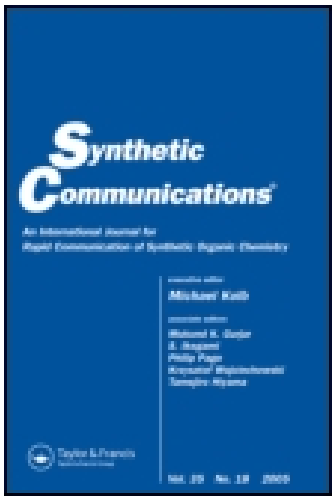

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Vandana Bansal [a] & R. N. Khanna [b]

[a] Department of Chemistry , Loyola University , Lakeshore Campus, Chicago, IL, 60626, U.S.A.

[b] Department of Chemistry , Delhi University , Delhi, 110 007, India

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REGIOSELECTIVE MONONITRATION OF COUMARINS USING CHROMIUM NITRATE AS NITRATING AGENT

Vandana Bansal[1,*] and R. N. Khanna[2]

[1]Loyola University, Department of Chemistry,
Lakeshore Campus, Chicago, IL 60626
[2]Department of Chemistry, Delhi University,
Delhi-110 007, India

ABSTRACT

A very efficient and simple method is presented for the regioselective mononitration of coumarins, using chromium nitrate in acetic anhydride, in high yields at room temperature.

Transition-metal nitrate salts have been used in the presence of strong mineral acids to nitrate organic compounds and quite a few examples are cited in patent literature. It was in 1925 when Menke[1] showed that transition-metal nitrate salts such as, copper nitrate in acetic anhydride can be used to nitrate aromatic compounds. However, not much work has been reported in the direct nitration of coumarins. Direct nitration of coumarins has been carried out with mixed acids[2] and thallium(III)nitrate,[3] but these methods suffer from the disadvantages of harsh acidic conditions, long reaction times, polynitration and side reactions such as oxidation,

*Corresponding author.

e.g., thallium(III)nitrate[3] gave nitrocoumarins after 7 days along with other side products.

Apart from the wide natural occurrence and biological activity[4] of coumarins, various nitro coumarins exhibit biological properties,[5,6] such as, 7-hydroxy-8-nitrocoumarin is cytotoxic[7] and 3-nitrocoumarin is bio-antioxidant,[8] neurotropic[9] and is useful in treatment of asthma, hay fever and rhinitis.[10] Nitrocoumarins are also useful as synthetic intermediates for the preparation of amino[11,12] and mercapto[13] coumarins and act as an activating group in various synthetic preparations of coumarin derivatives.[14,15]

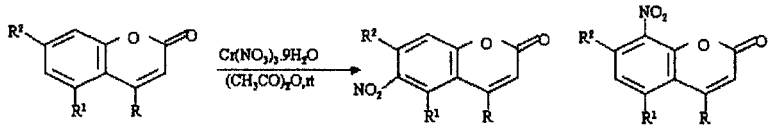
The wide biological and synthetic utility of nitrocoumarins and a relative absence of an efficient nitration method for coumarins, prompted us to investigate the nitration of coumarins. Chromium nitrate has been used to nitrate aromatic hydrocarbons,[16,17] polymeric compounds[18] and phenols.[19] But to the best of our knowledge it has not been used for the nitration of heterocyclic compounds. In this communication, we report a mild, efficient and regioselective mononitration of coumarins using chromium nitrate in high yields at room temperature without any side reactions, such as oxidation and coupling.

In a typical reaction, coumarins (**1a–f**) on treatment with $Cr(NO_3)_3{\cdot}9H_2O$ in acetic anhydride at room temperature give mononitrated products at 6 and 8 positions (**2b–f**, **3a–c**, **4f**) in 1–2 h (table, scheme).

Table. Nitration of Coumarins (**1a–f**) Using Chromium Nitrate in Acetic Anhydride at Room Temperature Giving Nitro Products (**2b–f**, **3a–c**, **4f**)

Substrate	Product[a]	Time (h)	Yield[b] (%)	M.P. (lit.) (°C)
1a	**3a**	2	69	192 (191)[20]
1b	**2b**	1	39	218 (219)[19]
	3b		40	246 (245)[21]
1c	**2c**	1.5	36	228 (229)[22]
	3c		40	257 (256)[23]
1d	**2d**	1.5	68	225
1e	**2e**	2	71	125–127
1f	**2f**	1	41	90–92
	4f		36	160

[a]Products are characterized by physical and spectral data.
[b]Yields refer to isolated pure products.



1a: R=R^1=R^2=H

1b: R=R^1=H; R^2=OH

1c: R=CH$_3$; R^1=H; R^2=OH

1d: R=R^1=H; R^2=OCH$_3$

1e: R=H; R^1=R^2=OCH$_3$

1f: R=Ph; R^1=H; R^2=OH

2b: R=R^1=H; R^2=OH

2c: R=CH$_3$; R^1=H; R^2=OH

2d: R=R^1=H; R^2=OCH$_3$

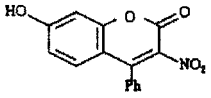
2e: R=H; R^1=R^2=OCH$_3$

2f: R=Ph; R^1=H; R^2=OH

3a: R=R^1=R^2=H

3b: R=R^1=H;R^2=OH

3c:R=CH$_3$;R^1=H;R^2=OH



4f

Scheme.

The general reaction shown in Eq. (1) may be written to describe the nitration of coumarins with chromium nitrate in acetic anhydride.

$$\text{Coumarin} + Cr(NO_3)_3 \cdot 9H_2O + \text{excess } (CH_3CO)_2O \longrightarrow \text{Coumarin} - NO_2 + CH_3CO_2Cr(NO_3)_2 + CH_3COOH \quad (1)$$

The reaction may proceed via in situ generation of "acetyl nitrate" which may dissociate to yield nitronium ion, as shown in Eq. (2).

$$(CH_3CO)_2O + Cr(NO_3)_3 \rightleftarrows CH_3C(O)ONO_2 + CH_3C(O)OCr(NO_3)_2$$
$$CH_3C(O)ONO_2 \rightleftarrows CH_3COO^- + NO_2^+ \quad (2)$$

Excess of acetic anhydride keeps the medium anhydrous as the metal salt is hydrated.

Both 7-hydroxycoumarin (**1b)** and 7-hydroxy-4-methyl-coumarin (**1c**) give 6 and 8-nitro products (**2b–c**, **3b–c**) in 1 to 1.5 h in good yields and 7-methoxy (**1d**) and 5,7-dimethoxycoumarin (**1e**) give only 6-nitro product (**2d–e**). However, coumarin (**1a**) gives only 8-nitro product (**3a**) and takes comparatively longer time. The yield of the product does not increase even when the reaction time is increased. This is in accordance with the typical nitration reaction where nitronium ion favors attack at ortho to the electron

donating group. In coumarins, the position with the highest electron density (C-8) is preferably attacked. Interestingly, 7-hydroxy-4-phenylcoumarin (**1f**) gives 3-nitro product (**4f**) also along with 6-nitro product (**2f**). It could be due to the high electron density at C-3 position because of the resonance stabilization of the positive charge at the C-4 position by phenyl ring. All the products have been characterized by physical and spectral data (^{1}H NMR, IR, CHN). The spectral data of the unknown compounds have been provided.

In conclusion, we have developed a mild and effective method for the regioselective mononitration of coumarins in good yields and short time.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Shimadzu IR-435 spectrophotometer (values in cm^{-1}). NMR spectra were recorded on Perkin-Elmer R-32 spectrophotometer (90 MHz). Chemical shifts are given in ppm (δ) with respect to tetramethylsilane and coupling constants (J) are in Hertz.

General Procedure

To a mixture of coumarin **1a** (146 mg, 1 mmol) and chromium nitrate·$9H_2O$ (400 mg, 1 mmol) was added 15 ml of acetic anhydride. The reaction mixture was stirred at room temperature for 2 h. After the completion of the reaction, as monitored on TLC, the reaction mixture was filtered and the filtrate was diluted with 100 ml of water. The contents were extracted with ether (2 × 20 ml) and dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the resulting crude product was subjected to column chromatography (hexane) when it afforded 8-nitrocoumarin (**3a**) in 69% yield; m.p. 192°C (lit m.p. 191°C).

SPECTRAL DATA

7-Methoxy-6-nitrocoumarin (2d)

^{1}H NMR (DMSO-d_6): 4.00 (s, 3H, OCH_3), 6.50 (d, $J = 9.5$ Hz, 1H, C_3-H), 7.00 (s, 1H, C_8-H), 7.80 (d, 1H, $J = 9.5$ Hz, C_4-H), 8.10 (s, 1H, C_5-H); IR (KBr): 910, 1365, 1520, 1725. Anal. calcd for $C_{10}H_7O_5N$: C, 54.29; H, 3.16; N, 6.33. Found: C, 54.27; H, 3.16; N, 6.32.

5,7-Dimethoxy-6-nitrocoumarin (2e)

^{1}H NMR (DMSO-d_6): 4.00 (s, 6H, OCH_3), 7.60 (d, 1H, $J = 7.0$ Hz, C_3-H), 7.80 (d, 1H, $J = 7.0$ Hz, C_4-H), 8.00 (s, 1H, C_8-H); IR (KBr): 910, 1360, 1520, 1725, 3220. Anal. calcd for $C_{11}H_9O_6N$: C, 52.59; H, 3.58; N, 5.57. Found: C, 52.58; H, 3.60; N, 5.59.

7-Hydroxy-6-nitro-4-phenylcoumarin (2f)

^{1}H NMR (DMSO-d_6): 6.20 (s, 1H, C_3-H), 7.20 (s, 1H, C_5-H), 7.30 (m, 5H, Ar-H), 8.10 (s, 1H, C_8-H); IR (KBr): 900, 1365, 1520, 1725, 3200. Anal. calcd for $C_{15}H_9O_5N$: C, 63.6; H, 3.17; N, 4.94. Found: C, 63.5; H, 3.18; N, 4.89.

7-Hydroxy-3-nitro-4-phenylcoumarin (4f)

^{1}H NMR (DMSO-d_6): 6.80 (d, 1H, $J = 7.0$ Hz, C_6-H), 7.10 (d, 1H, $J = 7.0$ Hz, C_5-H), 7.20 (m, 5H, Ar-H), 7.70 (s, 1H, C_8-H); IR (KBr): 900, 1365, 1520, 1725, 3200. Anal. calcd for $C_{15}H_9O_5N$: C, 63.6; H, 3.17; N, 4.94. Found: C, 63.5; H, 3.15; N, 4.89.

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