The current dye intermediate market – A cautionary tale and detective story; characterization and unambiguous synthesis of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole

Miloš Sedlák[a], Pavel Drabina[a], Illia Panov[a], Radka Kopřivová[a], Aleš Růžička[b] and Karel Ventura[c]

[a]Institute of Organic Chemistry and Technology, Faculty of Chemical Technology, University of Pardubice, nám. Čs. legií 565, 532 10 Pardubice, Czech Republic

[b]Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, nám. Čs. legií 565, 532 10 Pardubice, Czech Republic

[c]Department of Analytical Chemistry, Faculty of Chemical Technology, University of Pardubice, nám. Čs. legií 565, 532 10 Pardubice, Czech Republic

Abstract

Commercially delivered 2-chloro-5-methyl-1,4-phenylenediamine (1 metric ton) was not identical to the commonly used dye intermediate; it was found that the material was a pure but not yet described molecule. ^{1}H, ^{13}C NMR, MS, microanalysis and X-ray diffraction showed that the substance was in fact 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole. The manufacturer's mistake was explained by independent synthesis, which revealed that the key step was nitration of *N*-(5-chloro-2-methyl-4-nitrophenyl)acetamide giving *N*-(5-chloro-2-methyl-4,6-dinitrophenyl)acetamide, which requires Fe(III) catalysis. Subsequent reduction of *N*-(5-chloro-2-methyl-4,6-dinitrophenyl)acetamide with hydrogen and Pd/C catalyst exclusively gives *N*-(2,4-diamino-3-chloro-6-methylphenyl)acetamide. The ring closure reaction giving 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole takes place during the reduction with iron.

Keywords: Dye intermediates; 1*H*-Benzimidazoles; Heterocycles; Nitration; Ferric nitrate; X-ray diffraction

1. Introduction

The contemporary production of organic pigments [1] makes use of a variety of basic raw materials and intermediates. Indispensable components of such syntheses include substituted phenylenediamines [2]. For instance, 2-chloro-5-methyl-1,4-phenylenediamine [2] is a component in molecules of some azo pigments using 3-hydroxy-2-naphthoic acid amides as the coupling component [3] (**A**) or pigments based on substituted derivatives of anthraquinone [4] (**B**) (Fig. 1). Besides the syntheses of pigments, 2-chloro-5-methyl-1,4-phenylenediamine can also be used in the production of polyurea–polyurethane elastomers [5].

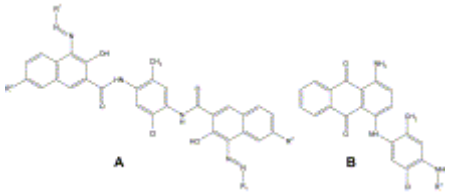


Fig. 1. Several pigments based on 2-chloro-5-methyl-1,4-phenylenediamine (A: R^1 = 1-nitro-2-naphthyl or a phenyl substituted with up to three substituents selected from H, Cl, Br, F, CH_3, OCH_3, CF_3, C(O)Oalkyl; R^2 = H, Cl, Br, F, CH_3, OCH_3, OC_2H_5, OC_3H_7; B: R^3 = $COCH_2Cl$, $COCH_2N(C_5H_5)_2$).

Until the early 1990s, manufacturers of organic dyes and pigments produced the necessary intermediates themselves, but extending world trade and the tightening of environmentalistic legislation in Europe have led to gradual transfer of this production to newly industrially developing countries outside Europe [1]. However, as documented in this article, trade in dye intermediates produced in developing countries may be associated with certain risks. Thus, a manufacturer of pigments ordered 1 metric ton of the dye intermediate, 2-chloro-5-methyl-1,4-phenylenediamine, from a supplier that will remain unnamed; the intermediate was designed for production of the above-mentioned pigments, but the material delivered by the supplier was not identical with the required dye intermediate. The substance was found to be a pure compound, not yet described in the literature. The aim of the present work was to establish the chemical structure of the substance and to prepare, by independent synthesis, a compound identical with the delivered sample. Moreover, a reconstruction of the synthesis is intended to be used in discussion and potential explanation of the supplier's mistake as well as evaluation of possible applications of this new compound.

2. Experimental

2.1. General

The starting *N*-(5-chloro-2-methylphenyl)acetamide (**1**) was purchased from Synthesia Comp. (the Czech Republic) and other chemicals were purchased from Sigma–Aldrich. The given melting points were not corrected. Structures of the products prepared were verified by means of ^{1}H and ^{13}C NMR. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 instrument. The chemical shifts δ are referenced to the solvent residual peaks δ (DMSO-d_6) = 2.55 ppm (^{1}H) and 39.6 ppm (^{13}C). The coupling constants J are given in Hz. The mass spectra were recorded on an Agilent Technologies Comp. gas chromatograph 6890N with a mass detector 5973 Network for samples dissolved in either ether or acetone. The microanalyses were performed on an apparatus of FISONS Instruments, EA 1108 CHN.

2.2. Crystallography

The X-ray data for colorless crystals of **4** were obtained at 150 K using Oxford Cryostream low-temperature device on a Nonius Kappa CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å), a graphite monochromator, and the $\Phi$and χ scan mode. Data reductions were performed with DENZO-SMN [6]. The absorption was corrected by integration methods [7]. Structures were solved by direct methods (Sir92) [8] and refined by full matrix least-square based on F^2 (SHELXL-97) [9]. Hydrogen atoms were mostly localized on a difference Fourier map, however, to ensure uniformity of treatment of crystal, all hydrogen were recalculated into idealized positions (riding model) and assigned temperature factors H_{iso}(H) = 1.2 U_{eq} (pivot atom) or of 1.5U_{eq} for the methyl moiety with C–H = 0.96, 0.97, and 0.93 Å for methyl, methylene and hydrogen atoms in aromatic ring, respectively, 0.86 and 0.82 Å for N–H and O–H groups, respectively. Hydrogen atoms connected to water molecules were localized

on a difference Fourier map and where possible the best orientation of H atoms for a connection with an acceptor atom chosen.

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 690 533for **4**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EY, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

2.3. *N*-(5-Chloro-2-methyl-4-nitrophenyl)acetamide (2)

A cooled solution (5 °C) of *N*-(5-chloro-2-methylphenyl)acetamide (**1**) (18.4 g; 0.1 mol) in 98% sulfuric acid (138 g; Fe ≤ 0.2 ppm) was treated with anhydrous nitric acid (7.3 g; 0.12 mol; Fe ≤ 0.2 ppm) added within 10 min. After 8 h stirring at the temperature of 5 °C, the reaction mixture was poured onto 300 g ice. The separated solid was collected by filtration, washed with water (100 mL), with a solution of $NaHCO_3$ (5%, 100 mL), and again with water (500 mL). The crude product obtained after drying (21.6 g) had the following composition (GC–MS): 96% acetamide **2**, 3% *N*-(5-chloro-2-methyl-6-nitrophenyl)acetamide (**5**), and 1% *N*-(5-chloro-2-methyl-4,6-dinitrophenyl)acetamide (**3**). The yield of pure product after recrystallization from ethanol was 18.4 g (81%), m.p. 181–182 °C. ^{1}H NMR: *δ* 2.21(s, 3H, CH_3), 2.34 (s, 3H, CH_3), 8.00 (s, 1H, Ar), 8.17 (s, 1H, Ar), 9.56 (bs, 1H, CONH); ^{13}C NMR: *δ* 17.3, 23.9, 123.4, 124.0, 127.8, 129.4, 141.8, 142.0, 169.5; EI-MS: *m*/*z* 228, 213, 198, 186, 170, 156, 140, 128, 104, 77, 43. Anal. calcd. for $C_9H_9ClN_2O_3$ (228.63): C, 47.28; H, 3.97; Cl, 15.51; N, 12.25. Found: C, 47.36; H, 4.09; Cl, 15.23; N, 15.63.

2.4. *N*-(5-Chloro-2-methyl-4,6-dinitrophenyl)acetamide (3)

A cooled solution (5 °C) of *N*-(5-chloro-2-methylphenyl)acetamide (**1**) (18.4 g; 0.1 mol) in 98% sulfuric acid (138 g) was treated with anhydrous nitric acid (12.6 g; 0.2 mol) added within 10 min. After 8 h stirring at the temperature of 5 °C, the reaction mixture was treated with a mixture of $Fe(NO_3)_3{\cdot}9H_2O$ (2 g; 5 mmol) and fuming sulfuric acid (5.5 g; 45 mmol SO_3) added within 15 min. After another 8 h stirring (5 °C), the reaction mixture was poured onto 300 g ice. The separated solid was collected by filtration, washed with water (100 mL), with a solution of $NaHCO_3$ (5%, 100 mL), and again with water (500 mL). The yield after recrystallization from ethanol was 24.3 g (89%), m.p. 202–204 °C. ^{1}H NMR: *δ* 2.07 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 8.40 (s, 1H, Ar), 10.31 (bs, 1H, CONH); ^{13}C NMR: *δ* 17.8, 22.4, 115.8, 128.7, 134.0, 139.3, 145.4,147.7, 169.1; EI-MS: *m*/*z* 273, 255, 243, 231, 201, 155, 139, 128, 104, 77, 43. Anal. calcd. for $C_9H_8ClN_3O_5$ (273.63): C, 39.50; H, 2.95; Cl, 12.96; N, 15.36. Found: C, 39.56; H, 2.82; Cl, 12.89; N, 15.43.

2.5. 5-Amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole sulfate (4) (reduction with iron, 3 → 4)

A mixture of *N*-(5-chloro-2-methyl-4,6-dinitrophenyl)acetamide (**3**) (5.5 g; 20 mmol), iron powder (12 g; 0.2 mol), and hydrochloric acid solution (10%, 80 mL) was stirred and refluxed for 3 h. After cooling, the reaction mixture was diluted with methanol (100 mL) and filtered. The filtrate was evaporated in vacuum, and the evaporation residue was dissolved in sulfuric acid (25%, 250 mL); the mixture obtained was boiled for a short period of time and hot filtered. The filtrate was concentrated in vacuum, cooled, and the separated solid was collected by filtration and recrystallized from water. Yield 8.1 g (84%). ^{1}H NMR: *δ* 2.41 (s, 3H,CH_3), 2.65 (s, 3H, CH_3), 5.63–6.41 (bs, 2H, NH) 6.71 (s, 1H, Ar); ^{13}C NMR: 13.0, 16.4, 97.2, 113.9, 122.9, 125.7, 132.3, 141.9, 149.6; EI-MS: *m*/*z* 195, 180, 161, 119. Anal. calcd for $C_9H_{10}ClN_3{\cdot}1/2H_2SO_4$ (244.69): C, 44.18; H, 4.53; Cl, 14.49; N, 17.17; S, 6.55. Found: C, 44.15; H, 4.62; Cl, 14.67; N, 17.33; S, 6.63.

2.6. *N*-(2,4-Diamino-3-chloro-6-methylphenyl)acetamide (6) (catalytic reduction, 3 → 6)

A solution of *N*-(5-chloro-2-methyl-4,6-dinitrophenyl)acetamide (**3**) (2.7 g; 10 mmol) in ethyl acetate (150 mL) with added Pd/C (5%; 0.1 g) was hydrogenated under a mild overpressure of hydrogen (ca 5 kPa) for a period of 3 h

at the temperature of 25 °C. Then the mixture was filtered and the filtrate was concentrated to give yellowish crystalline product which gradually turned brown. Yield 0.78 g (36%). EI-MS: *m*/*z* 213, 201, 167, 155, 119, 43.

2.7. 5-Amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole sulfate (4) (ring closure reaction 6 → 4)

A mixture of *N*-(2,4-diamino-3-chloro-6-methylphenyl)acetamide (**6**) (0.43 g; 2 mmol) and sulfuric acid (10%, 15 mL) was heated at the temperature of 80 °C. After 10 min, the reaction mixture was hot filtered with addition of charcoal, the filtrate was cooled, and the separated solid was collected by filtration and dried. Yield 0.16 g (33%); the product was identical with that of the previous experiment.

2.8. 7,4-[(4-Chloro-2,7-dimethyl-1-(1*H*)-benzimidazol-5-yl)azo]-3-hydroxy-2-naphthoic acid (7)

A solution of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole sulfate (**4**) (1 g; 4 mmol) in hydrochloric acid (30%, 3.5 mL) was cooled to the temperature of 0 °C and treated with a solution of sodium nitrite (0.29 g; 4 mmol) in water (1 mL) added drop by drop. After 10 min, the obtained solution of diazonium salt was added dropwise to a solution of 3-hydroxy-2-naphthoic acid (0.77 g; 4 mmol) in a solution of sodium hydroxide (0.66 g; 16 mmol) in water (20 mL) with added ice (10 g). After 1 h stirring, the reaction mixture was filtered. The obtained solid was washed with hydrochloric acid (1:1) and with water, dried and recrystallized from dimethylformamide. Yield 0.88 g (51%), m.p. >300 °C, decomp. ^{1}H NMR: δ 2.59 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 7.57 (t, 1H, *J* 7.2, ArH), 7.80 (t, 1H, *J* 10.7, ArH), 7.91 (s, 1H, Ar), 8.04 (d, 1H, *J* 7.2, ArH), 8.65 (s, 1H, ArH), 8.69 (d, 1H, *J* 8.2, ArH), 12.88 (bs, 2H, NH and OH), 16.75 (bs, 1H, COOH). Anal. calcd for $C_{20}H_{15}ClN_4O_3$ (394.81): C, 60.84; H, 3.83; Cl, 8,98; N, 14.19. Found: C, 60.59; H, 3.63; Cl, 9.21; N, 14.41. UV–vis (0.1 M CH_3ONa/CH_3OH) λ_{max}/nm (log ε) 438 (4.28), 496 (4.41); (0.05 M HCl/CH_3OH); λ_{max}/nm (log ε) 327 (3.93), 512 (4.37).

2.9. Study of the effect of ferric ion in the nitration mixture upon the ratio of nitration products 1 → 2 + 5

Experiment A. A mixture of *N*-(5-chloro-2-methylphenyl)acetamide (**1**) (1.84 g; 10 mmol), anhydrous sulfuric acid (7.5 g), anhydrous nitric acid (0.7 g; 10 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (0.4 g; 1 mmol), and fuming sulfuric acid (1.1 g; 9 mmol SO_3) was kept at the temperature of 5 °C.

Experiment B. A mixture of *N*-(5-chloro-2-methylphenyl)acetamide (**1**) (1.84 g; 10 mmol), anhydrous sulfuric acid (1.1 g), anhydrous nitric acid (0.7 g; 10 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (2.0 g; 5 mmol), and fuming sulfuric acid (5.5 g; 45 mmol SO_3) was kept at the temperature of 5 °C. After 24 h, samples of the reaction mixture were taken and analyzed by means of GC–MS (Table 1).

2.10. Study of the effect of ferric ion upon the nitration rate 2 → 3

Experiment C. A mixture of *N*-(5-chloro-2-methyl-4-nitrophenyl)acetamide (**2**) (2.28 g; 10 mmol), anhydrous sulfuric acid (7.5 g), anhydrous nitric acid (0.7 g; 10 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (0.4 g; 1 mmol), and fuming sulfuric acid (1.1 g; 9 mmol SO_3) was kept at the temperature of 5 °C.

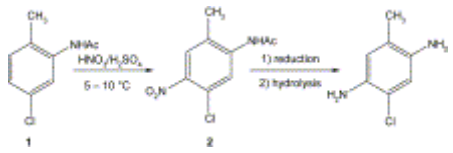
Experiment D. A mixture of *N*-(5-chloro-2-methyl-4-nitrophenyl)acetamide (**2**) (2.28 g; 10 mmol), anhydrous sulfuric acid (1.1 g), anhydrous nitric acid (0.7 g; 10 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (2.0 g; 5 mmol), and fuming sulfuric acid (5.5 g; 45 mmol SO_3) was kept at the temperature of 5 °C.

At definite time intervals, samples were taken from the reaction mixtures and analyzed by means of GC–MS (Table 2).

3. Results and discussion

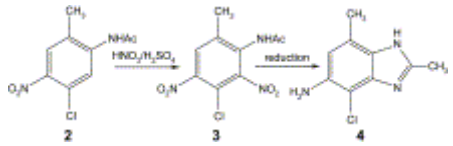
The supplied unknown substance is a white-grey amorphous powder which decomposes without melting above 360 °C. It is readily soluble in hot water, sparingly soluble in cold water. It is marginally soluble in most organic solvents (methanol, acetone, ethyl acetate, THF, toluene), both hot and cold. It dissolves in a solution of sodium

hydroxide, and the solution obtained is precipitated by addition of barium hydroxide. The empirical formula obtained by microanalysis is $(C_{18}H_{22}Cl_2N_6O_4S)_n$. The above findings indicate that the substance is a sulfate of an organic base. After subtracting the formula of sulfuric acid from the above empirical formula, the following empirical formula results $(C_{18}H_{20}Cl_2N_6)_n$. The GC–MS analysis of dichloromethane extract of the hydroxide solution of the unknown substance showed a single component with molecular peak *M* = 195, which means that the molecular formula of the free base corresponding to this peak is $C_9H_{10}ClN_3$ (*n* = 1/2). The ^{1}H NMR spectrum of the unknown substance shows only three signals for different H atoms, namely 2 × CH_3 (2.41 ppm and 2.65 ppm), a broadened signal in the region of 5.6–6.4 ppm, and one aromatic signal Ar–H at 6.71 ppm. The ^{13}C NMR spectrum shows signals for carbon atoms of 2 × CH_3 (13.0 ppm and 16.4 ppm), six quaternary carbon atoms in the aromatic region: 97.2, 122.9, 125.7, 132.3, 141.9, 149.6, and one CH signal at 113.9 ppm. However, according to Beilstein and Chemical Abstract databases the characteristics found do not correspond to any compound described so far. If we accept the presumption that the manufacturer's goal was to produce 2-chloro-5-methyl-1,4-phenylenediamine ($C_7H_9ClN_2$), then an additional nitrogen atom must have been introduced into one of the intermediates at some stage during the synthesis. One of the methods of production of 2-chloro-5-methyl-1,4-phenylenediamine starts from *N*-(5-chloro-2-methylphenyl)acetamide (**1**), which is nitrated to give **2** and then reduced and subsequently hydrolysed to give the required product [10], [10a] and [10b] (Scheme 1).



Scheme 1. Production of 2-chloro-5-methyl-1,4-phenylenediamine from *N*-(5-chloro-2-methylphenyl)acetamide (**1**).

The most likely source of the additional nitrogen atom in the molecule is the subsequent nitration of **2** to give dinitro compound **3**. If the latter was reduced, then the intermediate formed could be presumed to undergo subsequent ring closure reaction leading to formation of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**) (Scheme 2).



Scheme 2. Presumed formation of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**).

The found molecular mass of the unknown sample corresponds to the molecular mass of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**) (*M* = 195, $C_9H_{10}ClN_3$), which means that sulfate of benzimidazole **4** was delivered instead of the ordered 2-chloro-5-methyl-1,4-phenylenediamine. This conclusion is supported by all the physico-chemical characteristics including the ^{1}H and ^{13}C NMR spectra. Slow crystallization of the original sample from aqueous dimethylformamide gave a single crystal, whose X-ray diffraction confirmed the structure of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**) (Fig. 2). The picture shows that the crystal cell contains two molecules

of **4**, together with one sulfate ion and eight molecules of water ($2C_9H_{10}ClN_3 \cdot H_2SO_4 \cdot 8H_2O$). The benzimidazole **4** crystallizes in triclinic space group *P*-1 and two geometrically independent heterocyclic fragments are present. The cationic character of the heterocycle is compensated by sulfate anion and eight water molecules are present in the crystal unit cell as well. Views of **4** (Fig. 2 and Fig. 3) show almost planar arrangement of heterocyclic rings which are connected via numerous H-bonds.

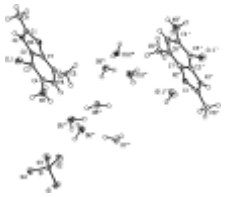


Fig. 2. ORTEP-diagram of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**) ($2C_9H_{10}ClN_3 \cdot H_2SO_4 \cdot 8H_2O$).

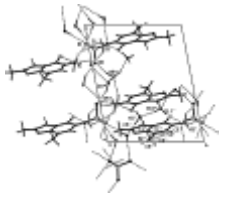


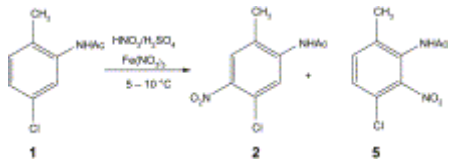
Fig. 3. View of H-bonding in 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**).

Distances C1–N2, C1–N1, C1′–N2′ and C1′–N1′ (see Fig. 2, [12]) in compound **4** reveal typical shortening attributable to a delocalization of π-electron density or double bond character with respect to the standard single bond $N(sp^3)\ldots C(sp^2)$ distance of 1.44 Å (Ref. [11]). Both C1–N1 and C1–N2 distances are very close in value and one hydrogen atom was placed to nitrogen atoms N1 and three hydrogen atoms to each of N3 to form positive charge. On the other hand, there is an alternative description of the structure, where one hydrogen is placed to each N1 and N2, respectively, and two hydrogen atoms to each N3 atom.

Another aim of this work was to verify the synthesis of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**) and thus identify the cause of its formation. According to Scheme 2, acetamide **3** is the key intermediate leading to benzimidazole **4**. Mono-nitro derivative **2** was prepared according to the literature [6] from acetamide **1** by nitration with the classical nitration mixture (H_2SO_4/HNO_3; 5 °C; 2 h) in a high yield (81%). The content of the isomeric nitro compound **5** was ca 3% under the conditions used. The subsequent step was designed to introduce the second nitro group into the molecule of substance **2**. However, the nitration giving derivative **3** proceeds very slowly under standard nitrating conditions. The second nitro group is not introduced (>5%) even after increasing twofold amount of nitric acid and prolongation of reaction time to 48 h (5–10 °C). In further experiments, reaction temperature was gradually increased to 30, 60 and 80 °C. Under these conditions, the nitration of amide **1** (with 2.2 equiv. HNO_3) gave decreasing yields of mono-nitro derivative **2** and increasing amounts of resinous side products. Decomposition and formation of these resinous products also took place in the case of adopting derivative **2** (with 1.1 equiv. HNO_3) as the starting substance. These results show that the manufacturer's mistake did not lie in exceeding the temperature, but the reason must lie in another factor. As this case concerns a medium-scale production of relatively cheap intermediate, application of another nitration agent (such as NO_2BF_4) which could lead to formation of derivative **3** cannot be presumed. Most probably the manufacturer used the

classical nitration mixture. The only difference between our experiments and the manufacturer's procedure can be in the quality of starting compounds and the apparatus used. In our case the apparatus was a jacketed glass reactor. The manufacturer probably used an enamelled reactor. It is generally known that in industrial enamelled reactors the enamel coating is damaged after some time, and iron ions are released into the reaction mixture. It is also known from the literature [13], [13a], [13b] and [13c] that ferric ions act in some cases as selective catalysts in nitrations of benzene derivatives with various substituents. In order to prove this hypothesis, we carried out the nitration **1** → **2** and then added into the nitration mixture another equivalent of nitric acid and the solution of $Fe(NO_3)_3 \cdot 9H_2O$ (5 mol%, relative to the starting substrate **1**) in fuming sulfuric acid. The following analysis of the reaction mixture showed that the consecutive nitration **2** → **3** began to take place and was finished after 8 h (complete conversion of mono-nitro derivative **2**), the yield of isolated dinitro derivative **3** being 89%. Our findings suggest that the manufacturer made a mistake in weighing the nitric acid, and due to a damaged reactor or contamination of starting materials with ferric ions the consecutive nitration **2** → **3** was significantly accelerated.

Further experiments were designed to test the effect of ferric ion upon the regioselectivity of the nitration **1** → **2** + **5** (Scheme 3).



Scheme 3. Study of effect of ferric ion upon regioselectivity of nitration of *N*-(5-chloro-2-methylphenyl)acetamide (**1**).

Table 1 shows that an increased amount of ferric ions in the reaction mixture increases the proportion of "*ortho*" product **5**. However, any further increase in proportion of derivative **5** in the reaction mixture is limited by restricted solubility of ferric nitrate. Table 2 summarises the effect of ferric ion upon the rate of nitration **2** → **3** (Scheme 2).

Table 1.

Effect of content of ferric ion in nitration mixture upon the ratio of nitration products **1** → **2** + **5**

Experiment	Fe(III) (mol%)[a]	2 (%)[b]	5 (%)[b]
A	10	92	8
B	50	80	20

[a] Relative to starting substrate **1**.

[b] The content of products **2** and **5** was determined by GC–MS after 24 h.

Table 2.

Effect of content of ferric ion in nitration mixture upon rate of nitration **2** → **3**

Experiment Fe(III) (mol%)[a]	Time (min)	15	60	90	120	300
C 10	**2** (%)[b]	82	52	40	34	10
	3 (%)[b]	18	48	60	66	90

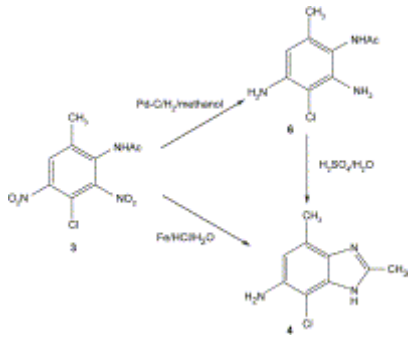
Experiment Fe(III) (mol%)[a]	Time (min)	15	60	90	120	300
D 50	**2** (%)[b]	70	11	5	3	1
	3 (%)[b]	30	89	95	97	99

[a] Relative to starting substrate **2**.

[b] The content of products **2** and **3** was determined by GC–MS.

The results given in Table 2 show that with the addition of 10 mol% Fe(III) to the starting substrate **2** the 90% conversion is attained after 5 h, and with the addition of 50 mol% Fe(III) the same conversion is already attained after 1 h.

The next key step consisted in verification of the reaction conditions during reduction of *N*-(5-chloro-2-methyl-4,6-dinitrophenyl)acetamide (**3**). It was found that hydrogenation of acetamide **3** catalyzed with Pd/C only gives *N*-(2,4-diamino-3-chloro-6-methylphenyl)acetamide (**6**). However, the acetamide **6** prepared was only characterized by means of GC–MS, because it is very unstable and undergoes fast oxidation giving mixtures of products that are difficult to analyze. When acetamide **6** was transferred into solution in diluted sulfuric acid immediately after its isolation, it underwent acid-catalyzed ring closure reaction giving 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole sulfate (**4**). The classical Béchamp's reduction [14], [14a] and [14b] of acetamide **3** with iron is accompanied by the acid-catalyzed ring closure reaction directly in the acidic reduction medium, hence the only isolated product was benzimidazole **4** (Scheme 4).



Scheme 4. Study of effect of reaction conditions during reduction of *N*-(5-chloro-2-methyl-4,6-dinitrophenyl)acetamide (**3**).

The last aim of our work was to test the applicability of 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**). With regard to its potential application for the synthesis of pigments, benzimidazole **4** was diazotized and coupled with 3-hydroxy-2-naphthoic acid to give this azo dyestuff **7**. The low field shift (16.75 ppm) of the =N–NH proton indicates that the azo dyestuff **7** exists as the hydrazone tautomer so enabling the carboxyl proton to be either bonded to the keto-carbonyl group (formula A, Fig. 4) [15], [15a], [15b], [15c] and [15d] or the carboxyl proton is moved to imidazole N afford the broad signal at 12.88 ppm (Fig. 4, formula B). The azo-hydrazo tautomerism would be better established by measuring of C=O shift in ^{13}C NMR spectra and shift of NH in ^{15}N NMR [15]. In our case we could not measure these shifts due to the poor solubility of the dyestuff **7**, which exhibits the typical insolubility characteristics of pigments. After recrystallization of the crude dyestuff from dimethylformamide, the dyestuff **7** was isolated in the form of fine dark-brown needles.

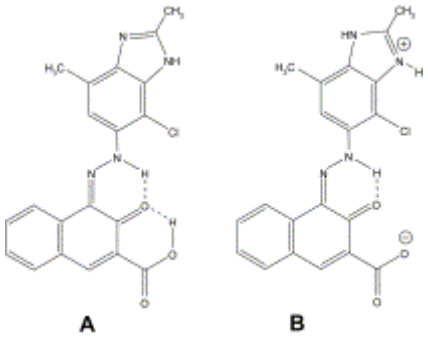


Fig. 4. Possible structural formulas of azo dyestuff **7**.

4. Conclusion

It was found that instead of the declared 2-chloro-5-methyl-1,4-phenylenediamine the manufacturer delivered 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**). The manufacturer's mistake consisted of using a larger amount of nitric acid used during preparation of **1**, resulting in the dinitration giving **3**. However, the use of excess of nitric acid alone or with prolonged reaction time and/or increased reaction temperature does not lead to the dinitration. The introduction of the second nitro group resulted from contamination of the reaction mixture with Fe(III) ions. These impurities were either present in the starting materials or were released into the reaction mixture from enamelled iron reactor with a damaged surface. Without catalysis by Fe(III) ions, the nitration **2** to dinitro compound **3** practically does not take place. The benzimidazole **4** is formed during the reduction **3** with iron. The given facts indicate that the supplier/manufacturer does not carry out any inter-operation checks and final analyzes. In addition, it was found that benzimidazole **4** can be diazotized under usual reaction conditions, and the obtained diazonium salt can be used for preparation of pigments intermediates. The benzimidazole **4** can also serve as a starting material for preparation of a variety of substituted benzimidazoles, which may have interesting biological properties [16].

Acknowledgement

The authors acknowledge Dr. Tomáš Weidlich for valuable discussion and the financial support from the MSMT-CR, MSM 002 162 7501.

References

[1] M.D. Hattori In: A. Sieidel, Editor, *Kirk-Othmer encyclopaedia of chemical technology* **vol. 9**, Wiley-Interscience, New York (2005), p. 265.

[2] R.A. Smiley In: B. Elners, S. Hawkins and G. Schluz, Editors (5th ed.), *Ullman's encyclopaedia of industrial chemistry* **vol. A19**, VCH-Weinheim (1991), p. 405.

[3] O. Tambieva, A.V. Khronov, R.K. Petrova, O.G. Ugol'nikov, R.K.-G. Feizulova and E.S. Fefilova, *RU Appl. 2001-12684, Chem Abstr* **140** (2003), p. 305379.

[4] I. Seben, I.D. Popescu, A. Ganea and I. Calota, *Confectii Texile* **35** (1984), p. 368.
Chem Abstr **102** (1985), p. 205402.

[5] Y. Saito, T. Watabe and N. Tunii, *JP 88-63596, Chem Abstr* **111** (1989), p. 116636.

[6] Z. Otwinowski and W. Minor, *Methods Enzymol* **276** (1997), p. 307.

[7] P. Coppens In: F.R. Ahmed, S.R. Hall and C.P. Huber, Editors, *Crystallographic computing*, Munksgaard, Copenhagen (1970), p. 255.

[8] A. Altomare, G. Cascarano, C. Giacovazzo and A. Guagliardi, *J Appl Crystallogr* **26** (1993), p. 343.

[9] G.M. Sheldrick, SHELXL-97, University of Göttingen, Göttingen (1997).

[10] (a)J. Kenner, C.W. Tod and E. Witham, *J Chem Soc* **127** (1925), p. 2343.
(b)J. Terč, *Chem Prům* **26** (1976), p. 641.
Chem Abstr **86** (1977), p. 155286.

[11] F.H. Allen, O. Kennard, D.G. Watson, L. Brammer, A.G. Orpen and R. Taylor, *J Chem Soc Perkin Trans* **2** (1987), p. S1.

[12] Crystallographic data for 5-amino-4-chloro-2,7-dimethyl-1*H*-benzimidazole (**4**): crystal system: triclinic; space group: *P*-1; *a* (Å): 10.2210(7); *b* (Å): 10.5600(4); *c* (Å): 13.2480(8); *α*(°): 99.978(5); *β* (°): 101364(5); *γ* (°): 94.278(5); *Z* = 2; *V*(Å): 1371.89(14); D_c/g cm^{-3}: 1.1534; crystal size (mm) 0.140 × 0.095 × 0.078; crystal shape: colorless block; *μ* (mm^{-1}): 0.383; *F* (000): 668; *h*;*k*;*l* range: −13,13;−13, 13; −17, 17; *θ* range/°: 1;27.5; reflection measured: 24,389; independent $R_{int} = \Sigma|F_o^2 - F_{o,mean}^2|/\Sigma F_o^2$): 6250(0.0898); observed [$I > 2\sigma(I)$] > 4055; parameters refined 352; max/min *δ ρ*/eÅ^{-3}: 0456/−0.485; GOF ($[\Sigma(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{1/2}$ for all data): 1.105; *R*/*wR* ($R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for observed data, $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{1/2}$ for all data): 0.0771/0.1572.

[13] (a)T. Mishra and K.M. Parida, *J Mol Catal A Chem* **121** (1997), p. 91.
(b)R.R. Bak and A. Smallridge, *Tetrahedron Lett* **42** (2001), p. 6767.
(c)V. Anuradha, P.V. Srinivas, P. Aparna and J.M. Rao, *Tetrahedron Lett* **47** (2006), p. 4933.

[14] (a)A. Béchamp, *J Ann Chim Phys* **42** (1854), p. 186.
(b)A. Courtin, *Helv Chim Acta* **62** (1980), p. 2280.

[15] (a)A. Lyčka and D. Šnobl, *Collect Czech Chem Commun* **46** (1981), p. 892.
(b)A. Lyčka and V. Macháček, *Dyes Pigments* **7** (1986), p. 171.
(c)A. Lyčka, M. Nečas, J. Jirman, J. Straka and B. Schneider, *Collect Czech Chem Commun* **55** (1990), p. 193.
(d)R.M. Claramunt, C. López, M.D. Santa María, D. Sanz and J. Elguero, *Prog Nucl Magn Reson Spectrosc* **49** (2006), p. 169.

[16] B. Pete, B. Szokol and L. Töke, *J Heterocycl Chem* **45** (2008), p. 343.