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ISOMERISATION OF BENZOPHENONES AND DIRECT OBSERVATION OF INTERMEDIATES IN THE AROMATIC ACYLATION OF PHLOROGLUCINOL DERIVATIVES WITH TRIFLUOROACETIC ANHYDRIDE

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Abstract—Acylation of methyl and benzylethers of orcinol with the same ethers of phloroglucinol carboxylic acid using trifluoroacetic anhydride (TFAA) in chloroform or dichloro methane afforded both unsymmetrical and symmetrical benzophenones. Magnetic resonance measurements were performed on the reactions between various deuterium labelled methylethers of phloroglucinol and phloroglucinol carboxylic acid. The reaction was found to proceed via several equilibria resulting in a total scrambling of the aromatic rings around the carbonyl function. The occurrence of an intermediate in the reaction was observed and is thought to consist of an ion pair between a protonated benzophenone and trifluoroacetate ion which rapidly catalyses an exchange between TFAA and TFA.

Trifluoroacetic anhydride is a useful reagent for promoting the acylation of activated aromatic compounds with suitable carboxylic acids.[1] It has been shown earlier[2,3] that the first step in the reaction is the formation of an unsymmetrical anhydride (acyl trifluoroacetate) between the acid and the reagent. The properties of such solutions have been studied extensively[2,4] and a mechanism for the acylation reaction has been suggested.[5-7] According to this, the acylating properties of such solutions are attributable to the formation of acylium ions derived from the ionisation of the acyl trifluoroacetates.

In this investigation, the occurrence of an intermediate was observed in the reaction with phloroglucinol derivatives. Mechanistic aspects are discussed.

RESULTS

In a previous investigation of the synthesis of polyhydroxy benzophenones,[8] reaction (I; Scheme 1) was carried out.

$$\mathbf{1a} + \mathbf{2a} \xrightarrow{TFAA,CH_2Cl_2} \mathbf{4a} + \mathbf{5a} \qquad (I)$$

$$\mathbf{1b} + \mathbf{2b} \xrightarrow{TFAA,CH_2Cl_2} \mathbf{4b} + \mathbf{5b} + \mathbf{6b} \qquad (II)$$

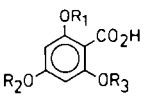
$$\mathbf{1a} + \mathbf{2b} \xrightarrow{TFAA,CH_2Cl_2} \mathbf{4c} + \mathbf{5b} + \mathbf{6a} \qquad (III)$$

The main product formed was the expected benzophenone **4a**, but the symmetrical benzophenone **5a** was also isolated.

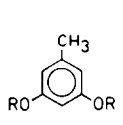
To see if by-products would be formed with other substrates, reactions (II and III) were performed. These reactions gave, in addition to the expected benzophenones **4**, the symmetrical products **6** together with **5**. The amount of by-products varied with the reaction conditions (for typical examples, see Experimental).

The formation of the unexpected products **5** and **6** called for a closer study of the reaction mechanism. Suitable systems for mechanistic studies were obtained by substituting orcinol ethers with phloroglucinol ethers and by labelling some of the OMe groups with deuterium.

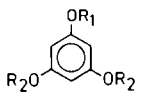
Quenching experiments. Equimolar amounts of **1c** and **3a** were reacted with a slight excess of TFAA in chloroform at 25°. The mixture was quenched in methanol and the products separated with TLC. After 1 min reaction time, the expected benzophenone was obtained as shown by the OMe part of the ^{1}H NMR spectrum ($\delta(C_3D_6O) = 3.64$ (*o*-OMe), 3.80 (*p*-OMe); ratio I(*o*-OMe)/I(*p*-OMe) = 1:1). When quenched after completion of the reaction (approx. 60 min), a mixture of benzophenones with a 2:1 ratio of the *o*/*p* OMe's was obtained. The mass spectrum of the mixture showed that three different types of benzophenones were formed: one without deuterium, one with two deuteriomethyl groups and one with four in a ratio of 1:2:1, and with molecular



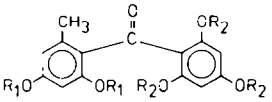
1a: $R_1 = R_2 = R_3 = CH_2C_6H_5$
b: $R_1 = R_2 = R_3 = CH_3$
c: $R_1 = R_3 = CD_3$, $R_2 = CH_3$
d: $R_1 = CH_3$, $R_2 = R_3 = CD_3$
e: $R_1 = R_2 = R_3 = CD_3$



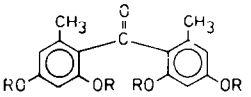
2a: $R = CH_2C_6H_5$
b: $R = CH_3$



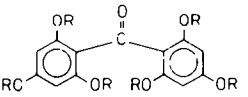
3a: $R_1 = R_2 = CH_3$
b: $R_1 = R_2 = CD_3$



4a: $R_1 = R_2 = CH_2C_6H_5$
b: $R_1 = R_2 = CH_3$
c: $R_1 = CH_3$, $R_2 = CH_2C_6H_5$



5a: $R = CH_2C_6H_5$
b: $R = CH_3$



6a: $R = CH_2C_6H_5$
b: $R = CH_3$

Scheme 1.

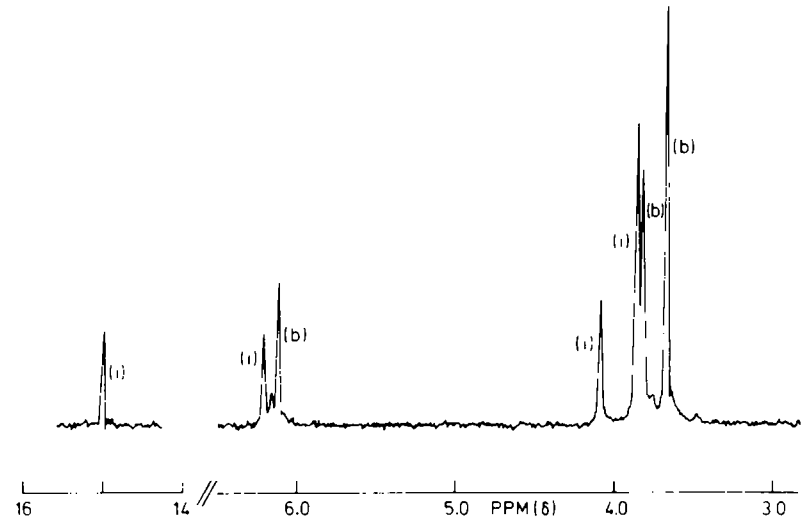


Fig. 1. ^{1}H NMR spectrum (60 MHz) of **6b** (0.32 M, $CDCl_3$) after addition of 7 moles TFAA and 1 mole TFA. (b) peaks from the benzophenone and (i) from intermediate.

ions at *m/e* 362, 368 and 374. In another experiment, **1c** was reacted with a catalytical amount (5%) of **3a**. The mixture was quenched in methanol after 24 hr and NMR analysis displayed that the methyl esters of **1d** and **1c** had formed in a ratio of 2:1 ($\delta(C_3D_6O) = 3.74$ and 3.83; *o*/*p*-ratio 2:1).

Direct NMR studies of the reaction. When acid **1c** and phenol ether **3b** were treated with TFAA in an NMR-tube, the *p*-OMe absorption (spectrum recorded after 5 min) appeared at $\delta = 4.10$, constituting approximately 70% of all absorption in this region. No other components of the mixture (including the benzophenone, see above) absorb at this value. With acid **1d** and ether **3b** the *o*-OMe signal was shifted to $\delta = 3.87$ using the same conditions.

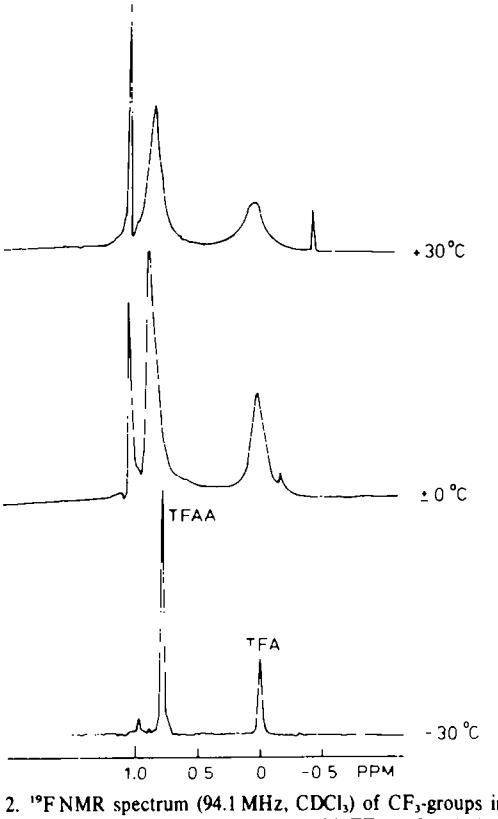
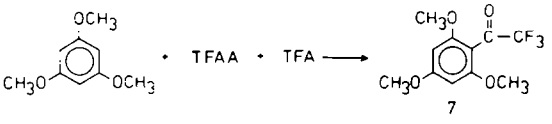


Fig. 2. ^{19}F NMR spectrum (94.1 MHz, $CDCl_3$) of CF_3-groups in the reaction of **1a** (0.5 M) and **3a** (0.5 M) with TFAA (3 moles) at different temperatures.

Further information was obtained by studying the reverse reaction. When benzophenone **6b** was treated with TFAA alone, no change was seen in the spectrum of **6b**. Addition of one mole trifluoroacetic acid (TFA) produced two new peaks in the OMe region with δ-values 3.87 and 4.10, exactly as in the above-mentioned experiments (Fig. 1). When the mixture was quenched immediately after the addition of TFA and the spectrum recorded after removal of the reagents, only the spectrum of **6b** was obtained. On prolonged standing (approx. 1 hr) the methyl ester of **1b** (after quenching in methanol) and ether **3a** were formed. Addition of pure TFA to the benzophenone did not give rise to the signals observed above, but on prolonged standing (approx. 2 hr) the benzophenone was cleaved (TLC, MS) to the same products as with both TFAA and TFA added.

The ^{19}F NMR spectrum of the reaction mixture (Fig. 2, TFA arbitrarily chosen as zero) was recorded at different temperatures. The broad peaks at higher temperature correspond to TFAA and TFA. The additional peak at high field is due to formation of the trifluoroacetyl derivative **7**,[9] but the peak at low field has not been satisfactorily assigned. A trifluoroacetylated compound corresponding to the latter absorption peak was not found in the quenched mixture and therefore this species must be stable in solution only.

Finally, the ^{13}C NMR spectrum of the intermediate is presented (Fig. 3b). The assignments of **6b** (Fig. 3a) have been made by off-resonance decoupling and by inference from reference compounds. By adding 4 moles of TFAA and 2 moles of TFA, the concentration of the intermediate could be maximized. Peaks from the carbonyl carbon and the reagents could not be assigned. The small additional peaks seen in the spectrum arise from the expected cleavage products.



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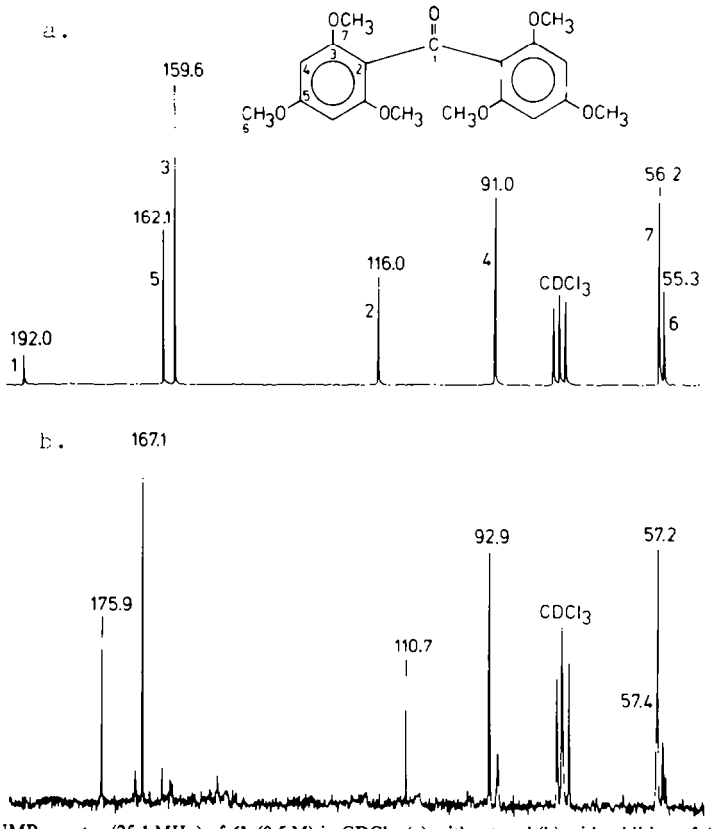


Fig. 3. FT ^{13}C NMR spectra (25.1 MHz) of **6b** (0.5 M) in $CDCl_3$; (a) without and (b) with addition of 4 moles TFAA and 2 moles TFA. Shift values from TMS. Data converted using $\delta_C^{CHCl_3} = 77.2$.

DISCUSSION

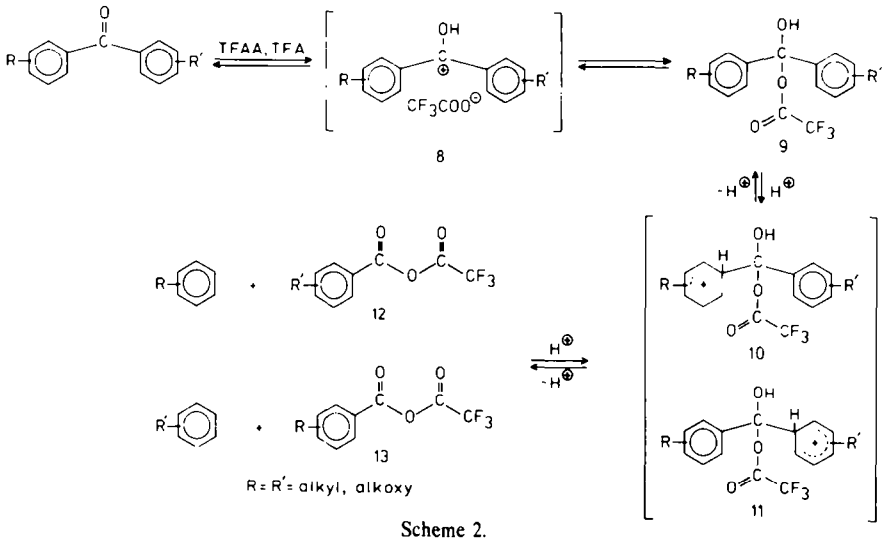
The results of the quenching experiments and mass spectrum product analysis indicate that the reaction proceeds via several equilibria, resulting in total scrambling of the aromatic rings around the carbonyl carbon of the benzophenone. Isomerisation of aromatic ketones (arylalkyl) has been previously observed,[10] although more drastic conditions were used ($AlCl_3$, high temperature). Since the system used is rather simple due to symmetry, and therefore the total number of equilibrium constants should be small, the kinetics of the reaction are complicated by the occurrence of side-reactions, viz. trifluoroacetylation of the phenol ethers[9] and decarboxylation of the acids by TFAA.[11] The products formed consequently vary with the reaction conditions. However, conclusions which could be drawn from spectroscopic evidence are not affected by this complication.

The ^1H NMR spectrum (Fig. 1) clearly demonstrates the presence of a species which is not identical with the final product but must be structurally similar to it and could therefore not be an acylium ion. The experiments also show that *both* TFAA and TFA are necessary for formation of this species. A low field shift for both aromatic and OMe protons are indicative of a system which is more electron deficient than the benzophenone **6a**. The low-field proton at $\delta = 15.0$ is sharp and suggests a protonated benzophenone.[12] However with only TFA added, which to some extent would protonate the benzophenone,[13] no intermediate was observed.

The broadening of the signals for both TFAA and TFA as seen in the ^{19}F NMR spectrum (Fig. 2), indicates that some species in the solution catalyses an exchange between the two reagents. (Broadening is not observed when a spectrum is recorded of a mixture of pure TFAA and TFA). This exchange is also inferred by the ^{13}C NMR spectrum (Fig. 3). The CO peak is missing, which would be expected by exchange, and significantly no sharp signals from the reagents were observed. Exchange with the aromatic protons of the benzophenone is not seen, since this would lead to broadening of the signals in both proton and carbon spectra. The structural similarity between benzophenone and the intermediate is also shown by the shift differences expected of a protonated benzophenone.[13,14] This similarity suggests formation of an ion-pair **8** (Scheme 2), between a protonated benzophenone and a trifluoroacetate ion in rapid equilibrium with TFAA and TFA. **8** may slowly collapse to the neutral compound **9**, which is protonated on either side of the aromatic rings at 1 or 1′ positions to form Wheeland-complexes **10** and **11** and finally the unsymmetrical anhydrides **12** and **13**.

The acylation reaction is known to be catalysed by acids[1] (general acid catalysis) and is, in this case, also responsible for the isomerisation process. More of the unexpected benzophenones **5** and **6** were formed when TFA was added to the reaction mixture, but because of side-reactions no attempts were made to quantify this.

The existence of **9** could explain the low-field absorption in the F-spectrum and would also be stable in solution only. A Wheeland-complex similar to **10** (and **11**) has been suggested in the mechanism for trifluoroacetylation of aromatic compounds.[10] Formation of the ion-pair could also be explained by an acylium ion mechanism, although in this case two separate reaction mechanisms operate: formation of the benzophenone and its subsequent cleavage.



Scheme 2.

The existence of observable intermediates was also tested for other systems (0,0-dimethylorcinol, 2-methylfuran) but was only found with phloroglucinol derivatives (e.g. 2,4,6-trimethoxytoluene) and may be attributable to their great ability to stablize a positive charge.

EXPERIMENTAL

All m.ps are uncorrected. ^{1}H NMR spectra were recorded on a Varian A60 D spectrometer, ^{19}F NMR spectra on a Varian XL 100 and ^{13}C NMR spectra on a Jeol FX 100. The ^{13}C NMR spectra (Fig. 3) were obtained in 10 mm tubes at 22°. Protons were noise-decoupled and the spectra are the Fourier transforms of 16 (Fig. 3a) and 25 (Fig. 3b) free induction decays. A 90° pulse angle was used but the pulse width had to be increased from 13 to 26 μs in the second experiment, probably due to changes in conductivity of the sample. A pulse repetition-rate of 120 s was employed. TMS was used as internal standard unless otherwise noted. TLC analyses (precoated silica gel plates (Merck), eluant: toluene–acetic acid (4:1)) of the quenched mixtures gave the following R_f-values: **6b** (0.12), methylester of **1b** (0.40), **7** (0.51), **3a** (0.57). IR spectra were measured on a Perkin–Elmer 177 (KBr discs) and mass spectra on a LKB 9000. Elemental analyses was performed by the Analytical Department, Institute of Chemistry, Uppsala.

Materials. Reagents and solvents were p.a. grade or >99% isotopically pure. TFAA was distilled from P_2O_5 before each experiment. Deuterated **1c** and **1d** were prepared from methyl 2,4,6-trihydroxybenzoate[15] by stepwise methylation with CD_3I (Ciba) and MeI by the usual methods. **3b** was prepared by decarboxylation of acid **1d**. The isotropic purity of the deuterated compounds was determined by mass spectrometry and found to be 96–97%.

1,1',3,3',5,5'-*Hexamethoxybenzophenone* (**6b**), was prepared from **1b** (2.12 g), **3a** (1.68 g) and TFAA (10 ml) in methylene chloride (100 ml) at 25°; reaction time 5 min. Recrystallisation from benzene after work-up yielded 2.9 g (80%), m.p. 151–52°. NMR(C_3D_6O)δ = 3.64 (s 6H), 3.80 (s 12H), 6.19 (s 4H). IR $\nu_{c=o}$ = 1662 cm^{-1}. (Found: C, 62.93; H, 6.13. Calc. for $C_{19}H_{22}O_7$: C, 62.96; H, 6.13%).

2,4,6-*Trimethoxy*-1',1',1'-*trifluoroacetophenone* (**7**), was prepared from **3a** (1.68 g), TFAA (3.8 ml) and TFA (2 ml) in methylene chloride (50 ml) at 25°. Reaction time 15 min. Recrystallisation after work-up gave 2.4 g (91%), m.p. 59–60° (light petroleum ether). NMR(C_3D_6O)δ = 3.88 (s 3H), 3.84 (s 6H), 6.34 (s 2H). IR $\nu_{c=o}$ = 1761 cm^{-1}. (Found: C, 50.13; H, 4.21. Calc. for $C_{11}H_{11}F_3O_4$: C, 50.00; H, 4.20%).

Reaction (I), has been described previously.[8]

Reaction (II), **2b** (152 mg) and **1b** (212 mg) were reacted with 300 μl TFAA in 20 ml methylene chloride at 25° under N_2. The mixture was evaporated *in vacuo* to 5 ml at 0°. Ether was added and the soln treated with $NaHCO_3$ and water. After drying ($MgSO_4$) and evaporation, the crude material was chromatographed on silica gel (Merck, precoated plates, 0.5 mm) with light petroleum ether-ether-THF (2:1:1) as eluent. Three bands were obtained: (1) R_f = 0.64–0.73. This was rechromatographed with light petroleum ether-ether (1:1) to give **7** (36 mg) and **5b** (62 mg). **5b** was recrystallized from benzene, m.p. 165–66°. NMR(C_3D_6O)δ = 2.29 (s 6H), 3.50 (s 6H), 3.80 (s 6H), 6.39 (q 4H, J = 1.95 Hz). IR $\nu_{c=o}$ = 1656 cm^{-1}. (Found: C, 69.02; H, 6.69. Calc. for $C_{19}H_{22}O_5$: C, 69.06; H, 6.72%). (2) R_f = 0.41 contained **4b** (79 mg, 23%)[8] and (3) R_f = 0.15 gave **6b** (50 mg).

Reaction (III). **2b** (152 mg) and **1a** (440 mg) were reacted with 350 μl TFAA as in reaction (II) during 2 hr. Chromatography (hexane-acetone (7:3)) gave three bands. (1) R_f = 0.43 gave **5b** (64 mg), (2) R_f = 0.38 gave **4c** (174 mg, 30%), which was recrystallized from hexane, m.p. 119, 5–20°. NMR(C_3D_6O)δ = 2.13 (s 3H), 3.43 (s 3H), 3.81 (s 3H), 5.00 (s 4H), 5.11 (s 2H), 6.32 (s 2H), 6.41 (s 2H), 7.25 (s 10H), 7.39 (s 5H). IR $\nu_{c=o}$ = 1665 cm^{-1}. (Found: C, 77.38; H, 5.96. Calc. for $C_{37}H_{34}O_6$: C, 77.32; H, 5.98%). (3) R_f = 0.30 gave **6a** (166 mg), m.p. 182–83° (benzene-light petroleum ether). NMR(C_3D_6O)δ = 4.82 (s 8H), 5.12 (s 4H), 6.32 (s 4H), 7.21 (s 20H), 7.42 (broad 10H). (Found: C, 80.61; H, 5.66. Calc. for $C_{55}H_{46}O_7$: C, 80.65; H, 5.67%).

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