Available online at www.sciencedirect.com

Tetrahedron Letters 45 (2004) 8615–8620

Tetrahedron Letters

Nitroarene catalyzed oxidation with sodium percarbonate or sodium perborate as the terminal oxidant

Hans-René Bjørsvik,* José Angel Vedia Merinero and Lucia Liguori

Department of Chemistry, University of Bergen, Allégaten 41, N-5007 Bergen, Norway

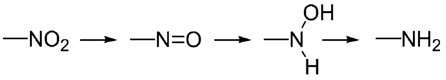
Received 18 August 2004; revised 20 September 2004; accepted 27 September 2004

Abstract—A new catalytic oxidation method for the preparation of aromatic carboxylic acids from methyl aryl ketones is reported. The method is an alternative to the haloform reaction; it is benign and affords the desired product without production of any harmful side products. The catalytic cycle is based on the use of an electron-deficient nitroarene as catalyst with either of the two cheap and green oxidants sodium percarbonate or sodium perborate. The method gives a good yield (87%) and shows excellent selectivity when the model substrate (acetophenone) is oxidized. A series of benzoic acids of industrial interest were prepared by means of this method.

Electron-deficient nitroarenes can be utilized as stoichiometric oxidants[1] or as catalysts with molecular oxygen as terminal oxidant.[2,3] Owing to several advantages from both research and industrial standpoints, we wanted to investigate the possibility of replacing oxygen with sodium perborate, $NaBO_3{\cdot}4H_2O$ (SPB) or sodium percarbonate, $Na_2CO_3{\cdot}1.5H_2O_2$ (SPC) as the terminal oxidant. SPB and SPC are both cheap, large-scale industrial chemicals that are nontoxic and relatively stable solids and are thus simple to handle on a large scale and permit accurate dosage. A few facets of the very complex nitroarene oxidation are outlined in Scheme 1. The nitro group was expected to possess a twofold role as the oxidizing species in the process, namely (1) as the electron acceptor in the single electron transfer process and (2) to act as the oxygen transfer reagent.

The enolate ion **2** (Scheme 1) is produced when acetophenone **1** is treated with a base. In a single electron transfer (SET) process the *C*-centred radical **5** and the radical anion **4** are formed, and then combined to form the labile anion **6**. Decomposition of **6** affords the partially oxidized intermediate anion **10** that is oxidized further to yield the target product **14** via a similar mechanism to that already described. The catalyst 1,3-dinitrobenzene **3** is regenerated from the reduction products 1-nitro-3-nitrosobenzene **7** and *N*-(3-nitrophenyl)-hydroxylamine **8** by treatment with base and by oxidation with SPB or SPC.[4]

Russell et al.[5–7] demonstrated that when a mixture of nitrosobenzene and *N*-hydroxyaniline is treated with base, two types of nitrosobenzene radical anions are formed, a reaction which corresponds to **7**+**8** → **9**. It is likely that both **7** and **8** may be formed during the oxidation process, since nitroarenes can be reduced over several steps (see Eq. 1).



$$—NO_2 \longrightarrow —N{=}O \longrightarrow —\underset{H}{\overset{OH}{N}} \longrightarrow —NH_2 \qquad (1)$$

The investigations by Russell and co-workers revealed moreover that if the reaction is performed in the presence of molecular oxygen, the radical anions are oxidized to yield two nitrobenzene radical anions that upon reaction with the nitroso group (e.g., compound **7**) afford the dinitrobenzene **3**. Here, the oxidation of the radical anion species **9** proceeds via the operation of either sodium perborate or sodium percarbonate.

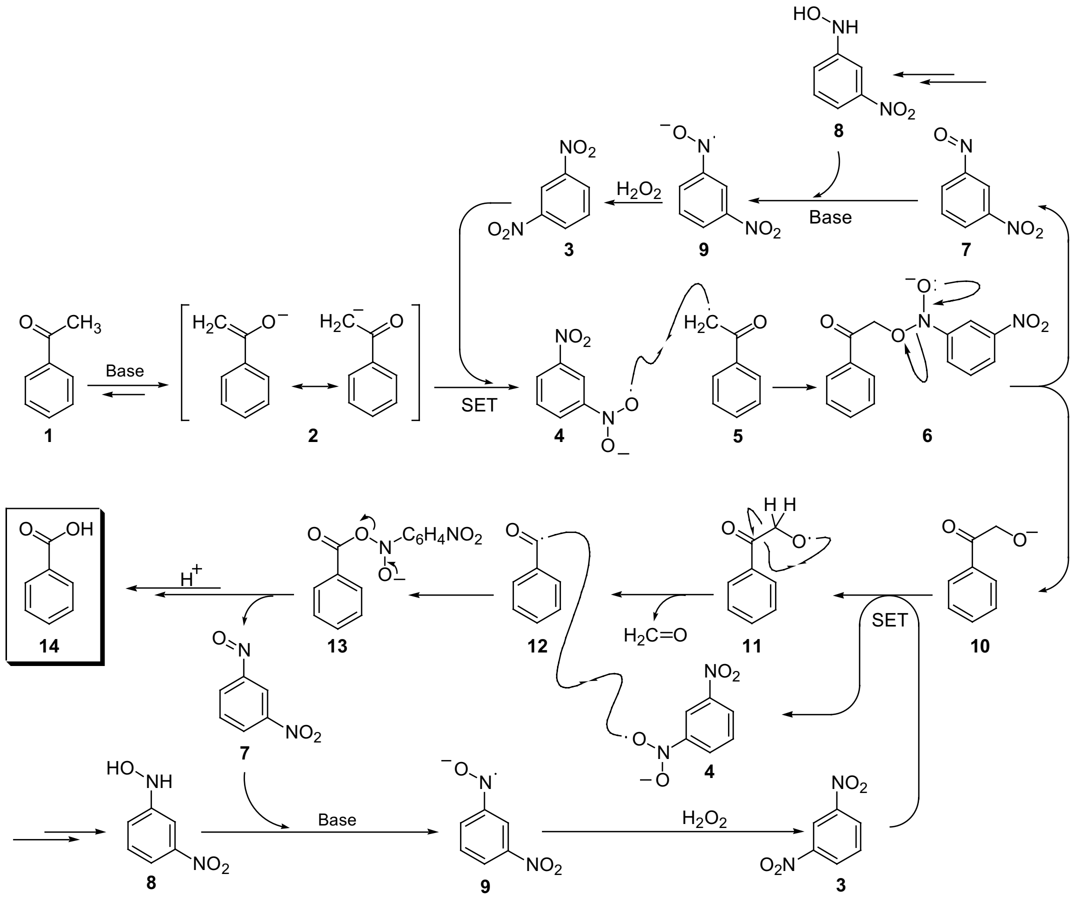
Initially, the proposed oxidation process, Scheme 2, was investigated by utilizing a small series of nitroarenes as catalysts: 1,8-dinitronaphthalene **15**, 2,4-difluoronitrobenzene **16**, 1,2,3-trifluoro-4-nitrobenzene **17**,

---

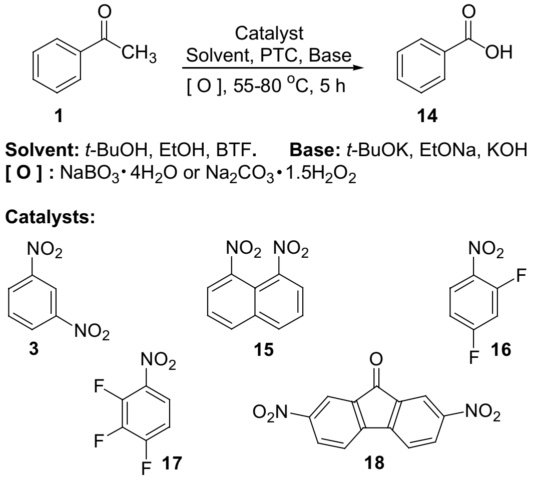
Keywords: Electron transfer; Green chemistry; Oxidations; Radicals; Radical reactions; Industrial chemistry.

* Corresponding author. Tel.: +47 55 58 34 52; fax: +47 55 58 94 90; e-mail: hans.bjorsvik@kj.uib.no

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.156



Scheme 1.



Scheme 2.

2,7-dinitro-9-fluorenone **18** and 1,3-dinitrobenzene **3**. The investigation comprised two reaction temperature ranges: 55–60 °C was used when SPB was present as the terminal oxidant, and 80 °C was used when SPC was utilized. This avoided potential decomposition of SPB and SPC while maintaining a slightly elevated reaction temperature as has been previously determined to be beneficial for the satisfactory operation of nitroarene oxidation.[2,3]

All of the investigated nitroarenes (**3** and **15**–**18**) operated as catalysts for the oxidation process. The major part of the investigation was, however, carried out with 1,3-dinitrobenzene **3** as catalyst, mainly for comparison purposes (with the aerobic oxidation process[3]), but also due to the low cost of the substance that will be highly advantageous for any eventual industrial application. Furthermore, most of the oxidation experiments were performed with SPC, since this appeared to give slightly higher yields than for experiments utilizing SPB as the oxidant.

Solvent and base screening were performed, which demonstrated that the solvents α,α,α,-trifluorotoluene (BTF) and *t*-BuOH and the bases NaOH, KOH and *t*-BuOK can be utilized (see Table 1). Furthermore, the use of the phase transfer catalyst tetrabutylammonium bromide (TBAB) and the addition of the terminal oxidant in several portions were investigated.

The rather large variations and moderate yield of the screening experiments (a few results are reported in Table 1), prompted us to continue the investigation by means of statistical experimental design and multivariate mod-

Table 1. Oxidation experiments with SPB or SPC and different nitroarenes as catalyst

#	Experimental conditions[a]										Results[b]		
	Subst. (mmol)	Cat.	TBAB (mmol)	Solvent	mL	Base	mmol	[O]	mmol	T (°C)	Conv. (%)	Yield (%)	Selec. (%)
1[c]	2.4	**15**	0.24	*t*-BuOH	12	KOH	8.0	SPC	3.00	80	58	26	45
2	2.4	**15**	0.24	BTF	12	KOH	5.0	SPB	2.40	55	16	15	92
3	2.4	**16**	0.24	BTF	12	KOH	5.0	SPB	2.40	55	16	10	59
4	2.4	**17**	0.24	BTF	12	KOH	5.0	SPB	2.40	55	16	14	89
5	1.2	**3**	0.12	BTF	6	*t*-BuOK	2.4	SPC	1.20	80	57	31	54
6	2.4	**3**	—	BTF	12	*t*-BuOK	4.8	SPC	2.40	80	37	28	76
7[d]	2.4	**18**	—	*t*-BuOH	12	*t*-BuOK	6.0	SPC	6.87	80	96	18	19
8[d]	2.4	**18**	—	*t*-BuOH	12	*t*-BuOK	6.0	SPB	6.87	60	94	31	34
9	1.2	**3**	0.12	BTF	6	NaOH	2.5	SPC	1.20	80	70	28	39
10	1.2	**3**	0.12	BTF	6	KOH	2.5	SPB	1.20	55	32	26	82
11	2.4	**3**	0.24	*t*-BuOH	12	*t*-BuOK	4.8	SPB	2.40	55	72	38	52
12	2.4	**3**	0.24	*t*-BuOH	12	NaOH	5.0	SPB	2.40	55	54	29	54

[a] Procedure: Acetophenone was used as substrate (Subst.) with 10 mol% of a nitroarene as catalyst. The nitroarenes were 1,3-dintrobenzene (DNB), 1,8-dinitronaphthalene (DNN), 2,4-difluoronitrobenzene (DFNB) or 1,2,3-trifluoro-4-nitrobenzene (TFNB). TBAB was used as phase transfer catalyst. The terminal oxidant was either SPC or SPB. The reaction time was 5 h performed at 55–80 °C under a nitrogen atmosphere.

[b] Conversion, yield and selectivity are based on isolated product and recovered substrate. Isolated products were corrected for impurities by GC. Moreover, isolated products were identified by GC–MS and NMR.

[c] The oxidant was added in two equal portions, 1.2 mmol, at the start and after 2 h.

[d] The oxidant was added in three portions, 3.12 mmol at the start, then 2.4 mmol after 1 h and 1.35 mmol after 2 h.

elling. For this investigation, *t*-BuOH was selected as solvent and *t*-BuOK as base. Furthermore, we decided not to use the phase transfer catalyst as no significant improvements were observed with TBAB as an additive. The oxidant SPC was added portion-wise, at the beginning of the reaction and then after 1 and 2 h of reaction time, respectively. The necessity for the somewhat large excess of oxidant may be due to partial thermal decomposition during heating of the reaction mixture.

Even though numerous experimental variables may influence the oxidation process, we have only studied two of the experimental variables, thoroughly, in terms of a statistical experimental design Table 2,[8] namely *the quantity of t-BuOK* [mmol] (x_1) and *the quantity of SPC* [mmol] (x_2).

The data from Table 2 was submitted to multivariate data analysis by means of multiple linear regression (MLR)[9–11] to establish an empirical mathematical predictive model, $y = f(x_1,x_2)$. In order to obtain a better fit of the response y to the model matrix $[\mathbf{1}\ \boldsymbol{x}_1\ \boldsymbol{x}_2\ \boldsymbol{x}_1 \times \boldsymbol{x}_2\ \boldsymbol{x}_1^2\ \boldsymbol{x}_2^2]$, the transformation of the response *yield* (y) was performed (Eq. 2). The estimated regression coefficients for the final model[12] with the *yield* as the response variable are given in Eq. 3.

$$\eta = \sqrt{y} = f(x_1, x_2) \tag{2}$$

Table 2. Statistical experimental design exploring the influence of the base (*t*-BuOK) and the oxidant (SPC)

#	Experimental conditions[a]		Measured responses[b]			
	x_1 (Base)	x_2 (SPC)	% **1**	% **2**	C%	S%
1	4.50	3.75	27	42	73	58
2	7.50	3.75	5	57	95	60
3	4.50	5.00	35	62	65	94
4	7.50	5.00	8	86	92	94
5	6.00	4.38	12	55	88	62
6	3.00	4.38	55	36	46	79
7	9.00	4.38	5	76	95	79
8	6.00	3.12	9	87	91	96
9	6.00	3.12	16	83	83	100
10	6.00	5.63	11	68	89	77
11	6.00	5.00	15	70	85	83
12	6.00	3.75	10	71	90	79
13	4.50	4.38	21	55	79	70
14	7.50	4.38	6	75	94	79

[a] Reaction conditions: x_1: *t*-BuOK (4.5–7.5 mmol), x_2: $Na_2CO_3 \cdot 1.5H_2O_2$ at the start of the reaction (3.75–5.00 mmol) were mixed in *t*-BuOH (12 mL) under a N_2 atmosphere. Following the addition of acetophenone (2.4 mmol, 0.28 mL) and 1,3-dinitrobenzene (0.24 mmol, 40.3 mg) as catalyst, the resulting solution was heated for 5 h at 80 °C. After 1 and 2 h reaction time, additional quantities of the oxidant $Na_2CO_3 \cdot 1.5H_2O_2$ were added (2.5 mmol after 1 h and 1.5 mmol after 2 h).

[b] Samples were analyzed by GC and the mol% estimated by means of 1-chloro-2,4-dinitrobenzene as internal standard. C% = percent conversion, and S% = percent selectivity.

$$\begin{aligned}\eta = f(x_1, x_2) &= 7.862 + 0.6526 \times x_1 \\ &\quad - 0.1296 \times x_1^2 + 0.2545 \times x_2^2 \qquad (3) \\ y &= \eta^2\end{aligned}$$

The model (Eq. 3) was used to create the response surface projected as an *iso*-contour map depicted in Figure 1. This map reveals that it is mandatory to apply a concomitant high quantity of the base *t*-BuOK and the oxidant SPC, or low quantities of oxidant but still with a high quantity of base. However, additional experiments under such conditions afforded no further improvement compared to the best results already included in the experimental design matrix portrayed in Table 2 (entries 8 and 9).

Application of the novel oxidation process. Functionalized aromatic carboxylic acids are highly valuable fine chemicals having a variety of applications. For example, veratric acid **8b** is used in the synthesis of the pharmaceuticals mebeverine and vesnarinone.[13] Various halogenated benzoic acids **10b**–**13b** are used in the synthesis of antibacterial agents,[14] cholesterol biosynthesis inhibitors[15] and herbicides.[16]

Thus, industrial interest in the production of such precursors has resulted in disclosures of various processes. For example, Hoechst have described a process for the preparation of halogenated benzoic acids by means of Baeyer–Villiger oxidation of appropriately halogenated benzophenones[17] using among others both sodium percarbonate and sodium perborate.

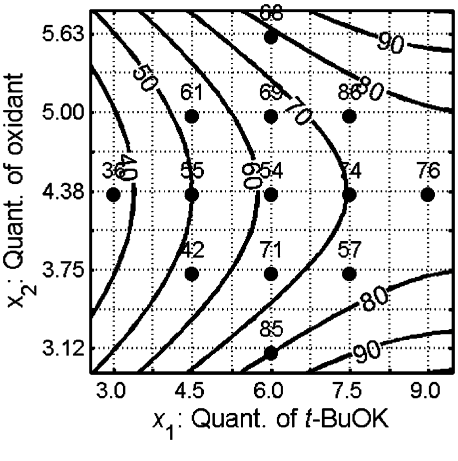
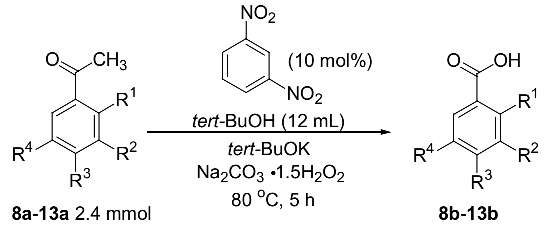


Figure 1. The *iso*-contour plot of the response surface shows the predicted yield as a function of two experimental variables, the quantity of the base *t*-BuOK (x_1), and the quantity of the oxidant sodium percarbonate (x_2). In the present plot, the contour lines show the yield of benzoic acid as a function of the two experimental variables x_1 and x_2 in the ranges 3.0–9.0 mmol and 3.12–5.63 mmol, respectively. The reactions were conducted by mixing the base *t*-BuOK (3.0–9.0 mmol) and the oxidant $Na_2CO_3 \cdot 1.5H_2O_2$ (3.12–5.63 mmol) in *t*-BuOH (12 mL) under a nitrogen atmosphere followed by adding acetophenone (2.4 mmol, 0.28 mL) and 1,3-dinitrobenzene (0.24 mmol, 40.3 mg) as catalyst. The resulting solution was heated for 5 h at 80 °C. After 1 and 2 h reaction time, additional quantities of the oxidant $Na_2CO_3 \cdot 1.5H_2O_2$ were added (2.5 mmol after 1 h and 1.5 mmol after 2 h). The black filled circles are the experiments included in the underlying model with their corresponding experimental values.



	R^1	R^2	R^3	R^4	Conv.%	Yield%	Selec.%
8	H	OCH_3	OCH_3	H	82	50	61
9	H	H	OCH_3	H	64	58	91
10	H	H	F	H	91	38	42
11	F	H	F	H	>99	23	23
12	H	H	Cl	H	98	73	74
13	Cl	H	Cl	F	98	35	34

Scheme 3.

As an alternative to the above method[17] we investigated the potential of our new catalytic oxidation method with a series of substituted fluoroacetophenones (see Scheme 3). The method operates with high levels of conversion when utilizing reaction conditions developed for acetophenone, however, only moderate yields and selectivity were obtained, except for the experiment where 4-chloroacetophenone **12a** was oxidized to 4-chlorobenzoic acid **12b** in 73% yield and 74% selectivity.

We have previously disclosed an optimized industrial process for the preparation of veratric acid **8b**, a process that was based on the oxidation of 3,4-dimethoxyacetophenone **8a** by means of the haloform reaction.[18] In view of the advantages of using a cheap solid and nontoxic substance as oxidant for fine chemical preparation, we have also tried to prepare veratric acid **8b** by means of the novel oxidation process using SPC. The conversion **8a**→**8b**, and 4-methoxyacetophenone **9a** to 4-methoxybenzoic acid **9b** demonstrated comparable results to our earlier disclosed aerobic oxidation process.[3]

The oxidation process optimized for the utilization of SPC was also attempted with SPB as the terminal oxidant. Since SPB decomposes at a reaction temperature above 60 °C, an extra trial was performed at this temperature. All the other experimental variables were kept at similar levels as for the optimized conditions (Table 2, entries 8 and 9).

Inferior results were achieved with SPB compared to the results obtained with SPC. The experiment performed at 60 °C resulted in a yield of 35% with a selectivity of 69%, while the experiment performed at 80 °C, resulted in 28% yield with a selectivity of 52%. Nevertheless, the experiments show that SPB may indeed be utilized as the terminal oxidant with 1,3-dinitrobenzene as catalyst. An improved yield and selectivity with SPB as the terminal oxidant may be accomplished if the process is submitted for a detailed study using statistical experimental multivariate modelling.

Conclusion. In summary, the oxidation method presented here, requires basic conditions and SPC as the terminal oxidant. SPB can be utilized as the terminal oxidant, but when operated under the conditions optimized for SPC, inferior results were obtained. However, we believe that comparable results may be accomplished if an optimizing study is performed for this oxidant as well. The oxidation method operates with the best selectivity at moderately elevated temperature (75–80 °C).

It is reasonable to believe that the oxidation operates according to a mechanism similar to that previously disclosed by us.[2] In the present case, however, the reduction products from the nitroarene are oxidized by means of SPC or SPB.

In contrast to the aerobic oxidation method[2,3] the present method is not specific for benzaldehydes and benzalcohols, since such functional groups are oxidized by both SPB and SPC. The investigations performed for the preparation of benzoic acids **8b**–**13b** revealed varying results with respect to the yield, but the method may be further improved for each of the substrates **8a**–**13a** as well as for other acetophenone derivatives in order to perform processes which are of industrial interest.

General oxidation procedure. Starting materials and reagents were purchased commercially and used without further purification. Acetophenone or derivative (2.4 mmol) was dissolved in a solution of potassium *tert*-butoxide (6.0 mmol) in *tert*-butanol (12.0 mL). The oxidant sodium percarbonate (3.12 mmol) was added at the start of the reaction followed by the catalyst 1,3-dinitrobenzene (0.24 mmol). A further two portions of SPC were added after 1 h (2.5 mmol) and after 2 h (1.5 mmol). The reaction mixture was stirred using a magnetic stirrer bar and heated at 80 °C for a total reaction time of 5 h under a nitrogen atmosphere in order to avoid any interaction of molecular oxygen. The reaction was quenched by dilution with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The aqueous phase was acidified using concd sulfuric acid to pH 1–2, then extracted with ethyl acetate (3 × 30 mL). After diluting with further ethyl acetate to 250 mL, a sample (10 mL) was mixed with internal standard (1-chloro-2,4-dinitrobenzene) solution (10 mL) and analyzed by GC.

All of the reaction products are known compounds. Isolated products were analyzed by GC[19] for impurities and samples were analyzed by GC–MS, ^{1}H NMR,[20] and by comparison with authentic samples.

Acknowledgements

Economic support from the Research Council of Norway (L.L.), Optimum Accipe and the Norwegian–Spanish cultural exchange program (J.A.V.M.) is gratefully acknowledged. Professor George Francis is acknowledged for linguistic assistance.

References and notes

1. Bjørsvik, H.-R.; Liguori, L.; Minisci, F. *Org. Process Res. Dev.* **2001**, *5* 136–140.
2. Bjørsvik, H.-R.; Liguori, L.; Rodríguez González, R.; Vedia Merinero, J. A. *Tetrahedron Lett.* **2002**, *43*, 4985–4987.
3. Bjørsvik, H.-R.; Liguori, L.; Vedia Merinero, J. A. *J. Org. Chem.* **2002**, *67*, 7493–7500.
4. (a) McKillop, A.; Tarbin, J. A. *Tetrahedron* **1987**, *43*, 1753–1758; (b) McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299–3306; (c) McKillop, A.; Sanderson, W. R. *Tetrahedron* **1995**, *51*, 6145–6166; (d) Muzart, J. *Synthesis* **1995**, 1325–1347; (e) McKillop, A.; Sanderson, W. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 471–476.
5. Russell, G. A.; Geels, E. J.; Smentowski, F. J.; Chang, K.-Y.; Reynolds, J.; Kaupp, G. *J. Am. Chem. Soc.* **1967**, *89*, 3821–3828.
6. Russell, G. A.; Geels, E. J. *J. Am. Chem. Soc.* **1965**, *87*, 122–123.
7. Geels, E. J.; Konaka, R.; Russell, G. A. *Chem. Commun.* **1965**, *23*, 13.
8. The statistical experimental design outlined in Table 2 is a composite design that allows the estimation of the main effects, the interaction effects and the quadratic effects for each of the experimental variables.
9. Draper, N. R.; Smith, H. *Applied Regression Analysis*, 3rd ed.; Wiley: New York, 1998.
10. Montgomery, D. C.; Peck, E. A. *Introduction to Linear Regression Analysis*; Wiley: New York, 1982.
11. (a) The multivariate calculations and graphical representations were performed by means of in-house developed procedures for MATLAB® version 6.1, which previously have been validated by comparison of the calculated results with computational results obtained from several commercial computer programs for statistics and mathematical model building. (b) *Using Matlab, Version 6*, The MathWorks Inc., Natick, MA, USA. (c) *Using Matlab Graphics Version 6*, The MathWorks Inc., Natick, MA, USA.
12. The product statistic of the model indicates an acceptable predictive capacity; $R^2 = 0.711$, $Q^2 = 0.547$, RMSEP = 0.521 and RSD = 0.562. Statistical analyses indicated that two of the experiments, entries 1–2 of Table 2 were both determined somewhat aberrantly, that is with high residuals ($y_{\text{measured}} - y_{\text{predicted}}$). If these were left out before the estimation of the regression coefficients, the product statistics indicated a slightly improved model, namely $R^2 = 0.813$, $Q^2 = 0.622$, RMSEP = 0.431 and RSD = 0.469. However, only minor variations of coefficients values were observed.
13. Bjørsvik, H.-R.; Liguori, L. *Org. Process Res. Dev.* **2002**, *6*, 279–290.
14. Culbertson, T. P.; Mich, T. F.; Domagala, J. M.; Nichols, J. B. (Warner-Lambert Co., USA) Patent 14 EP 153163 *Chem. Abstr.* **1986**, *104*, 34013.
15. Granzer, E.; Hammann, P.; Kirsch, R. (Hoechst A.-G., Germany). Patent EP 431480, *Chem. Abstr.* **1991**, *115*, 232218.
16. Wheeler, T. N.; Craig, T. A.; Morland, R. B.; Ray, J. A. *Synthesis* **1987**, *10*, 883–887.
17. Pfirmann, R. D. (Hoechst A.-G., Germany) Patent EP 600317, *Chem. Abstr.* **1994**, *121*, 133701.
18. Bjørsvik, H.-R.; Norman, K. *Org. Process Res. Dev.* **1999**, *3*, 341–346.

19. GLC analyses were performed on a capillary gas chromatograph equipped with a fused silica column (L 25 m, 0.20 mm i.d., 0.33 m film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector.
20. 4-Methoxybenzoic acid [100-09-4], 3,4-dimethoxybenzoic acid [93-07-2], 4-fluorobenzoic acid [456-22-4], 2,4-difluorobenzoic acid [1583-58-0], 4-chlorobenzoic acid [74-11-3], 2,4-dichloro-5-fluorobenzoic acid [86522-89-6].