Asian Journal of Chemistry; Vol. 29, No. 1 (2017), 91-93

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2017.20138

A Concise and Convenient Synthesis of 4-(Trifluoromethylthio)aniline

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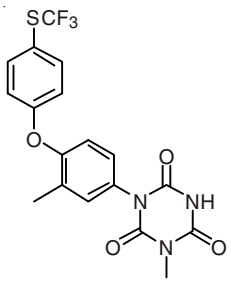
Received: 14 June 2016; *Accepted*: 6 September 2016; *Published online*: 29 October 2016; AJC-18104

4-(Trifluoromethylthio)aniline, a key agricultural intermediate, can be synthesized from 4-nitrobromobenzene. First 4-nitrothioanisole was obtained by the methylthiotriazine of 4-nitrobromobenzene with sodium salt of methyl mercaptan in the presence of phase-transfer catalyst in a 91.4 % yield; then 4-(trifuroromethylthio)nitrobenzene was produced through chlorination in a 83.7 % yield and fluorination in a 86.3 % yield; finally the hydrogenation in the presence of Pd/C can afford 4-(trifluoromethylthio)aniline with a 98 % yield.

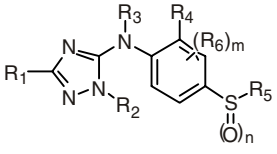
Keywords: Methylthiotriazine, Chlorination, Fluorination, Hydrogenation, Phase translation catalyst.

INTRODUCTION

4-(Trifluoromethylthio)aniline (**7**), a useful compound as a production intermediate, such as pesticides, agricultural chemicals and pharmaceutical industries [1-4]. It is a key intermediate for the preparation of toltrazuril (**1**) and anilinotriazoles (**2**). Toltrazuril is widely used in chickens, turkeys, pigs and cattle for prevention and treatment of coccidiosis, by administration *via* drinking water [5-7]. Anilinotriazoles a novel potential insecticidal and acaricidal agent showed potent bioactivities [8]. Several syntheses of 4-(trifluoromethylthio)-aniline (**7**) had also been reported in the literature [2,9]. Most of methods used were trifluoromethyl copper reagent for trifluoromethylation and iron powder for reduction [2]. A large quantity of iron mud pollution was produced in the iron powder reduction [10]. A clean and environmentally friendly hydrogenation technique needs to be used. This paper reported a convenient and efficient synthesis of 4-(trifluoromethylthio)-aniline utilizing methylthiotriazine, chlorination, fluorination and environment friendly hydrogenation reduction reaction using Pd/C catalyst in good yield.



Toltrazuril (1)



Anilinotriazoles (2)

EXPERIMENTAL

Reagents and solvents were obtained from commercial suppliers and were used without further purification. Melting points were determined on a XT34 binocular microscope (Shanghai Tech Instrument Co., China) and were not corrected. ^{1}H NMR spectra were recorded on Mercury plus 400 (300 MHz) spectrometer, chemical shifts (δ) were reported in parts per million relative to tetramethylsilane. Chemical shifts were reported in parts per million relative to the solvent resonance as the internal standard ($CDCl_3$, δ = 7.16 ppm). ^{19}F NMR assays with internal standard ($PhOCF_3$ or PhF or $PhCF_3$). Analytical TLC and column chromatography were performed on silica gel GF254 and silica gel H60, respectively. The following solvent mixtures were used: cyclohexane/ethyl acetate (3:1), cyclohexane/ethyl acetate (2:1), spots were visualized by short-wave UV light and iodine vapour.

4-Nitrothioanisole (4): A mixture of 4-nitrobromobenzene (**3**) (60.6 g, 0.30 mol), 20 % methyl mercaptan sodium salt in water (116 g, 0.33 mol), tetrabutyl ammonium bromide (4.8 g, 0.015 mol) and acetone (250 mL) was stirred at room temperature for 10 min. Then the resulting mixture was heated to reflux and left for 5 h. After the reaction finished, the acetone was removed *in vacuo*. The residue was then cooled to room temperature, poured into ice-water (350 mL) and stirred for 0.5 h. The solid precipitate was filtered off, washed with cold water and dry in vacuum. Recrystallized from ethanol to give a bright yellow solid 4-nitrothioanisole (**4**) (**Scheme-I**) (46.4 g) in 91.4 % yield, m.p.: 65-67 °C (lit. [12]; m.p.: 68-71 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 9.1 Hz, 2H), 7.26 (d, *J* = 9.1 Hz, 2H), 2.53 (s, 3H).

4-Nitrophenyl trichloromethylsulfide (5): A mixture of 4-nitrothioanisole (25.4 g, 0.15 mol), chloroform (250 mL) and 2,2'-azo-*bis*-isobutyronitrile (0.65 g, 4.0 mmol) was stirred at room temperature for 10 min. The resulting mixture was heated to reflux. Then, chlorine gas was bubbled through the resulting mixture during vigorous stirring for 3 h. After the completion of the reaction, chlorine gas was stopped introducing. Pass into nitrogen gas; extrude the excess chlorine gas and hydrogen chlorine. The reaction solution was poured into 100 mL of ice water, The chloroform layer was separated, washed twice with water and saturated brine and the organic phase was washed with non-anhydrous sodium sulfate and evaporated to dryness in chloroform to give the product of 4-nitrophenyl trichloromethylsulfide (**5**) (34.2 g) in 83.7 % yield, m.p.: 65-67 °C (lit. [13] m.p.: 71-72 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm), δ = 8.33 (m, 2H), 7.99 (m, 2H).

4-Nitrophenyl trifluoromethylsulfide (6): A mixture of 4-nitrophenyl trichloromethylsulfide (40.9 g, 0.15 mol), antimony trifluoride (30 g, 0.17 mol) and dichloromethane (275 mL) was stirred at room temperature for 10 min in a 500 mL polytetrafluoroethylene reactor. Then the resulting mixture was heated to 55-60 °C and stirred for 3 h. After the reaction finished, the reaction solution was poured into 1000 mL ice-water, the organic phase was separated and washed with saturated brine two times and the organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated to give the crude product of 4-nitrophenyl trifluoromethylsulfide. Recrystallized from hot ethanol to give a brown crystals of 4-nitrophenyl trifluoromethylsulfide (**6**) (28.9 g) in 86.3 % yields, m.p.: 92-92.5 °C (lit. [14]; m.p.: 94 °C). ^{1}H NMR (300 MHz, $CDCl_3$, ppm), δ, 8.32 (dd, *J* = 8.38, *J* = 2.14, 2H). 7.89 (dd, *J* = 8.38, *J* = 2.14, 2H). ^{19}F NMR (220 MHz, $CDCl_3$), δ = 41.4 (s, 3F, SCF_3).

4-Aminophenyl trifluoromethylsulfide (7): To a solution of 4-nitrophenyl trifluoromethylsulfide (**6**) (33.5 g, 0.15 mol) in ethanol (400 mL) was added palladium on carbon (10 % Pd/C, 3.5 g). The mixture was hydrogenated under 40 atmospheric pressure at room temperature for 8 h. After completion of the reaction, the reaction mixture was filtered through celite and thoroughly washed with ethanol. The filtrate was evaporated and the residue washed with water to give 28.4 g in a 98 % yield of 4-aminophenyl trifluoromethylsulfide (**7**) as a brown liquid. b.p.: 110-112 °C/1.70 KPa (lit. [14]; b.p.: 113 °C/1.73 KPa). ^{1}H NMR (300 MHz, $CDCl_3$), δ = 7.62 (d, *J* = 8.30, 2H), 7.42 (dd, *J* = 8.30, *J* = 1.90, 2H); 3.84 (s, 2H, NH_2). ^{19}F NMR (220 MHz, $CDCl_3$): δ: 44.5 (s, 3F, SCF_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.1, 138.2, 126.7, 115.3, 111.3.

RESULTS AND DISCUSSION

Recently, we studied a novel oxadiazine insecticide SICO-047 using a key intermediate 4-(trifluoromethylthio)aniline (**7**), which showed that the efficient synthesis of 4-nitrophenyl trifluoromethylsulfide (**6**) with hydrogen in the presence of Pd/C catalyst can produce 4-(trifluoromethylthio) aniline in very high yields. Meantime, the optimization of the synthetic conditions for 4-nitrothioanisole (**4**), 4-nitrophenyl trichloromethylsulfide (**5**) and 4-nitrophenyl trifluoromethylsulfide (**6**) were conducted.

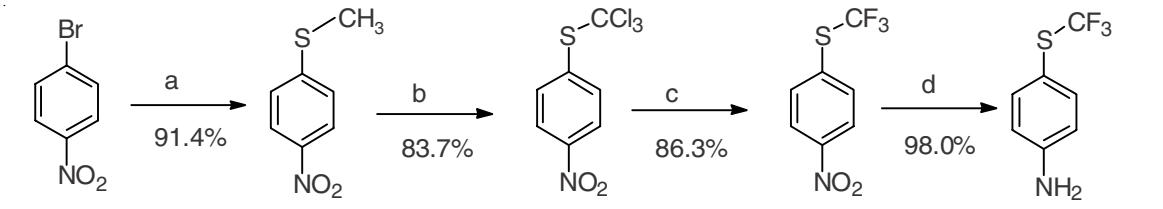
There were several methods to prepare 4-nitrothioanisol. It was reported to obtain 4-nitrothioanisol by the methylating of thiophenolate [12,15], the nitration of 4-(methylthio)bromobenzene under copper MOFs as catalysts [16], or the methylthiotriazine of 4-nitrobromobenzene [17]. A phase-transfer catalyst can accelerate the reaction process. It was found that the phase transfer catalyst tetrabutylammonium bromide can improve the methylthiotriazine of 4-nitrobromobenzene. The yield of methylthiotriazine was 91.4 %.

There were a few ways for halogenation such as free radical halogenation, electrophilic halogenation and halogen addition reaction. In this paper, it was used the chlorination with chlorine gas in presence of 2,2'-azo-*bis*-iso-butyronitrile as catalyst and fluorination with antimony trifluoride. The process is more suitable for a large-scale preparation in 72.2 % yields.

The traditional reducing process usually adopts iron powder reduction, which produces the serious pollution of iron mud. The hydrogenation reduction technique is an environment friendly process in the chemical industry. The 4-nitrophenyl trichloromethylsulfide was treated with hydrogenation reduction using Pd/C catalyst to give 4-(trifluoromethylthio)-aniline in 98 % yields (**Scheme-I**).

Conclusion

The Pd/C catalyst is an environment friendly process for the hydrogenation of 4-nitrophenyl trichloromethylsulfide. A convenient and concise process for the synthesis of 4-(trifluoromethylthio)aniline has been proven to be practical, This synthesis method presents a promising synthetic process for 4-(trifluoromethylthio)aniline because of the following advantages: (i) high yield because of phase transfer catalytic availability in methylthiotriazine, (ii) simplicity of process in chlorination, fluorination and hydrogenation, (iii) recycling of solvent, (iv) the experiment process reported in this paper can be easily developed into large-scale preparation of 4-(trifluoromethylthio)-aniline.



a. CH_3SNa, $(C_4H_9)_4NBr$, acetone b. Cl_2, $CHCl_3$, AIBN c. SbF_3, $ClCH_2CH_2Cl$ d. H_2, Pd/C, EtOH

Scheme-I

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