

Journal of Fluorine Chemistry 87 (1998) 65-67



# A practical synthesis of 2-methoxy-6-trifluoromethylaniline

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Received 9 April 1997; accepted 11 July 1997

# Abstract

A practical synthesis of 2-methoxy-6-trifluoromethylaniline is described via halogenation, nitration and reduction of 3-trifluoromethylanisole. © 1998 Elsevier Science S.A.

Keywords: 3-Trifluoromethylanisole; 2-Methoxy-6-trifluoromethylaniline

# 1. Introduction

2-Methoxy-6-trifluoromethylaniline, **1**, is a valuable intermediate for the synthesis of sulfonamide herbicides [1]. With the continued interest in the synthesis of 1,2,3-substituted benzenes and the development of *ortho* metallation of substituted aromatics [2–4], we report a practical synthesis of 2-methoxy-6-trifluoromethylaniline from 3-trifluoromethylanisole. The initial synthesis of **1** involved the carboxylation of 3-trifluoromethylanisole (Scheme 1). Although the yields of the process were satisfactory, the first step involved the use of *n*-butyl lithium at  $-78^{\circ}$ C. If the reaction temperature exceeded  $-55^{\circ}$ C, rapid decomposition was observed (J. Orvik, A. Gulbenkian, personal communication). The chemistry was not suitable for scale-up, and the present research was directed toward a practical synthesis of 2-methoxy-6-trifluoromethylaniline.

### 2. Results and discussion

An alternative synthetic approach to 1 involved the nitration of 2,4-dichloro-5-methylphenol (2) [5] (Scheme 2). However, photochlorination of the aromatic methyl group of the nitrophenol to the trichloromethyl moiety for HF exchange was unsuccessful and the approach was abandoned and the research directed toward the halogenation of 3-trifluoromethylanisole (3). Bromination of 3-trifluoromethylanisole in sodium acetate-buffered acetic acid gave a monobromo mixture, **4b**, in which the principal isomer was  $\sim 90\%$ . Nitration with 70% concentrated nitric acid in con-

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centrated sulfuric acid gave a mononitro isomer mixture, **5b**, with two principal isomers as shown by GC–MS analysis. Reduction of the mixture in aqueous ethanol with  $H_2$  and Pd/C in a sodium acetate buffer gave a mixture of three isomeric methoxytrifluoromethylanilines **6b**, in the rates of 64:6:30. Distillation gave a 55% yield of 2-methoxy-6-trifluorome

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thylaniline, that was identical in IR and NMR to material prepared via Scheme 1. The isomer with the lowest boiling point was the desired isomer. Chlorination of **3** under similar conditions to the bromination gave a monochloro isomeric mixture in the ratio of 12:62:26. Mononitration and reduction gave an isomeric mixture containing the desired 2-methoxy-6-trifluoromethylaniline in the ratio of 47:29:24. Distillation gave a 40% yield of **1**.

# 3. Conclusions

A practical route has been demonstrated for the preparation of 2-methoxy-6-trifluoromethylaniline by halogenation, nitration and reduction of 3-trifluoromethylanisole. Bromination is preferred over chlorination since the bromine route produces a higher percentage of the desired isomer. Reductive diazotization of the undesired isomers regenerates the starting material **3**.

### 4. Experimental details

#### 4.1. Bromination of 3-trifluoromethylanisole

3-Trifluoromethylanisole (67.0 g, 0.38 mol), sodium acetate (62.4 g, 0.76 mol), and acetic acid (250 ml) were placed in a 500 ml, three-necked round bottom flask equipped with mechanical stirrer, thermometer and dropping funnel. The contents were heated by an oil bath to 75°C and bromine (121.8 g, 0.76 mol) added dropwise from the addition funnel. The mixture was heated for 18 h, cooled, and the acetic acid removed in vacuo on a rotary evaporator. The residue was diluted with dichloromethane and the organic salts separated by filtration. Evaporation of the solvent gave 100 g of crude product. GC–MS analysis showed that a monobromo isomer constituted 90% of the product. MS m/z: 254(m+calcd for C<sub>8</sub>H<sub>6</sub>BrF<sub>3</sub>O: 254).

# 4.2. Nitration of monobromo-3-trifluoromethylanisoles (4b)

Nitric acid (28 g, 70%) was added dropwise to 37 g of concentrated sulfuric acid in a 100 ml, three-necked round bottom flask equipped with a magnetic stirrer, condenser and thermometer. The mixture was cooled in an ice bath and 20 g (0.078 mol) of bromo-3-trifluoromethylanisole prepared as described in Section 4.1 were added dropwise to maintain the temperature <40°C. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured onto ice and the product isolated by extraction with 1,2-dichloroethane, dried over MgSO<sub>4</sub> and the solvent evaporated. GC–MS analysis showed two principal isomers of monobromomononitro-3-trifluoromethylanisole. MS m/z: 299(m + calcd for C<sub>8</sub>H<sub>5</sub>BrF<sub>3</sub>NO<sub>3</sub>: 299).

### 4.3. 2-methoxy-6-trifluoromethylaniline

Bromonitro-3-trifluoromethylanisole mixture (20 g, 0.066 mol), sodium acetate (11 g, 0.134 mol), Pd/C (3 g, 10%) and 80% aqueous ethanol (125 ml) were placed in a 300 ml Hastelloy C Parr reactor. The reactor was pressurized with  $H_2$  to 200 psi and heated and stirred at 80°C until the pressure remained constant. Additional H2 was added during the reaction. After cooling and filtering the catalyst, the solvent was removed in vacuo on a rotary evaporator. The residue was diluted with 1,2-dichloroethane, washed with water, dried, and the solvent evaporated. GC-MS analysis showed the product to consist of isomers of 2-methoxy-trifluoromethylaniline in the ratio of 64:6:30. Distillation (Nester-Faust spinning band column) gave 7.0 g (55%) of 2-methoxy-6trifluoromethylaniline as the principal isomer, bp 80°C (20 mm). <sup>1</sup>H NMR (DMSO-d6)  $\delta$  3.82 (s, 3, OCH3); 5.1 (sb, 2, NH<sub>2</sub>); 6.65(m, 1, aromatic); 7.0 (m, 2, aromatic). MS m/z 191(m + calcd for C<sub>8</sub>H<sub>8</sub>F<sub>3</sub>NO: 191).

### 4.4. Chlorination of 3-trifluoromethylanisole

3-Trifluoromethylanisole (30 g, 0.17 mol), sodium acetate (28 g, 0.34 mol), and glacial acetic acid (250 ml) were placed in a 500 ml, three-necked round bottom flask equipped with temperature controller, gas sparger, condenser, and magnetic stirrer. The condenser was connected to a caustic scrubber and purged with nitrogen. The mixture was heated to ~70°C and gaseous chlorine introduced via the gas sparger. After chlorination was complete, the reaction mixture was cooled, filtered to remove inorganic solids, and the acetic acid removed in vacuo on a rotary evaporator. The residue was diluted with dichloromethane and washed with water to remove residual acid. The organic extract was dried over MgSO<sub>4</sub> and evaporated to give 28 g of product. GC–MS analysis showed three isomers. MS m/z 210(m + calcd for C<sub>8</sub>H<sub>6</sub>F<sub>3</sub>CIO: 210).

#### 4.5. Nitration of monochloro-3-trifluoromethylanisole (4a)

Monochloro-3-trifluoromethylanisole (95 g, 045 mol), prepared as described in Section 4.4, was added dropwise at ice bath temperature to a nitrating mixture prepared from 70% HNO<sub>3</sub> (133 g) and concentrated H<sub>2</sub>SO<sub>4</sub> (176 g). The addition of the anisole was controlled to maintain the reaction temperature <40°C. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was poured over ice and the product extracted with dichloromethane. After drying and solvent evaporation, 100 g of product was obtained. GC–MS analysis showed the mixture to consist of six monochloro-mononitro-3-trifluoromethylanisole. MS m/z 255(m+calcd for C<sub>8</sub>H<sub>6</sub>F<sub>3</sub>ClO: 255).

# 4.6. Preparation of 2-methoxy-6-trifluoromethylaniline from **5a**

Monochloro-mononitro-3-trifluoromethylanisole (100 g, 0.39 mol), sodium acetate (80 g, 0.98 mol), and Pd/C catalyst (5.0 g, 10% Pd/C) were added to a 600 ml Hastelloy C Parr reactor containing 80% aqueous ethanol (250 ml). The reactor was sealed and pressurized to 250 psi with  $H_2$  and heated to 85°C. Hydrogen was added as required and consumption ceased. The reactor was cooled and the catalyst removed by filtration and the solvent evaporated to give 65 g of product. GC–MS analysis showed the product to be a

mixture of three isomers in the ratio of 47:29:24. Distillation gave 30 g (40%) of 2-methoxy-6-trifluoromethylaniline.

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