Short Communication

Synthesis of 2-Nitrobenzaldehyde from 2-Nitrotoluene

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Abstract

Comparison of Arthur Lapworth' one-pot conversion of 2-nitrotoluene to 2-nitrobenzaldehyde with other published synthetic sequences revealed an environmental attractiveness of this reaction. Due optimisation of the procedure was made in order to enhance the safety of this process on a large scale. A highly selective one-pot preparative chemical synthesis of 2-nitrobenzaldehyde from 2-nitrotoluene is described.

Key words: 2-nitrotoluene, 2-nitrobenzaldehyde, 2-propylnitrite

Introduction

Manufacturing of nitroaromatic compounds with traditional synthetic procedures often leads to serious contamination of the environment by carcinogenic nitroaromatic compounds and the release of a large amounts of pollutants to both air and waste water. Considerable attention has been paid to the development of alternative, preferably catalytic, methods. Recently, release of waste sulphuric and nitric acids during traditional nitration of aromatic compounds was reduced by the application of perfluorinated solvents.[1] Homogeneous catalysis with tungstophosphoric acid was successfully applied to the oxidation of aromatic amines to nitroaromatic compounds.[2] Heterogeneous catalysis was used for nitration of fluorotoluene by nitric acid[3] and for highly selective preparations of 4-nitrobenzonitrile and 3-nitrophtalic acid from 4-nitrotoluene and 1-nitronaphtalene, respectively.[4] 2-Nitrobenzaldehyde is a key intermediate in heterocyclic chemistry. It is used in multi-ton quantities for the production of generic drugs, for example, Nifedipine.[5] In the synthesis of enantiomerically pure α-amino acids[6] it is a precursor for 2-aminobenzaldehyde,[7] which is an intermediate for preparation of α-methyl amino acids.[8] In spite of high-volume industrial applications of 2-nitrobenzaldehyde, the only preparative chemical synthesis of 2-nitrobenzaldehyde from cheap 2-nitrotoluene suitable for scaling-up has been published. Condensation of 2-nitrotoluene with diethyloxalate[9] in THF followed by hypochlorite oxidation to 2-nitrobenzaldehyde[10] in our hands led to predominant formation of 2-nitrobenzylidenedichl oride and only trace amount of 2-nitrobenzaldehyde. Bromination of 2-nitrotoluene to 2-nitrobenzylide nedibromide[11] followed by 4-nitosodimethylaniline oxidation to 2-nitrobenzaldehyde[10] requires application of expensive bromine compounds and carcinogenic 4-nitrosodimethylaniline. A three-step sequence including chlorination of 2-nitrotoluene followed by alkaline dimerisation to 2,2'-dinitrostilbene and ozonolysis suffers from low conversion rates and low selectivity in spite of intensive efforts made towards optimisation of the reaction conditions.[12,13] Poorly selective nitration of benzylchloride followed by separation of regioisomers could be used instead of chlorination of 2-nitrotoluene.[14] Both approaches employing 2-nitrobenzyl halides suffer from dangers of explosive decomposition of these compounds.[13] None of these methods are applicable for an environmentally-friendly preparation of 2-nitrobenzaldehyde.

A century ago Arthur Lapworth suggested the synthesis of 2-nitrobenzaldehyde from 2-nitrotoluene, amyl nitrite and anhydrous sodium ethoxide via the anti-oxime.[15] The synthesis is one-pot, does not require very toxic, carcinogenic or expensive raw materials. Diethyl ether was used as a solvent. In this work the preparative application of this approach is described.

Experimental

To a 4 M methanolic solution of sodium methoxide (700 mL), 500 mL of toluene was added followed by immediate removal of the methanol by distillation. After cooling, pentane (300 mL) was added to the resulting suspension. The flask was equipped with an ethanol cooled condenser (–20 °C) and a mixture of 2-nitrotoluene (118 mL, 1 mol) and 2-propylnitrite (111 mL, 1 mol) was added slowly with vigorous stirring. The temperature of the reaction mixture was controlled

by regulation of the rate of addition. After complete addition, the ethanol-cooled condenser was removed and a distillation head fitted. 600 mL of 36% HCl was added dropwise, following by controlled distillation of the solvent. Separation of the organic layer followed by its concentration in *vacuo* gave a solution of 2-nitrobenzaldehyde in 2-nitrotoluene.

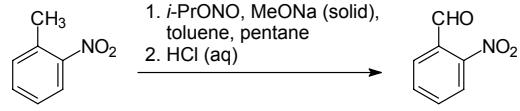
2-Nitrotoluene (85 g, 0.62 mol) was distilled off to give a crude sample of 2-nitrobenzaldehyde (36.3 g, 0.24 mol, yield 24%). Identity of the compound and its purity (>95%) were confirmed by capillary GC using purchased 2-nitrobenzaldehyde as a standard.

Results and discussion

In a first optimization step, diethyl ether was replaced by toluene in order to avoid possible problems with its peroxide. Reaction of 2-nitrotoluene, amyl nitrite and anhydrous sodium ethoxide in toluene leading to the oxime is highly exothermic. The procedure initially suggested by Lapworth[13] could only be applied on sub-gram scale due to the risk of fire.

It was known that 2-propylnitrite is used in industrial scale in both the pharmaceutical industry and as a rocket fuel. In spite of the facts that this compound can ignite by shock or friction and exothermic decomposition occurs in enclosed containers at about 60 °C, in England it is considered to be safe enough for industrial applications for the manufacture of pharmaceuticals. Animal experiments revealed possible carcinogenesis after long-time feeding with 2-propylnitrite-contaminated food.[16] For white rats and mice inhalation of non-lethal doses of 2-propylnitrite (less then 1 g/m^3) led to no observable long-term effects after a short recovery period.[17] Full recovery was reported after incidental acute intoxication of human being.[16] Acute toxicity of the compound was supposed to be due to formation of methemoglobin and nitrohemoglobin in blood and suppression of cytochrome oxidase activity in brain.[17] A GC-MS method was developed for monitoring of 2-propylnitrite levels in environment.[18] I hypothesised that the application of low-boiling 2-propylnitrite (bp 39 °C) instead of amyl nitrite (bp 97–99 °C) would slow down the reaction by heat transfer from the reaction by endothermic evaporation of 2-propylnitrite. The evaporation at the same time would decrease its concentration in the reaction mixture. In this experimental design an ethanol-cooled condenser (up to –30 °C) guaranteed no loss of 2-propylnitrite vapours. Experiment demonstrated that the replacement did not secure control over the reaction heat. Keeping in mind that heat transfer is a critical factor for scaling-up the synthesis, the next change in the reaction conditions was applied: one-half of toluene was replaced by low-boiling pentane (bp 35–36 °C) in order to co-distillate it with 2-propylnitrite and keep the reaction temperature below 40 °C (Scheme 1). In the case of uncontrolled heating of the reaction mixture, the concentration of 2-propylnitrite in the reaction mixture was decreasing due to its co-distillation with pentane leading to lowering of the reaction rate. Heat transfer was more efficient than in the previous case when only evaporation of 2-propylnitrite was used for this purpose. Sodium ethoxide was replaced by cheaper and more stable sodium methoxide.

The oxime was hydrolysed by aqueous HCl. Selectivity of the conversion of 2-nitrotoluene to 2-nitrobenzaldehyde is high, significant amounts of by-products were not found in the reaction mixture by GC. Unreacted 2-nitrotoluene was easily distilled from the reaction mixture for recycling.



Scheme 1

Conclusions

The original Lapworth procedure for the direct preparation of 2-nitrobenzaldehyde from 2-nitrotoluene was modified in order to make it suitable for high-scale production. The modification did not affect the low impact of the reaction to the environment. No heavy metals or highly carcinogenic compounds are used in the preparation. Additionally, low-boiling diethylether, which may contain explosive peroxides, was replaced by mixture of toluene and pentane. Use of highly flammable, explosive and physiologically active (hypotensive) 2-propylnitrite is the main disadvantage of the modified synthesis, an efficient fume hood is mandatory. Alternative chemical syntheses of 2-nitrobenzaldehyde from 2-nitrotoluene led to much higher amount of toxic waste; they also required toxic and often explosive intermediates.

The described modification of Lapworth' procedure should be useful in an industrial scaling-up and for the preparation of other 2-nitrobenzaldehydes bearing electron-acceptor substituents in the aromatic ring.

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Povzetek

Primerjava Arthur Lapworth-ovega postopka za pretvorbo 2-nitrotoluena v 2-nitrobenzaldehyd z ostalimi objavljenimi postopki pokaže njegovo večjo okoljsko sprejemljivost. Postopek smo optimizirali tako, da je primeren in varen za izvedbo procesa v večjih količinah.