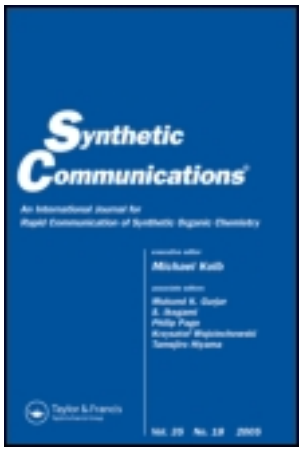


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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

Mono-nitration of Coumarins by Nitric Oxide

Liandi Lei [a] , Desuo Yang [a] , Zhongquan Liu [a] & Longmin Wu [a]

[a] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, China

Published online: 21 Aug 2006.

To cite this article: Liandi Lei , Desuo Yang , Zhongquan Liu & Longmin Wu (2004) Mono-nitration of Coumarins by Nitric Oxide, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:6, 985-992, DOI: 10.1081/SCC-120028628

To link to this article: http://dx.doi.org/10.1081/SCC-120028628

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 6, pp. 985–992, 2004

Mono-nitration of Coumarins by Nitric Oxide

Liandi Lei, Desuo Yang, Zhongquan Liu, and Longmin Wu*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, China

ABSTRACT

A novel methodology for the efficient and selective nitration of coumarins has been developed. The reaction of coumarins containing a hydroxy group with nitric oxide in CH_2Cl_2 or CH_3CN gave aromatic mono- and regio-specific-nitrated coumarins in various yields.

Key Words: Coumarins; Nitration; Nitric oxide.

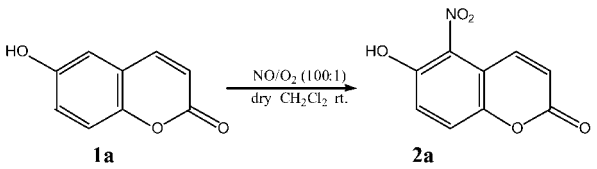
It is well known that coumarin derivatives exhibit pronounced medicinal effects.[1] In particular, the nitrated and hydroxylated coumarins play a therapeutic role in the treatment of renal cell carcinoma.[1a] Otherwise, nitrocoumarins may be utilized as precursors of aminocoumarins, which have become important raw materials for the production of bioactive chemicals.[2,3]

*Correspondence: Longmin Wu, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China; E-mail: nlaoc@lzu.edu.cn.

DOI: 10.1081/SCC-120028628 0039-7911 (Print); 1532-2432 (Online)

Usually, nitration of coumarins is catalyzed by concentrated strong acids.[4] Several methods have also been reported to it, including thallium salts in dry methanol,[5] cerium ammonium nitrate in acetic acid and hydrogen peroxide in water.[6] However, most of them have some drawbacks such as poor regio-selectivity, over-nitration, and competitive oxidation of substrates. In addition, the Kyotai-nitration of various kinds of aromatic compounds and the nitration of aromatic hydrocarbons with NO_2 were reported by Suzuki[7a] and Kochi,[7b] respectively. Although phenols[8] could be nitrated by NO_2, however, it gave various products except for nitro phenols, such as dienone, quinone, aldehyde and multi-nitro-compounds. Therefore, to seek mild and selective methods for the nitration of coumarins is still a challenge for organic synthesis.

Since nitric oxide (NO) plays a significant role in a variety of physiological processes,[9] papers involving its chemical reactions with biologically active compounds[10–13] have been increasing in recent years. The application of NO to the organic synthesis as a nitration or nitroso reagent was also developed.[14] Our interest in NO promoted us to study the reaction of NO with a series of coumarins containing a hydroxy group. We report herein a simple and effective method to nitrate selectively coumarins containing a hydroxy group with a gas mixture of NO and a small amount of O_2 in CH_2Cl_2 or CH_3CN. A representative reaction is outlined in Sch. 1.



1a **2a**

1a	6-Hydroxycoumarin	**2a**	6-Hydroxy-5-nitrocoumarin
1b	4- Hydroxycoumarin	**2b**	4-Hydroxy-3-nitrocoumarin
1c	7- Hydroxycoumarin	**2c$_1$**	7-Hydroxy-6-nitrocoumarin
		2c$_2$	7-Hydroxy-3-nitrocoumarin
		2c$_3$	7-Hydroxy-8-nitrocoumarin
1d	4-Methyl-7-hydroxycoumarin	**2d**	4-Methyl-7-hydroxy-6-nitrocoumarin
1e	8-Acetyl-7-hydroxycoumarin	**2e$_1$**	8-Acetyl-7-hydroxy-6-nitrocoumarin
		2e$_2$	8-Acetyl-7-hydroxy-3-nitrocoumarin
1f	6-Acetyl-7-hydroxycoumarin	**2f**	6-Acetyl-7-hydroxy-3-nitrocoumarin
1g	7-Benzyloxyl-8-hydroxycoumarin	**2g**	7-Benzyloxy-8-hydroxy-5-nitrocoumarin

Scheme 1.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

RESULTS AND DISCUSSION

All the compounds tested were nitrated to give almost exclusively the corresponding mono-nitro coumarins. Among them, coumarins **1a**–**b**, **1d** and **1f**–**g** gave unique products **2a**–**b**, **2d** and **2f**–**g**, respectively, in moderate to high yields (Table 1). Coumarins **1c** and **1e**, however, gave more than one product in different yields. The reactions were completed normally during 2 to 4 hours. It is worth pointing out especially that neither multi-nitro- nor nitroso-coumarins were detected in any case. We found that NO_2 or a more fraction of oxygen in the gas mixture of NO and O_2 led a complexity of products, as indicated in the literature,[8] so that decreased dramatically the yield of mono-nitro products. In the absence of oxygen, no products were obtained. Attempted nitration of coumarin itself failed under the present conditions. This indicated that the hydroxy group really activated coumarins towards nitration by NO.

Four issues of regioselectivity could be approached from the results: (a) the nitration occurred preferentially at the *ortho*-position with respect to the hydroxy group (entry 1–5); (b) if its *ortho*-position was occupied, the nitration would take place at the vinylogously *para* (entry 6) or the *para* (entry 7) to the hydroxy group; (c) when its *ortho*-position was alternative, the nitration occurred mainly at one. It seemed possible for **1a** that the nitration would occur at either the C-5 or C-7. The unique product **2a** indicated that the nitration occurred in favor at the C-5. Likewise, the nitration of **1d** took place only at the C-6. Although both the C-6 and C-8 in **1c** lied at as an *ortho*-position of the hydroxy group, the nitration tended to favor occur at the C-6; and (d) the C-8 was unavailable for the nitration.

Table 1. Nitration of coumarins with NO in CH_2Cl_2.

Entry	Substrate	Reaction condition	Product (yield, %)[a]	
1	**1a**	CH_2Cl_2, 4h	**2a**	(78)
2	**1b**	CH_2Cl_2, 1.5h	**2b**	(95)
3	**1c**	CH_2Cl_2, 3h	$\mathbf{2c_1}$	(63)
			$\mathbf{2c_2}$	(20)
			$\mathbf{2c_3}$	(5)
4	**1d**	CH_2Cl_2, 3h	**2d**	(80)
5[b]	**1e**	CH_3CN, 2h	$\mathbf{2e_1}$	(58)
			$\mathbf{2e_2}$	(31)
6	**1f**	CH_2Cl_2, 4.5h	**2f**	(56)
7	**1g**	CH_2Cl_2, 3h	**2g**	(72)

[a]Refer to isolated products.
[b]The reaction of **1e** was carried out in dry acetanitrile.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

Experiments involving the influence of solvents on the product yields indicated that no significant solvent effects were observed. Thus, dichloromethane, chloroform, 2-dichloroethane, benzene and acetonitrile were in favour for reactions, being subject to the solubility of substrates.

The above results and our EPR detection of radical intermediates formed in the reactions seem to assume that mechanistic pathways for the reaction via radicals are possible, as given in Sch. 2. NO oxidizes the phenolic function of coumarins to produce the phenoxyl radicals.[9,15] In general, phenoxyl radicals with an unpaired electron on the oxygen atom have a short life and tend to resonate to give rise to aromatic radicals.[16] As a radical species, NO_2 couples with one of the resonance forms of the phenoxyl radical to produce mono-nitrated coumarins.

In summary, we have found that NO could serve as an effective nitration agent for coumarins containing a hydroxy group. This reaction was quite general and gave the corresponding mono-nitro coumarins in moderate to high yields. In addition, the reaction conditions were mild and the reagents readily available. More significantly, this reaction has been used to achieve selective nitration of coumarins containing hydroxy group. We expect that this approach would be applied to the nitration of the other compounds in organic synthesis.

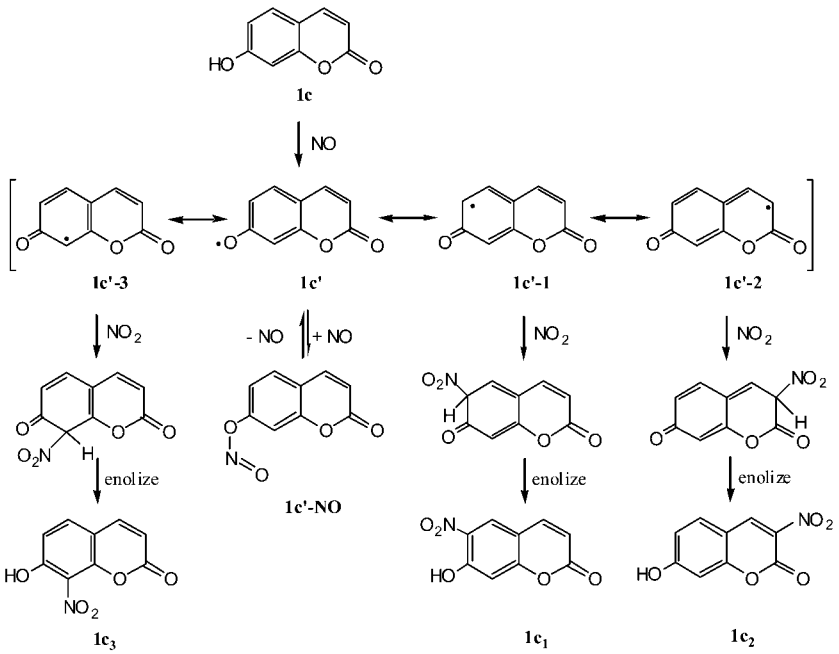
EXPERIMENTAL

7-Hydroxycoumarin and 4-hydroxycoumarin were purchased from Aldrich. Other chemicals were synthesized by reported methods.[17,18] ^{1}H NMR spectra data were recorded on a Bruker Avance 200 or AM 400 spectrometer. GC-MS was performed on a HP5988 spectrometer with an EI source. High resolution FTMS spectra were recorded with a Bruker Daltonics APEX II 47e spectrometer with an ESI source and had a precision of less than 1 ppm unless an individual sample (**2d**). IR (KBr) spectra were run on a Nicolet NEXUS 670 FT-IR instrument. Principal absorptions are reported in wave numbers (cm^{-1}). Melting points were measured on a Kofler apparatus and were uncorrected.

General Procedure for the Nitration of Coumarins

To a solution of coumarin (1 mmol) in dry CH_2Cl_2 (30 ml) was bubbled Ar gas for 10 min. Subsequently, a gas mixture of NO and O_2 (100 : 1 in vol.) was introduced to the solution for a specified time (Table 1). Reaction proceeding was inspected by TLC on silica gel GF254 plates with petroleum ether and ethyl acetone (3 : 1–8 : 1 v/v). The solvent was evaporated off after

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



Scheme 2.

completion of the reaction and the crude product was separated and purified by silica gel (200–300 mesh) column with a total length of 50 cm, using a mobile phase of petroleum ether and acetone (3 : 1–8 : 1 v/v).

Characterization Data for Products

2a: m.p. 158–160°C. IR (KBr) υ_{max} cm^{-1} 3077, 2917, 1741, 1662, 1548, 1381. ^1H NMR (200 MHz, acetone-d_6) δ 6.64 (d, $J = 10$ Hz, 1H, 3-H), 7.39 (d, $J = 9.4$ Hz, 1H, 5-H), 7.50 (d, $J = 9.2$ Hz, 1H, 8-H), 7.89 (d, $J = 10$ Hz, 1H, 4-H). MS (EI) m/z: 207 (M^+, 100%), 161 (21), 133 (16). HRMS (ESI): Found M-H = 206.0085, $C_9H_5O_5N$ require M-H = 206.0084.

2b: m.p. 166–168°C (from methanol). IR (KBr) υ_{max} cm^{-1} 3214, 3066, 1752, 1608, 1541, 1337. ^1H NMR (200 MHz, acetone-d_6) δ 7.18 (d, $J = 8.0$ Hz, 1H, 5-H), 7.25 (t, $J = 7.2$ Hz, 1H, 6-H), 7.61 (t, $J = 7.2$ Hz, 1H, 7-H), 8.08 (d, $J = 8.0$ Hz, 1H, 8-H). MS (EI) m/z: 207 (M^+, 100%), 163 (16). HRMS (ESI): Found M + H = 208.0239, $C_9H_5O_5N$ require M + H = 208.0240.

MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

2c$_1$: m.p. 188–190°C. IR (KBr) υ_{max} cm^{-1} 3237, 3066, 1732, 1635, 1528, 1357. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, $J = 9.7$ Hz, 1H, H-3), 7.05 (s, 1H, H-8), 7.70 (d, $J = 9.7$ Hz, 1H, H-4), 8.35 (s, 1H, H-5), 10.88 (s, 1H, 7-OH). MS (EI) m/z: 207 (M^+, 100%), 179 (58), 162 (10), 133 (21). HRMS (ESI): Found M-H = 206.0085, $C_9H_5O_5N$ require M-H = 206.0084.

2c$_2$: m.p. 178–180°C. IR (KBr) υ_{max} cm^{-1} 3277, 1742, 1618, 1601, 1560, 1381. ^{1}H NMR (400 MHz, acetone-d_6) δ 6.85 (d, $J = 2.2$ Hz, 1H, 8-H), 7.02 (dd, $J = 8.8$ Hz and 2.2 Hz, 1H, 6-H), 7.88 (d, $J = 8.8$ Hz, 1H, 5-H), 9.01 (s, 1H, 4-H). MS (EI) m/z: 207 (M^+, 100%), 179 (7), 162 (7). HRMS (ESI): Found M + H = 208.0242, $C_9H_5O_5N$ require M + H = 208.0240.

2c$_3$: decomposed at 218°C. IR (KBr) υ_{max} cm^{-1} 3240, 3120, 1732, 1617, 1535, 1377. ^{1}H NMR (200 MHz, acetone-d_6) δ 6.33 (d, $J = 9.7$ Hz, 1H, 3-H), 7.12 (d, $J = 8.8$ Hz, 1H, 5-H), 7.72 (d, $J = 8.8$ Hz, 1H, 6-H), 8.00 (d, $J = 9.7$ Hz, 1H, 4-H). MS (EI) m/z: 207 (M^+, 100%), 179 (21), 162 (15), 133 (21). HRMS (ESI): Found M-H = 206.0086, $C_9H_5O_5N$ require M-H = 206.0084.

2d: m.p. 252–254°C. IR (KBr) υ_{max} cm^{-1} 3234, 3051, 1730, 1633, 1531, 1377. ^{1}H NMR (200 MHz, acetone-d_6) δ 2.57 (s, 3H, 4-CH_3), 6.50 (s, 1H, 3-H), 7.16 (s, 1H, 8-H), 8.45 (s, 1H, 5-H). MS (EI) m/z: 221 (M^+, 100%), 193 (89), 176 (9), 147 (24). HRMS (ESI): Found M + H = 222.0417, $C_{10}H_7O_5N$ require M + H = 222.0397.

2e$_1$: decomposed at 214°C. IR (KBr) υ_{max} cm^{-1} 3450, 1767, 1730, 1599, 1541, 1369. ^{1}H NMR (200 MHz, acetone-d_6) δ 3.15 (s, 3H, 8-$COCH_3$), 6.96 (d, $J = 8.9$ Hz, 1H, 3-H), 7.97 (d, $J = 8.9$ Hz, 1H, 4-H), 9.02 (s, 1H, 5-H). MS (EI) m/z: 249 (M^+, 100%), 234 (60), 204 (20), 189 (28). HRMS (ESI): Found M-H = 248.0202, $C_{10}H_7O_5N$ require M-H = 248.0201.

2e$_2$: m.p. 122°C. IR (KBr) υ_{max} cm^{-1} 3442, 1610, 1552, 15241, 1345. ^{1}H NMR (300 MHz, acetone-d_6) δ 2.82 (s, 8-$COCH_3$), 6.51 (d, $J = 9.9$ Hz, 1H, 6-H), 8.15 (d, $J = 9.9$ Hz, 1H, 5-H), 8.64 (s, 1H, 4-H). MS (EI) m/z: 249 (M^+, 39%), 234 (100), 217 (89), 204 (5), 189 (14). HRMS (ESI): Found M-H = 248.0199, $C_{10}H_7O_5N$ require M-H = 248.0201.

2f: m.p. 176–178°C. IR (KBr) υ_{max} cm^{-1} 3415, 3064, 1759, 1645, 1574, 1371. ^{1}H NMR (200 MHz, acetone-d_6) δ 2.84 (s, 3H, 6-$COCH_3$), 6.92 (s, 1H, 5-H), 8.78 (s, 1H, 8-H), 9.09 (s, 1H, 4-H). MS (EI) m/z: 249 (M^+, 79%), 234 (100), 204 (15). HRMS (ESI): Found M-H = 248.0187, $C_{10}H_7O_5N$ require M-H = 248.0190.

2g: m.p. 209–210°C. IR (KBr) υ_{max} cm^{-1} 3348, 2925, 1729, 1617, 1518, 1368. ^{1}H NMR (200 MHz, acetone-d_6) δ 5.35 (s, 2H, 7-OCH_2), 6.51 (d, $J = 10.0$ Hz, 1H, 3-H), 7.26–7.33 (m, 3H, Ph), 7.45–7.49 (m, 2H, Ph), 7.84 (s, 1H, 6-H), 8.52 (d, $J = 10.2$ Hz, 1H, 4-H). MS (EI) m/z: 313 (M^+, 70%), 285 (60), 236 (100). HRMS (ESI): found M + H = 314.0653, $C_{10}H_7O_5N$ require M + H = 314.0659.

Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016

ACKNOWLEDGMENT

The authors thank The Natural Science Foundation of China for the financial support (The grant No 20272022).

REFERENCES

1. (a) Finn, G.J.; Kenealy, E.; Creaven, B.S.; Egan, D.A. In vitro cytotoxic potential and mechanism of action of selected coumarins, using human renal cell lines. Cancer Lett. **2002**, *183*, 61; (b) El-Sayed, A.M.; Ghattas, A.G.; El-Wassimy, M.T.; Allah, O.A.A. Synthesis of some new biologically-active coumarin derivatives. Farmaco **1999**, *54*, 56; (c) Oketch-Rabah, H.A.; Mwangi, J.W.; Lisgarten, J.; Mberu, E.K. A new antiplasmodial coumarin from Toddalia asiatica roots. Fitoterapia **2000**, *71*, 636.
2. Majumdar, K.C.; Ghosh, S.K. Studies on amine oxide rearrangements: regioselective synthesis of pyrano(3,2-e) indol-7-one. J. Chem. Soc. Perkin Trans. 1 **1994**, 2889.
3. Majumdar, K.C.; Biswas, P. Synthesis of bioreactive heterocycles: one pot regioselective synthesis of pyrano[3,2-*f*]benzo[*b*]thiophene derivatives. Tetrahedron **1999**, *55*, 1449.
4. Huebner, C.F.; Link, K.P. Studies on 4-hydroxycoumarin. VII. Reactions of 4-hydroxycoumarin with cationoid reagents. J. Am. Chem. Soc. **1945**, *67*, 99.
5. Banerji, A.; Nandi, G. Metal reagents in organic reactions: part V reactions of coumarins with thallium III salt. Heterocycles **1987**, *26* (5), 1221.
6. Ganguly, N.; Sukai, A.K.; De, S. Cerium (IV) ammonium nitrate mediated nitration of coumarins. Synthetic Commun. **2001**, *31* (2), 301.
7. (a) Mori, T.; Suzuki, H. Ozone-mediated nitration of aromatic compounds with lower oxides of nitrogen (the Kyodai-nitration). Synlett. **1995**, 383; (b) Bosch, E.; Kochi, J.K. Thermal and photochemical nitration of aromatic hydrocarbons with nitrogen dioxide. J. Org. Chem. **1994**, *59*, 3314.
8. (a) Riebsomer, J.L. The reactions of nitrogen tetroxide with organic compounds. Chem. Rev. **1945**, *36*, 157; (b) Brunton, G.; Cruse, H.W.; Riches, K.M.; Whittle, A. On the mechanism of nitration of 4-methyl-2,6-ditertiarybutylphenol by nitrogen dioxide in the liquid phase. Tetrahedron Lett. **1979**, *20*, 1093; (c) Fischer, A.; Mathivanan, N. Formation of dienones on the reaction of cresols, xylenols, and 2-naphthol with nitrogen dioxide: observation of keto tautomers of nitrophenols. Tetrahedron Lett. **1988**, *29*, 1869; (d) Coombes, R.G.; Hadjigeorgiou, P.; Jensen, D.G.J.; Morris, D.L. In *Nitration: Recent Laboratory and Industrial Development*; Albright, L.F., Carr, R.V.C., Schmitt, R.J., Eds.; ACS Symposium Series 623, American Chemical Society: 1996; Chap. 3.

9. (a) Moncada, S.; Palmer, R.M.; Higgs, E.A. Nitric oxide: physiology, and pharmacology. Pharmacol. Rev. **1991**, *43*, 109; (b) Galla, H.J. Nitric oxide, NO, and intercellular messenger. Angew. Chem. Int. Ed. Engl. **1993**, *32*, 378.
10. (a) Janzen, E.G.; Wilcox, A.L.; Manoharon, V. Reaction of nitric oxide with phenolic antioxidants and phenooxyl radicals. J. Org. Chem. **1993**, *58*, 3597; (b) Wilcox, A.W.; Janzen, E.G. Nitric oxide reaction with antioxidants in model systems: sterically hindered phenols and α-tocopherol in sodium dodecyl sulfate (SDS) micelles. J. Chem. Soc. Chem. Commun. **1993**, 1377; (c) Yenes, S.; Messeguer, A. A study of the reaction of different phenol substrates with nitric oxide and peroxynitrite. Tetrahedron **1999**, *55*, 14111.
11. Suzuki, T.; Yamaoka, R.; Nishi, M.; Ide, H.; Makino, K. Isolation and characterization of a novel product, 2′-deoxyguanosine, oligodeoxynucleotide, and calf thymus DNA treated by nitrous acid and nitric oxide. J. Am. Chem. Soc. **1996**, *118*, 2515.
12. Itoh, T.; Nagata, K.; Mastuya, Y.; Miyazaki, M.; Ohsawa, A. Reaction of nitric oxide with amines. J. Org. Chem. **1997**, *62*, 3582.
13. Wu, L.M.; Chen, W.; Liu, Z.L. Stable free radicals generated during the oxidation of 4-alkyl Hantzsch 1,4-dihydropyridines with nitrosonium – EPR evidence. Res. Chem. Intermed. **2001**, *27* (3), 219.
14. (a) Mukaiyama, T.; Hata, E.; Yamada, T. Convenient and simple preparation of nitroolifens niytration of olifens with nitric oxide. Chem. Lett. **1995**, 505; (b) Nagano, T.; Takizawa, H.; Hirobe, M. Reaction of nitric oxide with dioxygen. Tetrahedron Lett. **1995**, *36*, 8239; (c) Kelly, D.R.; Jones, S.; Adigun, J.O.; Kon, K.S.V.; Jackson, S.K. The addition of nitric oxide to 2,5-dimethyl-hexa-2,4-diene gives nitrogen dioxide adducts. Tetrahedron Lett. **1997**, *38*, 1245.
15. Zhu, X.Q.; Xian, M.; Wang, K.; Cheng, J.P. Is NO (nitric oxide) an electron acceptor or an electrophile? A detailed thermodynamic investigation on the mechanism of NO-initiated reactions with 3,6-dibromocarbazolide anion and related carbanion. J. Org. Chem. **1999**, 4187.
16. Thompson, M.J.; Zeegers, P.J. Studies on the two-phase nitration of phenols (part 2). Tetrahedron **1990**, *46*, 2661.
17. Degraw, J.I.; Tsakotellis, P. A convenient synthesis of 6-hydroxy coumarins. J. Chem. Eng. Data. **1969**, *14*, 509.
18. Ren, X.F.; Chen, X.C.; Peng, K.; Xie, X.G.; Xia, Y.M.; Pan, X.F. First enatioselective synthesis of daphneticin and its regioisomer. Tetrahedron: Asymmetry **2002**, *13*, 1799.

Received in Japan July 25, 2003