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Short communication

Unique sodium dithionite initiated coupling of $CF_3CHClBr$ with 1,3,5-trimethoxybenzene: Synthesis and structure of trifluoromethyl-bis(2,4,6-trimethoxyphenyl)methane

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ABSTRACT

Sodium dithionite initiated reaction of 1-bromo-1-chloro-2,2,2-trifluoroethane with 1,3,5-trimethoxybenzene (**1**) in an acetonitrile–water mixture gives trifluoromethyl-bis(2,4,6-trimethoxyphenyl)methane (**2**) as the only isolable product in over 32% yield. The structure of compound **2** was evidenced by spectral methods and X-ray crystal analysis.

1. Introduction

The reaction of perfluoroalkyl halides (R_FI, R_FBr) with sodium dithionite in acetonitrile–water or DMF–water medium, known as “sulfinatodehalogenation”, provides an easy way of generating perfluoroalkyl radicals. These electron-deficient radicals could be effectively trapped by electron-rich substrates like alkenes and alkynes to give addition products [1,2]. This reaction system could also be used for per- or polyfluoralkylation of electron rich aromatics, like phenolates and anilines [3,4], aromatic amines [5], methoxybenzenes and alkyl substitute benzenes [6]. In the preceding papers we reported that sulfinatodehalogenation procedure could also be successfully applied to 1-bromo-1-chloro-2,2,2-trifluoroethane, commercially available as Halothane® (inhalation anaesthetic), to generate $CF_3CHCl^\bullet$ radicals which readily reacted with unsaturated compounds like vinyl ethers [7,8], allylaromatics [9] and terpenes [10]. We have also found that the $CF_3CHCl^\bullet$ radicals react with pyrroles but in quite unusual way: instead of the expected CF_3CHCl substituted pyrroles, 5-(trifluoromethyl)dipyrromethanes were obtained in a 40–50% yields [11].

As an extension of our studies on applicability of the $CF_3CHClBr/Na_2S_2O_4$ system for fluoroalkylation, reactions with aromatic compounds were investigated.

2. Results and discussion

All the attempted reactions of $CF_3CHClBr$ with phenolates, aminobenzenes, toluene, xylenes, mono- and dimethoxybenzenes, both in the CH_3CN/H_2O and DMF/H_2O solutions and at the temperature range of 20–55 °C, totally failed; only unreacted substrates or complex mixtures were obtained. With 1,2,3-trimethoxybenzene and 1,2,4-trimethoxybenzene only low yields of complex mixtures of products which were not suitable for separation and identification. However, the reaction with 1,3,5-trimethoxybenzene (**1**) occurred more cleanly to afford reasonable yield of trifluoromethyl-bis(2,4,6-trimethoxy-phenyl)methane (**2**) as the only isolable product (Scheme 1).

The reaction proceeded at ambient temperature (with slight exothermic effect) under typical “sulfinatodehalogenation” conditions in acetonitrile–water solution using $Na_2S_2O_4$ as a free radical initiator and $NaHCO_3$ as a buffer. Compound **2** was easily isolated by column chromatography or, alternatively, by washing out all tar-like materials from the crude product with warm hexanes. The latter procedure was possible due to low solubility of **2** and high solubility of **1** and the impurities in this solvent. Both isolation procedures gave compound **2** of analytical purity.

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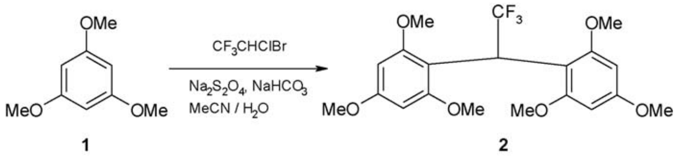


Scheme 1.

Compound **2** was found to be easily soluble in acetonitrile, chloroform, benzene and ethyl acetate.

Elemental analysis and mass spectrum gave unequivocal evidence that the molecule of **2** consists of two aromatic rings coupled *via* a $CHCF_3$ bridge. The presence of the $CHCF_3$ moiety is confirmed by quartets in the ^1H and ^{13}C NMR spectra ($^3J_{HF} = 11.8$ Hz, $^2J_{CF} = 32.2$ Hz) and a doublet in the ^{19}F NMR spectrum. The simplicity of the ^1H and ^{13}C NMR spectra (only two signals of the OCH_3 groups in both spectra) implies highly symmetric structure of compound **2**. Trifluoromethyl-bis(2,4,6-trimethoxyphenyl)methane (**2**) forms small, plate-like crystals, the structure of which, as proved by X-ray analysis (Fig. 1), is similar to the previously reported structures of 5-(trifluoromethyl)dipyrromethanes [11].

Formation of compound **2** probably involves a free radical chain mechanism, analogical to that previously suggested for the formation of 5-(trifluoromethyl)-dipyrromethanes [11], as depicted in Scheme 2. Perhaps, the driving force for the substitution of both halogen atoms in $CF_3CHClBr$ by the aryl groups, is rapid elimination of HCl from the primary aryl radical (i) to form radical (ii) which is stabilized by the CF_3 group and capable of attacking the second molecule of trimethoxybenzene (**1**).

In summary, the present paper describes the third (in addition to the previously reported [11]) example of rather unique sodium dithionite initiated reaction of 1-bromo-chlorotrifluoroethane with an aromatic molecule leading to diaryl(trifluoromethyl)methanes.

3. Experimental

Melting point was determined in a capillary and is uncorrected. ^1H NMR, and ^{19}F NMR spectra were recorded with a Varian 400 spectrometer in $CDCl_3$ solutions. Chemical shifts are quoted in p.p.m. from internal TMS for ^1H and ^{13}C and from internal $CFCl_3$ for ^{19}F nuclei. Coupling constants (*J*) values are in Hz. Mass spectrum was obtained with an AMD-604 spectrometer. X-ray diffraction experiment was performed on a MACH3 diffractometer.

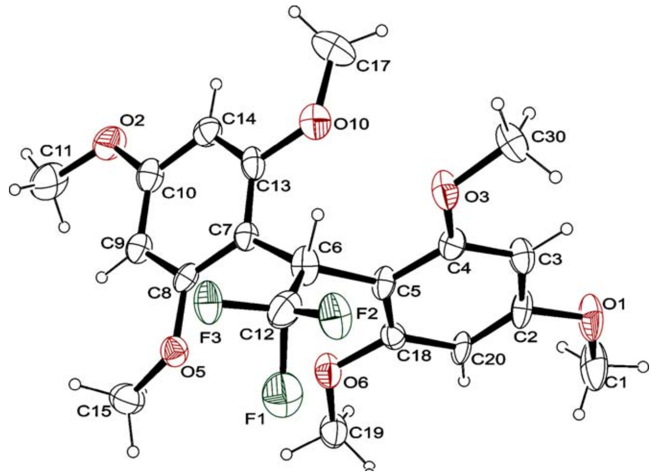
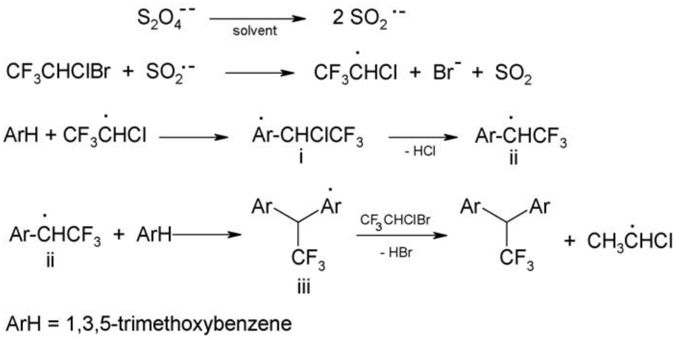


Fig. 1. X-ray crystal structure of **2** with crystallographic numbering scheme. Thermal ellipsoids shown at 20% probability level.



Scheme 2.

3.1. Trifluoromethyl-bis(2,4,6-trimethoxyphenyl)methane (2)

Sodium dithionite (2.0 g [85%], 10 mmol), sodium hydrogen carbonate (1.7 g, 20 mmol), 1,3,5-trimethoxybenzene (1.68 g, 10 mmol) and $CF_3CHClBr$ (3.0 g, 15 mmol) were added one by one to an acetonitrile–water solution (1:1, 20 ml) at ambient temperature (22 °C). The reaction mixture was vigorously stirred and after few minutes slow gas evolution (CO_2, formed by the reaction of SO_2 with $NaHCO_3$) began with a slight exothermic effect (the temperature rised to 30 °C). The temperature was kept at 30 °C for 3 h by external heating, after which time the reaction ceased (no more gas evolution) and most of inorganic salts dissolved. Stirring was continued overnight at ambient temperature, then the reaction mixture was poured into water (100 ml) to form a white oil which was extracted with diethyl ether, the extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a soft, slightly pink coloured solid (1.75 g) which was found by the TLC to consist mainly of the product and smaller amount of unreacted 1,3,5-trimethoxybenzene. The crude product was subjected to column chromagraphy (silica gel) to give two fractions: the first eluent (hexanes) contained only unreacted **1** (0.65 g) and the second eluent (hexanes/CH_2Cl_2, 1:1), after removal of the solvents, afforded pure compound **2** as white solid. Yield: 0.8 g (1.92 mmol, 38.4%). M.p. 181–182 °C. Analysis—found: C, 57.7; H, 5.8; F, 13.7%. Calculated for $C_{20}H_{23}F_3O_6$ (416.39): C, 57.7; H, 5.6; F, 13.7%. ^1H NMR: 3.73 (s, 4× CH_3); 3.77 (s, 2× CH_3); 5.65 (q, $^3J_{HF} = 11.8$ Hz, 1H); 6.09 (s, $4H_{arom}$). ^{19}F NMR: −64.8 (d, $^3J_{HF} = 11.8$ Hz, CF_3). ^{13}C NMR: 36.4 (q, $^2J_{CF} = 32.2$ Hz); 55.1 (s, OCH_3); 56.0 (s, OCH_3); 91.2 (s, aromatic C-3, C-5); 106.8 (s, aromatic C-1); 127.1 (q, $^1J_{CF} = 279$ Hz, CF_3); 159.8 and 160.1 (s, aromatic C-2, C-6 and C-4). MS (EI): *m*/*z* (rel. int., ion): 416 (50, M^+); 396 [16, $(M-HF)^+$]; 381 [22, $(M-CH_3)^+$]; 347 [97, $(M-CF_3)^+$]; 301 (11, $C_{17}H_{17}O_5^+$); 181 (100, $C_{10}H_{13}O_3^+$); 151 (10, $C_9H_{11}O_2^+$); 136 (10, $C_8H_8O_2^+$); 121 (17, $C_7H_5O_2^+$); 69 (5, CF_3^+).

In the alternative separation procedure unreacted **1** and all tar-like materials were removed from the crude product by washing with warm hexanes (3× 30 ml): the insoluble residue was pure **2** (0.67 g, yield 32%).

3.2. Crystal structure of 2

A colorless plate-like specimen of $C_{20}H_{23}F_3O_6$, approximate dimensions 0.01 mm × 0.10 mm × 0.10 mm, was used for the X-ray crystallographic analysis. The X-ray intensity data of compound **2** were measured using graphite monochromatised CuKα radiation (λ = 1.54178 Å). A total of 4394 frames were collected. The total data collection time was 12.21 h. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 5298 reflections to a maximum θ angle of 50.28° (1.00 Å resolution), of which 2004 were independent (average redundancy 2.644, completeness = 95.6%, R_{int} = 9.64%, R_{sig} = 14.58%) and 871 (43.46%) were greater than $2\sigma(F^2)$. The final cell constants of a = 13.9777(9) Å, b = 11.2507(5) Å, c = 12.8680(7) Å, β = 91.796(2)°, volume = 2022.6(2) Å^3, are based upon the refinement of the XYZ-centroids of 634 reflections above 20 σ(I) with $6.326^\circ < 2\theta < 88.17^\circ$. Data were corrected for absorption effects using the empirical multi-scan method (SADABS). The calculated minimum and maximum transmission coefficients (based on crystal size) are 0.9053 and 0.9899. The structure was solved and refined using the Bruker SHELXTL Software Package, using the space group $P2(1)/c$, with Z = 4 for the formula unit, $C_{20}H_{23}F_3O_6$. The final anisotropic full-matrix least-squares refinement on F^2 with 269 variables converged at R_1 = 0.053, for the observed data and $wR_2 = 0.2627$ for all data. The goodness-of-fit was 0.914. The largest peak in the final difference electron density synthesis was 1.118 e$^-$/Å^3 and the largest hole was −0.259 e$^-$/Å^3 with an RMS deviation of 0.079 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.367 g/cm^3 and $F(000)$, 872 e$^-$. The structure has been deposited in Cambridge Crystallographic Data Center (reference number CCDC 712754).

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