Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 16 Aug 2006.

To cite this article: N. Ganguly , A. K. Sukai & S. De (2001) CERIUM(IV) AMMONIUM NITRATE MEDIATED NITRATION OF COUMARINS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:2, 301-309, DOI: 10.1081/SCC-100000214

To link to this article: http://dx.doi.org/10.1081/SCC-100000214

SYNTHETIC COMMUNICATIONS, 31(2), 301–309 (2001)

CERIUM(IV) AMMONIUM NITRATE MEDIATED NITRATION OF COUMARINS

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ABSTRACT

A new convenient method of nitration of coumarins using cerium(IV) ammonium nitrate (CAN) has been developed. Higher regioselectivity is observed with CAN and hydrogen peroxide in aqueous medium in comparison with CAN in acetic acid for nitration of 7-hydroxycoumarin, 7-hydroxy-4-methyl coumarin and their derivatives.

The search for novel procedures of nitration of aromatics to replace the classical method based on nitric acid in sulphuric acid is an area of considerable current interest (1). Both the replacements of the solvent system (2) and the reagent (3) have been attempted to achieve higher regioselectivity, particularly to get less accessible isomers. Recently, aminocoumarins have been put to effective use as starting materials for the synthesis of bioactive pyrrolocoumarins (4) and pyrano[3,2-f]benzo[b]thiophenes (5). This led us to develop new simple procedures for the synthesis of nitrocoumarins that may be utilized as precursors of aminocoumarins. We decided to examine the scope of cerium(IV) ammonium nitrate for this purpose in view of its versatile uses (6–8) as the reagent for nitration

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of aromatic hydrocarbons (9–11). However, few reports (12) are documented concerning its use in this regard for heterocycles. Herein we report the results of CAN mediated nitration of coumarins with varying degree of electron availabilities in the carbocyclic as well as α-pyrone ring.

RESULTS AND DISCUSSION

Coumarin (**1a**) on treatment with one equivalent of CAN in acetic acid gave 6-nitrocoumarin as the sole product in excellent yield (92%). The presence of activating hydroxy and methoxy group, as in **(1b)** and (**1c**), respectively, also led to predominant nitration at C-6, accompanied by minor amounts of dinitro derivatives (**3b**) and (**3c**), respectively (Table 1). Regioselectivity in nitration substantially improved for both these substrates when CAN was used along with cooxidant 30% hydrogen peroxide in water. Thus, the ratio of 7-hydroxy-6-nitrocoumarin (**2b**)

Table 1. Nitration of Coumarins with CAN

Entry	Substrate	Reaction Conditions	Product[a] (Yield, %) [mp]
1	**1a**	CAN, HOAc, 2 h	**2a** (92) [186°]
2	**1b**	(a) CAN, HOAc, 1.5 h	**2b** (68) [219°], **3b** (18) [198–200°]
		(b) CAN, H_2O, 30% H_2O_2, 1 h, 50–60°	**2b** (71), **3b** (8)
3	**1c**	(a) CAN, HOAc, 1.5 h	**2c** (74) [216°], **3c** (10) [121°]
		(b) CAN, H_2O, 30% H_2O_2, 1 h, 50–60°	**2c** (68), **3c** (4)
4	**1d**	(a) CAN, HOAc, 1.5 h	**2d** (72) [195°], **3d** (8) [224°]
		(b) CAN, H_2O, 30% H_2O_2, 45 min, 50°	**2d** (76)
		(c) CAN (4moles), 6N $HClO_4$, 80°, 1 h	**2d** (75), **3d** (7)
		(d) CAN (1 mole), 30% H_2O_2 (1 ml per mmol of substrate), HOAc	**3d** (68), **4d** (8) [240°(d)]
5	**1e**	(a) CAN, HOAc, 1.5 h	**2e**, **3e** (1:1)
		(b) CAN, H_2O, 30% H_2O_2, 45 min, 50°	**2e**, **3e** (3:1)
6	**1f**	CAN, HOAc, 2 h	No reaction
7	**1g**	CAN, HOAc, 8 h	No reaction

[a]Refers to isolated yields after chromatography; the products were characterized from their spectroscopic data.

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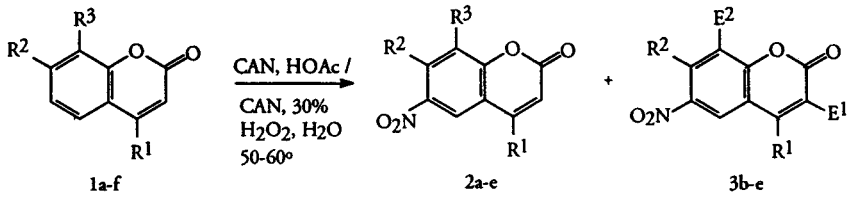
to 7-hydroxy-6, 8-dinitrocoumarin (**3b**) increased to 9:1 with CAN in the aqueous medium. Interestingly, cleavage of the deactivating lactone ring of (**1c**) with methanolic sodium methoxide to methyl 4′-methoxycoumarate (**4c**), its nitration with CAN in acetic acid to (**5c**) followed by reclosure of the lactone ring, provided a simple reaction sequence (Scheme 1) leading to (**2c**) exclusively in high overall yield. Predominant nitration in the carbocyclic ring was also observed for 7-hydroxy-4-methylcoumarin (**1d**); however, the presence of C-4 methyl activated the lactone ring towards nitration, giving some 3,6-dinitrocoumarin derivative (**3d**). Attempted oxidation of C-4 methyl of (**1d**) in 6N perchloric acid failed. Better selectivity in favor of the mononitro compound was also found in the aqueous medium here. Treatment of (**1d**) with CAN (1 mole) and 30% hydrogen peroxide in acetic acid led to the formation of some trinitro compound, 7-hydroxy-4-methyl-3,6,8-trinitrocoumarin (**4d**), as well as (**2d**), suggesting increased nitrating ability of CAN and hydrogen peroxide combination in acetic acid. 7-Methoxy-4methylcoumarin (**1e**) gave an inseparable mixture of mono and dinitro products in the ratio of 1:1 (analyzed from ^{1}H NMR spectrum of the mixture). Attempt to bias the nitration in favor of the mononitro derivative (**2e**) was a limited success with the ratio of (**2e**) to (**3e**) increasing to 3:1. The presence of deactivating acetoxy group at C-7 (**1f**) inhibited nitration in acetic acid (2 h). With 7-hydroxy-8-iodocoumarin (**1g**), nitration did not occur with CAN in acetic acid even after longer reaction time (8 h), presumably due to steric effect. The results of these experiments are summarized in Table 1.

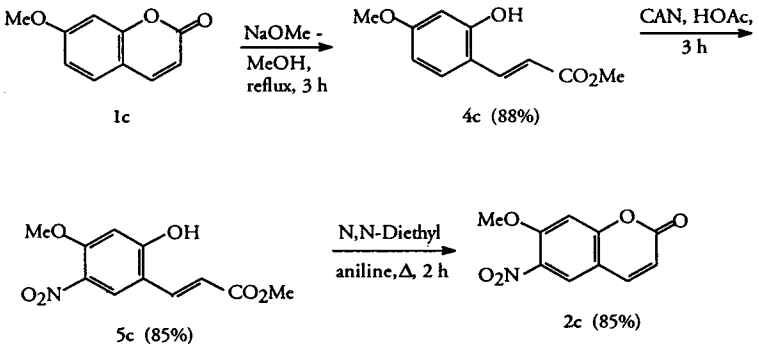


1a-f 2a-e 3b-e

1a, $R^1=R^2=R^3=H$
1b, $R^1=R^3=H$, $R^2=OH$
1c, $R^1=R^3=H$, $R^2=OMe$
1d, $R^1=Me$, $R^2=OH$, $R^3=H$
1e, $R^1=Me$, $R^2=OMe$, $R^3=H$
1f, $R^1=R^3=H$, $R^2=OAc$
1g, $R^1=H$, $R^2=OH$, $R^3=I$

3b, $E^1=H$, $E^2=NO_2$
3c, $E^1=H$, $E^2=NO_2$
3d, $E^1=NO_2$, $E^2=H$
3e, $E^1=NO_2$, $E^2=H$

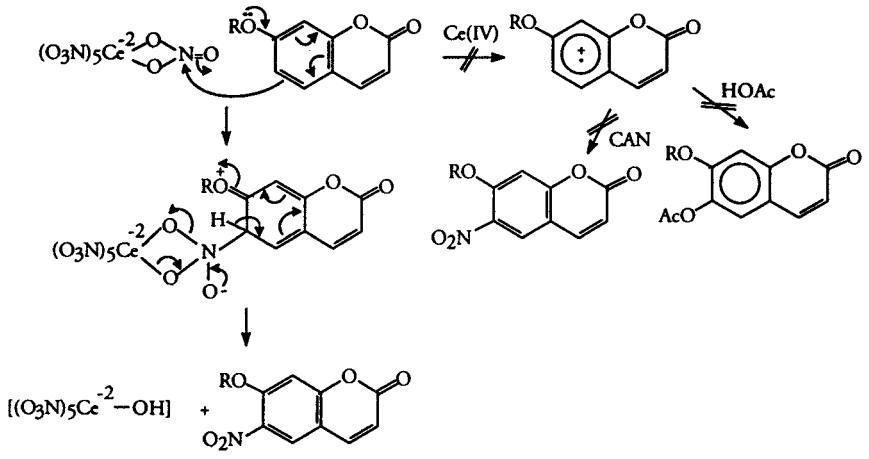
Nitration of coumarins with CAN is unlikely to involve oxidative mechanism (13,14) requiring generation of radical cation intermediate from an electron deficient benzannelated pyrone system. The nonformation of acetoxylated products (13) formed by solvolytic capture by a carbocation intermediate supports this view. Our observation that nitration was optimal with one equivalent of CAN per



Scheme 1.

equivalent of substrate is also consistent with a ligand transfer mechanism, with bidentate nitrato structure (15) of CAN the key to its nitrating ability (Scheme 2). This mechanism obviates direct involvement of free NO_2^+ and NO_2 in nitration. In fact, the addition of ammonium nitrate to the nitrating mixture did not affect the rate of reactions, thereby suggesting noninvolvement of free NO_2^+ generated by the action of acetic acid on NO_3^- from CAN. The pruning of nitrating ability of CAN and H_2O_2 in water seems to result from the reduced electrophilic character of Ce(IV) consequent upon entry of the more electron donating ligands water/hydroperoxide anion into its coordination sphere, replacing one or more NO_3.

In conclusion, nitration of coumarins with CAN adds a new reaction manifold of CAN. Coumarin, 7-hydroxycoumarin, 7-hydroxy-4-methylcoumarin, and



Scheme 2.

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their derivatives have been nitrated using CAN in acetic acid and water in the presence of hydrogen peroxide. The combination of CAN and hydrogen peroxide provides better regioselective nitration at C-6 of 7-hydroxycoumarins and their derivatives.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were run for KBr disks (solid) or liquid film on a Perkin Elmer 1310 instrument. ^{1}H NMR were recorded on a Jeol FX 100 (100 MHz) and Bruker AM-300L instruments with TMS as internal standard. Mass spectra were carried out at RSIC, CDRI, Lucknow. Silica gel (60–120 mesh) was used for chromatographic separation and silica gel G was used for TLC.

General Procedure for the Nitration of Coumarins with CAN in Acetic Acid

To an ice-cold solution of coumarin (3 mmol) in acetic acid (5 mL) was added CAN (3 mmol) in three portions over 10 min. The mixture was then stirred at room temperature for the specified time (Table 1). After the completion of the reaction, the reaction mixture was poured into water (30 mL) and extracted with chloroform/ethyl acetate, washed with brine, sodium bicarbonate solution, and dried (Na_2SO_4). Concentration of the combined organic extracts and chromatographic separation afforded the products.

General Procedure for the Nitration of Coumarins with CAN and Hydrogen Peroxide in Water

The substrate (1 mmol) was charged in two portions to a solution of CAN (1 mmol) in water (5 mL) to which 30% hydrogen peroxide (1 mL) was already added. The resulting mixture was heated at 50°–60°C with continuous vigourous stirring for 1 h. After the completion of the reaction, the reaction mixture was cooled, diluted with water (20 mL), and extracted with chloroform (3 × 30 mL). Removal of solvent from the dried concentrated extract amd chromatographic purification afforded the products.

Conversion of 7-Methoxycoumarin (1c) to Methyl 4′-methoxycoumarate (4c)

Metallic sodium (1.7 g) was dissolved in absolute methanol (20 mL) and the mixture was refluxed for 1 h. To it was added **1c** (175 mg, 1 mmol) and the mixture

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was refluxed for 3 h under nitrogen cover. Then the reaction mixture was cooled and quenched by pouring into ice (40 g), acidified with 6N hydrochloric acid, and extracted with chloroform (3 × 20 mL). Removal of solvent, drying (Na_2SO_4), and chromatographic purification gave a light yellow crystalline product **3c** (182 mg, 88%) mp 143°C (ethyl acetate-light petrol), lit. (16) 140°–142°C.

Nitration of (4c) with CAN in Acetic Acid to Methyl-4′-Methoxy-5′-Nitrocoumarate

5c (100 mg, 0.48 mmol) was allowed to react with CAN (260 mg, 0.48 mmol) in acetic acid (3 mL) for 3 h at room temperature. Usual work-up and chromatography yielded yellow crystals (**4c**) as the sole product (104 mg, 85%), mp 228°C (ethylacetate-light petrol).

Ring Closure of (5c) to (2c) in Refluxing N,N-Diethylaniline

A mixture of (**5c**) (152 mg, 0.6 mmol) in N,N-diethylaniline (3 mL) was refluxed for 2 h. The reaction mixture was cooled, poured into ice-cold 6N hydrochloric acid (20 mL), and extracted with chloroform (3 × 20 mL). The chloroform layer was washed with water and dried over Na_2SO_4. Usual concentration and chromatography gave (**2c**) (113 mg, 85%).

Characterization Data for Products

(2b)

IR (KBr) ν_{max} (cm^{-1}) 3220, 1720, 1600, 1560, 1515, 1300, 900, 820. ^1H NMR (100 MHz, DMSO-d_6) δ 6.40 (1H, *d*, J = 9.5 Hz, H-3), 6.98 (1H, *s*, H-8), 8.04 (1H, *d*, J = 9.5 Hz, H-4), 8.42 (1H, *s*, H-5). MS *m*/*z* (%) 207 (M^+, 100), 190 (6.2), 179 (28.8), 177 (10.8), 149 (22.2). Anal. calcd for $C_9H_5NO_5$: C, 52.17; H, 2.42; N, 6.76. Found: C, 52.04; H, 2.36; N, 6.71.

(3b)

IR (KBr) ν_{max} (cm^{-1}) 3250, 1735, 1615, 1565, 1530, 1320, 870, 830. ^1H NMR (300 MHz, DMSO-d_6) δ 6.29 (1H, *d*, J = 9.6 Hz, H-3), 7.98 (1H, *d*, J = 9.6 Hz H-4), 8.45 (1H, *s*, H-5). MS *m*/*z* (%) 252 (M^+, 45.2), 224 (3.6), 207 (100), 179 (37). Anal. calcd for $C_9H_4N_2O_7$: C, 42.86; H, 1.59; N, 11.11. Found: C, 42.75; H, 1.52; N, 10.98.

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(2c)

IR (KBr) ν_{max} (cm^{-1}) 3020, 2940, 1720, 1610, 1520, 1310, 1280, 1095, 980, 810. ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.97 (3H, *s*, 7-OMe), 6.36 (1H, *d*, J = 10 Hz, H-3), 7.30 (1H, *s*, H-8), 7.95 (1H, *d*, J = 10 Hz, H-4), 8.30 (1H, *s*, H-5). MS *m/z* (%) 221 (100), 220 (13), 191 (17.2), 190 (12.3), 175 (11.4). Anal. calcd for $C_{10}H_7NO_5$: C, 54.30; H, 3.17; N, 6.33. Found: C, 54.18; H, 3.34; N, 6.21.

(3c)

IR (KBr) ν_{max} (cm^{-1}) 3040, 2950, 1750, 1620, 1600, 1550, 1530, 1365, 1225, 1020, 980, 835. ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.03 (3H, *s*, 7-OMe), 6.51 (1H, *d*, J = 10 Hz, H-3), 7.75 (1H, *d*, J = 10 Hz, H-4), 8.30 (1H, *s*, H-5). MS *m/z* (%) 266 (100), 236 (37.5), 220 (2.6), 192 (4.2). Anal. calcd for C_{10},$H_6N_2O_7$: C, 45.11; H, 2.26; N, 10.53. Found: C, 45.25; H, 2.12; N, 10.48.

(4c)

^{13}C NMR (25 Hz, $CDCl_3$): δ_C 51.54 (2′-CO_2*Me*), 55.29 (4′-OMe), 101.06 (C-3′), 107.06 (C-6′), 114.99 (C-5′), 130.40 (C-2), 140.78 (C-1), 154.88 (C-1′), 157.04 (C-2′), 162.58 (C-4′), 169.23 (2′-CO_2Me). Anal. calcd for $C_{11}H_{12}O_4$: C, 63.46; H, 5.77. Found: C, 63.32; H, 5.65.

(5c)

IR (KBr) ν_{max} (cm^{-1}) 3180, 2950, 1670, 1620, 1575, 1530, 1310, 1210, 1090, 1000, 980, 880, 845. ^{1}H NMR (100 MHz, DMSO-d_6) δ 3.72, 3.88 (each 3H, *s*, CO_2Me, OMe), 6.66 (1H, *d*, J = 16 Hz, H-2), 6.71 (1H, *s*, H-3′), 7.70 (1H, *d*, J = 16 Hz, H-1), 8.32 (1H, *s*, H-6′). MS *m/z* (%) 253 (65.3), 236 (9.4), 222 (51.5), 221 (100), 194 (3.5), 193 (12.7), 191 (15.3), 163 (11.7). Anal. calcd for $C_{11}H_{11}NO_6$: C, 52.17; H, 4.35; N, 5.53. Found: C, 51.98; H, 4.24; N, 5.67.

(2d)

IR (KBr) ν_{max} (cm^{-1}) 3125, 3060, 1730, 1620, 1530, 1390. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (3H, *s*, 4-Me), 6.39 (1H, *s*, H-3), 7.39 (1H, *s*, H-8), 8.47 (1H, *s*, H-5). MS *m/z* (%) 221 (100), 220 (11.1), 191 (14.4), 175 (6.1), 174 (4.2), 163 (24.8). Anal. calcd for $C_{10}H_7NO_5$: 54.30; H, 3.17; N, 6.33. Found: C, 54.18; H, 3.08; N, 6.46.

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(3d)

IR (KBr) ν_{max} (cm^{-1}) 3220, 1730, 1620, 1565, 1520, 1340, 1150, 1060, 850, 830, 750. ^{1}H NMR (100 MHz, DMSO-d_6) δ 2.50 (3H, *s*, 4-Me), 7.08 (1H, *s*, H-8), 8.52 (1H, *s*, H-5). MS m/z (%) 266 (100), 249 (10.9), 220 (2.3), 208 (44.2). Anal. calcd for $C_{10}H_6N_2O_7$: C, 45.11; H, 2.26; N, 10.53. Found: C, 45.02; H, 2.14; N, 10.41.

(4d)

IR (film) ν_{max} (cm^{-1}) 3160, 3080, 1765, 1640, 1550, 1535, 1365, 1100, 840. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.47 (3H, *s*, 4-Me), 8.37 (1H, *s*, H-5), 11.23 (1H, *s*, 7-OH). MS m/z (%) 311 (100), 253 (23.3), 208 (4.1), 173 (29.9). Anal. calcd for $C_{10}H_5N_3O_9$: C, 38.59; H, 1.60; N, 13.50. Found: C, 38.44; H, 1.47; N, 13.58.

(2e) and (3e) (in 1:1 mixture)

^{1}H NMR (100 MHz, DMSO-d_6) δ 2.44, 2.56 [each 3H, *s*, 4-Me *s* of (**2e**) and (**3e**)], 4.04, 4.08 [each 3H, *s*, 7-OMe s of (**2e**) and (**3e**)], 6.36 [1H, *s*, H-3 of (**2e**)], 7.36 and 7.56 [each 1H, *s*, H-8s of (**2e**) and (**3e**)], 8.3 and 8.6 [each 1H, *s*, H-5s (**2e**) and (**3e**)].

ACKNOWLEDGMENTS

AKS is thankful to the University of Kalyani for a research fellowship.

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Received in the UK November 9, 1999

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