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Grignard Reagent-Mediated Conversion of an Acyl Nitroso-anthracene Cycloadduct to a Nitrone

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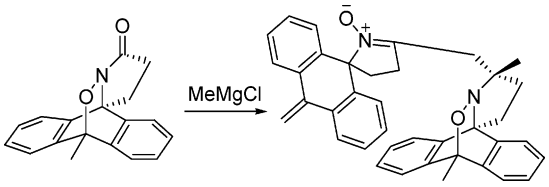

An intramolecular hetero-Diels−Alder cycloadduct of an acyl nitroso compound and a 9,10-dimethyl anthracene derivative was prepared as a potential nitroxyl (HNO) donor. This compound did not release HNO under any of the conditions tested. Treatment of this cycloadduct with excess MeMgCl resulted in the formation of a nitrone, whose structure was confirmed by X-ray crystallography. A mechanism where MeMgCl acts as a nucleophile, strong base, and Lewis acid possibly explains the formation of this product.

The cycloadducts of acyl nitroso compounds and 9,10-dimethylanthracene (**1**, Scheme 1) undergo thermal decomposition through retro-Diels−Alder reactions to produce acyl nitroso compounds (**2**, Scheme 1) under nonoxidative conditions and relatively mild temperatures (40−100 °C).[1−4] Decomposition of these compounds provides a particularly clean method for the formation of acyl nitroso compounds, which are highly reactive N−O heterodienophiles. Acyl nitroso compounds also hydrolyze to release nitroxyl (HNO), the one-electron reduced form of the biologically important messenger molecule, nitric oxide (NO).[5−9] Nitroxyl has drawn considerable recent interest as it demonstrates distinct biological effects to NO in various systems.[10,11] Such activities and the inherent chemical instability of HNO also have focused efforts on the development of chemically and mechanistically unique nitroxyl releasing systems.

Our recent studies show HNO release from functionalized *N*-hydroxyurea-derived acyl nitroso-9,10-dimethylanthracene cycloadducts (**1**, R = -NHR) through the pathway depicted in Scheme 1.[12,13] Generation of an equivalent of the water-insoluble and immunotoxic 9,10-dimethylanthracene (**3**, 9,10-DMA) in this sequence remains a major limitation of this method of HNO formation.[14] The introduction of functional groups that act as hydrogen-bond donors or acceptors on the 9,10-DMA portion of these molecules should increase water solubility and reduce toxicity.[15] Compound **4**, the product of an intramolecular hetero-Diels−Alder reaction of acyl nitroso compound (**5**), fulfills this requirement by producing the carboxylic acid (**6**) after retro-Diels−Alder reaction and hydrolysis (Scheme 1). We wish to report the preparation of **4**, its ability to act as an HNO donor, and a unique molecular rearrangement upon treatment with an excess amount of Grignard reagent.

Scheme 2 depicts the synthesis of the target compound **4**. Horner−Wadsworth−Emmons olefination of commercially available 10-methylanthracene-9-carboxaldehyde (**7**) yields a mixture of the α,β-unsaturated esters **8** and **9** (**8**:**9** = 5.8:1, 92% overall yield, Scheme 2). Reduction of **8** and **9** proved difficult with $NaBH_4/NiCl_2$ and hydrogenation on Pd/C yielding mixtures as a result of the concurrent reduction of the anthracene moiety.[16,17] However, $Pd(OAc)_2/HCO_2K$ in DMF at 50 °C selectively reduces **8** and **9** to **10** in quantitative yield.[18] Condensation of **10** with NH_2OH hydrochloride/KOH gives hydroxamic acid (**11**) in 85% yield at −10 °C.[19] Tetra-*n*-butylammonium periodate oxidation of **11** at 0 °C produces **4** through an intramolecular Diels−Alder reaction of the highly reactive acyl nitroso compound intermediate (**5**, Scheme 2).[19,20] The structure of **4** was assigned unambiguously by single-crystal X-ray diffraction analysis (Supporting Information).

The preparation of **4** allows the investigation of the ability of this compound to release HNO through thermal decomposition. Identification of nitrous oxide (N_2O), the dimerization and dehydration product of HNO, provides strong evidence for the intermediacy of HNO.[21] Gas chromatographic headspace analysis of the thermal decomposition of **4** in a 1:1 mixture of water−acetonitrile at 40 °C fails to detect the formation of any N_2O,

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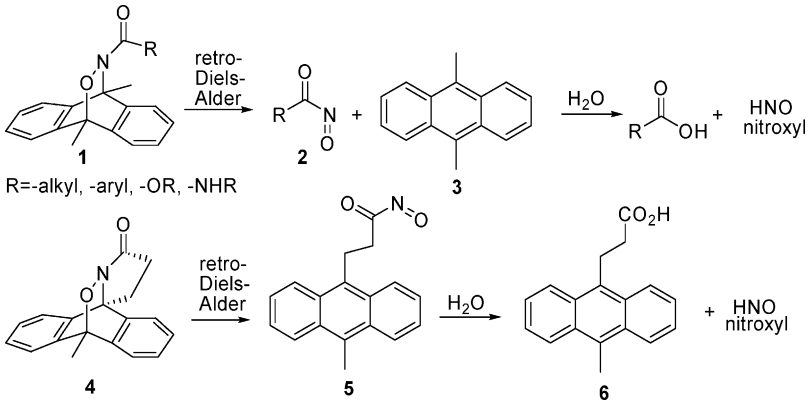
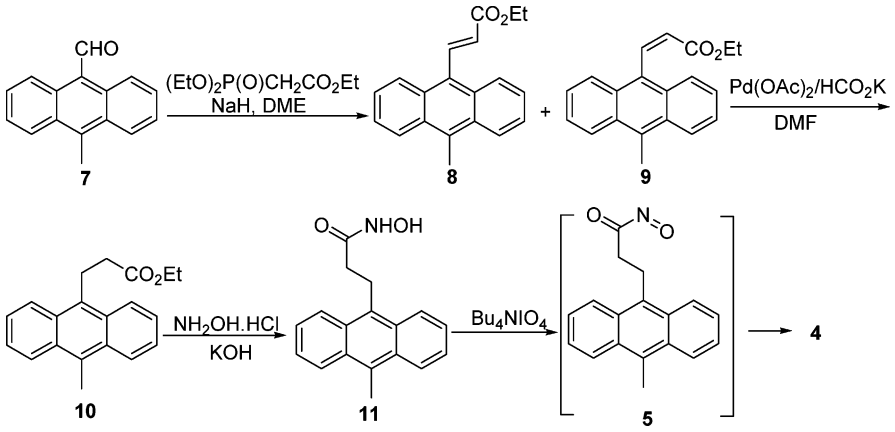
SCHEME 1



SCHEME 2



as a measure of HNO. TLC and NMR analysis shows only **4** in the reaction mixture. Similar reactions at higher temperatures (60, 80, and 100 °C) also fail to generate N_2O, indicating the stability of **4**. Treatment of **4** with NaOH (1.0 N) at 80 °C for 10 h partially converts **4** to **6** in 11% yield, but no N_2O was detected. While cycloadducts of acyl nitroso compounds derived from hydroxamic acids generally show greater stability than those derived from *N*-hydroxyureas, such cycloadducts should decompose at these temperatures.[1−4] These results highlight the preference for the intramolecular cycloadduct (**4**) over the acyl nitroso compound (**5**) in this system. The failure of **4** to release HNO under these conditions prompted further structural elaboration.

Cycloadducts similar to **4** have been recognized as bicyclic forms of Weinreb amides.[22] Previous work shows that the addition of Grignard reagents to 1,3-cyclopentadiene-acyl nitroso compound-derived cycloadducts in the presence of catalytic copper salts results in regiospecific ring opening of the bicyclic system (and not attack at the amide with ketone formation).[26] However, such reactions with 9,10-DMA-acyl nitroso cycloadducts have not been reported, and we wished to explore the possibility of Grignard reagent (MeMgCl) attack of the carbonyl group to yield unique acyl nitroso-anthracene-derived cycloadducts as possible HNO donors. Such a reaction would yield a ketone (**12**) that in the presence of excess Grignard reagent would further react to give an alcohol (**13**, Scheme 3). Both **12** and **13** meet the previously mentioned requirements of potentially improved HNO donors that would release functionalized versions of 9,10-DMA upon retro-Diels−Alder decomposition. Treatment of **4** with 1 or 2 equiv of MeMgCl yields a complex mixture of products by TLC. Surprisingly, treatment of **4** with excess MeMgCl gives a solid product that single-crystal X-ray diffraction studies reveal as the nitrone (**14**, Scheme 3) in 76% yield. In addition to the unambiguous X-ray diffraction analysis (Figure 1), the structure of **14** is supported by both ^{1}H and ^{13}C NMR (including DEPT experiments that show six CH_2 groups (δ 20.49, 30.42, 36.42, 37.34, 40.27, 110.80 ppm)), elemental analysis, and mass spectrometry (Supporting Information).

The structure of **14** appears to be a combination of two anthracene-derived cycloadducts with the addition of two methyl groups. The exocyclic double bond of the anthracene moiety depicted in the left part of the molecule (Figure 1) may arise

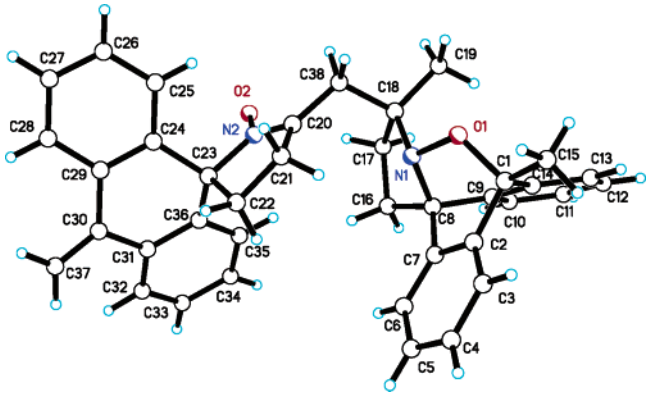


FIGURE 1. X-ray crystallographic structure of **14**.

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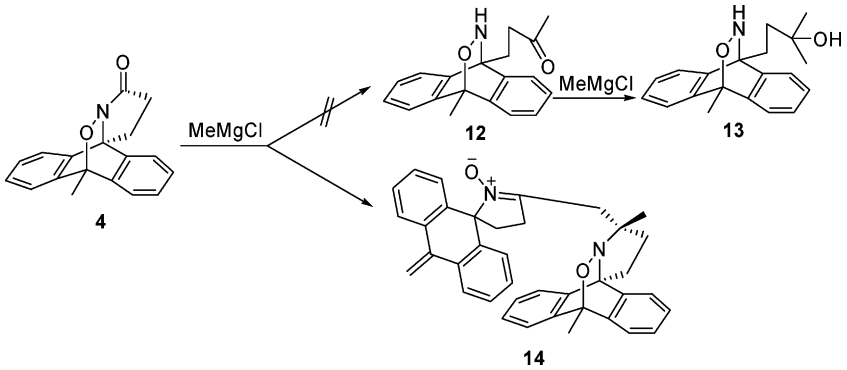
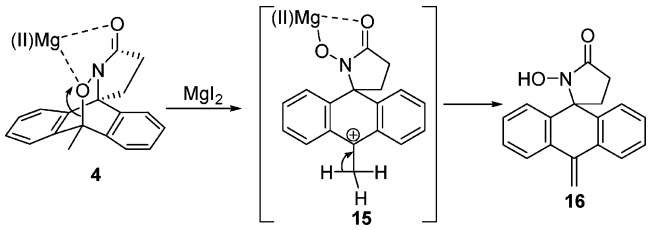
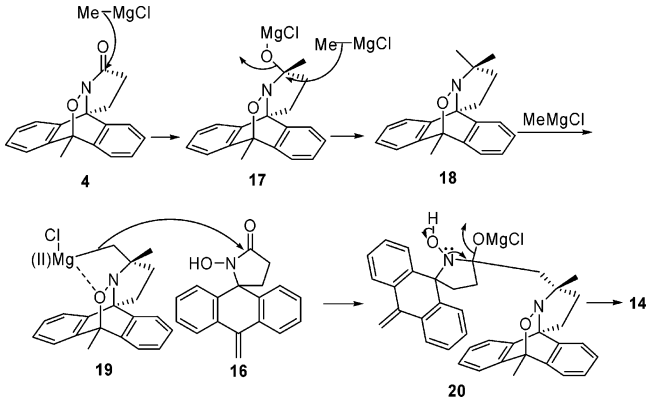
SCHEME 3



SCHEME 4



SCHEME 5



from a Mg (II)-mediated ring opening of **4**. To confirm this idea, treatment of **4** with MgI_2 (prepared from I_2 and Mg in ether) yields a red solution that was purified by flash chromatography on silica gel to give hydroxamic acid (**16**, Scheme 4) as a white solid in a quantitative yield. The red color may reflect a complex of **16** with Mg (II) or possibly small amounts of the nitroxide radical of **16**. The formation of the intermediate carbocation **15**, stabilized by two phenyl groups, likely represents the driving force for this skeletal rearrangement of **4**.[23−26]

While the crystallographic studies confirm the structure of **14**, a mechanism for its formation remains unclear. Scheme 5 depicts a possible pathway that combines nucleophilic attack of MeMgCl on the carbonyl group of **4** with Mg (II)-mediated ring opening of **4** to **16**. Initial nucleophilic attack of the carbonyl group of **4** by MeMgCl would yield **17** that may be susceptible to a second attack by MeMgCl (possibly through an iminium ion-like intermediate) to give **18**. Simultaneously, Mg (II)-mediated opening of **4** would yield **16** as supported by the previously described reactions with MgI_2. Reaction of **18** with a third equivalent of MeMgCl acting as a base could produce a new Grignard species (**19**, Scheme 5) that could condense with **16** to give intermediate (**20**, Scheme 5). Final loss of −-OMgCl (or water) from **20** would yield **14**. This mechanism suggests three roles for MeMgCl: (1) carbon nucleophile, (2) strong base, and (3) Lewis acid. The formation of the new Grignard species **19** may be facilitated by coordination of Mg (II) to oxygen to form a five-membered ring (Scheme 5).

In summary, compound **4**, the product of an intramolecular hetero-Diels−Alder reaction of an acyl nitroso compound and a 9,10-dimethyl anthracene derivative, was prepared using straightforward synthetic schemes. However, **4** did not undergo facile retro-Diels−Alder decomposition and did not act as an HNO donor under any of the conditions tested. Treatment of **4** with excess MeMgCl resulted in the formation of a unique nitrone (**14**), whose structure has been unambiguously confirmed by X-ray crystallography. Tentatively, a mechanism in which the Grignard reagent acts as a nucleophile, strong base, and Lewis acid has been forwarded as a possible explanation for the formation of this unusual product.

Experimental Section

9-[2′-(Ethoxycarbonyl)vinyl]-10-methylanthracenes (8 and 9). A solution of triethyl phosphonoacetate (12 g, 53.6 mmol) in DME (12 mL) was added dropwise to a stirred suspension of NaH (1.32 g, 55.0 mmol) in dry DME (40 mL) at 0 °C. After stirring at room temperature for 2 h, 10-methylanthracene-9-carboxaldehyde (2.5 g, 11.4 mmol) was added in one portion, and the reaction mixture was stirred at 50 °C for 4 h. After cooling, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography on silica gel (gradient: 3−10% ethyl acetate in hexane) to give a mixture (5.8:1) of esters **8** and **9** (3.04 g, 92%) as a yellow solid. **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 16.2 Hz, 1H), 8.23−8.56 (m, 4H), 7.47−7.58 (m, 4H), 6.38 (d, J = 16.2 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 3.11 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H).

9-[2′-(Ethoxycarbonyl)ethyl]-10-methylanthracene (10). A mixture of **8** and **9** (0.77 g, 2.65 mmol), HCO_2K (4.2 g, 50 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol), and DMF (10 mL) was stirred in a sealed glass tube under argon at 50 °C for 18 h. After cooling, the reaction mixture was diluted with ethyl acetate and filtered through Celite, which was washed with additional ethyl acetate. This organic filtrate was washed with water and brine, and the

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organic phase was dried over Na_2SO_4. After concentration, water was added to this DMF-contaminated residue to give a solid, which was filtered and dried to afford **10** (0.76 g, 98%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28−8.38 (m, 4H), 7.48−7.58 (m, 4H), 4.21 (q, J = 7.2 Hz, 2H), 3.97 (t, J = 8.5 Hz, 2H), 3.11 (s, 3H), 2.78 (t, J = 8.3 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H).

***N*-Hydroxy-3-(10-methylanthracen-9-yl)propanamide (11).** A solution of KOH (4.31 g, 77.0 mmol) in MeOH (15 mL) was added dropwise to a solution of hydroxylamine hydrochloride (2.67 g, 38.4 mmol) in MeOH (10 mL) at −10 °C, and the mixture was stirred for 30 min. A solution of **10** (1.12 g, 3.84 mmol) in MeOH (5 mL) was added dropwise, and this white suspension was stirred overnight at −10 °C. At this time, water was added to the mixture, and the pH was adjusted to 6 with concentrated HCl. The mixture was extracted with ethyl acetate, and the extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by flash chromatography on silica gel (gradient: 2−10% MeOH in CH_2Cl_2) to afford **11** (0.91 g, 85%) as a pale yellow powder. mp 112.0−115.0 °C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$) δ 10.54 (s, 1H), 8.82 (s, 1H), 8.31−8.43 (m, 4H), 7.52−7.63 (m, 4H), 3.82 (t, J = 8.1 Hz, 2H), 3.05 (s, 3H), 2.40 (t, J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$) δ 168.3, 131.5, 129.5, 129.0, 128.7, 125.49, 125.46, 125.0, 124.6, 34.0, 23.6, 13.9. ESIMS m/z 278 ($M^+ - 1$, 100%). Anal. Calcd for $C_{18}H_{17}NO_2 \cdot 0.5H_2O$: C, 75.00; H, 6.25; N, 4.86. Found: C, 74.67; H, 6.19; N, 4.66.

Cycloadduct (4). A solution of **11** (0.4 g, 1.43 mmol) in MeOH/CH_2Cl_2/H_2O (1:1:0.1, 21 mL) was added to a solution of tetra-*n*-butylammonium periodate (1.24 g, 2.86 mmol) in MeOH/CH_2Cl_2 (1:2, 15 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, quenched with saturated aqueous $Na_2S_2O_3$, and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography on silica gel (gradient: 40−70% ethyl acetate in hexane) to give **4** (0.4 g, 100%) as colorless needles. mp 202.0−204.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.46 (m, 2H), 7.26−7.36 (m, 6H), 2.99 (t, J = 8.1 Hz, 2H), 2.65 (t, J = 8.1 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 140.7, 139.5, 127.8, 127.7, 121.9, 119.7, 82.4, 65.4, 28.6, 17.4, 14.7. ESIMS m/z 278 ($M^+ + 1$, 100%). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.05. Found: C, 78.04; H, 5.44; N, 5.04.

Compound (14). A solution of MeMgCl (10 mL of a 3.0 M solution in ether, 30 mmol) was added to a stirred solution of **4** (138 mg, 0.5 mmol) in dry THF (20 mL) at −78 °C. After being stirred for 30 min at −78 °C, the solution was warmed to 0 °C and stirred overnight. At this time, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography on silica gel (gradient: 50% ethyl acetate in hexane to 100% ethyl acetate) to give **14** (105 mg, 76%) as a white powder. Evaporative recrystallization from ethyl acetate/hexane provided crystals suitable for X-ray analysis. mp 175.0−177.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.78 (m, 2H), 7.16−7.41 (m, 14H), 5.74 (s, 2H), 2.58−2.98 (m, 7H), 2.21−2.34 (m, 1H), 2.05−2.19 (m, 5H), δ 0.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 143.6, 141.9, 140.4, 136.1, 136.0, 134.0, 134.0, 128.4, 127.6, 127.1, 126.9, 126.6, 126.4, 124.5, 124.3, 121.5, 121.2, 120.2, 119.6, 110.8, 81.5, 69.1, 65.3, 40.3, 37.3, 36.4, 30.4, 23.9, 20.5, 15.3. ESIMS m/z 573 (M^+ + Na, 100%). Anal. Calcd for $C_{38}H_{34}N_2O_2$: C, 82.91; H, 6.18; N, 5.09. Found: C, 82.83; H, 6.23; N, 4.96.

Compound (16). A mixture of I_2 (0.25 g, 1 mmol) and Mg (small turnings, 0.24 g, 10 mmol) in dry ether (20 mL) was stirred at room temperature for 4 h, and the excess Mg was removed by filtration to give a colorless solution of MgI_2. This solution of MgI_2 (1 mmol) was added to a stirred solution of **4** (138 mg, 0.5 mmol) in dry THF (20 mL) at −78 °C. After 30 min, the solution was allowed to warm to 0 °C and stirred for 4 h to give a red solution. The reaction mixture was washed with saturated aqueous $Na_2S_2O_3$ and extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography on silica gel (gradient: 2−10% MeOH in CH_2Cl_2) to give **16** (136 mg, 98%) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.34 (br s, 1H), 7.75−7.81 (m, 2H), 7.33−7.54 (m, 6H), 5.77 (s, 2H), 2.56 (t, J = 8.1 Hz, 2H), 2.16 (t, J = 8.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 140.5, 136.6, 134.4, 128.4, 127.7, 124.7, 123.7, 110.9, 68.7, 35.3, 26.1. ESIMS m/z 278 ($M^+ + 1$, 100%). Anal. Calcd for $C_{18}H_{15}NO_2 \cdot H_2O$: C, 73.22; H, 5.76; N, 4.75. Found: C, 73.02; H, 5.95; N, 4.83.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the synthetic intermediates and final products and structures of **4** and **14** (CIF). This material is free of charge via the Internet at http://pubs.acs.org.

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