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SYNTHESIS OF 2,6-DIFORMYL-4-TRIFLUOROMETHYLPHENOL

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SUMMARY

A convenient method for the synthesis of the previously unknown 2,6-diformyl-4-trifluoromethylphenol is reported by a seven-stage synthesis. A methyl ether is used to protect the phenol moiety and the key-step involves a copper-mediated trifluoromethylation of a bromoanisole prepared from 4-bromophenol.

INTRODUCTION

Binuclear copper complexes have been the subject of a large number of publications over the past few years in order to elucidate problems such as the nature of active sites in the oxygen-binding protein hemocyanin and multicopper oxidases [1], copper mixed-valency [2], low dimensional conductors [3] and exchange coupled polymetallic systems [4].

Because of its macrocyclic structure and its reversible redox behavior, a large interest was devoted to the homonuclear complex 1a synthesized by N.H. Pilkington and R. Robson [5].

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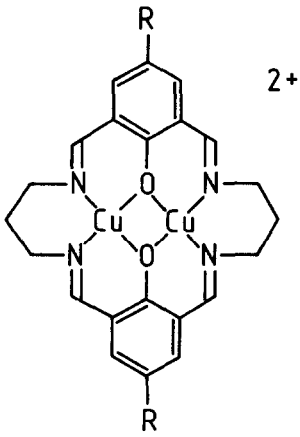
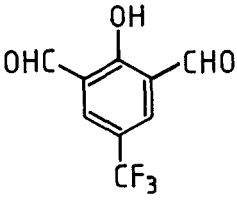


1a R=CH_3
b R=CF_3

With the aim of modifying electronic properties of such a complex without causing a significant change of geometry, we looked at replacement of the methyl groups on the phenolic residue by trifluoromethyl substituents. As the ligand in complex 1a is a symmetric tetra-Schiff base derived by condensing two equivalents of 2,6-diformyl-4-methylphenol with two equivalents of 1,3-diaminopropane, we needed the 2,6-diformyl-4-trifluoromethylphenol (2) to prepare the complex 1b by a similar way.



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SYNTHESES

Our initial approach to prepare this dialdehyde (2) from 4-trifluoromethylphenol by the procedure described for 4-cresol [6] (*vide-infra*) failed, because of the lability of the fluorine atoms in basic media. Consequently, we planned to introduce the trifluoromethyl group on the

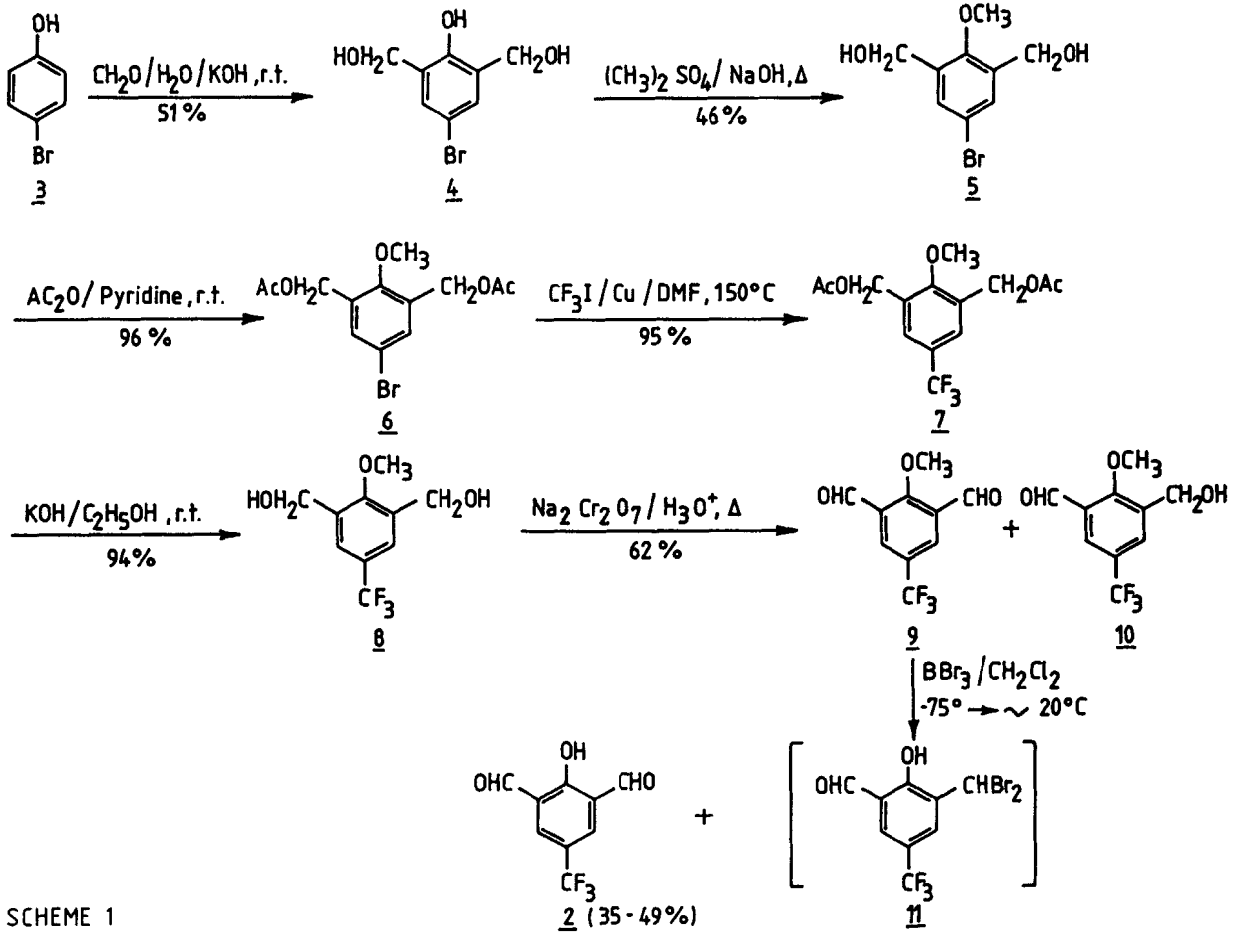
aromatic ring by substitution of an halogen atom. Usually, copper-mediated trifluoromethylations are performed on iodoarenes, when available, for better yields [9c]. However, we observed in the present synthesis that this coupling with the trifluoromethyl iodide can be done in a high yield in the case of a particular bromoarene.

For the synthesis of 2,6-diformyl-4-trifluoromethylphenol (2), we used 4-bromophenol (3) as starting material (Scheme 1). This latter, upon treatment with an aqueous formaldehyde solution in the presence of potassium hydroxide, following the reaction developed for 4-cresol [6] and later applied to 4-chlorophenol [7], gave 4-bromo-2,6-di(hydroxymethyl) phenol (4) in 51 % yield. Inexplicably, we were unable to produce this compound by a slightly different procedure recently described [8] and attempts to prepare the 4-iodo analogue of 4, which we initially selected as the best substrate for subsequent trifluoromethylation, led only to tars. When 4 was submitted to a copper-mediated coupling with trifluoromethyl iodide in *N,N* -dimethylformamide at 130°C [9], no tractable product could be found in the reaction mixture. We attributed this failure to the thermal instability of the expected 2,6-di(hydroxymethyl) -4-trifluoromethylphenol, if formed.

To circumvent problems due to the presence of several hydroxy functions, the phenolic hydroxy group of 4 was converted into its methyl ether by dimethyl sulfate [10] to give 4-bromo-2,6-di(hydroxymethyl) anisole (5). This diol was acetylated into the fully protected compound 6 which was submitted to a thermal copper-mediated coupling with trifluoromethyl iodide (4 equivalents) in *N,N*-dimethylformamide (9). In the conditions we selected (28-30 h heating at 150°C), complete conversion of 6 into 2,6-di(hydroxymethyl)-4-trifluoromethylanisole diacetate (7) was obtained in remarkably high yield (up to 95 % of isolated product, with respect to 6).

Cleavage of the diacetate 7 was achieved by treatment with ethanolic potassium hydroxide at ambient temperature and the resultant diol 8 was oxidized with sodium dichromate dihydrate/sulfuric acid, in water, to give 2,6-diformyl-4-trifluoromethylanisole (9) in 62 % yield, after column chromatography. About 15 % of the diol 8 was only semi-oxidized into 10 which was easily separated from 9 during the chromatographic purification step.

The demethylation of the anisole 9 was readily performed with boron tribromide (3.5 equivalents) in dichloromethane (-75 ⟶ 20°C) [11] giving the desired 2,6-diformyl-4-trifluoromethylphenol (2) in moderate yields


OH
Br
3
CH2O/H2O/KOH, r.t.
51 %
HOH2C
CH2OH
4
(CH3)2 SO4/ NaOH, Δ
46 %
OCH3
5
AC2O/ Pyridine, r.t.
96 %
AcOH2C
CH2OAc
6
CF3I / Cu / DMF, 150°C
95 %
CF3
7
KOH/C2H5OH, r.t.
94%
8
Na2 Cr2 O7 / H3O+, Δ
62 %
OHC
CHO
9
10
BBr3 /CH2Cl2
-75° → ~ 20°C
CHBr2
11
2 (35 - 49%)

SCHEME 1

(35-49 %), although ^{1}H-NMR spectra of the crudes indicated almost pure products. Upon prolonged contact at room temperature, extensive formation of the benzalbromide 11 occurred. The formation of this dibromide agrees with the report of Lansinger *et al.* since they observed the formation in high yield of benzalbromide starting from benzaldehyde itself, when treated with boron tribromide at room temperature [11d]. The same authors found boron triiodide to be far more reactive and milder than boron tribromide for the cleavage of methoxybenzaldehydes. Nevertheless, as the reported yields for an *ortho* situation of the methoxy group *vs.* the formyl function lie in the range 47 to 58 %, in our case, boron tribromide can be considered as relatively convenient with respect to the multifunctionality of the phenol to be deprotected.

The new trifluoromethylphenol 2 has recently been successfully used for the synthesis of complex 1b [12] as its perchlorate, *ie.* $[Cu_2(LCF_3)](ClO_4)_2$, the crystal structure of which was fully resolved, showing the molecular frame to be non planar. Electrochemical properties of 1b were investigated and compared to that of 1a. As expected, the replacement of CH_3 by CF_3 in the ligand makes the species more reducible. This effect is moderate. Nevertheless, the new trifluoromethylated phenol 2 remains an attractive synthon in the area of complexes of macrocyclic ligands.

EXPERIMENTAL

^{1}H and ^{19}F NMR spectra were recorded at 60 MHz and 56.4 MHz on a Varian EM-360L NMR spectrometer equipped with a proton/fluorine probe. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) downfield relative to internal tetramethylsilane. ^{19}F NMR chemical shifts (δ) are given in ppm downfield relative to fluorotrichloromethane. Infrared spectra were recorded on a Perkin-Elmer 167 spectrometer. Melting points are uncorrected and were measured in open capillaries on a Mettler FP 61 instrument. Mass spectra were recorded on a AEI MS-30 apparatus. Elemental analyses were performed either by the Service Central d'Analyse du CNRS, Vernaison or by the Service de Microanalyse, Université P. et M. Curie, Paris. The copper powder (copper bronze) was purchased from KochLight Ltd, Haverhill, Suffolk, England. The molar solution of boron tribromide in dichloromethane is a commercial material.

4-Bromo-2,6-di(hydroxymethyl) phenol (4)

To a stirred solution of 4-bromophenol (86.05 g, 0.5 mol) in aqueous potassium hydroxide (35 g in 100 ml of water) was added an aqueous solution of formaldehyde (37 %, 115.5 ml). The mixture was then allowed to stand at 35-40°C for 48 h. Cooling and acidification of the resultant brownish mixture with 10 % aqueous acetic acid (400 ml) precipitated crude 4 which was filtered off and well washed with water (*ca* . 1500 ml). Further purification was achieved by crystallization from boiling water (*ca* . 50 g of dried crude 4 in 2.5 l of water. Decolorizing charcoal (Norit) was added to the hot solution) to give, after filtration and on cooling overnight, 4 as beige to orange needles (59 g, 51 %), mp 130.4-131.1°C ; ^{1}H NMR (CD_3COCD_3) δ : 4.76 (s,4H,CH_2), 6.0 (br s, OH), 7.30 (s,2H, H_{arom}). Anal. calcd. for $C_8H_9BrO_3$: C 41.22, H 3.89, Br 34.28 ; found : C 40.95, H 3.69, Br 34.48.

4-Bromo-2,6-di(hydroxymethyl)anisole (5)

In a 1 l round-bottomed flask fitted with a reflux condenser and equipped with a mechanical stirrer, the phenol 4 (92.5 g, 0.397 mol) was dissolved in refluxing ethanol (370 ml). The source of heat was then removed and a solution of sodium hydroxide (18.6 g in 46 ml of water) and dimethyl sulfate (46.4 ml) were alternatively added in five instalments (the brown colour developed by the base slowly discharged to yellow after each addition of dimethylsulfate). After the addition was complete (final temperature : *ca*. 55°C), the reaction mixture was made alkaline by the further addition of 5 g of sodium hydroxide in 10 ml of water and was allowed to reflux for 3 h. The ethanol was removed by rotary evaporation *in vacuo* at 60°C and the residual fibrous solid was taken off with water, filtered and thoroughly washed with water, giving crude 5. Recrystallization from water/decolorizing charcoal (Norit) afforded pure anisole 5 as colourless tiny needles (44.6 g, 46 %), mp 129.2-130.2°C ; ^{1}H NMR (CD_3COCD_3) δ : 3.76 (s,3H, OCH_3), 4.26 (dd, 2H, J=6.0, 5.2Hz, OH), 4.70 (br d, 4H, J=5.6Hz, CH_2), 7.53(s, 2H, H_{arom}). Anal. calcd. for $C_9H_{11}BrO_3$: C 43.75, H 4.49, Br 32.34 ; found C 43.78, H4.30, Br 32.46.

4-Bromo-2,6-di(hydroxymethyl) anisole diacetate (6)

To a stirred mixture of acetic anhydride (175 ml) and pyridine (175 ml) was added the diol 5 (43.6 g, 0.177 ml). Stirring was continued at room temperature overnight then the excess of reagents was removed by rotary

evaporation under vacuum at 40°C. The oily residue was diluted with ether (200 ml) and washed with *ca.* 1.2 N hydrochloric acid. The ether layer was washed with water (100 ml) and then stirred for 1/2 h with a saturated sodium hydrogen carbonate solution (200 ml) and solid sodium hydrogen carbonate (*ca.* 10 g). After separation, the ether phase was washed with water until neutral and then with a saturated sodium chloride solution (100 ml). After drying over magnesium sulfate, removal of the ether by rotary evaporation (water pump) then under good vacuum (0.03 Torr) left the diacetate 6 as a waxy, colourless solid (56.4 g, 96 %), mp 41.7°C ; ^{1}H NMR ($CDCl_3$) δ : 2.13 (s, 3H, $COCH_3$), 3.82 (s, 3H, OCH_3), 5.14 (s, 4H, CH_2), 7.48 (s, 2H, H_{arom}). Anal. calcd. for $C_{13}H_{15}BrO_5$: C 47.15, H 4.56, Br 24.16 ; found : C 46.90, H 4.70, Br 23.87.

2,6-Di(hydroxymethyl)-4-trifluoromethylanisole diacetate (7)

A 50 ml stainless steel autoclave was charged with dry dimethylformamide (20 ml), copper powder (4.7 g, 73.9 mmol) and 6 (5 g, 15.1 mmol). The autoclave was stopped and cooled to *ca* . -70°C then liquid trifluoromethyl iodide, pre-condensed at -70°C (*ca.* 12 g, 61.2 mmol) was quickly introduced. The autoclave was securely closed, placed in a rocking oven and heated at 150°C for 30 h. After cooling and degassing, the mixture was filtered through a pad of Celite, the autoclave and the solid phase being washed with ether (80 ml). To the filtrate, water (50 ml) was added and the shaken mixture was filtered once more through Celite. The ether layer was separated and the water phase was extracted with ether (3x70 ml). The combined organic phases were washed with water (50 ml) then with a saturated sodium chloride solution (50 ml). After drying over magnesium sulfate and evaporation of the solvent *in vacuo* , the remaining oil was distilled off through a short path condenser (oil-bath at 150°C/0.03 Torr) to give 7 as a pale-yellow to colourless oil (4.56 g, 95 %). ^{1}H NMR ($CDCl_3$)δ: 2.13 (s, 3H, $COCH_3$), 3.88 (s, 3H, OCH_3), 5.20 (s, 4H, CH_2), 7.67 (s, 2H, H_{arom}) ; ^{19}F NMR ($CDCl_3$) δ : -62.8 (s), unidentified impurity at -85.5 ppm (s). Anal. calcd. for $C_{14}H_{15}F_3O_5$: C 52.50, H 4.72 ; found : C 52.52, H 4.77.

2,6-Di(hydroxymethyl)-4-trifluoromethylanisole (8)

To a stirred 5 N solution of ethanolic potassium hydroxide (80 ml, prepared from 95-96 % ethanol) was added 7 (14.0 g, 43.7 mmol). Stirring was continued for 5 h at room temperature then the ethanol was partially removed by rotary evaporation at 30-40°C to a final volume of *ca* . 60 ml.

The residual brown syrup was diluted with water (250 ml) and extracted with ether (4x90 ml). The combined organic phases were washed with *ca* . 1.2 N hydrochloric acid (60 ml) then with water (80 ml) and a saturated sodium chloride solution (80 ml). The ether phase was dried over magnesium sulfate. Evaporation of the solvent *in vacuo* afforded 8 as a yellowish solid suitable for the next step (9.65 g, 94 %), mp 93.3°C (water ; colourless needles). ^{1}H NMR (CD_3COCD_3) δ: 3.82 (s, 3H, OCH_3) ; 4.32 (dd,2H, J=6.0, 4.8 Hz, OH), 4.73 (br d, 4H, J=5.4 Hz, CH_2), 7.73 (s, 2H, H_{arom}) ; ^{19}F NMR (CD_3COCD_3) δ : -61.3 (s). Anal. calcd for $C_{10}H_{11}F_3O_3$: C 50.85, H 4.69, F 24.13 ; found : C 50.30, H 4.70, F 24.02.

2,6-Diformyl-4-trifluoromethylanisole (9)

2,6-Di(hydroxymethyl)-4-trifluoromethylanisole (8) (9.5 g, 40.2 mmol) was added to water (68 ml) containing sulfuric acid (d 1.83, 6 ml). The stirred mixture was refluxed in an oil bath at 110°C and a solution of sodium dichromate dihydrate (8.2 g, 27.5 mmol) in water (6.2 ml) was added dropwise, the heating source being removed. At the end of the addition, the mixture was allowed to cool to 50°C and then heated at this temperature for 3 h. After cooling, the mixture was poured into water (200 ml) and ether (100 ml) was added. After shaking, the mixture was filtered through a pad of Celite. The organic layer was separated and the water phase extracted with ether (3 x 80 ml). The combined organic phases were washed with water (100 ml) then with a saturated sodium chloride solution (50 ml), and dried over magnesium sulfate. The green pasty solid obtained after evaporation of the solvent *in vacuo* was flash chromatographed (silica gel Merck 60, 0.040-0.063 mm ; dichloromethane as eluent) to give 9 as a white solid (5.8 g, 62 %) ; an analytical sample was obtained by sublimation (60°C/0.02 Torr), mp 62.5°C ; ^{1}H NMR ($CDCl_3$) δ : 4.16 (s, 3H, OCH_3), 8.32 (s, 2H, H_{arom}), 10.4 (s, 2H, CHO); ^{19}F NMR ($CDCl_3$) δ : -63.6 (s) ; ir (CCl_4) ν_{max} : 1718 cm^{-1}. Anal. calcd. for $C_{10}H_7F_3O_3$: C 51.74, H 3.04, F 24.55 ; found : C 51.25, H 2.87, F 24.57. The semi-oxidized compound 10 was recovered by further elution of the chromatography column with dichloromethane/ethyl acetate (1/1) as eluent (0.94 g, viscous oil) ; ^{1}H NMR ($CDCl_3$) δ: 3.5 (br s, 1H, OH), 4.0 (s, 3H, OCH_3), 4.83 (s, 2H, CH_2), 7.98 (s, 2H, H_{arom}), 10.32 (s, 1H, CHO) ; ^{19}F NMR ($CDCl_3$) δ : -63.3 (s) ; MS (70 eV) *m/e* =234 (M^+).

2,6-Diformyl-4-trifluoromethylphenol (2)

A dried, argon (or nitrogen) -flushed round- bottomed flask equipped with a mechanical stirrer, was charged with a solution of the anisole 9 (1.0 g, 4.31 mmol) in dry dichloromethane (60 ml). The flask was cooled to between -70 to -75°C and a molar solution of boron tribromide in dichloromethane (15.1 ml, 15.1 mmol) was added dropwise in *ca.* 20 min., under a vigorous stirring, to give a yellow gel. After 15 min. at this temperature, the mixture was allowed to reach room temperature (in *ca.* 30 min.), turning homogeneous on warming. Stirring was continued for 45 min. and then the mixture was poured into ice/water (100 ml) and vigorously stirred for 30 min. After decantation, the aqueous phase was extracted with dichloromethane (2 x 50 ml). The combined extracts were washed with water (2 x 50 ml) then with a saturated sodium chloride solution (50 ml) and dried over magnesium sulfate. After removal of the solvent by rotary evaporation *in vacuo* , the residual solid (moistened by an unidentified oil) was dissolved in boiling *n*-hexane (15 ml, decolorizing charcoal Norit may be added). The hot solution was decanted into a flask from a small amount of brown oil (or filtered if charcoal had been added), leaving crystals of the phenol 2 at the surface of the glass. The crystals were filtered, washed with a minimum amount of *n*-hexane, then dried for a short time *in vacuo* and finally sublimed (oil bath temperature : 80°C/0.03 Torr) to give pure phenol 2 as a white powder (0.42 g, 45 %), mp 98.3°C ; ^{1}H NMR ($CDCl_3$) δ : 8.24 (s, 2H, H_{arom}), 10.32 (s, 2H, CHO), 11.97 (s, 1H, OH) ; ^{19}F NMR ($CDCl_3$) δ = -63.2 (s) ; ir ($CHCl_3$) ν_{max} : 1691, 1668 cm^{-1} ; MS(70 eV) *m/e* (relative intensity)=218 (M^+, 39), 190 (100). Anal. calcd. for $C_9H_5F_3O_3$: C 49.56, H 2.31, F 26.13 ; found : C 49.48, H 2.28, F 25.17. Identification of compound 11 : ^{1}H NMR ($CDCl_3$) δ : 7.07 (s, 1H, $CHBr_2$), 7.87 (d, 1H, H_{arom}), 8.35 (d, 1H, H_{arom}), 9.96 (s, 1H, CHO), 11.97 (s, 1H, OH) ; MS(70 eV) *m/e* =341, 343, 345(M^+-19).

Caution ! Skin contact with 2,6-diformyl-4-trifluoromethylphenol leaves a deep yellow stain which will persist for several days.

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