

A re-investigation of the reaction of hemimellitic acid with sulphur tetrafluoride. A simple preparation of 2,6-bis(trifluoromethyl)benzoic acid

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Abstract

The reaction of hemimellitic acid (**1**) with SF₄/HF gives a 1 : 3.5 : 13 mixture of 1,2,3-tris(trifluoromethyl)benzene (**2**), 1,1,3,3-tetrafluoro-4-trifluoromethyl-1,3-dihydroisobenzofuran (**3**) and 2,6-bis(trifluoromethyl)benzoyl fluoride (**4**). Treatment of the crude reaction mixture with aqueous KOH, followed by acidification of the water phase, gives a good yield of pure 2,6-bis(trifluoromethyl)benzoic acid (**5**). © 1997 Elsevier Science S.A. All rights reserved.

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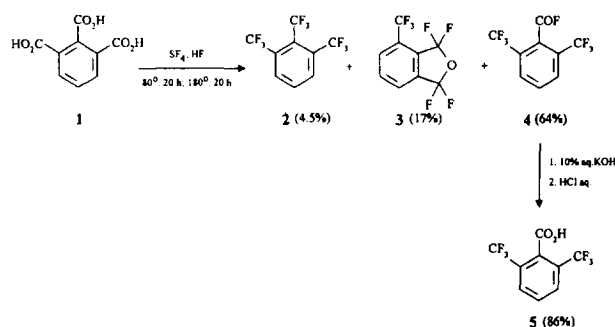
1. Introduction

It was reported a long time ago that the treatment of hemimellitic acid (1,2,3-benzenetricarboxylic acid) with sulphur tetrafluoride at 100–175 °C results in the conversion of the 1- and 3-carboxylic groups into trifluoromethyl groups, whereas the reaction of the central 2-carboxylic group stops at the acid fluoride stage; 2,6-bis(trifluoromethyl)benzoyl fluoride was obtained in 84% yield and identified by stepwise conversion to isophthalic acid [1]. The low reactivity of the internal fluorocarbonyl group formed is undoubtedly due to the steric hindrance exerted by the two neighbouring CF₃ groups. Later, it was found that all three carboxylic groups of hemimellitic acid can be converted into CF₃ groups to give a 71% yield of 1,2,3-tris(trifluoromethyl)benzene by applying extreme reaction conditions (320 °C, 10 h, large excess of SF₄ and HF) [2]. In both reports [1,2], probably because of the lack of appropriate analytical techniques, no mention was made of the formation of any isomeric products.

2. Results and discussion

We have found that the reaction of hemimellitic acid (**1**) with an SF₄/HF mixture at 80–180 °C results in three prod-

ucts: 1,2,3-tris(trifluoromethyl)benzene (**2**), 1,1,3,3-tetrafluoro-4-trifluoromethyl-1,3-dihydroisobenzofuran (**3**) and 2,6-bis(trifluoromethyl)benzoyl fluoride (**4**) in a 1 : 3.5 : 13 ratio.



Gas chromatography-mass spectrometry (GC-MS) analysis of the crude reaction mixture shows a molecular ion $m/z = 282$ for the minor, most volatile, product thus identifying it as tris(trifluoromethyl)benzene **2**. The two other components of the reaction mixture exhibit identical molecular ions, $m/z = 260$, but different fragmentation patterns, indicating isomeric compounds with the molecular formula C₉H₃F₇O. Vacuum distillation of the reaction mixture allowed the isolation of the least volatile product, which was then identified by ¹H and ¹⁹F nuclear magnetic resonance (NMR) spectroscopy as the acid fluoride (**4**). Spectroscopic investigations

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of the most volatile fraction, after the hydrolytic removal of **4** as described below, permitted the identification of compounds **2** and **3**. The ^{19}F NMR spectrum of **3** shows one CF_3 group signal and two AB spin systems for CF_2 groups with small geminal coupling constants (approximately 4.2 Hz), thus indicating slight magnetic non-equivalence of the fluorines in each CF_2 group. This non-equivalence is also demonstrated by the two coupling constants (dd) of CF_3 to the neighbouring CF_2 fluorines. The formation of cyclic tetrafluoroethers is typical for reactions of SF_4 with benzenepolycarboxylic acids and 1,2-benzenedicarboxylic acids flanked on both sides with bulky substituents, such as CF_3 , Cl or CH_3 groups [3]; the present result seems to be the first example of the cyclization of two *ortho*-carboxylic groups sterically hindered from one side only.

The cyclic structure of **3** is also confirmed by its hydrolytic stability under basic conditions. This is in contrast with the acid fluoride **4** which, on prolonged treatment with 10% aqueous potassium hydroxide at 100 °C, fully hydrolyses to the potassium salt of the corresponding acid **5**, while compounds **2** and **3** remain unchanged. Thus the hydrolysis of the reaction mixture containing **2**, **3** and **4** leaves an organic layer containing only **2** and **3**. Acidification of the aqueous phase gives a precipitate of 2,6-bis(trifluoromethyl)benzoic acid (**5**) of high purity and over 85% yield (approximately 55% yield in relation to **1**). This provides a simple and efficient method for the preparation of 2,6-bis(trifluoromethyl)benzoic acid (**5**), which is competitive with the method reported recently involving the low-temperature metallation of 1,3-bis(trifluoromethyl)benzene with an *n*-BuLi/*tert*-BuOK reagent followed by carboxylation [4].

3. Experimental details

^1H and ^{19}F NMR spectra were recorded in CDCl_3 with a Varian Gemini 200 spectrometer at 200 and 188 MHz respectively. Chemical shifts are quoted in parts per million from internal tetramethylsilane (TMS) for protons (positive downfield) and from internal CFCl_3 for fluorine nuclei (positive upfield). GC-MS analyses were performed with a Hewlett-Packard 5890 apparatus (70 eV) using a 30 m capillary column coated with an HP5 oil. IR spectra were obtained with a Perkin-Elmer 1640 instrument.

3.1. Reaction of hemimellitic acid with sulphur tetrafluoride

Hemimellitic acid (**1**) (25 g, 0.119 mol) was placed in a 250 ml stainless steel autoclave; the autoclave was immersed in a dry ice-acetone bath and anhydrous hydrogen fluoride (28 g, 1.4 mol) followed by sulphur tetrafluoride (42 g, 0.4 mol) were condensed into it. The charged autoclave was placed in a rocking furnace and heated overnight at 80 °C. After cooling to ambient temperature, gaseous products were released (SOF_2 , unreacted SF_4); the autoclave was again

cooled in a dry ice-acetone bath, refilled with sulphur tetrafluoride (64 g, 0.6 mol) and heated overnight at 180 °C. The gaseous products were released, the liquid residue was dissolved in methylene chloride (150 ml) and dry sodium fluoride (15 g) was added as an HF scavenger. The solution was left overnight and then filtered and the solvent was distilled off to give a crude mixture of products (26.7 g). GC-MS analysis revealed three components which were later identified by ^1H and ^{19}F NMR spectroscopy as compounds **2** (5.6%), **3** (19.8%) and **4** (74.6%). Vacuum distillation gave three fractions (1, 7.2 and 16 g, boiling range 92–106 °C/80 Torr) containing compounds **2**, **3** and **4** in various ratios and a residue (2.5 g) consisting of almost pure (97%) acid fluoride **4**. The first fraction (92–98 °C/80 Torr) was agitated with 10% aqueous KOH at 80–100 °C for 6 h; the remaining organic layer consisted of compounds **2** and **3** only, which were subjected to NMR investigations.

1,2,3-Tris(trifluoromethyl)benzene (**2**): GLC yield, 4.5%. ^1H NMR, AB_2 system δ : 7.84 (t, $^3J_{\text{HH}} = 7.9$ Hz, 1H), 8.10 (d, $^3J_{\text{HH}} = 7.9$ Hz, 2H) ppm. ^{19}F NMR δ : 55.3 (hept., $^5J_{\text{FF}} = 15.9$ Hz, 1CF_3), 58.2 (q, $^5J_{\text{FF}} = 15.9$ Hz, 2CF_3) ppm. GC-MS m/z (% assignment): 282 (69, M^+), 263 (92 ($\text{M}^+ - \text{F}$)), 232 (24 ($\text{M}^+ - \text{CF}_2$)), 213 (100 ($\text{M}^+ - \text{CF}_3$)), 163 (26 ($\text{M}^+ - \text{C}_2\text{F}_5$)), 144 (13 ($\text{M}^+ - 2\text{CF}_3$)), 194 (10 ($\text{M}^+ - \text{CF}_4$)), 69 (18, CF_3^+).

1,1,3,3-Tetrafluoro-4-trifluoromethyl-1,3-dihydroisobenzofuran (**3**): GLC yield, 17%. ^1H NMR δ : 7.86–8.06 (complex ABC system) ppm. ^{19}F NMR δ : 61.4 (dd, $^5J_{\text{FF}}$ approximately 10.8 and 10 Hz, CF_3), two AB systems 67.63 and 67.65 (dq, $^2J_{\text{FF}} \approx 4.2$ Hz, $^5J_{\text{FF}} \approx 10$ –10.8 Hz, CF_2), 69.70 and 69.72 (d, $^2J_{\text{FF}} \approx 4.2$ Hz, CF_2). GC-MS m/z (% assignment): 260 (32, M^+), 241 (29 ($\text{M}^+ - \text{F}$)), 213 (100 ($\text{M}^+ - \text{COF}$)), 194 (12 ($\text{M}^+ - \text{CF}_2\text{O}$)), 163 (18 ($\text{M}^+ - \text{C}_2\text{F}_3\text{O}$)), 144 (14 ($\text{M}^+ - \text{C}_2\text{F}_4\text{O}$)), 125 (10 ($\text{M}^+ - \text{C}_2\text{F}_5\text{O}$)), 75 (11, C_6H_3^+), 69 (8, CF_3^+).

2,6-Bis(trifluoromethyl)benzoyl fluoride (**4**): GLC yield, 64.4%. ^1H NMR, AB_2 system δ : 7.86 (t, $^3J_{\text{HH}} = 7.7$ Hz, 1H), 8.02 (d, $^3J_{\text{HH}} = 7.7$ Hz, 2H) ppm. ^{19}F NMR δ : -58.30 (hept., $^5J_{\text{FF}} = 5.0$ Hz, COF), 60.37 (d, $^5J_{\text{FF}} = 5.0$ Hz, 2CF_3) ppm. GC-MS m/z (% assignment): 260 (55, M^+), 241 (68 ($\text{M}^+ - \text{F}$)), 232 (100 ($\text{M}^+ - \text{CO}$)), 213 (59 ($\text{M}^+ - \text{COF}$)), 191 (33 ($\text{M}^+ - \text{CF}_3$)), 182 (22 ($\text{M}^+ - \text{C}_2\text{F}_2\text{O}$)), 163 (95 ($\text{M}^+ - \text{CF}_3 - \text{CO}$)), 143 (18, $\text{C}_7\text{H}_2\text{F}_3^+$), 75 (19, C_6H_3^+), 69 (30, CF_3^+). IR (film) (cm^{-1}): 1849 (COF) (literature 1860 cm^{-1} [1]).

3.2. Preparation of 2,6-bis(trifluoromethyl)benzoic acid (**5**)

A mixture composed of compounds **2** (5.5%), **3** (20.5%) and **4** (74%) (22.2 g) and 10% aqueous KOH was vigorously agitated at 100 °C for 48 h. The remaining organic layer was separated and the water phase was extracted with Et_2O (3 × 20 ml) and strongly acidified with concentrated hydrochloric acid. After removal of the residual Et_2O on a rotary evaporator, a white precipitate of acid (**5**) was formed. The precipitate was filtered off, washed twice with a small

amount of cold water and dried under vacuum over P_5O_{10} . Yield, 14 g (85.7% in relation to **4**). M.p., 134–136 °C (in capillary, uncorrected) (literature 133–135 °C [4]). Analysis: calculated for $C_9H_4F_6O_2$: C, 41.88%; H, 1.56%; F, 44.16%; found: C, 41.90%; H, 1.64%; F, 44.00%. 1H NMR, AB₂ system δ : 7.75 (t, $^3J_{HH} = 7.85$ Hz, 1H), 7.96 (d, $^3J_{HH} = 7.85$ Hz, 2H), 8.16 (broad, COOH) ppm. ^{19}F NMR δ : 60.05 (s, CF₃) ppm. GC-MS m/z (% assignment): 258 (75, M⁺), 241 (100 (M⁺ – OH)), 219 (32 (M⁺ – HF₂)), 213 (36 (M⁺ – CO₂H)), 194 (52 (M⁺ – CO₂H – F)), 163 (30, C₇H₃F₄⁺), 144 (20, C₇H₃F₃⁺), 125 (12, C₇H₃F₂⁺), 99

(5, C₅HF₂⁺), 75 (8, C₆H₃⁺), 69 (5, CF₃⁺), 45 (4, CO₂H⁺). IR (nujol) (cm⁻¹): 1722 (CO), 2853–3033 (OH).

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