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A Highly Selective Aerobic Oxidation Process Catalyzed by Electron-Deficient Nitroarenes via Single Electron Transfer Processes

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A versatile and simple method for aerobic oxidation of various aromatics containing an oxygen-functionalized benzylic carbon is reported. Results from oxidation experiments with methyl aryl ketones, benzaldehydes, benzylic alcohols, and mandelic acid are reported; all provide high yields of the corresponding aromatic carboxylic acids. By means of response surface methodology and mechanistic interpretation it is revealed that the oxidation process operates catalytically using electron-deficient nitroarenes, such as 1,3-dinitrobenzene, 1,2,3-trifluoro-4-nitrobenzene, and 2,4-difluoro-1-nitrobenzene, with molecular oxygen as the terminal oxidant. The reaction is carried out in a basic solution of potassium *tert*-butoxide in *tert*-butyl alcohol. Since the terminal oxidant is molecular oxygen and only 5−10 mol % of, e.g., 1,3-dinitrobenzene as catalyst is used, the new method represents an environmentally benign alternative to, for example, the well-known haloform reaction. The method is also a convincing alternative when transition metal free conditions are required.

Introduction

Functionalized aromatic carboxylic acids boast a vast application area ranging from monomers for bulk polymers and special polymers to fine chemicals and key intermediates for the synthesis of numerous pharmaceutical chemicals. 3,4-Dimethoxybenzoic acid (veratric acid) is such a compound and is used in the synthesis of mebeverine,[1] vesnarinone,[2] and itopride,[3] which are antispasmodic cardiotonic and gastric prokinetic agents, respectively. Acetovanillone, industrially obtained as a side product from the lignosulfonate oxidation process for production of vanillin,[4] is used as industrial feedstock for veratric acid. Veratric acid is produced industrially from acetovanillone through a simple two-step process constituted by a methylation and an oxidation step. The latter utilizes the haloform reaction as recently improved and optimized by us.[5] As a part of this process improvement and development project we initiated several other investigations of more basic character to look for other oxidation methods that hopefully could be converted into benign and environmentally friendly industrial scale processes. We have recently reported two new oxidation processes as results of these investigations: (1) using manganese and cobalt nitrates as catalysts with air or oxygen as the terminal oxidant,[6] and (2) using 1,3-dinitrobenzene as a stoichiometric oxidant for obtaining carboxylic acids from methyl aryl ketones benzaldehydes and benzylic alcohols.[7] The latter method was developed on the basis of the alkaline nitrobenzene oxidation method,[8−10] which has been widely used in oxidation and structure elucidation studies of lignin. The original nitrobenzene oxidation method requires rather drastic reaction conditions using a very alkaline environment and elevated temperature (180−190 °C) and pressure (10−12 atm.). Our recently reported method,[7] which utilizes the more powerful oxidant 1,3-dinitrobenzene, requires considerably less drastic conditions. A reaction temperature of only 100 °C at atmospheric pressure is now required, but a strong alkaline medium is still crucial for the process.

Nevertheless, an obvious drawback exists even with our modified alkaline nitrobenzene oxidation process; the fact that the process requires the oxidant in stoichiometric quantities implies production of reduction products of 1,3-dinitrobenzene.

On the basis of analogous single electron transfer (SET) processes such as in the stoichiometric 1,3-dinitrobenzene oxidation method,[7] we have recently com-

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[1] Kralt, T.; Moed, H. O.; Lindner, A.; Asma, W. J. (N.V. Philips' Gloeilampenfabrieken). Patent DE 1126889; *Chem. Abstr.* **1963**, *58*, 27206.

[2] Yang, Y. H.; Tominaga, M.; Nakagawa, K.; Ogawa, H. (Otsuka Pharmaceutical Co., Ltd., Japan). Patent BE 890942; *Chem. Abstr.* **1982**, *97*, 72386.

[3] Itoh, Y.; Kato, H.; Koshinaka, E.; Ogawa, N.; Nishino, H.; Sakaguchi, J. (Hokuriku Pharmaceutical Co., Ltd., Japan). Patent EP 0 306 827; *Chem. Abstr.* **1989**, *111*, 153371.

[4] Bjørsvik, H.-R.; Minisci, F. *Org. Process Res. Devel.* **1999**, *3*, 330.

[5] Bjørsvik, H.-R.; Norman, K. *Org. Process Res. Dev.* **1999**, *3*, 341.

[6] Minisci, F.; Recupero, F.; Fontana, F.; Bjørsvik, H.-R.; Liguori, L. *Synlett* **2002**, 610.

[7] Bjørsvik, H.-R.; Liguori, L.; Minisci, F. *Org. Process Res. Dev.* **2001**, *5*, 136.

[8] Freudenberg, K.; Lautsch, W.; Engler K. *Ber. Dtsch. Chem. Ges.* **1940**, *73*, 167.

[9] Lautsch, W.; Plankenhorn, E.; Klink, F. *Angew. Chem.* **1942**, *53*, 108.

[10] Leopold, B. *Acta Chem. Scand.* **1950**, *4*, 1523.

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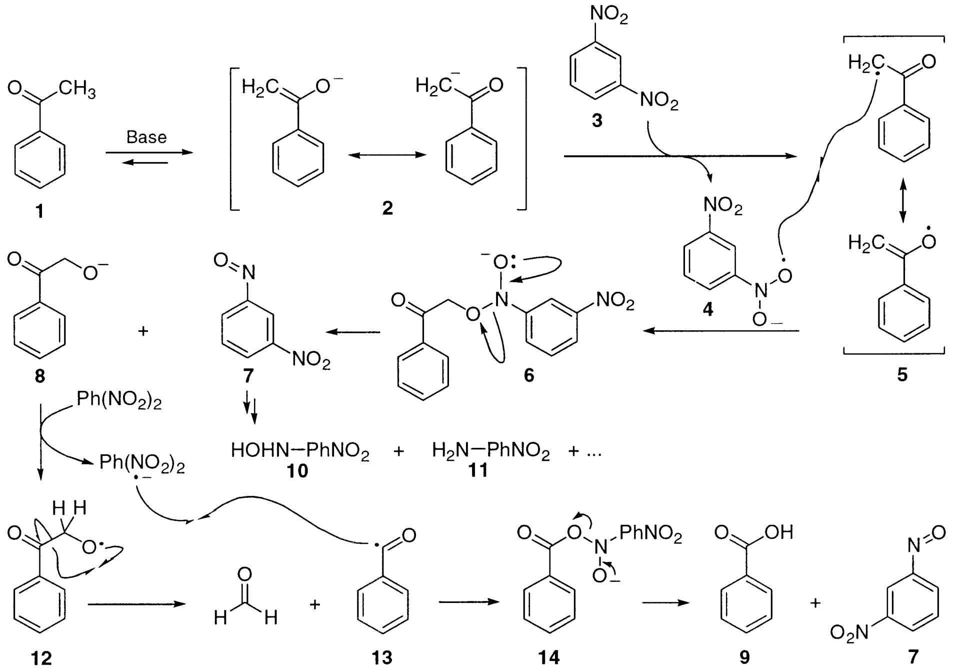
SCHEME 1



municated[11] a new catalytic oxidation process that we believed to be made up by a base-catalyzed autoxidation path and a pathway catalytic in 1,3-dinitrobenzene with molecular oxygen as the terminal oxidant. This paper presents a full account of this new oxidation process providing improved conditions as well as new insights into the mechanism of the highly selective and high yielding catalytic oxidation process. The oxidation process is still based on molecular oxygen as the terminal oxidant with an electron-deficient nitroarene, e.g., 1,3-dinitrobenzene, as mediator for the oxidation of aromatics containing oxygen-functionalized benzylic carbon.

Methods and Results

Russell and co-workers[12] and Ayscough and co-workers[13] have reported conclusive evidence that carbanions react with nitroarenes by SET processes with formation of nitroarene radical anions and carbon-centered radicals. On the basis of these studies we believe that the intrinsic principle of the 1,3-dinitrobenzene oxidation process we have recently reported[7] relies on an initial SET step. The mechanism of this process is clearly complex; our proposal of a mechanism for the SET process is reproduced with several extensions in Scheme 1. The SET step is based on a carbanion or alkoxide ion **2** that carries out a single electron transfer to the electron-deficient aromatic ring of 1,3-dinitrobenzene **3**. The reaction yields a nitro-group-centered radical anion **4** and a carbon- or oxygen-centered radical in the substrate **5**. During our exploration of this reaction we have discovered that it is essential to use a substantial quantity of a strong base in order to produce a sufficient amount of the enolate anion **2** from the methyl aryl ketone **1**. In the following step a coupling reaction between the nitroarene radical anion **4** and the carbon-centered radical **5** leads to formation of the labile anion **6**. The succeeding step entails fission of the weak N−O bond as indicated in Scheme 1. This bond fission gives nitrosoarene **7** as the first reduction product and 2-oxo-2-phenylethanoic anion **8** as the partly oxidized product. Nitrosoarene **7** and 2-oxo-2-phenylethanoic anion **8** may be formed via a "cage recombination" of the radicals **4** and **5**. This is also a highly reasonable mechanism since the solvent and the reaction temperature have been shown to be two very important factors in enabling the process to operate.

Further oxidation of the anion **8** gives the ultimate oxidation product **9** according to the reaction pathway **8** → **12** → **13** → **14** → **9** of Scheme 1 that is analogous to the steps **1** → ... → **8**. The mechanism in Scheme 1 provides a framework that we have used to develop a new catalytic oxidation cycle using molecular oxygen as the terminal oxidant.

In an endeavor to develop this oxidation process into a catalytic process we have investigated several methods that could hopefully oxidize the different reduction products, viz., 1-nitro-3-nitrosobenzene **7**, *N*-(3-nitrophenyl)hydroxylamine **10**, 3-nitrophenylamine **11**, etc., back to 1,3-dinitrobenzene **3**. Scheme 2 summarizes two such systems that were tried for the in situ oxidation of these compounds. The first system tried used transition metal salt ($Cu,^{2+}$ $Co,^{2+}$ or Mn^{2+})-catalyzed oxidation of the reduction products of 1,3-dinitrobenzene with molecular oxygen as the terminal oxidant. The yields achieved are reported in Scheme 2 and correspond, although only roughly, to the quantity of 1,3-dinitrobenzene used as catalyst. Thus it was concluded that the only oxidation mechanism operating was the stoichiometric one as described in Scheme 1 or autoxidation as described later in this section. Investigations using transition metal salts as cocatalyst with molecular oxygen as the terminal oxidant were therefore abandoned.

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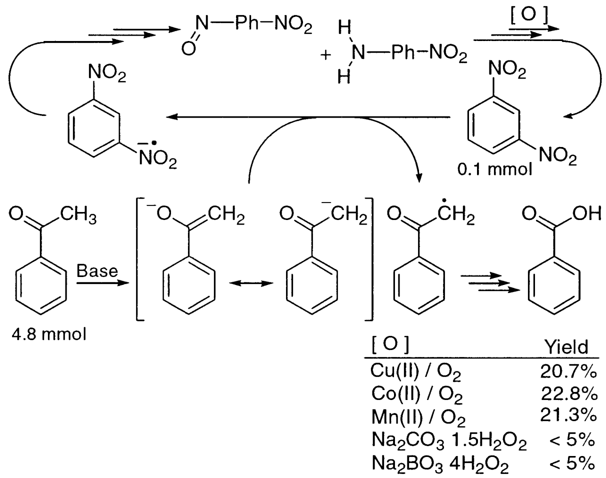
[11] Bjørsvik, H.-R.; Liguori, L.; Rodríguez González, R.; Vedia Merinero, J. A. *Tetrahedron Lett.* **2002**, *43*, 4985.

[12] Russell, G. A.; Janzen, E. G. *J. Am. Chem. Soc.* **1962**, *84*, 4153.

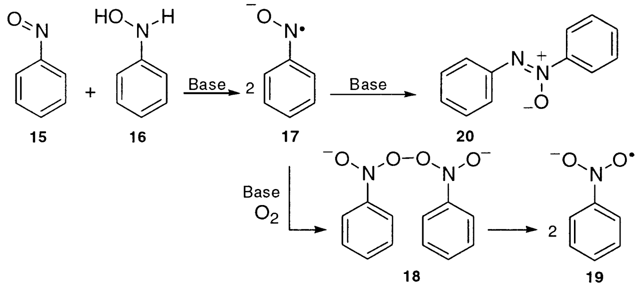
[13] Ayscough, P. B.; Sargent, F. P.; Wilson, R. *J. Chem. Soc.* **1963**, 5418.

SCHEME 2



[O]	Yield
Cu(II) / O_2	20.7%
Co(II) / O_2	22.8%
Mn(II) / O_2	21.3%
Na_2CO_3 1.5H_2O_2	< 5%
Na_2BO_3 4H_2O_2	< 5%

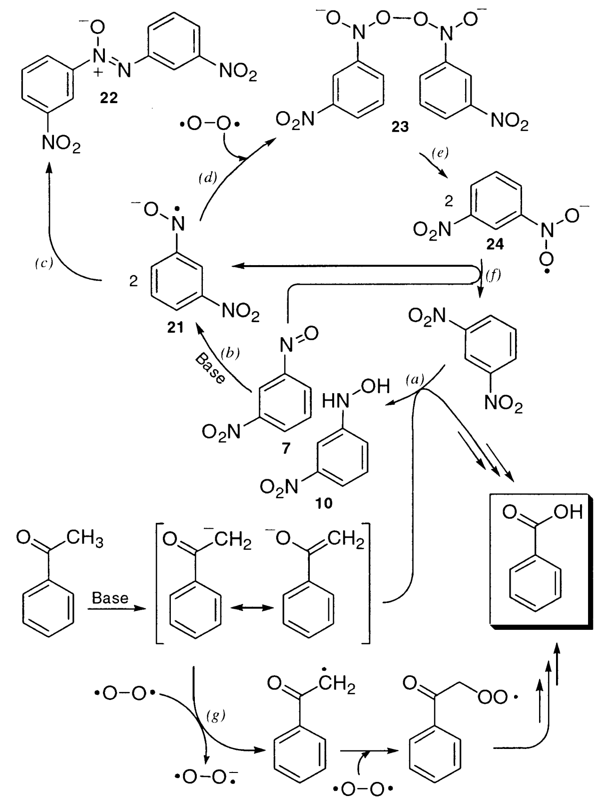
SCHEME 3



However, analogous catalytic oxidation using 1,3-dinitrobenzene as the working mediator was further investigated.

McKillop and co-workers[14–16] have demonstrated perborates and percarbonates as superb oxidants for the oxidation of anilines and derivatives into the corresponding nitroderivatives. Using these oxidants, we have set up a comparable catalytic oxidative scheme using either sodium perborate or sodium percarbonate as the terminal oxidant with 1,3-dintrobenzene as the working oxidant for the methyl aryl ketone. However, only traces or very modest yields were obtained from these experiments. In earlier studies of the nitroarene oxidation a reaction temperature of 80−100 °C was found to be necessary for the oxidation of acetophenones using the modified alkaline nitrobenzene method.[7] At the melting point of 60 °C sodium perborate ($NaBO_3 \cdot 4H_2O$) decomposes, and it is thus reasonable to assume that the decomposition temperature of $NaBO_3 \cdot 4H_2O$ and the required oxidation temperature result in a mismatch for this oxidative cycle.

SCHEME 4



ESR studies performed several years ago by Russell and co-workers[17–19] have shown that nitrosobenzene **15** and hydroxylaniline **16** (Scheme 3) react in basic medium to form two nitrosobenzene radical anions **17**. Moreover these ESR studies also revealed that if the reaction was performed in the presence of molecular oxygen, the radical anions **17** were oxidized to yield two nitrobenzene radical anions **19**. On the other hand, if the reaction was performed without oxygen present, the nitrosobenzene radical anions **17** dimerized to *N*,*N*′-diphenyldiazene *N*-oxide **20**.

This knowledge of the behavior of nitrosobenzene and hydroxylaniline derivatives has been utilized to construct a catalytic cycle using 1,3-dinitrobenzene as catalyst with molecular oxygen as the terminal oxidant. The catalytic cycle is outlined in Scheme 4.

Pathway (*a*) shows the initiation step that also operates as the oxidation step for the catalytic cycle. Step (*a*) is constituted by the mechanism that operates in the stoichiometric oxidation process[7] as proposed in Scheme 1. The basic conditions originally present for the production of the enolate anion of the acetophenone now serve a dual purpose, since basic conditions are crucial for the regeneration of the reduced nitroaryl as shown by Russell and co-workers[17] (Scheme 3). In the present oxidation process the products **7** and **10** formed during the oxidation reaction are converted into the reactive species **21** (nitrosoradical anion) following pathway (*b*). In the presence of molecular oxygen the reoxidation proceeds to provide the coupling product **23**, which decomposes to form the nitrobenzene radical anion **24** (reaction pathways (*d*) and (*e*)). The radical anion **24** is as the ultimate step (*f*) of the catalytic cycle oxidized in a SET reaction to afford 1,3-dinitrobenzene. This can be explained by the fact that nitrosobenzene is a better electron acceptor than nitrobenzene, as has been demonstrated by ESR experiments.[17] A termination reaction arises when two 1-nitro-3-nitrosobenzene radical anions **21** react following pathway (*c*) to give *N*,*N*′-bis(3-nitrophenyl)diazene *N*-oxide **22**.

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(14) McKillop, A.; Tarbin, J. A. *Tetrahedron* **1987**, *43*, 1753.

(15) McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299.

(16) McKillop, A.; Sanderson, W. R. *Tetrahedron* **1995**, *51*, 6145.

(17) Russell, G. A.; Geels, E. J.; Smentowski, F. J.; Chang, K.-Y.; Reynolds, J.; Kaupp G. *J. Am. Chem. Soc.* **1967**, *89*, 3821.

(18) Russell, G. A.; Geels, E. J. *J. Am. Chem. Soc.* **1965**, *87*, 122.

(19) Geels, E. J.; Konaka, R.; Russell, G. A. *Chem. Commun.* **1965**, 13.

TABLE 1. Experiments Performed for Exploration and Optimization of the 1,3-Dinitrobenzene-Catalyzed Aerobic Oxidation Process

	reaction conditions[a]				measured responses[b]		
entry	*t*-BuOK [mmol]	*T* [°C]	O_2	1,3-Ph$(NO_3)_2$ [mmol]	conv [%]	selectivity [%]	yield [%]
1	2.4	20	+	0.12	55.8	23.1	13.0
2	2.4	20	+		44.7	25.9	11.6
3	4.8	20	+	0.12	67.0	59.6	39.9
4	4.8	20	+		52.0	51.7	26.9
5	7.2	20	+	0.12	73.0	57.7	42.3
6	7.2	20	+		69.2	44.6	31.0
7	2.4	50	+	0.12	50.0	71.6	35.8
8	2.4	50	+		64.5	53.8	34.7
9	4.8	50	+	0.12	74.6	71.5	53.5
10	4.8	50	+		66.8	71.2	47.6
11	7.2	50	+	0.12	76.6	92.9	71.3
12	7.2	50	+		85.0	53.9	45.8
13	2.4	80	+	0.12	75.8	44.0	34.0
14	2.4	80	+		70.5	48.1	33.9
15	4.8	80	+	0.12	72.9	84.0	61.2
16	4.8	80	+		88.3	39.2	34.6
17	7.2	80	+	0.12	92.5	87.4	80.8
18	7.2	80	+		91.7	63.6	58.2
19[c]	8.0	90	+	0.12	75.8	98.9	75.2
20	8.0	90	+		94.2	53.5	50.6
21[c]	7.2	90	+	0.12	87.9	86.0	75.6
22	7.2	90	+		95.6	66.1	63.2
23[c]	7.6	85	+	0.12	91.4	80.0	72.9
24	7.6	85	+		94.6	59.9	56.8
25[c]	8.0	80	+	0.12	95.8	87.8	84.2
26	8.0	80	+		96.2	66.2	63.7
27[d]	7.2	80	−	0.12	13.3	60.0	<9
28[e]	15.0	80	+	0.12			

[a] Procedure: Acetophenone (0.288 g 2.4 mmol) was dissolved in *t*-BuOH (12 mL), followed by addition of *t*-BuOK and 1,3-dinitrobenzene (0.12 mmol) with oxygen bubbling through the reaction mixture. The reaction mixture was heated with stirring for a period of 5 h. [b] Conversion selectivity and yield are based on isolated products and recovered substrates. Isolated substances are corrected for impurities by GC analysis. Moreover, isolated substances were also analyzed on GC-MS and NMR for identification. [c] Experiment based on model for searching optimized conditions. [d] Experiment performed without bubbling oxygen but under nitrogen atmosphere. The isolated product was impure. [e] NaOH was used as base. NaOH was added as 30% (7.5 M) aqueous solution.

It is reasonable to believe that the reaction following pathway (*c*) may be restrained by increased oxygen pressure that would favor oxidation over dimerization of the 1-nitro-3-nitrosobenzene radical anions **21**.

The new oxidation method described above is performed in the absence of water and with a strong base present for the formation of enolate anion from the methyl aryl ketone and for the regeneration of reduction products **7**, **10**, **11**, etc. derived from the mediator **3**. 1,3-Dinitrobenzene is used in catalytic quantities (initially we used 5 mol %) with molecular oxygen as the terminal oxidant. When water is used as solvent as in the stoichiometric process,[7] the oxidation cycle fails (entry 28, Table 1).

It has been shown by ESR studies[13] that proton interaction between the aromatic anion and the solvent (i.e., hydrogen bonding) or a polarizing effect of the oriented ionic environment as existing in the polar solvents may influence change in the nitro group electronic distribution. Water has a higher dielectric constant versus *t*-BuOH or other alcohols, so the influence is stronger and can inhibit the redox process.

The introduction of *tert*-butyl alcohol as solvent and potassium *tert*-butoxide as base allowed the oxidation method to operate successfully to afford desired carboxylic acid. We believe that the *tert*-butoxide anion operates only as a base without involvement in the SET process, which is in agreement with earlier reports.[12,20−22] Except from the substrate and the corresponding carboxylic acid, no other compounds were observed in the reaction mixture. Experiments that demonstrated low selectivity (Tables 1−3) contained only tars in addition to desired carboxylic acid. In general, absence of 1,3-dinitrobenzene disfavored the desired oxidation reaction and resulted in lowered yield and selectivity.

An experiment performed without bubbling oxygen (entry 27, Table 1) but with 5 mol % of 1,3-dinitobenzene present afforded less than 10% of benzoic acid and thus supported our belief that the reaction could be ascribed to the stoichiometric oxidation with 1,3-dinitrobenzene as oxidant, Scheme 1.

When the oxidation process was performed without the mediator 1,3-dinitrobenzene present (entry 26, Table 1), a surprisingly high yield of benzoic acid was determined, namely, 63.7% with a conversion of 96.2%, which however corresponds to a selectivity of only 66.2%. The base-catalyzed autoxidation indicated as pathway (*g*) of Scheme 4 thus seems to be a substantial contributor to the overall picture. Such a base-catalyzed aerobic oxidation of methyl aryl ketones was described in the old literature.[23] Later reports by Wallace et al.[24] and Petrič et al.[25] describe similar processes. These processes suffer however from serious "environmental drawbacks" because the two processes require the rather environmentally unfriendly solvents hexamethylphosphoramide (HMPA) and dimethylformamide (DMF), respectively. Moreover the process using HMPA as reaction medium is also burdened by a very long reaction time.

Depending on the experimental conditions large variations of the obtained yield and selectivity were observed for what we initially assumed to be the composite process outlined in Scheme 4. These variations were explored systematically when a series of experiments comprising entries 1−26 of Table 1 were performed. The experiments of Table 1 constitute a $2^1 \times 3^2$ factorial design.[26] The two experimental variables x_1, quantity of *t*-BuOK, and x_2, reaction temperature, were initially explored on three levels, while a third variable x_3, quantity of the catalyst 1,3-dinitrobenzene, was explored at two experimental levels. An empirical model shown in eq 1 relates the yield

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[20] Guthrie, R. E.; Weisman, G. R.; Burdon, L. G. *J. Am. Chem. Soc.* **1974**, *96*, 6955.

[21] Guthrie, R. E.; Weisman, G. R. *J. Am. Chem. Soc.* **1974**, *96*, 6962.

[22] Guthrie, R. E.; Pendygraft, G. W.; Young, A. T. *J. Am. Chem. Soc.* **1976**, *98*, 5877.

[23] Miller, W.; Rohde, A. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 2095.

[24] Wallace, T. J.; Pobiner, H.; Schriesheim, A. *J. Org. Chem.* **1965**, *30*, 3768.

[25] Zabjek, A.; Petric, A. *Tetrahedron Lett* **1999**, *40*, 6077.

[26] Factorial design is a type of statistical experimental design constructed for gaining maximum information from a minimum number of experiments. The regression models obtained from such experimental plans comprise terms that explain the interaction between the different experimental variables. A full account of such methodology is give in (a) Box, G. E. P.; Hunter, W. G.; Hunter, J. S. *Statistics for Experimenters, An Introduction to Design Data Analysis and Model Building*; Wiley: New York, 1978. (b) Box, G. E. P.; Draper, N. R. *Empirical Model-Building and Response Surfaces*; Wiley: New York, 1987.

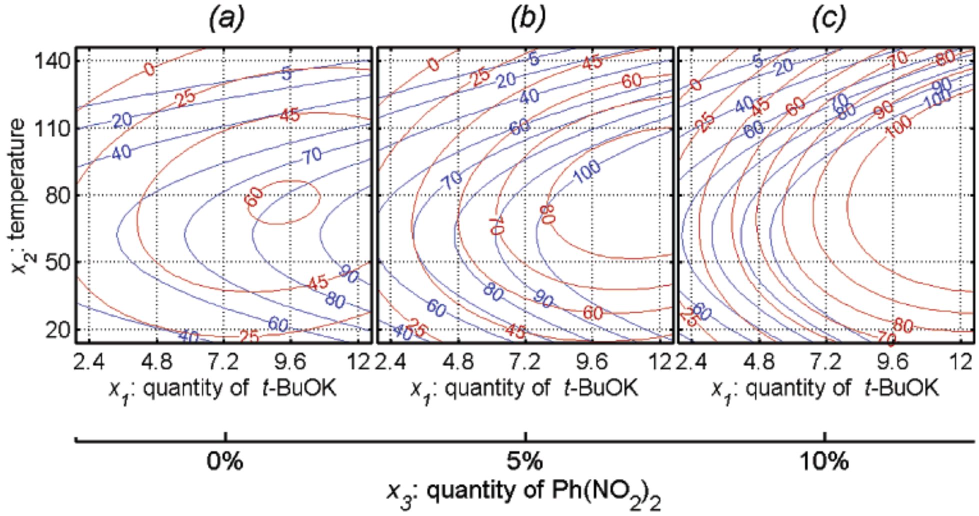

FIGURE 1. Multidimensional contour plot showing the predicted yield and selectivity as a function of three experimental variables x_1, x_2, and x_3 produced by in-house developed routines for MATLAB version 6. The multidimensional contour plot (response surface) describes variation in one or more responses given by the contour lines and two or more experimental variables, in the present case, three experimental variables. The plot is used in the following way: consider the outer axis that shows the variation of the quantity of the catalyst 1,3-$C_6H_4(NO_2)_2$ at three discrete levels (0%, 5%, 10%). Above this axis three subplots are shown where the contour projections of two response surfaces are exposed when the two experimental variables, the quantity of potassium *tert*-butoxide and the reaction temperature, are varied continuously over the ranges 2.4−12 mmol and 20−140 °C, respectively. The contour lines show the variation in the yield (the red lines) and the selectivity (the blue lines).

of the carboxylic acid y to the three experimental variables x_1, x_2, and x_3; the two-factor interactions x_1x_2, x_1x_3, and x_2x_3; and the quadratic terms x_1^2 and x_2^2. The model parameters were estimated by means of the multiple linear regression method (MLR).[27] Evaluation of the model on a confidence level of 95% shows that the regression coefficients α_0, α_1, α_2, α_3, $\alpha_{2\times2}$, and $\alpha_{1\times3}$ should be included in the model. The regression coefficients $\alpha_{1\times2}$ and $\alpha_{1\times1}$ were found to be "boarder line cases", but both were included in the final model. The product statistics of the final model indicate an excellent fit of the experimental data with $R^2 = 0.947$, $Q^2 = 0.892$, and RSD = 5.511. The final model $y = f(x_1, x_2, x_3)$ describing the yield y as a function of the experimental variables x_1, x_2, and x_3 is given by

$$y = 50.641 + 14.431x_1 + 12.110x_2 + 5.716x_3 - 3.493x_1^2 - 9.419x_2^2 + 2.506x_1x_2 + 3.741x_1x_3 \quad (1)$$

A similar model using the MLR method[27] was also derived for the selectivity of the reaction $s = F(x_1, x_2, x_3)$. The evaluation of the model at confidence level of 95% shows that the regression coefficients β_0, β_1, β_2, β_3, $\beta_{2\times2}$, and $\beta_{1\times3}$ should be included. The product statistics indicate a reasonable good model with $R^2 = 0.796$ $Q^2 = 0.640$, and RSD=10.483. The model is given by

$$s = 66.941 + 12.437x_1 + 10.530x_2 + 8.279x_3 - 13.921x_2^2 + 3.741x_1x_3 \quad (2)$$

The two models $y = f(x_1, x_2, x_3)$ and $s = F(x_1, x_2, x_3)$, eqs 1 and 2, respectively, were used for the production of the contour maps of Figure 1. The red contour lines of Figure 1 show the changes in the yield as the setting of the experimental variables x_1 (quantity of *t*-BuOK) and x_2 (reaction temperature) are varied. The corresponding selectivity can be read from the blue contour lines. Moving from the contour map of Figure 1a to Figure 1b and further on to Figure 1c represents a change in the experimental variable x_3 (the quantity of 1,3-dinitrobenzene catalyst). Figure 1a shows the isocontour projections without any 1,3-dinitrobenzene as catalyst present, Figure 1b shows the isocontour projection when 5% of 1,3-dinitrobenzene is present, and Figure 1c shows the expected (predicted) response surface if 10% of 1,3-dinitrobenzene is used.

Comparing the response surfaces of Figures 1a and 1b it is evident that both the selectivity and the yield increases when 1,3-dinitrobenzene is introduced as a catalyst in a quantity of 5 mol %. Figure 1a, which shows the response surface for the base-catalyzed autoxidation pathway (*g*) only, reveals the expected yield passing a maximum of 60% with an expected selectivity of some 80%. The best setting is established when the reaction temperature is set within a range of 75−85 °C and a quantity of 8.4−10.8 mmol of *t*-BuOK is used. Considering the identical experimental domain of the response surface when 5 mol % of 1,3-dinitrobenzene is used as mediator, Figure 1b, a completely different response surface is shown. The expected yield is some 80%, which corresponds to a relative increase of 33%, and the expected selectivity is 100%.

Initially we believed that the oxidation process proceeded by a composite mechanism following the two independent reaction pathways, the 1,3-dinitrobenzene catalyzed reaction (*a*) → (*b*) → ... → (*f*), and the base-catalyzed autoxidation pathway (*g*).

However, if these two pathways operate simultaneously one would have expected that the pathway (*g*)

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[27] See, for example: (a) Draper, N. R.; Smith, H. *Applied Regression Analysis*, 3rd ed.; Wiley: New York, 1998. (b) Montgomery, D. C.; Peck, E. A. *Introduction to Linear Regression Analysis*; Wiley: New York, 1982.

also contributed to a diminished selectivity of the entire oxidation process. Experiments performed with the nitroarene present reveal however a practically 100% selectivity when the optimized reaction conditions are used. Therefore we believe that the nitroarene-mediated process composed by the pathway (*a*) → (*b*) → ... → (*f*) is the principally operating mechanism, which moreover is supported by the fact that SET is very rapid and much faster than nuclear motions, 10^{-16} s and 10^{-13} s, respectively (see, e.g., ref 28 and references therein).

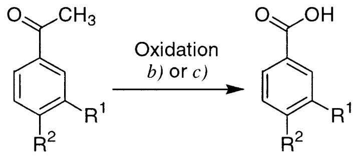
In Figure 1c the models eqs 1 and 2 have been used to represent (by extrapolation) the response surface for when 10 mol % of the nitroarene catalyst is used. The response surface Figure 1c envisages that a quantitative yield (and thus also a 100% selectivity) is to be expected when acetophenone (2.4 mmol), *t*-BuOK (8.4 mmol), and 1,3-dinitrobenzene (0.24 mmol, i.e., 10 mol %) are dissolved in *t*-BuOH (12 mL) and heated at 74 °C for 5 h with oxygen bubbling through the reaction mixture. An experiment performed using these conditions confirmed the validity of the model, as a yield of 92.4% was isolated in practice. The conversion was 92.9%, which corresponded to a selectivity of 99.4%.

An optimized yield when only 5% of the catalyst is used is envisaged to be obtainable (80% yield and 100% selectivity) when acetophenone (2.4 mmol), *t*-BuOK (8 mmol), and 1,3-dinitrobenzene (0.12 mmol) are dissolved in *t*-BuOH (12 mL) heated at 80 °C for 5 h with oxygen bubbling through the reaction mixture. An experiment performed using these conditions confirmed the validity of the model; a yield of 84.5% was isolated in practice with a selectivity of practically 100%.

The optimal oxidation conditions that were attained for acetophenone were also used for the oxidation of a small selection of substituted methyl aryl ketones, reported in Table 2. The experiments were performed with two different quantities (5 and 10 mol %) of the mediator present. Even though the optimal oxidation conditions for these substances may differ from those for acetophenone, the results achieved demonstrate that electronic effects did not have any major influence on the entire oxidation process.

The rate of the enolization of methyl-aryl ketones, most probably the rate-limiting step in the oxidation process, is restrained by electron-donating groups, which on the contrary favor the SET process. 3,4-Dimethoxyacetophenone (entry 5 of Table 2) reacts slightly less rapidly than the acetophenone, affording a high selectivity but slightly lower conversion. The reactivity may however be increased by other more powerful oxidants, for example, 1,3,5-trinitrobenzene. 1,3,5-Trinitrobenzene was tried as mediator for the oxidation system but afforded only degradation products (tars). 2,4-Difluoro-1-nitrobenzene and 1,2,3-trifluoro-4-nitrobenzene have also been tested. The results of these experiments are represented graphically in Figure 2 together with the results of experiment 1 (procedure II) of Table 2 for purpose of comparison. In all three cases the conversion is >85%. A selectivity of ~100% is observed when 1,3-dinitrobenzene is used as the mediator. The fluorinated nitroarenes afford both less yield and less selectivity compared to 1,3-dinitrobenzene, which so far is the best mediator for the new aerobic oxidation process. The experimental tendency is confirmed by theoretical calculations. As a rough estimates of the electron affinity EA = $-\epsilon_{\mathrm{LUMO}}$ may be used. The electron affinity is directly and qualitatively related to

TABLE 2. Results from Oxidation of Methyl Aryl Ketones with Molecular Oxygen with 1,3-Dinitrobenzene as Mediator



			measured responses[a]					
			procedure I[b]			procedure II[c]		
entry	R_1	R_2	conv [%]	yield [%]	selectivity [%]	conv [%]	yield [%]	selectivity [%]
1	H	H	95.8	84.2	87.8	92.9	92.4	99.4
2	CH_3	H	82.0	81.9	100	90.5	79.1	87.4
3	H	F	92.9	80.0	86.1	91.3	74.7	81.8
4	H	Cl	89.3	68.2	76.4	94.5	72.4	76.6
5	CH_3O	CH_3O	78.3	78.3	100	82.8	44.0	53.2
6	NO_2	H	100		0			
7	H	NO_2	90.5	55.5	61.3	63.7	33.4	52.4

[a] Conversion selectivity and yield are based on isolated products and recovered substrates. Isolated substances are corrected for impurities by GC analysis. Moreover, isolated substances were also analyzed on GC-MS and NMR for identification. [b] Procedure I: Acetophenone (0.288 g, 2.4 mmol) was dissolved in *t*-BuOH (12 mL), followed by addition of *t*-BuOK (8 mmol, 0.898 g) and 1,3-dinitrobenzene (0.12 mmol, 5 mol %) with oxygen bubbling through the reaction mixture. The reaction mixture was heated at 80 °C with stirring for 5 h. [c] Procedure II: Acetophenone (0.288 g 2.4 mmol) was dissolved in *t*-BuOH (12 mL), followed by addition of *t*-BuOK (8.4 mmol, 0.9425 g) and 1,3-dinitrobenzene (0.24 mmol, 10 mol %) with oxygen bubbling through the reaction mixture. The reaction mixture was heated at 74 °C with stirring for 5 h.

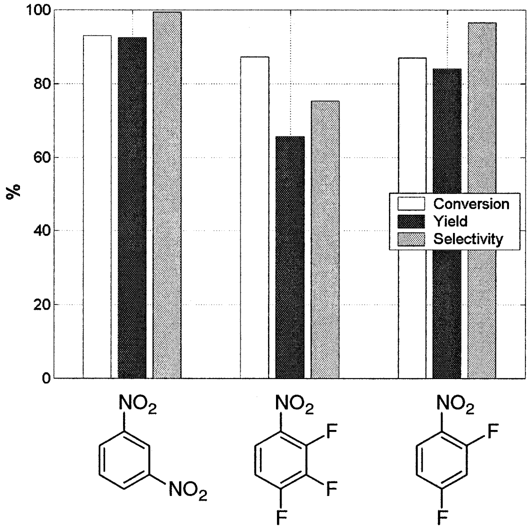


FIGURE 2. Results from oxidation experiments with three different nitroarenes: 1,3-dinitrobenzene, 1,2,3-trifluoro-4-nitrobenzene, and 2,4-difluoro-1-nitrobenzene. The conditions that were used for the three experiments correspond to the optimized conditions when 1,3-dinitrobenzene was used. The three different shaded bars show the conversion yield and selectivity, respectively.

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(28) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; HarperCollins Publishers: New York, 1987, p 229.

the reduction potential (see, e.g., ref 29). Thus comparison of the different electron affinities reveals an order of reactivity to be 1,3,5-trinitrobenzene (EA = 2.29 eV) > 1,3-dinitrobenzene (EA = 1.95 eV) > 1,2,3-trifluoro-4-nitrobenzene (EA = 1.93 eV) > 2,4-difluoro-1-nitrobenzene (EA = 1.58 eV). Estimates for EA, the $-\epsilon_{\mathrm{LUMO}}$, values were calculated by means of the PM3 semiempirical method[30] in the MOPAC package incorporated in the ChemBats3D software.[31] The apparent deviation observed for 1,2,3-trifluoro-4-nitrobenzene may be attributed to side reactions where the catalyst is involved resulting in diminished yield and selectivity.

Returning to the results listed in Table 2, entries 6 and 7 reveal somewhat divergent results reporting quantitative conversion and diminished selectivity (entry 7) and complete degradation (entry 6). This is most probably related to concomitant or consecutive reduction of the nitro group of the substrate, which results in degradation and random polymerization in consecutive steps. As predicted by the model, Figure 1c, increased yields and selectivity were to be expected if 10 mol % of the catalyst were used as compared to when 5 mol % of the catalyst was used. For other methyl aryl ketones, entries 2−5, Table 2, the conversion increases but the yield and selectivity are slightly diminished (except for 4). This shows that the oxidation reaction becomes more powerful with more catalyst present. The model was however developed for acetophenone and does not take account of the substitution pattern on the aromatic ring.

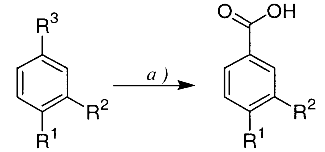
Functional groups such as OH, CN, and NH_2 were not included in the test compound set, since in our previous report[7] we have already demonstrated that when such groups are submitted to oxidative conditions, random polymerization and oxidative degradation occur to form tars. Further exploration of the oxidation methods revealed that benzylic alcohols, benzaldehydes, and mandelic acid all afforded excellent yields of the corresponding benzoic acids when exposed for the determined optimized oxidation conditions for acetophenone even when using only 5 mol % of catalyst. In the case of benzaldehydes we have previously found[7] that Cannizzaro disproportionation[32] contributes approximately 12% to the oxidation of the benzaldehydes under basic conditions such as those used in the present experiments. Since the method operates also for the oxidation of benzyl alcohols a high selectivity is obtained for benzaldehydes.

Phenylacetic acid and (3,4-dimethoxyphenyl)acetic acid were also submitted to the oxidative conditions, entries 5 and 6 of Table 3. The yields of the corresponding carboxylic acids were rather restricted in these experiments. Only the nonsubstituted phenylacetic acid gave the product, although in only approximately 5%.

Conclusions

We have developed a new simple and versatile nonmetal-catalyzed method applicable for the aerobic oxidation of aromatics with oxygen-functionalized benzylic carbon. The presence of at least one nitro group in the mediator is essential for the operation of the method because of the direct involvement of the nitro group in the oxygen transfer to the compound being oxidized (Scheme 1).

TABLE 3. Results from Oxidation of Benzylic Alcohols and Benzaldehydes with Molecular Oxidation with 1,3-Dinitrobenzene as Mediator in Alkaline Media



				measured responses[b]		
entry	R^1	R^2	R^3	conv [%]	yield [%]	selectivity [%]
1	H	H	CH_2OH	95.0	93.8	98.7
2	H	H	CHO	100	100	100
3	OCH_3	H	CH_2OH	92.5	70.0	75.7
4	OCH_3	OCH_3	CHO	95.5	93.0	97.4
5	H	H	CH_2COOH	12.1	5.4	44.8
6	OCH_3	OCH_3	CH_2COOH	0.0		
7	H	H	CH(OH)COOH	100	93.0	93.0

[a] Procedure: The substrate (2.4 mmol) was dissolved in *t*-BuOH (12 mL), followed by addition of *t*-BuOK (8 mmol 0.898 g) and 1,3-dinitrobenzene (0.12 mmol) with oxygen bubbling through the reaction mixture. The reaction mixture was heated at 80 °C with stirring for 5 h. [b] Conversion selectivity and yield are based on isolated products and recovered substrates. Isolated substances are corrected for impurities by GC analysis. Moreover, isolated substances were also analyzed on GC-MS and NMR for identification.

The oxidation proceeds to the ultimate oxidation product, the aromatic carboxylic acid, in excellent yields when benzylic alcohols benzaldehydes mandelic acid and methyl aryl ketones are oxidized. The method provides an efficient, benign, and environmentally friendly alternative to both the well-known haloform reaction and the stoichiometric nitroarene oxidation method recently reported by Bjørsvik et al.[5,7] Moreover the method is particularly interesting as an alternative to transition metal catalyzed oxidation methods[6] when metal-free environments are required.

Schemes 1 and 4 show some facets of the complex reaction mechanism. The outlined mechanism is deduced from response surface models together with previous reports of Russell et al.[12,17,18] that described conclusive evidence for the single electron transfer reduction of nitroarenes in basic media and above all for the formation of carbon-centered radicals and nitroarene radical anions by reactions of carbanions with nitroarenes. Thus it is highly reasonable that in the strongly basic medium the carbanion in equilibrium with the ketone in Scheme 1 is oxidized by a SET process with the formation of an α-ketoalkyl radical that can react rapidly with the nitrobenzene radical anion. The regeneration of the reduction products from the nitroarenes proceeds by the formation of the nitroso radical anions due to the strongly basic environment.

A substantial base-catalyzed autoxidation of the acetophenone in basic medium, pathway (*g*) of Scheme 4, was also revealed during this investigation, even though it had a much lower selectivity than that with the electron-deficient nitroarene-catalyzed pathway.

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(29) Haman, C. H.; Hamnett, A.; Vielstich, W. *Electrochemistry* Wiley-VCH: Weinheim, 1998.

(30) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.

(31) *ChemBats3D Molecular Modeling and Analysis*, version 6.0; CambridgeSoft: Cambridge, MA.

(32) Cannizzaro, S. *Liebigs Ann. Chem.* **1985**, *88*, 129.

Advantages and Limits of the Methods. The new method appears as a "green" alternative to the haloform reaction and when metal-free conditions are required. The new oxidation process can be used for several aromatics with oxygen-functionalized benzylic carbon: methyl aryl ketones, benzylic alcohols, benzaldehydes, and mandelic acids. In the most of the cases the selectivity is high. The process is catalytic in an electron-deficient nitroarene with oxygen as a cheap terminal oxidant.

Functional groups such as CN, NH_2, and OH present in the substrate are not tolerated because of their participation in degradation processes. The necessity of the expensive base *t*-BuOK and the fact that the method so far only can be utilized for aromatic substrates are currently the two major limitations of the method.

The method may hopefully be fitted to future industrial application by the introduction of cheaper bases, for example, by using KOH or NaOH supported by a phase transfer catalyst (tetrabutylammonium bromide TBAB).[11]

Experimental Section

General Methods. GLC analyses were performed on a capillary gas chromatograph equipped with a fused silica column (25 m × 0.20 mm, 0.33 μm film thickness) from at a helium pressure of 200 kPa, split less/split injector and flame ionization detector.

Mass spectra were obtained on a GC-MS instrument using a gas chromatograph equipped with fused silica column (30 m × 0.25 mm, 0.25 μm film thickness) 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.

General Procedure for the Oxidation. The methyl aryl ketone, benzaldehyde, or benzylic alcohol (2.4 mmol), potassium *tert*-butoxide (8.0 mmol), and 1,3-dinitrobenzene (0.12 mmol-0.24 mmol) are added to *tert*-butanol (12.0 mL). The reaction mixture was stirred (magnetic stirrer bar) and heated to and held for 5 h at a temperature of 80−74 °C at atmospheric pressure while bubbling oxygen through the mixture. After a few minutes reaction time the mixture became dark red and during the course of the reaction changed further to orange-brown. The reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 × 80 mL). This organic phase contained the unreacted substrate, the unconsumed oxidant (1,3-dinitrobenzene), and the reaction products from the oxidant (3-nitroaniline, 1,3-phenylenediamine, etc). The basic water phase is acidified using concentrated H_2SO_4 to pH 1−2 and extracted with ethyl acetate (3 × 80 mL). This organic phase contains almost only the pure benzoic acid derivatives.

All of the reaction products were known compounds. The reaction mixtures of the oxidation experiments were worked up for isolation of the aromatic carboxylic acids and unconsumed substrates. The isolated products were analyzed by GC for the correction of impurities. The samples were analyzed on GC-MS, ^{1}H NMR, and by comparison with authentic samples for the purpose of identification.

Spectroscopic Data. ***m*-Methylbenzoic acid**, [99-04-7], $C_8H_8O_2$, MW 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*-Fluorobenzoic acid**, [456-22-4], $C_7H_5FO_2$, MW 140.11. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 8.20−7.80 (m, 2H), 7.21−6.98 (m, 2H). MS (*m*/*e*) 140 ($M^{+\bullet}$) 123 ($M^{+\bullet}$ − OH) 95, 75, 69, 63, 57.

***p*-Chlorobenzoic acid**, [74-11-3], $C_7H_5ClO_2$, MW 156.56. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.995 (d, 2H, J = 8.83 Hz), 7.48 (d, 2H, J = 8.83 Hz). MS (*m*/*e*) 156 ($M^{+\bullet}$), 139 ($M^{+\bullet}$ − OH), 128, 111, 85, 75, 65.

3,4-Dimethoxybenzoic acid, [93-07-2], $C_9H_{10}O_4$, MW 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-Nitrobenzoic acid, [62-23-7], $C_7H_5NO_4$, MW 167.12. MS (*m*/*e*) 167 ($M^{+\bullet}$), 150 ($M^{+\bullet}$ − OH), 137, 121, 109, 103, 93, 81, 75, 65, 50.

4-Methoxybenzoic acid, [100-09-4], $C_8H_8O_3$, MW 152.14. ^{1}H NMR (400 MHz, CD_3OD, ppm) δ 7.96 (d, 2H, J = 8.81 Hz), 6.97 (d, 2H, J = 8.81 Hz), 3.85 (s, 3H, CH_3). MS (*m*/*e*) 152 ($M^{+\bullet}$), 135 ($M^{+\bullet}$ − OH), 121 ($M^{+\bullet}$ − OCH_3), 107 ($M^{+\bullet}$ − COOH), 92, 81, 77, 74, 63.

Multivariate Calculations and Graphics. Calculations and the graphical representations were performed by means of procedures developed in-house for MATLAB version 6.1.[33] The in-house developed MATLAB modeling procedures have previously been validated by comparison of the calculated results with computational results obtained from several commercial computer programs for statistics and mathematical model building.

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(33) (a) Using *Matlab*, version 6; The MathWorks Inc.: Natick, MA. (b) Using *Matlab Graphics*, version 6; The MathWorks Inc.: Natick, MA.