Nitrophenol Derivatives Oxidized by Cerium(IV) Ammonium Nitrate (CAN) and their Cytotoxicity

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Oxidation of a series of phenols with cerium(IV) ammonium nitrate (CAN) in acetonitrile under mild conditions yields the mixture of corresponding nitrophenols. In the cases of methylphenols and hydroxycarboxylic acids, the steric effect may reduce the nitration reaction. Compounds **3a** and **4b** showed selective activities to Hep 3B and Hep G2 cancer cell lines, respectively. Compound **2c** showed selective activities to Hep G2 and MDA-MB-231 cancer cell lines. Furthermore, compound **10b** showed selective activities to Hep G2, Hep 3B, MCF-7 and MDA-MB-231 cancer cell lines.

Keywords: Cerium(IV) ammonium nitrate; Nitrophenols; Oxidative addition; Cytotoxicity.

INTRODUCTION

For decades, the strong oxidizing properties of CAN have been shown to be extremely useful in synthetic organic chemistry.[1] It has also been employed adsorbed on silica gel for oxidative nitration of polynuclear arenas.[2] Nitration of phenols as a special case has been studied using various nitrating agents under different conditions.[3] CAN has proved to be an ideal reagent because the mild conditions involved. CAN in protic solvent (acetonitrile, water/acetonitrile or methanol) has been widely employed for the oxidative addition of 2-hydroxynaphthoquinone to dienes,[4] oxidative demethylation of 1,4-dimethoxyphenyl derivatives,[5] and oxidation of benzylamines or benzylalcohols into benzaldehydes.[6] Oxidative addition of soft anions to alkenes mediated by CAN in protic solvent has also been shown to offer a practical method carbon-heteroatom (C-O, C-S, and C-Br) bond formation.[7,8] In our previous investigation, we have reported the use of CAN for the esterification of aliphatic carboxylic acids with simple primary and secondary alcohols[9] and esterification-nitration of *ortho*-hydroxyphenyl carboxylic acids and benzoic acids with CAN.[10] Seeking milder conditions, we focused on the use of CAN, which has been employed for nitration purposes. In 1994, Chakrebarty and Batabyal have reported the nitration of carbazols by CAN in acetonitrile in the presence of (not adsorbed on) silica gel at 70-75 °C.[11] Unfortunately the reaction did not take place without silica gel. Grenier et al. have reported the ring nitration of electron-rich methoxyphenyl derivatives with CAN/SiO_2 in 1999.[12] Moridani et al. have reported the quantitative structure toxicity relationships for phenols in isolated rat hepatocytes in 2003.[13] Now we report, herein, the ring nitration of several phenol derivatives with CAN. An important purpose of this paper is to clarify the reaction conditions and to refocus attention on the ability of CAN to both ring nitration and oxidative addition of phenol derivatives. The cytotoxicities toward Hep G2, Hep 3B, MCF-7, and MDA-MB-231 cells, and the structure-activity relationship of the isolated products are also revealed for the first time.

RESULTS AND DISCUSSION

We reacted several phenol derivatives with CAN in acetonitrile from 20 min to 24 h (in the case of no reaction or low yield after 20 min) at room temperature. Results are reported in Table 1. Furthermore, the cytotoxicities of the isolated products toward various cancer cells were evaluated.

Under these conditions, phenol **1** gave 2-nitrophenol **1a** and 4-nitrophenol **1b** in 41% and 28% yields, respectively (entry 1, Table 1). Methylphenols **2-4** gave nitrophenols. In addition, 2-methylphenol **2** and 4-methylphenol **4** gave oxidative addition derivatives as minor products. In the reaction of **2**, the products were 6-methyl-2-nitrophenol **2a**, 2-meth-

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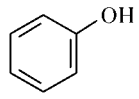
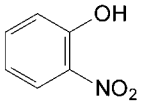
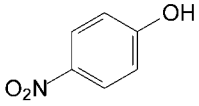
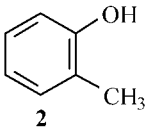
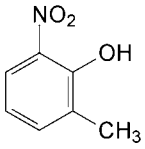
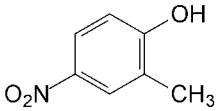
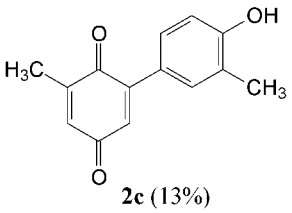
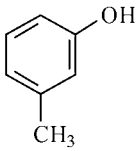
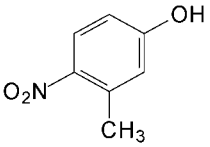
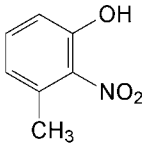
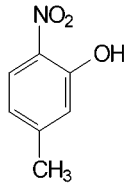
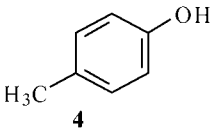
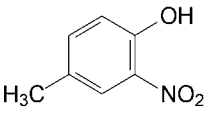
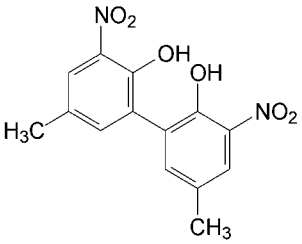
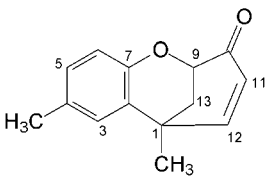
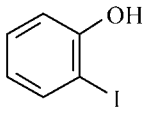
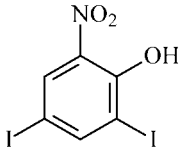
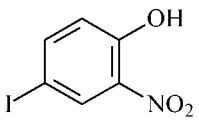
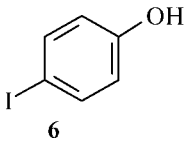
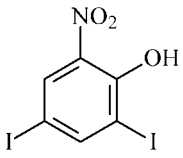
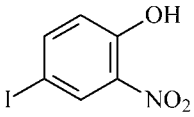
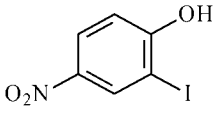
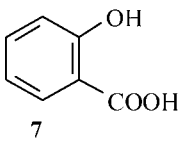
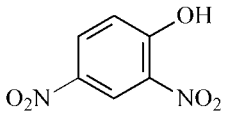
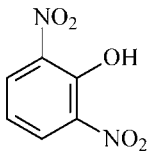
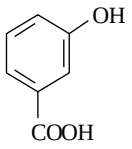
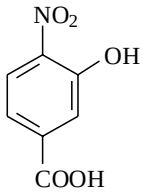
Table 1. Reaction of phenols with CAN in acetonitrile at room temperature

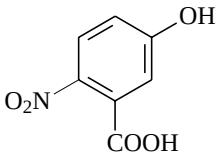
Entry	Substrate	Time	Products	Yields (%)*	
1	 **1**	24 h	 **1a** (41%)	 **1b** (28%)	
2	 **2**	24 h	 **2a** (36%)	 **2b** (27%)	 **2c** (13%)
3	 **3**	24 h	 **3a** (40%)	 **3b** (21%)	 **3c** (22%)
4	 **4**	12 h	 **4a** (77%)	 **4b** (12%)	 **4c** (10%)
5	 **5**	2 h	 **5a** (22%)	 **5b** (18%)	
6	 **6**	2 h	 **5a** (17%)	 **5b** (27%)	 **6a** (10%)
7	 **7**	12 h	 **7a** (95%)	 **7b** (3%)	



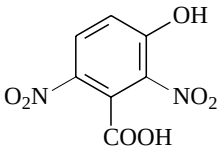
8



8a (50%)

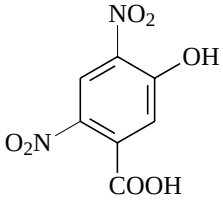


8b (18%)



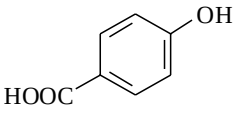
8c (14%)

8 12 h



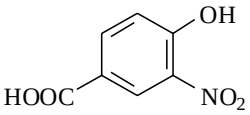
8d (10%)

9

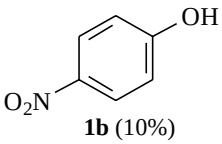


9

20 min

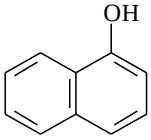


9a (84%)



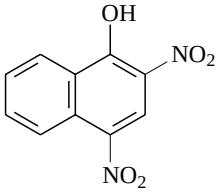
1b (10%)

10

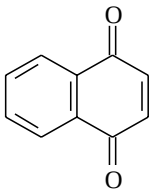


10

20 min

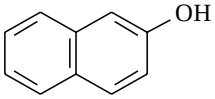


10a (42%)



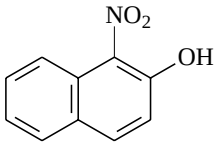
10b (31%)

11



11

2 h



11a (41%)

* Yields refer to the isolated yields. All of the compounds were assigned in view of ^{1}H NMR, ^{13}C NMR and MS spectra data.

yl-4-nitrophenol **2b**, and the oxidative addition product, 2-(4-hydroxy-3-methylphenyl)-6-methylcyclohexa-2,5-diene-1,4-dione **2c** in 36, 27, 13% yields, respectively after 24 h (entry 2, Table 1). 3-Methylphenol **3** led to the 3-methyl-4-nitrophenol **3a**, 3-methyl-2-nitrophenol **3b**, and 5-methyl-2-nitrophenol **3c** in 40%, 21% and 22% yields, respectively after 24 h (entry 3, Table 1). Compound **4** led to the 4-methyl-2-nitrophenol **4a** as major products, along with the oxidative addition products, 2-(2-hydroxy-5-methyl-3-nitrophenyl)-4-methyl-6-nitrophenol **4b** and 1,4-dimethyl-8-oxatricyclo-[7.3.1.0<2,7>]trideca-2(7),3,5,11-tetraen-10-one **4c** as minor products in 77%, 12% and 10% yields, respectively after 12 h (entry 4, Table 1). The structure of **4c** was established by spectroscopic data. The ^{1}H NMR signal at δ 4.69 (1H, m) was assigned to the oxymethine proton attached to the ring junction carbon C-9. The methylene protons at δ 3.04 (1H, ddd, *J* = 19.6, 4.0, 1.0 Hz) and δ 2.79 (1H, dd, *J* = 19.6, 4.0 Hz) were assigned to H-13. The reaction of **4** is apparently faster than those of **2** and **3**, indicating that the steric hindrance affects the rate of nitration of methylphenols. Interestingly, from the reactions of iodophenols **5** and **6** for 2 h, 4,6-diiodo-2-nitrophenol **5a** and 4-iodo-2-nitrophenol **5b** were isolated as the major products (entries 5, 6, Table 1). Iodonation, mononitration, and nitrodeiodonation reactions occur in these two

cases. Moreover, the reaction rates of iodophenols are apparently faster than those of methyl phenols or hydroxyl benzoic acids by the comparison of their reaction time.

In another series of reactions, we reacted some hydroxybenzoic acids **7**-**9** which possess an additional electron-withdrawing group under the same reaction conditions. 2-Hydroxybenzoic acid **7** underwent simultaneous nitrodecarboxylation and mononitraton reactions to give in high yield a mixture of 2,4-dinitrophenol **7a** and 2,6-dinitrophenol **7b** in 95% and 3% yields, respectively, whereas 3-hydroxybenzoic acid **8** gave mononitrophenols, **8a** (50%) and **8b** (18%), as well as dinitrophenols, **8c** (14%) and **8d** (10%) after 12 h. 4-Hydroxybenzoic acid **9** gave mononitrophenol, **9a** (84%) along with nitrodecarboxylation product **1b** (10%) as minor product after 20 min. The reaction of **9** is faster than those of **7** and **8**, indicating the steric hindrance also affects the rate of nitration reaction of hydroxybenzoic acids. In the reactions of naphthols, 1-naphthol **10** afforded dinitronaphthol **10a** (42%) and the oxidized product, naphthalene-1,4-dione **10b** (31%) after 20 min, whereas 2-naphthol **11** gave mononitronaphthol **11a** (41%) after 2 h.

The cytotoxicities of compounds **1a**, **1b**, **2a-2c**, **3a-3c**, **4a-4c**, **5a-5b**, **6a**, **7a**, **9a**, **10a**, **10b**, **11a** were evaluated against the cell lines of human hepatocellular carcinoma Hep G2 and Hep 3B, human breast carcinoma MCF-7 and MDA-MB-231. The results are presented in Table 2. Compound **2c** showed selective activities to Hep G2 and MDA-MB-231 cancer cell lines with IC_{50} values 5.75 and 5.43 μg/mL, respectively. Compound **3a** showed selective activity to a Hep 3B cancer cell line with IC_{50} value 1.22 μg/mL. Compound **4b** showed selective activity to a Hep G2 cancer cell line with IC_{50} value 3.92 μg/mL. Compound **10b** showed selective activities to Hep G2, Hep 3B, MCF-7 and MDA-MB-231 cancer cell lines with IC_{50} values 1.79, 6.47, 2.14, and 0.85 μg/mL, respectively. However, the other compounds exhibited weak or no effect to the growth inhibition of Hep G2, Hep 3B, MCF-7, and MDA-MB-231 cell lines.

In conclusion, we have shown that CAN in acetonitrile is an efficient and mild nitrating agent of phenols. Numerous functionalities (e.g.; $-CH_3$, -I, $-CO_2H$) were tolerated in the reaction conditions. In the cases of methylphenols and hydroxycarboxylic acids, the steric effect may reduce the nitration reaction. The limitations are due to (1) low regioselectivity of most substrates; (2) the strong oxidizing power of CAN often leads to over-oxidized products; and (3) competition with the oxidative addition reaction in the cases of 4-methylphenols and 2-methylphenols. Furthermore, compounds **3a** and **4b** showed selective activities to Hep 3B and Hep G2 cancer cell lines, respectively. Compound **2c** showed selective activities to Hep G2 and MDA-MB-231 cancer cell lines. Compound **10b** showed selective activities to Hep G2, Hep 3B, MCF-7 and MDA-MB-231 cancer cell lines. Three main points are apparent from these results. Firstly, the *p*-nitrophenol functionality in such nitrophenol compounds **1b**, **2b**, and **3a** seems to play an important role in cytotoxicities to Hep G2 and Hep 3B cancer cell lines. Secondly, the *o*-nitrophenols does not show the activity due to hydrogen bond while compound **4b** shows activity that may be driven by intercalation. Thirdly, the para-quinone moiety in compounds **2c** and **10b** has a large influence on cytotoxicities to Hep G2, Hep 3B, MCF-7 and MDA-MB-231 cancer cell lines.

Table 2. Cytotoxicity of phenol derivatives against various cancer cell lines

	Cytotoxicity IC_{50} (μg/mL)			
Compounds	Hep G2	Hep 3B	MCF-7	MDA-MB-231
1a	> 30.00	> 30.00	> 30.00	> 30.00
1b	**27.21**	**22.28**	> 30.00	> 30.00
2a	> 30.00	> 30.00	> 30.00	> 30.00
2b	**18.96**	**19.40**	**26.67**	**23.59**
2c	**5.75**	**18.10**	**18.52**	**5.43**
3a	**18.30**	**1.22**	> 30.00	> 30.00
3b	> 30.00	> 30.00	> 30.00	> 30.00
3c	> 30.00	> 30.00	> 30.00	> 30.00
4a	> 30.00	> 30.00	> 30.00	> 30.00
4b	**3.92**	> 30.00	> 30.00	> 30.00
4c	**17.91**	**21.79**	> 30.00	**29.09**
5a	> 30.00	> 30.00	> 30.00	> 30.00
5b	> 30.00	> 30.00	> 30.00	> 30.00
6a	> 30.00	> 30.00	> 30.00	> 30.00
7a	> 30.00	> 30.00	> 30.00	> 30.00
9a	> 30.00	> 30.00	> 30.00	13.72
10a	**18.54**	**18.59**	> 30.00	> 30.00
10b	**1.79**	**6.47**	**2.14**	**0.85**
11a	> 30.00	> 30.00	> 30.00	> 30.00

EXPERIMENTAL SECTION

General

^1H and ^{13}C NMR spectra were acquired on a Varian Germini 200 MHz FT-NMR running at 200 Mz (^1H) or 50 MHz (^{13}C), respectively. Chemical shifts (δ) were reported in ppm relative to residual solvent signals. The multiplicities of ^1H signals are designated by the following abbreviations: s = singlet; d = doublet; t =triplet; q = quartet; br = broad; m =

multiplet. All coupling constants, *J*, are reported in Hertz. ^{13}C NMR spectra were acquired on a broad band decoupled mode and the multiplicities were obtained using DEPT sequences. Melting points were determined using a Fargo MP-1D melting point apparatus and are uncorrected. Mass spectra were recorded on a JEOL TMSD-100 Mass spectrometer. Flash column chromatography was carried out using silica gel 60 (Merck, 230-400 mesh). Analytical thin layer chromatography (TLC) was performed using precoated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation. Analytical grade solvents were used as received. The CAN used for the reactions was purchased from Lancaster Co. and was used without purification.

General procedure for CAN mediated nitration of phenols

To a solution of phenols (1.6 mmol) in acetonitrilel was added a solution of CAN (1.26 g, 2.3 mmol) in acetonitrile at room temperature. The mixture was stirred for 20 min or more. The solvent was removed on a rotary evaporator and the residue was diluted with saturated aqueous NaCl solution and extracted with EtOAc (3 × 15 mL). The extracts were dried over anhydrous $MgSO_4$. After the removal of the solvent, the residue was subjected to column chromatography on silica gel to afford the corresponding products.

Cytotoxicity Assays

Compounds were assayed for cytotoxicity against Hep G2, Hep 3B, MCF-7, and MDA-MB-231 cells using the MTT method. Freshly trypsinized cell suspensions were seeded in 96-well microtitre plates at densities of 5,000-10,000 cells per well with tested compounds added from DMSO-diluted stock. After 3 days in culture, attached cells were incubated with MTT (0.5 mg/mL, 1 hr) and subsequently solubilized in DMSO. The absorbency at 550 nm was then measured using a microplate reader. The IC_{50} is the concentration of agent that reduced cell growth by 50% under the experimental conditions.

2-Nitrophenol (1a)

Compound **1a** was prepared according to general procedure and after 24 h the product was isolated as yellow needles. mp 44-45 °C (lit.[14] 46 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 10.59 (s, 1H), 8.11 (dd, 1H, *J* = 8.4, 1.8 Hz), 7.59 (td, 1H, *J* = 7.8, 1.6 Hz), 7.16 (dd, 1H, *J* = 8.4, 1.2 Hz), 6.99 (td, 1H, *J* = 8.0, 1.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 165.5, 155.3, 137.7, 125.2, 120.4, 120.1.

4-Nitrophenol (1b)

Compound **1b** was prepared according to general procedure and after 24 h the product was isolated as white needles. mp 115-116 °C (lit.[15] 114 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.16 (dd, 2H, *J* = 9.2, 2.4 Hz), 6.93 (dd, 2H, *J* = 9.2, 2.4 Hz), 6.41 (br s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 161.9, 141.3, 126.3, 126.3, 115.7, 115.7. EI-MS *m/z* (rel. int. %): 139 (M^+, 100), 109 (47), 65 (72), 43 (72).

6-Methyl-2-nitrophenol (2a)

Compound **2a** was prepared according to general procedure and after 24 h the product was isolated as a yellow solid. mp 70-71 °C (lit.[16] 71 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 10.90 (s, 1H, -OH), 7.94 (d, 2H, *J* = 8.6 Hz), 7.43 (d, 2H, *J* = 7.4 Hz), 6.86 (dd, 2H, *J* = 8.6, 7.4 Hz), 2.32 (s, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.5, 137.9, 132.0, 129.2, 122.3, 119.0, 15.5. EI-MS *m/z* (rel. int. %): 153 (64), 107 (19), 105 (17), 77 (100), 52 (51).

2-Methyl-4-nitrophenol (2b)

Compound **2b** was prepared according to general procedure and after 24 h the product was isolated as a white solid. mp 95-96 °C (lit.[17] 94 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 8.05 (d, 1H, *J* = 2.8 Hz), 8.00 (dd, 1H, *J* = 8.8, 2.8 Hz), 6.87 (d, 1H, *J* = 8.8 Hz), 6.71 (br s, 1H, -OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 160.2, 141.0, 126.9, 125.4, 123.7, 114.8, 15.80. EI-MS *m/z* (rel. int. %): 153 (22), 123 (14), 77 (100), 67 (25), 51 (30), 43 (64).

2-(4-Hydroxy-3-methylphenyl)-6-methylcyclohexa-2,5-diene-1,4-dione (2c)

Compound **2c** was prepared according to general procedure and after 24 h the product was isolated as a red solid. mp 148-149 °C (lit.[18] 149-150 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 7.28 (d, 1H, *J* = 1.6 Hz), 7.25 (dd, 1H, *J* = 8.0, 2.4 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 6.74 (d, 1H, *J* = 2.4 Hz), 6.65 (qd, 1H, *J* = 1.6, 1.6 Hz), 5.24 (br s, 1H, -OH), 2.28 (s, 3H), 2.12 (d, 1H, *J* = 1.6 Hz). EI-MS *m/z* (rel. int. %): 228 (100), 213 (13), 200 (27), 185 (26), 157 (15), 132 (27), 68 (21).

3-Methyl-4-nitrophenol (3a)

Compound **3a** was prepared according to general procedure and after 24 h the product was isolated as an orange red solid. mp 129-130 °C (lit.[19] 129 °C). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, 1H, *J* = 9.6 Hz), 6.76 (dd, 1H, *J* = 9.6, 3.2 Hz), 6.75 (d, 1H, *J* = 3.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 159.8, 137.5, 127.9, 118.9, 113.6, 113.2, 21.5. EI-MS *m/z*

(rel. int. %): 153 (M^+, 48), 136 (100), 77 (54).

3-Methyl-2-nitrophenol (3b)

Compound **3b** was prepared according to general procedure and after 24 h the product was isolated as yellow green liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.36 (br s, 1H, -OH), 7.38 (t, 1H, *J* = 8.0 Hz), 7.01 (dt, 1H, *J* = 8.0, 0.8 Hz), 6.84 (dt, 1H, *J* = 8.0, 0.8 Hz), 2.63 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.4, 136.8, 135.2, 130.0, 124.0, 117.6, 22.4.

5-Methyl-2-nitrophenol (3c)

Compound **3c** was prepared according to general procedure and after 24 h the product was isolated as yellow needles. mp 127-128 °C (lit.[20] 128 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.61 (s, 1H, -OH), 7.97 (d, 1H, *J* = 8.6 Hz), 6.93 (d, 1H, *J* = 2.0 Hz), 6.78 (dd, 1H, *J* = 8.6, 2.0 Hz), 2.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 155.1, 149.8, 131.8, 124.9, 121.6, 119.6, 21.8.

4-Methyl-2-nitrophenol (4a)

Compound **4a** was prepared according to general procedure and after 12 h the product was isolated as yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.40 (s, 1H, -OH), 7.84 (d, 1H, *J* = 2.2 Hz), 7.37 (dd, 1H, *J* = 8.6, 2.2 Hz), 7.02 (d, 1H, *J* = 8.6 Hz), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 153.0, 138.7, 133.0, 130.1, 124.3, 119.5, 20.1. EI-MS *m/z* (rel. int. %): 153 (100), 136 (18), 123 (15), 107 (13), 77 (32).

2-(2-Hydroxy-5-methyl-3-nitrophenyl)-4-methyl-6-nitrophenol (4b)

Compound **4b** was prepared according to general procedure and after 12 h the product was isolated as a yellow solid. mp 211-212 °C (lit.[21] 210-212 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.82 (s, 2H, -OH), 8.00 (d, 2H, *J* = 2.0 Hz), 7.43 (d, 2H, *J* = 2.0 Hz), 2.40 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.0, 151.0, 140.3, 140.3, 133.6, 133.6, 129.4, 129.4, 127.1, 127.1, 124.8, 124.8, 20.4, 20.4. EI-MS *m/z* (rel. int. %): 304 (88), 286 (21), 269 (100), 182 (21), 152 (26).

1,4-Dimethyl-8-oxatricyclo[7.3.1.0<2,7>]trideca-2(7),3,5,11-tetraen-10-one (4c)

Compound **4c** was prepared according to general procedure and after 12 h the product was isolated as a yellow solid. mp 123-124 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.01 (d, 1H, *J* = 1.6 Hz, H-3), 6.99 (dd, 1H, *J* = 7.8, 1.6 Hz, H-5), 6.71 (d, 1H, *J* = 7.8 Hz, H-6), 6.46 (dd, 1H, *J* = 10.0, 2.0 Hz, H-12), 5.92 (dd, 1H, *J* = 10.0, 1.0 Hz, H-11), 4.69 (m, 1H, H-9), 3.04 (ddd, 1H, *J* = 19.6, 4.0, 1.0 Hz, H-13), 2.79 (dd, 1H, *J* = 19.6, 4.0 Hz, H-13), 2.32 (s, 3H), 1.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 195.1, 156.7, 149.6, 132.2, 131.1, 129.7, 125.8, 123.2, 110.1, 86.5, 45.1, 37.5, 21.4, 20.9. EI-MS *m/z* (rel. int. %): 214 (100), 199 (87), 171 (55), 128 (41), 115 (41). HREIMS *m/z* Found 214.0995 (Calcd for $C_{14}H_{14}O_2$ 214.0993).

4,6-Diiodo-2-nitrophenol (5a)

Compound **5a** was prepared according to general procedure and after 2 h the product was isolated as yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 11.27 (br s, 1H, -OH), 8.41 (d, 1H, *J* = 2.2 Hz), 8.34 (d, 1H, *J* = 2.2 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 154.1, 153.8, 133.6. EI-MS *m/z* (rel. int. %): 391 (13), 218 (14), 189 (15), 91 (45), 61 (100).

4-Iodo-2-nitrophenol (5b)

Compound **5b** was prepared according to general procedure and after 2 h the product was isolated as yellow needles. mp 81-82 °C (lit.[22] 81 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 10.51 (br s, -OH), 8.41 (d, 1H, *J* = 2.2 Hz), 7.82 (dd, 1H, *J* = 8.8, 2.2 Hz), 6.95 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): 154.8, 145.9, 134.5, 133.2, 124.0, 122.0. EI-MS *m/z* (rel. int. %): 265 (73), 219 (12), 207 (15), 191 (12), 127 (15), 92 (68), 63 (100).

2-Iodo-4-nitrophenol (6a)

Compound **6a** was prepared according to general procedure and after 2 h the product was isolated as brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (d, 1H, *J* = 1.6 Hz), 8.17 (dd, 1H, *J* = 8.8, 1.6 Hz), 7.07 (d, 1H, *J* = 8.8 Hz), 6.27 (br s, 1H, -OH). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 134.4, 133.8, 127.2, 126.1, 114.6. EI-MS *m/z* (rel. int. %): 265 (70), 235 (26), 92 (100), 63 (76).

2,4-Dinitrophenol (7a)

Compound **7a** was prepared according to general procedure and after 12 h the product was isolated as colorless needles. mp 143-144 °C (lit.[23] 144 °C). ^{1}H NMR (CD_3OD, 200 MHz): δ 8.83 (d, 1H, *J* = 2.8 Hz), 8.23 (dd, 1H, *J* = 9.4, 2.8 Hz), 7.02 (d, 1H, *J* = 9.4 Hz). ^{13}C NMR (CD_3OD, 50 MHz): δ 164.7, 138.0, 136.9, 130.5, 123.9, 123.8. EI-MS *m/z* (rel. int. %): 184 (M^+, 94), 154 (100), 98 (36).

2,6-Dinitrophenol (7b)

Compound **7b** was prepared according to general procedure and after 12 h the product was isolated as colorless needles. mp 61-62 °C (lit.[24] 63.5 °C). ^{1}H NMR (CD_3OD, 200 MHz): δ 8.07 (d, 2H, *J* = 8.0 Hz), 6.66 (d, 1H, *J* = 8.0 Hz). ^{13}C NMR (CD_3OD, 50 MHz): δ 160.9, 160.9, 145.2, 145.2, 131.7,

108.1. EI-MS *m/z* (rel. int. %): 184 (M^+, 59), 139 (100), 109 (60), 81 (64), 69 (63).

3-Hydroxy-4-nitrobenzoic acid (8a)

Compound **8a** was prepared according to general procedure and after 12 h the product was isolated as a pale yellow solid. mp 232-233 °C (lit.[25] 231-237 °C). ^{1}H NMR (CD_3OD, 400 MHz): δ 8.09 (d, 1H, *J* = 8.8 Hz), 7.72 (d, 1H, *J* = 1.6 Hz), 7.58 (dd, 1H, *J* = 8.8, 1.6 Hz). ^{13}C NMR (CD_3OD, 50 MHz): δ 167.5, 154.5, 138.9, 129.9, 126,4, 122.0, 121.4. EI-MS *m/z* (rel. int. %): 183 (24, M^+), 153 (11), 119 (26), 97 (43), 81 (45), 63 (100).

5-Hydroxy-2-nitrobenzoic acid (8b)

Compound **8b** was prepared according to general procedure and after 12 h the product was isolated as an orange red solid. mp 128-129 °C (lit.[26] 128-130 °C). ^{1}H NMR (CD_3OD, 200 MHz): δ 7.93 (d, 1H, *J* = 8.8 Hz), 6.67 (d, 1H, *J* = 3.6 Hz), 6.65 (dd, 1H, *J* = 8.8, 3.6 Hz). ^{13}C NMR (CD_3OD, 50 MHz): δ 166.0, 159.0, 133.0, 126.5, 118.3, 106.9, 106.2.

3-Hydroxy-2,6-dinitrobenzoic acid (8c)

Compound **8c** was prepared according to general procedure and after 12 h the product was isolated as an orange red solid. mp 181-182 °C (lit.[27] 180.5-181.5 °C). ^{1}H NMR (CD_3OD, 200 MHz): δ 7.84 (d, 1H, *J* = 8.6 Hz), 6.46 (d, 1H, *J* = 8.6 Hz). ^{13}C NMR (CD_3OD, 50 MHz): δ 157.9, 138.5, 126.4, 115.7, 114.8, 107.1.

5-Hydroxy-2,4-dinitrobenzoic acid (8d)

Compound **8d** was prepared according to general procedure and after 12 h the product was isolated as a yellow solid. mp 189-190 °C (lit.[28] 188-188.5 °C). ^{1}H NMR (CD_3OD, 200 Mhz): δ 8.74 (s, 1H), 6.64 (s, 1H). ^{13}C NMR (CD_3OD, 50 MHz): δ 169.7, 144.6, 128.0, 127.6, 126.0, 123.5, 115.4. EI-MS *m/z* (rel. int. %): 228 (25), 198 (15), 154 (14), 135 (19), 107 (28), 79 (59), 63 (88), 53 (100).

4-Hydroxy-3-nitrobenzoic acid (9a)

Compound **9a** was prepared according to general procedure and after 20 min the product was isolated as a white solid. mp 185-186 °C (lit.[29] 187 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.98 (br s, 1H, -OH), 8.91 (d, 1H, *J* = 2.0 Hz), 8.30 (dd, 1H, *J* = 8.8, 2.0 Hz), 7.27 (d, 1H, *J* = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0, 158.7, 138.3, 133.3, 128.2, 121.8, 120.5. EI-MS *m/z* (rel. int. %): 183 (100), 153 (43), 125 (25).

2,4-Dinitronaphthol (10a)

Compound **10a** was prepared according to general procedure and after 20 min the product was isolated as a brown solid. mp 129-130 °C (lit.[30] 139.5 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.03 (s, 1H), 8.75 (d, 1H, *J* = 8.6 Hz), 8.66 (d, 1H, *J* = 8.6 Hz), 7.99 (t, 1H, *J* = 8.6 Hz), 7.80 (t, 1H, *J* = 8.6 Hz). ^{13}C NMR (CD_3OD, 50 MHz): δ 167.9, 151.5, 144.7, 133.1, 130.6, 127.6, 127.2, 127.1, 124.9. EI-MS *m/z* (rel. int. %): 234 (26), 129 (36), 113 (42), 69 (85), 55 (100).

Naphthalene-1,4-dione (10b)

Compound **10b** was prepared according to general procedure and after 20 min the product was isolated as a yellow solid. mp 122-123 °C (lit.[31] 124.3-125.3 °C). ^{1}H NMR (CD_3OD, 200 MHz): δ 8.05 (m, 2H), 7.81 (m, 2H), 7.00 (s, 2H). ^{13}C NMR (CD_3OD, 50 MHz): δ 186.3, 139.8, 135.1, 133.3, 127.2. EI-MS *m/z* (rel. int. %): 158 (100), 130 (67), 102 (98), 76 (38).

1-Nitronaphthalen-2-ol (11a)

Compound **11a** was prepared according to general procedure and after 2 h the product was isolated as a yellow solid. mp 106-107 °C (lit.[32] 104 °C). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 12.18 (s, 1H, -OH), 8.89 (d, 1H, *J* = 8.8 Hz), 7.98 (d, 1H, *J* = 9.2 Hz), 7.80 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.71 (td, 1H, *J* = 8.0, 2.0 Hz), 7.49 (td, 1H, *J* = 8.0, 1.0 Hz), 7.23 (d, 1H, *J* = 9.0 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 158.8, 139.1, 130.9, 129.3, 128.6, 128.2, 126.8, 125.6, 123.2, 119.3. EI-MS *m/z* (rel. int. %): 189 (78), 131 (35), 115 (100), 103 (46), 89 (62).

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