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A PRACTICAL SYNTHESIS OF 2,4-DICHLORO-3-METHYL-6-NITROPHENOL

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ABSTRACT: 2,4-Dichloro-3-methyl-6-nitrophenol **2** was prepared by KOH/H_2O hydrolysis of a product mixture obtained from chlorination of p-nitrotoluene in the presence of a phase transfer catalyst. A 95-99% yield of **2** based on 2,3,6-trichloro-4-nitrotoluene, **4** (major chlorination product) was achieved in >95% purity.

2,4-Dichloro-3-methyl-6-aminophenol (**1**, commercial name **Konica A**) is a very useful color photographic chemical providing dye images with good stability and excellent balance in resistance to light, heat and moisture.[1] It is made by hydrogenation of 2,4-dichloro-3-methyl-6-nitrophenol, **2**, with H_2/Pt. The synthesis of 2,4-dichloro-3-methyl-6-nitrophenol, **2**, from 4-chloro-3-methylphenol or other phenols had been reported.[2-7] However, the reported routes have many disadvantages. For example, only low overall yields for the multi-step reactions were achieved and difficult byproduct and impurity separation steps were necessary.[1,8,9] Synthesis of 2,4-dichloro-3-alkyl-6-nitrophenols (where alkyl=C_2-C_6 chains) from the corresponding 1-alkyl-4-nitrobenzenes was effected by chlorination

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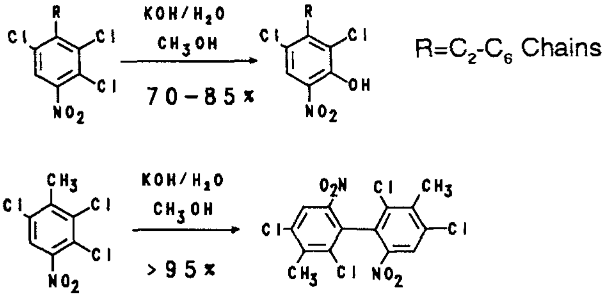
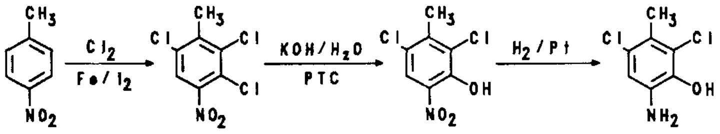


Scheme 1. Hydrolysis of 1,2,5-trichloro-4-alkylnitrobenzenes

followed by hydrolysis with potassium hydroxide in aqueous methanol.[1,9] The hydrolysis products from 2,3,5-trichloro-4-alkylnitrobenzenes, where the alkyl groups are C_2-C_6 chains, were the desired 2,4-dichloro-3-alkyl-6-nitrophenols in high (70-85%) yields (Scheme 1).[1] This convenient route, however, did not work if the 3-alkyl function was a methyl group.[1] Hydrolysis of 2,3,6-trichloro-4-nitrotoluene, **4**, produced almost no **2**. Instead, dimerization occurred in >95% yield to give the biphenyl derivative shown in Scheme 1.[1] Therefore, a practical, high yield synthesis of **2**, hence **1**, has not appeared previously in the literature.

Herein the synthesis of 2,4-dichloro-3-methyl-6-nitrophenol, **2**, by chlorination of *p*-nitrotoluene, **3**, to give 2,3,6-trichloro-4-nitrotoluene, **4**, followed by hydrolysis of **4** with KOH/H_2O in the presence of a phase transfer catalyst (PTC) is reported. PTCs such as poly(ethylene glycol) (PEG), tetrabutylammonium chloride (TBA), or benzyl-trimethylammonium chloride (BTA) were used. This route gave the title compound, **2**, in a high yield (overall yield 85% based on *p*-nitrotoluene) and purity (>95%), permitting a practical and improved synthesis of **1** (see Scheme 2).

The heterogeneous phase transfer catalyzed hydrolysis of **4** to **2** with KOH/H_2O is also compared to the hydrolysis of **4** to **2** with KOH/H_2O in several homogeneous solution systems.



3 4 2 1

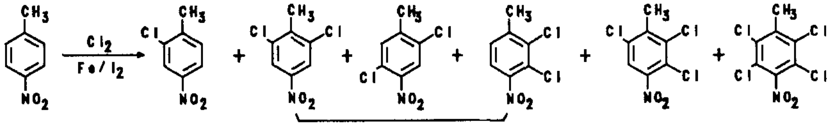
Scheme 2. Synthesis of 2,4-dichloro-3-methyl-6-aminophenol (**1**)

I. Preparation of 2,3,6-trichloro-4-nitrotoluene (4):

The 2,3,6-trichloro-4-nitrotoluene, **4**, was prepared by the chlorination of *p*-nitrotoluene (PNT) with chlorine gas in the presence of iron powder and iodine. The components of the chlorination reaction were characterized by GC and GC-MS. Four products were present in the reaction mixture. The structures for these products are shown in Scheme 3. By varying the reaction time and temperature 89-90% yields of **4** were achieved.

I-1. Effect of reaction time on composition of products:

The dependence of product composition on the reaction time in the chlorination at 40 °C is shown in Figure 1. If the reaction was stopped at 4 hrs., the percentage of product **4** in the chlorination mixture was over 82% by GC. However, if the reaction was stopped at 2 hrs., the percentage of other products, notably monochloro-4-nitrotoluene, in the mixture was 98%. None of the desired **4** was present. At 3 hrs. the product composition was 75% of 2-chloro-*p*-nitrotoluene, 22% of dichloro-*p*-



PNT 1Cl-PNT 2Cl-PNT **4** 4Cl-PNT

Scheme 3. The chlorination of 4-nitrotoluene (PNT)

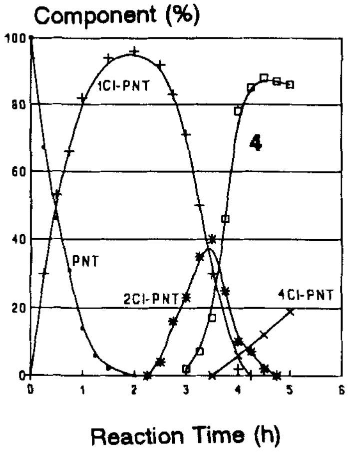


Fig. 1. Chlorination of PNT at 40 °C

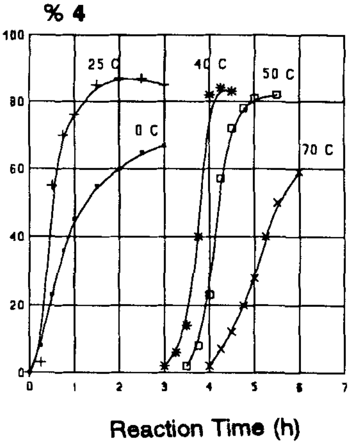


Fig. 2. Effect of temperature on chlorination yield.

nitrotoluene and 3% of **4**; at 5 hrs., the product composition was 80% of **4** and 19% of tetrachloro-*p*-nitrotoluene. Thus, it is necessary to control reaction time to obtain the desired product **4** in high yield and high purity.

I-2. Effect of temperature on product composition:

The dependence of product composition on reaction time in the chlorination of *p*-nitrotoluene at 0 °C, 25 °C, 40 °C, 50 °C, and 70 °C, respectively, was studied (see results in Figure 2). It is evident that the chlorination rate exhibits long induction periods with increasing temperature. To obtain a high yield of **4**, the reaction would have to be carried out for 4 hrs. at 40 °C, for 5 hrs. at 50 °C, or more than 6 hrs. at 70 °C, respectively. In addition, an examination of the slopes of the curves in Figure 2 shows that the rate decreases going from 40 to 70 °C possibly due to a drop in chlorine solubility. When the temperature was lowed to 0 °C the chlorination rate also slowed. The most suitable temperature range to obtain high yields of **4** at high purity in this chlorination was 25-50 °C.

Table 1. Hydrolysis of **4** with KOH/H_2O in heterogeneous PTC systems

RXN	**4** (g)	Solvent & PTC* (mL) (g)	KOH (g)	H_2O (mL)	Temp (°C)	Time (h)	Yield (%)
1	10	toluene 20; PEG, 3.3g	10	5	85	4	99
2	10	DCE, 30; PEG, 2.2g	10	6	85	5	95
3	10	heptane 30; PEG, 2.2g	10	6	85	4	95
4	10	hexane 30; PEG, 2.2g	10	6	85	4	98
5	10	skelly B 30; PEG, 2.2g	10	6	85	4	75
6	4	toluene 30; TBA, 0.9g	10	10	85	4	94
7	4	toluene 100; BTA,0.4g	10	10	85	4	55

* PTC (Phase-transfer-catalysts): PEG-200, poly(ethylene glycol), molecular weight 200; TBA, tetrabutylammonium chloride; BTA, benzyl-trimethylammonium chloride.

** Solvents: DCE, dichloroethane; skelly B, petroleum ether, bp.60-90 °C.

II. Preparation of 2,4-dichloro-3-methyl-6-nitrophenol, 2, from 2,3,6-trichloro-4-nitrotoluene, 4:

II-1. Heterogenous hydrolysis of 2,3,6-trichloro-4-nitrotoluene, 4, with KOH/H_2O catalyzed by PTC:

2,4-Dichloro-3-methyl-6-nitrophenol, **2**, was synthesized by the hydrolysis of **4** using KOH/H_2O in toluene, benzene, chloroform, carbon tetrachloride or other solvents in the presence of a PTC such as PEG or a quaternary ammonium salt. The results are shown in Figure 3 and are summarized in Table 1. Methanol, which had been used in the successful hydrolysis of 2,3,6-trichloro-4-nitroethylbenzene to 2,4-dichloro-3-ethyl-6-nitrophenol[1] (Scheme 1), could not be used in the hydrolysis of **4** to **2**.

It is evident from Table 1 that very high yields (95-99%) of 2,4-dichloro-3-methyl-6-nitrophenol, **2**, were obtained by the KOH/H_2O hydrolysis of **4** in the presence of phase-transfer-catalysts. Many organic solvents such as toluene, benzene, xylene, chloroform, 1,2-dichloroethane, hexane, heptane, cyclohexane, petroleum ethers, etc., may be used. The use of phase-transfer-catalysts in the KOH/H_2O hydrolysis of the crude chlorination mixture (containing 89% **4**, 8% tetrachloro-PNT and 2% monochloro-PNT) greatly increased both the yield and reactor utility. Furthermore, the resulting compound **2** was sufficiently pure to be used directly in the subsequent nitro group reduction to Konica A, **1**.

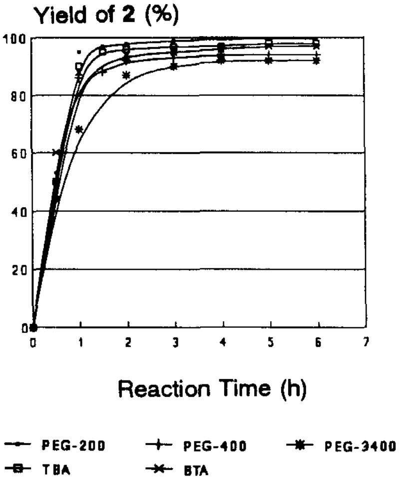


Fig. 3. Heterogeneous hydrolysis of **4** to **2**

The relatively high purity of **2** achieved in this process was due to the resistance of dichloro-, tetrachloro-, and traces of monochloro-*p*-nitrotoluene to hydrolyze. Therefore, these three compounds remained in the organic phase while the desired hydrolysis product, **2**, precipitated as a phenol salt from in the water phase. This was very easy to separate from the combined byproducts in the organic phase by filtration. After acidification of the phenol salt, the desired product **2** was collected by filtration. Compound **2** was used without further purification to generate **1** by catalytic hydrogenation (Scheme 2).

Two types of PTCs, quaternary ammonium salts and polyethers, were used for the hydrolysis. Representative results are summarized in Table 2. The quaternary ammonium salts used included tetrabutylammonium chloride (TBA) and benzyltrimethylammonium chloride (BTA). The polyethers studied were poly(ethylene glycols) (PEG) of varying molecular weight including: PEG-200 (M.W. 200); PEG-400 (M.W. 400); PEG-1000

Table 2. Effect of different phase transfer catalysts on the conversion of 2,3,6-trichloro-4-nitrotoluene **4** to 2,4-dichloro-3-methyl-6-nitrophenol **2**

RXN	(4) (g)	Toluene (mL)	KOH (g)	Water (mL)	PTC* (g)	Yield in 4 h (%)
8	4.0	100	10	10	BTA, 0.4 (2.1 mmol)	61
9	4.0	100	10	10	TBA, 0.6 (2.1 mmol)	82
10	4.0	100	10	10	PEG-200, 1.0	79
11	4.0	100	10	10	PEG-400, 1.0	94
12	4.0	100	10	10	PEG-1000, 1.0	68
13	4.0	100	10	10	PEG-3400, 1.0	91
14	4.0	100	10	10	PEM-2000, 1.0	82

* PTC: phase transfer catalysts used in heterogenous hydrolysis systems.

(M.W. 1000); PEG-3400 (M.W. 3400). Also, poly(ethylene glycol methyl ether), PEM-2000 (M.W. 2000), was used.

The data in Table 2 demonstrated that the catalytic activity of TBA (Bu_4NCl) is higher than that of BTA ($PhCH_2NMe_3Cl$). Generally, the PEG and PEM catalysts having an average degree of polymerization above 7 (M.W.=400) function better as a PTC. In addition, for both quaternary ammonium salts and poly(ethylene glycol), higher concentrations of PTC give faster rates of conversion of **4** into **2**. About 1% by wt. of PTC with respect to total wt. of the reaction solution was sufficient. The effect of the amount and concentration of KOH used on the yield of product **2** was studied and optimized. In general, the use of a **4**/KOH mole ratio of 1/6 and a high concentration of KOH in water gave higher yields of product **2**.

II-2. Homogeneous hydrolysis of 2,3,6-trichloro-4-nitrotoluene, 4, to 2,4-dichloro-3-methyl-6-nitrophenol, 2, with KOH/H_2O:

2,4-Dichloro-3-methyl-6-nitrophenol, **2**, was also synthesized successfully by hydrolysis of **4** with KOH/H_2O in several homogeneous solvent systems. Representative results are summarized in Table 3. The solvent has a major effect on yield (Table 3 and Figure 4). Some solvents were satisfactory and others were poor. A high yield of **2** was obtained using pyridine/*p*-dioxane (3:2, v/v). However, the yield and purity of **2** achieved with pyridine/*p*-dioxane (3:2, v/v) was still much lower than those achieved from the heterogeneous hydrolyses (see Table 1 and Figure 3)

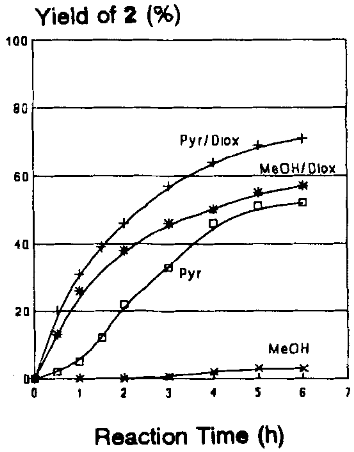


Fig. 4. Hydrolysis of **4** to **2**

Table 3. Typical hydrolyses of **4** to **2** in homogeneous systems

RXN	**4** (g)	Solvent system* (mL)	KOH (g)	Water (mL)	Temp (°C)	Time (h)	Yield of **2** (%)
15	1.0	pyr./dioxane (30+20)	2	3	95	5	80
16	1.0	pyr./dioxane (40+10)	2	3	95	5	42
17	1.0	pyr./dioxane (20+30)	2	3	95	5	52
18	1.0	pyr./dioxane (10+40)	2	3	95	5	27
19	1.0	MeOH/diox. (20+40)	2.5	3	75	30	50
20	1.0	pyridine (30)	1.5	1	50	6	57
21	1.0	methanol (30)	2	3	50	10	4
22	1.0	ethanol (50)	2	3	50	8	0
23	1.0	$MeOCH_2CH_2OH$ (30)	2	3	50	8	0

* Solvents: Pyr., pyridine; diox. or dioxane, *p*-dioxane.

EXPERIMENTAL

1. Preparation of 2,3,6-trichloro-4-nitrotoluene, 4, from 4-nitrotoluene

1-1. General chlorination procedure:

p-Nitrotoluene (7.0 g, 0.005 mol), iron powder (0.5 g, 0.008 mol), iodine (0.1 g, 0.0008 mol), and dichloroethane, 80 mL, were added to a 3-necked flask and stirred at 25 °C. Chlorine gas was passed into the reaction system at the desired temperature. The reaction was followed to completion by GC. The products were also examined by GC-MS. When the reaction was complete, the chlorination mixture was washed with 5% HCl and water until pH=7. The organic layer was separated and dried with $CaCl_2$. Solvent was removed in vacuo to give 11.8 g of crude product (**4** 88.9%, dichloro-*p*-nitrotoluene 6.0%, tetrachloro-*p*-nitrotoluene 5.2% by GC). The crude product was used for the next step reaction without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ: **4**, 7.81 (s, 1H, Ar$\underline{H}$), 2.66(s, 3H, $C\underline{H}_3$); 2,3,5,6-tetrachloro-4-nitrotoluene, 2.64 (s, 3$\underline{H}$, $C\underline{H}_3$).

1-2. Scale up of the chlorination reaction:

The chlorination reaction was scaled up by a factor of 10 with no significant change in yield. Thus, 31.5 g of *p*-nitrotoluene gave 54.5 g of the product. Analysis of the crude product by GC: monochloro-*p*-nitrotoluene, 1.92% (wt.); **4**, 89.1% (wt.); tetrachloro-*p*-nitrotoluene, 8.3% (wt.). The yield of **4** was 87.4%

2. Heterogeneous hydrolysis of 2,3,6-trichloro-4-nitrotoluene, 4 with KOH/H_2O in the presence of a phase-transfer-catalyst (PTC):

The crude product (4 g, 0.015 mol of **4**) of the chlorination of *p*-nitrotoluene (89% **4**), KOH (85% purity, 10 g, 0.152 mol), toluene (100 mL) and water (10 mL) were added into a three-necked flask fitted with a stirrer, a condenser and a thermometer. After stirring for 5 minutes at 85-90 °C, a 1 mL sample was taken to determine the initial concentration of **4**. Then 0.5 - 2.2 g of a phase-transfer catalyst, such as either tetrabutylammonium chloride (TBA) or poly(ethylene glycol), (average M.W. 400), was added.

The color of the reaction mixture immediately changed from light yellow to dark red. A reddish black precipitate was formed. The reaction was followed by determining the amount of **4** present via GC until none remained. The precipitate was filtered, acidified with H_2SO_4(25%) to pH=1, and stirred for 2 hrs. at 25 °C. The precipitate was filtered, washed three times with water (50 x 3 mL) and then dried at 60 °C in vacuo for 3-5 days to give 3.1 g (isolated yield 94%) of **2**. ^1H NMR ($CDCl_3$, 300 MHz) δ: 2,4-dichloro-3-methyl-6-nitrophenol, **2**, 11.0 (s, 1H, O$\underline{H}$), 8.12 (s, 1H, Ar$\underline{H}$), 3.37(s, 3H, C$\underline{H_3}$). This hydrolysis was scaled up by a factor of 2.5 with no yield loss (10 g of **4** gave 8.05 g of **2**, yield 97%, purity 95% by GC).

3. Homogeneous hydrolysis of 2,3,6-trichloro-4-nitrotoluene, 4, with KOH/H_2O in a mixed solvent system:

3-1. In pyridine and *p*-dioxane solvent system:

Crude product from the chlorination of *p*-nitrotoluene (1.0 g, 89% **4**, 3.72 mmol), KOH (2.0 g, purity 85%, 30.3 mmol), *p*-dioxane (20 mL), pyridine (30 mL) and water (3 mL) were added into a three-necked flask fitted with a stirrer, a condenser and a thermometer. The reaction mixture was heated to 90-98 °C and the progress of the reaction was followed by GC. The color of the solution changed from light yellow to dark red after 5 minutes. After stirring 2-7 hrs., the reaction mixture was cooled to room temperature and chloroform (50 mL) was added into the reaction mixture. A dark red precipitate was formed. This dark precipitate was filtered, washed twice with chloroform (2 x 5 mL), acidified with H_2SO_4 (25% by wt.) to pH=1 and stirred for 2 hrs. The red precipitate was then filtered and washed with water (3 x 20 mL). The product was dried at 60 °C in vacuo for 48 hrs. to give **2** (0.72 g, yield 87%, purity >85% by GC analysis).

3-2. Hydrolysis of 2,3,6-trichloro-4-nitrotoluene, 4, in other solvents:

The crude product from chlorination of *p*-nitrotoluene (1.2 g, 89% **4**, 4.46 mmol), KOH (2.5 g of 85% KOH), *p*-dioxane (40 mL), methanol (20 mL) and water (3 mL) were added into a 100 mL three-necked flask fitted with a stirrer, a condenser and a thermometer. The reaction was heated to 75 °C and followed by GC. When no starting material remained, 30 mL H_2SO_4 (25%) was added into the reaction mixture and the solution was stirred for 2 hrs. A dark red precipitate was formed. This precipitate was filtrated, washed with water (3 x 30 mL) and dried in vacuo to give 2,4-dichloro-3-methyl-6-nitrophenol, **2**, (4.1 g, yield=50%, purity 75% by GC).

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