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$CoCl_2$ Catalyzed Trifluoroacetylation versus Dimerization of Methoxyaromatics Using Trifluoroacetic Anhydride

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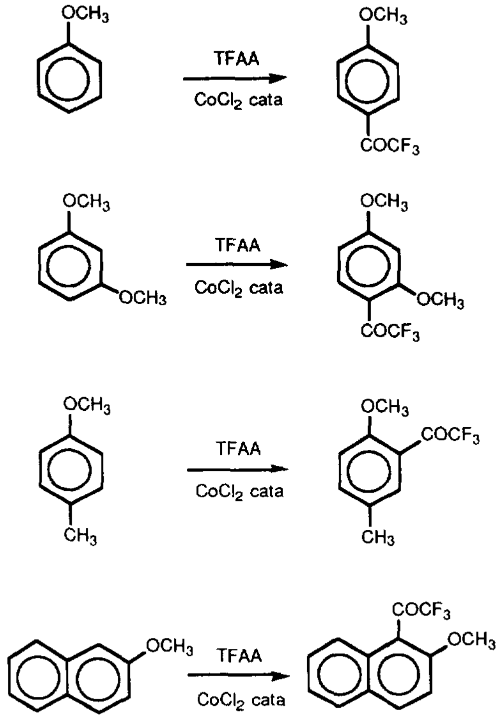
Abstract: Anisole, resorcinol dimethyl ether, *p*.methylanisole, and β-methoxynaphthalene undergo regiospecific trifluoroacetylation in neat trifluoroacetic anhydride (TFAA) at 100 °C in the presence of 0.1 eq. $CoCl_2$ as catalyst; with a 1:1 anisole/TFAA ratio, only paradimerization of anisole is observed.

The trifluoroacetylation of aromatics usually requires sub-stoichiometric amounts of Al_2Cl_6 and trifluoroacetyl chloride whose boiling point, -27 °C, brings about difficulties of handling.[1] Apart from some specially reactive aromatics whose trifluoroacetylation can proceed using trifluoroacetic anhydride (TFAA) at 200 °C or triflate at 80 °C,[2] the usual synthesis of trifluoroacetophenones involves a reaction between a Li, Mg, Zn or Mn derivative and trifluoroacetic acid or ethyl or Li trifluoroacetate.[3] Finally, a recently reported method uses trifluoroacetoxy-2-pyridine, but requires recycling of this compound.[4] No research has been published up to now on truly catalytic trifluoroacetylation. Catalysis studies have recently emerged as an important field of Friedel-Crafts reactions, however.[5] We report here our first results on the $CoCl_2$ catalyzed trifluoroacetylation and dimerization of anisole and the trifluoroacetylation of other mono- and dimethoxy aromatics using TFAA.

Methoxyaromatics such as anisole, *p*.methylanisole, β-methoxynaphthalene, and *m*.dimethoxybenzene (resorcinol dimethyl ether) undergo trifluoroacetylation in neat TFAA at 100 °C for 15 h in an autoclave in good yields on a 20 mmol scale when these reactions are carried out in the presence of 0.1 eq. $CoCl_2$ (Table I).

The reaction mixture was extracted using ether, washed with water and with a saturated aqueous solution of sodium bicarbonate, the organic phase was dried with sodium sulfate and ether was removed *in vacuo*. The trifluoroacetylated aromatic product and/or the dimer was purified by distillation or crystallization (Table I). No reaction occurs in the absence of catalyst. The presence of the methoxy group is necessary and orientates the trifluoroacetylation in the para position. However, when this position is occupied by a substituent such as in *p*.methylanisole and β-methoxynaphthalene, trifluoroacetylation occurs in the ortho position. The reaction is always regiospecific (Scheme 1).



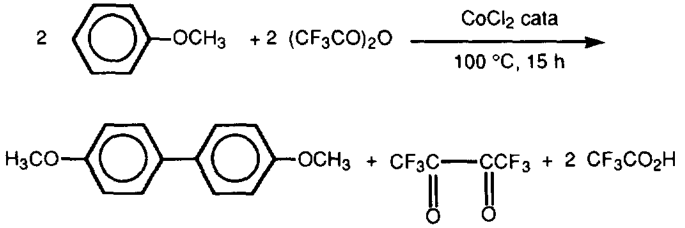
Scheme 1

Table I: $CoCl_2$ Catalyzed Trifluoroacetylation of Methoxyaromatics in neat TFAA.

Aromatic	Yield in $ArCOCF_3$ (%)	TFAA: aromatic	Site
anisole	60	80	para
m.dimethoxyanisole	87	5	para
p.methylanisole	40	5	ortho
β-methoxynaphthalene	68	5	1-ortho

All the reactions were carried out at 100 °C for 15 hours in the presence of 0.1 eq. catalyst (vs arene). The TFAA/anisole ratio was 80 in order to obtain only trifluoroacetylation. With this ratio, the yield was 25% after one month at room temperature. When the TFAA/anisole ratio was 5:1, a 34% yield of *p*.trifluoroacetylanisole and a 54% yield of the para dimer (see text) were obtained. Only the *p*.dimer was obtained using a 1:1 ratio (yield 96%). For all the entries of Table I, the complements to 100% were essentially unreacted aromatics (tars were found above 100 °C) and the yields are reported for reaction products purified by distillation for the two first entries and by crystallization for the next ones. The yields have not been optimized. (1.2-trifluoromethylmethoxynaphthalene was obtained with 100% conversion). All the products were identified by 250 MHz ^1H and 62.9 MHz ^{13}C NMR and infrared spectra and gas chromatography by comparison with authentic samples and literature data.

This regiospecificity is noteworthy for instance in the case of β-methoxynaphthalene which sometimes reacts at the 6 position (in zeolites).[6] Under our reaction conditions, 1,2,3,4-tetramethylbenzene and veratrole are reproducibly unreactive whereas ferrocene is oxidized to ferricinium. The lack of reactivity of veratrole is somewhat surprising since it is more easily oxidized than anisole (*vide infra*), but could be due to its ability to form an unreactive Co^{III} chelate. The case of anisole is of special interest since para dimerization also occurs when the TFAA/anisole ratio is reduced in the reaction medium. Thus with a 1:1 ratio, only para dimerization is found in 96% yield (Scheme 2).



Scheme 2

The $CoCl_2$ catalyzed acetylation of anisole was also reported by Iqbal to yield a dimer as a side product but an ortho-ortho structure was asigned in that case for the dimer.[7] The cobalt chloride catalyzed trifluoroacetylation and dimerization reactions are inhibited by acetonitrile or triphenylphosphine, which emphasizes the role of the coordination in these catalytic processes. The formation of the dimer and the oxidation of ferrocene indicate that Co^{III} intermediates are formed under the reaction conditions (eq. 1). Thus the catalysis by Co^{II} is not a simple electrophilic activation. The Co^{III} species is a strong oxidant[8] which can either oxidize the aromatic (eq. 2) or undergo electrophilic attack (eq. 3). Thus the trifluoroacetylation must occur either subsequently to electrophilic attack (eq. 3) or to coupling between the aromatic radical cation and Co^{III} (eq. 4). This latter possibility was proposed by Iqbal in the case of acetylation.[7] The arene dimer should result from coupling between the arene radical cation and the neutral arene (eqs. 5 and 6). Overall, the mechanism is not yet clear.

$$2\,[Co^{II}Cl_2] + (CF_3CO)_2O \rightarrow [Co^{III}Cl_2(CF_3CO)] + [Co^{III}Cl_2(CF_3CO_2)] \qquad \text{(eq. 1)}$$

$$[Co^{III}Cl_2(O_2CCF_3)] + PhOCH_3 \rightarrow [Co^{II}Cl_2] + (PhOCH_3)^{\bullet +}.CH_3CO_2^- \qquad \text{(eq. 2)}$$

$$PhOMe + [Co^{III}Cl_2(COCF_3)] \rightarrow p\text{-}CF_3COPhOCH_3 + [Co^{III}(H)(Cl)_2] \qquad \text{(eq. 3)}$$

$$PhOMe^{\bullet +} + [Co^{III}Cl_2(COCF_3)] \rightarrow p\text{-}CF_3COPhOCH_3 + [Co^{II}Cl_2] + H^+ \qquad \text{(eq. 4)}$$

$$PhOCH_3^{\bullet +} + PhOCH_3 \rightarrow \text{dimer H} + H^+ \qquad \text{(eq. 5)}$$

$$\text{dimer H} + [Co^{III}(O_2CCF_3)(Cl)_2] \rightarrow \text{dimer} + CF_3CO_2H + Co^{II} \qquad \text{(eq. 6)}$$

In conclusion, we have found the first truly catalytic trifluoroacetylation of methoxyaromatics together with para dimerization in the case of anisole. We have shown that, depending on the TFAA/anisole ratio, either the paratrifluoroacetylation or the para dimerization of anisole could be obtained exclusively. The $CoCl_2$ catalyzed trifluoroacelylation of monomethoxy aromatics appears to be a general reaction occurring in good yields when it is carried out in neat TFAA at 100 °C. When the para position is blocked by a substituent, no side product is obtained which makes this procedure a valuable and practical trifluoroacetylation method.

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