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New Selective Oxidation Reactions by Nitroarenes in Basic Medium Involving Electron-Transfer Processes

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Abstract:

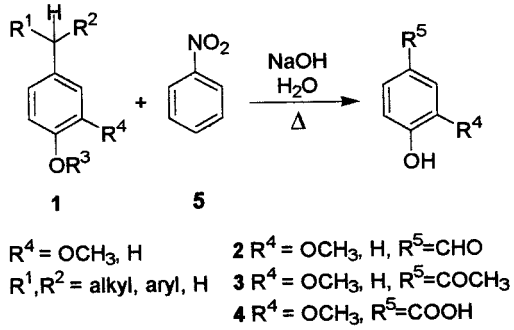
A new synthetic process for oxidation of methyl ketones into their corresponding carboxylic acids using a modified alkaline nitrobenzene method is described. By introduction of a more powerful oxidant, such as 1,3-dinitrobenzene, the oxidation reaction proceeds smoothly in aqueous alkaline solution at 100 °C. The procedure can also be used for oxidation of benzaldehydes and benzyl alcohols into carboxylic acids and to oxidise mandelic acid into its α-keto form, whereas prolonged reaction time results in decarboxylation and gives thus also in this case benzoic acid.

Introduction

In 1940 Freudenberg et al.[1] discovered a method for oxidative degradation of spruce lignin **1** that gave vanillin **2**, acetovanillon **3**, vanillic acid **4**, and several other low-molecular weight phenolic compounds as oxidation products. This method is currently known as the alkaline nitrobenzene oxidation method. In subsequent years the method was further investigated and developed by Lautsch et al.[2] and Leopold,[3] and has since then been extensively applied within the area of wood chemistry regarding the oxidative degradation process[4] and for elucidation of structural elements of the lignin biopolymer.

Despite these former results, few synthetic applications have been reported for the oxidation by nitrobenzene **5** or nitroarenes in general. Leopold[3] has reported that guaiacol derivatives were oxidised to give high yields of vanillin under the rather drastic conditions of the alkaline nitrobenzene oxidation. The method requires a reaction temperature of 170−190 °C, a pressure of 10−12 atm, and a pH of 13−14. Furthermore, nitrosobenzene **6**, the first stable reduction product of the nitro group (**5**), is reported[5,6] to be a very specific oxidant, giving aldehydes from benzyl halides and tosylates, and α-dicarbonyl compounds from α-halo ketones. In the Skraup synthesis[7,8] nitrobenzene **5** is used for dehydrogenation of the dihydroquinoline intermediate to quinoline.

Scheme 1



Methods and Results

Recently, in our laboratories we have studied and optimised different hydrolysis−oxidation processes for synthesis of vanillin from lignosulfonates,[4] also including the alkaline nitrobenzene method. Our studies revealed that this last method was more selective than any of the other methods we tried as well as other methods reported in the past[4] for the synthesis of vanillin, even if we developed the less selective oxidation by oxygen for industrial application suggested by economical reasons.[4] During the oxidation process using the alkaline nitrobenzene oxidation method, the lignin biopolymer is degraded into low molecular weight phenolic compounds that also contain carbonylic groups: ketones, aldehydes, and carboxylic acids are formed (Scheme 1)

In this process, nitrobenzene **5**, used as oxidant, is stepwise reduced to aniline **8**, following the reaction path nitrobenzene **5** → nitrosobenzene **6** → phenylhydroxylamine **7** → aniline **8**, Scheme 2. Thus, the intermediates **6** and **7** also function as oxidants as well as nitrobenzene itself. Besides the reaction products **6**, **7**, and **8**, azoxybenzene **9**, azobenzene **10,** and hydroxyazobenzene **11** have also been determined in the reaction mixtures after such oxidation experiments. This shows that the oxidation is a rather complex process and it proceeds by several steps since compounds **9**−**11** are condensation products of nitrosobenzene and hydroxylamine derivatives.

As mentioned above, the alkaline nitrobenzene oxidation process requires rather drastic conditions, which obviously are very unfavourable for synthetic applications. However, the reactions that take place under this oxidation process could be in principle a valuable tool for the synthetic organic

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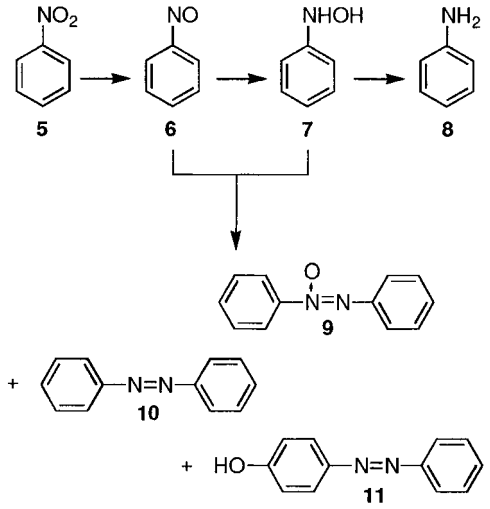
Scheme 2



process chemist, as the reaction involves C−C bond fissions and ether bond cleavages. Thus, on the basis of our gained knowledge and experiences from lignin oxidation studies,[4] we tried to further develop the alkaline nitrobenzene oxidation into a more applicable method for synthetic purposes and also to investigate the mechanistic aspects of the oxidation process.

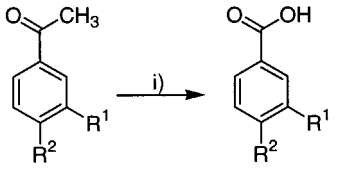
Our primary interests and goal in this context were to develop a new halogen-free oxidation process, a substitute for the haloform reaction[9] that we earlier have developed for application for oxidation of acetoveratron into veratric acid.[10]

Our synthetic experimental results using the alkaline nitrobenzene method for oxidation of simple low-molecular weight organic compounds revealed that an elevated temperature was necessary to carry out the oxidation. However, by introduction of the more powerful oxidant, 1,3-dinitrobenzene, the oxidation reaction proceeded smoothly at atmospheric pressure and much lower reaction temperature (100 °C). The oxidation reactions were performed in strong alkaline water solution: upon heating a few minutes, the reaction mixture becomes dark red, which during the course of the reaction changed to black.

A variety of methyl aryl ketones (Table 1) have all been oxidised into their corresponding benzoic acids using the new method. Moreover, the method was also tried with some benzyl alcohols (Table 2) and benzaldehydes (Table 3); both functionalities also gave the corresponding benzoic acid in high yields. Esters have also been determined as reaction products, although in small quantities and only when benzylic alcohols are oxidised with a low sodium hydroxide concentration. The reaction products from dinitrobenzene (*m*-nitroaniline, 1,3-phenyldiamine, azoxy-nitrobenzene resulting from condensation of nitrosobenzene and hydroxylamine derivatives) were characterised only qualitatively, because tars are often formed due to further oxidation of the amino derivatives. However, in one experiment (entry 1 of Table 2) the azoxyderivative was isolated as pale yellow crystals in high yield (96%). The dinitrobenzene radical anion is the origin for the dark red colour that initially is observed in the oxidation reaction, as it is well documented in literature.[11] The colouring of the reaction mixture is observed when alcohols, aldehydes, or acetophenones are oxidised.

We have also used the modified alkaline nitrobenzene oxidation method to oxidise hydroxy-phenyl-acetic acid **12**

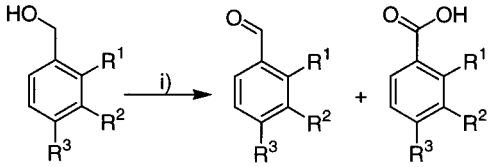
Table 1. **Results from Oxidation of Acetophenones with the Modified Alkaline Nitrobenzene Method**



	R_1	R_2	conv.	yield of acid
1	H	H	100	62.1
2	H	Ph	>97	24.2
3[a]	H	CH_3	>96	59.2
4	CH_3	H	>95	66.2
5	H	Br	>98	63.8
6	H	Cl	100	72.7
7	H	F	~97	60.0
8	H	CH_3O	>99	56.2
9	CH_{3O}	CH_3O	>98	57.9
10	H	HO	100	−
11[b]	H	H_2N	>93	25.4
12	NO_2	H	100	58.7
13	H	NO_2	100	−
14	H	CN	100	−

[i] Reaction conditions: The ketone (2.4 mmol) and the oxidant 1,3-dinitrobenzene (1.8 mmol) are added to an aqueous solution (12 mL) of NaOH (30%) and heated at $T = 100$ °C for $t = 2.5$ h. [a]A minor quantity (13.7%) of terephthalic acid was also formed during the oxidation reaction. [b] A trace (~1%) of benzoic acid was also formed during the oxidation reaction.

Table 2. **Results from Oxidation of Benzylic Alcohols with the Modified Alkaline Nitrobenzene Method**



	R_1	R_2	R_3	conv.	yield aldehyde	yield acid
1[a]	H	NO_2	H	100	−	44.0
2	H	H	Cl	82.2	7.4	63.4
3	H	CH_3O	CH_3O	84.2	38.3	42.7
4	H	H	CH_3O	100	53.0	22.5
5	NO_2	H	H	100	−	17.0
6	H	CH_3O	H	67.6	1.6	65.8

[i] Reaction conditions: The alcohol (2.4 mmol) and the oxidant 1,3-dinitrobenzene (1.8 mmol) are added to an aqueous solution (12 mL) of NaOH (30%) and heated at $T = 100$ °C for $t = 2.5$ h. [a] In this experiment, a reduction product from the oxidant 1,3-dinitrobenzene was isolated as pale yellow crystals of azoxynitrobenzene in a yield of 96% (248 mg).

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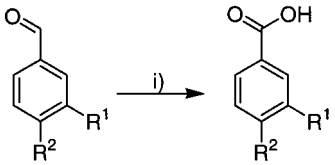
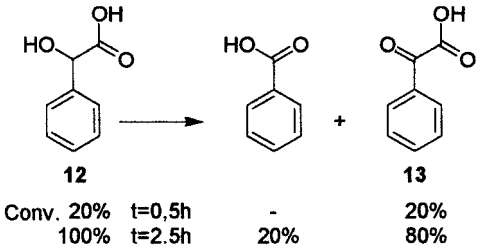
Table 3. **Results from Oxidation of Benzaldehydes with the Modified Alkaline Nitrobenzene Method**



	R_1	R_2	conv.	yield of acid
1	H	H	100	96.0
2	H	Cl	100	89.1
3	CH_3O	CH_3O	100	59.5
4	H	CH_3O	>50	47.6
5	H	CH_3	70.3	41.3

[i] Reaction conditions: The aldehyde (2.4 mmol) and the oxidant 1,3-dinitrobenzene (1.8 mmol) are added to an aqueous solution (12 mL) of NaOH (30%) and heated at $T = 100$ °C for $t = 2.5$ h.

Scheme 3



(mandelic acid) in an attempt to obtain oxo-phenyl-acetic acid **13**, Scheme 3.

After a short reaction time of 0.5 h, 20% of hydroxy-phenyl-acetic acid **12** is converted into oxo-phenyl-acetic acid **13**. Prolonging of the reaction time (2.5 h.), leads to quantitative conversion affording 80% of the oxo-phenyl-acetic acid **13** and 20% of benzoic acid, by further oxidising. Also, in the present experiment oxidising the hydroxy-phenyl-acetic acid **12**, the dark red colour of the dinitrobenzene radical anion is observed in the beginning of the reaction.

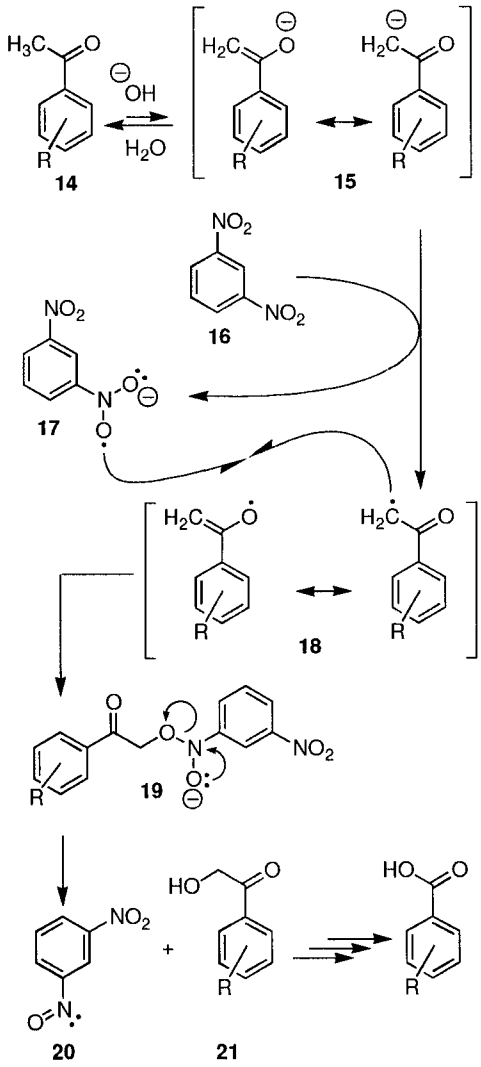
Conclusions

We have developed a simple and versatile method for oxidation of acetophenones into their corresponding benzoic acids. Moreover, the method is also suitable for oxidation of benzaldehydes and benzylic alcohols to the corresponding carboxylic acids and the oxidation of hydroxy-phenyl acetic acid **12** into oxo-phenyl-acetic acid **13** as well as oxidative decarboxylation, only by prolonging the reaction time.

The reaction mechanism of the oxidation is clearly complex. Some general mechanistic aspects, however, can be emphasised: electron-transfer processes are involved according to our interpretation. For example we suggest Scheme 4 for the first steps of the ketone oxidation.

The reactions were carried out in a sealed tube in air or nitrogen atmosphere as well as in an "open beaker", all affording similar results. In any case, however, the amount of air is too small so that molecular oxygen could significantly contribute to the reaction mechanism, even if the "cage" coupling of Scheme 4 may successfully compete with

Scheme 4



the oxygen involvement. G. Russell and co-workers[11,12] have reported many years ago conclusive evidence for the electron-transfer reduction of nitroarenes in basic media and above all for the formation of carbon-centred radicals and nitroarene radical anions by reactions of carbanions with nitroarenes. It is, therefore, highly reasonable that in the strongly basic medium the carbanion in equilibrium with the ketone in Scheme 4 is oxidised by an electron-transfer process with the formation of an α-ketoalkyl radical and dinitrobenzene radical anion. Russell's results were further supported by other authors.[13−15]

The oxidation of aromatic alcohols and aldehydes to carboxylic acids can be related to the initial oxidation of the alcohol to the aldehyde by an electron-transfer process and in some degree (∼12%) competitive Canizzaro disproportionation of the aldehyde to the carboxylic acid and benzylic alcohol, which is further oxidised, and direct oxidation of the aldehyde. Of particular interest appears to be the

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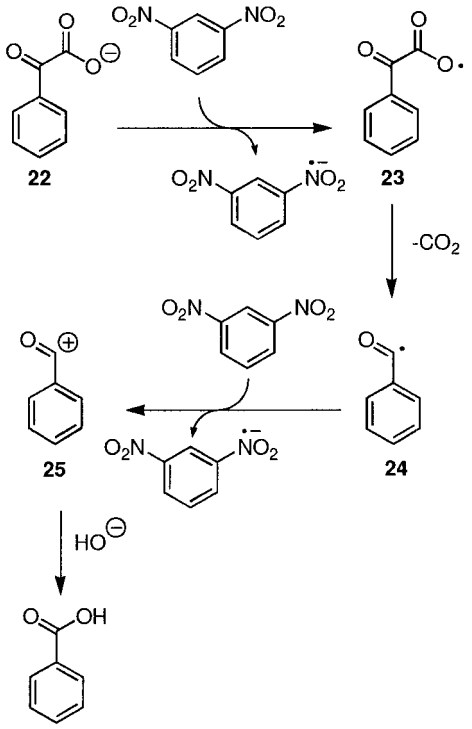
Scheme 5



oxidation of mandelic acid, which initially leads to the α-keto acid **13** which is further oxidised to benzoic acid (Scheme 3). We suggest for this oxidative decarboxylation the two electron-transfer steps shown by Scheme 5.

The α-keto acid **13** is deprotonated in the strong alkaline solution giving the anion form **22**. The first electron-transfer step proceeds under formation of the oxygen-centred radical **23**, which easily decarboxylates under formation of CO_2, and the acyl radical **24**, which has a marked nucleophilic character, and their easy electron-transfer oxidations to acyl cations **25** is well-documented.[16−20] The acyl cations **25** obviously react fast with hydroxyl ions of the very strong basic water solution, giving benzoic acid.

Experimental Section

General Methods. GLC analyses were performed on a capillary gas chromatograph (HP 5890) equipped with a fused silica column (*L* 25 m, 0.20 mm i.d., 0.33 μm film thickness) from Hewlett-Packard at a helium pressure of 200 kPa, splitless/split injector and flame ionisation detector.

Mass spectra were performed on a GC−MS VG 7070 E instrument, using a HP 5890 series II gas chromatograph equipped with a fused silica column (*L* 30 m, 0.25 mm i.d., 0.25 μm film thickness) from Chrompack, CP-Sil 8 CB low bleed/MS and He as carrier gas.

^{1}H NMR spectra were recorded on a NMR spectrometer operating at 400 MHz. Chemical shifts were referenced to internal TMS.

Starting materials and reagents were purchased commercially and used without further purification. All of the reaction products were known and were analysed by GC and GC−MS, ^{1}H NMR, and by comparison with authentic samples.

General Procedure. To a solution of NaOH (12 mL of 30% solution) was added the substrate (methyl ketones, benzylic alcohols, benzaldehyde, or mandelic acid) (4.3 mmol), 1,3-dinitrobenzene (0.606 g, 3.6 mmol). The reaction mixture was stirred (magnetic stirrer bar) and heated to a temperature of 100 °C at atmospheric pressure or slightly elevated pressure by means of a closed reaction tube for 2 h 30 min. After a few minutes reaction time, the reaction mixture became dark red, which during the course of the reaction changed to black. The basic water phase was diluted with water (150 mL) and extracted with CH_2Cl_2 (200 mL). This organic phase contained the unreacted substrate, the unconsumed oxidant 1,3-dinitrobenzene, and the reaction product from the oxidant *m*-nitroaniline, 1,3-phenylenediamine, and azoxynitrobenzene. In one experiment (entry 1 of Table 2) the azoxynitrobenzene was isolated as pale yellow crystals in high yield (96%). In some cases, the separation of the organic and water phases was difficult due to the presence of tars that probably were formed from the polymerisation of aniline compounds (reaction products of the oxidant). The basic water phase is acidified using concentrated HCl until pH 1−2 and extracted with CH_2Cl_2 (200 mL). This organic phase contains almost only the pure benzoic acid derivative.

An experiment under the same conditions with benzaldehyde in the absence of dinitrobenzene revealed that only 12% of the aldehyde undergoes the Cannizzaro disproportionation in benzoic acid and benzyl alcohol.

Spectroscopic Data. *p*-Phenylbenzoic acid: $C_{13}H_{10}O_2$ [198.21]. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 8.10 (d, 2H, J = 8.18 Hz), 7.74−7.38 (m, 7H). MS (*m*/*e*) 198 ($M^{+\bullet}$), 181 ($M^{+\bullet}$ − OH), 152, 126, 115, 102, 75.

***p*-Methylbenzoic acid:** $C_8H_8O_2$ [136.14]. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.90 (d, 2H, J = 8.18 Hz), 7.16 (d, 2H, J = 8.18 Hz), 2.40 (s, 3H, CH_3). MS (*m*/*e*) 136 ($M^{+\bullet}$), 119 ($M^{+\bullet}$ − OH), 107, 91, 77, 65.

***m*-Methylbenzoic acid** $C_8H_8O_2$ [136.14]. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.85−7.75 (m, 1H), 7.50−7.30 (m, 1H), 7.13−7.09 (d, 2H, J = 6.29 Hz), 2.40 (s, 3H, CH_3). MS (*m*/*e*) 136 ($M^{+\bullet}$), 119 ($M^{+\bullet}$ − OH), 91, 65.

***p*-Bromobenzoic acid:** $C_7H_5BrO_2$ [201.01]. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.91 (d, 1H, J = 8.18 Hz), 7.63 (d, 1H, J = 8.18 Hz). MS (*m*/*e*) 202 ($M^{+\bullet}$), 183, 157, 104, 75, 65.

***p*-Chlorobenzoic acid**: $C_7H_5ClO_2$ [156.56]. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.995 (d, 1H, J = 8.83 Hz), 7.48 (d, 1H, J = 8.83 Hz). MS (*m*/*e*) 156 ($M^{+\bullet}$), 139 ($M^{+\bullet}$ − OH), 128, 111, 85, 75, 65.

***p*-Fluorobenzoic acid:** $C_7H_5FO_2$ [140.11]. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 8.20−7.80 (m, 2 H), 7.21−6.98 (m, 2 H). ^{19}H NMR (400 MHz, CD_3OD, ppm) δ (−105.9)−(−106.2) (m), (−113.9)−(−114.1) (m). MS (*m*/*e*) 140 ($M^{+\bullet}$), 123 ($M^{+\bullet}$ − OH), 95, 75, 69, 63, 57.

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3,4-Dimethoxybenzoic acid: $C_9H_{10}O_4$ [182.17]. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.67 (d, 1H, J_o = 8.81 Hz, J_m = 1.89 Hz), 7.555 (d, 1H, J_m = 1.89 Hz), 7.15 (d, 1H, J_o = 8.81 Hz), 3.90 (s, 3H, CH_3), 3.84 (s, 3H, CH_3). MS (*m*/*e*) 182 ($M^{+\bullet}$), 167 ($M^{+\bullet} - CH_3$), 139, 121, 111, 107, 95, 79, 68, 63, 55.

4-Methoxybenzoic acid $C_8H_8O_3$ [152.14]. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.96 (d, 1H, J = 8.81 Hz), 6.97 (d, 1H, J = 8.81 Hz), 3.85 (s, 3H, CH_3). MS (*m*/*e*) 152 ($M^{+\bullet}$), 135 ($M^{+\bullet} - CH_3$), 109, 92, 81, 77, 74, 63.

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