

Solid-state regioselective nitration of activated hydroxyaromatics and hydroxycoumarins with cerium (IV) ammonium nitrate

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Predominant *ortho*-selective mononitration of low-melting and liquid phenols and hydroxycoumarins in moderate to high yields has been accomplished upon grinding with solid cerium (IV) ammonium nitrate (CAN). Microwave-assisted expeditious CAN-mediated nitration of relatively high melting phenols and hydroxycoumarins with high efficiency and selectively under solvent-free conditions has been also developed to address the problems of sluggishness and low yield for these reluctant substrates.

Keywords: regioselective nitration, hydroxyaromatics, hydroxycoumarins, cerium (IV) ammonium nitrate

Nitro derivatives of aromatics and heteroaromatics constitute a useful class of organic compounds which are widely utilised as chemical feedstocks for dyes, pharmaceuticals, plastics and perfumes. Traditional nitration employing an excess of a mixture of potent nitric acid and sulfuric acid results in excess acid waste streams¹ coupled with frequent low selectivity due to formation of polynitro derivatives and oxidative byproducts along with the desired mononitro product. To alleviate these problems, considerable contemporary efforts have been focused on alternative nitrating reagents and media.² With the emerging trend of developing solvent-free solid-state organic reactions³ with their green features including elimination of volatile organic solvents, high selectivity, recyclability, some attempts have been made to develop solvent-free nitration protocols using metal nitrates, such as copper(II) nitrate on montmorillonite K-10 clay support,⁴ clayfen/clayan,⁵ stoichiometric quantity of nitric acid and acetic anhydride in the presence of zeolite beta,⁶ and nitrogen dioxide.⁷ In our continuing search to find conditions of regioselective nitration using CAN,^{8,9} we were prompted to evaluate the hitherto unstudied efficacy of this lanthanide nitrate as a nitrating agent in the solid state with and without microwave irradiation. Herein we report the results of nitration of a wide range of substrates of varying reactivity levels, as summarised in Table 1.

Results and discussion

Phenols (entries 1-6 and 11), upon thorough aggregation with solid CAN in an agate mortar, undergo predominant, if not exclusive, *ortho*-selective nitration in good-to-moderate yields. However, 2-allylphenol (entry 2) represents an exception presumably due to steric encumbrance offered by pendant allylic moiety to initial complex formation of the hydroxy group with CAN. Grinding of these substrates with solid CAN was attended with immediate colour change to brownish-black and rheological change suggesting initial complex formation with oxyphilic cerium(IV). The solid mixture of phenol and CAN showed a good rhombic anisotropic EPR signal showing directional property (Fig. 1) and was consistent with the formation of phenoxy radicals in the solid matrix.

Interestingly, nitration of relatively high-melting activated phenols, such as resorcinol and β -naphthol were sluggish and gave comparatively poor yields even after prolonged exposure to the reagent suggesting a purely diffusion-controlled solid-solid reaction^{10,11} which is rarely observed. In contrast, the complete nitration of lower melting or liquid phenols (entries 2 and 3) with ease and excellent yields is compatible with liquid melt formation facilitating substrate and product movement. To demonstrate this mechanistic point further, we chose hydroxycoumarins as substrates which are characterised

by relatively high melting points and acceptable reactivity levels. 7-Hydroxycoumarins (entries 7–10) underwent exclusive sluggish *ortho*-selective mononitration at C-6. However, improved regioselectivity was a poor compensation for disappointingly slow reaction rates and lower yields in comparison to solution phase nitration in glacial acetic acid.⁹ Remarkably no nitration was observed at the electron-rich vinylogous C-3 positions of 7-hydroxycoumarin (entry 7) and 7-hydroxy-4-methylcoumarin (entry 8). The lower yields and sluggishness are consistent with the solid-solid nature of nitration of hydroxycoumarins with CAN. Intrinsic reactivity factors which are also crucial in solid-state reactions^{12,13} definitely play their part, and the deactivating effect of the α -pyrone ring impedes nitration of hydroxycoumarins to a significant extent. Substrates lacking free hydroxy group such as 7-methoxycoumarin were totally resistant to nitration with solid CAN (96 h) upon grinding. Very significantly, no such huge rate differential is observed in the homogeneous nitration with CAN in glacial acetic acid.⁹ In general, solid-state nitration of hydroxycoumarins and phenols displayed improved selectivity over CAN-mediated nitration under homogeneous conditions,^{9,14a,b} although yields were not very encouraging for hydroxycoumarins. Interestingly, moderately activated phenyl acetate (entry 12) underwent exclusive *para*-selective nitration in acceptable yield presumably because initial complex formation was precluded in contrast to the behaviour of phenol. It is likely that oxidative nitration is not favoured for less reactive substrates, such as 7-hydroxycoumarins where considerable electron-withdrawal from the 7-OH group to the deactivating α -pyrone ring occurs and the hydroxy group is responsible for α chaperon effect facilitating delivery of the nitro group to an *ortho* position by a ligand transfer mechanism.^{14a,b} No allylic or benzylic oxidation^{14c} which often characterises CAN-based reactions occurred with this reagent system.

This mode of solid-state nitration was mechanistically intriguing in view of the fact that it allows one to correlate

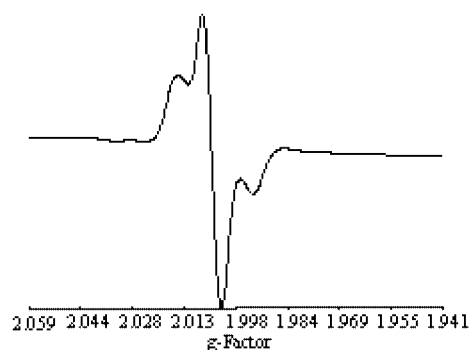




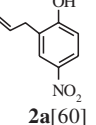
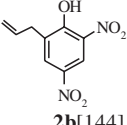

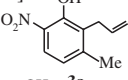


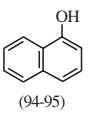
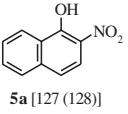
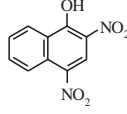
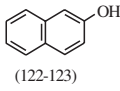
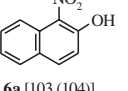
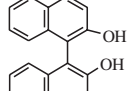
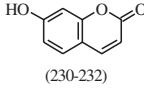
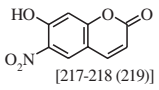
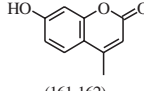
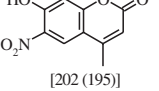
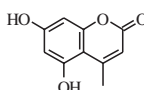
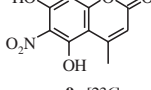
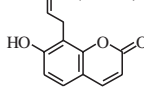
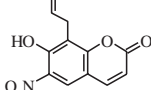
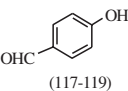
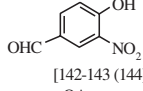




Fig. 1

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Table 1 Solid-state nitration of aromatics and heteroaromatics with CAN

Entry	Substrate (m.p./°C)	Product (s) [m.p./°C (lit ¹⁷ /°C)]	Reaction conditions, time; [Yield/% ^c] of products
1	 (42-43)	 1a [43 (45)]  1b [113 (114)]	(a) 30 min; 1a [84], 1b [5] (b) 2 min; 1a [95]
2		 2a [60]  2b [144]	(a) 45 min; 2a [72], 2b [18] (b) 2 min; 2a [86]
3		 3a	(a) 1 h; [80] (b) 1 min; [85]
4	 (108-110)	 [120 (122)]	(a) 10 h; [70] (b) 2 min; [95]
5	 (94-95)	 5a [127 (128)]  5b [138 (140)]	(a) 2 h; 5a [78], 5b [12] (b) 2 min; 5a [75]
6	 (122-123)	 6a [103 (104)]  6b [216 (218)]	(a) 12 h; 6a [25], 6b [35] (b) 5 min; 6a [65], 6b [28]
7	 (230-232)	 [217-218 (219)]	(a) 72 h; [68] (b) 8 min; [80]
8	 (161-162)	 [202 (195)]	(a) 80 h; [58] (b) 4 min; [98]
9	 (265-267)	 9a [236]	(a) 70 h; [60] (b) 4 min; [92]
10	 (148-150)	 10a [128]	(a) 10 h; [82] (b) 6 min; [85]
11	 (117-119)	 [142-143 (144)]	(a) 14 h; [72] (b) 8 min; [85]
12		 [80 (82)]	(a) 10 h; [75] (b) 3 min; [95]

^aReaction conditions: substrate, CAN (1:1 molar ratio), ground in a mortar, rt.

^bSubstrate:CAN (1:1 molar ratio), ground, MW, 600W.

^cYields refer to chromatographically isolated pure products which were identified by their spectral characteristics (IR, ¹H NMR, ¹³C NMR, EIMS) and comparison with authentic samples (m.p. co-TLC, IR) when available; attempt to expedite nitration of 7-hydroxycoumarin (entry 7) by heating the ground mixture at 100 °C led to runaway reaction in one experiment.

reaction time and yield not only with the intrinsic reactivity of the substrate but also to its melting point. However, the low yield¹⁵ and long reaction time for high melting substrates were compelling reasons to evaluate a microwave-assisted solvent-free protocol of nitration with solid CAN, particularly for reluctant substrates. Previously, we reported⁸ expeditious CAN-mediated nitration with montmorillonite K-10 clay support under microwave irradiation for 6-hydroxycoumarins. Herein, we report an expeditious and efficient nitration

protocol employing CAN without any solid support under microwave irradiation. An intimate mixture of 1,3-dihydroxybenzene (entry 4) and solid, thoroughly powdered CAN, upon irradiation with microwave (600W), was attended with initial formation of brown fumes that gradually faded away as the reaction progressed. Nitration was complete within 2 min affording 1,3-dihydroxy-4-nitrobenzene in excellent yield (95%). Formation of brown fumes has been also observed in the oxidation of alcohols to ketones with metallic nitrates

supported on silica gel.¹⁶ Microwave-assisted thermal homolytic cleavage of one of the nitrate groups of CAN presumably generates the nitrogen dioxide radical which acts as nitrating agent. Remarkably, solid-state nitration with nitrogen dioxide⁷ gas gives *ortho*-selective nitration supporting our view.

The microwave-assisted procedure works well for activated low-melting phenols as well as relatively high-melting phenols and hydroxycoumarins. However, solid-state nitration with CAN by the aggregation method works well for phenols but not as well for hydroxycoumarins. It offers an excellent balance of selectivity, yield, reaction time and non-aqueous simple work-up and is therefore synthetically more attractive. Hopefully this will become the method of choice of the nitration for phenols and hydroxycoumarins.

Experimental

Representative procedure for solid-state nitration with CAN: Solid phenol (200 mg, 2.1 mmol) was ground intimately with solid CAN (1.15 g, 2.1 mmol) in an agate mortar when the solid mixture becomes a brownish-black paste immediately. It was removed to a vial where it was kept closed for 30 min. It was directly charged into a silica gel column and chromatographed using chloroform-ethyl acetate (98:2) as the eluent to afford 2-nitrophenol, m.p. 43 °C (lit.^{17b} 45 °C) (130 mg, 84%) as the major product along with 4-nitrophenol, m.p. 113 °C (lit.^{17b} 114 °C) in a yield of 20 mg (5%).

General procedure for the microwave-assisted solvent-less nitration with CAN: The substrate and thoroughly-powered CAN (in 1:1.1 molar equivalents) were ground in a mortar for 2–4 min. This aggregate was irradiated with microwave for the specified time (Table 1) at 600W in a domestic microwave oven (BPL India, 2450 MHz). For microwave irradiations exceeding 3 min, the total reaction time corresponded to cycles of 3 min with cooling periods 30 s in between two cycles. This time interval was also utilised to monitor the progress of reaction by TLC. After the reaction was over, the reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 5 ml for 1 mmol scale). Removal of solvent under vacuum yielded a residue that was chromatographed over silica gel (60–120 mesh) for separation or purification of products.

2-Allyl-4-nitrophenol (2a): m.p. 60 °C. IR (KBr) ν_{\max} (cm⁻¹) 3340, 3060, 2500, 1590, 1480, 1430, 1330, 1270, 1200, 1060, 940. ¹H NMR (300 MHz, CDCl₃): δ 3.46 (2H, d, *J* = 6.3 Hz, ArCH₂), 5.15–5.24 (2H, m, -CH=CH₂), 5.93–6.04 (1H, m, -CH₂-CH=CH₂), 6.41 (1H, bs, OH), 6.90 (1H, d, *J* = 8.4 Hz, H-6), 8.03 (1H, d, *J* = 3 Hz, H-3), 8.06 (1H, dd, *J* = 8.4 Hz, 3 Hz, H-5). ¹³C NMR (CDCl₃): δ_c 34.50 (ArCH₂), 115.85 (C-6), 117.83 (-CH=CH₂), 124.23 (C-5), 126.38 (C-3), 126.87 (C-2), 134.70 (-CH=CH₂), 141.80 (C-4), 159.88 (C-1). MS *m/z* (%) 179 (50.6), 177 (100), 163 (18.9), 162 (20.0), 148 (35.7), 132 (37.7), 131 (46.3), 130 (31.2), 117 (43.3), 114 (26.9), 105 (42.3), 103 (59.3). Anal. calcd. for C₉H₉NO₃: C, 60.3; H, 5.0; N, 7.8. Found: C, 60.2; H, 5.0; N, 7.9.

2-Allyl-4,6-dinitrophenol (2b): m.p. 144 °C. IR (KBr) ν_{\max} (cm⁻¹) 3260, 3064, 2945, 1600, 1546, 1490, 1456, 1335, 1316, 1245, 1228, 1136, 1012, 986. ¹H NMR (300 MHz, CDCl₃): δ 3.56 (2H, d, *J* = 3.4 Hz, ArCH₂), 5.15–5.20 (2H, m, -CH=CH₂), 5.96–6.07 (1H, m, -CH=CH₂), 7.65 (1H, s, H-5), 8.16 (1H, s, H-3), 10.95 (1H, bs, OH). ¹³C NMR (CDCl₃): δ_c 33.79 (ArCH₂=CH-), 117.16 (-CH=CH₂), 120.61(-CH=CH₂), 130.44 (C-5), 132.56 (C-3), 133.88 (C-2), 134.71 (C-6), 135.53 (C-4), 152.85 (C-1). Anal. calcd. for C₉H₈N₂O₅: C, 48.2; H, 3.6; N, 12.5. Found: C, 48.2; H, 3.5; N, 12.5.

2-Allyl-3-methyl-6-nitrophenol (3a): viscous oil. IR (neat) ν_{\max} (cm⁻¹) 3230, 3158, 3057, 2932, 1620, 1608, 1590, 1572, 1467, 1354, 1317, 1267, 1243, 1158, 1025, 940. ¹H NMR (300 MHz, CDCl₃): δ 2.50 (3H, s, 3-Me), 4.63 (2H, d, *J* = 5.1 Hz, ArCH₂), 5.32–5.44 (2H, m, -CH=CH₂), 5.96–6.12 (1H, m, -CH=CH₂), 7.02 (1H, d, *J* = 8.4 Hz, H-4), 8.21 (1H, d, *J* = 8.4 Hz, H-5), 10.2 (1H, bs, -OH). (This is formally a tentative characterisation based on the spectroscopic data available and the products from the other reactions.)

5,7-Dihydroxy-4-methyl-6-nitrocoumarin (9a): m.p. 236 °C. IR (KBr) ν_{\max} (cm⁻¹) 3090, 1670, 1590, 1505, 1390, 1290, 1185, 1110. ¹H NMR (300 MHz, DMSO-d₆): δ 2.01 (3H, s, 4-Me), 6.21 (1H, s, H-3), 6.74 (1H, s, H-8). MS *m/z* (%) 237 (100), 219 (5.3), 210 (8.3), 209 (64.8), 202 (3.0), 192 (6.5), 191 (4.9), 190 (7.3), 179 (9.6), 178 (4.6). Anal. calcd. for C₁₀H₇NO₆: C, 50.6; H, 2.95; N, 5.9. Found: C, 50.6; H, 3.0; N, 5.9.

8-Allyl-7-hydroxy-6-nitrocoumarin (10a): m.p. 128 °C. IR (KBr) ν_{\max} (cm⁻¹) 3260, 3060, 1720, 1610, 1450, 1420, 1390, 1320. ¹H NMR (300 MHz, DMSO-d₆): δ 3.52–3.54 (2H, m, ArCH₂), 4.96–5.04 (2H, m, -CH=CH₂), 5.86–5.99 (1H, m, -CH=CH₂), 6.45 (1H, d, *J* = 9.5 Hz, H-3), 8.09 (1H, d, *J* = 9.6 Hz, H-4), 8.46 (1H, s, H-5). MS *m/z* (%) 247 (100), 229 (69.8), 228 (19.0), 219 (4.5), 199 (44.6), 171 (63.0), 170 (25.3), 143 (13.5), 142 (10.0). Anal. calcd. for C₁₂H₉NO₅: C, 59.0; H, 3.6; N, 5.7. Found: C, 58.2; H, 3.6 N, 5.6.

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