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The selective ortho-methoxylation of pentafluorobenzoic acid – a new way to tetrafluorosalicylic acid and its derivatives

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Abstract

A simple and efficient preparation of tetrafluorosalicylic acid has been developed which involves a selective substitution of fluorine in pentafluorobenzoic acid with methoxyl group by magnesium methoxide. The synthesis of 2,6-dimethoxy-3,4,5-trifluorobenzoic acid, 4,5,6-trifluororesorcinol and its dimethoxy ether is described.

Keywords: Pentafluorobenzoic acid; Tetrafluorosalicylic acid; 4,5,6-trifluororesorcinol

1. Introduction

Nucleophilic substitution is the most typical reaction for fluoroaromatic compounds. Its direction and rate are determined by the presence of electron-withdrawing (or donating) substituents in the benzene ring. Electron-withdrawing groups orientate an attack of a nucleophile mainly to the *para*-position [1,2]. *Ortho*-substituted products (in a mixture with *para*-) may be obtained when the acceptor substituent forms hydrogen bonds with the attacking nucleophile. The reaction must be carried out in a low-polar solvent to stabilize the complex. Examples of these are the reactions of nitropentafluorobenzene, methylpentafluorophenylsulphone and ethylpentafluorobenzoate with sodium ethylate in diethyl ether [2,3]. Pentafluorobenzoic acid reacts similarly with magnesium benzyl(methyl)halides to form *ortho*-substituted products [4], while the reaction of this acid with alkali metal alkoxides gives only *para*-derivatives [5].

We have studied the selective *ortho*-substitution of fluorine atoms in pentafluorobenzoic acid with magnesium methoxide with a purpose to prepare fluoroaromatic synthons, in particular, tetrafluorosalicylic acid. Nonfluorinated salicylic acid is widely used in organic chemistry for the preparation of heterocyclic compounds. The use of tetrafluorosalicylic acid and its derivatives is emphasized by the synthesis of quinolone class of antibiotics on the basis of *ortho*-methoxytetrafluorosalicylic acid [6,7]. Tetrafluorosalicylic acid and its alkoxy derivatives are not obtained by direct substitution of fluorine atoms in pentafluorobenzoic acid due to the *para*-orientation effect of the carbonyl substituent. Hitherto methods for the preparation of tetrafluorosalicylic acid involved splitting of fluorinated heterocycles [8,9] and tetrafluorobenzene metallation [10]. In this connection, the development of a simple and effective method for synthesis of tetrafluorosalicylic acid will open a way to its active use in organic synthesis.

2. Experimental details

Infrared spectra were measured on a Specord 75 IR spectrophotometer. ^{1}H NMR spectra were recorded on a Tesla BS-567A instrument (^{1}H: 100 MHz) using TMS as an internal standard. ^{19}F NMR spectra were recorded on a Tesla BS-587A instrument (^{19}F: 75 MHz) using $CFCl_3$ as an internal standard. Microanalyses were performed with a Carlo Erba CHNS-O EA 1108 elemental analyzer. Melting points were measured in open capillaries and are reported uncorrected.

2.1. Tetrafluorosalicylic acid (3)

A stirred suspension of Mg (shavings) (6.7 g, 27.6 mmol) in absolute MeOH (55 ml) was warmed to 60°C. To the suspension was added anhydrous diglyme (50 ml) at 60–80°C. The reaction mass was stirred to fully dissolve the Mg at 60–80°C after 3–4 h. Methanol was removed at 160°C from the reaction mixture. After cooling to 100°C the

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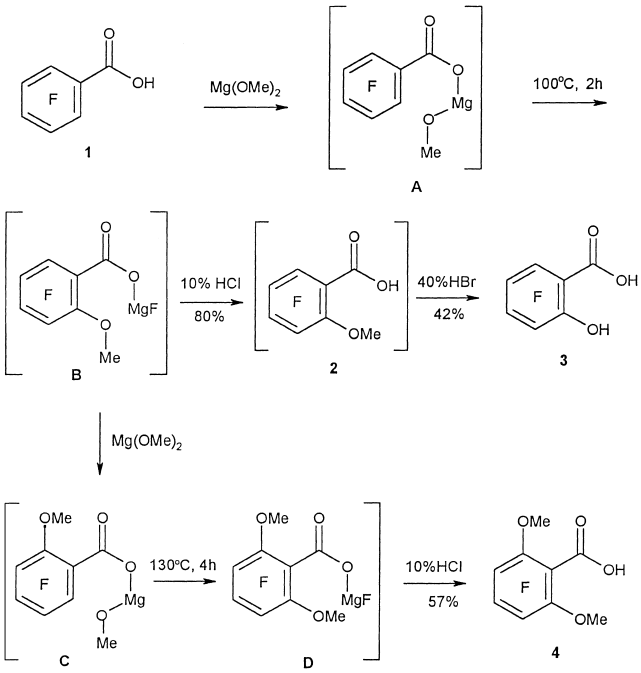


Scheme 1.

mixture was added to a solution of pentafluorobenzoic acid (**1**) (5 g, 23.6 mmol see Scheme 1) in anhydrous diglyme (30 ml). The reaction mixture was stirred at 100°C for 2 h. The solvent was removed in vacuo, the residue was treated with 10% HCl (190 ml). The resulting solution was extracted with $CHCl_3$ (3 × 50 ml) and Et_2O (100 ml). The extracts were combined, dried (over $MgSO_4$) and the solvents were removed in vacuo. The oily residue was refluxed in 40% HBr (50 ml) for 12 h. The mixture was cooled and the precipitate filtered off, recrystallized from H_2O to give **3** (2.1 g, 42%) as colorless crystals (mp 170–173°C) ([1], 169–172°C). ^{1}H NMR and IR spectra matched literature values [1].

2.2. 2,6-dimethoxy-3,4,5-trifluorobenzoic acid (**4**) (nc)

To a well-stirred suspension of magnesium methoxide (6.7 g, 27.6 mmol) prepared by the procedure described above was added a solution of **1** (5 g, 23.6 mmol) in anhydrous diglyme (30 ml) at 130°C. The stirred reaction mixture was heated at 130°C for 4 h. The solvent was removed in vacuo. The residue was treated with 10% HCl (190 ml). The resulting solution was cooled to 0°C and stored for 2 h. The precipitate was filtered off and washed with H_2O. The crude product was crystallized from heptane and dried to give **4** (2.1 g, 57%) as colorless crystals (mp 107–109°C). ^{1}H NMR (acetone-d_6) (δ (ppm) = 4.10 (6H, d, $2CH_3$, $J_{(H–F)} = 1.9$ Hz,), 11.22 (1H, s, COOH). ^{19}F NMR (acetone-d_6) (δ (ppm) = −157.12 (2F, dq, F^3, F^5, $J_{(F–F)} = 19.5$ Hz, $J_{(H–F)} = 1.9$ Hz), −154.26 (1F, t, F^4, $J_{(F–F)} = 19.5$ Hz). IR (cm^{-1}): 2750–2450 (OH); 1700 (C=O); 1490 (C=C); 1060 (CF). *Anal*. Calc. for $C_9H_7F_3O_4$: C, 45.78; H, 2.99; F, 24.14. Found: C, 45.51; H, 2.99; F, 24.27%.

2.3. 4,5,6-Trifluororesorcinol dimethoxy ether (**5**) (nc)

A mixture of **4** (1 g, 4.23 mmol) and Bu_3N (20 ml) was refluxed for 2 h, then distilled under reduced pressure. The distillate was cooled to room temperature. The precipitated solid was collected by filtration, washed with the saturated solution of $NaHCO_3$ (50 ml), recrystallized from heptane to give **5** (0.15 g, 18.5%) as colorless crystals (mp 92–94°C). ^{1}H NMR (acetone-d_6) (δ (ppm) = 3.93 (6H, s, $2CH_3$), 6.73 (1H, td, CH, $J_{(H–Fmetha)} = 8$ Hz, $J_{(H–Fpara)} = 2.6$ Hz). ^{19}F NMR (acetone-d_6) (δ (ppm) = −167.53 (2F, dd, F^4, F^6, $J_{(F–F)} = 19.5$ Hz, $J_{(H–Fmetha)} = 8$ Hz), −160.24 (1F, dt, F^5, $J_{(F–F)} = 19.5$ Hz, $J_{(H–Fpara)} = 2.6$ Hz). IR (cm^{-1}): 1510 (C=C); 1060 (CF) *Anal*. Calc. for $C_8H_7F_3O_2$: C, 50.01; H, 3.67; F, 29.66. Found: C, 50.09; H, 3.58; F, 29.63%.

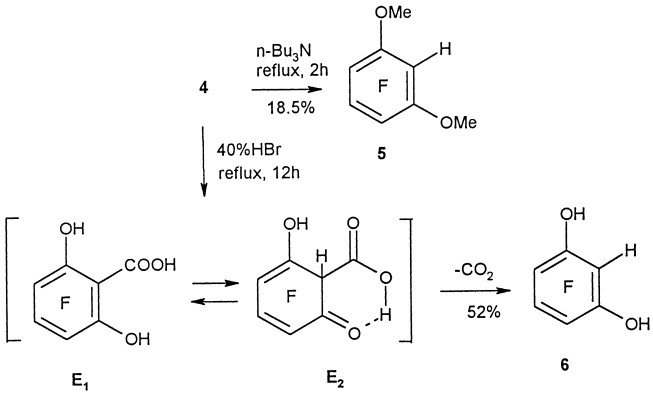
2.4. 4,5,6-Trifluororesorcinol (**6**) (nc)

A mixture of **4** (1.1 g, 4.66 mmol) and 40% HBr (25 ml) was refluxed for 12 h, than poured into water (30 ml). The product was extracted with Et_2O (3 × 50 ml). The extract was washed with the saturated solution of $NaHCO_3$ (100 ml). The solvent was evaporated, the residue was recrystallized from CCl_4 to give **6** (0.4 g, 52%) as colorless crystals (mp 128–128.5°C). ^{1}H NMR (acetone-d_6) (δ (ppm) = 6.47 (1H, td, CH, $J_{(H–Fmetha)} = 7.8$ Hz, $J_{(H–Fpara)} = 2.3$ Hz), 8.78 (1H, s, OH). ^{19}F NMR (acetone-d_6) (δ (ppm) = −170.01 (2F, dd, F^4, F^6, $J_{(F–F)} = 20$ Hz, $J_{(H–Fmetha)} = 7.8$ Hz), −160.67 (1F, td, F^5, $J_{(F–F)} = 20$ Hz, $J_{(H–Fpara)} = 2.3$ Hz). IR (cm^{-1}): 3355 (OH); 1630, 1510 (C=C); 1060 (CF). *Anal*. Calc. for $C_6H_3F_3O_2$: C, 43.92; H, 1.84; F, 34.73. Found: C, 43.98; H, 1.73; F, 34.65%

3. Results and discussion

In present work, it has been found that interaction of pentafluorobenzoic acid (**1**) with magnesium methoxide in benzene, toluene, bis(2-methoxyethyl)ether (diglyme) or methanol leads to selective *ortho*-substitution of a fluorine atom by methoxyl group to form 2-methoxy-3,4,5,6-tetrafluorobenzoic acid (**2**). Compound **2** was not isolated from the reaction mass as a pure sample, but in the ^{19}F spectrum of the resulting mixture four equivalent multiple resonance signals at δ = −142.08, −145.00, −155.50 and 163.17 ppm were attributed to the fluorine atoms of **2**.

Treatment of **2** with 40% hydrogen bromide affords tetrafluorosalicylic acid (3) (Scheme 1). Incomplete conversion of starting **1** does not allow preparation of **3** in good yield. Increase of the reaction time and/or temperature leads to displacement of the second fluorine atom to form 2,6-dimethoxy-3,4,5-trifluorobenzoic acid (**4**) (via intermediate C) (Scheme 1). Optimal conditions for preparative synthesis



Scheme 2.

of tetrafluorosalicylic acid (**3**) were diglyme at 100°C, 2 h and for 2,6-dimethoxy-3,4,5-trifluorobenzoic acid **(4)** diglyme at 130°C, 4 h.

It is notable that displacement of fluorine in the reaction of pentafluorobenzoic acid with magnesium methoxide does not occur in the *para*-position as in the interaction of **1** with alkaline metal alkoxides [5].

Compound **4** was used as precursor for synthesis of 4,5,6-trifluororesorcinol (**6**) and its dimethoxy ether (**5**) (Scheme 2).

Trifluororesorcylic acid (E_1) was not obtained. This is probably due to its decarboxylation, which is possible when acid exists in keto-form (E_2) and occurs like decarboxylation of 1,3-keto-acids. Such tautomerism for resorcinol derivatives is expected [11].

Thus, the present reactions provide a useful method for preparation of tetrafluorosalicylic acid and its derivatives.

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