Facile, high-yield, regioselective synthesis of *ortho*-nitro derivatives of hydroxy heterocycles using cerium (IV) ammonium nitrate

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Abstract

A series of hydroxy heterocycles with two different unsubstituted *ortho* sites undergo exclusive regioselective nitration with the CAN/$NaHCO_3$ reagent at the less hindered *ortho* site. Neither dinitro nor oxidized products were observed. The hydroxy heterocycles studied include: some derivatives of 7-hydroxycoumarins, sesamol, 2,3-dihydrobenzo[*b*]furan-3-one, 6-hydroxy-1,3-benzoxathiol, 5-hydroxybenzothiazol, 5-hydroxyindole, 7-benzofuranol, and (5-isoxazolyl)phenols. A mechanism is proposed in which an initial oxidation of the phenol to a radical cation by CAN occurs. Another molecule of CAN subsequently reacts with the phenolic radical cation to give an radical adduct from which an NO_2 radical is transferred to the less hindered carbon *via* a tight ion-radical pair yielding the Wheland complex that furnishes the nitrophenol after proton loss.

Keywords: Nitration, cerium (IV) ammonium nitrate, regioselective, *ortho* addition

Introduction

We[1] recently reported that certain phenols possessing at least one unsubstituted *ortho* position underwent rapid, regioselective *ortho* nitration with CAN (cerium (IV) ammonium nitrate) in the presence of $NaHCO_3$ at room temperature to yield *o*-nitrophenols in high yields. Substituents tolerating these nitration conditions ranged from the ring activating methoxy and methyl groups to the moderately ring-deactivating Cl, Br, CHO and CO_2Me groups. In contrast, phenols which contained a strongly deactivating group such as nitro, cyano or 2,6-disubstituted phenols were not nitrated by the CAN/$NaHCO_3$ reagent. We have extended this reaction to include several hydroxy heterocycles (**1a—k**) and report the results herein.

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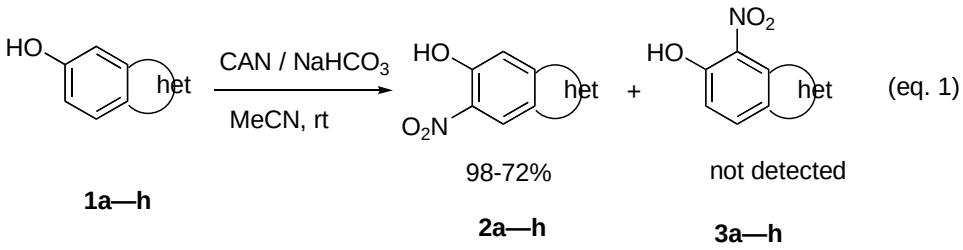
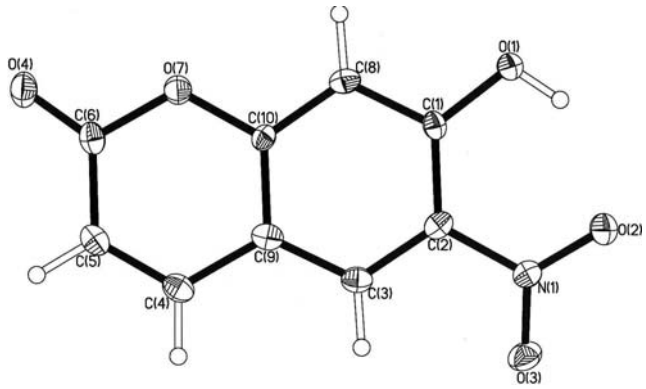
Results and Discussion

We first studied the hydroxy compounds (**1a—h**) which, in principle, can give two different *ortho* nitration products, namely compounds (**2a—h**), in which substitution of H by NO_2 occurs at the less hindered carbon and compounds, and (**3a—h**) in which substitution of H by NO_2 occurs at the more hindered carbon.



As shown in eq. 1, nitration occurred, in all cases, regioselectively at the less hindered position to give **2a—h** in yields ranging from 98-72%. The regiochemistry was confirmed by ^{1}H NMR spectroscopy (the two *para* hydrogens appear as two slightly broadened singlets) and, in the case of **2a**, by X-ray crystallographic analysis. An ORTEP drawing of **2a** is shown below.



ORTEP Compound (**2a**)

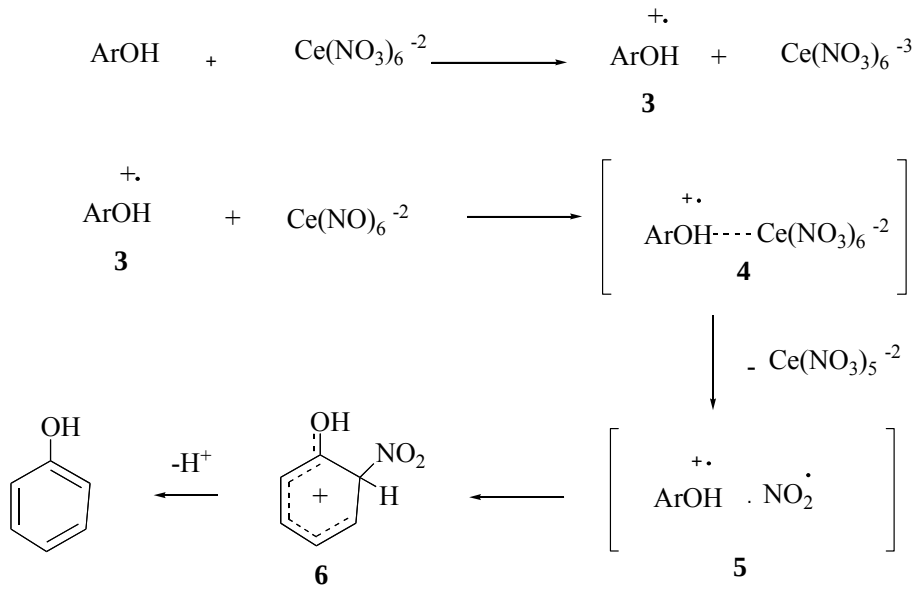
A few of the nitro compounds listed in Table 1 had been prepared previously using other nitrating reagents. However, these were obtained in lower yields and as mixtures of mono-nitro and/or dinitro- compounds. For example, as shown in Table 1, 6-hydroxycoumarin (**1a**) was nitrated regioselectively using CAN/$NaHCO_3$ to give 6-hydroxy-7-nitrocoumarin (**2a)** in 84% yield; no other positional isomers or dinitrated products were detected. On the other hand, the use of CAN in acetic acid gave both **2a** and 8-nitro-6-nitrocoumarin in 68% and 18% yields, respectively.[2] The nitration of **1a** using chromium nitrate gave nearly equal amounts of the aforementioned isomers.[3] Recently, Wu *et al.*[4] found that nitration of **1a** with NO/O_2 gave **2a** in

only 63% yield as well as 7-hydroxy-3-nitro- and 7-hydroxy-8-nitrocourmarin in 20% and 5%, respectively.

Interestingly the 6-nitro-3-cyanocoumarin derivative (**2f**) in which the cyano group is not on the phenolic ring was obtained by CAN/$NaHCO_3$ nitration of the corresponding 3-cyanocoumarin derivative (**1f**). We showed previously that phenols possessing a cyano group such as 3-cyanophenol did not undergo nitration with this reagent.[1]

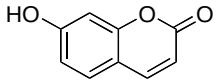
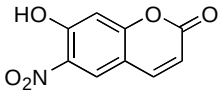
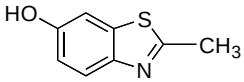
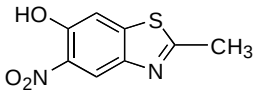
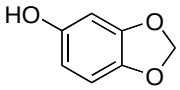
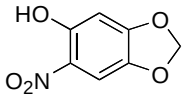
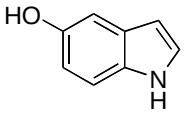
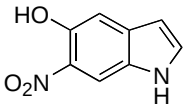
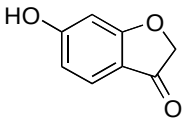
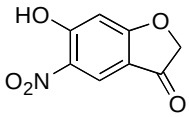
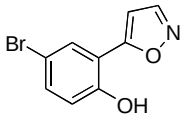
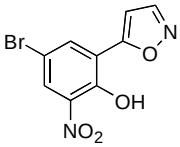
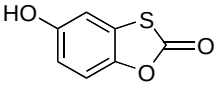
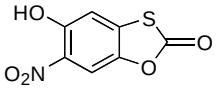
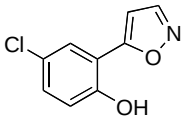
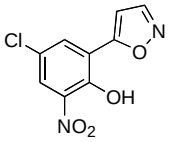
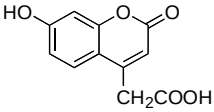
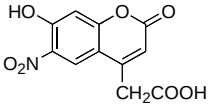
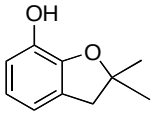
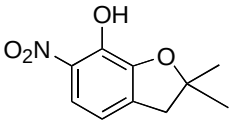
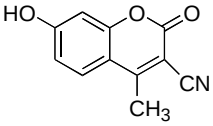
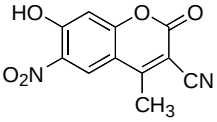
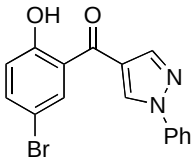
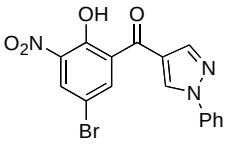
The generality of the regioselective CAN/$NaHCO_3$ nitration at the less hindered *ortho* site of hydroxy heterocycles with two different *ortho* sites prompted us to reinvestigate our previous finding that nitration of 3-bromophenol occurred at the more hindered site to give 3-bromo-2-nitrophenol.[1] The result of our reinvestigation showed that assignment to be incorrect; CAN/$NaHCO_3$ nitration does indeed occur at the less hindered site affording 3-bromo-4-nitrophenol.

The results from this study are consistent with an elegantly conceived oxidative mechanism of nitration proposed by Ganguly *et al.*[5] for the CAN regioselective *ortho* nitration of coumarins. Accordingly, an electron-rich phenol react with $Ce(NO_2)_6^{-2}$ to give a phenolic radical cation species **3** by one-electron transfer. In this process $Ce(NO_2)_6^{-2}$ is reduced to $Ce(NO_2)^{-3}$ (the ammonium ion have been omitted for simplicity). A second molecule of $Ce(NO_2)_6^{-2}$ then forms a complex with **3** from which a NO_2 radical is transferred *via* a tight ion radical pair **5** yielding the Wheland complex (**6**) that furnishes the nitrophenol after proton loss. It is not clear what the exact nature of complex, but there probably is some type of interaction between the Ce and O atoms to account for the observed *ortho* regioselectivity. This mechanism is shown in Scheme 1.



Scheme 1

Table 1. Yields of hydroxy nitro heterocycles (**2a-n)**

Hydroxy heterocycle	Hydroxy nitro heterocycle	Yld, %	Hydroxy heterocycle	Hydroxy nitro heterocycle	Yld, %
 **1a**	 **2a**	82	 **1g**	 **2g**	86
 **1b**	 **2b**	98	 **1h**	 **2h**	74
 **1c**	 **2c**	92	 **1i**	 **2i**	91
 **1d**	 **2d**	94	 **1j**	 **2j**	89
 **1e**	 **2e**	79	 **1k**	 **2k**	94
 **1f**	 **2f**	84	 **1l**	 **2l**	66

We next studied the CAN/$NaHCO_3$ nitration of the hydroxy heterocycles **1i—l**. Our nterest in compounds **1i**, **j** and **l** was to confirm that a single *ortho* nitrated product is obtained and to see if the oxazole and pyrazol rings in these compounds could tolerate the CAN reagent. Compound **1k** was investigated to see if *ortho* nitration would prevail over *para* nitration. The data in Table 1 shows that these compounds gave the expected *ortho* nitrated product and that the two aforementioned rings did indeed tolerate the CAN/$NaHCO_3$ reagent.

In conclusion, we have shown that the CAN/$NaHCO_3$ reagent provides a facile way to introduce a single nitro group regioselectively to the *ortho* position of a wide range of hydroxy heterocycles. To our knowledge no other nitrating reagent can match this. It should become an important tool in organic synthesis.

Experimental Section

General procedures. Melting points were in open capillaries and are uncorrected. All reactions were carried out under an atmosphere of dry nitrogen. Hydroxy heterocycles (**1a—l**), CAN, and acetonitrile were purchased from commercial sources. The nitration reactions were monitored by GC/MS. Low-pressure chromatography was carried out by applying air pressure to Pyrex columns packed with silica gel 60 (0.040-0.063 mm particle size, 230-400 mesh). Routine ^{1}H NMR spectra were recorded on a FT NMR instrument at 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz.

General procedure for the synthesis of 7-hydroxy-6-nitrocoumarin (**2a**)
A sample of CAN (5.07g, 9.3 mmol) was added to a stirred mixture containing 1.0g (6.3 mmol) of appropriate 7-hydroxycoumarin (**1a**), $NaHCO_3$ (1.5g), and 30 ml of anhydrous MeCN at rt. The resulting mixture was stirred for 1h during which time the solution developed a yellow color. The mixture was filtered, washed with water, and extracted with $CHCl_3$ (3x20ml). The combined $CHCl_3$ extracts were dried (Na_2SO_4), and the solvent evaporated in vacuo to give 7-hydroxy-6-nitrocoumarin (**2a**). Prior to purification of **2a**, an aliquot was subjected to GC/MS analysis, which confirmed the absence of the 7-hydroxy-8-coumarin positional isomer or other dinitrated products. 7-Hydroxy-6-nitrocoumarin (**2a**) was purified by column chromatography using hexane-ethyl acetate (9:1) as eluent. Compounds **2b-l** were synthesized according this procedure, and their physical and spectral properties as well as those of **2a** are given below.
6-Hydroxy-7-nitrocoumarin (2a). Yellow needles ($CHCl_3$), mp: 225°C (lit.[4], 232°). ^{1}H NMR (400MHz, $CDCl_3$): δ 6.42 (d, *J* = 9.5Hz, 1H), 7.06 (s, 1H), 7.68 (d, *J* = 9.5Hz), 8.35 (s, 1H), 10.89 (s, OH); ^{13}C NMR (100MHz, $CDCl_3$): δ 105.9 (d), 112.0 (d), 115.0 (d), 127.2 (s), 135.0 (d), 144.3 (d), 155.9 (s), 158.1(s), 160.0 (s).
4,5-Methylenedioxy-2-nitrophenol (2-nitrosesamol) (2b). Yellow needles ($CHCl_3$), mp: 92-93°C (lit.,[8] 93-94 °C): ^{1}H NMR (400MHz, $CDCl_3$): δ 6.09 (s, OCH_2O), 6.58 (s, 1H), 7.48 (s, 1H), 11.40 (s, OH); ^{13}C NMR (100MHz, $CDCl_3$): δ 99.1(t), 102.8 (d), 103.4 (s), 142.2 (d), 156.0 (s), 156.3 (s).
5-Nitro-2,3-dihydro-6-hydroxy[*b*]furan-3-one (2c). Yellow needles (hexane), mp: 191°C: ^{1}H NMR (400MHz, $CDCl_3$): δ 4.77 (s, 2H), 6.81 (s, 1H), 8.61 (s, 1H), 11.37 (s, OH): ^{13}C NMR (100MHz, DMSO-d_6): δ 77.2 (t), 101.4 (d), 113.6 (s), 123.1 (d), 134.8 (s), 161.1(s), 176.0 (s), 197.2 (s). Anal. Calcd for $C_8H_5NO_5$: C, 49.24; H, 2.58; N, 7.18. Found: C, 49.28; H, 2.66; N, 7.24.

6-Hydroxy-7-nitro-1,3-benzoxathiol-2-one (2d). Yellow needles (EtOAc), mp: 130°C: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.12 (s, 1H), 8.23 (s, 1H), 10.91 (s, OH): ^{13}C NMR (100MHz, DMSO-d_6): δ 102.9 (d), 114.0 (s), 121.7 (d), 135.0 (s), 152.7 (s), 154.0 (s), 170.0 (s). Anal. Calcd for $C_7H_3NO_5S$: C, 39.44; H, 1.42; N, 6.57. Found: C, 39.55; H, 1.57; N, 6.78.

6-Hydroxy-7-nitrocoumarin-4-acetic acid (2e). Light red solid, mp: 95-96°C: ^{1}H NMR (400MHz, DMSO-d_6): δ 3.94 (s, 2H), 6.44 (s, 1H), 7.01 (s, 1H), 8.30 (s, 1H), 12.05 (bs, OH): ^{13}C NMR (100MHz, DMSO-d_6): δ 38.1 (t), 103.1(d), 112.2 (s), 112.8 (s), 113.9 (d), 127.6 (s), 151.0 (s), 155.9 (d), 161.0 (s), 162.0 (s), 171.5 (s). Anal. Calcd for $C_{11}H_7NO_7$: C, 49.82; H, 2.66; N, 5.28. Found: C, 49.88; H, 2.75; N, 5.32.

3-Cyano-6-hydroxy-4-methyl-7-nitrocoumarin (2f). Yellow solid, mp 110°C: ^{1}H NMR (400MHz, $CDCl_3$): δ 2.73 (s, 3H), 7.28 (s, 1H), 8.59 (s, 1 H), 11.02 (s, 1 H).; ^{13}C NMR (100MHZ, $CDCl_3$): δ 30.1 (t), 108.0 (d), 112.6 (d), 113.4 (d), 125.2 (d), 131.8 (s), 155.4 (s), 158.6 (s), 159.6 (s), 166.3 (s). Anal. Calcd for $C_{11}H_6N_2O_5$: C, 53.67; H, 2.46; N, 11.38. Found: C, 53.76; H, 2.51; N, 11.48.

5-Hydroxy-2-methyl-6-nitrobenzothiazol (2g). Yellow needles ($CHCl_3$), mp: 130-132°C: ^{1}H NMR (400MHz, $CDCl_3$): δ 2.96 (s, CH_3), 7.28 (s, 1H), 8.82 (s, 1H), 10.95 (bs, OH): ^{13}C NMR (100MHz, $CDCl_3$): δ 21.6 (q), 121.2 (d), 128.4 (s), 132.2 (s), 133.5 (d), 146.1 (s), 150.8 (s), 180.4 (s). Anal. Calcd for $C_8H_6N_2O_3S$: C, 45.71; H, 2.88; N, 13.33. Found: C; 45.79; H, 2.97; N, 13.44.

5-Hydroxy-6-nitroindole (2h). Yellow needles ($CHCl_3$), mp: 104-105°C: ^{1}H NMR (400MHz, $CDCl_3$): δ 5.37 (bs, NH), 6.45 (d, *J* = 4.2 Hz, 1H), 6.80 (dd, J = 4.2 Hz, 1 H), 7.07 (s, 1H), 7.65 (s, 1 H)), 11.15 (s, 1 H, OH): ^{13}C NMR (100MHz, $CDCl_3$): δ 102.5 (d), 105.5 (d), 112.0 (d), 112.2 (s), 125.7 (s), 129.0 (s), 131.6 (s), 149.9 (d). Anal. Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.73. Found: C, 54.02; H, 3.43; N, 15.87.

4-Bromo-2-(5-isoxazolyl)-6-nitrophenol (2i). Yellow needles (hexane), mp: 120-121°C: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.08 (s, 1H), 8.37 (d, *J* = 2.2Hz, 1H), 8.41 (s, 1H), 8.45 (d, *J* = 2.2Hz, 1H), 11.50 (s, OH): ^{13}C NMR (100MHz, $CDCl_3$): δ 105.5 (d), 112.3 (s), 120.7 (s), 128.7 (d), 134.9 (s), 138.0 (d), 151.1(s), 151.6 (d), 161.7 (s). Anal. Calcd for $C_9H_5BrN_2O_4$: C, 37.92; H, 1.77; N, 9.83. Found: C, 37.99; H, 1.83; N, 9.88.

4-Chloro-2-(5-isoxazolyl)-6-nitrophenol (2j). Yellow needles (hexane), mp: 128-129°C: ^{1}H NMR (400MHz, $CDCl_3$): δ 7.09 (s, 1H), 8.20 (d, *J* = 2.3Hz, 1H), 8.32 (d, *J* = 2.1Hz, 1H), 8.42 (d, *J* = 1.2Hz, 1H), 11.49 (s, OH): ^{13}C NMR (100MHz, $CDCl_3$): δ 105.4 (d), 120.4 (s), 125.7 (d), 125.9 (s), 134.6 (s), 135.2 (d), 150.7 s), 151.7 (d), 161.7 (s). Anal. Calcd for $C_9H_5ClN_2O_4$: C, 44.93; H, 2.09; N, 11.64. Found: C, 45.03; H, 2.15: N, 11.76.

2,3-Dihydro-2,2-dimethyl-6-nitro-7-benzofuranol (2k). Yellow solid ($CHCl_3$), mp: 178-179°C : ^{1}H NMR (400MHz, $CDCl_3$) δ 1.53 (s, CH3), 1.57 (s, CH3), 3.61 (d, *J* = 15.3Hz, 2H), 7.27 (d, *J* = 15.4Hz, 1H), 8.61 (d, *J* = 15.8Hz, 1H), 10.71 (s, OH): ^{13}C NMR (100MHz, $CDCl_3$): δ 28.6 (q), 45.2 (t), 91.6 (s), 113.8 (d), 131.7 (d), 133.4 (s) 137.1 (s), 144.9 (s), 150.2 (s). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.54; H, 5.40; N, 6.74.

(5-Bromo-3-nitro-2-hydroxyphenyl)-(1-phenyl-1*H*-pyrazol-4-yl)ketone (2l). Light yellow solid, mp, 110-111°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.47 (m, 5 H), 8.29 (s, 1H), 8.72 (s, 1 H), 8.92 (s, 1H), 8.95 (s, 1 H), 11.64 (s, 1H, OH). ^{13}C NMR (100MHz, $CDCl_3$): δ 115.0 (d), 120.4 (d), 120.5 (s), 121.0 (s), 126.3 (d), 127.8 (d), 128.8 (s), 128.9 (s), 130.2 (d) 130.3 (s), 135.2 (s), 140.2 (d), 142.8 (d), 180.0 (s) Anal. Calcd for $C_9H_5BrN_2O_4$: C, 37.92; H, 1.77; N, 9.83. Found: C, 37.99: H, 1.73; N, 9.86.

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