

A New Approach to the Photochemical Trifluoromethylation of Aromatic Compounds

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Using silver trifluoroacetate as a source of $\text{CF}_3\cdot$ radicals and powdered TiO_2 as a photocatalyst, electrophilic substitution of the trifluoromethyl group for hydrogen occurs in moderate to good yield for a variety of aromatic compounds.

Recent research involving the preparation of trifluoromethyl-substituted organic compounds has attracted increasing attention, because these compounds are of interest in biomedical and biochemical applications.¹ There are essentially four synthetic approaches to trifluoromethyl compounds: the conversion of a methyl group to a trifluoromethyl group,² the use of trifluoromethyl-copper (or -cadmium, -zinc *etc.*),³ the generation of the trifluoromethyl radicals from precursors⁴ and electrochemical methods.⁵ However, these routes often employ reagents that are toxic, expensive, and/or difficult to handle, and convenient alternatives are needed.

We report a novel photochemical route to trifluoromethyl-aromatic compounds that uses safe and conveniently handled

reagents: silver trifluoroacetate as the source of $\text{CF}_3\cdot$ radicals and TiO_2 as the photocatalyst. This method is based on the photo-Kolbe decarbonylation of carboxylic acids, RCO_2H , adsorbed on the surface of illuminated TiO_2 to produce an intermediate $\text{R}\cdot$ radical.⁶ While $\text{CF}_3\cdot$ radicals represent the most interesting case and are explored in this preliminary report, because of the ease with which perfluorocarboxylic acids can be prepared by direct fluorination of the analogous hydrogen-containing esters,⁷ this method should be generally applicable to the preparation of aromatic perfluoroalkyl compounds.

The photochemical procedure for trifluoromethylation is as follows. An acetonitrile solution (2 ml) of the appropriate

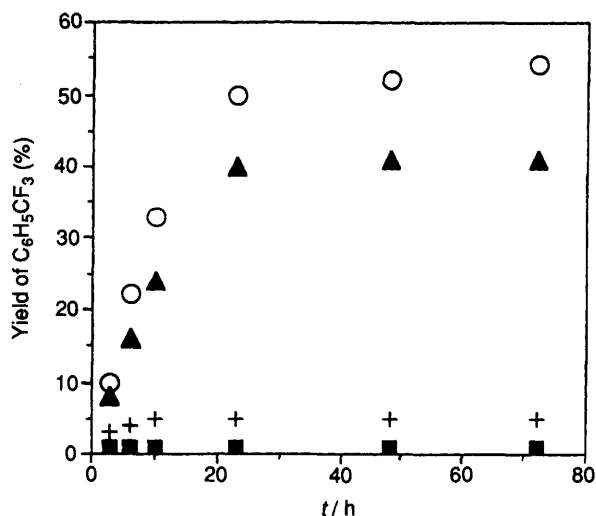


Fig. 1 Product yield vs. time for the trifluoromethylation of benzene using anatase and rutile as photocatalysts: ○ anatase; ▲ rutile; + no catalyst; ■ no light

arene (0.25 mmol), silver trifluoroacetate (1 mmol),[†] anatase TiO₂ powder (2 mmol) and trifluoroacetic acid (0.1 mmol) was placed into a 10 ml vacuum-tight quartz flask, and then deoxygenated *via* freeze-pump-thaw cycles. The mixture was warmed to room temperature and then illuminated with a 500 W Hg lamp for 24 hours. The light beam was filtered by a 10 cm Pyrex water jacket (to remove IR irradiation) and a 340 nm broad band filter. The photolysis procedure has been described previously.⁸ During the course of the reaction, Ag⁺, which serves as a scavenger for conduction band electrons, is reduced to elemental silver and deposited on the surface of the TiO₂ powder. The reaction products were identified by means of ¹⁹F and ¹H NMR spectroscopy and GC-MS.

Table 1 shows the results of photochemical trifluoromethylation of some aromatic compounds using silver trifluoroacetate as the fluorinating agent and anatase as a catalyst. In all cases only a single trifluoromethyl group is substituted for H. The substitution occurs preferentially at electron-rich positions on the arene rings, consistent with the electrophilic character of the trifluoromethyl radical. For example, in the case of naphthalene, the HOMO electron densities at α - and β -positions are 0.3517 and 0.1422, respectively.^{4b} The α -position is preferentially trifluoromethylated. Compounds 5–7, which contain electron-withdrawing groups, gave lower yields compared to 1–4 and 8.

In previous experiments, we have studied the photochemical replacement of the -CO₂H group by -F, using either AgF of AgF·HF as the fluorinating agent and TiO₂ as a photocatalyst.^{8,9} The reaction mechanism involves in that case two-electron oxidation of RCO₂H to form the carbocation R⁺. Formation of the one-electron oxidation product (R·) leads to undesirable side-reactions, and is significant when the second oxidation potential of RCO₂H is $\geq +1.8$ V vs. the saturated calomel electrode (SCE). This threshold is medium-dependent, shifting to more positive potentials as the F⁻ ions (which adsorb strongly at the TiO₂ surface) are complexed by HF. Interestingly, we find that while the first oxidation potential of CF₃CO₂Ag is *ca.* +1.82 V vs. SCE in acetonitrile solution[‡] CF₃· radical addition products are efficiently formed

[†] A twofold excess of CF₃CO₂Ag was used to compensate for the loss of trifluoromethyl as C₂F₆.

[‡] Electrochemical measurements were carried out in a standard one compartment, three electrode cell. The solution was acetonitrile containing 10 mol l⁻¹ CF₃CO₂Ag, with 40 mmol l⁻¹ tetrabutylammonium perchlorate as a supporting electrolyte. A scan rate of 100 mV s⁻¹ was used. Other details are described in ref. 8.

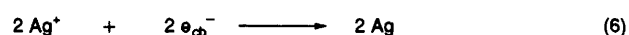
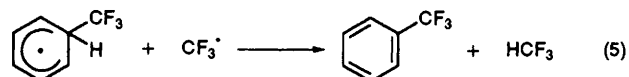
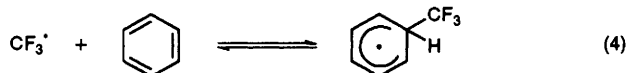
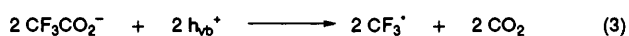
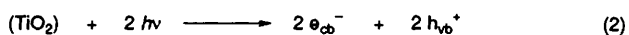
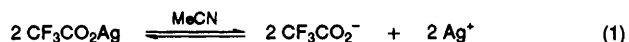
Table 1 Photochemical trifluoromethylation of various aromatic compounds

Compound	Products ^a	¹⁹ F NMR ^b	m/z	Yield ^c (%)
		-63.0 ^d	146	50
		-63.2 ^e	214	45
		-62.5(ρ) ^f -62.7(o) -62.8(m)	226	46
		-61.8(ρ) ^f -62.7(o) -63.1(m)	160	38
		-60.2(a) ^e -63.0(b)	238	20
		-61.7(m) -62.2(o) -62.7(p)	204	26
		-61.0	239	10
		-60.1(α) ^g -62.7(β)	196	50

^a Products were identified by ¹⁹F NMR and GC-MS analyses. ^b Parts per million upfield from CFCl₃; CFCl₃ was used as internal standard. Assignments were consistent with literature values. ^c Yield, reported are from integration of NMR spectra and GC results, and represent the total amount of product if more than one isomer was formed. ^d Ref 12. ^e Ref. 4(c). ^f Ref. 13. ^g Ref. 14.

in the present case. Apparently, in the absence of adsorbed fluoride ions, the valence band-edge potential of TiO₂ is sufficiently positive to effect one-electron oxidation of CF₃CO₂⁻, but not two-electron oxidation. Of the two available polymorphs of TiO₂, rutile is less active as a trifluoromethylation catalyst than anatase (Fig. 1). This difference most likely arises from the slightly larger band-gap of anatase relative to rutile [E_g (anatase) = 3.23 eV and E_g (rutile) = 3.02 eV], and greater oxidizing power of photogenerated holes at the anatase particle surface.^{6c} Similar effects have been previously observed in other photocatalytic oxidation reactions involving TiO₂.^{6,10,11} Fig. 1 also shows that the photocatalyst is essential for this reaction.

Product analysis (by ¹⁹F NMR and GC-MS) in the trifluoromethylation reaction of benzene showed that Ph-CF₃ and by-products HCF₃, CO₂ and C₂F₆ were formed. The production of the CF₃· radical as a reaction intermediate is strongly suggested by the formation of its dimerization product, C₂F₆. The fact that oxygen, a radical scavenger, suppresses the formation of trifluoromethyl substitution products lends further support to the intermediacy of CF₃· in the reaction. From Fig. 1 one can see that the starting materials are consumed within 24 hours of photolysis, and the yield of product is determined by competition between electrophilic substitution of the arene and dimerization of CF₃·. A plausible mechanism (benzene as substrate) is illustrated by reactions (1)–(7).



In conclusion, we have described a convenient and novel photochemical method for introducing the trifluoromethyl group into electron-rich arenes. The method may be generally applicable to perfluoroalkyl substitution, using the appropriate perfluorocarboxylic acid, and furthermore may be applicable to biochemically interesting arenes, such as heterocycles, and electron-rich olefins. The full scope of this reaction is currently under investigation.

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