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Preparation of 2,6-difluoro-*n*-alkylbenzenes from 1,3-difluorobenzene Transformation of 2,6-difluorotoluene to the corresponding benzaldehyde via benzyl chloride

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Abstract

Reactions of *n*-alkyl chlorides with the 2,6-difluorophenyl anion prepared from 1,3-difluorobenzene by the action of sodium amide in liquid ammonia give 2,6-difluoro-*n*-alkylbenzenes in high yields. 2,6-Difluorotoluene reacts with chlorine at 80°C to give 2,6-difluorobenzyl chloride in 92% yield. 2,6-Difluorobenzaldehyde has been obtained from this chloride through Sommelet's reaction in 62% yield.

Keywords: 2,6-Difluoro-*n*-alkylbenzene; Alkylation; Chlorination; 2,6-Difluorophenyl derivatives; Liquid ammonia

1. Introduction

A number of compounds containing 2,6-difluorophenyl or corresponding benzyl fragments are well known as efficient pesticides and medicines [1]. 2,6-Difluorobenzyl chloride and 2,6-difluorobenzaldehyde can be used as starting substrates in the synthesis of these bioactive materials [2–6]. 2,6-Difluorobenzaldehyde had been prepared [7,8] by formylation of 2,6-difluorophenyl lithium in THF/heptane, and converted to 2,6-difluorobenzyl derivatives such as the alcohol by direct hydrogenation or amine via oxoimidation followed by hydrogenation [7,8]. However, the direct incorporation of a methyl group into 1,3-difluorobenzene followed by its chlorination and nucleophilic substitution of the benzylic chlorine would appear a more convenient synthetic route since the first and second stages could be carried out without organic solvents.

We report here (cf. Ref. [9,10]) the easy preparation of 2,6-difluoro-*n*-alkyl-benzenes in 85–90% yields through the interaction of *n*-alkyl chlorides with the 2,6-difluorophenyl anion generated from 1,3-difluorobenzene by the action of $NaNH_2$ in liquid ammonia. Corresponding toluene, ethyl- and *n*-butylbenzene were prepared in this manner. A typical experimental procedure of a 2,6-difluoro-*n*-alkylbenzene preparation is described below for the toluene. In addition, we describe in detail the preparation of 2,6-difluorobenzyl chloride by the thermally induced chlorination of 2,6-difluorotoluene; the reaction initiated by UV irradiation (cf. Ref. [11]) had principally led to formation of 2,6-difluorobenzal chloride. The chlorination of 2,6-difluoroethylbenzene under conditions mentioned above gave the corresponding α- and β-monochlorinated products in a 2:3 ratio (according to the ^1H and ^{19}F NMR data), but these compounds were not isolated individually. Also 2,6-difluorobenzyl chloride has been converted into 2,6-difluorobenzaldehyde through Sommelet's reaction.

2. Experimental details

Melting points were determined in sealed capillaries and boiling points were measured during distillation, both are uncorrected. ^1H and ^{19}F NMR spectra were recorded in CCl_4/acetone-d_6, 10:1 vol., using a Bruker WP-200 SY spectrometer at 200.1 and 188.3 MHz, respectively. Chemical shifts are reported with respect to TMS and C_6F_6. IR spectra were obtained with a Specord M80 spectrometer. GLPC analysis was performed on a HP 5890 instrument using the HP G1800A GCD system (capillary GC column 0.26 mm/30 m, 0.25 μm film HP-5 phase).

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2.1. 2,6-Difluorotoluene

In a three-necked flask, equipped with thermometer, stir-bar, and gas outlet, a suspension of sodium amide was prepared from 23.3 g of metallic sodium in 500 ml of liquid ammonia at −60°C in the usual manner [12]. Then 1,3-difluorobenzene (88.9 g) and, after stirring the reaction mixture for 15 min, liquid methyl chloride (55.5 ml) were added dropwise at a temperature below −60°C, and stirring was continued for 20 min under the same conditions. Unreacted sodium amide was quenched by ammonium chloride (10.7 g). After evaporation of ammonia, the residue was steam distilled. The distillate thus obtained was separated into layers, the lower organic phase was dried by granulated calcium chloride and redistilled on a Vigreux distilling column of 150 mm length and 19 mm i.d. The 2,6-difluorotoluene (85.5 g, 84.5% yield) was collected at b.p. 110–112°C (lit. data: b.p. 112°C [11]) as a colorless liquid. The GLPC purity was 99.3% (2,6-difluoroethylbenzene was a by-product, 0.7%). ^{1}H NMR (δ, ppm): 1.8 (3H, s, α-H), 7.3 (1H, m, H^4), 7.0 (2H, m, H^{3,5}), and ^{19}F (δ, ppm): 47.8 (m).

Procedures analogous to that described for 2,6-difluorotoluene have been used to prepare other 2,6-difluoro-*n*-alkylbenzenes.

2.2. 2,6-Difluoroethylbenzene

A total of 17.0 g of 2,6-difluoroethylbenzene as a colorless liquid {85% yield; >99.0% GLPC purity; b.p. 129–130°C. Anal. calc. for $C_8H_8F_2$: C 67.6, H 5.05, F 26.7%. Found: C 67.9, H 4.72, F 26.8%; ^{1}H NMR: 2.7 (2H, q, CH_2, J_{HH} 7.5 Hz), 1.2 (3H, t, CH_3,), 7.3 (1H, m, H^4), 7.0 (2H, m, H^{3,5}), and ^{19}F: 45.8 (m)} were prepared from 15.0 g of 1,3-difluorobenzene, sodium amide (from 3.4 g of sodium), and 12.6 g of ethyl chloride in 150 ml of liquid ammonia.

2.3. 2,6-Difluoro-n-butylbenzene

A total of 4.0 g of 2,6-difluoro-*n*-butylbenzene as a colorless liquid {90% yield; >99.0% GLPC purity; b.p. 63–73°C/15 mm. Anal. calc. for $C_{10}H_{12}F_2$: C 70.6, H 7.06, F 22.3%. Found.: C 69.6, H 6.90, F 22.4%; ^{1}H NMR: 0.8–1.6 (7H, m, β, γ-CH_2, -CH_3), 2.6 (2H, t, α-CH_2, J_{HH} 7.0 Hz), 7.2 (1H, m, H^4), 6.95 (2H, m, H^{3,5}), and ^{19}F: 46.0 (m)} were prepared from 3.0 g of 1,3-difluorobenzene, sodium amide (from 0.7 g of sodium), and 5.4 g of *n*-butyl chloride in 100 ml of liquid ammonia.

2.4. 2,6-Difluorobenzyl chloride

A flask, equipped with stir-bar, thermometer, reflux condenser, and bubbler for gaseous chlorine was charged with 85.0 g of 2,6-difluorotoluene. The chlorine was passed through the liquid at a rate of ~4–5 l/h over 4–6 h with continuous stirring at 82–86°C. The consumption of starting material in the reaction mixture was controlled by GLPC analysis. The mixture was cooled after the complete conversion of 2,6-difluorotoluene, and purged from residual chlorine and hydrogen chloride with nitrogen to give 108.0 g of crude product containing 93–95% of 2,6-difluorobenzyl chloride, 5–6% of 2,6-difluorobenzal chloride and traces of 2,6-difluorotoluene. This product was rectified on a column, and the fraction boiling at 170–173°C was drawn off as pure 2,6-difluorobenzyl chloride crystallizing at 33–34°C (100.0 g, 92.5% yield; >99.0% GLPC purity. Lit. data: b.p. 76°C/22 mm, m.p. 32°C [11]). ^{1}H NMR: 4.65 (2H, α-H), 7.3 (1H, m, H^4), 6.9 (2H, m, H^{3,5}) and ^{19}F: 47.5 (m).

2.5. 2,6-Difluorobenzaldehyde

A flask, equipped with reflux condenser, was charged with 2,6-difluorobenzyl chloride (12.4 g), hexamethylenetetramine (10.6 g), glacial acetic acid (25 ml) and water (25 ml), and heated on a water-bath until the mixture was homogenized and then separated into layers. The orange oil thus obtained was distilled to give 6.7 g of 2,6-difluorobenzaldehyde (62% yield, b.p. 76–80°C/13–15 mm, >98.0% GLPC purity. Lit. data: 82–84°C/15 mm [7,8]). ^{1}H NMR: 10.3 (1H, α-H), 7.6 (1H, m, H^4), 7.0 (2H, m, H^{3,5}), and ^{19}F: 47.3 (m). IR (cm^{-1}): 1720 (C=O), 2780–2880 ($C_{C=O}$–H).

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