

# PATENT SPECIFICATION

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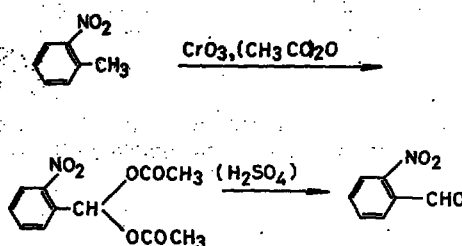
## (54) PROCESS FOR THE PREPARATION OF 2-NITROBENZALDEHYDE AND 2-NITROBENZYLIDENECHLORIDE

(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a new, unobvious process for the preparation of 2-nitrobenzylidene chlorides and 2-nitrobenzaldehydes, which can be used as intermediate products for the preparation of, for example the pharmaceutically active 4-nitrophenyl-1,4-dihydropyridine derivatives.

2-Nitrobenzaldehydes have hitherto been extremely difficult to obtain, since most of the conventional processes of aldehyde synthesis fail in this case. Thus, H. Cassebaum, (J. pr. Chem. [4], 29, (1965), (1)) reports as follows: "Though 2-nitrobenzaldehyde has been known for more than 80 years and has occasionally even been manufactured industrially for the production of indigo salt T, an advantageous method of preparation of this frequently required substance is still lacking in the literature even at the present time". In (L. F. and M. Fieser, Organische Chemie (Organic Chemistry), 2nd edition, Verlag Chemie (1968), page 1004 (2), 2-nitrobenzaldehyde is described as "a very useful starting product for syntheses, which is difficult to obtain by most processes".

The chromic acid oxidation of 2-nitrotoluene in acetic anhydride, recommended in Organic Syntheses Coll. Vol. III, page 641, (3), gives very low yields



(23—24%) (74%)  
 Total yield 17%

and suffers from the disadvantages that the reaction volumes are large and that tarry, smelly by-products, which are difficult to separate off, are produced.

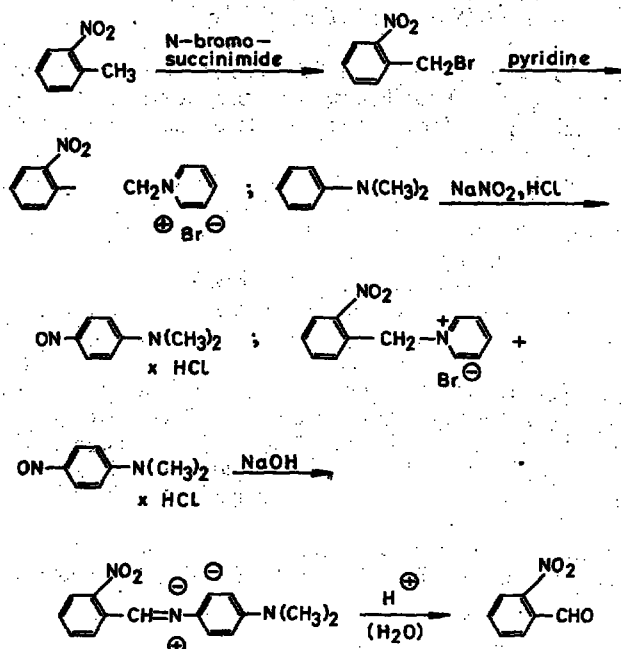
Numerous methods of preparation of 2-nitrobenzaldehyde use 2-nitrobenzyl chloride or 2-nitrobenzyl bromide as starting material, but these very compounds are difficult to obtain (literature (1)). The literature does not give any usable instructions, the statements of which can be followed satisfactorily. Thus 2-nitrotoluene reacts with chlorine in the presence of iodine only in glass vessels which transmit UV, to give 2-nitrobenzyl chloride in a yield of only 15%.

2-Nitrobenzylidene chloride, which is substantially more suitable still for the preparation of 2-nitrobenzaldehyde is not obtainable at all by direct chlorination of 2-nitrotoluene and instead has hitherto only been prepared from the aldehyde itself with phosphorus pentachloride (Kliegl, Ber. dtsh. chem. Ges. 40, 4939 (1907), (4)).

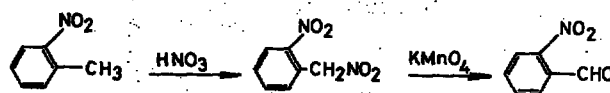
2-Nitrotoluene can be reacted with bromine in radical form (bromine in UV light, or N-bromosuccinimide) to give 2-nitrobenzyl bromide, in 45—60% yield (H. Cassebaum, Z. Chem. 1969, 340 (5) and Organic Syntheses Vol. 46, 81 (1966) (6)). However, industrially these methods can only be utilised unsatisfactorily. A dihalogenation was not observed even under these drastic conditions.

2-Nitrobenzylidene bromide has been obtained in 33% yield by reaction of 2-nitrophenyl-pyruvic acid with sodium hypobromite solution (A. Reissert, Ber. dtsh. chem. Ges. 30, 1030 (1897) (7)). Apart from the low yield (which, when rechecked by the applicant company, was found to be distinctly lower still), this method has the disadvantage of a large reaction volume.

2-Nitrobenzyl bromide can be converted to 2-nitrobenzaldehyde by a Kröhnke reaction, though there the expensive N-bromosuccinimide has to be employed and 4-nitrosodimethylaniline, which is carcinogenic, is used (6). Furthermore, this Kröhnke process comprises numerous reaction stages, as is shown by the following scheme:

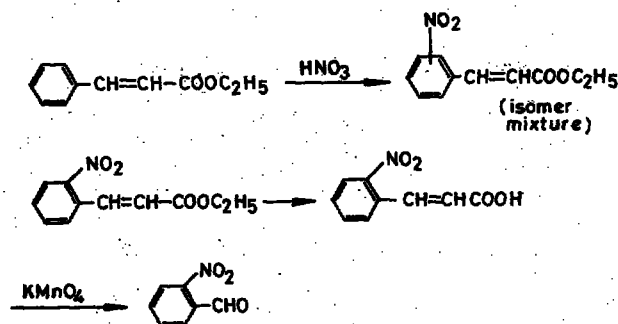


Another method known from the literature is the side-chain nitration of 2-nitrotoluene and subsequent oxidation of the 2-nitrophenylnitromethane with potassium permanganate (1).



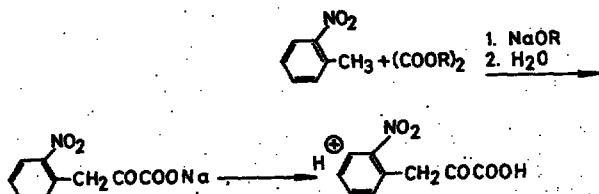
However, only 134 g (=10% of theory) of 2-nitrophenylnitromethane can be obtained from 1,000 g of 2-nitrotoluene by this process, so that this reaction is also industrially uninteresting.

A further method (J. Chem. Soc [London] 1950, 204 (8)) comprises the nitration of cinnamic acid ethyl ester, which produces an isomer mixture of 2- and 4-nitrocinnamic acid ethyl ester which can only be separated with difficulty. After saponification to nitrocinnamic acid and after separation of the isomers, an oxidation with potassium permanganate then gives the aldehyde, as can be seen from the following equations:



In addition to the expensive separation of the isomers and the low yield implicit therein, the large reaction volume is also an argument against the use of this synthesis of 2-nitrobenzaldehyde.

The reaction of 2-nitrotoluene with diesters of oxalic acid, under catalysis by an alcoholate, to give 2-nitrophenylpyruvic acid esters can also be regarded as belonging to the state of the art (6, 8). The enolate salts of these esters are hydrolysed with water to give the alkali metal salts of 2-nitrophenylpyruvic acid, from which free 2-nitrophenylpyruvic acid can then be obtained by reaction with mineral acids.



The large number of the abovementioned methods hitherto followed in order to obtain 2-nitrobenzaldehyde, which is very valuable for syntheses, and in particular the poor yields and results of these methods, show clearly that hitherto no satisfactory and industrially utilisable process for the preparation of 2-nitrobenzaldehyde, which had diverse uses, has been disclosed.

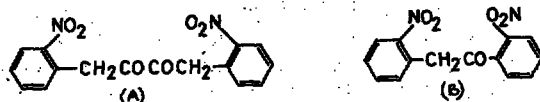
According to the present invention, we provide a process for the preparation of a 2-nitrobenzaldehyde comprising reacting an alkali metal salt of 2-nitrophenylpyruvic acid with an aqueous solution of an alkali metal hypochlorite and hydrolysing the resulting 2-nitrobenzylidene chloride at a temperature of from 20 to 150°C in the presence of water.

We also provide in accordance with this invention a process for the preparation of a 2-nitrobenzylidene chloride, comprising reacting an alkali metal salt of a 2-nitrophenylpyruvic acid with an aqueous alkali metal hypochlorite solution the aqueous solution in which the reaction is carried out preferably is itself alkaline.

Desirably, the salt of the 2-nitrophenylpyruvic acid is prepared by reacting 2-nitrotoluene with an oxalic acid diester of the formula  $(\text{COOR})_2$ , in which R represents an alkyl group of from 1 to 6 carbon atoms or an aralkyl group.

It must be described as distinctly surprising that 2-nitrobenzaldehydes can be obtained in such good yields and such high purity in accordance with the process of the invention, since it had to be expected from the state of the art that the dihalogenation of 2-nitrotoluene would not take place or would at most take place with very poor yields.

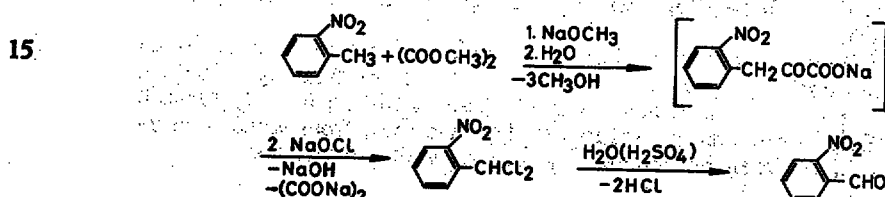
Equally it is distinctly surprising that in the reaction of the alkali metal salt of 2-nitrophenylpyruvic acid with sodium hypochlorite the 2-nitrobenzylidene chloride was obtained in such high yields, since Reissert (Ber. dtsch. Chem. Ges. 30, 1030 (1897)) was only able to isolate a solid of melting point 160°C from the reaction of 2-nitrophenylpyruvic acid with the chemically equivalent calcium hypochlorite; he ascribed the structure of a dinitrodibenzyl diketone (A) to this solid. 40 years later it proved possible to clarify the structure of this compound, which is dinitrodesoxybenzoin (B) (compare P. Ruggli and A. Dinger, Helv. Chim. Acta 22, 908 (1939)).



The formation of (B) is not observed in the case of the reaction according to the invention.

The processes according to the invention have a number of advantages. Thus, the 2-nitrotoluenes and oxalic acid diesters used as starting products are accessible conveniently and in adequate quantity. The end product is obtained from the hydrolysis in high yield and high purity. The preparations of the 2-nitrophenylpyruvic acid and the subsequent preparation of the 2-nitrobenzylidene chloride can be conducted without isolation of the 2-nitrophenylpyruvic acid, so that the process is technically easy to carry out. 60% of the oxalic acid diester employed are recovered in the form of dialkali metal oxalate in the hypochlorite reaction stage and this oxalate can be reconverted to the ester without difficulty.

If 2-nitrotoluene, oxalic acid dimethyl ester and sodium methylate are used as starting materials, the course of the reaction can be represented by the following equation:



The starting products usable according to the invention are known or can be prepared according to known methods.

The term alkali metal denotes lithium, sodium or potassium, especially sodium or potassium.

In the formula  $(\text{COOR})_2$ , R preferably represents an alkyl group with from 1 to 6 carbon atoms, especially methyl, ethyl, propyl, isopropyl, butyl, tert.-butyl, pentyl and hexyl, or represents benzyl.

The hypochlorite reaction can be carried out in aqueous solution and the 2-nitrobenzylidene chloride can be isolated by extraction with a water-immiscible solvent, but preferably the process is carried out directly in a two-phase system (for example toluene/water) and the 2-nitrobenzylidene chloride is obtained by separating off the organic phase and working it up by distillation.

The hydrolysis of the 2-nitrobenzylidene chloride can also be carried out in an alkaline medium, but preferably the hydrolysis is carried out under acid conditions. Aqueous organic and inorganic acids can be used as the acids. Preferably the reaction is carried out with sulphuric acid (50—98% strength by weight  $\text{H}_2\text{SO}_4$ , preferably 85—95% strength by weight  $\text{H}_2\text{SO}_4$ ). The reaction is carried out at 20—150°C, preferably at 60—80°C.

In carrying out the hypochlorite reaction 2—3.5 mols of alkali metal hypochlorite are preferably employed per mol of the alkali metal salt of 2-nitrophenylpyruvic acid. The temperature will usually be between -5 and +50°C, preferably between 0 and 20°C.

The reactions can be carried out under normal pressure but also under elevated pressure. Preferably, they are carried out at pressures of between 1 and 2 atmospheres, especially in the case of the hydrolysis reaction step.

A subsequent purification with sodium bisulphite solution is advisable in order to purify the resulting 2-nitrobenzaldehyde to a purity of >99%.

2-Nitrobenzaldehyde is used, inter alia, as an intermediate product for the preparation of coronary-dilant and peripheral-dilant pharmaceuticals which lower the blood pressure (compare German Offenlegungsschrift (German Published Specification) 1,670,827). Thus, for example, the reaction of 2-nitrobenzaldehyde with  $\beta$ -dicarbonyl compounds and amines produces pharmacologically active 1,4-dihydropyridines.

The process according to the invention will be described with the aid of the following examples:

#### Example 1

##### a) 2-Nitrobenzylidene chloride (from 2-nitrotoluene)

144 g (2.67 mols) of sodium methylate are dissolved in 570 ml of ethanol and a mixture of 365 (2.5 mols) of oxalic acid diethyl ester and 395 g (2.88 mols) of 2-nitrotoluene is poured in at 35°C. The mixture is then briefly heated under reflux and cooled to 65°C, 75 ml of cold water are next added and after addition of a further 640 ml of water (60°C) the mixture is then boiled under reflux for 1½ hours. A steam

distillation is then carried out until two phases no longer pass over. The nitrotoluene from the steam distillate is separated off and recovered by distillation.

The residues of the steam distillation are made up to a volume of 3.3 l with water and 150 g of sodium carbonate are dissolved therein. This solution is added dropwise, at 10°C, to a mixture of 1,700 ml of aqueous sodium hypochlorite solution (150 g of NaClO/l) and 60 g of sodium hydroxide in 1,500 ml of water and 1,200 ml of toluene. The mixture is then stirred for a further hour at +10°C and the solid sodium oxalate is filtered off. The toluene phase is separated from the filtrate and concentrated in vacuo. 279.5 g of 2-nitrobenzylidene chloride, boiling point<sub>12mm</sub> 140°C are obtained. Yield, 77% of theory, based on 2-nitrotoluene converted.

b) Analogously, 301 g of 2-nitrobenzylidene chloride (82.5%) were obtained starting from 230 g of potassium ethylate, 365 g of oxalic acid diethyl ester and 395 g of 2-nitrotoluene, with 149 g of 2-nitrotoluene being recovered. Yield, 82.5% of theory.

#### Example 2

2-Nitrobenzylidene chloride (from 2-nitrophenylpyruvic acid)

A solution of 358 g (1.715 mol) of 2-nitrophenylpyruvic acid (melting point 115°C) and sodium carbonate in water is slowly added dropwise to a mixture of sodium hydroxide solution, sodium hypochlorite solution (162 g of NaClO/l) and 1.35 l of toluene at +10°C. The mixture is stirred for a further hour at +10°C and the solid (sodium oxalate) is filtered off. The toluene phase is separated from the filtrate. The filter residue is rinsed with 1.35 l of toluene and the aqueous phase is re-extracted therewith. The combined toluene phases are dried with anhydrous sodium sulphate and concentrated in vacuo. 294.5 g (83.5% of theory) of 2-nitrobenzylidene chloride are obtained.

#### Example 3

2-Nitrobenzylidene chloride (produced continuously from 2-nitrophenylpyruvic acid)

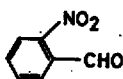
The stirred volume of two stirring flasks with an overflow totalled 1.05 l. 1,692 ml of an aqueous solution of the Na salt of 2-nitrophenylpyruvic acid (prepared from 163 g of 2-nitrophenylpyruvic acid), 1,692 ml of sodium hypochlorite solution (80 g of NaOCl/l) and 716 ml of toluene were added dropwise per hour (making a total of 4.0 l so that the residence time is 15.7 minutes). The temperature was kept at +10°C in both flasks by cooling. After starting the continuous operation, 4 l per hour of the issuing reaction mixture are collected in a collecting vessel and worked up as follows:

The mixture was filtered, the phases separated, the aqueous phase extracted with toluene, and the toluene phases were combined, dried with sodium sulphate and concentrated on a rotary evaporator, for 1 hour at 80°C.

After 4 hours' continuous operation, 15.85 l of the 16 l volume employed were recovered. Working up gave 500.0 g=77.8% of theory of 2-nitrobenzylidene chloride.

#### Example 4

2-Nitrobenzaldehyde



492.5 g (2.39 mols) of 2-nitrobenzylidene chloride in 2 kg of aqueous sulphuric acid (90% strength by weight H<sub>2</sub>SO<sub>4</sub>) are warmed to 70°C. The mixture is stirred until the evolution of hydrogen chloride has ceased, and is then poured onto crushed ice. Thereafter, the mixture is extracted by stirring with 1,300 ml of toluene for 30 minutes, insoluble material is filtered off and the toluene phase is separated from the filtrate. The aqueous phase is re-extracted with toluene. The combined toluene phases are twice extracted by stirring with 20% strength aqueous sodium bisulphite solution. The bisulphite solution is brought to pH 12.5 with sodium hydroxide solution and extracted with toluene. The toluene phase is dried with sodium sulphate and evaporated in vacuo. After 1 hour at 80°C, the residue which remains is 277.5 g (77% of theory) of very pure 2-nitrobenzaldehyde, which on cooling immediately solidifies to crystals. Melting point 42–43°C.

The method of the invention can be used to prepare not only 2-nitrobenzaldehyde and 2-nitrobenzylidene themselves, but also simple substituted derivatives thereof, in which cases the appropriately substituted 2-nitrophenyl pyruvic acid salt will be used.

## WHAT WE CLAIM IS:—

1. A process for the preparation of a 2-nitrobenzaldehyde comprising reacting an alkali metal salt of 2-nitrophenylpyruvic acid with an aqueous solution of an alkali metal hypochlorite and hydrolysing the resulting 2-nitrobenzylidene chloride at a temperature of from 20 to 150°C in the presence of water.

2. A process for the preparation of a 2-nitrobenzylidene chloride, comprising reacting an alkali metal salt of a 2-nitrophenylpyruvic acid with an aqueous alkali metal hypochlorite solution.

3. A process according to claim 1 or claim 2 wherein the said salt of 2-nitrophenylpyruvic acid is prepared by reacting 2-nitrotoluene with oxalic acid diesters of the formula



in which R represents an alkyl group of from 1 to 6 carbon atoms or an aralkyl group.

4. A process according to claim 3, wherein the oxalic acid diesters are oxalic acid dialkyl esters.

5. A process according to any one of claims 1 to 4 wherein the alkali metal hypochlorite is sodium hypochlorite.

6. A process according to any one of claims 1 to 5 wherein from 2 to 3.5 moles of alkali metal hypochlorite are used per mole of the 2-nitrophenylpyruvic acid.

7. A process according to any one of claims 1 to 6 wherein the reaction between the alkali metal hypochlorite and the 2-nitrophenylpyruvic acid is effected at a temperature of from 0 to 20°C.

8. A process according to any one of claims 1 to 3 wherein the 2-nitrophenylpyruvic acid is reacted with the alkali metal hypochlorite in a solvent system comprising water and a water-immiscible organic solvent.

9. A process according to claim 1, or any one of claims 2 to 8 when dependant upon claim 1, wherein the 2-nitrobenzylidene chloride is hydrolysed under acid conditions.

10. A process according to claim 9 wherein the 2-nitrobenzylidene chloride is hydrolysed with aqueous sulphuric acid.

11. A process for the preparation of 2-nitrobenzylidene chloride substantially as hereinbefore described in either one of Examples 1 and 2.

12. A process for the preparation of 2-nitrobenzaldehyde substantially as hereinbefore described in Example 4.

13. 2-nitrobenzaldehyde whenever prepared by a process according to claim 1, claim 12 or any one of claims 3 to 10 when dependent upon claim 1.

14. 2-nitrobenzylidene chloride whenever prepared by a process according to claim 2, claim 11 or any one of claims 3 to 10 when dependent upon claim 2.

15. A process according to any one of claims 1 to 12 wherein the preparation of the 2-nitrobenzylidene chloride is carried out as a continuous process.

16. A process for the preparation of 2-nitrobenzylidene chloride substantially as hereinbefore described in Example 3.

17. 2-nitrobenzylidene chloride whenever prepared by a process according to claim 15 or claim 16.

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