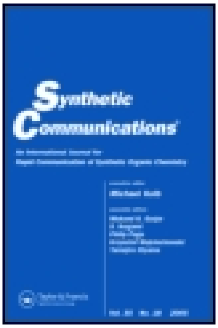

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NITRODECARBOXYLATION AND NITRODEFORMYLATION OF SOME ELECTRON-RICH BENZOIC ACIDS AND BENZALDEHYDES

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Abstract: The nitration ipso to a carboxylic or formyl group of disubstituted and trisubstituted benzoic acids and benzaldehydes using nitric acid in acetic acid is described.

INTRODUCTION

The ipso substitution [1], in which a leaving group X is displaced by a nitro group, has long been known, occuring when X = alkyl, acyl, $-SiR_3$, $-SO_3H$, -Cl, -CHO or -COOH [2-6]. Nitration ipso to a carboxylic group has also been reported using cerium (IV) ammonium nitrate as nitration agent [7-8].

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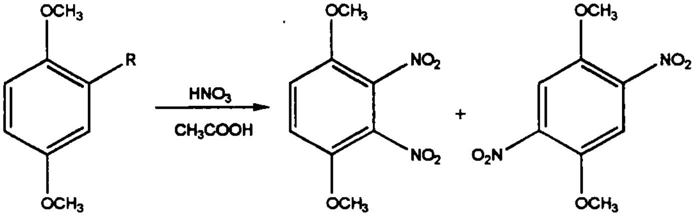
However, nitrodecarboxylation and nitrodecarbonylation require strong acidic medium (fuming nitric acid).

We report herein the nitration of some electron-rich di and trisubstituted benzoic acids and benzaldehydes by dilute nitric acid in acetic acid.

RESULTS AND DISCUSSION

The nitration of 2,5-dimethoxybenzaldehyde **1** and benzoic acid **2** by nitric acid in acetic acid afford 6-nitro and 4-nitro derivatives in a ratio of about 4:1 [9-10] in overall yields up to 80%. However, the action of more concentrated nitric acid on **1** or **2** yields 2,5-dimethoxy-1,6-dinitrobenzene and 2,5-dimethoxy-1,4-dinitrobenzene in a ratio of 4:1 (scheme 1). These results suggest that the first step of the reaction is an aromatic nitration para or ortho to the formyl or carboxylic group and the second step is an ipso substitution of the formyl or carboxylic group. (An ipso substitution followed by an aromatic nitration would give a ratio 1,6-dinitro/1,4-dinitro of about 9:1 [11]).

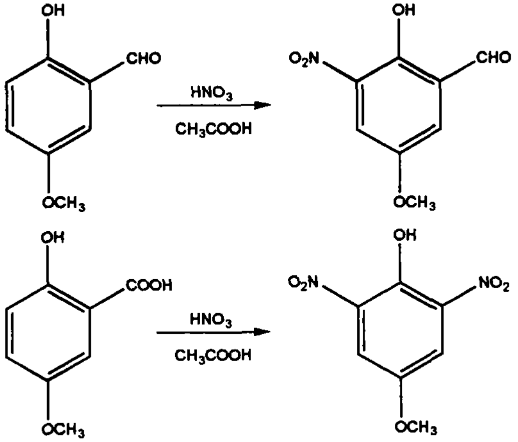


R= CHO **1**
R= COOH **2**

Scheme 1

The behaviours of 2-hydroxy-5-methoxybenzaldehyde **3** and benzoic acid **4** are more contrasted. Indeed whereas **3** yields 2-hydroxy-5-methoxy-3-

nitrobenzaldehyde in 70% yield as previously shown by Baker and Castro [12], **4** affords 4-methoxy-2,6-dinitrophenol in 50% yield (scheme 2).

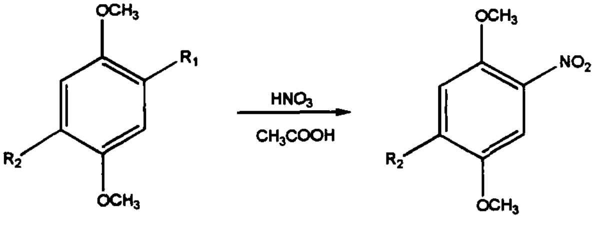


3

4

Scheme 2

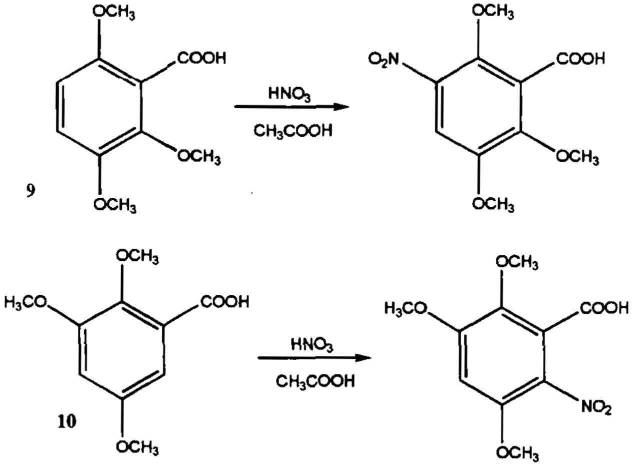
In the series of trisubstituted derivatives, i.e., 2,4,5-trimethoxybenzaldehyde **5** and benzoic acid **6** and 4-bromo-2,5-dimethoxybenzaldehyde **7** and benzoic acid **8**, the nitration ipso to the carbon group is the sole reaction (scheme 3).



Scheme 3

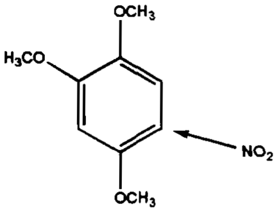
Here again dilute nitric acid is necessary; stronger conditions lead to the total oxidation of the aromatic ring and no organic material can be obtained. **5** and **6** give 1,2,4-trimethoxy-5-nitrobenzene in 68% and 84% yields respectively and **7** and **8** give 1-bromo-2,5-dimethoxy-4-nitrobenzene in 87% and 90% yields respectively. The carboxylic group is more sensitive to the ipso nitration than the formyl group: the yields are better with benzoic acids than with benzaldehydes.

Finally, in order to determine the primordial parameters in the ipso substitution, 2,3,6-trimethoxybenzoic acid **9** and 2,3,5-trimethoxybenzoic acid **10** were submitted to our nitration conditions. In the two cases, a "normal" nitration occurs (scheme 4) leading to only one isomer in each case. The position of the nitration was determinated by nOe's.



Scheme 4

From these results, we postulate that the nitration occurs at a sole position on carbon 5 (see scheme 5) even if this position is occupied by a carboxylic or a formyl group.



Scheme 5

In conclusion, we have shown that the ipso substitution can be used as a possible synthetic way in the synthesis of polysubstituted nitrobenzenes. The ipso nitration can be predicted in the cases of electron-rich benzaldehydes and benzoic acids. It occurs when the carboxylic or formyl group is attached at the most electronic rich position of the aromatic ring.

EXPERIMENTAL

TLC analyses were performed on a 3*10 cm plastic sheet precoated with silica gel 60F254 (Merck) (Solvent system: ethyl acetate/hexane 1:1). Melting points were obtained on a Reichert Thermopan microscope and are uncorrected. NMR spectra were recorded on a AC 300 Bruker spectrometer in the appropriate solvent with TMS as internal reference. Mass spectra were recorded on a Ribermag R 10-10 (Electron Impact, 60eV). Elemental analysis were performed by CNRS laboratories (Vernaison) and were within 0.4% of the theorical value.

Compounds **1-6** were purchased from Aldrich-Chimie (St Quentin-Fallavier). Compounds **7** and **8** were obtained as previously described by Rubinstein[13]. Compounds **9** and **10** were synthesized by known methods[14,15].

The nitration reaction: a solution of nitric acid (85%, 3ml, 58mmol for **1** and **2**, 70%, 3ml, 48mmol for **3-10**) in acetic acid (10ml) was added dropwise to a cooled and stirred solution of the compound to be nitrated in acetic acid (40 mmol in 20ml) at 10-15°C. after being stirred for 1 H, water (50ml) was added and the solid was filtered off and crystallized from the appropriate solvent.

1 and **2** give a crude mixture of 2,5-dimethoxy-1,6-dinitrobenzene and 2,5-dimethoxy-1,4-dinitrobenzene in a ratio of 4:1 (measured from the ^1H spectra of the crude mixture)(the overall yields are 85% and 92% respectively): 2,5-dimethoxy-1,6-dinitrobenzene, m.p. 186-187°C (litt[11]: m.p. 186-187°C); 2,5-dimethoxy-1,4-dinitrobenzene, m.p. 205°C (litt[11]: m.p. 203-204°C).

3 gives 2-hydroxy-5-methoxy-3-nitrobenzaldehyde in 68% yield, m.p. 132°C [litt[12]: m.p. 132-133°C (AcOH)].

4 gives 4-methoxy-2,6-dinitrophenol (50% yield), m.p. 96-98°C [litt[16]: m.p. 100-101°C (EtOH-H_2O)]. δ_H ($CDCl_3$): 10.99 (1H, bs, OH), 7.86 (2H, s, ArH), 3.90 (3H, s, OCH_3); SM (EI, 60eV): 214 (100), 123 (17), 95 (26), 79 (19), 53 (43).

5 and **6** give 1,2,4-trimethoxy-5-nitrobenzene (68% and 84% yield respectively), m.p. 130°C [litt[17]: m.p. 129°C (EtOH)]; δ_H ($CDCl_3$): 7.59 (1H, s, ArH), 6.59 (1H, s, ArH), 4.00 (6H, s, OCH_3), 3.92 (3H, s, OCH_3); SM (EI, 60eV): 213 (100), 198 (23), 137 (29), 109 (24).

7 and **8** give 1-bromo-2,5-dimethoxy-4-nitrobenzene (87% and 90% yield respectively), m.p. 150-152°C [litt[17]: m.p. 156°C (EtOH)]; δ_H ($CDCl_3$): 7.39 (1H, s, ArH), 7.27 (1H, s, ArH), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3); SM (EI, 60eV): 263 (81), 261 (82), 246 (20), 244 (19), 53 (100).

9 gives 2,3,6-trimethoxy-5-nitrobenzoic acid (90% yield), m.p. 133°C (EtOH); δ_H (DMSO-6d): 12.60 (1H, bs, COOH), 7.60 (1H, s, ArH), 4.02 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 3.93 (3H, s, OCH_3); SM (EI, 60eV): 257 (100), 209 (83), 181 (34), 166 (22); Elemental analyses for $C_{10}H_{11}NO_7$: Calcd C: 46.70; H: 4.31; N: 5.45; O: 43.54; Found C: 47.02; H: 4.28; N: 5.54; O: 43.27.

10 gives 2,3,5-trimethoxy-6-nitrobenzoic acid (41% yield), m.p. 194°C (EtOH); δ_H (DMSO-6d): 12.90 (1H, bs, COOH), 6.98 (1H, s, ArH), 3.96 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.71 (3H, s, OCH_3); SM (EI, 60eV): 257 (100), 242 (25), 181 (18), 166 (14); Elemental analyses for $C_{10}H_{11}NO_7$: Calcd C: 46.70; H: 4.31; N: 5.45; O: 43.54; Found C: 46.39; H: 4.27; N: 5.51; O: 43.68.

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