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PAPER

Protolytic defluorination of trifluoromethyl-substituted arenes†‡

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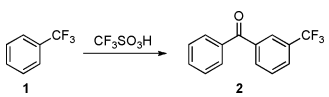
A series of trifluoromethyl-substituted arenes were studied in their reactions with Brønsted superacids. The products from these reactions suggest the formation of reactive electrophiles, such as carbocations, acylium cations or equivalent electrophilic species. As such, Friedel–Crafts-type reactions occur between these species and arene nucleophiles. NMR studies were done, and the results suggest the formation of an acyl group from the trifluoromethyl groups in the superacid.

Introduction

Perfluorinated alkyl groups can be incorporated into organic compounds to influence the charge distributions within the structure, lipophilicities of the compounds and to impart other effects. In particular, many drugs and pharmaceutical agents utilize the trifluoromethyl group to give these desirable properties. While the trifluoromethyl group is generally considered to be a reasonably stable functional group, it can undergo decomposition reactions with some transition metal catalysts,[1] Lewis acids,[2] metal hydrides[3] and in base-catalyzed conditions.[4] Ionization of the C–F bond by strong Lewis acids is also a well-known route to carbocationic structures.[5] Although ionization of the C–F bond by Brønsted acids is known, this chemistry has not been studied in great detail.[6] Dissociative attachment of protons to 1-fluoroadamantane has been shown to give the stable 1-adamantyl cation (by the loss of HF) in the gas phase and several theoretical studies have examined the protonation of alkyl fluorides.[7] Fornarini and co-workers have studied the gas-phase protonation of α,α,α-trifluorotoluene using FT-ICR methods and *ab initio* calculations.[8] Both experimental and theoretical results indicated that protonation occurs at the fluorine atoms with the subsequent loss of HF. Recently, Bell and co-workers described a synthesis of benzoyl fluoride from α,α,α-trifluorotoluene (**1**), Nb_2O_3 (and other metal oxides), trifluoroacetic acid, trifluoroacetic anhydride and molecular oxygen. They proposed a mechanism involving protonation of the fluorine atoms along with interactions at the catalyst surface.[9] A report by Hu and Wang also described Friedel–Crafts acylations involving α,α,α-trifluorotoluene (and related substrates) in reactions with arenes in CF_3SO_3H.[10] A proposed mechanism involved protonation of the fluorine atoms and the formation of benzylic cations.

During the course of our studies related to superacid chemistry, we observed that reactions of α,α,α-trifluorotoluene (**1**) in the Brønsted superacid CF_3SO_3H (triflic acid) often contained small amounts of benzoic acid or benzoyl fluoride in the product mixtures. We also observed a reaction in which compound **1** gave a small amount of 3-trifluoromethylbenzophenone (**2**, eqn (1)). These results prompted us to further examine the chemistry of trifluoromethyl-substituted arenes in superacids. The results of these studies are presented in this article.



(1)

Results and discussion

Our initial studies examined the conversions of trifluoromethyl-substituted arenes in Friedel–Crafts-type reactions with benzene using CF_3SO_3H as the acid (Table 1). We observed four basic types of reactivity patterns from these conversions. Several of the trifluoromethyl-substituted arenes formed both the benzophenone derivative and the triarylmethanol derivative (entries 1–3). In most cases, the product ratio varied little with temperature. Compound **1** gives almost equal amounts of benzophenone (**11**, 41%) and triphenylmethanol (**20**, 54%) at 0 °C. At 25 °C, the ratio shifts to **11**, 56% and **20**, 44%. Compound **1** does not react with benzene in the weaker acids of 98% H_2SO_4 or CF_3CO_2H. Several compounds were capable of preferentially forming either the ketone (entries 5–8) or the alcohol (entries 4 and 9). Finally, some substrates were found to be completely unreactive with benzene in CF_3SO_3H, including the benzophenone derivative (**29**) and the heterocyclic derivative (**30**). We also examined the effects of added metal oxide catalyst (Nb_2O_3), but the presence of this catalyst had only minor effects on reactivities and product distributions. While our results are similar to the recent work of Hu and Wang,[10] the formation of triarylmethanols has not been previously reported in reactions involving trifluoromethyl-substituted arenes.

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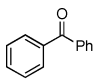
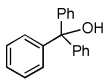
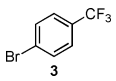
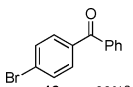
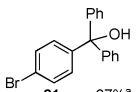
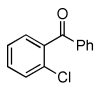
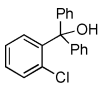
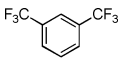
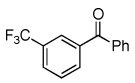
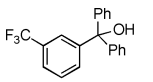
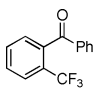
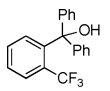
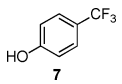
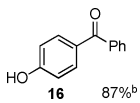
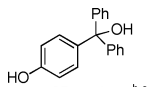
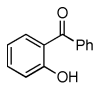
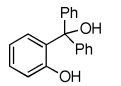
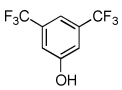
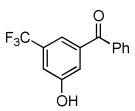
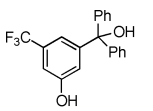
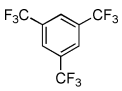
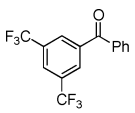
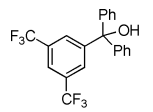
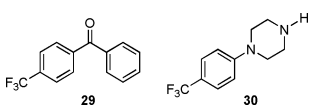
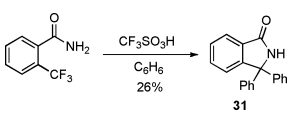
Table 1 Products and yields from the reactions of trifluoromethyl-substituted arenes with benzene in CF_3SO_3H

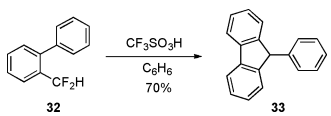
Entry	Substrate	Products and yields	
1	 **1**	 **11** 56%[a]	 **20** 44%[a]
2	 **3**	 **12** 33%[a]	 **21** 67%[a]
3	 **4**	 **13** 65%[a]	 **22** 35%[a]
4	 **5**	 **14** trace[c,d]	 **23** 62%[b,d]
5	 **6**	 **15** 84%[b]	 **24** trace[c]
6	 **7**	 **16** 87%[b]	 **25** trace[b,c]
7	 **8**	 **17** 75%[b]	 **26** trace[b,c]
8	 **9**	 **18** 79%[b,e]	 **27** trace[c,e]
9	 **10**	 **19** not formed	 **28** 32%[b]

[a] Relative yield determined by GC-FID. [b] Isolated yield. [c] Detected by GCMS. [d] Reaction done at 0 °C. [e] Reaction done at 80 °C.


29 **30**

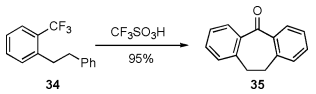
An interesting conversion was observed from the reaction of 2-(trifluoromethyl)benzamide with benzene in CF_3SO_3H (eqn (2)). Only unreacted starting material was recovered from the reaction at room temperature. However at 90 °C, 1-isoindolinone **31** is formed in a fair yield with some unreacted starting material. A clean cyclization is observed in the reaction of difluoromethyl derivative **32** with benzene in CF_3SO_3H (eqn (3)).


31 (2)

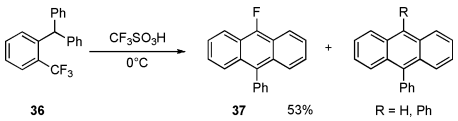

32 **33** (3)

In the absence of benzene, products of cyclizations and dimerizations are obtained. When 1-phenethyl-2-(trifluoromethyl)benzene (**34**) is reacted with CF_3SO_3H, 5-suberone (**35**) is formed as the exclusive product (eqn (4)).[11] Triarylmethane **36** undergoes cyclization in CF_3SO_3H; however, a mixture of substituted anthracenes is formed (eqn (5)). 9-Fluoro-10-phenylanthracene (**36**) is the major product, isolated in 53% yield. Reactions of 1-chloro-2-(trifluoromethyl)benzene (**4**) and 2-(trifluoromethyl)-phenol (**8**) in neat CF_3SO_3H provide the dimerization products in high yields (eqn (6) and eqn (7)). There is

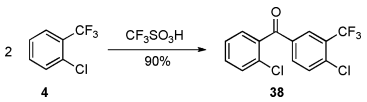
no evidence for further reaction (*i.e.*, trimerization), so formation of the benzophenone derivatives (**38** and **39**) must deactivate the remaining trifluoromethyl group to ionization. We have also found that some trifluoromethyl-substituted arenes provide clean conversions to the carboxylic acids (**40** and **41**) from superacidic reactions and a hydrolytic work-up (eqn (8) and eqn (9)). These results are in accordance with an earlier study with H_2SO_4, which showed the formation of benzoic acids from electron deficient trifluoromethyl-substituted arenes.[12]



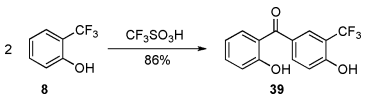
(4)



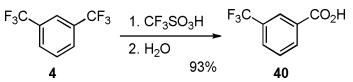
(5)



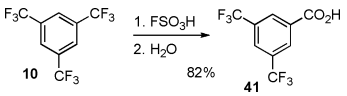
(6)



(7)



(8)



(9)

The reactions of trifluoromethyl-substituted arenes in CF_3SO_3H give products that suggest the formation of carbocationic or acylium ion intermediates. This is consistent with the mechanisms proposed by both Bell and Hu.[9,10] In order to gain further mechanistic insights into this chemistry, ^{13}C NMR experiments were undertaken. Our initial experiments were done by reacting α,α,α-trifluorotoluene (**1**) in CF_3SO_3H (H_o −14); however, the spectra were dominated by the ^{13}C signals arising from the solvent CF_3SO_3H, and the intermediate(s) appeared to rapidly convert to the dimeric product (**2**). In order to simplify the ^{13}C spectra, FSO_3H (H_o −15) was used as the acid and 1,3,5-tris(trifluoromethyl)benzene (**10**) was used as the arene substrate. We reasoned that the deactivating effects of the trifluoromethyl groups should prevent dimerization, and any unreacted trifluoromethyl groups could serve as an internal NMR standard. When compound **10** was mixed with FSO_3H, an up-field ^{13}C signal slowly appeared as a singlet at about δ 180 (Fig. 1, spectrum B). This suggests the formation of a carbonyl group, and since the peak is a well-defined singlet, there can be no fluorine atoms remaining on the carbon. The observed ^{13}C spectrum is consistent with the formation of a mixed carboxylic acid anhydride. To test this hypothesis, 3,5-bis(trifluoromethyl)benzoyl chloride (**42**) was dissolved in FSO_3H and the ^{13}C spectrum recorded (Fig. 1, spectrum A). Very similar spectra were observed from both

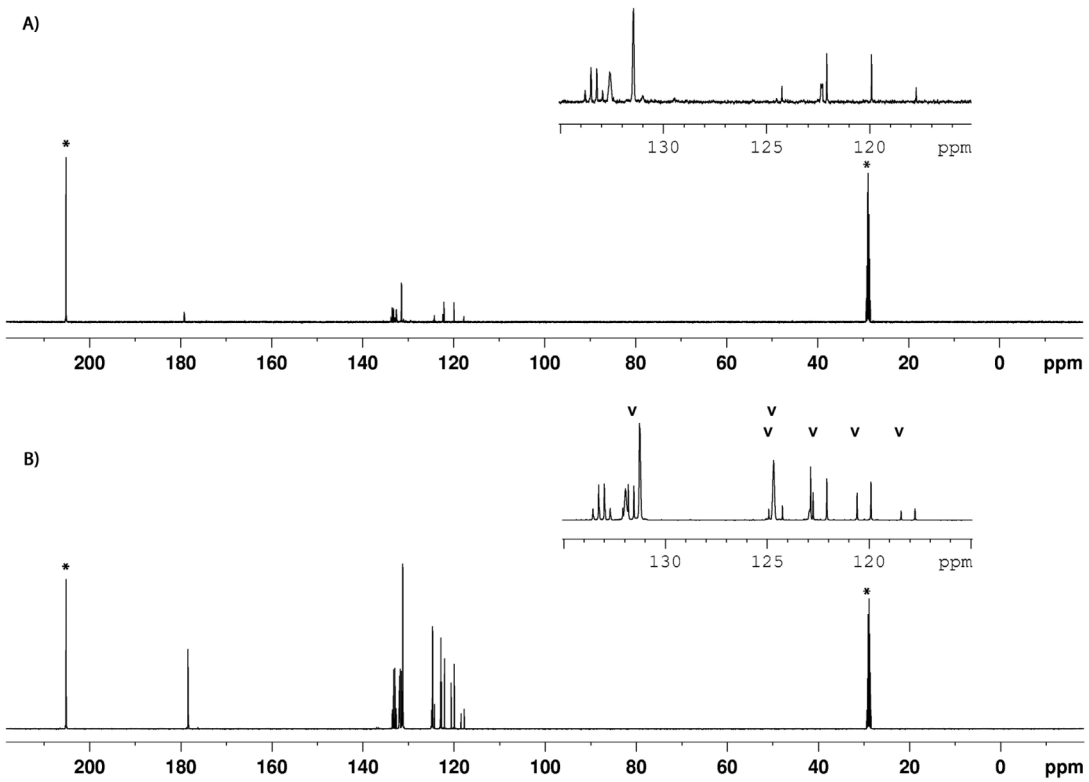
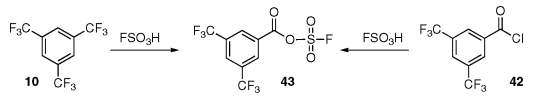


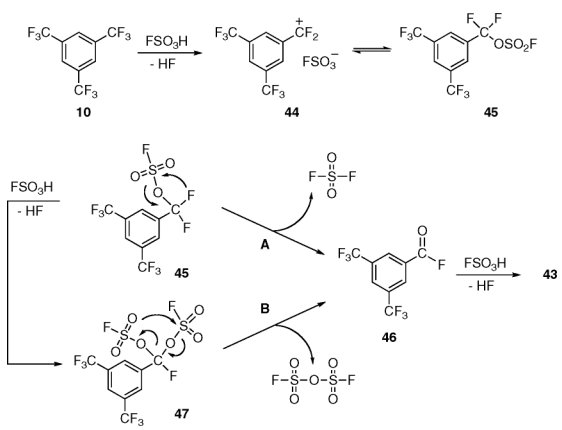
Fig. 1 ^{13}C NMR spectrum A: 3,5-bis(trifluoromethyl)benzoyl chloride (**42**) in FSO_3H with d_6-acetone external standard (labeled as *); ^{13}C NMR spectrum B: 1,3,5-tris(trifluoromethyl) benzene (**10**) in FSO_3H with d_6-acetone external standard (labeled as *); peaks arising from unreacted **10** are indicated by a **v** designation).

compounds **10** and **42**, although signals arising from unreacted **10** were present in its mixture (spectrum B). We propose that these substances form the same species in the superacid—the mixed anhydride (**43**) with the fluorosulfonic acid (eqn (10)).



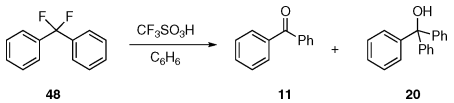
(10)

While the conversion of **42** to mixed anhydride **43** would involve the loss of HCl, it is less obvious how **10** leads to **42** in the Brønsted acid. Based on the observed chemistry of trifluoromethyl-substituted arenes, we propose that anhydride **43** is formed by protonation(s) of the trifluoromethyl group, with some involvement of the fluorosulfonate group (Scheme 1). Initial protonation of a fluorine atom forms benzylic carbocation **44** by the loss of a molecule of HF. Despite being an exceptionally weak nucleophile, the fluorosulfonate anion most likely reacts with **44** to form sulfonate ester **45**. Formation of the carbonyl group may occur by one of two routes. Based on Bell's proposed mechanism for the conversion of α,α,α-trifluorotoluene to the benzoyl fluoride,[8] sulfuryl fluoride may eliminate to directly provide the acid fluoride (**45**, route **A**). Presumably, such a step requires a four-center transition state. If a second protonation were to occur and another sulfonate ester group be formed, compound **47** would be generated. This unusual intermediate could then provide **46** by elimination of the acid anhydride. Alternative mechanisms can be formulated involving intermolecular attack of a sulfonate anion at a sulfonic ester group. In accordance with this mechanism, triflic anhydride has been observed as a by-product in the dimerization of **1** in CF_3SO_3H. Presumably, the initial ionization of **10** is the slow step, because the ^{13}C NMR spectrum shows only the carbonyl product (**43**) and the unreacted starting material (**10**). None of the intermediates are formed as persistent, observable species.

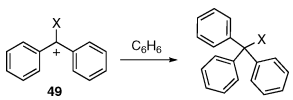


Scheme 1 Proposed mechanism for the conversion of **10** to **43** in FSO_3H.

The suggested mechanism provides a reasonable explanation for the observed chemical conversions of the trifluoromethyl-substituted arenes. For example, a mixed anhydride (*i.e.*, **43**) is expected to be a good source of the aroyl group, leading to dimers (**38** and **39**) and the benzoic acid derivatives (**40** and **41**). We found that benzophenone itself does not react with benzene in CF_3SO_3H solution, so the ketone products are not the direct source of the triarylmethanols (**20–28**). As a mechanistic test, we also reacted difluorodiphenylmethane with benzene in CF_3SO_3H (eqn (11)). Benzophenone and triphenylmethanol were formed in roughly equal amounts. Thus, the triarylmethanol products may arise from the reaction of a benzylic cation (*i.e.*, **44**) with benzene. The intermediate product would be a difluorodiarylmethane, which is further ionized in the superacid and leads to the triarylmethanol (eqn (12)). Benzophenone is completely protonated in superacidic triflic acid (**49**, X = OH), but the reaction requires a more electrophilic species. This suggests that either the fluorine-substituted (**49**, X = F) or the triflate-substituted (**49**, X = OTf) carbocation reacts with benzene, leading to triphenylmethanol (**20**).

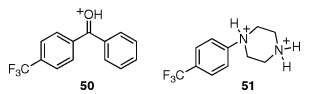


(11)



(12)

As described by Wang and Hu,[10] protonation of the fluorine atoms leads to carbocations and related intermediates. Since the initial ionization of the trifluoromethyl group produces a benzylic carbocation, arenes with electron-deficient ring systems are expected to be less reactive. Compounds such as **29** and **30** did not undergo reaction because they are protonated in the superacid, giving ions **50** and **51**. Evidently, further ionization of the C–F bond is inhibited by the existing cationic centers.



Conclusions

In summary, trifluoromethyl-substituted arenes react in superacids to give Friedel–Crafts-type products with benzene. Both intra and intermolecular reactions can give products in good yields. The products are consistent with the formation of carbocations or their equivalent reactive intermediates. These reactions are evidently facilitated by benzylic-type stabilization of the carbocationic species. Low temperature ^{13}C NMR experiments suggest the formation of mixed acid anhydrides in some reactions of trifluoromethyl-substituted arenes. The results further confirm that carbon–fluorine bonds may be efficiently cleaved in the condensed phase by Brønsted acids.

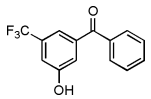
Experimental

General details

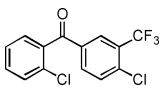
All the reactions were performed with oven-dried glassware and conducted under an Ar atmosphere. Trifluoromethanesulfonic acid (CF_3SO_3H) was distilled from an Ar atmosphere prior to its use. All commercially available compounds and anhydrous solvents were used as received. ^1H and ^{13}C NMR spectra were obtained using a 500 MHz spectrometer and low resolution mass spectra were obtained from a capillary GC (DB-5 column) equipped with a mass selective detector. High-resolution mass spectra were obtained from the analytical services department at the University of Illinois, Champaign-Urbana.

General synthetic method A (products 11–28, 31 and 33). The trifluoromethyl-substituted arene (1 mmol) was dissolved in C_6H_6 (2 mL). If the reaction was performed at 0 °C, then $CHCl_3$ (1 mL) was added as a co-solvent. Trifluoromethanesulfonic acid (2 mL) was then added. The mixture was stirred for at least 4 h, after which it was poured over several grams of ice. The solution was extracted twice with chloroform and the organic extracts washed with water followed by brine (2×). The solution was dried over sodium sulfate and the products isolated by removal of the solvent. In some cases, the major product(s) could be isolated by column chromatography (hexane : ether). However, some of the benzophenone/triarylmethanol product mixtures (**11/20**, **12/21**, **13/22**) were inseparable by column chromatography.

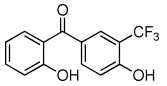
General synthetic method B (products 35, 37, 40 and 41). The trifluoromethyl-substituted arene (1 mmol) was dissolved in $CHCl_3$ (2 mL). Trifluoromethanesulfonic acid (2 mL) was then added. The mixture was then stirred for at least 4 h, after which it was poured over several grams of ice. The solution was extracted twice with chloroform and the organic extracts washed with water followed by brine (2×). The solution was dried over sodium sulfate and the products isolated by removal of the solvent.



3-Hydroxy-5-(trifluoromethyl)benzophenone (18). mp 77–79 °C (C_6H_6). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (m, 2H), 7.65 (m, 1H), 7.55 (m, 4H), 7.27 (s, 1H), 6.89 (bs, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.1, 156.6, 139.5, 136.5, 133.4, 132.3 (q, J_{C-F} = 33 Hz), 130.2, 128.7, 123.3 (q, J_{C-F} = 271 Hz), 119.9, 119.0 (q, J_{C-F} = 4 Hz), 116.7 (q, J_{C-F} = 3 Hz). Low resolution mass spectroscopy (EI): m/z 266 [M$^+$], 189, 161, 105, 77. High resolution mass spectroscopy (EI): calc. $C_{14}H_9O_2F_3$ 266.05547, found 266.05635.



2′,4-Dichloro-3-(trifluoromethyl)benzophenone (38)[13]. mp 138–139 °C (hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (s, 1H), 7.86 (dd, J = 1.5, 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.51–7.48 (m, 2H), 7.43–7.40 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.9, 137.9, 137.2, 135.1, 134.0, 132.0, 132.0, 131.4, 130.4, 129.3, 129.2 (q, J_{C-F} = 32 Hz), 129.1 (q, J_{C-F} = 5 Hz), 127.1, 122.3 (q, J_{C-F} = 271 Hz). Low resolution mass spectroscopy (EI): m/z 320/318 [M$^+$], 209/207, 181/179, 141/139, 113/111. High resolution mass spectroscopy (EI): calc. $C_{14}H_9OF_3Cl_2$ 317.98262, found 317.98381.



2′,4-Dihydroxy-3-(trifluoromethyl)benzophenone (39). mp 77–79 °C (CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.2 (s, 1H), 8.10 (dd, J = 0.4, 2.0 Hz, 1H), 7.76 (d, J = 1.9 Hz, 1H), 7.69–7.66 (m, 1H), 7.59–7.56 (m, 1H), 7.45–7.40 (m, 2H), 7.07 (d, J = 8.5 Hz, 1H), 7.02 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 162.3, 147.5, 136.9, 133.1, 130.6, 127.1 (q, J_{C-F} = 4 Hz), 126.4, 124.3, 123.4 (q, J_{C-F} = 31 Hz), 122.8 (q, J_{C-F} = 271 Hz), 119.8, 117.9, 111.3. Low resolution mass spectroscopy (EI): m/z 282 [M$^+$], 162, 142, 121, 93. High resolution mass spectroscopy (EI): calc. $C_{14}H_9O_3F_3$ 282.05039, found 282.05132.

Acknowledgements

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