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Acetoxymethylation of Coumarins by Manganese(III) Acetate

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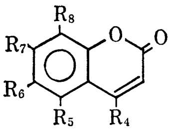
The reactions of 4-methoxy-, 7-methoxy-, 6,7-dimethoxy-, and 7,8-dimethoxycoumarins with manganese(III) acetate in boiling acetic acid containing acetic anhydride gave 3-(acetoxymethyl)coumarins as the major product. The reactions of coumarin, and 6-methoxy- and 8-methoxycoumarins with manganese(III) acetate yielded a mixture of 3-(diacetoxymethyl)- and nuclear acetoxymethylated coumarins. The reaction of 7-methoxycoumarin with lead(IV) acetate gave 7-methoxy-3-methylcoumarin.

In a previous publication[1)] we have reported the oxidation of 2-hydroxybenzophenones with manganese(III) acetate, that gave 9-xanthenones and acetoxymethylated 9-xanthenones. The reactions of aromatic hydrocarbons,[2,3)] aromatic ethers,[4)] and benzofuran,[5)] with manganese(III) acetate have been reported to give acetoxymethylated products. The reaction mechanisms were discussed by Heiba *et al.*[2)] However, these papers were primarily concerned with the product analyses and the reaction mechanisms, and the synthetic utility was not investigated in detail. In this paper we will describe the reaction of methoxy-substituted coumarins with manganese(III) acetate, that gave 3-(acetoxymethyl)-, 3-(diacetoxymethyl)-, and di(acetoxymethyl)-coumarins. We have also carried out the reaction of 7-methoxycoumarin with lead(IV) acetate, which yielded mainly 7-methoxy-3-methylcoumarin.

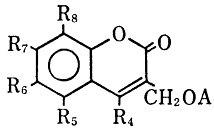
The coumarins studied were coumarin (**1a**), 4-methoxycoumarin (**1b**), 6-methoxycoumarin (**1c**), 7-methoxycoumarin (**1d**), 8-methoxycoumarin (**1e**), 6,7-dimethoxycoumarin (**1f**), and 7,8-dimethoxycoumarin (**1g**). The reactions were carried out in boiling acetic acid containing acetic anhydride, and in boiling acetic anhydride, using 6—12 equivalents of manganese(III) acetate dihydrate for 1 equivalent of the substrate. The reactions were continued until the color of manganese(III) acetate disappeared.

The reaction of **1d** in acetic acid containing acetic anhydride in the substrate/oxidant ratio of 1 : 6 gave an acetate (**2d**) (entry 4). The NMR spectrum indicated the presence of an acetoxymethyl group {δ 2.24 (3H, singlet) and δ 5.03 (2H, doublet, J=1.0 Hz)}. The acetoxymethyl group can be located at 3-position, since the methylene protons at δ 5.03 couple with a lower field proton which appeared at δ 7.69 (1H, broad singlet) as was confirmed by a decoupling experiment. An ABX pattern of three aromatic protons was found in the spectrum {δ 6.75—6.90 (2H, multiplet) and 7.48 (1H, m)}. The yield of **2d** increased with increase of the molar ratio of manganese(III) acetate and the maximum yield was attained for the substrate/oxidant ratio of 1 : 10 (entry 6). When the reaction was conducted for this molar ratio, another product (**4d**) was isolated from the reaction mixture, the structure of which was elucidated as before by the NMR spectrum. It showed the presence of two acetoxyl group at δ 2.15 and a doublet proton at δ 7.66 (J=1.0 Hz), indicating that a diacetoxymethyl group is present in the molecule. The presence of an ABX pattern of three aromatic protons and a lower field proton (δ 7.80, broad s) suggested that the diacetoxymethyl group can be located at 3-position (Fig. 1). When the reaction of **1d** with manganese(III) acetate was conducted in acetic anhydride, a complex mixture of products was obtained. In acetic acid, on the other hand, the reaction did not take place. **1b**, **1f**, and **1g** gave the corresponding 3-(acetoxymethyl)coumarin, **2b**, **2f**, and **2g** in the reaction, respectively (entries 2, 13, and 14). In the case of **1g**, 3,6-di(acetoxymethyl)-7,8-dimethoxycoumarin (**5g**) was obtained in a low yield.

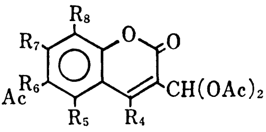
In contrast to the coumarins described above, the reactions of **1a**, **1c**, and **1e** with manganese(III) acetate showed a very different product distribution. In the case of **1a**, 3-(diacetoxymethyl)coumarin (**4a**) was the major product and a small amount of impure 3-(acetoxymethyl)coumarin (**2a**) was isolated (entry 1). **1c** gave 3-(diacetoxymethyl)-6-methoxycoumarin (**4c**) and a mixture of 5- and 7-(acetoxymethyl)coumarins (**3c** and **3c′**). The reaction of **1e** with manganese(III) acetate gave three products: **3e**, **4e**, and **6e** (entry 12). The structure of **3e** was elucidated by the NMR analysis: the chemical shifts of an AB system due to the protons at 6- and 5-positions (δ_A=7.00 and δ_B=7.21, J_{AB}=9.0 Hz) are characteristic of the 7,8-disubstituted



1a—g

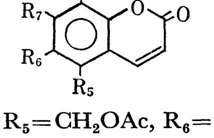


2a, b, d, f, g

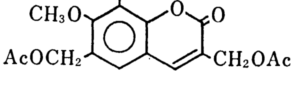


4a, c, d, e

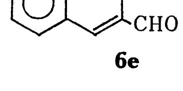
1, 2, and 4
a: $R_4=R_5=R_6=R_7=R_8=H$
b: $R_5=R_6=R_7=R_8=H, R_4=OCH_3$
c: $R_4=R_5=R_7=R_8=H, R_6=OCH_3$
d: $R_4=R_5=R_6=R_8=H, R_7=OCH_3$
e: $R_4=R_5=R_6=R_7=H, R_8=OCH_3$
f: $R_4=R_5=R_8=H, R_6=R_7=OCH_3$
g: $R_4=R_5=R_6=H, R_7=R_8=OCH_3$



3c : $R_5=CH_2OAc, R_6=OCH_3, R_7=R_8=H$
3c′: $R_5=R_8=H, R_6=OCH_3, R_7=CH_2OAc$
3e : $R_5=R_6=H, R_7=CH_2OAc, R_8=OCH_3$



5g



6e

7d

Table 1. The reactions of coumarins with manganese(III) acetate and lead(IV) acetate

Entry	Substrate	Reaction conditions$^{a)}$				Product (yield$^{b)}$/%)			
		Oxidant	Molar ratio of **1**: oxidant	Solvent	Time / min	Monoacetate	Diacetate	Aldehyde	3-Methylcoumarin
1	**1a**	Mn(OAc)$_3$	1: 10	AcOH, Ac$_2$O	60	**2a**(5)	**4a**(19)		
2	**1b**	Mn(OAc)$_3$	1: 10	AcOH, Ac$_2$O	120	**2b**(39)			
3	**1c**	Mn(OAc)$_3$	1: 10	AcOH, Ac$_2$O	50	**3c**(4.5$^{c)}$), **3c′**(2.5$^{c)}$)	**4c**(4)		
4	**1d**	Mn(OAc)$_3$	1: 6	AcOH, Ac$_2$O	140	**2d**(24)			
5	**1d**	Mn(OAc)$_3$	1: 8	AcOH, Ac$_2$O	110	**2d**(70)			
6	**1d**	Mn(OAc)$_3$	1: 10	AcOH, Ac$_2$O	200	**2d**(87)	**4d**(7)		
7	**1d**	Mn(OAc)$_3$	1: 12	AcOH, Ac$_2$O	170	**2d**(46)	**4d**(19)		
8	**1d**	Mn(OAc)$_3$	1: 12	Ac$_2$O	90	intractable			
9	**1d**	Pb(OAc)$_4$	1: 5	AcOH	30	**2d**(6)			**7d**(5)
10	**1d**	Pb(OAc)$_4$	1: 5	Ac$_2$O	10	**2d**(4)	**4d**(2)		**7d**(5)
11	**1d**	Pb(OAc)$_4$	1: 5	C$_6$H$_6$	6480				**7d**(23)
12	**1e**	Mn (OAc)$_3$	1: 8	AcOH, Ac$_2$O	105	**3e**(9)	**4e**(9)	**6e**(4)	
13	**1f**	Mn(OAc)$_3$	1: 10	AcOH, Ac$_2$O	80	**2f**(54)			
14	**1g**	Mn(OAc)$_3$	1: 10	AcOH, Ac$_2$O	90	**2g**(55)	**5g**(3)		

a) The reactions were carried out at reflux temperature.
b) Yields are based on the amount of coumarin consumed.
c) The values were estimated from the NMR spectrum.

coumarin (**1g**), in which the corresponding protons appeared at δ 6.91 and 7.23.

The results described above showed that coumarins bearing a methoxyl group at 4- or 7-position react with the carboxymethyl radical,2) which is formed from the decomposition of manganese(III) acetate, predominantly at the 3-position, where the electron density is much greater than in the other positions owing to the resonance effect of the methoxyl groups. In coumarins bearing no methoxyl group in either position, the competitive reactions occur at the 3-position and at *ortho*-positions to the methoxyl group on the aromatic nucleus. Diacetoxymethylation takes place in the case when a substrate has no sufficient activating group at 4- or 7-position (entries 1, 3, and 12) or when the oxidant is used in large excess (entry 7). On the contrary, the reaction of **1d** with lead(IV) acetate gave 7-methoxy-3-methylcoumarin (**7d**), when treated with 5 equivalents of lead(IV) acetate in boiling benzene. The methylation of aromatic compounds by lead(IV) acetate has precedence.1,6) The reaction of **1d** with lead(IV) acetate in acetic acid yielded **2d** and **7d** and in acetic anhydride **2d**, **4d**, and **7d**, but they have no synthetic values.

It is thus concluded that the reaction of coumarins bearing a methoxyl group at 4- or 7-position with manganese(III) acetate can give the corresponding 3-(acetoxymethyl)coumarin in moderately good yields.

Experimental

All ^{1}H chemical shifts (δ) were recorded for the deuteriochloroform solution with a Hitachi R 24 NMR spectrometer with TMS as an internal standard. The IR spectra were recorded for the chloroform solution with a JASCO IRA-1 grating spectrometer. The mass spectrum was recorded with a JEOL JMS-01 SG-2 mass spectrometer. Melting points were determined on a Yanagimoto hot-stage and are uncorrected. The compounds were recrystallized from ethanol, unless otherwise stated, and the yields are summarized in Table 1.

Coumarins. Coumarin (**1a**) was commercially available. 4-Methoxycoumarin (**1b**) was obtained from commercial 4-hydroxycoumarin by methylation.7) 6-Methoxycoumarin (**1c**) was obtained from coumarin (**1a**) by potassium peroxodisulfate oxidation followed by methylation.8) 7-Methoxycoumarin (**1d**) was prepared by the Pechmann reaction9) of resorcinol and malic acid, followed by methylation. 8-Methoxycoumarin (**1e**) was obtained by the reaction of *o*-vaniline and acetic anhydride.10) 6,7-Dimethoxycoumarin (**1f**) and 7,8-dimethoxycoumarin (**1g**) were prepared by the Pechmann reaction of the corresponding phenols and malic acid.

Oxidations of Coumarins (1a—g) with Manganese(III) Acetate. A typical oxidation of coumarin was as follows. A mixture of a coumarin (2 mmol), manganese(III) acetate dihydrate3) (12—24 mmol), and a solvent (50 ml) (if acetic acid was used as the solvent, acetic anhydride (24—48 mmol) was added) was heated under reflux for the time shown in Table 1. After the removal of the solvent *in vacuo*, the resulting mixture was extracted with chloroform. The chloroform solution was evaporated and chromatogrammed on TLC using chloroform as the developing solvent.

1a yielded 3-(acetoxymethyl)coumarin (**2a**). Mp: 106.5—107.5 °C; IR 1740 cm^{-1}; NMR 2.15 (3H, s, OAc), 5.07 (2H, d, J=1.0 Hz, –CH$_2$–), 7.1—7.7 (4H, m, aromatic), and 7.74 (1H, t, J=1.0 Hz, H$_{(4)}$); 3-(diacetoxymethyl)coumarin (**4a**): Mp 139—140 °C; IR 1750 and 1780 cm^{-1}; NMR 2.18 (6H, s, 2×OAc), 7.1—7.7 (4H, m, aromatic), 7.75 (1H, d, J=1.0 Hz, >CH–), and 7.92 (1H, broad s, H$_{(4)}$); MS *m/e* 276 (M$^+$), 233, 216, 191, 176, 175, 174, 173, 149, and 146 (Found: C, 60.99; H, 4.41%. Calcd for C$_{14}$H$_{12}$O$_6$: C, 60.87; H, 4.38%).

1b gave 3-(acetoxymethyl)-4-methoxycoumarin (**2b**). Mp: 114—115 °C; IR: 1740 cm^{-1}; NMR: 2.10 (3H, s, OAc), 4.16 (3H, s, OCH$_3$), 5.18 (2H, s, –CH$_2$–), 7.15—7.90 (4H, m, aromatic) (Found: C, 63.00; H, 4.92%. Calcd for C$_{13}$H$_{12}$O$_5$: C, 62.90; H, 4.87%).

1c yielded a mixture of 5-(acetoxymethyl)- and 7-(acetoxymethyl)-6-methoxycoumarins (**3c** and **3c′**). Mp: 119—123 °C.

(Found: C, 63.22; H, 4.90%. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87%); 3-(diacetoxymethyl)-6-methoxycoumarin (**4c**). Mp: 175—177 °C; IR: 1745 and 1778 cm^{-1}; NMR: 2.15 (6H, s, 2×OAc), 3.85 (3H, s, OCH_3), 6.9—7.4 (3H, m, aromatic), 7.70 (1H, d, $J=1.0$ Hz, >CH–), and 7.83 (1H, broad s, $H_{(4)}$) (Found: C, 58.62; H, 4.62%. Calcd for $C_{15}H_{14}O_7$: C, 58.82; H, 4.61%).

1d gave 3-(acetoxymethyl)-7-methoxycoumarin (**2d**). Mp: 118—119 °C; IR: 1725 and 1755 cm^{-1}; NMR: 2.24 (3H, s, OAc), 3.86 (3H, s, OCH_3), 5.03 (2H, d, $J=1.0$ Hz, $-CH_2-$), 6.75—6.90 (2H, m, $H_{(6)}$ and $H_{(8)}$), 7.48 (1H, m, $H_{(5)}$), and 7.69 (1H, broad s, $H_{(4)}$) (Found: C, 62.72; H, 4.93%. Calcd for $C_{13}H_{12}O_5$: C, 62.90: H, 4.87%); 3-(diacetoxymethyl)-7-methoxycoumarin (**4d**). Mp: 147—149 °C; IR: 1745 and 1775 cm^{-1}; NMR: 2.15 (6H, s, 2×OAc), 3.89 (3H, s, OCH_3), 6.79—6.95 (2H, m, $H_{(6)}$ and $H_{(8)}$), 7.40 (1H, d, $J=9.5$ Hz, $H_{(5)}$), 7.66 (1H, d, $J=1.0$ Hz, >CH–), and 7.80 (1H, broad s, $H_{(4)}$) (Found: C, 58.72; H, 4.69%. Calcd for $C_{15}H_{14}O_7$: C, 58.82; H, 4.61%).

1e yielded 7-(acetoxymethyl)-8-methoxycoumarin (**3e**). Mp: 121—122 °C; IR: 1750 cm^{-1}; NMR: 2.05 (3H, s, OAc), 3.92 (3H, s, OCH_3), 5.21 (2H, s, $-CH_2-$), 6.48 (1H, d, $J=10.0$ Hz, $H_{(3)}$), 7.00 (1H, d, $J=9.0$ Hz, $H_{(6)}$), 7.21 (1H, d, $J=9.0$ Hz, $H_{(5)}$), and 7.90 (1H, d, $J=10.0$ Hz, $H_{(4)}$) (Found: C, 62.73; H, 5.18%. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87%); 3-(diacetoxymethyl)-8-methoxycoumarin (**4e**). Mp: 130—131 °C (CCl_4); IR: 1752 and 1775 cm^{-1}; NMR: 2.15 (6H, s, 2×OAc), 3.96 (3H, s, OCH_3), 6.8—7.4 (3H, m, aromatic), 7.70 (1H, d, $J=1.0$ Hz, >CH–), 7.85 (1H, broad s, $H_{(4)}$) (Found: C, 58.90; H, 4.72%. Calcd for $C_{15}H_{14}O_7$: C, 58.82; H, 4.61%); 3-formyl-8-methoxycoumarin (**6e**). Mp: 166—168 °C; IR: 1724 and 1750 cm^{-1}; NMR: 3.97 (3H, s, OCH_3), 7.24 (3H, s, aromatic), 8.36 (1H, s, $H_{(4)}$), and 10.17 (1H, s, CHO) (Found: C, 64.70; H, 3.89%. Calcd for $C_{11}H_8O_4$: C, 64.70; H, 3.95%).

1f gave 3-(acetoxymethyl)-6,7-dimethoxycoumarin (**2f**). Mp: 140—141 °C; IR: 1730 and 1740 cm^{-1}; NMR: 2.14 (3H, s, OAc), 3.91 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 5.06 (2H, d, $J=1.0$ Hz, $-CH_2-$), 6.85 (1H, s, $H_{(5)}$ or $H_{(8)}$), 6.91 (1H, s, $H_{(5)}$ or $H_{(8)}$), and 7.70 (1H, broad s, $H_{(4)}$). Found: C, 60.30; H, 5.15%. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07%.

1g yielded 3-(acetoxymethyl)-7,8-dimethoxycoumarin (**2g**). Mp: 140 °C; IR: 1750 cm^{-1}; NMR: 2.14 (3H, s, OAc), 3.95 (6H, s, $2\times OCH_3$), 5.00 (2H, d, $J=1.0$ Hz, $-CH_2-$), 6.92 (1H, d, $J=9.0$ Hz, $H_{(6)}$), 7.22 (1H, d, $J=9.0$ Hz, $H_{(5)}$), and 7.69 (1H, t, $J=1.0$ Hz, $H_{(4)}$) (Found: C, 60.32; H, 5.02%. Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07%); 3,6-di(acetoxymethyl)-7,8-dimethoxycoumarin (**5g**). Mp: 159—160 °C; IR: 1750 cm^{-1}; NMR: 2.09 (3H, s, OAc), 2.14 (3H, s, OAc), 3.96 (6H, s, $2\times OCH_3$), 5.00 (2H, d, $J=1.0$ Hz, $-CH_2-$), 5.23 (2H, s, $-CH_2-$), 6.91 (1H, s, $H_{(5)}$), and 7.87 (1H, t, $J=1.0$ Hz, $H_{(4)}$) (Found: C, 58.59; H, 5.25%. Calcd for $C_{17}H_{18}O_8$: C, 58.28; H, 5.18%).

*Oxidation of **1d** with Lead(IV) Acetate.* A mixture of **1d** (2 mmol), lead(IV) acetate[11] (10 mmol), and a solvent (50 ml) was heated under reflux for the time shown in Table 1. After the removal of the solvent *in vacuo*, the resulting mixture was extracted with chloroform. The chloroform solution was evaporated and then chromatogrammed on TLC, giving **2d**. Mp: 118—119 °C. **4d**. Mp: 147—149 °C. 7-Methoxy-3-methylcoumarin (**7d**). Mp: 144 °C (lit,[12] mp 144 °C); IR: 1725 cm^{-1}; NMR: 2.17 (3H, d, $J=1.5$ Hz, CH_3), 3.85 (3H, s, OCH_3), 6.65—6.90 (2H, m, $H_{(6)}$ and $H_{(8)}$), 7.39 (1H, m, $H_{(5)}$), and 7.44 (1H, q, $J=1.5$ Hz, $H_{(4)}$).

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