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Fluoroanalogs of DDT: Superacidic BF_3-H_2O Catalyzed Facile Synthesis of 1,1,1-Trifluoro-2,2-diarylethanes and 1,1-Difluoro-2,2-diarylethanes

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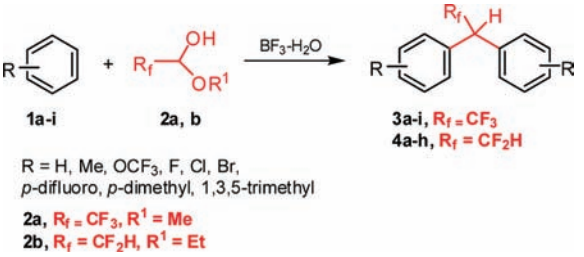
ABSTRACT



The one-pot synthesis of 1,1,1-trifluoro- and 1,1-difluoro-2,2-diarylethanes from arenes and fluorinated hemiacetals in the BF_3-H_2O system is described. The reaction is simple, clean, and convenient, eliminating the use of organic solvents and other expensive acid systems. BF_3-H_2O is economic, is easy to prepare, and offers ample acidity required for this reaction.

Organofluorine compounds have special properties and are used in various fields such as medicine and agrochemicals. In particular, trifluoromethylated and difluoromethylated compounds are found to have a large number of industrial and pharmaceutical applications.[1] Fluorinated drugs containing the trifluoromethyl and difluoromethyl groups are highly important due to their unique physical and biological properties.[2] Some of the well-known drugs containing the "CF_3" group are Prozac (antidepressant), Casodex (anticancer agent), Celecoxib (Celebrex, anti-inflammatory),[2] and Trifluridine (Viroptic, antiherpesvirus antiviral).[3] Roflumilast (anti-inflammatory)[2] and Eflornithine (Ornidyl, α-difluoromethylornithine or DFMO, anticancer)[4] are examples of drugs containing the "CF_2H" group.

The preparation of di- and trifluoromethylated compounds has often been achieved by direct di- and trifluoromethylation techniques using nucleo- or electrophilic fluoromethylating agents. Prakash and co-workers have carried out significant work in the development of novel nucleophilic trifluoromethylation based on $TMS-CF_3$ (the Ruppert–Prakash reagent).[5] The synthesis of fluoroalkylated compounds can also be achieved using various trifluoromethyl containing building blocks. Trifluoroacetaldehyde (CF_3CHO) is a highly useful synthon for this purpose. The strong electron-withdrawing effect of the trifluoromethyl group increases the electrophilicity at the carbonyl carbon and enhances its reactivity. Since fluoral (CF_3CHO) is a gas and its preparation and handling are difficult, its hydrate and hemiacetal derivatives are used as convenient trifluoroacetaldehyde equivalents. They are stable

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(1) (a) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359.

(2) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303.

(3) Wu, Y. C.; Chen, Y. J.; Li, H. J.; Zou, X. M.; Hu, F. Z.; Yang, H. Z. *J. Fluorine Chem.* **2006**, *127*, 409.

(4) Jun, J. Y.; Griffith, J. W.; Bruggeman, R.; Washington, S.; Demers, L. M.; Verderame, M. F.; Manni, A. *Breast Cancer Res. Treat.* **2007**, *105*, 29.

(5) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(6) Begue, J. P.; Bonnet-Delpon, D.; Crousse, B.; Legros, J. *Chem. Soc. Rev.* **2005**, *34*, 562.

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and commercially available at a reasonable cost.[6] Trifluoroacetaldehyde ethyl hemiacetal has been used for the synthesis of a wide variety of trifluoromethylated compounds such as β-hydroxy-β-trifluoromethyl ketones,[7] α-trifluoromethyl amines, α-trifluoromethyl alcohols,[8] β-trifluoromethylated amino acids, amino alcohols, amino esters,[6] heterocycles (β-lactams, piperidines, quinolines),[6,9] and aryl-α-trifluoromethyl amino alcohols.[10] Similarly, the synthesis of a variety of difluoromethylated analogs including nitrocarbinols and sugar analogs[10,11] has been achieved using difluoroacetaldehyde ethyl hemiacetal. Though much work has been done in this field, there are only a few reports on Friedel–Crafts hydroxyalkylation reactions of fluoral or fluoroketones with arenes in the literature and in all cases the reactions stopped at the carbinol stage.[12] To the best of our knowledge, there are only two reports in the literature on hydroxyalkylation reaction of 2,2,2-trifluoroacetophenone with aromatics in the presence of trifluoromethanesulfonic acid (triflic acid) leading to 1,1,1-triaryl-2,2,2-trifluoroethanes.[12d,e]

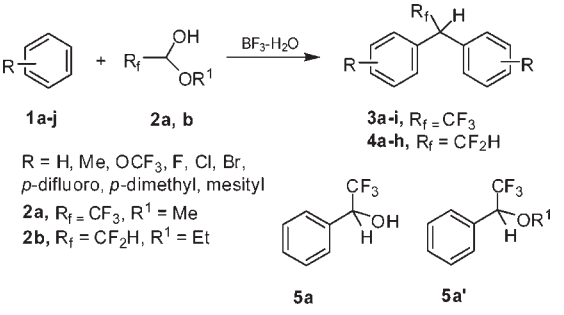
1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT) has been used worldwide as an effective pesticide to control insect-borne diseases such as malaria. DDT has been prepared by the acid catalyzed condensation of chloral with chlorobenzene.[13] Today, the use of DDT is banned in many countries because of its hydrophobic nature and persistence due to its chemical stability, leading to bioaccumulation and biomagnification in food chains. However, DDT is still used in some countries to combat disease-carrying insects due to its efficacy as a potent insecticide.[14]

Trifluoroethyl aromatics have received significant attention in agriculture as insecticides and fungicides.[15] However, there are limited studies on the synthesis of trifluoroethyl aromatics, which include reduction of diaryl trifluoromethyl carbinols (obtained by addition of aryl Grignard reagent to ethyl trifluoroacetate),[16a] replacement of chlorine by fluorine of 2,2,2-trichloroethyl aromatics,[16b] Friedel–Crafts reaction of α-trifluoromethyl benzyl alcohol (prepared by reduction of α-trifluoromethyl acetophenone),[16c] and treatment of arenes in trifluoroacetic acid with sodium borohydride.[16d] All these methods have many disadvantages such as high toxicity of reagents, poor yields, and the involvement of multistep procedures.

During our recent studies on Friedel–Crafts reactions and acid catalyzed synthetic transformations under various superacidic conditions, we found that boron trifluoride monohydrate (BF_3–H_2O) is a very effective acid catalyst for the preparation of sulfides from carbonyl compounds,[17] nitration of aromatics and preparation of alkyl nitrates using metal nitrates,[18] halogenation of deactivated arenes using *N*-halosuccinimide,[19] the Fries rearrangement of phenolic esters,[20] and preparation of di- or triarylmethane derivatives from heteroaromatic and aromatic carboxaldehydes, respectively, and anthracene derivatives from phthalic dicarboxaldehyde under relatively mild conditions.[21]

Herein, we describe the synthesis of 1,1,1-trifluoro-2,2-diarylethanes (**3a**–**i**) and 1,1-difluoro-2,2-diarylethanes (**4a**–**h**) from arenes and fluorinated acetaldehyde hemiacetals in a single step in BF_3–H_2O without the use of any other organic solvents. 1,1,1-Trifluoro-2,2-diarylethane and 1,1-difluoro-2,2-diarylethane derivatives are the fluoroanalogs of DDT.[22] BF_3–H_2O plays a dual role, as an efficient acid catalyst as well as a suitable medium for this reaction.

Scheme 1. Synthesis of 1,1,1-Trifluoro-2,2-diarylethanes (**3a**–**i**), 1,1-Difluoro-2,2-diarylethanes (**4a**–**h**) under BF_3–H_2O Catalyzed Conditions and Mixture of Carbinol **5a** and Ether **5a′** under Less Acidic Conditions



In 1986 Guy et al. reported trifluoroethylation of benzene using various acid catalysts such as $AlCl_3$, $SbCl_5$,

(7) (a) Funabiki, K.; Matsunaga, K.; Nojiri, M.; Hashimoto, W.; Yamamoto, H.; Shibata, K.; Matsui, M. *J. Org. Chem.* **2003**, *68*, 2853. (b) Funabiki, K.; Nagaya, H.; Ishihara, M.; Matsui, M. *Tetrahedron* **2006**, *62*, 5049.

(8) Yuefa, G.; Katsuya, K. *Curr. Org. Chem.* **2004**, *8*, 1659.

(9) (a) Billard, T.; Gille, S.; Ferry, A.; Barthelemy, C.; Christophe, C.; Langlois, B. R. *J. Fluorine Chem.* **2005**, *126*, 189. (b) Yanai, H.; Mimura, H.; Kawada, K.; Taguchi, T. *Tetrahedron* **2007**, *63*, 2153.

(10) Gosselin, F.; Roy, A.; O'Shea, P. D.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2004**, *6*, 641.

(11) Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302.

(12) (a) Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597. (b) Prakash, G. K. S.; Yan, P.; Török, B.; Olah, G. A. *Synlett* **2003**, 527. (c) Abid, M.; Török, B. *Adv. Synth. Catal.* **2005**, *347*, 1797. (d) Kray, W. D.; Rosser, R. W. *J. Org. Chem.* **1977**, *42*, 1186 and references therein. (e) O'Connor, M.; Boblak, K. N.; Spitzer, A. D.; Gucciardo, P. A.; Baumann, A. M.; Peter, J. W.; Chen, C. Y.; Peter, R.; Mitton, A. A.; Klumpp, D. A. *Tetrahedron Lett.* **2010**, *51*, 4984.

(13) Klumpp, D. A.; Garza, M.; Sanchez, G. V.; Lau, S.; Leon, S. *J. Org. Chem.* **2000**, *65*, 8997.

(14) Monguchi, Y.; Kume, A.; Sajiki, H. *Tetrahedron* **2006**, *62*, 8384.

(15) (a) Uneyama, K.; Momota, M.; Hayashida, K.; Toshiyuki, I. *J. Org. Chem.* **1990**, *55*, 5364 and references therein. (b) Ciongrad; B. M.; Iancu, V. S.; Mate, S.; Stark, V. F.; Buzasiu, A.; Condoros, F.; Juhasz, E. Rom. (1984), RO 82-109278.

(16) (a) Kaluszyner, A.; Reuter, S.; Bergmann, E. D. *J. Am. Chem. Soc.* **1955**, *77*, 4164. (b) DePuy, C. H.; Schultz, A. L. *J. Org. Chem.* **1974**, *39*, 878. (c) Jarczewski, A.; Shroeder, G.; Galezowski, W. *Can. J. Chem.* **1985**, *63*, 576. (d) Nutaitis, C. F.; Gribble, G. W. *Synthesis* **1985**, 756.

(17) Olah, G. A.; Wang, Q.; Trivedi, N; Prakash, G. K. S. *Synthesis* **1992**, 465.

(18) (a) Olah, G. A.; Wang, Q.; Li, X. Y.; Bucsi, I. *Synthesis* **1992**, 1085. (b) Olah, G. A.; Wang, Q.; Li, X. Y.; Prakash, G. K. S. *Synthesis* **1993**, 207.

(19) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770.

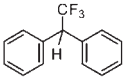
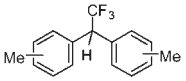
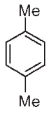
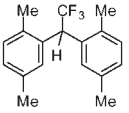
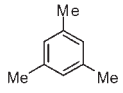
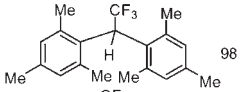
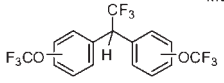
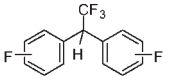
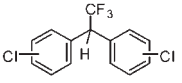
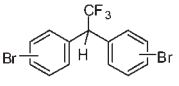
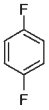
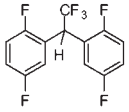
(20) Prakash, G. K. S.; Panja, C.; Mathew, T.; Olah, G. A. *Catal. Lett.* **2007**, *114*, 24.

(21) (a) Prakash, G. K. S.; Paknia, F.; Chacko, S.; Mathew, T.; Olah, G. A. *Heterocycles* **2008**, *76*, 783. (b) Prakash, G. K. S.; Panja, C.; Shakhmin, A.; Shah, E.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2009**, *74*, 8659.

(22) (a) Abernathy, C. O.; Hodgson, E.; Guthrie, F. E. *Biochem. Pharmacol.* **1971**, *20*, 2385. (b) Cohen, S.; Tahori, A. S. *J. Agric. Food Chem.* **1957**, *5*, 519. (c) Bornstein, J.; Blum, M. S.; Pratt, J. J., Jr. *J. Org. Chem.* **1957**, *22*, 1210.

$FeCl_3$, and H_2SO_4.[23] 1,1,1-Trifluoro-2,2-diphenylethane was obtained only when 100% H_2SO_4 was used (70% conversion). Formation of carbinols **5a** and ether **5a′** was observed in other cases. However, in our present method fluoral hemiacetal **2a** and difluoroacetaldehyde ethyl hemiacetal **2b** undergo condensation reactions with aromatics in an excess of BF_3-H_2O to afford 1,1,1-trifluoro-2,2-diarylethanes and 1,1-difluoro-2,2-diarylethanes in excellent yields (Scheme 1). These reactions are examples of the Friedel–Crafts type reactions known as hydroxyalkylation.[24] Our group and others[12b,c,13,21,25,26] have used similar methodologies for the synthesis of various biologically active heteroaryl systems.

Table 1. Reaction of Fluoral Hemiacetal (**2a**) and Arenes (**1a–i**) in Presence of BF_3-H_2O

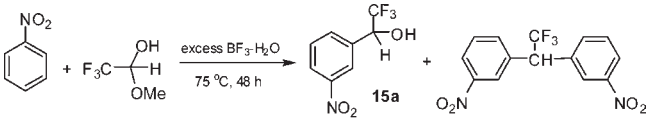
entry	arene (1a-i)	temp (°C)	time (h)	product (3a-i)	yield (%)	isomer ratio (*p-p:others*)[a]
a		rt	24		90	-
b		rt	24		96	63:37
c		rt	4		98	-
d		rt	3		98	-
e		30	6		86	87:13
f		60	1		88	84:16
g		60	1		87	65:35
h		75	12		90	69:31
i		85	24		90	-

[a] The ratio of regioisomers was calculated based on ^{19}F NMR of the mixture before column chromatography.

Activated aromatics are found to undergo hydroxyalkylation reactions readily with fluoral hemiacetal in BF_3-H_2O. Reactions with electron-rich aromatics such as *p*-xylene and mesitylene were carried out at room temperature over a short period of time leading to the expected 1,1,1-trifluoro-2,2-diarylethanes (Table 1, entries c, d). However, in the case of deactivated arenes, the reaction conditions were varied depending on the degree of deactivation. Reactions of fluorobenzene and chlorobenzene with trifluoroacetaldehyde methyl hemiacetal in BF_3-H_2O (50 equiv) at 60 °C resulted in the formation of the products in high yields (87–88%) (Table 1, entries f, g). For bromobenzene, when the temperature was elevated to 75 °C, the corresponding product **3h** was obtained in 90% yield. Condensation of monosubstituted arenes with fluoral hemiacetal led to *para–para′* diaryl compounds as the major products along with other regioisomers (Table 1).

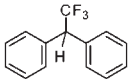
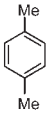
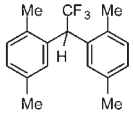
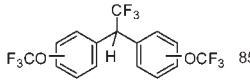
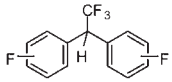
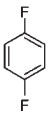
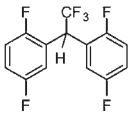
The reaction of fluoral hemiacetal with nitrobenzene did not afford the corresponding trifluorodiarylethane product **3j** even when the amount of BF_3-H_2O and reaction time were increased (75 equiv, 75 °C, 48 h). However, the intermediate carbinol **5j** was obtained in 56% yield (Scheme 2).

Scheme 2. Condensation of Fluoral Hemiacetal with Nitrobenzene in Presence of BF_3-H_2O



As a comparative study, we also conducted the hydroxyalkylaton of aromatics with fluoral hemiacetal **2a** using triflic acid having an acidity greater than BF_3-H_2O. The reaction was faster as expected, and the reaction had to be properly controlled to avoid undesired side reactions (Table 2).

Table 2. Reaction of Fluoral Hemiacetal **2a** and Arenes in Presence of Triflic Acid

entry	arene (1)	temp	time	product (3)	yield (%)	isomer ratio (*p-p:others*)[a]
a		rt	2 h		94	-
c[b]		0 °C	1 min		85	-
d		rt	2 h		85	92:8
e		rt	45 min		95	84:16
h		45 °C	6 h		78	-

[a] The ratio of regioisomers was calculated based on ^{19}F NMR of the mixture before column chromatography. [b] Traces of transalkylated products were also observed in NMR. Reaction was also carried out at −40 °C for 30 min. However, the product was obtained in lower yield (76%).

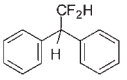
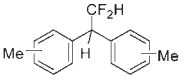
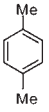
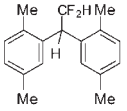
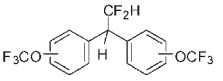
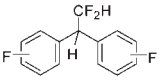
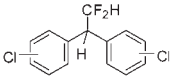
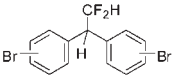
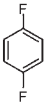
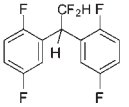
(23) Guy, A.; Lobgeois, A.; Lemair, M. *J. Fluorine Chem.* **1986**, *32*, 361.

(24) (a) Olah, G. A. *Friedel-Crafts and Related Reactions*; Wiley-Interscience: New York, 1963. (b) Olah, G. A.; Rasul, G.; York, C.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1995**, *117*, 11211.

(25) (a) Klumpp, D. A.; Garza, M.; Jones, A.; Mendoza, S. *J. Org. Chem.* **1999**, *64*, 6702. (b) Klumpp, D. A.; Kindelin, P. J.; Li, A. *Tetrahedron Lett.* **2005**, *46*, 2931. (c) Klumpp, D. A.; Lau, S. *J. Org. Chem.* **1999**, *64*, 7309.

(26) Olah, G. A. Klumpp, D. A. *Superelectrophiles and their Chemistry*; Wiley-Interscience: Hoboken, NJ, 2008.

Table 3. Reaction of Difluoroacetaldehyde Ethyl Hemiacetal (**2b**) and Arenes (**1a**–**h**) in Presence of BF_3–H_2O

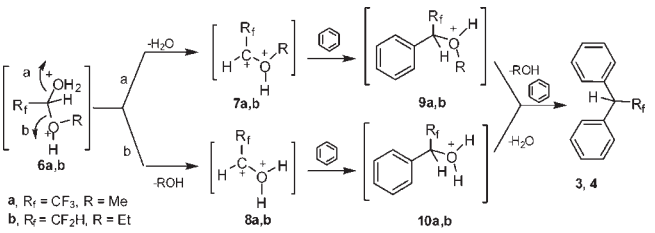
entry	arene (**1a-h**)	temp (°C)	time (h)	product (**4a-h**)	yield (%)	isomer ratio (*p*-*p*:*others*)[a]
a		0	0.5		45	-
b		0	1		96	85:15
c		0	0.5		98	-
d		0	1		86	98.5:1.5
e		0	0.33		88	92:8
f[b]		0-rt	1		87	89:11
g[b]		0-rt	2		90	91:9
h		rt	5		90	-

[a] The ratio of regioisomers was calculated based on ^{19}F NMR of the mixture before column chromatography. [b] Reactions were carried out at 0 °C for 30 min followed by gradual warming to room temperature.

The hydroxyalkylation reaction of aromatics was also carried out with difluoroacetaldehyde ethyl hemiacetal **2b** to afford the desired 1,1-difluoro-2,2-diarylethane. The results are summarized in Table 3. Reaction of **2b** with benzene at 0 °C led to 1,1-difluoro-2,2-diarylethane **4a** in 45% yield in 30 min. Hydroxyalkylation of arenes (particularly activated arenes) with difluoroacetaldehyde ethyl hemiacetal was carried out at low temperatures under controlled conditions. Reactions of trifluoromethoxybenzene and fluorobenzene with **2b** were completed within 60 and 20 min, respectively, at 0 °C (Table 3, entries d, e). Reactions of chlorobenzene and bromobenzene were carried out at 0 °C in 0.5 h followed by gradual warming to room temperature over 0.5 and 1.5 h, respectively. (Table 3, entries f, g). Reactions of deactivated arenes such as *p*-difluorobenzene required more time (Table 3, entry h). Condensation of monosubstituted arenes with **2b** proceeded with high regioselectivity (> 85%) to afford *para*–*para*′ diaryl compounds as the major products.

Similar to other superacid-catalyzed hydroxyalkylation reactions reported earlier,[25,26] the mechanism of hydroxyalkylation of aromatics using fluorinated hemiacetals is believed to involve superelectrophilic activation of the hemiacetal and subsequent reaction of the resulting gitonic 1,3-dicationic species **7a,b**/**8a,b** with the arene to give **9a,b**/**10a,b**. The reaction between benzene and fluoral hemiacetal **2a** was periodically monitored, and formation of carbinol **5a** and ether **5a**′ (Scheme 1) was observed after just 1 h. Formation of carbinol **5a** and ether **5a**′ requires two types of intermediates **7a** and **8a**, respectively. Protonated ether **9a,b** and carbinol **10a,b** in BF_3–H_2O undergo subsequent reaction with arenes to give the corresponding final fluoroalkyldiaryl compounds **3** and **4** (Scheme 3).

Scheme 3. Plausible Mechanism for Reaction of Fluorinated Hemiacetals with Arenes under BF_3–H_2O Catalyzed Conditions



In summary, the direct synthesis of 1,1,1-trifluoro-2,2-diarylethanes and 1,1-difluoro-2,2-diarylethanes has been achieved by BF_3–H_2O-catalyzed Friedel–Crafts hydroxyalkylation of arenes with trifluoroacetaldehyde methyl hemiacetal and difluoroacetaldehyde ethyl hemiacetal, respectively, in high yields and purity. BF_3–H_2O plays a dual role, both as an acid catalyst and as a solvent, eliminating the use of expensive acids and organic solvents. This methodology can be widely applied for the development of fluoroanalogs of DDT, which are potentially biodegradable with greater insecticidal and pesticidal activities.

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Supporting Information Available. General experimental procedure and spectroscopic data of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.