Monatshefte für Chemie 133, 9–22 (2002)

Monatshefte für Chemie
Chemical Monthly

A New Approach to the Synthesis of 2-Nitrobenzaldehyde. Reactivity and Molecular Structure Studies

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Summary. New approaches to the synthesis of 2-nitrobenzaldehyde by formation and selective isomer separation of 2-nitrophenyl-1,3-dioxolane and further hydrolysis are reported. In this route, the same acidic heterogeneous catalyst is used for 1,3-dioxolane formation and hydrolysis; it can be recycled several times without loss of efficiency. The *ortho*/*meta* isomers of 2-nitrophenyl-1,3-dioxolane can be separated by a combination of stereoselective crystallization and fractionated distillation. This new route reduces safety and environmental hazards in the synthesis of 2-nitro- and 3-nitro-benzaldehydes. The molecular structures of the nitro derivatives were confirmed by ^{1}H and ^{13}C NMR spectroscopy. The results are in accordance with a non-coplanar conformer of the 2-nitro derivatives (2-nitrobenzaldehyde and 2-(2′-nitrophenyl)-1,3-dioxolane), where the nitro group is twisted with respect to the phenyl ring. In contrary, both the carbonyl and the nitro group are coplanar with the phenyl ring in 3-nitrobenzaldehyde. This result is consistent with the reactivity of the compounds.

Keywords. Aldehydes; Catalysis; Chemoselectivity; Isomers; NMR spectroscopy.

Introduction

The nitro derivatives of benzaldehyde are used as intermediates in the synthesis of fine chemicals. They are very important for the preparation of dyes, pesticides, non-linear optic materials [1], and pharmaceutical drugs. In pharmacy, they serve as raw materials for the synthesis of benzodiazepines and new cardiovascular drugs of the dihydropyridine group like nifedipine, nisoldipine, nitrendipine, nicardipine, *etc*. [2]. Besides, the study of these substances is very interesting for the environment since they are highly toxic and weakly biodegradables [3]. Many organic nitroaromatic compounds have mutagenic properties, the nitro group playing an important role in the biological activity [4]. Surprisingly, the *ortho*-mononitro derivative of benzaldehyde is difficult to obtain in good yield and high purity [5]. All these factors have pushed up the number of patents [2, 6–9] and papers [10, 11] reporting new syntheses of *o*-nitrobenzaldehyde published in recent years.

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The partial oxidation of 2-nitrotoluene gives low yields and selectivity [12], especially for 2-nitrobenzaldehyde [13, 14]. Other routes of nitrobenzaldehyde preparation *via* α-halo-nitrotoluenes have been reported [7, 8]. However, this route presents some safety problems due to the low thermal stability of these molecules. Several papers refer to the possible explosive decomposition of *o*-nitrobenzyl halides [15, 16], and a violent explosion during the drying of one of these compounds in a fine chemicals factory has been reported [17]. In particular, *o*-nitrobenzyl chloride decomposes exothermically and violently [18]. Another synthesis route towards *o*-nitrobenzaldehyde proceeds *via* ozonolysis of *o*-nitrostyrene [19]. Recently, the reductive ozonolysis of 2,2′-dinitrostilbene has been reported to yield directly *o*-nitrobenzaldehyde with *o*-nitrobenzoic acid as by-product [5]. The nitration of benzaldehyde is the classical method of mono-nitrobenzaldehyde synthesis; it affords predominantly 3-nitrobenzaldehyde [20]. The proportion of 2-nitrobenzaldehyde can be increased using acetic acid derivatives as reagents [21]. The main problem of this route is the safety hazard in the nitration reaction [22], and some explosions have been reported in this context [23]. A variation of the method, proposed in this work, overcomes this problem.

The isomer separation by fractionated distillation also presents safety hazards [24]. Alternatively, the isomers can be converted to their dimethyl acetals separated afterwards by fractionated distillation. However, this method requires long reaction times and large amounts of reactants [25]. One of the aims of this work is to demonstrate the formation of cyclic acetals of these isomers by an improved method and their separation by a combination of fractionated distillation and stereoselective crystallisation.

Results and Discussion

Nitration

The results of benzaldehyde nitration are summarized in Table 1. The main isomer of nitrobenzaldehyde is the *meta* species in all cases as expected. On the contrary, a very small proportion of *para* isomer ($< 2\%$) was obtained throughout. Within the range of experiments, a higher proportion of HNO_3 yielded a slightly higher amount of *ortho* isomer. The nitration in *ortho* position is very unlikely due to steric hindrance and low nucleophilic character of this position. However, when the HNO_3 concentration is high, the aldehyde group can coordinate the NO_2^+ ion, thus promoting *ortho*-substitution (Fig. 1) [26]; this generally leads to an abnormally high *o*/*m* ratio in the electrophylic nitration of aromatics with electron withdrawing substituents. Probably, the aldehyde group is more solvated in the strongly protic system H_2SO_4–HNO_3 at higher proportions of H_2SO_4, thus disfavouring the assistance of the aldehyde group and decreasing the relative amount of *ortho* product.

The temperature control during reactant addition is difficult, and direct mixing of nitrating agent and benzaldehyde is dangerous. This can be overcome using an intermediate inert solvent (methylene chloride or 1,2-dichloroethane) which neither affects the isomer proportions nor the selectivity. Nevertheless, it allows using additions above room temperature (74°C) and affords higher amounts of

Table 1. Nitration of benzaldehyde

Entry	H_2SO_4/HNO_3[a]	Solvent[b] (cm^3/mmol)	Addition		Reaction		Conversion (%)	Selectivity[c] (%)	*ortho*/*meta*[d]
			T/°C	*t*/min	*T*/°C	*t*/h			
1	7.7/0.86	–	(−5)/5	7[e]	(−5)/0	3	73	88	18/82
2	7.7/0.92	–	(−5)/(−2)	15[e]	(−5)/5	5.5	97	83	17/83
3	5.0/0.86	–	(−5)/0	15	(−5)/5	7	89	77	13/87
4	5.0/0.92	–	(−5)/12	27[e]	(−5)/5	5	94	87	20/80
5	5.0/0.92	–	(−5)/(−3)	64	(−5)/5	6	98	96	21/79
6	4.0/1.5	–	(−5)/5	30[e]	(−5)/5	3.5	100	92	20/80
7	2.0/1.5	–	15/20	12[e]	15/20	2.3	100	95.5	24/76
8	2.2/0.86	0.6	(−5)/0	14	(−5)/0	6.3	84	100	21/79
9	2.2/1.0	0.9	20/25	14	(−5)/0	4.75	99	93	24/76
10	2.0/1.5	1.0	22/25	20	30/38	3.7	100	91.2	23.7/76.3
11	2.0/1.5	0.75	20/35	25	20	4.0	100	95	25/75
12	2.0/1.5	0.5	20/30	96	20	4.0	99.5	95	25/75
13	2.0/1.5	0.35	20/40	270	20	6.0	100	100	24.5/75.5
14	2.0/1.5	0.4	20/28	150	20	6.0	100	98	23.7/76.3
15	2.0/1.5	1	66/78	20	74	1.0	97	83	25.5/74.5
16	NO_3Ac	Ac_2O	0/10	60	8/18	2.0	80	90	30/47/23

[a] Molar ratio with respect to benzaldehyde; [b] CH_2Cl_2, molar ratio with respect to benzaldehyde; 1,2-dichloroethane was used in entry 15; [c] in mononitro benzaldehyde; [d] ratio without considering the 4-nitro isomer, whose proportion was $< 2\%$ in most of the cases except in entry 16 where it is specified; [e] addition of benzaldehyde to the nitrating mixture; in the rest of experiments, the nitrating mixture is added to the organic phase

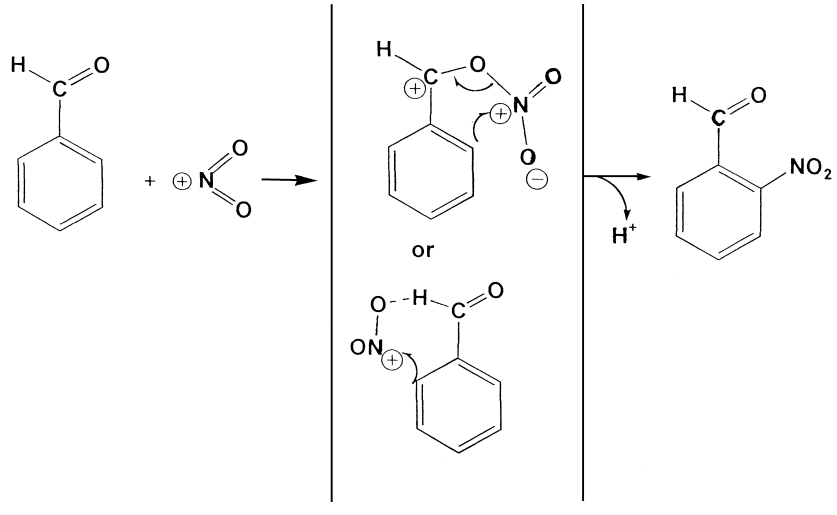

Fig. 1. Scheme of aldehyde group assistance in the nitration of benzaldehyde

ortho isomer. Similar results have been obtained by *Strazzolini et al*. [26] for *ortho*/*para* directing substituents (*Chaperon* effect). From all variables of this reaction, the concentration of HNO_3 is the most important factor to obtain a high proportion of *ortho* isomer.

This work presents a modified method of benzaldehyde nitration that yields a significant proportion of 2-nitrobenzaldehyde by using a non-expensive nitrating agent. The classical method of benzaldehyde nitration yields mainly, and sometimes only, 3-nitrobenzaldehyde [20, 22] with important safety risks in the scale-up. The procedure presented in this work allows using a lower amount of sulfonitric mixture with a higher ratio of HNO_3 at room temperature, yielding both a high selectivity and proportion of *ortho* isomer. Other authors obtained a higher proportion of 2-nitrobenzaldehyde in the benzaldehyde nitration with HNO_3/Ac_2O or HNO_3/CF_3CO_2H. Nitration of benzaldehyde with acetyl nitrate also afforded a higher proportion of the *ortho* isomer (Table 1, entry 16). However, the formation of *para* isomer is also important in this case, and the presence of a significant amount of all three mononitro isomers will render isomer separation difficult. Besides, this procedure involves two steps (nitration + hydrolysis), and the reactants are more expensive at an industrial scale.

A kinetic study of benzaldehyde nitration using the sulfonitric method (Fig. 2a) shows that at the beginning of the reaction the *ortho*/*meta* ratio is 18/82; the *ortho* proportion increases slightly until 25/75 later on. Obviously, the *meta* position is more favoured, both thermodynamically and kinetically; this would result in a constant *ortho*/*meta* ratio. Hence, the higher proportion of the *ortho* isomer at longer reaction times can be explained by the participation of the aldehyde group in the nitration at the *ortho* position. The reaction of formation of the complex intermediate (Fig. 1) will be favoured when the relative concentration of NO_2^+ increases with respect to that of benzaldehyde.

Acetalization

Acetalization reactions of nitrobenzaldehyde mixtures are summarized in Table 2. Initially, the formation of methyl acetals of nitrobenzaldehyde was studied by the classical method using mineral acids as catalysts (HCl) [25, 27]. However, this procedure requires long reaction times. Experiments at higher temperatures yielded a selectivity below 50%. Besides, the industrial scale-up of this procedure needs two reaction steps, handling of Na alkoxides, and wastewater treatment. However, the use of heterogeneous acid catalysis with a ion exchange resin, Amberlite IR 120 (nuclear sulfonic acid type) [27] yielded better results at shorter reaction times. In addition, this method allows recycling the catalyst, thus overcoming environmental problems. Experiments with ethylene glycol yielded better results than with other alcohols. Furthermore, cyclic acetals of nitro-substituted benzaldehydes are of interest because of their anti-cancer activity [28]. These considerations and others concerning isomer separation (discussed later) promoted a firm interest in the formation of 1,3-dioxolane derivatives.

The increase of catalyst content increases slightly the selectivity, reaching 100% in nitrophenyl acetals by using 0.8 g of resin per g of aldehyde with an optimum

Table 2. Acetalization of nitrobenzaldehyde

Entry	*R*OH	Molar ratio of *R*OH[a]	H^{+} [b]	[Aldehyde]/g · dm^{-3}	*T*/°C	*t*/h	Selectivity	Conversion
1	MeOH/MeONa	solvent	0.5	1000	25	6 days	80	100
2	EtOH	4	0.12	116	80	6.5	82	85
3	$(CH_2OH)_2$	1.8	0.10	300	80	4.5	95	95
4	$(CH_2OH)_2$	1.8	0.11	94	80	5	98	97
5	$(CH_2OH)_2$	1.8	0.19	63	80	6	97	100
6	$(CH_2OH)_2$	1.8	0.25	120	80	4.5	97	98
7	$(CH_2OH)_2$	1.8	0.25	333	80	5	96	100
8	$(CH_2OH)_2$	1.7	0.72	295	80	5	99.5	99.5
9	$(CH_2OH)_2$	1.6	0.8	169	80	6	100	99
10	$(CH_2OH)_2$	1.7	0.72		25	22	95	53[c]
11	$(CH_2OH)_2$	1.7	0.72		25	46	98.6	71[d]
12	$(CH_2OH)_2$	1.8	0.25	333	80	5	97	98[e]
13	MeCHOHCHOH	1.7	0.17		80	6	90	

[a] Molar ratio with respect to nitrobenzaldehyde; solvent is benzene in all cases except in entry 1 where MeOH was used as solvent; [b] acid catalyst (g per g of aldehyde; in entry 1, HCl was employed); [c] *ortho*:*meta* ratio: 22:77 (initial), 34:66 (aldehyde, final), 8:92 (acetal, final); [d] *ortho*:*meta* ratio: 22:77 (initial), 44:56 (aldehyde, final), 12:88 (acetal, final); [e] recycled catalyst

range of aldehyde concentration of 60–300 g/dm^3. Nevertheless, further experiments have to be performed to obtain the optimal conditions for all parameters depending on the scale-up level. Similar results were obtained with 1,2-propylene glycol with a slightly lower yield, though only one condition was tested. *ortho*-Nitrobenzaldehyde is slightly less reactive than the *meta* derivative in the acetalization with ethylene glycol due to steric hindrance. A kinetic study of the formation of 1,3-dioxolanes at room temperature for each isomer shows that the initial rate of the *meta* isomer is higher than that of the *ortho* compound (Fig. 2b). At longer reaction times and/or higher temperatures (70°C), this stereoselectivity was lower or absent.

One of the advantages of this method is the catalyst recycling. Using the catalyst directly from a previous reaction, 90% of nitrophenyl acetals were obtained under the same conditions (0.17 g of catalyst per g of aldehyde). When the catalyst was washed with dilute HCl and water prior to reuse, the reaction yielded similar results as with a new catalyst. This result was maintained at least during 5 recycling steps. Therefore, our reaction conditions in this preparation of 2-nitrophenyl-1,3-dioxolanes by means of heterogeneous acid catalysis established a good acetalization method, improving the selectivity and reaction time (5 h instead of 30 h [27]).

One alternative way to this method might be the nitration of benzaldehyde acetals. However, other authors have already studied the nitration of aromatic acetals, and for benzaldehyde acetals, deacetalization preceded the nitration and no nitration product was obtained [29].

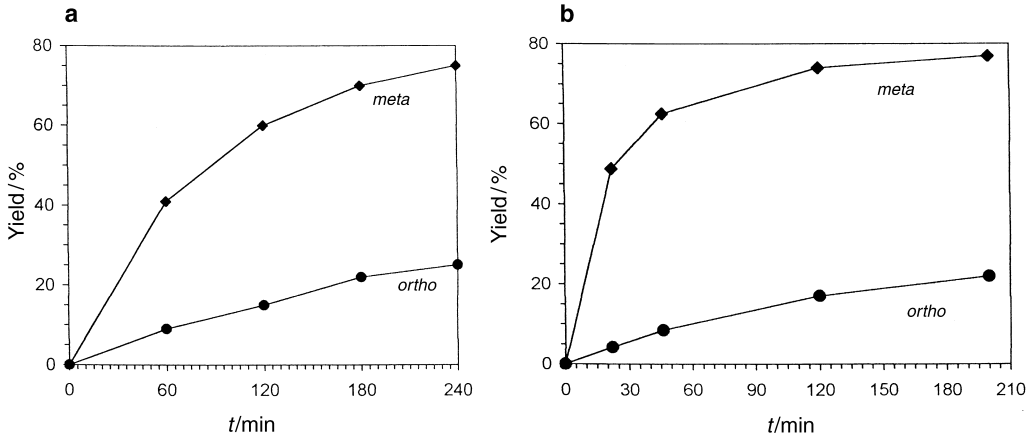

Fig. 2. Stereoselectivity between *ortho* and *meta* isomers; formation of *ortho* and *meta* isomers during the nitration of benzaldehyde (a; conditions of entry 13, Table 1) and formation of 2-nitrophenyl-1,3-dioxolanes (b; conditions of entry 12, Table 2)

Isomer separation

The boiling point difference between the *ortho* and *meta* nitro isomers of the dialkyl and ethylene acetals of the aldehydes is low (6–12°C) (Table 3). Nevertheless, the separation of nitrobenzaldehydes as acetals by fractionated distillation is better than direct separation as aldehydes, overcoming safety hazards. Previous studies have reported that the ethylene acetals are significantly less reactive (30–35 times) than dialkyl acetals with respect to hydrolysis [30]. This could suggest that the thermal stability of ethylene acetals would be higher than that of dialkyl acetals. One important aspect for preventing safety hazards is the exothermic behaviour of these derivatives as tested by differential scanning calorimetry (DSC). In Fig. 3, the profile of the exothermal heat flow *vs.* temperature of *ortho*/*meta* mixtures of 2-nitrophenyl-1,3-dioxolane ($o:m = 32{:}65$) is compared with that of other nitro derivatives synthesized as standards (a mixture of 3-nitrobenzaldehyde and 3,5-dinitrobenzoic acid). The 1,3-dioxolane mixture presents no exothermicity at temperatures below 200°C. The exothermicity detected in the range of 200–280°C is not significant, taking into account the profile of a mixture of 3-nitrobenzaldehyde and 3,5-dinitrobenzoic acid which

Table 3. Boiling points of *ortho*/*meta* isomers of nitrobenzaldehyde and acetal derivatives (reduced pressure (in parentheses) is expressed in mm Hg units)

Compound	*ortho*	*meta*
Nitrobenzaldehyde	153°C (23)	164°C (23)
Dimethyl acetal	146–149°C (27) 125–127°C (14)	128–130°C (10)
Ethylene acetal	90–100°C (0.6–0.8) 146–149°C (7.5) 180–189°C (30)	106–116°C (0.6–0.8) 155–157°C (7.5) 196–198°C (30)

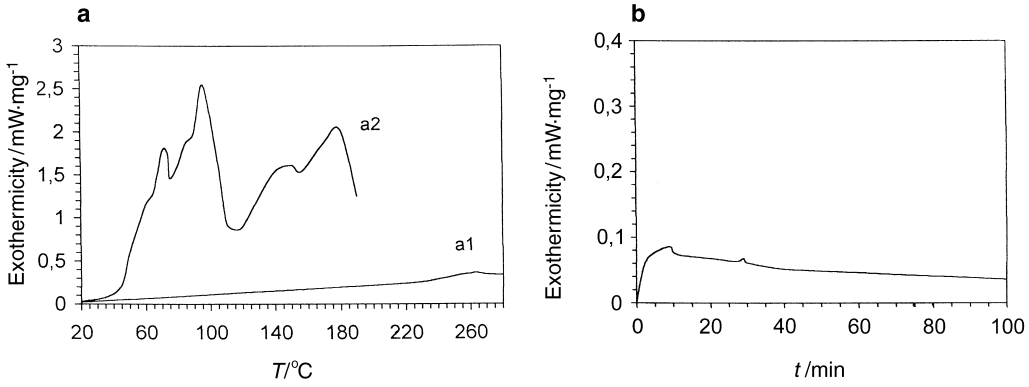

Fig. 3. DSC curves of 2-nitrophenyl-1,3-dioxolanes (a1) and 3-nitrobenzaldehyde (a2) with 3,5-nitrobenzoic acid; exothermicity *vs.* temperature (a) and exothermicity of the dioxolanes at 240°C (b)

presents a much higher exothermicity at lower temperatures (Fig. 3a). The dioxolane mixture did not produce any significant exothermicity even at 240°C (Fig. 3b). Therefore, these ethylene acetals can be treated at least until 280°C without safety hazard risk and were thus selected for the separation of isomers by fractionated distillation.

In the present method, the initial mixture of 2-nitrophenyl-1,3-dioxolanes had an *ortho*/*meta* ratio of 22:77. Initially, it was tried to separate these isomers only by means of fractionated distillation. 9% of a mixture were obtained containing more than 85% *ortho* product. The rest of fractions, collected at higher temperatures, were mixtures with a *meta* below 86%. Hence, this procedure required a high number of repetitions. A similar selectivity was obtained in the fractionated distillation of dimethyl acetals of nitrobenzaldehyde. Nevertheless, the fractionated distillation of a 50:50 *ortho*:*meta* mixture of 1,3-dioxolanes yielded a 51% of a mixture with *ortho*/*meta* ratio of 76:22, leaving behind a mixture of *ortho*:*meta* = 21.5:78.5. The distillated fraction was redistillated fractionally, yielding 64% of *ortho* isomer with a purity above 90%. The residue in the distillation flask consisted of a mixture with an *ortho*/*meta* ratio of 45:55.

Taking into account the molecular structure of these compounds, the probability of intermolecular interactions will be higher in the *meta* isomer than in *ortho* isomer (see below), and the crystallization of the *meta* product would be more favoured than that of the *ortho* species. Therefore, a stereoselective crystallization would allow the separation of both isomers. Different solvents were tested, and the best results were obtained with toluene, yielding 51% of 2-(3′-nitrophenyl)-1,3-dioxolane (purity >98%). The mother liquors contained a mixture with an *ortho*/*meta* ratio of 50:50, and no more *meta* isomer could be separated by further crystallization. This procedure was tested also with dimethyl acetals of nitrobenzaldehyde, but no isomer separation was possible.

Both procedures, stereoselective crystallization and fractionated distillation, were combined for the separation of the isomers following the scheme of Fig. 4. Starting from an *ortho*/*meta* mixture (*o*:*m* = 22:77) as obtained from synthesis, the *meta* isomer is separated by crystallization, and the mother liquors (*o*:*m* = 50:50)

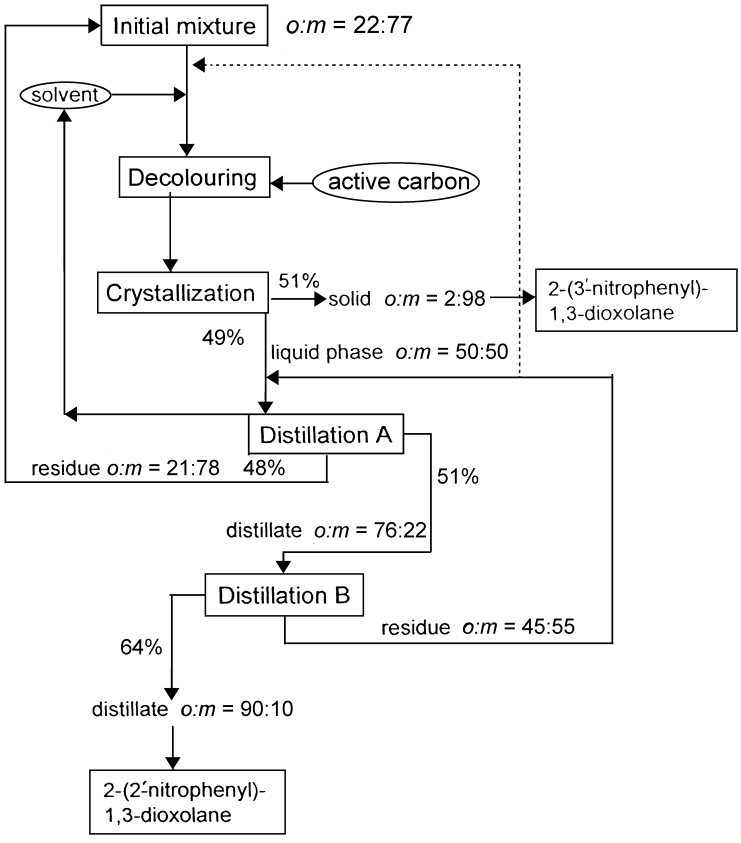

Fig. 4. Scheme of combination of stereoselective crystallization and fractionated distillation for the *ortho*/*meta* isomer separation of 2-nitrophenyl-1,3-dioxolane

are used as input for distillation A. The solvent and non-distillated residue of distillation A (o:$m = 21.5$:78.5) are added to the input of the crystallization process. The tars produced during the distillation can be eliminated by a decolouring treatment with active carbon prior to the crystallization step. The *ortho* isomer is separated by the distillation B step, and the residue (o:$m = 45$:55) is again added to the input of distillation A.

Hydrolysis of dioxolanes

The hydrolysis of ethylene acetals of nitrobenzaldehydes is catalyzed by acids (Table 4). The reaction catalyzed by HCl is faster than that catalyzed by acid resin, but the latter provides higher selectivity and yields. The reactivity of the *ortho* isomer is slightly lower than that of the *meta* product in the hydrolysis reaction due to steric hindrance; however, this stereoselectivity is not sufficient for applying this reaction to isomer separation. The use of a heterogeneous acid catalyst, like IR 120 resin, allows recycling of the catalyst. Several experiments similar to entry 6 (Table 4) were performed using recycled catalyst without previous acid regeneration treatment; the yield was always higher than 90% for at least 5 cycles.

Table 4. Hydrolysis of 2-nitrophenyl)-1,3-dioxolanes

Entry	Catalyst[a]	H_2O[b]	*T*/°C	*t*/h	Yield/%	*ortho*/*meta*	
						Acetal	Aldehyde
1	HCl (4 cm^3)	50	25	3.5	66	33/67	13.5/86.5
2	IR 120 (0.5 g)	50	25	0.5	24		
3	IR 120 (1 g)	50	25	2.5	24	23/76.5	8.5/91.5
4	IR 120 (0.55 g)	10	25	3 days	23	23/76	10/90
5	IR 120 (0.55 g)	10	25	6 days	68	43/57	11/89
6	IR 120 (1 g)	20	40–50	7	>95		

[a] Amount of catalyst per g of substrate; [b] cm^3 per g of substrate

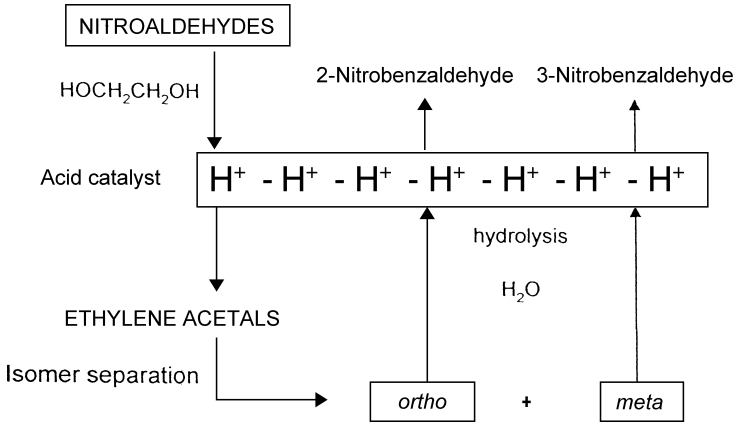

Fig. 5. Combination of heterogeneous acid catalysis in nitrobenzaldehyde acetalization and 2-nitrophenyl-1,3-dioxolane hydrolysis

It is remarkable that the type of resin used in the hydrolysis reaction is the same as that used for acetalization. Besides, the same catalytic solid used in the acetalization can also catalyze the hydrolysis. Some hydrolysis experiments were performed employing the catalyst used previously in the acetalization process without acid regeneration treatment. The results were similar to those obtained with a new fresh catalyst. Therefore, the same catalyst can be used consecutively in both acetalization and hydrolysis and recycled for a new acetalization/hydrolysis cycle (Fig. 5). This procedure overcomes environmental scale-up problems.

Molecular structure

Most of the experimental results shown above can be related to the molecular structure of the compounds which accounts for the high reactivity of the nitrobenzaldehydes, the stereoselectivity in the acetalization and acetal hydrolysis reactions, the crystallization process, the isomeric differences in boiling points, and the spectroscopic data. From the ^{13}C NMR chemical shifts of the aromatic carbons it can be deduced that the electron withdrawing effect of the nitro group on the *ipso*

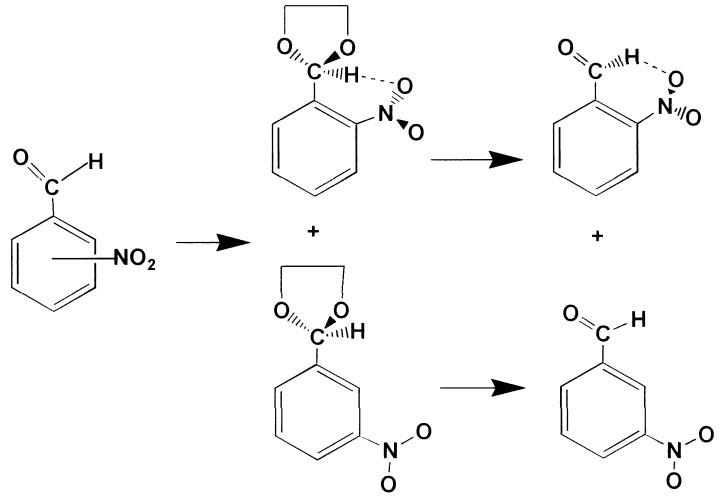

Fig. 6. Separation of *ortho*/*meta* isomers of nitrobenzaldehyde *via* 1,3-dioxolane derivatives; molecular structure of *ortho* and *meta* isomers of nitrobenzaldehyde and 1,3-(nitrophenyl)-dioxolane

carbon is slightly higher in the *meta* isomer ($\delta = 148.2$ ppm) than in the *ortho* compound ($\delta = 146.3$ ppm). This can be explained by a better coplanarity of the nitro and phenyl moieties in the *meta* derivative (Fig. 6). Significant differences can be observed in the ^{1}H NMR chemical shifts. In the 1,3-dioxolane derivatives, the shift of H_α in the *ortho* isomer ($\delta = 6.49$ ppm) is significantly higher than that in the *meta* compound ($\delta = 5.89$ ppm), which is close to the value for the ethylene acetal of benzaldehyde ($\delta = 5.82$ ppm). The shift of the aromatic H vicinal to the nitro group is higher in the *meta* ($\delta = 8.36$ ppm) than in the *ortho* ($\delta = 7.91$ ppm) isomer. This difference is especially significant for H_4 atom (joined to C_4), whose shift is much higher in the *meta* ($\delta = 8.23$ ppm) than in the *ortho* ($\delta = 7.63$ ppm) compound. These differences cannot be explained by the electronic effect of nitro group alone, but some H-bonding or anisotropic effect should be also considered. Previous quantum mechanical studies have shown a non-coplanar twisted conformation of the nitro group with respect to the phenyl ring in 2-nitrobenzaldehyde [5]. Intramolecular H-bonding interactions with the nitro group oxygens have also been found (Fig. 6). These intramolecular H-bonding interactions and the twisted conformation of the nitro group in the 2-nitro derivatives could explain the differences between the isomers with respect to reactivity and crystallization-distillation (different intermolecular interactions).

Conclusions

Different approaches to the synthesis of nitrobenzaldehydes were studied. Each step of the synthesis was modified and improved. An important claim of this work is the combination strategy to establish an alternative synthesis of 2-nitrobenzaldehyde. This modified route avoids the safety and environmental hazards of previous methods. A modified benzaldehyde nitration, using a low proportion of sulfonitric mixture with high HNO_3 content and an intermediate inert solvent,

yields a high selectivity of mononitrobenzaldehydes with a high proportion of *ortho* the isomer (*ortho*:*meta* = 25:75). This procedure appears amenable to scale-up on an industrial level due to the low exothemicity of the process. The main handicap is the isomer separation because of safety risks. This work has set up a procedure to overcome this problem by means of nitrobenzaldehyde acetalization, isomer separation, and acetal hydrolysis. The 2-nitrophenyl-1,3-dioxolanes are good candidates for application in cancer therapy and exhibit low exothermicity at the maximal distillation temperature. One important point in the strategy of this route is to use an acid heterogeneous catalyst for acetalization and hydrolysis. Besides, the same catalyst can be used for both steps without intermediate regeneration, and the same catalyst can be recycled several times without losing efficiency in both reactions. This point is very important for environmental aspects with respect to scale-up. The best strategy for the isomer separation is the combination of stereoselective crystallization and fractionated distillation. This procedure allows to obtain the *meta* isomer by crystallization and the *ortho* isomer by distillation.

Experimental

Materials

Unless otherwise noted, high quality commercial materials and solvents shown to be free of interfering impurities by GLC were used as received.

Analytical methods

IR spectra were obtained with a Perkin-Elmer IR spectrometer. The peak intensity is designated as s (strong), m (medium), and w (weak). NMR spectra were measured at 200 MHz (for ^{1}H NMR) and at 50.3 MHz (for ^{13}C NMR) with a Varian VXR 200 spectrometer using *TMS* as internal reference. A DEPT pulse sequence was used as a help for assignment. MS analysis was performed using a Hewlett Packard 5985B spectrometer. TLC analysis was conducted on 0.25 mm E. Merck silica gel plates (60F-254) using UV light (254 nm) for detection and toluene or benzene:cyclohexane = 1:1 as the mobile phase. In the analytical GLC studies, a Perkin-Elmer 8500 chromatograph was used with a flame ionization detector and a 2 m $\times \frac{1}{4}$ inch column with 5% XE-60 in Chromosorb WHP 80/100. The quantitative analysis was performed using hexadecane and hexadecanol as internal standards. Differential scanning calorimetry (DSC) was performed using a Mettler DSC calorimeter with a temperature rate of 1 K/min in the range of 50–300°C. All reactions were monitored by TLC and GLC.

Nitration of benzaldehyde

a) With sulfonitric mixture: A mixture of discoloured nitric acid (97%) and sulfuric acid (96%) was added slowly to a solution of benzaldehyde in CH_2Cl_2 under heavy stirring (Table 1). The reactor should have both a cooling system and an independent heating system for careful temperature control. For safety reasons, a discharge system (over an ice/water container) should be installed at the bottom of the reactor. The reaction was monitored by TLC until total conversion. At the end of the reaction, the mixture was poured into ice/water. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. All organic phases were collected, washed with water, and concentrated under reduced pressure to give a red liquid that

was analyzed by GC, showing it to consist of a mixture of 2-, 3-, and 4-nitrobenzaldehydes and small amounts of by-products (Table 1).

b) With acetyl nitrate: Discoloured nitric acid (30 cm^3, 97%) was added slowly (1 h) to a solution of benzaldehyde (12 g) in 100 cm^3 of acetic anhydride under heavy stirring, maintaining the temperature at 0–10°C. After 2 h at 8–18°C the reaction mixture was poured into 200 cm^3 of ice/water and extracted with 2×100 cm^3 of $CHCl_3$. The organic phase was washed with H_2O and concentrated under reduced pressure, affording a dark reddish liquid. This product was analysed by GC and IR, showing it to consist of a mixture of benzaldehyde, 2- and 3-nitrobenzaldehyde, and the diacetate derivatives of benzaldehyde, 2-nitro-, and 4-nitrobenzaldehyde. A portion of the above reaction product (18.6 g) was treated with Na_2CO_3 (4 g), ethylene glycol (10 cm^3), and H_2O (20 cm^3) under reflux for 2 h. The reaction mixture was diluted with H_2O, extracted with $CHCl_3$, and concentrated under reduced pressure to yield a red liquid (mixture of 71.5% nitrobenzaldehyde (30, 47, and 23% of 2-nitro-, 3-nitro-, and 4-nitrobenzaldehyde, respectively) and 28.5% benzaldehyde with other by-products by GC).

Dimethyl acetal of nitrobenzaldehyde

Concentrated HCl (10 cm^3) was added to a methanolic solution of 50 g of nitrobenzaldehyde mixture (*ortho*:*meta* = 22:77). After 6 days, 0.6 g of freshly prepared MeONa were added at room temperature under heavy stirring. The reaction mixture was filtered, washed with H_2O, extracted with diethyl ether, and concentrated under reduced pressure to yield a brown-reddish liquid (GC: *ortho*:*meta* = 19:81). This product was fractionally distilled at reduced pressure with a reflux ratio of 50/1, affording two fractions of b.p. 124–126°C (14 mm Hg) and 128–130°C (10 mm Hg) which after chromatographic purification showed to be 1-(dimethoxymethyl)-2-nitrobenzene and 1-(dimethoxymethyl)-3-nitrobenzene, respectively. 1-(dimethoxymethyl)-2-nitrobenzene: $m/z = 180$ (M^+, 5%), 166 (100), 165 (22), 149 (11), 135 (30), 119 (9), 105 (22), 104 (9), 91 (38), 90 (17), 77 (41), 76 (14), 75 (25), 65 (12), 59 (22), 51 (35); 1-(dimethoxymethyl)-3-nitrobenzene: $m/z = 197$ (M^+, 1%), 166 (100), 120 (32), 105 (5), 91 (10), 77 (11), 75 (24).

Hydrolysis of 1-(dimethoxymethyl)-2-nitrobenzene

A freshly obtained fraction of dimethyl acetal of 2-nitrobenzaldehyde (1.4 g) was added to 2 *N* sulfuric acid (7 cm^3). After 3 h at room temperature with gentle stirring, the reaction mixture was extracted with CH_2Cl_2. The organic phase was washed with H_2O and concentrated under reduced pressure, yielding 0.9 g of pure 2-nitrobenzaldehyde (GC; m.p.: 40–42°C; caution: toxic and irritant by inhalation). MS: $m/z = 151$ (M^+, 97%), 150 (75), 105 (43), 104 (18), 77 (100), 76 (32), 51 (95).

2-Nitrophenyl-1,3-dioxolanes

A mixture of ethylene glycol (208 g) and previously washed and dried IR 120 acid resin (21.5 g, dry weight) was added to a solution of 295 g freshly prepared nitrobenzaldehyde (*ortho*:*meta* = 24:75) in C_6H_6. The reaction was monitored by TLC and by following the H_2O generation. After 5 h under reflux using a *Dean-Stark* trap for concomitant removal of H_2O, the theoretical amount of H_2O was collected (final volume: 43 cm^3). The reaction mixture was filtered, and the solid was washed with hot C_6H_6. The liquid phase was washed with 100 cm^3 of an aqueous solution of $NaHCO_3$ at *pH* 8.3 and 100 cm^3 of H_2O. The aqueous phases were extracted with CH_2Cl_2. All organic phases were concentrated at reduced pressure to yield a brown-reddish liquid (381 g). This product was analyzed (GC and NMR) and was identified as a mixture of 2-(2′-nitrophenyl)- and 2-(3′-nitrophenyl)-1,3-dioxolane (*ortho*:*meta* = 22:77) and 0.5% of nitrobenzaldehydes as by-products (yield: 99.5%).

Isomer separation: The above mixture was crystallized from toluene to give a solid (yield: 65%) with an *ortho*/*meta* ratio of 2:98 which, after chromatographic purification, yielded pure 2-(3′-nitrophenyl)-1,3-dioxolane (m.p.: 55–56°C).

IR (nujol): $\nu = 1530$ (s), 1380 (s), 1280 (m) 1220 (m), 1095 (m), 1070 (s), 985 (s), 950 (m), 905 (m) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 4.0$–4.2 (m, 4H, OCH_2–CH_2O), 5.89 (s, 1H, O–CH–O), 7.57 (t, 1H, $J = 7.9$ Hz, H–C_5), 7.81 (ddt, 1H, $J = 7.9$, 2.1, and 1.3 Hz, H–C_6), 8.23 (ddd, 1H, $J = 7.9$, 2.1, and 1.3 Hz, H–C_4), 8.36 (t, 1H, $J = 2.1$ Hz, H–C_2) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 65.5$ (OCH_2), 102.2 (O–CH–O), 121.7 (C_2), 124.0 (C_4), 129.4 (C_5), 132.7 (C_6), 140.3 (C_1), 148.2 (C–NO_2) ppm.

The mother liquor was discoloured with active carbon and concentrated under reduced pressure. The concentrate was fractionally distilled at reduced pressure to give 2-(2′-nitrophenyl)-1,3-dioxolane (yield: 45%) with 3% of *meta* isomer (b.p.: 100°C at 0.6 mm Hg). After chromatographic purification, pure 2-(2′-nitrophenyl)-1,3-dioxolane was obtained.

IR (neat): $\nu = 1530$ (s), 1360 (s), 1200 (s), 1110 (s), 1070 (s), 950 (m), 890 (s) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 4.0$–4.2 (m, 4H, OCH_2–CH_2O), 6.49 (s, 1H, O–CH–O), 7.5 (dt, 1 H, $J = 7.7$ and 1.4 Hz, H–C_5), 7.63 (dt, 1 H, $J = 7.7$ and 1.4 Hz, H–C_4), 7.82 (dd, 1 H, $J = 7.7$ and 1.4 Hz, H–C_6), 7.91 (dd, 1H, $J = 7.7$ and 1.4 Hz, H–C_3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 65.32$ (OCH_2), 65.45 (OCH_2), 99.6 (O–CH–O), 124.4 (C_3), 127.6 (C_6), 129.7 (C_4), 132.9 (C_5), 133.2 (C_1), 146.3 (C–NO_2) ppm.

Hydrolysis of 2-nitrophenyl-1,3-dioxolanes

A freshly obtained fraction of 2-(3′-nitrophenyl)-1,3-dioxolane (1 g) was added to a suspension of IR 120 acid resin in H_2O with high stirring. The reaction was monitored by TLC and IR until complete conversion. 20 cm^3 CH_2Cl_2 were added to the reaction mixture which was then filtered. The organic phase was washed with H_2O, dried, and concentrated under reduced pressure to give 3-nitrobenzaldehyde (yield: 95%).

M.p.: 58°C; ^1H NMR ($CDCl_3$): $\delta = 7.8$ (ddd, 1H, $J = 7.7$ and 1.4 Hz, H–C_5), 8.26 (dt, 1H, $J = 7.7$ and 1.4 Hz, H–C_6), 8.51 (ddd, 1H, $J = 7.7$ and 1.4 Hz, H–C_4), 8.73 (m, 1H, $J = 7.7$ and 1.4 Hz, H–C_2), 10.14 (d, 1H, $J = 0.4$ Hz, HC=O) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 124.4$ (C_2), 128.6 (C_4), 130.4 (C_5), 134.7 (C_6), 137.4 (C_1), 148.7 (C–NO_2), 189.8 (C=O) ppm.

A similar procedure was applied to 2-(2′-nitrophenyl)-1,3-dioxolane, affording 2-nitrobenzaldehyde.

Acknowledgements

The author thanks Ercros S.A. and U.E.E. S.A. for financial support and Dr. *J. Santaolalla* for useful discussions.

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Received January 22, 2001. Accepted (revised) July 18, 2001