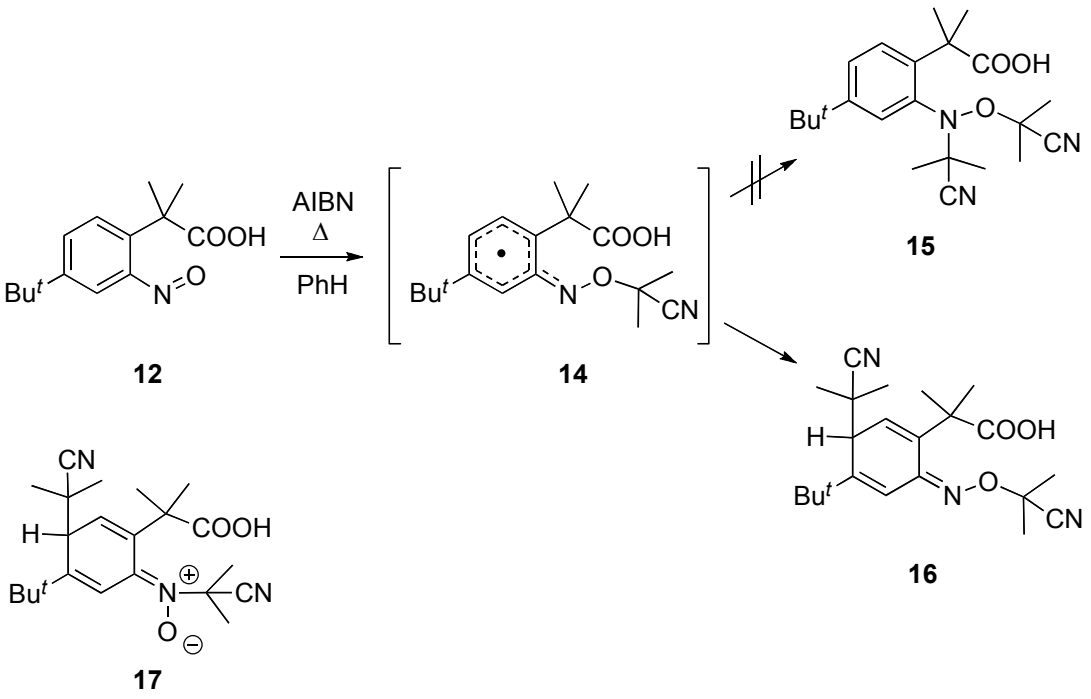
We have earlier reported on a convenient photochemical access to 1-hydroxyindolin-2-ones, among them compound **10**.[12] During the investigation of its reactions it was found that **10** could readily be transformed into the title compound **12** in 72% yield by treatment with a slight excess of potassium hexacyanoferrate(III) in alkaline solution followed by hydrolytic ring opening of the presumed oxoammonium intermediate[8a,13] **11** (Scheme 3).



Scheme 3

Compound **12** was characterized by its ready oxidation to the corresponding nitro compound **13** (80%) and spectroscopically (i) by its long wavelength absorption at λ_{max} = 770 nm (log ε = 1.5) in methanol, and (ii) by its ^{1}H NMR spectrum: due to the diamagnetic anisotropy of the nitroso group[14] the proton vicinal to that group (3'-H) gives rise to a signal at δ = 6.15 ppm in $CDCl_3$ solution similar to δ = 5.85 ppm (3'-H, in $CDCl_3$) reported earlier[14] for compound **2**. ^{1}H Chemical shifts in nitrosobenzenes are conformation-dependent: upfield shifts (compared to the parent compounds not bearing the nitroso group) are expected for protons or groups *syn* to the nitroso oxygen atom and shifts to lower field for protons or groups *anti* to the oxygen atom with the preferred coplanar arrangement of the N=O bond and the benzenoid ring.[14] The δ value for 3'-H in **12** (6.15 ppm) is 0.3 ppm to lower field compared to the corresponding value (5.85 ppm) for compound **2**, which may be interpreted by a slight deviation from coplanarity of the benzenoid ring and the N=O bond.

Compound **12** can be regarded as a water-soluble analogue of **2**. The carboxyl group might serve as an anchor to hook this potential spin trap to a substrate. We therefore wanted to test compound **12** in the addition reactions of 2-cyanoprop-2-yl radicals. When AIBN was thermolyzed in a benzene solution of **12** at reflux temperature for 30 minutes, to our surprise the sole product formed was not the trisubstituted hydroxylamine **15** (analogous to **3)** but an 'abnormal' product **16** (31%) presumably via the delocalized aminyl radical **14** (Scheme 4).



Scheme 4

The six-membered ring in **16** clearly is not benzenoid, since in the ^{1}H NMR spectrum the AB subsystem originally present in **12** [δ_A = 7.74 (5'-H), δ_B = 7.67 ppm (6'-H), $^3J_{AB}$ = 8.3 Hz] has been replaced by an AX system [δ_A = 6.20 (3'-H), δ_X = 3.69 ppm (4'-H), $^3J_{AX}$ = 5.8 Hz], thus the second CMe_2CN radical must have been connected to C-4' and not to C-2'. Further, while the chemical shift of the geminal 2-Me_2 in **12** is 1.86 (6H), the corresponding signal for **16** is split (δ = 1.48 and 1.49 for 3H each) which points to the presence of a distant chiral center (C-4'). An analogous splitting for 2-Me_2 is observed in the ^{13}C NMR spectrum of **16**. In the mass spectrum of **16** there is no indication of fragmentation of an O-atom from the molecular ion, which renders structure **17** highly unlikely in accord with the finding that only small and primary radicals are prone to be added at the nitrosoarene N atom.[7]

Conclusions

In contrast to the N,O-bis-addition of 2-cyanoprop-2-yl radicals to 1,4-di-*t*-butyl-2-nitrosobenzene **2**, replacement of one methyl group in the *ortho*-*t*-butyl group as in **12** by carboxyl severely enhances the steric encumbrance of the nitroso group and thereby drives the bis-addition of the teriary radicals CMe_2CN completely into the 'abnormal' mode. Whether this behaviour is (at least in part) due to the suspected non-coplanarity of the N=O bond and the benzenoid ring, or whether intramolecular OH···N hydrogen bonding impedes the normal addition, cannot be ascertained at present.

Experimental Section

General Procedures. Melting points were determined using a Kofler hot stage microscope "Reichert Thermovar". Elemental analyses were determined on a Carlo Erba model 1106 Elemental Analyzer. For EI mass spectra, an AMD 605 instrument was used in connection with a direct inlet system (inlet temperature given). IR spectra were recorded on a Perkin Elmer 285 instrument using KBr pellets. A Bruker WM 300 NMR spectrometer operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C was used on $CDCl_3$ solutions containing TMS as an internal standard.

2-(4-*t*-Butyl-2-nitrosophenyl)-2-methylpropanoic acid (12). A sample of 10.1 g (43 mmol) of 6-*t*-butyl-1-hydroxy-3,3-dimethylindolin-2-one[12] **10** was dissolved with gentle warming in 400 mL of 0.2 M aqueous NaOH. The mixture was then diluted with water to 1000 mL, a solution of 34.00 g (103 mmol) of potassium hexacyanoferrate(III) in 500 mL of 0.2 M NaOH was added all at once and the mixture was stirred at room temperature for 2 h. The resultant olive-green mixture was filtered. The filtrate was washed with diethyl ether (3 x 300 mL) to remove any neutral byproducts and acidified to pH 4-5 with dilute sulfuric acid. The green precipitate formed on standing for 24 h was collected by suction filtration to give 7.72 g (72%) of emerald-green crystals, mp 159 °C (with decomp., from ethyl acetate/cyclohexane); UV/Vis (methanol): λ_{max} (log ε) = 294 (3.87), 317 (3.86), 770 nm (1.50); IR: ν = 3300-2350 (COOH), 2965, 2870, 1710 (C=O), 1486, 1470, 1361, 1295, 1282, 1241, 1183, 1171, 1143, 1112 cm^{-1}; ^{1}H NMR: δ = 1.25 (s, 9H, *t*-Bu), 1.86 (s, 6H, Me_2), ABX [δ_A = 7.74 (5'-H), δ_B = 7.67 (6'-H), δ_X = 6.15 (3'-H), $^{3}J_{AB}$ = 8.3 Hz, $|^{4}J_{AX}|$ = 2.1 Hz, $^{5}J_{BX}$ ~ 0 Hz], 10.8 (broad, COOH); ^{13}C NMR: δ = 28.6 (C*Me*$_2$), 31.0 (C*Me*$_3$), 34.6 (*C*Me$_3$), 45.9 (C-2), 102.6 (C-5'), 126.7 (C-6'), 133.2 (C-3'), 146.0 (C-4'), 150.2 (C-1'), 161.2 (C-2'), 184.0 (COOH); MS (122 °C): *m*/*z* (%) = 249 (13) [M^+], 204 (20) [M^+ - COOH], 163 (17) [M^+ - NO - H_2C=CMe_2], 148 (14), 57 (100).- Calcd. for $C_{14}H_{19}NO_3$ (249.31): C, 67.45; H, 7.68; N, 5.62% Found: C, 67.35; H, 7.66; N, 5.64%

2-(4-*t*-Butyl-2-nitrophenyl)-2-methylpropanoic acid (13). To a solution of 5.008 g (20.1 mmol) of **12** in 500 mL of glacial acetic acid, 5 mL of hydrogen peroxide solution (32%) were added, and the mixture was stirred at 80 °C for 24 hrs. After tlc indicated the complete conversion of **12,** the mixture was concentrated to a few mL and left at room temperature for 2 days. Thus, acid **13** was obtained as a total of 4.249 g (80%) of pale yellow crystals, mp 235 °C (with decomp., from acetic acid/cyclohexane); UV (methanol): λ_{max} (log ε) = 430-420 (shoulder, 1.1), 261 (3.55), 218 nm (4.00); IR: ν = 2969, 2874, 2400-3200 (COOH), 1696 (COOH), 1530 and 1385 (NO_2) cm^{-1}; ^{1}H NMR: δ = 1.29 (s, 9H, *t*-Bu), 1.55 (s, 6H, Me_2), 7.64 (d, ^{3}J = 8.4 Hz, 6'-H), 7.72 (dd, ^{3}J = 8.4 Hz, ^{4}J = 2.2 Hz, 5'-H), 7.82 (d, ^{4}J = 2.2 Hz, 3'-H), 12.45 (broad, 1H, COOH); ^{13}C NMR: δ = 27.5 (C*Me*$_2$), 30.8 (C*Me*$_3$), 34.6 (*C*Me$_3$), 45.6 (C-2), 121.8 (C-3'), 128.6 (C-5'), 130.5 (C-6'), 136.3 (C-1'), 148.7 (C-2'), 150.9 (C-4'), 176.6 (COOH); MS (120 °C): *m*/*z* (%) = 265 (0.4) [M^+], 250 (4) [M^+ - 15], 221 (6) [M^+ - CO_2], 220 (15) [M^+ - COOH], 219 (39)

[M^+ - NO_2], 163 (23), 57 (100); Anal. Calcd. for $C_{14}H_{19}NO_4$ (265.31): C, 63.38; H, 7.22; N, 5.28% Found: C, 63.40; H, 7.18; N, 5.31%

2-[5-*t*-Butyl-1-(1-cyano-1-methylethoxy)imino-4-(1-cyano-1-methylethyl)cyclohexa-2,5-dien-2-yl]-2-methylpropanoic acid (16). A solution of 927 mg (3.7 mmol) of compound **9** and 1427 mg (8.7 mmol) of AIBN in 20 mL of benzene was maintained at reflux temperature for 30 min then extracted with 40 mL of 0.2 M NaOH. To effect complete phase separation, the mixture was centrifuged for 35 min at 3250 r.p.m. The alkaline phase was washed with ether (20 mL), and acidified with 0.1 M H_2SO_4 to pH ~ 3. After 12 h, 445 mg (31%) of colorless crystals, mp 162-163 °C were collected; IR: ν = 2992, 2973, 2942, 2876; 3300-2300 (COOH); 2229 (CN), 1710 (COOH) cm^{-1}; ^{1}H NMR: δ = 1.12 (s, 3H, 4'-C(CN)*Me*), 1.34 (s, 9H, *t*-Bu), 1.42 (s, 3H, 4'-C(CN)*Me*), 1.48 and 1.49 (2s, 3H each, 2-C*Me*$_2$), 1.65 and 1.68 (2s, 3H each, O-C*Me*$_2$CN), 3.69 (d, ^3J = 5.8 Hz, 4'-H), 6.20 (d, ^3J = 5.8 Hz, 3'-H), 6.90 (s, 1H, 6'-H), 10.0 (broad, 1H, COOH); ^{13}C NMR: δ = 21.7 and 24.7 (2-*Me*$_2$), 25.7 and 25.9 (4'-C*Me*$_2$CN), 26.0 and 27.6 (O-C*Me*$_2$CN), 31.4 (C*Me*$_3$), 36.4 (*C*Me$_3$), 37.1 (4'-*C*Me$_2$CN), 44.2 (C-2), 44.5 (C-4'), 47.5 (O-*C*Me$_2$CN), 118.0 (C-3'), 121.0 (4'-CMe$_2$*C*N), 126.1 (OCMe$_2$*C*N), 129.4 (C-6'), 140.7 (C-5'), 148.8 (C-2'), 158.3 (C-1'), 181.6 (COOH); MS (155 °C): *m*/*z* (%) = 385 (0.5) [M^+], 367 (0.4) [M^+ - 18], 318 (13) [M^+ - H_2C=CMeCN], 317 (49) [M^+ - CMe_2CN], 300 (16) [317 - OH], 250 (42) [318 - CMe_2CN or 317 - H_2C=CMeCN], 233 (31), 232 (100) [300 - CMe_2CN], 205 (21) [250 - COOH], 204 (91), 202 (16), 190 (18), 176 (26); Anal.: Calcd. for $C_{22}H_{31}N_3O_3$ (385.51): C, 68.28; H, 8.07; N, 10.81% Found: C, 68.54; H, 8.10; N, 10.90%

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