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Development of optimised synthesis of 4-amino-*N*-(4-carbamoylphenyl)benzamide for industrial application

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Abstract An efficient two-step synthetic route for preparation of the important Pigment Yellow 181 intermediate 4-amino-*N*-(4-carbamoylphenyl)benzamide is described. The synthetic pathway reflects requirements that are important for industrial applications. Optimisation of the reaction steps was performed to improve yields and procedures. The overall yield was higher than 78 %.

Keywords Organic technology · Pigment Yellow 181 · *N*-(4-carbamoylphenyl)-4-nitrobenzamide · 4-Amino-*N*-(4-carbamoylphenyl)benzamide · Catalytic reduction

Introduction

Pigment Yellow 181 (P.Y. 181) is an extremely heat stable, very light-fast reddish yellow pigment. Its main area of application is in plastics, especially polyolefins. It is a suitable pigment for other polymers which are processed at high or very high temperatures. The list includes polyester, polyacetal, and various other technical plastics. P.Y. 181 is also frequently used to colour spin-dyed viscose rayon and viscose cellulose. In these media the pigment satisfies the particularly stringent specifications regarding light-fastness and weather-fastness for use in automobile interiors. This is a purpose for which only very few organic yellow pigments are suited [1].

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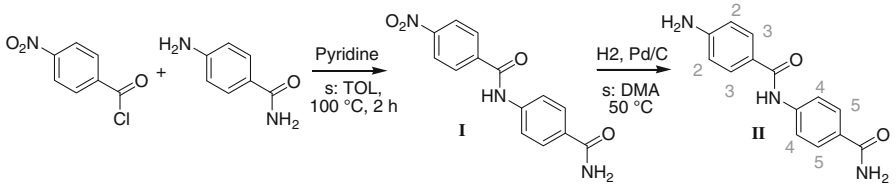
4-Aminobenzoylbenzamide (4-amino-*N*-(4-carbamoylphenyl)benzamide) is an important intermediate in the production of P.Y. 181. Suitable methodology for laboratory preparation of this compound is available in the literature [2]. This synthetic pathway, however, includes reduction of polymer-bound nitroarenes, which is unsuitable for the industrial production, because of low yields, and the use of toxic *N*,*N*-dimethylformamide as solvent [2]. Hence, a two-step, safe, inexpensive, and high-yield industrial synthetic pathway has been developed and tested for synthesis of 4-aminobenzoylbenzamide.

Results and discussion

The synthetic pathway is shown in Scheme 1. The synthesis of 4-aminobenzoylbenzamide **II** was designed as a two-step reaction with isolation of *N*-(4-carbamoylphenyl)-4-nitrobenzamide **I** as intermediate.

The first step is the preparation of *N*-(4-carbamoylphenyl)-4-nitrobenzamide **I**. It was decided to prepare this compound by direct reaction of 4-nitrobenzoyl chloride (4-NBC) and 4-aminobenzoyl amide (4-ABA). The synthesis of intermediate **I** is described in the literature [3]. This synthetic pathway is not suitable for industrial production. For formation of this type of amide bond, a procedure known from the literature was chosen. In generally, formation of this bond is realised in dichloromethane in the presence of a base, for example triethylamine (TEA) [4, 5] or pyridine (Py) and sodium hydrogen carbonate [6], and eventually in Py [7]. Because of health risks associated with dichloromethane, in some studies this solvent was substituted with tetrahydrofuran and sodium hydrogen carbonate [8]. However, tetrahydrofuran is also not suitable for technological use because of the possibility of formation of unstable peroxides and its high flammability.

For the purpose of this study, toluene was chosen as solvent for the reaction, and *N*,*N*-dimethylaniline (DMA), TEA, and Py were tested as bases. Individual experiments were performed under the same conditions and using the same amounts of starting materials. All experiments and their results are listed in Table 1. The procedure was performed as follows: 4-ABA, toluene, and a base were placed in a reactor ($V = 1.5$ L). To this suspension solid 4-NBC was slowly added (temperature was maintained at 40 °C). After addition of the chloride, the reaction mixture was heated to 80 °C. The product was collected by use of hot filtration. When DMA



Scheme 1 Developed synthetic pathway. *Grey* numbers are used for assignment of proton resonances in the "Experimental" section

Table 1 Conditions used in optimisation of the preparation of the *N*-(4-carbamoylphenyl)-4-nitrobenzamide **I**

Exp. no.	Reactants and solvents					Addition temp (°C)	Finishing temp (°C)	Yield (g)	Yield (%)
	4-ABA (mol)	4-NBC (mol)	Toluene (mL)	Base (g)	EtOH (mL)				
1	0.316	0.372	400	50.5^{DMA}	–	60	80	0	0
2	0.316	0.372	400	40.0^{TEA}	1,000	40	80	14.6	16.2
3	0.316	0.372	400	33.0^{Py}	1,000	40	80	68.7	76.3
4	0.316	0.372	400	33.0^{Py}	500	60	100	73.4	81.5
5	0.316	0.372	400	33.0^{Py}	500	60	100	72.4	80.5
6	0.316	0.372	400	33.0^{Py}	500	80	100	69.9	77.6

DMA N,*N*-dimethylaniline; *TEA* triethylamine; *Py* pyridine

was used as the base, it was not possible to isolate the product by filtration, and this experiment was terminated. This base was not used subsequently.

In other experiments, in which TEA or Py was used, the crude product was easily isolated by filtration and then suspended in water to remove hydrochloride salts. After this operation, NMR spectroscopy of the isolated products was performed. When TEA was used, the desired product **I** was produced in 20 % yield whereas Py gave a product in approximately a 70 % yield. Other compounds, for example 4-ABA and 4-nitrobenzoic acid, products of hydrolysis of 4-NBC, and other, unknown, impurities were also detected. To refine the product, ethanol was used. The crude product **I** was suspended in hot ethanol for 15 min. The product was filtered while hot and this material was dried and analysed by NMR spectroscopy. Compound **I** was obtained without any impurities. The unsuccessful step of purification with hot water was performed again in the future experiments. Py was identified as an optimum base for this reaction and hot ethanol was used to eliminate pyridinium hydrochloride from the reaction mixture.

The next stage of the research focussed on modification of the reaction conditions. First, the temperature during addition of 4-NBC was increased to 60 °C and the temperature at the end of the reaction was increased to 100 °C. The yield of this experiment increased to 81 % whereas experiments at lower temperatures gave yields of 76 %. A further increase in temperature (addition temperature 80 °C and finishing temperature 100 °C) did not change the yield or purity of the compound.

In experiments 4, 5, and 6, the amount of ethanol used during refining was reduced from 1 L to 500 mL. In experiment 6, addition of 4-NBC as a solution in toluene was also investigated. Both changes were without any significant effect on the reaction yields of product **I**. All the experiments and their results are listed in Table 1.

The second step of the synthesis was reduction of intermediate **I** to the final product, 4-aminobenzoylbenzamide **2**. The classic Béchamp reduction process [9] could not be used because of the production of a large amount of wastewater containing iron oxides. Therefore, attention was focussed on Pd-catalytic reduction using hydrogen. The optimum solvent for this reaction was investigated. It should

Table 2 Solubility of 4-amino-*N*-(4-carbamoylphenyl)benzamide **II**, and toxicity and boiling points of solvents

Solvent	Solubility of **II**	LD_{50} (mg/kg)[a]	Boiling point (°C)
Toluene	Insoluble	3–8.41	111
Ethanol	Slightly soluble	10,300	78.1
Tetrahydrofuran	Insoluble	1,650	66
Butanol	Insoluble	3,500	117.7
Dioxane	Insoluble	4,200	101
Dimethyl sulfoxide	Soluble	$14–28 \times 10^3$	189
N-methylpyrrolidone	Soluble	3,914	204.3
N,*N*-dimethylformamide	Soluble	2,800	153
N,*N*-dimethylacetamide	Soluble	4,250	166.1

[a] ORL-RAT

be an inexpensive and non-toxic solvent in which compound **II** is soluble. The most commonly used solvents for reductions are ethanol [10], tetrahydrofuran [11], toluene, 1,4-dioxane [12], dimethyl sulfoxide, *N*-methylpyrrolidone, *N*,*N*-dimethylformamide [13], and *N*,*N*-dimethylacetamide (DMAC) [14]. Regeneration should be possible by single distillation or other conventional methods. For the purpose of this study, most of the solvents commonly used for catalytic reductions are not suitable, because of their toxicity or the lack of solubility of the starting material. In Table 2, possible solvents are listed, together with their important properties.

The relatively non-toxic DMAC was chosen as the optimum solvent. The solubility of **II** is high, and the solvent can be regenerated by distillation. All experiments were performed in this solvent. Reductions were performed under hydrogen pressure (1.5 MPa) in a non-corrosive autoclave ($V = 1$ L). Palladium

Table 3 Investigation of reaction conditions and yields of the reduction of *N*-(4-carbamoylphenyl)-4-nitrobenzamide **I** in DMAC as solvent

Exp. no.	Reagents					Reaction conditions		Product **II**		
	Compd **I** (g)	DMAC	c **I** (g/100 mL)	3 % Pd/C (g)	H_2 (L)	Temp (°C)	Time (min)	Yield (g)	Yield (%)	HPLC area 220 nm (%)
7	10	300	3.33	3	2.3	50–55	60	7.27	81.4	99
8	25	300	8.33	5	6.5	50–65	45	20.7	92.4	93
9	34	300	11.33	5	9	50–65	60	29.3	96.2	95.6
10	50	300	16.67	4	12.5	50–75	30	9.31	20.8	99.6
11	44.7	450	9.93	3	12.0	60–80	15	36.9	92.2	98.17
12	50	450	11.11	1.5	12.5	70–80	45	42.3	94.4	98.22
13	50	450	11.11	1.5* + 0.5	13.5	60–80	65	41.8	93.3	98.77

* Catalyst was separated from experiment 6 and 0.5 g of fresh catalyst was used

Table 4 Time dependence of hydrogen consumption of chosen experiments 11, 12 and 13

Exp. no.	Time (min)	Temperature (°C)		Pressure (Mpa)		Hydrogen consumption (L)	
		Reactor	Thermostat	Reactor	H_2 tank	Change	Total
11	0	51	60	1.5	68	0	0
	1	60	60.4	1.5	67	1.0	1.0
	2	64.3	61.8	1.5	66	1.0	2.0
	5	69.5	80	1.5	62.5	3.5	5.5
	8	71.6	80	1.5	60	2.5	8.5
	15	81.1	80	1.5	56	4.0	12.5
	25	79.8	80	1.5	56	0	12.5
	70	79.8	80	1.5	56	0	12.5
12	0	69.3	80	1.5	35	0	0
	4	83	80	1.5	31	4.0	4.0
	9	81.8	80	1.5	26	5.0	9.0
	15	79	80	1.5	24	2.0	11.0
	25	79	80	1.5	23.5	0.5	11.5
	35	79.9	80	1.5	22.5	1.0	12.5
	45	79.9	80	1.5	22.5	0	12.5
	55	79.9	80	1.5	22.5	0	12.5
	100	79.8	80	1.5	22.5	0	12.5
13	0	59.4	66	1.5	44	0	0
	9	79.3	76.6	1.5	37.5	6.5	6.5
	15	81.4	80.6	1.5	35	2.5	9.0
	25	81.2	80.8	1.5	32	3.0	12.0
	35	81.0	80.8	1.5	31	1.0	13.0
	45	80.8	80.8	1.5	30.5	0.5	13.5
	55	80.8	80.8	1.5	30.5	0	13.5
	65	80.8	80.8	1.5	30.5	0	13.5
	115	80.8	80.8	1.5	30.5	0	13.5

(3 %) in activated carbon as a 50 % paste with water was used as catalyst. Hydrogen consumption was monitored by the pressure decrease in the 1-L hydrogen high-pressure tank. The optimum concentration of **I**, the amount of catalyst, and the temperature course of reduction was investigated. The experimental conditions and yields are summarised in Table 3.

Table 3 shows that the concentrations of the starting material increased from 3.33 g/100 mL DMAC in experiment 1, to 16.67 g/100 mL of DMAC in experiment 4. The highest concentration is the maximum solubility of **I** and the starting material crystallised in the reaction mixture. The optimum concentration of the starting material **I** is approximately 11 g in 100 mL of DMAC. Half of the amount of catalyst used in experiment 6 was used. In comparison with experiment 5, the reaction time was extended. The yield of the desired product **II** was then higher

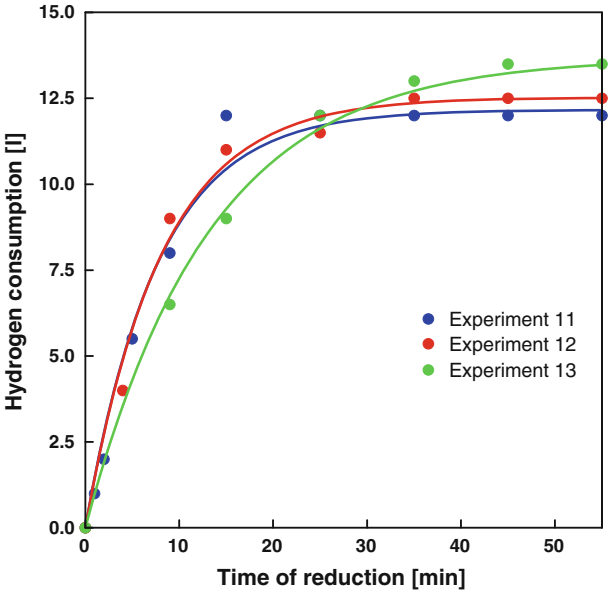


Fig. 1 Graphical representation of the time-dependence of hydrogen consumption

than 90 %. In experiment 7, the catalyst isolated from experiment 6 was used with 0.5 g new catalyst. The yield of this experiment was also comparable with that of experiments 5 and 6. The purity of isolated products was monitored using HPLC, and the optimum concentration was higher than 98 % for all experiments.

The course of hydrogenation in experiments 11, 12, and 13 was monitored. The time dependence of hydrogen consumption is shown in Table 4.

The course of hydrogenation in these experiments is shown graphically in Fig 1. It was concluded that use of half the amount of catalyst in experiment 13 does not dramatically affect the reaction rate (green line).

In all of the experiments, the same procedure was used for isolation of product **II**. When hydrogenation complete, the reaction mixture was stirred for 1 h at 80 °C. The catalyst was then removed by filtration and washed with DMAC (100 mL, 55 °C). Part of the solvent was removed at low pressure. Cooling of the mixture and the addition of distilled water caused precipitation of the desired product **II**. This was isolated by filtration and dried at 80 °C to constant weight. This material was then analysed by use of HPLC and ^{1}H and ^{13}C NMR spectroscopy.

Conclusion

A short and efficient synthesis of 4-amino-*N*-(4-carbamoylphenyl)benzamide **II** has been described. This study provides new ideas for synthesis of this important intermediate. The developed procedure also helped to eliminate undesirable impurities, which can be a major problem with low-quality products. The overall yield was higher than 78 %, and the prepared compound can be used directly into

the next step of the synthesis of P.Y. 181. The developed methodology is now ready for industrial application.

Experimental

General information

All reagents and solvents were purchased from commercial sources and were technical grade. NMR spectra were measured in DMSO-d_6 solutions at ambient temperature on a Bruker Avance 500 (500 MHz for ^{1}H, 125.77 MHz for ^{13}C). Coupling constants are presented in Hz. Proton chemical shifts in DMSO-d_6 are referenced to the middle of the solvent multiplet ($\delta = 2.50$). ^{13}C NMR spectra were measured by using an APT pulse sequence. Carbon chemical shifts are referenced to the middle of the solvent multiplet ($\delta = 39.5$ in DMSO-d_6). A LaChrom Merck Hitachi HPLC separation module and a LaChrom Merck Hitachi L7450 photodiode array detector were used. A Symmetry Shield RP-18 5 μm, 4.0 mm × 150 mm, chromatographic column was used. A mixture of MeOH p.a. (40 %) and Milli-Q HPLC-grade H_2O (60 %) was used as mobile phase; the flow rate was 1.0 mL/min, the injection volume 10 μL, and the column temperature 25 °C, all at ambient sample temperature. The detection wavelength was 220 nm.

General procedure for preparation of compound **I**, and its characterisation

N-(4-Carbamoylphenyl)-4-nitrobenzamide (**I**) (experiment no. 5). Toluene (400 mL), 4-ABA (43 g, 0.316 mol), and Py (33 g, 0.417 mol) were placed in a nitrogen-flushed autoclave (V = 1.5 L). The mixture was heated to 60 °C and 4-NBC (69 g, 0.372 mol) was slowly added. The reaction mixture was than heated to 100 °C and stirred at this temperature for 2 h. The precipitate was isolated by filtration and washed with hot toluene (200 mL, 80 °C). Crude intermediate **I** was put back in the autoclave and 96 % ethanol (500 mL) was added. The suspension was heated to reflux and then stirred for 2 h. The product was isolated by filtration while hot and washed with hot ethanol (200 mL, 70 °C). The product was dried in an oven (80 °C) to constant weight, to give 72.4 g of desired intermediate **I** with purity higher than 99 % (HPLC).

White solid, yield 70.7 %. ^{1}H NMR (500,13 MHz, DMSO-d_6): δ 10.84 (1H, s, NH–CO); 8.39 (2H, d, $J = 8{,}7$ Hz, H2); 8.19 (2H, d, $J = 8{,}7$ Hz, H3); 8.04 (1H, s, NH_2–CO); 7.92 (2H, d, $J = 8{,}7$ Hz, H5); 7.86 (2H, d, $J = 8{,}7$ Hz, H4); 7.33 (1H, s, NH_2–CO). ^{13}C NMR (125,77 MHz, DMSO-d_6) : δ• 168.1; 164.8; 149.6; 141.7; 140.7; 129.9; 129.8; 128.7; 124.0; 120.1.

General procedures for preparation of compound **II**, and its characterisation

4-Amino-*N*-(4-carbamoylphenyl)benzamide (**II**) (experiment no. 12). *N*-(4-Carbamoylphenyl)-4-nitrobenzamide **I** (50 g), DMAC (400 mL) and Pd/C 3 % (water paste 1.5 g) were placed in a non-corrosive pressure autoclave ($V = 1$ L).

The reaction mixture was heated to 50 °C and hydrogen was introduced under the surface of the mixture (the pressure of hydrogen was constant at 1.5 MPa during the operation). The temperature of reaction mixture was maintained between 60 and 80 °C. When hydrogen consumption was constant for more than hour, reduction was terminated. The reaction mixture was filtered through a pressure filter to remove the catalyst and the isolated catalyst was washed with DMAC (50 mL, 55 °C). DMAC (280 g) was removed from the filtrates under reduced pressure (26 mBar). The content of the autoclave was cooled to 30 °C and distilled water (200 mL) was slowly added. The reaction mixture was stirred for another 1 h. Precipitated product **II** was isolated by filtration, washed with water (100 mL), and dried in oven (80 °C) to constant weight, to give 42.3 g of desired 4-amino-*N*-(4-carbamoylphenyl)benzamide **II** with purity higher than 98 % (HPLC).

White solid, yield 94.4 %. ^{1}H NMR (500,13 MHz, DMSO-d_6) : δ 10.06 (1H, s, NH–CO); 8.00 (1H, s, NH_2–CO); 7.84 (4H, m, H4, H5); 7.75 (2H, d, $J = 8{,}6$ Hz, H3); 7.26 (1H, s, NH_2–CO); 6.66 (2H, d, $J = 8{,}6$ Hz, H2); 5.80 (2H, s, NH_2). ^{13}C NMR (125,77 MHz, DMSO-d_6): δ 168.5; 166.3; 152.8; 142.9; 130.1; 130.0; 128.6; 121.1; 119.8; 113.2.

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