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CAN-Mediated Oxidations for the Synthesis of Xanthones and Related Products

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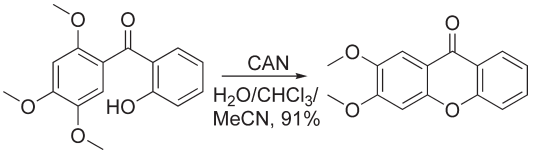

Reaction of (2,4,5-trimethoxyphenyl)(2-hydroxyphenyl)-methanone with ceric ammonium nitrate furnished the xanthone, 2,3-dimethoxy-9*H*-xanthen-9-one. Under the same conditions the related (1,4-dimethoxynaphthalen-2-yl)(2-hydroxyphenyl)methanone resulted in the formation of 12a-methoxy-5*H*-benzo[*c*]xanthenes 5,7(12a*H*)-dione. Other examples of this novel transformation are also outlined.

The xanthone nucleus is present in numerous natural products that exhibit interesting biological activity. For example, the antitumor compound bikaverin **1**,[1] (Figure 1) mangeferin **2**[2] isolated from the mangosteen fruit, the anticancer compound psorospermin **3**,[3] and the anti-HIV compound swertifrancheside **4**[4] all have a xanthone nucleus.

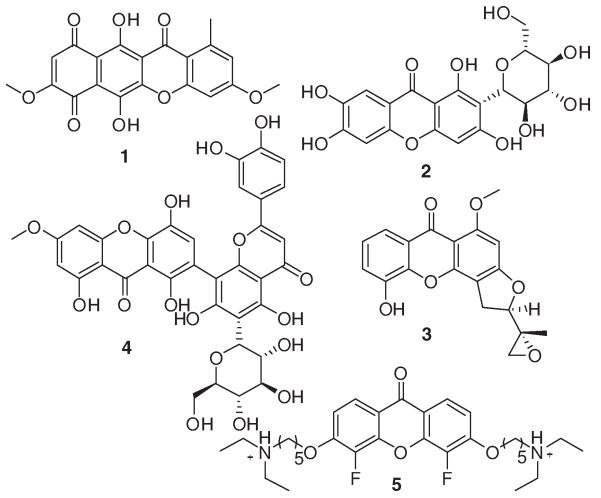

FIGURE 1. Examples of naturally occurring and synthetic xanthone-containing compounds.

Finally, compound **5**, a synthetic antimalarial, represents an example of a synthetic xanthone.[5]

There are a number of reported methods for the synthesis of xanthones.[6] In our laboratories we have been interested in developing new synthetic methods for the assembly of aromatic compounds in general,[7] and this paper outlines new methodology for the synthesis of xanthones and related compounds.

Commercially available 1,4-dimethoxynaphthalene **6** was subjected to 1 molar equiv of *N*-bromosuccinimide (NBS) to afford the desired known brominated compound **7**[8] in good yield. This compound was then treated with *n*-BuLi and the benzyl ester **8** to yield the aromatic ketone **9** in good yield (89%) as shown in Scheme 1. Selective removal of the *O*-benzyl substituent then yielded the required phenol **10**. Exposure of **10** to 5 molar equiv of CAN[9] in the presence of acetonitrile, water, and chloroform, with the hope of

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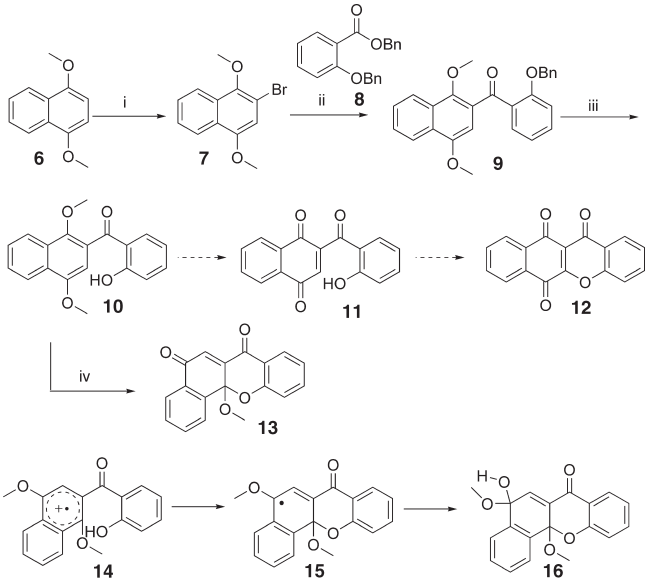
SCHEME 1[a]



[a]Reagents and conditions: (i) NBS, CH_2Cl_2, 90%; (ii) (a) *n*-BuLi, THF, −78°C, (b) **8**, THF, 89%; (iii) H_2, 5% Pd/C, 4.5 atms, 97%; (iv) CAN, H_2O/MeCN/$CHCl_3$, rt, 72%.

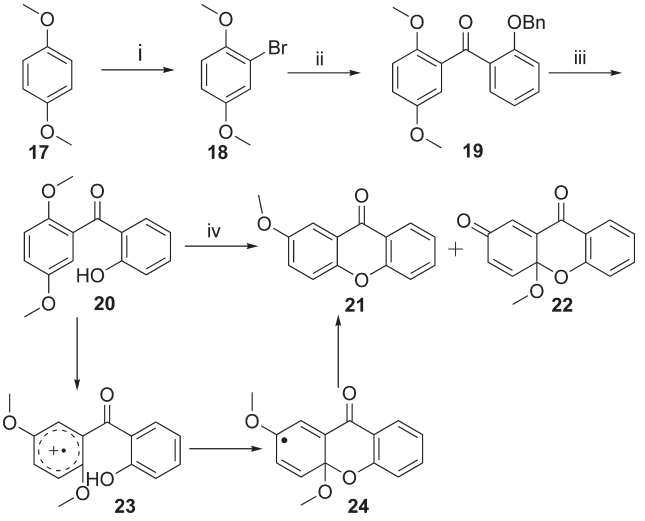
producing the quinone **11** or the corresponding xanthone **12**, unexpectedly met with failure. The ^{1}H NMR spectrum of the product that was isolated after chromatography contained what appeared to be a methoxy as part of an acetal at δ 3.03, as well as a quinone-like singlet at δ 7.26. An X-ray crystal structure indicated that we had formed a xanthone-related product, dione **13** (see figure in Supporting Information).[10]

A possible mechanism for the synthesis of **13** involves CAN-mediated oxidation of **10** to afford radical cation **14**.[11] Nucleophilic addition of the phenol to the aromatic radical cation of **14** will then afford radical **15**, which can undergo further oxidation with another 1 equiv of CAN to afford a cation to which water can add to yield **16**. Compound **13** is then formed by elimination of methanol from **16**. Alternatively, the phenoxy radical of **10** could be formed, which on addition to the naphthalene would result in the formation of the same radical **15**. This reaction appears to represent new methodology for the synthesis of a xanthone-like product.

After this unexpected result we decided to try the reaction on related substrates to gauge the versatility of this novel reaction. Instead of using 1,4-dimethoxynaphthalene **6** as the starting material, 1,4-dimethoxybenzene **17** was used in this investigation.

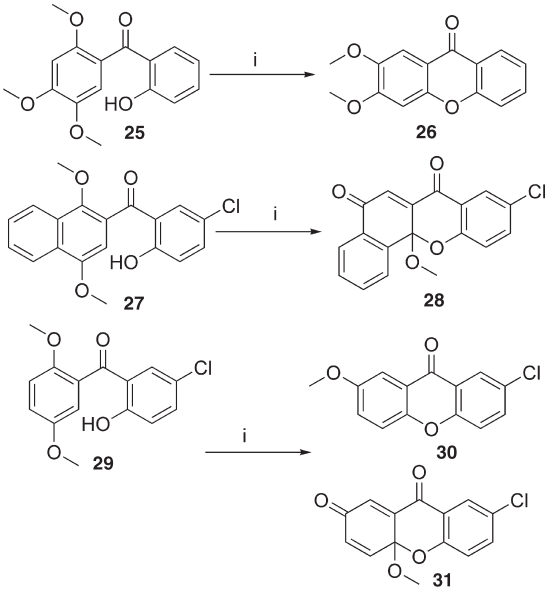
In a similar manner, reaction of 1,4-dimethoxybenzene **17** with NBS afforded the halogenated product **18** (Scheme 2). Exposure of this compound to *n*-BuLi and the same ester **8** furnished the required compound **19**. Removal of the benzyl substituent of **19** yielded the desired substrate **20** on which we could attempt our novel CAN-mediated reaction. Treatment of **20** with 5 molar equiv of CAN afforded the same type of dione **22** obtained previously, although this time it was the minor product (15%). The major product isolated was the xanthone **21**, which was produced in 74% yield. The identity

SCHEME 2[a]



[a]Reagents and conditions: (i) NBS, CH_2Cl_2, 89%; (ii) (a) *n*-BuLi, THF, −78°C, (b) **8**, THF, 72%; (iii) H_2, 5% Pd/C, 1 atm, 89%; (iv) CAN, H_2O/MeCN/$CHCl_3$, rt, **21**, 74%, **22**, 15%.

SCHEME 3[a]



[a]Reagents and conditions: (i) CAN, H_2O/MeCN/$CHCl_3$, rt, **26**, 91%, **28**, 93%, **30**, 63% and **31** 17%.

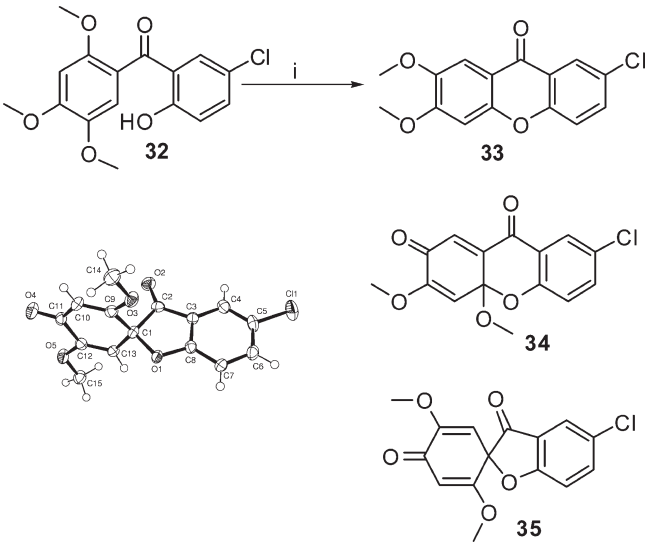
of this product was confirmed by X-ray crystallography (see figure in Supporting Information).

It would appear that xanthone **21** could be formed in a similar manner as the dione **13**. CAN oxidation again results in the formation of a radical cation **23**, which cyclizes by nucleophilic addition of the phenol to yield **24**. The radical **24** then undergoes elimination of a methoxy radical, which results in the reformation of the aromatic ring to give the observed product, xanthone **21**. Presumably in this case, the lack of an extra aromatic ring, as compared to the naphthalene example, results in the major product being the fully aromatic xanthone **21**.

(10) For the use of $K_3[Fe(CN)_6]$ to prepare one related compound, see: Franck, B.; Zeidler, U. *Chem. Ber.* **1973**, *106*, 1182–1197.

(11) Tanoue, Y.; Terada, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2039–2045.

SCHEME 4[a]



[a]Reagents and conditions: (i) CAN, H_2O/MeCN/$CHCl_3$, rt, **33**, 21%, **34**, 29%, **35**, 9%.

As a result of the success of this reaction, three other related transformations were carried out. The methodology for the synthesis of precursor **25**, **27**, and **29** is described in the Supporting Information and follows a synthetic sequence similar to that described previously. Reaction of **25** with 5 molar equiv of CAN resulted in the formation of the xanthone **26** in an excellent yield of 91%, and reaction of **27** with CAN gave the dione **28** in 93% yield. In addition, the phenol precursor **29** furnished the xanthone **30** and dione **31**, in 63% and 17% yield, respectively, as depicted in Scheme 3.

One final example of this CAN-mediated transformation was attempted on substrate **32** (Scheme 4), and to our surprise the reaction yielded the expected products **33** and **34** as well as an unexpected product **35**. The structure of this compound (**35**) was confirmed by X-ray crystallography (Scheme 4). Presumably the oxygen substituent in the *para* position to the newly formed five-membered ring facilitates the reaction.

In conclusion, we have developed new methodology for the synthesis of xanthones and related products, using CAN as an oxidant, from readily prepared precursors. Current work in our laboratories includes further investigations into the scope and limitation of the CAN reaction as well as attempts to elucidate details of the mechanism of the reaction.

Experimental Section

12a-Methoxy-5*H*-benzo[*c*]xanthene-5,7(12a*H*)-dione (13). CAN (13.3 g, 24.3 mmoles) in water (25 mL) was added dropwise to a stirring mixture of (1,4-dimethoxynaphthalene-2-yl)(2-hydroxyphenylmethanone (**9**) (1.50 g, 4.86 mmoles) in MeCN (25 mL) and $CHCl_3$ (5 mL). The mixture was then stirred at rt for 10 min. The reaction mixture was filtered through Celite and washed with EtOAc (3 × 25 mL). The organic layer was washed consecutively with a saturated aqueous $NaHCO_3$ solution (25 mL), brine (25 mL), and water (25 mL). The organic layer was then dried over $MgSO_4$. The solvent was removed *in vacuo*, and column chromatography with (5% EtOAc/hexane) afforded the product **13** as orange rod-like crystals (1.02 g, 72%). Mp 125−127 °C (EtOAc); IR (solid) ν_{max} (cm^{-1}) 1713, 1689, 1667, 1636, 1607, 1596, 1459; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, J = 7.8, 1H), 8.07−8.02 (m, 2H), 7.83−7.57 (m, 3H), 7.24−7.08 (m, 3H), 3.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.0, 181.0, 157.8, 143.8, 137.0, 136.6, 133.9, 130.8, 130.6, 130.2, 127.6, 126.9, 126.5, 123.2, 121.5, 118.6, 96.5, 51.5; MS (m/z) 293.07 (M^+, 100%), 294.09 (22); HRMS (m/z) calcd for $C_{18}H_{12}O_4$, 292.0736, found 292.0778.

2-Methoxy-9*H*-xanthen-9-one (21) and 4a-Methoxy-2*H*-xanthene-2,9(4a*H*)-dione (22). CAN (1.06 g, 1.94 mmoles) in water (5 mL) was added dropwise to a stirring mixture of (2,5 dimethoxyphenyl)(2-hydroxyphenyl)methanone (**20**) (0.100 g, 0.388 mmoles) in MeCN (10 mL) and $CHCl_3$ (2.5 mL). The mixture was then stirred at rt for 24 h. The reaction mixture was filtered through Celite and washed with EtOAc (3 × 25 mL). The organic layer was washed consecutively with a saturated aqueous $NaHCO_3$ solution (25 mL), brine (25 mL), and water (25 mL). The organic layer was then dried over $MgSO_4$. The solvent was removed *in vacuo*, and column chromatography (5% ethyl acetate/hexane) afforded the products **21** and **22** as white needles (0.065 g, 74%) and orange grains, respectively (0.015 g, 15%). 2-Methoxy-9*H*-xanthen-9-one (**21**): mp 131−133 °C (EtOAc), lit.[12] mp 134−135 °C; IR (solid) ν_{max} (cm^{-1}) 1647, 1614, 1488, 1462, 1430; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.25 (dd, J = 8.0, 1.6, 1H), 7.65−7.55 (m, 2H), 7.42−7.31 (dd, J = 7.8, 1.4, 1H), 7.29 (s, 1H), 7.28−7.14 (m, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0, 155.0, 154.9, 149.9, 133.5, 125.6, 123.8, 122.7, 121.0, 120.2, 118.4, 116.9, 104.8, 54.9; MS (m/z) 227.10 (M^+, 100%), 228.10 (12), 249.08 (5); HRMS (m/z) calcd for $C_{14}H_{10}O_3$, 226.0630, found 226.0620. 4a-Methoxy-9*H*-xanthen-2,9(4a*H*)-dione (**22**): mp 110−112 °C (EtOAc); IR (solid) ν_{max} (cm^{-1}) 1693, 1669, 1644, 1604, 1577, 1464; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, J = 7.8, 1H), 7.53 (t, J = 7.8, 1H), 7.11 (t, J = 7.5, 1H), 7.03 (d, J = 10.0, 1H), 6.81 (s, 1H), 6.37 (dd, J = 10.4, 1.9, 1H), 3.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185.1, 180.9, 157.0, 144.5, 140.1, 137.0, 130.7, 128.5, 127.5, 123.3, 121.6, 118.5, 95.1, 51.3; MS (m/z) 243.12 (M^+, 100%), 244.12 (15); HRMS (m/z) calcd for $C_{14}H_{10}O_4$, 242.0479, found 242.0568.

X-ray Crystallography. All three data sets were collected using ω-scans on a APEX II CCD area detector diffractometer.

Crystal data for **13**: $C_{18}H_{12}O_4$, M_r 292.28 g mol^{-1}; crystal dimensions (mm) 0.49 × 0.28 × 0.25; crystal system, monoclinic; space group, $P2_1/n$; unit cell dimensions and volume, a = 13.0183(7) Å, b = 13.0356(6) Å, c = 15.9224(7) Å, α = 90°, β = 98.662(3)°, γ = 90°, V = 2671.2(2) $Å^3$, no. of formula units in the unit cell Z = 8; calculated density r_{calcd} 1.454 Mg/m^3; linear absorption coefficient, m 0.103 mm^{-1}; radiation and wavelength, Mo Kα = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 19971 and 6440; R_{int} = 0.0773; R [$I > 2.0\sigma(I)$] = 0.0789, wR = 0.1979, GoF = 0.983, refined on F; residual electron density, 1.129 and −0.306 e $Å^{-3}$.

Crystal data for **21**: $C_{14}H_{10}O_3$, M_r 226.22 g mol^{-1}; crystal dimensions (mm) 0.60 × 0.07 × 0.06; crystal system, monoclinic; space group, $P2_1/n$; unit cell dimensions and volume, a = 4.7765(2) Å, b = 14.2280(5) Å, c = 15.4365(6) Å, α = 90°, β = 93.426(2)°, γ = 90°, V = 1047.19(7) $Å^3$, no. of formula units in the unit cell Z = 4; calculated density r_{calcd}, 1.435 Mg/m^3; linear absorption coefficient, m 0.101 mm^{-1}; radiation and wavelength, Mo Kα = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 28.00°; no of measured and independent reflections, 15813 and 2533; R_{int} = 0.0446; R [$I > 2.0\sigma(I)$] = 0.0466, wR = 0.1070, GoF = 1.026, refined on F; residual electron density, 0.287 and −0.273 e $Å^{-3}$.

Crystal data for **35**: $C_{15}H_{11}ClO_5$, M_r 306.69 g mol^{-1}; crystal dimensions (mm) 0.49 × 0.05 × 0.03; crystal system, monoclinic; space group, $P2_1/c$; unit cell dimensions and volume, a = 5.2102(3) Å, b = 30.1686(16) Å, c = 8.4028(5) Å, α = 90°, β = 94.569(4)°, γ = 90°, V = 1316.59(13) $Å^3$, no. of formula

(12) Bennett, O. F.; Bouchard, M. J.; Mallot, R.; Derven, P.; Saluti, G. *J. Org. Chem.* **1972**, *37*, 1359–1376.

units in the unit cell $Z = 4$; calculated density r_{calcd}, 1.547 Mg/m^3; linear absorption coefficient, m 0.310 mm^{-1}; radiation and wavelength, Mo Kα = 0.71073 Å; temperature of measurement, 173(2) K, 2 Q_{max} 25.00°; no of measured and independent reflections, 12081 and 2315; R_{int} = 0.0479; R [$I > 2.0\sigma(I)$] = 0.0479, wR = 0.0886, GoF = 1.039, refined on F; residual electron density, 0.220 and −0.243 e Å^{-3}.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including crystallographic data for compounds **13** (CCDC 799882), **21** (CCDC 799883), and **35** (CCDC 799884). This material is available free of charge via the Internet at http://pubs.acs.org.