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Electrophilic Nitration of Electron-Rich Acetophenones

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Summary. It is demonstrated that electron-rich disubstituted acetophenones react according to various electrophilic nitration conditions that generally lead to *ipso* substitution accompanying the conventional reaction. The hydroxy substituent does not seem prone to favor such behaviour.

Keywords. Nitration; *Ipso* substitution; Polysubstituted acetophenones.

Introduction

In the past, there have been regular references to the *ipso* electrophilic aromatic substitution reaction [1–3] and a few authors have reported examples of it [4, 5]. *Ipso* substitution in which X is displaced by a nitro group has long been known occurring in cases where $X =$ alkyl [6], acyl [7], or trialkylsilyl [8]. In cases where it occurs in reactions other than nitration, such as bromination [9], it is called ''non-conventional'' [10]. This type of substitution may also be induced by radical initiation [11]. We have recently demonstrated [12] that the nitration of electron-rich benzoic acids and benzaldehydes occurs at the most reactive position whatever that substituent, *i.e.* hydrogen, formyl, or carboxylic group. An *ipso* reaction has also been reported in the case of the nitration of polymethoxyacetophenones under concentrated nitric acid conditions [13].

In our general projects devoted to the synthesis of highly susbtituted heterocycles [14], we required efficient syntheses of new, diversely substituted *ortho*-aminoacetophenones. Therefore, we embarked on a systematic study of the nitration of acetophenones substituted with a *para* nitrogen atom and a *meta* oxygen atom. In this paper, we demonstrate that *ipso* substitution may be

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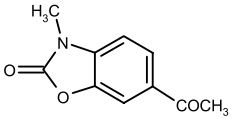
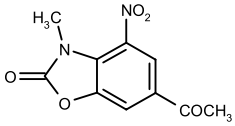
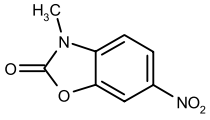
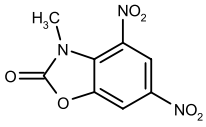
controlled depending on reaction conditions and the nature of the substituents leading to highly polysubstituted anilines or acetophenones in satisfactory yields.

Results and Discussion

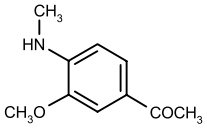
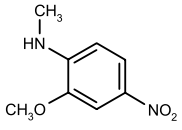
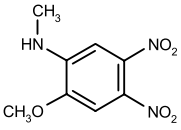
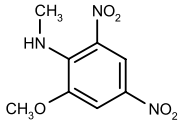
Three acetophenones, 6-acetyl-3-methyl-3*H*-benzoxazol-2-one (**1**) [15], 4-acetyl-2-methoxy-*N*-methylaniline (**2**) and 4-acetyl-2-hydroxy-*N*-methylaniline (**3**) [16] were subjected to five different nitration conditions. Structures of known compounds were established by 2D NMR and results are reported in Tables 1–3. Classical nitration conditions (methods A–C) were first tested using different co-solvents and reaction temperatures. Tin(IV) chloride was used as catalyst under

Table 1. Nitration of **1**

Method	Products (yield/%)[a]			
				
	1	**4**	**5**	**6**
A[b]		0	76	0
B[c]		16	50	0
C[d]		0	0	48
D[e]		0	0	0
E[f]		14	50	0

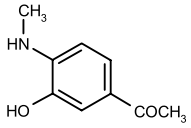
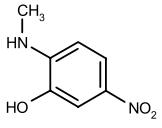
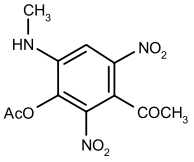
[a] Pure isolated products; [b] 68% HNO_3, 0°C, 3 h, see Experimental; [c] 68% HNO_3, 8 eq, $(CH_3CO)_2O$, 0°C, 3 h, see Experimental; [d] 68% HNO_3, 8 eq, H_2SO_4, CF_3COOH, 0°C, 1 h, see Experimental; [e] Fuming HNO_3, $SnCl_4$, CH_2Cl_2, −25°C, 3 h, see Experimental; [f] Claycop (Aldrich, 26/30 nitrate/clay), 1 eq, $(CH_3CO)_2O$, CH_2Cl_2, room temperature, 16 h, see Experimental

Table 2. Nitration of **2**

Method	Products (yield/%)[a]			
				
	2	**7**	**8**	**9**
A		0	0	32
B[b]		0	63	0
C		0	0	53
D		5	0	33
E		30	0	0

[a] Footnotes as in Table 1 except for method B; [b] 68% HNO_3, 8 eq, $(CH_3CO)_2O$, −40°C, 3 h, see Experimental

Table 3. Nitration of **3**

Method	Products (yield/%)[a]		
			
3	**10**	**11**	
E[b]	0	45	

[a] Pure isolated products; [b] Claycop (Aldrich, 26/30 nitrate/clay), 1 eq, $(CH_3CO)_2O$, CH_2Cl_2, room temperature, 16 h, see Experimental

mild conditions (−25°C, methylene chloride) [17] in method D, whereas Claycop (clay-supported cupric nitrate) was used in method E according to the *Laszlo*'s procedure [18]. Details are given in footnotes of Table 1.

The results show that the reactivities of **1**–**3** are very different and depend strongly on the reaction conditions. Compounds **1** and **2**, which appear to be the least reactive molecules of the series, give mainly, and in the case of **2**, even exclusively, products of *ipso* nitration. Reaction of **1** (Table 1) gives (i) 6-acetyl-3-methyl-4-nitro-3*H*-benzoxazol-2-one (**4**) in only 14–16% yields using acetic anhydride as solvent and nitric acid or Claycop as nitronium ion source (methods B and E), (ii) 3-methyl-6-nitrobenzoxazolone (**5**) [19] as the main product (50% yields, methods B and E) or as the sole product (76% yield, method A), whereas it is recovered according to method D. Under more acidic conditions the *ipso* derivative **6** [20] was isolated in 48% yield (method C).

Whatever the conditions used, the *ipso* nitration of **2** occurred (Table 2) but the structure of the products strongly depends on the reaction conditions. Whereas Claycop (method E) gives the *ipso* nitration product **7** [21], the dinitro product **9** is obtained as the main compound using method C. Unexpectedly, 2-methoxy-4,5-dinitro-*N*-methylaniline (**8**) is obtained in good yield using nitric acid in acetic anhydride at −40°C, whereas its 2,4-dinitro isomer **9** is the major product in the other cases. These *ipso* reactions constitute the best method for obtaining these dinitromethoxyanilines. The 2,4-dinitro isomer **9** has never been obtained using this procedure and the 4,5-dinitro isomer **8** had previously been obtained by photosubstitution (36% yield) from 4,5-dinitroveratrole [22].

Unlike the apparently dissimilar results, acetophenone **3**, which is expected to be the most reactive species, leads invariably (Table 3) to a dark residue from which no organic compound could be isolated, except in the case of method E where 2-acetoxy-4-acetyl-3,5-dinitro-*N*-methylaniline (**11**) was obtained in a moderate yield. Whereas 3,4-dimethoxyacetophenone is efficiently nitrated at position 6 in good yield using the classical method A (68% nitric acid), the replacement of the methoxy group at position 4 with a nitrogen atom dramatically increases the reactivity of **1**–**3**. *Ipso* nitration occurs almost exclusively for **1** and **2** whereas compound **3** is too reactive to allow for the isolation of organic material. Even milder conditions, *i.e. Laszlo*'s reagent, do not improve the yield in conventional

nitration products from **1** or **2** whereas a dinitroacetophenone is cleanly obtained from **3**.

The generation of different dinitro compounds from **2** may be tentatively explained by a difference in the order of occurrence of *ipso* nitration and conventional electrophilic substitution. At low temperature (method B), conventional nitration may occur first, *ortho* to the acetyl group (same position as in the case of 3,4-dimethoxyacetophenone) and, after that, *ipso* nitration leads to the 4,5-dinitro derivative. Conversely, under the other reaction conditions, *ipso* nitration occurs first and the second step is conventional nitration leading to the 2,4-dinitro compound.

In conclusion, we describe here the efficient preparation of some new, highly substituted anilines that may lead to a diversity of heterocycles. In addition, the yield of the known 2-methoxy-4,5-dinitro-*N*-methylaniline (**8**) was significantly improved. These new examples illustrate the difficulties encountered when the synthesis of highly substituted aryl compounds bearing electron-rich substituents is envisaged.

Experimental

TLC analyses were performed on 3×10 cm plastic sheets precoated with silica gel $60F_{254}$ (Merck), solvent system: ethyl acetate/cyclohexane. SiO_2, 230–400 mesh (Merck), was used for flash column chromatography. Melting points were obtained on a Büchi 510 melting point apparatus. IR spectral measurements were carried out with a Bruker Vector 22 spectrometer. ^1H NMR spectra were obtained on an AC 300P Bruker spectrometer in the appropriate solvent with TMS as internal reference. Mass spectra were taken with a Finningan TSQ 700 apparatus. Elemental analyses were performed by the Service Central d'Analyse-Département Analyse Elémentaire, CNRS, F-69390 Vernaison and were within 0.4% of the theoretical values.

Method A

Acetophenone (10 mmol) was added portionwise to 3 cm^3 68% HNO_3 (46 mmol) cooled to 0–5°C. The mixture was stirred for 3 h at this temperature. The solution was poured into 100 cm^3 H_2O, and the *pH* was adjusted to 8 with 10% aqu. K_2CO_3. The solution was extracted with CH_2Cl_2. The organic layer was dried ($CaCl_2$) and evaporated under reduced pressure. The products were separated by column chromatography and recrystallized.

Method B [23]

Nitric acid (68%, 5.30 cm^3, 80 mmol) cooled to 0–5°C (−40°C for **2**) was added dropwise to a solution of 10 mmol acetophenone in 20 cm^3 of acetic anhydride at the same temperature. The mixture was stirred at 0–5°C (−40°C for **2**) for 3 h. The precipitate was filtered, washed with H_2O and ether. The products were separated by column chromatography and recrystallized.

Method C [24]

A mixture of 68% HNO_3 (5.30 cm^3, 80 mmol) and 4 cm^3 96% H_2SO_4 cooled to 0–5°C was added dropwise to a solution of 10 mmol acetophenone in 5 cm^3 *TFA* at the same temperature. The mixture was stirred at 0–5°C for 1 h. The solution was poured into 100 cm^3 H_2O. The precipitate was filtered and washed with H_2O. The products were separated by column chromatography and recrystallized.

Method D [17]

A solution of 10 mmol acetophenone in 30 cm^3 CH_2Cl_2 was cooled to −25°C. A mixture of 1.15 cm^3 $SnCl_4$ (30 mmol) and 1.30 cm^3 of fuming HNO_3 (30 mmol) in 10 cm^3 CH_2Cl_2 was added. The solution

was stirred at −25°C for 3 h and hyrolyzed with 30 cm^3 H_2O. The organic layer was washed with 5% aqu. K_2CO_3, dried ($CaCl_2$) and evaporated under reduced pressure. The products were purified by column chromatography and recrystallized.

Method E [18]
Acetophenone (10 mmol) was dissolved in 30 cm^3 CH_2Cl_2 before Claycop (mixture of $Cu(NO_2)_2 \cdot H_2O$ and Montmorillonite K10 (26/30)) (10 mmol) and 9.40 cm^3 of acetic anhydride (100 mmol) were added. The mixture was stirred for 16 h at room temperature. The solution was filtered and evaporated under reduced pressure. The products were purified by column chromatography and recrystallized.

4-Acetyl-2-methoxy-N-methylaniline (**2**, $C_{10}H_{13}NO_2$)
Sodium hydride was added at room temperature to a solution of 3-hydroxy-4-methylaminoacetophenone [25] (0.5 g, 30 mmol) in *THF*. After stirring for 30 min, 0.23 cm^3 of iodomethane (36 mmol) were added. After 24 h, the mixture was poured into 50 cm^3 H_2O and extracted with ether. The organic layer was dried ($CaCl_2$) and evaporated under reduced pressure to give 0.33 g of orange solid (61%). Mp 105–106°C (cyclohexane); ^{1}H NMR (300 MHz, *DMSO*-d_6): $\delta = 2.55$ (s, 3H, COCH_3), 2.90 (d, 3H, $J = 4.9$ Hz, NCH_3), 3.90 (s, 3H, OCH_3), 4.85 (bs, 1H, N*H*), 6.50 (d, 1H, $J = 8.3$ Hz, H-5), 7.40 (dd, 1H, $J = 1.6$ Hz, H-2), 7.55 (dd, 1H, $J = 8.3$ Hz, 1.6 Hz, H-6); IR (KBr): $\bar{\nu} = 3381$, 1649 cm^{-1}.

6-Acetyl-3-methyl-4-nitro-3H-benzoxazol-2-one (**4**, $C_{10}H_8N_2O_5$)
Yellow solid; chromatography eluent: CH_2Cl_2, petroleum ether 1/1; $R_f = 0.5$ (CH_2Cl_2); Mp 175–176°C (*Et*OH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.65$ (s, 3H, COCH_3), 3.70 (s, 3H, NCH_3), 8.05 (d, 1H, $J = 1.6$ Hz, H-7), 8.45 (d, 1H, $J = 1.6$ Hz, H-5); IR (KBr): $\bar{\nu} = 1760$, 1680 cm^{-1}.

2-Acetoxy-4-acetyl-3,5-dinitro-N-methylaniline (**11**, $C_{11}H_{11}N_3O_7$)
Yellow solid; chromatography eluent: *Et*O*Ac*, cyclohexane 1/1; $R_f = 0.7$ (*Et*O*Ac*); Mp 155–156°C (*Et*OH 95%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.97$ (bs, 1H, N*H*), 2.36 (s, 3H, COCH_3), 2.71 (s, 3H, COCH_3), 3.24 (s, 3H, NCH_3), 8.36 (s, 1H, H-5); IR (KBr): $\bar{\nu} = 1715$, 1685, 1535, 1345 cm^{-1}; MS (70 eV): $m/z = 297$ (M^+).

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