Regioselective Introduction of a Methoxy Group at the Benzylic Position of Isochromane Derivatives by Cerium(IV) Oxidation in Methanol

Kimiaki ISOBE,*[,a] Naoko TAKEDA,[a] Kunihiko MOHRI,[a] and Yoshisuke TSUDA[b]

Showa College of Pharmaceutical Sciences,[a] 5-1-8 Tsurumaki, Setagaya-ku, Tokyo 154, Japan and Faculty of Pharmaceutical Sciences,[b] Kanazawa University, 13-1 Takara-machi, Kanazawa 920, Japan. *Received May 1, 1989*

The oxidation of methoxy-isochromans and -isochromanones with ceric ammonium nitrate in methanol introduced a new methoxy group regioselectively at a benzylic position *para* to the methoxy function on the aromatic nucleus.

Keywords ceric ammonium nitrate (CAN); methanol; regioselective methoxylation; isochromane; methoxyisochroman-3-one; benzylic oxidation; methoxylation

An efficient method of introducing a methoxy group at the benzylic position of aromatic compounds would have considerable value in organic synthesis, since such introduction may provide useful synthetic intermediates and there are some natural products bearing a methoxy group at this position.[1] Although many reports are available on benzylic oxidation ($Pb(OAc)_4$, 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), *etc.*),[2] few of the procedures are regio- and chemo-selective.

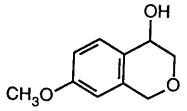
Ceric ammonium nitrate (CAN) is a reagent widely used for qualitative analysis of alcohols, oxidation of phenols or methoxybenzenes to quinones,[3] and oxidation of benzyl alcohols to benzaldehydes.[4] Several workers[5] have reported that the oxidation of toluenes with CAN in acetic acid gave benzyl acetates. Another group[6] reported that ceric trimethylammonium nitrate mediated the addition of alcohols to tetrahydrofuran, giving rise to 2-alkoxyfurans. These reactions were considered[5b] to proceed through the generation of a stabilized cation species, benzyl or α-oxa carbocation, by two one-electron oxidations with a cerium (IV) compound, followed by trapping by the solvent.

We considered that aromatic compounds bearing a methoxy group *para* to the benzylic position would more easily give a benzyl cation, which might be greatly stabilized by the methoxy group already present, and thus regioselective substitution at the particular benzylic position by a new

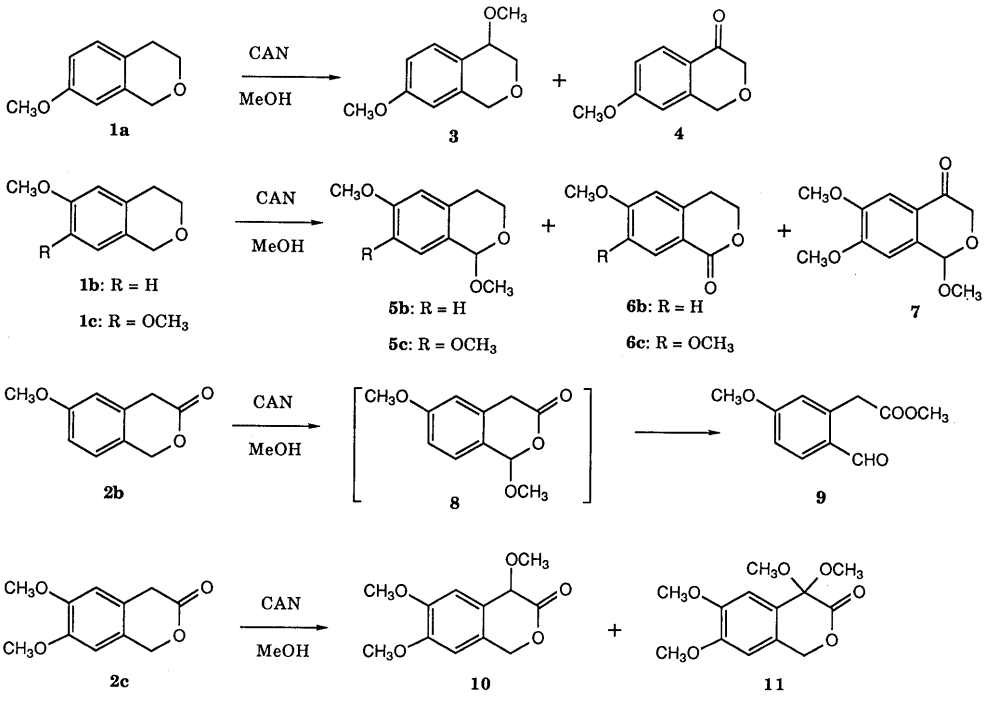
TABLE I. Reaction of Methoxybenzene Derivatives with CAN in Methanol

Entry	Substrate	Reaction condition[a] (min)	Product (yield, %)[b]
1	**1a**	10	**3** (38), **4**[c] (15)
2	**1b**	10	**5b** (58), **6b** (3)
3	**1c**	30	**5c** (50), **6c** (21), **7** (9)
4	**2b**	40	**9** (71)
5	**2c**	30	**10** (49), **11** (24)
6[d]	**2c**	30	**10** (16), **11** (47)

a) At room temperature. *b*) Isolated yield. *c*) Isolated as an alcohol **12** after reduction of a mixture of **3** and **4** with $NaBH_4$. *d*) 4.4 mol eq of CAN was used.



12



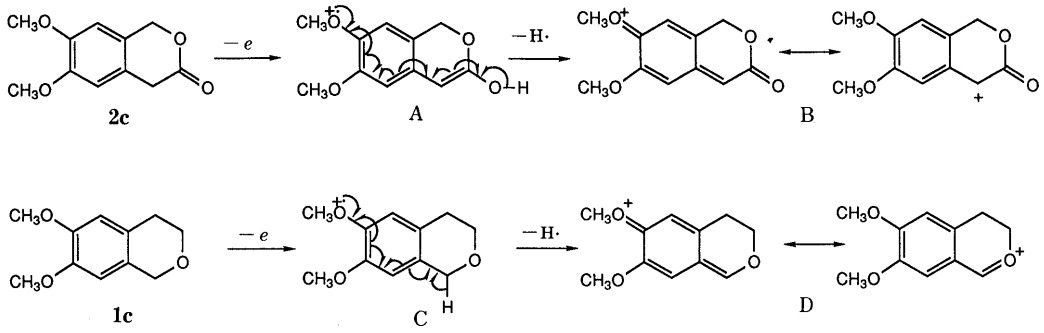


Chart 2

methoxy group would be achieved when the CAN oxidation was carried out in methanol. To test this possibility, CAN oxidation of some methoxyisochromans and methoxyisochromanones in methanol was examined.

The results of the oxidation are listed in Table I. The structure of each product was elucidated spectroscopically after isolation by medium-pressure liquid chromatography. As we expected, the oxidation always occurred regioselectively at the benzylic position *para* to the methoxy group already present on the aromatic nucleus to give the monomethoxylated compound as a major product. The by-products found in this reaction were only those of over-oxidaton at the same position (except for entry 6). Thus, oxidation of **1a** or **1b** gave only one regioisomer **3** or **5b** in satisfactory yield. 6-Methoxyisochroman-3-one **2b** also gave **9**, which is the product derived from the expected 1-methoxy derivative **8**.

Oxidation of 6,7-dimethoxyisochroman **1c** gave the 1-methoxy derivative **5c**, the 4-methoxy isomer being not isolated. In contrast, oxidation of 6,7-dimethoxyisochroman-3-one (**2c**) gave the 4-methoxy derivative **10** regioselectively. The only isolable by-product was the 4,4-dimethoxylated derivative **11**, the formation of which was increased by using an excess of CAN. Of the two benzylic positions *para* to the methoxy group, particular positions were oxidized regioselectively in these examples, one is α to oxygen in **1c** and the other α to carbonyl in **2c**. This difference in reactivity can be rationalized by considering the ease of formation of the intermediate cation. In the oxidation steps leading to the intermediate cation, B or D, the removal of a hydrogen radical from the oxonium cation radical, A or C, is accelerated by the contribution of an enol form conjugated with the aromatic group in A. However, the stability of the cation B should be lowered by the presence of an adjacent carbonyl group. Hence the position in this situation is the most vulnerable to oxidation. On the other hand, the presence of an oxa function adjacent to the benzylic position in C does not accelerate the removal of hydrogen, but greatly stabilizes the resulting cation D. These are the factors favoring regioselectivity in a CAN oxidation.

In conclusion, CAN in methanol always oxidizes the benzylic position *para* to the methoxy group on the aromatic nucleus, introducing a new methoxy group at the position. The oxidation usually occurs regioselectively to give only one isomer even when two methoxy groups are present on the aromatic nucleus. Among such benzylic positions, the oxidation occurs in the order of α to carbonyl, α to oxygen, then at the benzylic position.

Experimental

Unless otherwise stated, the following procedures were adopted. Melting points were taken on a Yanagimoto micro hot-stage melting point apparatus, and are uncorrected. Infrared (IR) spectra were taken in KBr with a Jasco IR-810 spectrophotometer and are given in cm^{-1}. Proton nuclear magnetic resonance (^{1}H-NMR) (100 MHz) spectra were taken in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal standard on a JEOL FX-100 spectrometer. Mass spectra (MS) were recorded on a JEOL JMS-D300 spectrometer. Preparative medium-pressure liquid chromatography was performed on a silica gel column (Kusano CPS-HS-221-1) with ethyl acetate–hexane as an eluent.

6,7-Dimethoxyisochroman (1c) 3,4-Dimethoxyphenethyl alcohol (10 g, 55 mmol) and paraformaldehyde (2 g) in CF_3COOH (100 ml) were stirred for 10 min at room temperature. After the usual work-up, the product was purified by column chromatography on silica gel; yield 6.8 g (64%); mp 79—81 °C.[7]

7-Methoxyisochroman (1a) This was prepared as described above in 8.6% yield; oil. IR (neat): 1610 cm^{-1} (arom.). ^{1}H-NMR δ: 2.78 (2H, t, J=5.6 Hz), 3.77 (3H, s), 3.95 (2H, t, J=5.6 Hz), 4.74 (2H, s), 6.51 (1H, d, J=2.5 Hz), 6.73 (1H, dd, J=8, 2.5 Hz), 7.03 (1H, d, J=8 Hz). High-resolution MS m/z: Calcd for $C_{10}H_{12}O_2$ (M^+): 164.0838. Found 164.0845.

6-Methoxyisochroman (1b) A mixture of 3-methoxyphenethyl alcohol (1 g, 6.6 mmol) and boron trifluoride etherate (5 ml) in methylal (20 ml) was stirred for 10 min at room temperature. On the usual work-up, **1b** was obtained in 18% yield as an oil. IR (neat): 1610 cm^{-1} (arom.). ^{1}H-NMR δ: 2.82 (2H, t, J=6 Hz), 3.77 (3H, s, J=6 Hz), 6.65 (1H, d, J=2.4 Hz), 6.72 (1H, dd, J=8, 2.4 Hz), 6.89 (1H, d, J=8 Hz). High-resolution MS m/z: Calcd for $C_{10}H_{12}O_2$ (M^+) 164.0838. Found 164.0854.

6,7-Dimethoxyisochroman-3-one (2c) and 6-Methoxyisochroman-3-one (2b) These compounds were prepared by condensation of arylacetic acids with paraformaldehyde in HCl–acetic acid acccording to the known procedure.[8]

Oxidation with CAN in Methanol (General Procedure) A solution of the substrate (1 mmol) and CAN (2.2 mmol) in methanol (20 ml) was stirred for 5—30 min at room temperature, then CH_2Cl_2 was added and the mixture was washed with water. The organic layer was dried over $MgSO_4$ and concentrated to dryness. The residue was subjected to a preparative medium pressure liquid chromatography using ethyl acetate–hexane as an eluent to separate the oxidation products. For details, see Table I.

3: Oil. IR (neat): 1620 cm^{-1}. ^{1}H-NMR δ: 3.45 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.81 (1H, dd, J=12, 3 Hz, 3-H), 4.18—4.25 (2H, m, 3-H and 4-H), 4.64 (1H, d, J=15 Hz, 1-H), 4.81 (1H, d, J=15 Hz, 1-H), 6.54 (1H, d, J=3 Hz, 8-H), 6.81 (1H, dd, J=8, 3 Hz, 6-H), 7.31 (1H, d, J=8 Hz, 5-H). High-resolution MS m/z: Calcd for $C_{11}H_{14}O_3$ (M^+) 194.0941. Found 194.0940.

12: The crude oxidation products of **1a** showed a carbonyl absorption, at 1690 cm^{-1} suggesting the presence of **4**. This mixture was reduced with $NaBH_4$ in ethanol for 10 min at room temperature to give **12** (15%) together with **3** (38%) after chromatographic separation. mp 60—63 °C. IR: 3430 cm^{-1}. ^{1}H-NMR δ: 3.79 (3H, s, OCH_3), 3.81 (1H, dd, J=12, 2.5 Hz, 3-H), 4.09 (1H, dd, J=12, 2.5 Hz, 3-H), 4.48 (1H, br s, 4-H), 4.62 (1H, d, J=9 Hz, 1-H), 4.70 (1H, d, J=9 Hz), 6.49 (1H, d, J=3 Hz, 8-H), 6.82 (1H, dd, J=8, 3 Hz, 6-H), 7.35 (1H, d, J=8 Hz, 5-H). *Anal.* Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.39; H, 6.88.

5b: mp 42—45 °C. IR: 1620 cm^{-1}. ^{1}H-NMR δ: 2.57 (1H, m, 4-H), 3.0 (1H, m, 4-H), 3.52 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.92 (1H, dd, J=12, 6 Hz, 3-H), 4.05 (1H, dd, J=12, 4 Hz, 3-H), 5.41 (1H, s, 1-H), 6.63 (1H, d, J=2 Hz, 5-H), 6.77 (1H, dd, J=8, 2 Hz, 7-H), 7.15 (1H, d, J=8 Hz). *Anal.*

Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.31; H, 7.51.

5c: mp 95—97 °C. IR: 1610 cm^{-1}. ^{1}H-NMR δ: 2.5 (1H, m, 4-H), 3.0 (1H, m, 3-H), 3.53 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.0 (2H, m, 3-H), 5.39 (1H, s, 1-H), 6.59 (1H, s, ArH), 6.72 (1H, s, ArH). *Anal.* Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.55; H, 7.25.

6b: mp 63—64 °C. IR: 1710 cm^{-1}. ^{1}H-NMR δ: 3.02 (2H, t, J=6 Hz, 4-H), 3.87 (3H, s, OCH_3), 4.51 (2H, t, J=6 Hz, 3-H), 6.72 (1H, d, J=3 Hz, 5-H), 6.89 (1H, dd, J=9, 3 Hz, 7-H), 8.03 (1H, d, J=9 Hz). *Anal.* Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.13; H, 5.71.

6c: mp 140—141 °C (lit.[9] mp 140—141 °C). IR: 1720 cm^{-1}. ^{1}H-NMR δ: 2.99 (2H, t, J=6 Hz, 4-H), 3.92 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.52 (2H, t, J=6 Hz, 3-H), 6.69 (1H, s, ArH), 7.55 (1H, s, ArH).

7: mp 98—100 °C. IR: 1700 cm^{-1}. ^{1}H-NMR δ: 3.62 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.22 (1H, d, J=17 Hz, 3-H), 4.61 (1H, d, J=17 Hz, 3-H), 5.57 (1H, s, 1-H), 6.78 (1H, s, ArH), 7.45 (1H, s, ArH). *Anal.* Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.20; H, 5.82.

9: mp 41—43 °C. IR: 1730, 1680 cm^{-1}. ^{1}H-NMR δ: 3.71 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.03 (2H, s, $ArCH_2CO$), 6.79 (1H, d, J=3 Hz, ArH), 6.96 (1H, dd, J=8, 3 Hz, ArH), 7.77 (1H, d, J=8 Hz, ArH), 9.96 (1H, s, CHO). *Anal.* Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.82. Found: C, 63.39; H, 5.81.

10: mp 97—98 °C. IR: 1750 cm^{-1}. ^{1}H-NMR δ: 3.72 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.69 (1H, s, 4-H), 5.28 (2H, s, 1-H), 6.75 (1H, s, ArH), 7.04 (1H, s, ArH). *Anal.* Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.73; H, 5.94.

11: mp 130—131 °C. IR: 1760 cm^{-1}. ^{1}H-NMR δ: 3.39 (6H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.28 (2H, s, 1-H), 6.73 (1H, s, ArH), 7.23 (1H, s, ArH). *Anal.* Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.21; H, 5.97.

References

1) S. F. Dyke and S. N. Quessy, "The Alkaloids," Vol. 18, ed. by R. G. A. Rodrigo, Academic Press, Inc., New York, 1981, pp. 1—98.
2) *a*) D. J. Rawlinson and G. Sosnovsky, *Synthesis*, **1973**, 567; *b*) D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).
3) *a*) T-L. Ho, *Synthesis*, **1973**, 354; *b*) T. Fukuyama, A. A. Laird, and L. M. Hotchkiss, *Tetrahedron Lett.*, **1985**, 6291.
4) Y. Hatanaka, Y. Imamoto, and M. Yokoyama, *Tetrahedron Lett.*, **1983**, 2399.
5) *a*) D. M. Piatak and L. S. Eichmeier, *J. Chem. Soc., Chem. Commun.*, **1971**, 772; *b*) W. S. Trahanovsky and L. B. Young, *J. Org. Chem.*, **31**, 2033 (1966).
6) A. M. Maione and A. Romeo, *Synthesis*, **1987**, 250.
7) W. Schneider and E. Kaemmerer, *Arch. Pharm.*, **299**, 817 (1966).
8) R. J. Spangler, B. G. Beckmann, and J. H. Kim, *J. Org. Chem.*, **42**, 2989 (1977).
9) N. K. Bose and D. M. Chaudhury, *Tetrahedron*, **20**, 49 (1964).