Monatshefte für Chemie 113, 73—79 (1982)

Monatshefte für Chemie
Chemical Monthly
© by Springer-Verlag 1982

Nitration, Amination, and Halogenation of Di-*O*-methylphloracetophenone

John P. Acton, Dorothy J. Donnelly, and **John A. Donnelly***

Chemistry Department, University College, Dublin 4, Ireland

(Received 14 April 1981. Accepted 27 April 1981)

Chlorination of the title compound gave 5′- and 3′-chloro-2′-hydroxy-4′,6′-dimethoxyacetophenone. The nitration of its acetate, followed successively by reduction, diazotization, and reaction with cuprous chloride, gave the 3′-substituted series, 2′-acetoxy-4′,6′-dimethoxy-3′-nitroacetophenone, 3′-amino-2′-hydroxy-4′,6′-dimethoxyacetophenone, and 3′-chloro-2′-hydroxy-4′,6′-methoxyacetophenone, respectively. The orientation of substituents in the products was proved. The amino and chloro members of the isomeric 5′-substituted series were available *via* 2′-hydroxy-4′,6′-dimethoxy-5′-phenylazoacetophenone, the product of the reaction of the title compound with benzenediazonium chloride.

(Keywords: Acetophenone; Aromatic substitution; Nuclear regioselectivity)

Nitrierung, Aminierung und Halogenierung von Di-O-methylphloracetophenon

Chlorierung der Titelverbindung gab 5′- und 3′-Chlor-2′-hydroxy-4′,6′-dimethoxyacetophenon. Die Nitrierung des Acetats, gefolgt von Reduktion, Diazotierung und Reaktion mit CuCl ergab die 3′-substituierte Reihe: 2′-Acetoxy-4′,6′-dimethoxy-3′-nitroacetophenon, 3′-Amino-2′-hydroxy-4′,6′-dimethoxyacetophenon und 3′-Chlor-2′-hydroxy-4′,6′-dimethoxyacetophenon. Die Orientierung der Substituenten wird diskutiert. Die Amino- und Chlorderivate der isomeren 5′-substituierten Reihe sind über 2′-Hydroxy-4′,6′-dimethoxy-5′-phenylacetophenon zugängig, dem Produkt der Reaktion der Titelverbindung mit Phenyldiazoniumchlorid.

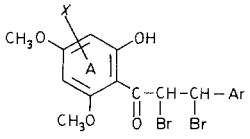
Introduction

A-ring halogenated and nitrated chalcone dibromides (**1**) derived from phloracetophenone, were required for a study[1] of the steric and electronic effects that control the *Emilewicz—von Kostanecki* cyclization of chalcone dihalides to naturally-occurring flavones or aurones. It was, therefore, sought to nitrate and halogenate, directly and indirectly, 2′-hydroxy-4′,6′-dimethoxyacetophenone (**2**).

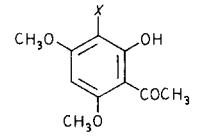
0026-9247/82/0113/0073/$ 01.40

Results and Discussion

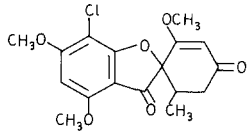
Grove and co-workers have shown[2] that griseofulvin (**9**) is related to 3′-chloro-2′-hydroxy-4′,6′-dimethoxyacetophenone (**3**) and have synthesised this acetophenone by the *Friedel-Crafts* reaction of acetyl chloride with 2-chloro-3,5-dimethoxyphenol; the orientation of substituents in the phenol was proved unambiguously by a series of



1 X = Hal ; NO_2



	X
2	H
3	Cl
4	Br
5	J
6	NO_2
7	NH_2
8	$N(CH_3CO)_2$



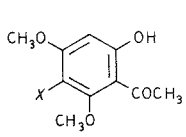
9

reactions and that of the acyl group in the derived acetophenone (**3**) by colour tests and infrared spectroscopy. It has now been found that this 3′-chloroacetophenone (**3**) is the minor component (15%) of the mixture obtained by chlorinating 2′-hydroxy-4′,6′-dimethoxyacetophenone (**2**); it precipitated cleanly and completely from the reaction when carbon tetrachloride was used as solvent. The major product (57%) was 5′-chloro-2′-hydroxy-4′,6′-dimethoxyacetophenone (**10**).

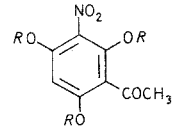
Bromination of 2′-hydroxy-4′,6′-dimethoxyacetophenone (**2**) is known[3] to give 3′-bromo-2′-hydroxy-4′,6′-dimethoxyacetophenone (**4**). This reaction was repeated but did not prove to be analogous to the chlorination in that no trace of a possibly more soluble 5′-bromo-2′-hydroxy-4′,6′-dimethoxyacetophenone (**11**) was detected; the 3′-bromoacetophenone (**4**) was the sole product. Iodination of 2′-hydroxy-4′,6′-dimethoxyacetophenone (**2**) is also reported[4] to give only 2′-hydroxy-3′-iodo-4′,6′-dimethoxyacetophenone (**5**). It would appear, therefore, that the 5′-position of 4′,6′-di-*O*-methylphloracetophenone (**2**) is unable, for steric reasons, to compete with the 3′-position for the larger halogens, bromine and iodine, even though it is more competitive than the 3′-position towards chlorine.

The nitration of 2′-hydroxy-4′,6′-dimethoxyacetophenone (**2**) in acetic anhydride with nitric acid in acetic acid gave 2′-hydroxy-4′,6′-dimethoxy-3′-nitroacetophenone (**6**) but in very poor yield (2%). Many other reagents such as concentrated or dilute nitric acid in acetic acid, urea nitrate in polyphosphoric acid, and aluminium nitrate in acetic

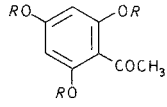
anhydride, failed. When attempts were made to synthesise 2′,4′,6′-trihydroxy-3′-nitroacetophenone (**15**) and 2′,4′,6′-trimethoxy-3′-nitroacetophenone (**16**) by the nitration of phloracetophenone (**17**) and its trimethyl ether (**18**), with the intention of dimethylating the former and monodemethylating the latter, nitrodeacylation *ipso* reactions[5] occurred with the formation of 1,3,5-trihydroxy-2-nitrobenzene (**19**) and 1,3,5-trimethoxy-2-nitrobenzene (**20**), respectively.



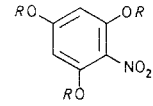
	X
10	Cl
11	Br
12	$-N{=}NC_6H_5$
13	NH_2
14	$N(COCH_3)_2$



	R
15	H
16	CH_3



	R
17	H
18	CH_3

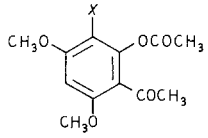


	R
19	H
20	CH_3
21	$COCH_3$

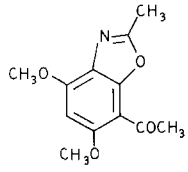
Nitration prior to acylation was scarcely more successful. A low yield (20%) of 2′,4′,6′-trihydroxy-3′-nitroacetophenone (**15**) was obtained from the reaction of 1,3,5-trihydroxy-2-nitrobenzene (**19**) with acetic anhydride and aluminium chloride in nitrobenzene. When this reaction was carried out in carbon tetrachloride, only 1,3,5-triacetoxy-2-nitrobenzene (**21**) was obtained. Methylation of 2′,4′,6′-trihydroxy-3′-nitroacetophenone (**15**) with dimethyl sulphate gave 2′,4′,6′-trimethoxy-3′-nitroacetophenone (**16**). 1,3,5-Trimethoxy-2-nitrobenzene (**20**) failed to react with acetic anhydride and aluminium chloride.

The successful nitration of a 4′,6′-di-*O*-methylphloracetophenone derivative was eventually achieved using 2′-acetoxy-4′,6′-dimethoxyacetophenone (**22**); it reacted in acetic anhydride with nitric acid in acetic acid to give 2′-acetoxy-4′,6′-dimethoxy-3′-nitroacetophenone (**23**) in 52% yield. The orientation of the nitro group is shown by its reactions (see below).

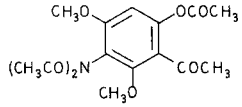
The reduction of 2′-acetoxy-4′,6′-dimethoxy-3′-nitroacetophenone (**23**) was carried out in the presence of an anti-oxidant, stannous chloride, using zinc dust in acid solution. The yellow solid product, 3′-amino-2′-hydroxy-4′,6′-dimethoxyacetophenone (**7**), was unstable in



	X
22	H
23	NO_2



24



25

air, turning into a red oil. It was characterised as its hydrochloride. It reacted with acetic anhydride to form 3′-diacetylamino-2′-hydroxy-4′,6′-dimethoxyacetophenone (**8**) rather than the benzoxazole (**24**), so frustrating an attempt to establish the orientation of the amino group. This was achieved, however, by diazotizing the aminoacetophenone (**7**) and treating it with cuprous chloride; the orientation of substituents in the product, 3′-chloro-2′-hydroxy-4′,6′-dimethoxyacetophenone (**3**), is known.

In the belief that the weakly electrophilic diazonium cation, $C_6H_5N_2^+$, would be sterically suited for attacking the hindered 5′-position of 4′,6′-di-*O*-methylphloracetophenone (**2**) and so make available 5′-halogenated derivatives of this acetophenone, the last-mentioned was treated with benzenediazonium chloride. It yielded 2′-hydroxy-4′,6′-dimethoxy-5′-phenylazoacetophenone (**12**). This was reduced to 5′-amino-2′-hydroxy-4′,6′-dimethoxyacetophenone (**13**) which was more stable than its 3′-amino isomer. When diazotized, this amine reacted with cuprous chloride to give 5′-chloro-2′-hydroxy-4′,6′-dimethoxyacetophenone (**10**), identical with the major product from the chlorination of 2′-hydroxy-4′,6′-dimethoxyacetophenone (**2**). It failed to give 5′-bromo-2′-hydroxy-4′,6′-dimethoxyacetophenone (**11**) after diazotization and reaction with mercuric bromide; the only product isolated was the deaminated compound, 2′-hydroxy-4′,6′-dimethoxyacetophenone (**2**). It reacted with acetic anhydride to give a mixture of 5′-diacetylamino-2′-hydroxy-4′,6′-dimethoxyacetophenone (**14**) and the corresponding acetate, 2′-acetoxy-5′-diacetylamino-4′,6′-dimethoxyacetophenone (**25**).

Experimental

^{1}H N.m.r. spectra of all products were obtained at 60 MHz in $CDCl_3$ with $SiMe_4$ as internal reference. Hydroxy-signals were identified by deuteriation. M.p.s. were taken with a *Kofler* hot-stage apparatus. Mixtures were fractioned

by preparative thin layer chromatography (p.l.c.) on silica gel; products are mentioned in order of decreasing R_F values.

Chlorine (2 g) in carbon tetrachloride (50 ml) was added to a solution of 2'-hydroxy-4',6'-dimethoxyacetophenone (5 g) in carbon tetrachloride (100 ml). After 18 h, the precipitated 3'-chloro-2'-hydroxy-4',6'-dimethoxyacetophenone[2b] (**3**) was filtered off; it crystallized from ethanol in needles (0.865 g), m.p. 191—192 °C; δ 2.67 (s, *Ac*), 3.98 (s, 4'-O*Me*), 4.02 (s, 6'-O*Me*), 6.09 (s, 5'-H), 14.46 (s, OH). The filtrate was evaporated to dryness and the residue crystallized from ethanol, giving *5'-chloro-2'-hydroxy-4',6'-dimethoxyacetophenone* (**10**) in needles (3.354 g), m.p. 91 °C; δ 2.74 (s, *Ac*), 3.96 (s, 4'- and 6'-O*Me*), 6.36 (s, 3'-H), 13.63 (s, OH). $C_{10}H_{11}ClO_4$.*.

Nitric acid ($d = 1.42$, 1.6 ml) in acetic acid (2 ml) was added slowly to an ice-cold solution of 2'-hydroxy-4',6'-dimethoxyacetophenone (4.781 g) in acetic anhydride (20 ml). After 8 h, the mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with diethyl ether. The extract was washed, dried, and purified by p.l.c., giving *2'-hydroxy-4',6'-dimethoxy-3'-nitroacetophenone* (**6**) which crystallized from aqueous ethanol (96%) in yellow prisms (0.118 g), m.p. 104-105 °C; δ 2.73 (s, *Ac*), 3.87 (s, 4'-O*Me*), 3.98 (s, 6'-O*Me*), 6.40 (s, 5'-H), 13.11 (s, OH). $C_{10}H_{11}NO_6$.

Nitric acid ($d = 1.42$; 0.4 ml) in sulphuric acid (2 ml) was added slowly to an ice-cold solution of 2',4',6'-trihydroxyacetophenone (1.503 g) in dilute sulphuric acid (50%, 50 ml). After 3 h, the mixture was diluted with water (50 ml) and extracted with diethyl ether. The extract was washed, dried, and evaported to dryness, giving 1,3,5-trihydroxy-2-nitrobenzene[6] (**19**) which crystallized from chloroform in red prisms (0.762 g), m.p. 191-192 °C.

An ice-cold mixture of nitric acid ($d = 1.42$, 0.2 ml) and acetic acid (1.2 ml) was added to a similar mixture of 2',4',6'-trimethoxyacetophenone (0.22 g) in acetic anhydride (5 ml). After 12 h, the mixture was diluted with water and extracted with chloroform. The extract was washed with saturated aqueous sodium bicarbonate and water, then dried and purified by p.l.c. giving 1,3,5-trimethoxy-2-nitrobenzene[7] (**20**) (0.155 g), m.p. 146-148 °C.

Acetic anhydride (6 ml) was added to a mixture of anhydrous 1,3,5-trihydroxy-2-nitrobenzene (9.507 g) and aluminium chloride (19.14 g) in nitrobenzene (100 ml) and heated on a steambath for 7 h. The mixture was cooled, treated with dilute hydrochloric acid, and steam-distilled, giving *2',4',6'-trihydroxy-3'-nitroacetophenone* (**15**) (2.40 g), m.p. 131-132 °C; δ 2.01 (s, *Ac*), 5.90 (s, 5'-H), 10.49 (bs, 2'-, 4'-, and 6'-OH). $C_8H_7NO_6$. Aluminium chloride (20.0 g) was added to an ice-cold suspension of 1,3,5-trihydroxy-2-nitrobenzene (16.47 g) in acetic anhydride (50 ml) and carbon tetrachloride (100 ml). After 4 h, the mixture was refluxed for 5 h, cooled, treated with dilute hydrochloric acid, and extracted with diethyl ether. The extract was washed with saturated aqueous sodium bicarbonate and water and dried, giving 1,3,5-triacetoxy-2-nitrobenzene[6b] (**21**) which crystallized from aqueous ethanol (96%) in plates (4.051 g), m.p. 105-107 °C.

A mixture of 2',4',6'-trihydroxy-3'-nitroacetophenone (0.147 g) and potassium carbonate (2 g) in anhydrous acetone (30 ml) and dimethyl sulphate (3 ml) was refluxed under nitrogen for 48 h, filtered, and diluted with water. The precipitated *2',4',6'-trimethoxy-3'-nitroacetophenone* (**16**) (0.027 g) crystallized from aqueous ethanol (96%), m.p. 93-94 °C; δ 2.53 (s, *Ac*), 3.90 (s, 4'-O*Me*), 3.95 (s, 6'-O*Me*), 3.99 (s, 2'-O*Me*), 6.43 (s, 5'-H). $C_{11}H_{13}NO_6$.

* All new compounds gave satisfactory elemental analyses (C, H, N).

Nitric acid ($d = 1.42$, 1 ml) in acetic acid (9 ml) was added to a solution of 2′-acetoxy-4′,6′-dimethoxyacetophenone (3.368 g) in acetic anhydride, kept at 0 °C for 4 days, and diluted with water, giving *2′-acetoxy-4′,6′-dimethoxy-3′-nitroacetophenone* (**23**) which crystallized from aqueous ethanol (96%) in needles (2.075 g), m.p. 114–115 °C; δ 2.29 (s, O*Ac*), 2.50 (s, *Ac*), 4.00 (s, 4′- and 6′-O*Me*), 6.53 (s, 5′-H). $C_{12}H_{13}NO_7$.

A hot solution of stannous chloride (0.197 g) in hydrochloric acid (1 ml) was added to a solution of 2′-acetoxy-4′,6′-dimethoxy-3′-nitroacetophenone (0.241 g) in ethanol (5 ml) containing zinc dust (2.47 g). The mixture was heated on a steambath for 10 min and then concentrated under reduced pressure to an oil which was purified by p.l.c., giving *3′-amino-2′-hydroxy-4′,6′-dimethoxyacetophenone* (**7**) as a yellow solid (0.086 g), m.p. 118–119 °C; δ 2.68 (s, *Ac*), 3.66 (bs, NH_2), 3.92 (s, 4′-O*Me*), 3.99 (s, 6′-O*Me*), 6.19 (s, 5′-H), 13.80 (s, OH); i.r. ($CHCl_3$) cm^{-1} 3 600 (NH_2), 3 405 (OH), 1 630 (C=O). $C_{10}H_{13}NO_4$. A solution of the 3′-nitroacetophenone (0.047 g) in ethanol (5 ml) was treated with zinc dust (0.120 g) and a solution of stannous chloride (0.255 g) in hydrochloric acid (1 ml), heated on a steambath for 5 min, diluted with water, and extracted with chloroform. Removal of the solvent gave *3′-amino-2′-hydroxy-4′,6′-dimethoxyacetophenone hydrochloride* as a white solid (0.024 g), m.p. 171°. $C_{10}H_{13}NO_4 \cdot HCl$.

Stannous chloride (0.133 g) in hydrochloric acid (1 ml) solution was added to a hot solution of 2′-acetoxy-4′,6′-dimethoxy-3′-nitroacetophenone (0.162 g) in ethanol (5 ml) containing zinc dust (1.592 g), heated on a steambath for 15 min, and filtered. The filtrate was added to sodium acetate (0.277 g) and acetic anhydride (5 ml), heated on a steambath for 2 days, diluted with water, and extracted with chloroform. The extract was washed with saturated aqueous sodium bicarbonate and water, dried, and evaporated to dryness, giving *3′-diacetylamino-2′-hydroxy-4′,6′-dimethoxyacetophenone* (**8**) which crystallized from hexane/chloroform in plates (0.058 g), m.p. 178–179 °C; δ 2.33 (s, N*Ac*$_2$), 2.68 (s, *Ac*), 3.93 (s, 4′-O*Me*), 4.00 (s, 6′-O*Me*), 6.09 (s, 5′-H), 14.18 (s, OH). $C_{14}H_{17}NO_6$.

An aqueous solution (1 ml) of sodium nitrite (0.057 g) was added to a solution of 3′-amino-2′-hydroxy-4′,6′-dimethoxyacetophenone at 0 °C, kept in an ice-bath for 0.5 h, and treated with a solution of cuprous chloride (0.5 g) in hydrochloric acid (1 ml). After 12 h, the mixture was diluted with water, precipitating 3′-chloro-2′-hydroxy-4′,6′-dimethoxyacetophenone (**3**) which crystallized from aqueous ethanol (96%) in white prisms (0.010 g), m.p. 190 °C.

Sodium nitrite (1.016 g) dissolved in water (5 ml) was added to aniline (1.430 g) in dilute hydrochloric acid (20%, 30 ml) at 0–4 °C, stirred in an ice-bath for 0.5 h and added to a solution of 2′-hydroxy-4′,6′-dimethoxyacetophenone (2.973 g) in ethanol (60 ml) and aqueous sodium hydroxide (10%, 20 ml) at 4–8 °C. After 72 h, the mixture was acidified, precipitating *2′-hydroxy-4′,6′-dimethoxy-5′-phenylazoacetophenone* (**12**) which crystallized from aqueous ethanol (96%) in red needles (4.076 g), m.p. 97 °C; δ 2.77 (s, *Ac*), 3.92 (s, 4′- and 6′-O*Me*), 6.43 (s, 3′-H), 7.45–8.12 (m, *Ph*), 13.87 (s, OH). $C_{16}H_{16}N_2O_4$.

Stannous chloride (0.132 g), dissolved in hydrochloric acid (1 ml), was added to a hot solution of 2′-hydroxy-4′,6′-dimethoxy-5′-phenylazoacetophenone (0.165 g) in ethanol (30 ml) containing zinc dust (1.05 g), heated on a steambath for 4 h, filtered, diluted with water, and extracted with chloroform. The extract was purified by p.l.c., giving *5′-amino-2′-hydroxy-4′,6′-dimethoxyacetophenone* (**13**) which crystallized from light petroleum (b.p. 60–80 °C) in yellow needles (0.085 g), m.p. 75 °C; δ 2.75 (s, *Ac*), 3.60 (bs, NH_2), 3.88 (s, 4′-O*Me*), 3.99 (s, 6′-O*Me*), 6.40 (s, 3′-H), 13.05 (s, OH). $C_{10}H_{13}NO_4$.

Stannous chloride (0.33 g) dissolved in hydrochloric acid (3 ml) was added to a solution of 2′-hydroxy-4′,6′-dimethoxy-5′-phenylazoacetophenone (0.355 g) in ethanol (10 ml) containing zinc dust (1.203 g), heated on a steambath for 2 h under nitrogen, filtered, cooled in an ice-bath and treated with an aqueous solution (1 ml) of sodium nitrite (0.091 g) at 0–4 °C. This solution was added to cuprous chloride (1 g), dissolved in hydrochloric acid (5 ml), at 4–8 °C, heated on a steambath for 10 min, diluted with water, and extracted with chloroform. The extract was purified by p.l.c., giving 5′-chloro-2′-hydroxy-4′,6′-dimethoxyacetophenone (**10**) which crystallized from aqueous ethanol (96%) in needles (0.028 g), m.p. 90–91 °C. $C_{10}H_{11}ClO_4$.

The above reaction was repeated but, after the addition of sodium nitrite, mercuric bromide (0.31 g) was added. No precipitation of a mercuric bromide complex occurred. The mixture was stirred for 5 h, and excess potassium bromide was added. It was then heated on a steambath for 0.5 h and extracted with chloroform. The extract was washed, dried, and evaporated to dryness, giving 2′-hydroxy-4′,6′-dimethoxyacetophenone (**2**) as a white solid (0.023), m.p. 80–81 °C.

A solution of 5′-amino-2′-hydroxy-4′,6′-dimethoxyacetophenone (0.582 g) in acetic anhydride (5 ml) was heated on a steambath for 12 h, evaporated to an oil under reduced pressure, and fractioned by p.l.c. This gave *5′-diacetylamino-2′-hydroxy-4′,6′-dimethoxyacetophenone* (**14**) which crystallized from ethanol in prisms (0.085 g), m.p. 141–142 °C; δ 2.35 (s, N*Ac*$_2$), 2.71 (s, *Ac*), 3.83 (s, 4′-O*Me*), 3.91 (s, 6′-O*Me*), 6.45 (s, 3′-H), 13.75 (s, OH), ($C_{14}H_{17}NO_6$), and its *acetate* (**25**) which crystallized from aqueous ethanol (96%) in needles (0.282 g), m.p. 116–117 °C; δ 2.23 (s, O*Ac*), 2.34 (s, N*Ac*$_2$), 2.55 (s, *Ac*), 3.97 (s, 4′-O*Me*), 4.01 (s, 6′-O*Me*), 6.60 (s, 3′-H). $C_{16}H_{19}NO_7$.

References

1 *Donnelly D. J., Donnelly J. A., Keegan J. R.*, Tetrahedron **33**, 3289 (1977).

2 (a) *Grove J. F., MacMillan J., Mulholland T. P. C., Zealley J.*, J. Chem. Soc. **1952**, 3967; (b) *Duncanson L. A., Grove J. F., MacMillan J., Mulholland T. P. C.*, ibid. **1957**, 3555.

3 *Donnelly J. A.*, Tetrahedron Letters **1959**, No. 19, 1.

4 *Chen F. C., Chang C. T., Chen T. S.*, J. Org. Chem. **27**, 85 (1962).

5 *Moodie R. B., Schofield K.*, Accounts Chem. Res. **9**, 287 (1976); *Nightingale D. V.*, Chem. Rev. **40**, 117 (1947); *Beirne J. J., Coyle A. M., Donnelly J. A.*, Tetrahedron **26**, 3809 (1970).

6 (a) *Dubiel S. V., Zuffanti Z.*, J. Org. Chem. **19**, 1359 (1954); (b) *Kampouris E. M.*, J. Chem. Soc. (C) **1967**, 2568.

7 *Price D., Bogert M. T.*, J. Amer. Chem. Soc. **56**, 2449 (1934).