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A Site Selective Functionalisation of 1,3-Bis(trifluoromethyl)benzene

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Abstract

1,3-Bis(trifluoromethyl)benzene was regioselectively metalated and subsequently carboxylated at position 2 to give 2,6-bis(trifluoromethyl)benzoic acid. Treatment of the acid with sulphur tetrafluoride gave 2,6-bis-(trifluoromethyl)benzoyl fluoride which was readily converted to 2,6-bis(trifluoromethyl)benzyl alcohol and further to 2,6-bis(trifluoromethyl)benzaldehyde. Bromination of 2,6-bis(trifluoromethyl)benzoic acid with 1,1-dibromo-5,5-dimethylhydantoin proceeded regioselectively affording 4-bromo-2,6-bis(trifluoromethyl)benzoic acid almost quantitavely. The latter was fluorinated to the corresponding acid fluoride which on treatment with methanolic sodium methoxide gave 4-methoxy-2,6-bis(trifluoromethyl)benzoic acid or its methyl ester, depending on the reaction conditions. 4-Methoxy-2,6-bis(trifluoromethyl)benzoic acid, *via* its acid fluoride, was also transformed, first to the corrsponding benzyl alcohol, then to the benzaldehyde. Lithiation of 4-methoxy-2,6-bis(trifluoromethyl)benzoic acid, followed by methylation, proceeded with low selectivity, nevertheless, methyl 4-methoxy-3-methyl-2,6-bis(trifluoromethyl)benzoate was formed as the main product which was stepwise converted to 4-methoxy-3-methyl-2,6-bis(trifluoromethyl)benzyl alcohol and 4-methoxy-3-methyl-2,6-bis(trifluoromethyl)-benzaldehyde, albeit in low total yield .

Keywords: Fluorine compounds; Benzenes; Metalation; Regioselective control

1. INTRODUCTION

A unique character of the trifluoromethyl group [1,2] means that the introduction of this substituent into biologically important molecules has attracted much attention; trifluoromethylated aromatics are common structural fragments of modern drugs and pesticides [2 - 7]. For this reason, a search for synthetic methods leading to suitable trifluoromethylated molecules is of considerable importance [1 - 8]. The aim of the present work was the synthesis of aldehydes **1a-c** useful as

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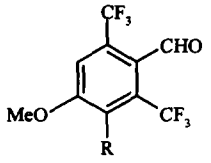
intermediates to trifluoromethylated analogs of aromatic retenoids which have been applied with remarkable success to treatment of *psoriasis* [9].



1a, R = H
1b, R = CH_3
1c, R = CF_3

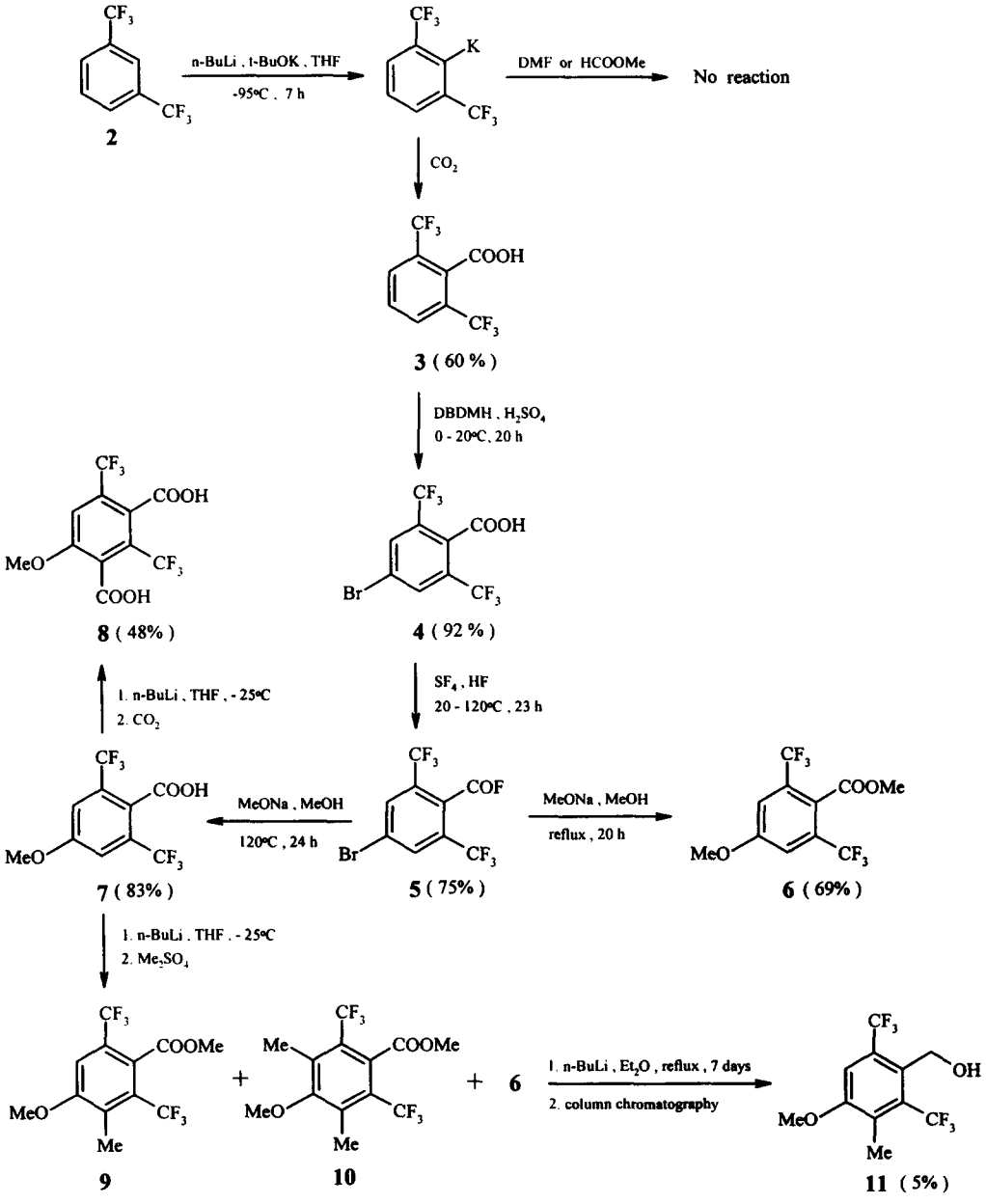
In the previous paper we reported functionalization of 3,5-bis(trifluoromethyl)anizole [10]. That compound, however, independently of reagent or reaction conditions, undergoes metallation exclusively at the position *ortho* to the methoxy group and therefore it could not be functionalised between the two CF_3 groups. To avoid the strong directing power of the methoxy group, the present strategy for the synthesis of compounds of type **1** involves regioselective functionalisation of 1,3-bis(trifluoromethyl)benzene in position 2, prior to introduction of the methoxy group.

2. RESULTS AND DISCUSSION

The reaction sequence started from the low temperature metallation of commercially available 2,3-bis(trifluoromethyl)benzene (**2**) with a n-BuLi/tert-BuOK ("LIKOR") reagent using a slightly modified procedure described by Schlosser *et al* [11]. The attempted direct formylation of the formed 2,6-bis(trifluoromethyl)phenylpotassium (**i**) with DMF or ethyl formate failed; only substrate **2** was regenerated. However, carboxylation with large excess of solid carbon dioxide gave 2,6-bis(trifluoromethyl)benzoic acid (**3**) in good yield and high purity, as described previously [11], thus confirming highly regioselective metallation at the kinetically most favourable position, between the two CF_3 groups. The acid **3** was alternatively obtained by fluorination of hemimellitic acid with sulphur tetrafluoride [12].

The bromination of acid **3** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) in sulphuric acid also preceeded regioselectively to give 4-bromo-2,6-bis(trifluoromethyl)benzoic acid (**4**) almost quantitatively. Substitution of the methoxy group for bromine in **4** was achieved by conversion to the fluoride **5** followed by treatment of the latter with sodium methoxide in methanol. Substitution of the bromine could not be carried out directly on the acid **4** because formation of carboxylate ion in an alkaline medium strongly retards nucleophilic attack on the benzene ring. To avoid this, the carboxylic group should be converted into an non-ionic moiety, *e.g.* an ester group. However, it has been reported that 2,6-bis(trifluoromethyl)benzoic acids, possibly because of steric hindrance, could

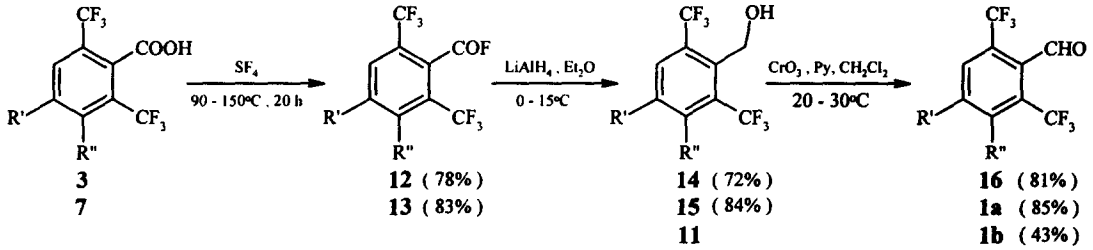
not be directly esterified by conventional methods [13]. Acid **4** was then converted into 4-bromo-2,6-bis(trifluoromethyl)benzoyl fluoride (**5**) by treatment with sulphur tetrafluoride. Reaction of the fluoride **5** with methanolic sodium methoxide at the reflux temperature resulted in simultaneous replacement of both acyl fluorine and aromatic bromine to give methyl 4-methoxy-2,6-bis(-trifluoromethyl)benzoate (**6**). Addition of **5** to an MeONa\MeOH solution occurred with an exothermic effect but, anyway, when the reaction was quenched at an early stage only **6** and



unreacted **5** were present in the product and none of the expected methyl 4-bromo-2,6-bis(trifluoromethyl)benzoate was found. When the reaction mixture was heated at 120°C for 24 hour in a sealed tube, total cleavage of the ester function occurred to give 4-methoxy-2,6-bis(trifluoromethyl)benzoic acid (**7**) in high yield.

Lithiation of acid **7** with two equivalents of n-butyllithium followed by treatment with solid carbon dioxide gave 4-methoxy-2,6-bis(trifluoromethyl)isophthalic acid (**8**) in reasonable yield. However, lithiation of **7** did not always proceed with good selectivity. In other experiments, after quenching the reaction with dimethyl sulphate a mixture of three compounds was obtained: the desired methyl 4-methoxy-3-methyl-2,6-bis(trifluoro-methyl)benzoate (**9**), methyl 4-methoxy-2,6-bis(trifluoromethyl)benzoate (**6**) and methyl 4-methoxy-3,5-dimethyl-2,6-bis(trifluoromethyl)benzoate (**10**) in a 67 : 16 : 4 ratio. This mixture of esters was subjected to reduction with lithium aluminium hydride in refluxing diethyl ether but the reaction was very sluggish and not clean. After seven days a very complex mixture was formed from which the required 4-methoxy-3-methyl-2,6-bis(trifluoro-methyl)benzyl alcohol (**11**) was isolated by a column chromatography in a *ca.* 5% yield with respect to acid **7**. In contrast to the mixture of esters, acid fluorides **12** and **13**, obtained by treatment of acids **3** and **7** with sulphur tetrafluoride, were found to react exothermically with $LiAlH_4$ to afford, respectively, 2,6-bis(trifluoromethyl)benzyl alcohol (**14**) and 4-methoxy-2,6-bis(trifluoromethyl)benzyl alcohol (**15**) in high yields. The observed drastically different susceptibility of the ester and the fluorocarbonyl groups to reduction with $LiAlH_4$ could be interpreted in terms of much better leaving group ability of the fluoride ion as compared to the methoxide ion and, probably, also by less steric crowding in fluorides **12** and **13** than in esters **6**, **9** and **10**.

The oxidation of benzyl alcohols **14** and **15** with a CrO_3-pyridine complex in methylene chloride, by following the literature procedure [14], proceeded cleanly to give, respectively, 2,6-bis(trifluoromethyl)benzaldehyde (**16**) and 4-methoxy-2,6-bis(trifluoromethyl)benzaldehyde (**1a**) in over 80% yield and the oxidation of alcohol **11** afforded 4-methoxy-3-methyl-2,6-bis(trifluoromethyl)benzaldehyde (**1b**) in a 43% yield.



3 **7**

12 (78%)
13 (83%)

14 (72%)
15 (84%)
11

16 (81%)
1a (85%)
1b (43%)

3, 12, 14, 16 : R' = R" = H
7, 13, 15, 1a : R' = MeO, R" = H
11, 1b : R' = MeO, R" = Me

The attempted fluorination of isophthalic acid **8** to 4-methoxy-2,3,6-tris(trifluoromethyl)benzoyl fluoride and then conversion of the latter to compound **1c**, failed; the fluorination resulted in a complex mixture containing 4-methoxy-2,6-bis(trifluoromethyl)isophthaloyl difluoride as the main product.

3. EXPERIMENTAL

Melting points were determined in open capillaries and boiling points during distillation; both are uncorrected. Elemental analyses for C, H, and N, were done with a Perkin-Elmer 240 Elemental Analyzer. The fluorine was determined by a Rowley and Churchill method [15] after combustion of samples in an atmosphere of oxygen in a Schöniger flask [16]. ^{1}H- and ^{19}F-NMR spectra were recorded with a Varian Gemini 200 spectrometer at 200 and 188 MHz, respectively; chemical shifts are in p.p.m. from internal TMS for protons and from internal $CFCl_3$ for fluorine nuclei (positive upfield). GC-MS analyses were carried out with a Hewlett-Packard 5890 apparatus (70eV) using a 30 m capillary coated with a HP-5 oil. Mass spectra of isolated compounds were obtained with an AMD-604 spectrometer and IR spectra were measured with a Perkin-Elmer 1640 instrument.

*3.1. 2,6-Bis(trifluoromethyl)benzoic acid (**3**)*

The reaction was carried out in a cylindrical glass vessel of *ca.* 400 ml capacity (ϕ = 45 mm, l = 300 mm) fitted with a rubber septum, magnetic stirring bar and a valve connected to a rubber balloon filled with dry nitrogen. Dry THF (200 ml) was placed in the vessel, the vessel was purged with nitrogen then freshly sublimed *tert*-BuOK (13.6 g, 0.12 mol) was added at room temperature and the mixture was stirred until almost clear solution was obtained. The solution was cooled to *ca.* -30°C and 1,3-bis(trifluoromethyl)benzene (**2**) (19.3 g, 0.09 mol) was added with a syringe (yellow colour appeared) while stirring, then the solution was cooled to -95°C (n-hexane-liquid nitrogen bath) and n-BuLi (0.94 mol, 37.5 ml of 2.5 M solution in hexane) was added dropwise in such a rate to not allow the temperature rise above -90°C (*ca.* 15 min). The deep-violet reaction mixture was stirred at -95°C for seven hours after which time freshly crushed dry ice (*ca.* 300 g) was added portionwise (Notice: intensive foaming), the reaction vessel was removed from the cooling bath, placed in an empty Dewar flask (to prevent rapid warming up) and left overnight after which time the colour changed to brown. The solvents were removed on a rotary evaporator and the remaining solid was dissolved in water (500 ml), strongly alkalized with KOH and any water insoluble organic material was removed by extraction with ether (5 x 100ml; the last extract was colourless). The aqueous layer was separated, and after removal of the residual ether on a rotary evaporator, strongly acidified with concentrated hydrochloric acid (a white precipitate was immediately formed) and left for one hour in a refrigerator (*ca.* 4°C). The precipitate was filtered off, washed with small amount

of cold water and dried in vacuum over P_4O_{10}; yield: 13.8 g (59.5%); m.p. 134 - 136 °C. This product was used for further transformations. Analytical sample was obtained by recrystallisation from n-hexane: white needles: m.p. 136 - 137°C [lit.: 133 - 135°C] [11]. Analysis: Found: C, 41.9; H, 1.64; F, 44.0 %. $C_9H_4F_6O_2$ requires: C, 41.88; H, 1.56; F, 44.16 %. ^{1}H NMR ($CDCl_3$): AB_2 system, δ: 7.75 (t, J_{AB} = 7.85 Hz, 1H) and 7.96 (d, J_{AB} = 7.85 Hz, 2H); 8.16 (br., COOH) ppm. ^{19}F NMR ($CDCl_3$) δ: 60.05 (s) ppm. MS m/e (rel.int., ion): 258 (75%, M^+); 241 [100, $(M\text{-}OH)^+$]; 219 [32, $(M\text{-}HF_2)^+$]; 213 [36, $(M\text{-}COOH)^+$]; 194 [52, $(M\text{-}F\text{-}COOH)^+$]; 163 (30, $C_7H_3F_4^+$); 144 (20, $C_7H_3F_3^+$); 125 (12, $C_7H_3F_2^+$); 99 (5, $C_5HF_2^+$); 75 (8, $C_6H_3^+$); 69 (5, CF_3^+). IR (nujol) ν (cm^{-1}): 1720 (C=O); 2853 - 3033 (OH).

3.2. 4-Bromo-2,6-bis(trifluoromethyl)benzoic acid (4)

1,3-Dibromo-5,5-dimethylhydantoin (DBDMH) (11 g, 38.5 mmol) was dissolved at r.t. in conc. sulphuric acid (40 ml), the solution was cooled to 0°C then 2,6-bis(trifluoromethyl)benzoic acid (**3**) (10 g, 38.7 mmol) was added. The slurry was stirred at 0 - 5°C for 2 hours followed by stirring overnight at ambient temperature after which time it was poured into iced water (500 ml), decolourized with Na_2SO_4 and left in a refrigerator (ca.4°C) for two hours. The white precipitate was filtered off and dried in vacuo over P_4O_{10}; yield: 12 g (92 %); m.p. 188 - 190°C. Analytical sample was obtained by sublimation (160°C, 5 Torr): m.p. 190 - 192°C (in a sealed capillary). Analysis: Found: C, 32.06; H, 0.81, Br, 23.86; F, 33.79 %. $C_9H_3BrF_6O_2$ requires: C, 32.08; H, 0.90; Br, 23.71; F, 33.82 %. ^{1}H NMR ($CDCl_3$) δ: 8.085 (s, H_{arom}); 9.086 (broad s, H_{COOH}) ppm. ^{19}F NMR ($CDCl_3$) δ: 60.2 (s) ppm. MS m/e(rel.int., ion): 338,336 (100%, M^+); 321,319 [90, $(M\text{-}OH)^+$]; 299,279 [15, $(M\text{-}HF_2)^+$]; 293,291[15, $(M\text{-}CO_2H)^+$]; 274, 272 [15, $(M\text{-}CO_2H\text{-}HF)^+$]; 212 [20, $(M\text{-}CO_2H\text{-}Br)^+$], 193 (18, $C_8H_2F_2^+$); 162 (16, $C_7H_2F_4^+$); 143 (15, $C_7H_2F_3^+$); 69 (5, CF_3^+). IR (nujol) ν (cm^{-1}): 1726 (C=O); 2990 - 3089 (OH).

3.3. 4-Bromo-2,6-bis(trifluoromethyl)benzoyl fluoride (5)

4-Bromo-2,6-bis(trifluoromethyl)benzoic acid (**4**) (25 g, 74.2 mmol) and water (1.8 ml, an equivalence of 0.2 mol HF) were placed in a 100 ml stainless steel autoclave; the autoclave was immersed in a dry-ice-acetone bath, evacuated, the sulphur tetrafluoride (25 g, 0.23 mol) was condensed into it. The charged autoclave was heated in a rocking muffle furnace at 20°C for 20 hours followed by 3 hours at 120°C. After the autoclave had cooled to ambient temperature, gaseous products (SOF_2, HF, unreacted SF_4) were released and a liquid product was dissolved in CH_2Cl_2 (150 ml). The solution was washed with 10% aqueous K_2CO_3 followed by water untill neutral and dried over $MgSO_4$. The solvent was distilled off under atmospheric pressure and the residue was vacuum distilled to give a colourless liquid boiling at 126 -130°C/85 Torr. The GC-MS analysis revealed the presence of only trace amounts of 3,4,5-tris(trifluoromethyl)bromobenzene. Yield 19 g (75%). Analysis: Found: C, 31.40; H, 0.57; Br, 23.73; F, 39.12 %. $C_9H_2BrF_7O$ requires: C, 31.89; H, 0.59;

Br, 23.57; F, 39.23 %. ^{1}H NMR ($CDCl_3$) δ: 8.14 (s) ppm. ^{19}F NMR ($CDCl_3$) δ: -58.3 (sept., $^5J_{FF}$ = 5.0 Hz, COF); 60.5 (d, $^5J_{FF}$ = 5.0 Hz, CF_3). MS m/e(rel.int., ion): 340,338 (35%, M^+); 312,310 [70, $(M-CO)^+$]; 293,291 [20, $(M-COF)^+$]; 243,241 [28, $(M-CO-CF_3)^+$]; 231 [80, $(M-Br-CO)^+$]; 212 [42, $(M-Br-COF)^+$]; 181 (45, $C_7H_2F_5^+$); 162 (82, $C_7H_2F_4^+$); 143 (65 $C_7H_2F_3^+$); 123 (28, $C_7HF_2^+$); 112 (18, $C_6H_2F_2^+$); 93 (35, $C_6H_2F^+$); 74 (40, $C_6H_2^+$); 69 (100, CF_3^+); 47 (18, COF^+). IR (film) ν (cm^{-1}): 1852 (COF).

3.4. Methyl 4-methoxy-2,6-bis(trifluoromethyl)benzoate (6)

Sodium metal (0.3 g, 13 mmol) was dissolved in methanol (5 ml) then 4-bromo-2,6-bis-(trifluoromethyl)benzoyl fluoride (**5**) (1 g, 2.9 mmol) was added and the solution was refluxed under nitrogen for 20 hours. Methanol was removed on a rotary evaporator, water (10 ml) and diethyl ether (10 ml) were added, the mixture was well agitated, the ether layer was separated and dried over $MgSO_4$. Evaporation of the solvent gave colourless oil which by GC-MS was found to be almost pure compound **6**: yield: 0.6 g (69 %). Analysis: Found: C, 43.60; H, 2.75; F, 37.80 %. $C_{11}H_8F_6O_3$ requires: C, 43.72; H, 2.67; F, 39.56 %. ^{1}H NMR ($CDCl_3$) δ: 3.927 (s, CH_3); 3.932 (s, CH_3); 7.36 (s, H_{arom}) ppm. ^{19}F NMR ($CDCl_3$) δ: 60.65 (s, CF_3) ppm. GC-MS m/e (rel.int., ion): 302 (20%, M^+); 283 [5, $(M-F)^+$]; 271 [100, $(M-MeO)^+$]; 243 [3, $(M-CO_2Me)^+$]. IR (film) ν (cm^{-1}): 1748 (C=O).

Acidification of the water layer gave a precipitate (0.2 g) which was found by GC-MS to consist mostly of 4-bromo-2,6-bis(trifluoromethyl)benzoic acid (**4**).

3.5. 4-Methoxy-2,6-bis(trifluoromethyl)benzoic acid (7)

To a solution of sodium methoxide prepared from sodium metal (4.6 g, 0.2 mol) and freshly distilled methanol (60 ml) 4-bromo-2,6-bis(trifluoromethyl)benzoyl fluoride (**5**) (9 g, 26.5 mmol) was added was added dropwise, while stirring, under atmosphere of nitrogen. An exothermic reaction occurred and a white precipitate was immediately formed. When the exothermic reaction ceased, the mixture was transfered into a 200 ml pressure glass tube fitted with a Rotaflo valve, the tube was immersed in an oil bath and warmed up to 120°C. The precipitate disappeared and after a few minutes another, dense precipitate was formed. A sample taken after two hours at 120°C, after work up as above, was found to contained methyl 4-methoxy-2,6-bis(trifluoromethyl)benzoate and the unreacted acid fluoride in the ether layer and some acid precititated by acidifying the water layer. The heating was continued for additional 24 hours, then methanol was removed on a rotary evaporator. The solid residue was dissolved in water (200 ml), the solution was washed with ether (3 x 30 ml), and the residual ether was removed from the water solution on a rotary evaporator. Acidification with hydrochloric acid afforded a white precipitate which was filtered off and dried in vacuo over P_4O_{10}. Yield: 6.3 g (83 %); m.p. 169 - 171°C. An analytical sample with m.p. 172 - 174°C was obtained by boiling in water (the acid is practically insoluble in hot water; this procedure removes inorganic impurities), filtering (after cooling to ambient temperature) and drying

as above. Analysis: Found: C, 41.53; H, 2.02; F, 39.48 %. $C_{10}H_6F_6O_3$ requires: C, 41.68; H, 2.10; F, 39.56 %. ^{1}H NMR ($CDCl_3$) δ: 3.94 (s, CH_3); 5.36 (broad, H_{COOH}); 7.38 (s, H_{arom}) ppm. ^{19}F NMR ($CDCl_3$) δ: 55.4 (s) ppm. MS m/e (rel.int., ion): 288 (50, M^+); 271 [100, $(M\text{-}OH)^+$]; 249 [15, $(M\text{-}HF_2)^+$]; 200 [10, $(M\text{-}CF_3\text{-}F)^+$]; 181 [10, $(M\text{-}CF_3\text{-}2F)^+$]; 69 (5, CF_3^+). IR ($CDCl_3$) ν (cm^{-1}): 1719.5 (C=O); 3000 - 3100 (broad, OH). IR ($CDCl_3$) ν (cm^{-1}): 1719.5 (C=O); 3000 - 3100 (broad, OH).

*3.6. 4-Methoxy-2,6-bis(trifluoromethyl)isophtalic acid (**8**)*

The reaction was carried out under atmosphere of dry nitrogen. 4-Methoxy-2,6-bis-(trifluoromethyl)benzoic acid (7) (3.8 g, 16.7 mmol) was dissolved in dry THF (60 ml), the solution was cooled to -30°C then n-butyllithium (30 mmol, 12 ml of a commercial 2.5 M solution in n-hexane) was added dropwise in such a rate to keep the temperature within the range -28 to -25°C (ca. 30 min). The reaction mixture was stirred at this temperature range for additional 3 hours after which time a large amount (ca. 150 g) of freshly crushed solid carbon dioxide was added and the reaction mixture was left to warm slowly to ambient temperature (overnight). Water (150 ml) and small amount of KOH (two pelllets) were added, THF was removed on a rotary evaporator and the remaining aqueous solution was washed with ether (3 x 50ml, removal of insoluble organic impurities), separated, and the residual ether was evaporated. Acidification with hydrochloric acid gave a white precipitate which was filtered off, dissolved in boiling water (200 ml), the yellow solution was decolourized with charcoal and filtered while hot. Evaporation of of water gave a white solid which was dried in vacuo over P_4O_{10}; yield: 2.66 g (48 %); m.p. 274 - 276°C (decomp.). Analysis: Found: C, 39.7; H, 1.7; F, 34.35 %. $C_{11}H_6F_6O_5$ requires: C, 39.8; H, 1.8; F, 34.3 %. ^{1}H NMR (acetone-d_6) δ: 4.10 (s, CH_3); 6.3 (v.broad, COOH); 7.76 (s, H_{arom}) ppm. ^{19}F NMR (acetone-d_6) δ: 55.5 (s); 59.1 (s) ppm. MS m/z (rel.int., ion): 332 (100, M^+); 315 [20, $(M\text{-}OH)^+$]; 295 [68. $(M\text{-}OH\text{-}HF)^+$]; 288 [10, $(M\text{-}CO_2)^+$]; 275 [38, $(M\text{-}OH\text{-}2HF)^+$]; 274 [38, $(M\text{-}H_2O\text{-}2HF)^+$]; 265 [28, $(M\text{-}CHF_2O)^+$]; 246 [30, $(M\text{-}CF_3\text{-}OH)^+$]; 244 [10, $(M\text{-}2CO_2)^+$]. IR (nujol) ν (cm^{-1}): 1710.7 and 1740.0 (C=O); ca. 3100 (OH).

*3.7. Conversion of 4-methoxy-2,6-bis(trifluoromethyl)benzoic acid (7) into 4-methoxy-3-methyl-2,6-bis(trifluoro-methyl)benzyl alcohol (**11**)*

n-Butyllithium (42.5 mmol, 17 ml of 2N solution in n-hexane) was added dropwise, to a solution of 4-methoxy-2,6-bis(trifluoromethyl)benzoic acid (7) (5.8 g, 20 mmol) in dry THF (100 ml), precooled to -30°C and stirred under atmosphere of dry nitrogen, in such a rate to keep the temperature below -25°C and to avoid an appearance of yellow colouration (*ca.* 30 min). After completion of the n-BuLi addition, the reaction mixture was stirred at -25°C for 1.5 hour (yellow-brown colour appeared) then dimethyl sulphate (10 g, 80 mmol) was added dropwise while keeping the temperature with the range of -15 to -10°C. The reaction mixture was allowed to warm to room temperature then refluxed for three hours (a fine precipitate of Li_2SO_4 deposited). The solvent (THF)

was removed on a rotary evaporator, water was added (100 ml), and the solution was made alkaline by portionwise addition of solid K_2CO_3 then extracted with ether (4x50 ml). The extract was found by the GC-MS to contain three compounds: *methyl 4-methoxy-3-methyl-2,6-bis(trifluoromethyl)benzoate* (**9**) (67%, m/e 316, M^+), *methyl 4-methoxy-2,6-bis-(trifluoromethyl)benzoate* (**6**)(16%, m/e 302, M^+) and *methyl 4-methoxy-3,5-dimethyl-2,6-bis(trifluoromethyl)benzoate* (**10**) (4%, m/e 330, M^+). The extact was well dried over $MgSO_4$ and evaporated to ca. 50 ml. Lithium aluminium hydride (1.5 g, 40 mmol) was added and the suspension was refluxed under nitrogen. The reaction was monitored by GLC. After seven days 94% of the esters were consumed and a complex mixture of products were formed which contained, amongst numerous minor components, *ca.* 40% the required alcohol (**11**) (GC-MS determined). The reaction was quenched with 10% hydrochloric acid, extracted with ether (5x50 ml) and the combined extracts were dried over $MgSO_4$. Evaporation of the solvent gave a dark-brown oil (4 g) which was subjected to column chromatography on silica-gel (240 - 400 mesh) using n-pentane/CH_2Cl_2 (4 : 1) as an eluent. A fraction (550 mg) containg 90% of (**11**) was isolated and recrystallized from n-hexane to give pure compound (400 mg, total yield 5%) as a colourless solid: mp 73 - 75°C. Analysis: Found: C, 46.0; H, 3.6; F, 39.7 %. $C_{11}H_{10}F_6O_2$ (288.19) requires: C, 45.85; H, 3.5; F, 39.55 %. ^{1}H NMR ($CDCl_3$) δ: 2.40 (q, $^5J_{HF}$ = 2.6 Hz,, CH_3); 3.91 (s, OCH_3); 4.86 (s,broad, CH_2); 7.28 (s, H_{arom}) ppm. ^{19}F NMR ($CDCl_3$) δ: 53.3 (broad s); 57.8 (s) ppm. GC-MS m/z (rel.int., ion): 288 (50, M^+); 271 [10, $(M\text{-}OH)^+$]; 259 [100, $(M\text{-}CHO)^+$]; 253 [30, $(M\text{-}CH_3\text{-}HF)^+$]; 249 [25, $(M\text{-}HF_2)^+$]; 239 [55, $(M\text{-}CH_2O\text{-}F)^+$]; IR($CCl_4$): no carbonyl absorption.

*3.8. 2,6-Bis(trifluoromethyl)benzoyl fluoride (***12***)*

2,6-Bis(trifluoromethyl)benzoic acid (**3**) (2.6 g, 10 mmol) and sulphur tetrafluoride (2 g, 18 mmol) were reacted in a 30 ml stainless steel autoclave at 90°C for 20 hours. The liquid product was dissolved in CH_2Cl_2 (25 ml) and sodium fluoride (ca. 2 g) was added to bind hydrogen fluoride formed in the reaction. After two days sodium fluoride was filtered off, the solvent was distilled off under atmospheric pressure and the residue was vacuum distilled to give a colourless liquid boiling at 113°C/80 Torr ; yield: 2.05 g (78.5 %). The spectral data (^{1}H and ^{19}F NMR, MS and IR) were in agreement with those reported earlier [12].

*3.9. 4-Methoxy-2,6-bis(trifluoromethyl)benzoyl fluoride (***13***)*

4-Methoxy-2,6-bis(trifluoromethyl)benzoic acid (**7**) (9.3 g, 32 mmol) and sulphur tetrafluoride (14 g, 130 mmol) were reacted in a 30 ml stainless steel autoclave at 150°C for 20 hours. The semi-liquid product was dissolved in CH_2Cl_2 (25 ml) and sodium fluoride (ca. 2 g) was added to bind hydrogen fluoride formed in the reaction. The next day, sodium fluoride was filtered off, the solvent was distilled off under atmospheric pressure and the residue was vacuum distilled to give (**13**) as a colourless low melting solid. Yield: 7.7 g (83 %); b.p. 136 - 138°C / 52 Torr. GC-MS m/z

(rel.int., ion): 290 (60, M^+); 271 [50, $(M-F)^+$]; 262 {100, $(M-CO)^+$]; 247 [30, $(M-CO-Me)^+$]. IR (film) ν (cm^{-1}): 1845 (vs, COF).

*3.10. 2,6-Bis(trifluoromethyl)benzyl alcohol (***14***)*

A solution of 2,6-bis(trifluoromethyl)benzoyl fluoride (**12**) (1.8 g, 6.9 mmol) in dry ether (10 ml) was added dropwise, while stirring, to a suspension of $LiAlH_4$ (0.4 g, 10.4 mmol) in ether (40 ml) precooled to 0°C. An exothermic reaction occured with rapid temperature rise to 15°C. The reaction mixture was cooled again to 0°C and stirred for two hours then quenched by slow addition of 10% hydrochloric acid and stirred until homogenous solution was obtained. The ether layer was separated, aqueous layer extracted with ether (3 x 10 ml) and the combined ether solutions were dried over $MgSO_4$. The GLC examination shawed the presence of one compound only. Evaporation of the solvent under atmospheric pressure afforded a colourless liquid; yield: 1.22 g (72.5 %). Crystalizes when stored in a refrigerator. Analysis: Found: C, 44.25; H, 2.6; F, 46.6 %. $C_9H_6F_6O$ requires: C, 44.3; H, 2,5; F, 46.7 %. ^1H NMR ($CDCl_3$) δ: 2.0 (broad, OH); 4.94 (s, CH_2); 7.59 (t, $^3J_{HH}$ = 7.9 Hz, H_{arom}); 7.94 (d, $^3J_{HH}$ = 7.9 Hz, $2H_{arom}$) ppm. ^{19}F NMR ($CDCl_3$) δ: 58.6 (s) ppm. MS m/z (rel.int., ion): 244 (25, M^+); 227 [8, $(M-OH)^+$]; 223 [15, $(M-H_2F)^+$]; 222 [10, $(M-H_3F)^+$]; 214 [8, $(M-CH_2O)^+$]; 205 [25, $(M-HF_2)^+$]; 196 [30, $(M-CHFO)^+$]; 195 [100, $(M-CH_2FO)^+$]; 175 [45, $(M-CH_3F_2O)^+$]. IR(film): no carbonyl absorption.

*3.11. 4-Methoxy- 2,6-bis(trifluoromethyl)benzyl alcohol (***15***)*

A solution of 4-methoxy- 2,6-bis(trifluoromethyl)benzoyl fluoride (**13**) (7.5 g, 25.8 mmol) in dry ether (30 ml) was added dropwise during 20 minutes, while stirring, to a suspension of $LiAlH_4$ (1.52 g, 40 mmol) in ether (150 ml) precooled to 3°C. An exothermic reaction occured with the temperature rise to 10°C. The reaction mixture was cooled again to 5°C and stirred for two hours then worked up as described above. The residue obtained after evaporation of the solvent was vacuum distilled to afford a colourless oil; yield: 6.0g (84.5 %); b.p. 132 - 134°C / 20 Torr. Analysis: Found: C, 43.6; H, 2.8; F, 41.5 %. $C_{10}H_8F_6O_2$ requires: C, 43.8; H, 2,95; F, 41.6 %. ^1H NMR ($CDCl_3$) δ: 1.9 (broad, OH); 3.93 (s, OCH_3); 4.86 (s, CH_2); 7.40 (s, H_{arom}) ppm. ^{19}F NMR (in $CDCl_3$) δ: 58.9 (s) ppm. GC-MS m/z (rel.int., ion): 274 (55, M^+); 257 [40, $(M-OH)^+$]; 245 [100, $(M-CHO)^+$]; 235 [45, $(M-HF_2)^+$]; 225 [90, $(M-CH_2O-F)^+$]. IR(film): no carbonyl absorption.

*3.12. 2,6-Bis(trifluoromethyl)benzaldehyd (***16***)*

Pyridine (6 g, 76 mmol), chromium trioxide (3 g, 30 mmol) and methylene chloride (50 ml) were stirred at ambient temperature for one hour to from a deep-orange solution then 2,6-bis-(trifluoromethyl)benzyl alcohol (**14**) (0.9 g, 3.7 mmol) dissolved in CH_2Cl_2 (10 ml) was added (exothermic reaction with the temperature rise to 28°C). The reaction mixture was stirred overnight at ambient temperature and chromium salts were removed by filtration under nitrogen atmosphere

through a 10 cm layer of silica gel. The colourless eluent was washed with 10% hydrochloric acid (removal of pyridine), followed by water, and dried over $MgSO_4$. Removal of the solvent gave a yellowish oil (0.73 g, yield: 81.5%) which was found by GLC to consist practically of a single component (98%). Vacuum distillation gave a colourless oil: b.p. 84°C/12 Torr. Analysis: Found: C, 44.5; H, 1.6; F, 47.0 %. $C_9H_4F_6O$ requires: C, 44.65; H, 1.7; F, 47.1%. ^1H NMR ($CDCl_3$) δ: 7.76 (t, $^3J_{HH}$ = 8.1 Hz, 1H); 7.98 (d, $^3J_{HH}$ = 8.1 Hz, 2H); 10.58 (septet, $^5J_{HF}$ = 2,5 Hz, CHO) ppm. ^{19}F NMR ($CDCl_3$) δ: 57.6 ppm (d, $^5J_{HF}$ = 2,5 Hz) ppm. MS m/z (rel.int., ion): 242 (40, M^+); 241 [100, $(M-H)^+$)]; 223 [22, $(M-F)^+$); 214 [15, $(M-CO)^+$]; 213 [40, $(M-CHO)^+$]; 195 [25, $(M-CO-F)^+$]; 194 [38, $(M-CHO-F)^+$]; 164 (13, $C_7H_4F_4^+$); 163 (18, $C_7H_3F_4^+$); 145 (28, $C_7H_4F_3^+$); 144 (23, $C_7H_3F_3^{+)}$; 125 (15, $C_7H_3F_2^+$); 75 (8, $C_6H_3^+$); 69 (5, CF_3^+). IR (film) ν (cm^{-1}): 1726.6 (CHO).

*3.13. 4-Methoxy-2,6-bis(trifluoromethyl)benzaldehyd (***1a***)*

Pyridine (28.8 g, 0.36 mol), chromium trioxide (14.5 g, 0.145 mol) and methylene chloride (150 ml) were stirred at ambient temperature (25°C) for one hour to from a deep-orange solution then 4-methoxy-2,6-bis(trifluoromethyl)benzyl alcohol (**15**) (5.2 g, 19 mmol) dissolved in CH_2Cl_2 (30 ml) was added (slightly exothermic reaction with the temperature rise to 32°C). The reaction mixture was stirred overnight at ambient temperature and worked up as described for the preparation of (**16**) to give a colourless low melting material (4.3 g, yield: 85%) which was found by GLC to consist practically of a single component (>98%). . Analysis: Found: C, 43.95; H, 2.1; F, 41.85 %. $C_{10}H_6F_6O_2$ requires: C, 44.1; H, 2.2; F, 41.9%. ^1H NMR ($CDCl_3$) δ: 3.98 (s, CH_3O); 7.44 (s, H_{arom}); 10.45 (septet, $^5J_{HF}$ = 2,35 Hz, CHO) ppm. ^{19}F NMR ($CDCl_3$) δ: 57.8 ppm (d, $^5J_{HF}$ = 2,4 Hz) ppm. MS m/z (rel.int., ion):272 (50, M^+); 271[100, $(M-H)^+$]; 253 [12, $(M-F)^+$]; 244 [5, $(M-CO)^+$]; 243 [4, $(M-CHO)^+$]. IR (film) ν (cm^{-1}): 1718.4 (CHO).

*3.14. 4-Methoxy-3-methyl-2,6-bis(trifluoromethyl)benzaldehyd (***1b***)*

Pyridine (2.5 g, 32 mmol), chromium trioxide (1.2 g, 12 mmol) and methylene chloride (25 ml) were stirred at ambient temperature (25°C) for one hour to from a deep-orange solution then 4-methoxy-3-methyl-2,6-bis(trifluoromethyl)benzyl alcohol (**11**) (0.4 g, 1.4 mmol) dissolved in CH_2Cl_2 (5 ml) was added (slightly exothermic reaction with the temperature rise to 28°C). The reaction mixture was stirred overnight at ambient temperature and worked up as described for the preparation of (**16**) to give a colourless oil (170 mg, yield: 43%). The product crystallized when stored at room temperature for a few days. HRMS: 286.04236. $C_{11}H_8F_6O_2$ requires: 286.04285. ^1H NMR ($CDCl_3$) δ: 2.40 (q, $^5J_{HF}$ = *ca.* 2 Hz, CH_3); 3.97 (s, CH_3O); 7.27 (s, H_{arom}); 10.48 (m, CHO) ppm. ^{19}F NMR ($CDCl_3$) δ: 53.4 (sext., $^5J_{HF}$ = 2.3 Hz); 57.1 ppm (d, $^5J_{HF}$ = 2,7 Hz) ppm. MS m/z (rel.int., ion):286 (40, M^+); 285[100, $(M-H)^+$]; 267 [12, $(M-F)^+$]; 258 [8, $(M-CO)^+$]; 243 [10, $(M-CO-CH_3)^+$]; 227 [10, $(M-CO-CH_3O)^+$]. IR (film) ν (cm^{-1}): 1720.0 (CHO).

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