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Trifluoroethyl Phenyl Iodonium Triflate: Modified Preparation and N-trifluoroethylation of Amino Alcohols.

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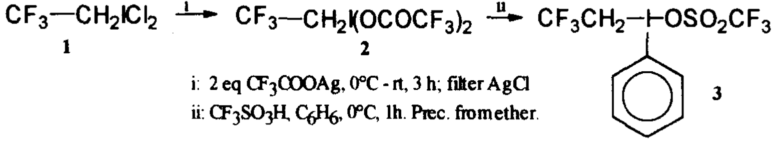
Abstract: The title iodinane **3** (Umemoto's FMITS-1) is prepared in two steps from the readily accessible $CF_3CH_2ICl_2$ (**1**). **1** and 2 eq. of CF_3COOAg react in $CFCl_2CF_2Cl$ (FC 113) to give $CF_3CH_2(OCOCF_3)_2$ (**2**) which is converted into **3** by the known method. With this modification, chlorine and nontoxic FC 113 replace 60-80% H_2O_2 and trifluoroacetic anhydride as the oxidant and the solvent, respectively, in the synthesis of the intermediate **2**. The N-trifluoroethylation of some aminoalcohols by FMITS-1 is also reported.

Fluorinated organic compounds with peculiar and desirable characteristics can be obtained by trifluoroethylation of heteroatom or carbon nucleophiles[1]. When the trifluoroethylating agent is CF_3CH_2X, X = Cl, Br, OTf, the reaction is seldom possible, and then under forcing conditions[1]. The fundamental work by Yagupol'skii,[2] later extended by Umemoto,[1a,b] produced the very stable and effective perfluoroalkylating agents $R_fI(Ph)X$ and $R_fCH_2I(Ph)X$, X being an electronegative ligand. In all reported syntheses of these materials, the first step is the oxidation of a perfluoro or polyfluoro alkyl iodide to the (bis-trifluoroacetoxy)iodonium compound with 60-80% H_2O_2 in $(CF_3CO)_2O$. Hydrogen peroxide of this grade is not commonly available, and the optimized preparations in the literature involve large amounts of the expensive anhydride. (Dichloroiodo)polyfluoroalkanes $R_fCH_2ICl_2$ are easily obtained from the iodides and chlorine, as recently shown.[3a,b] (1-dichloroiodo)-2,2,2-trifluoroethane **1** is the most readily available from commercial trifluoroethyl iodide. Herein we report the two-step conversion of **1** into the title iodinane **3** (Scheme 1), and the trifluoroethylation of aminoalcohols **4 a-d** (Table), which does not require protection of the hydroxy group.

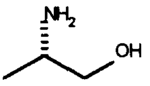
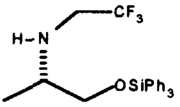
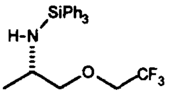
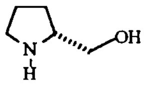
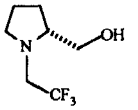
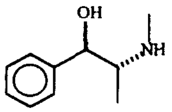
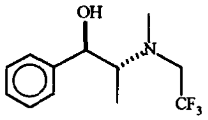
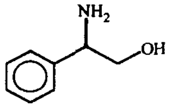
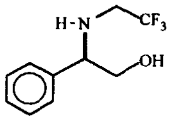


Scheme 1

(2,2,2-Trifluoroethyl)phenyliodonium triflate (**3**): 1-(dichloroiodo)-2,2,2-trifluoroethane (**1**, 4.21 g, 15 mmol) was added into an ice-cold suspension of silver trifluoroacetate[6]

(7.70 g, 35 mmol) in 50 mL FC113. The mixture was stirred under nitrogen and allowed to 22°C during 3 hrs. Silver chloride was filtered off on a glass frit. The resulting clear or pale yellow solution of **2** was placed in a 100 mL flask with thermometer and nitrogen inlet, and cooled in ice-salt to -10°C. Triflic acid (1.10 mL, 12.5 mmol) was added by syringe in ca 10 min, keeping the temperature below 0°C. The solution became a milky suspension. Benzene (1.75 mL, 20 mmol) was added in the same way. After one hour at 0°C, the solvent was rotary evaporated at 22°C, the residual amber syrup was pumped in high vacuum. The resulting solid was dissolved in 3-4 mL of CHCl$_3$, cooled in ice, and 50-60 mL of ice-cold ether were stirred in to form a voluminous white precipitate. Filtering on a glass frit and drying in vacuum gave **3** as a white nonhygroscopic powder, 4.46-4.70 g (68-72% from **1**, 82-86% relative to the limiting reagent triflic acid). Mp 89-90.5 °C (lit^{1b}. 88-89°C). This product was pure by NMR. It was stored refrigerated (+ 5°C) when not in use^{1b}.

Table. N-Trifluoroethyl Amino Alcohols

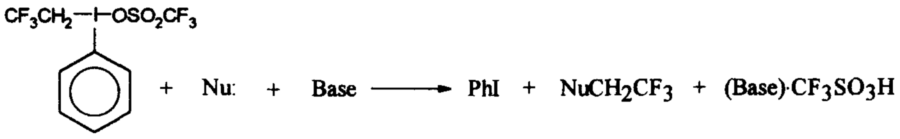
Starting compound	Entry	Product	No.	Yield %^{a}
	4 a		5 a	79^b
			6a	8^{b,c}
	4 b		5 b	88
	4 c		5 c	76
	4 d		5 d	85

(a) Isolated yields. (b) Note 4 (c) Calcd by NMR.

The reactions (Scheme 2) between FMITS-1 (**3**) and the aminoalcohols **4 a-d** were carried out under the conditions given for amines in Ref. 1a. For example, into a solution of phenylglycinol **4d** (274 mg, 2 mmol) and 2,4,6-collidine (245 mg, 2.02 mmol) in dry CH$_2$Cl$_2$ (4 mL) blanketed with nitrogen were added portionwise 880 mg (2.02 mmol) of **3**, then the homogeneous solution was stirred at 22°C under nitrogen for two hours. Flash chromatography (hexanes/ethyl acetate = 4/1) gave 374 mg (85%) of **5d** as a white crystalline powder, mp 36.5-38 °C. NMR: see Note 5.

The fluoroalkylation reaction proceeds most probably[7] by displacement of the leaving group ligand, in this case triflate, by the nucleophile. The labile intermediate thus formed decays rapidly to iodobenzene, triflic acid, and the desired product. The reaction is driven to completion by trapping the liberated acid with a base. The trifluoroethylation of alcohols is reported [1a] to proceed rapidly in CH_2Cl_2 in the presence of LiH, not collidine. However in our case, the O-trifluoroethylation is in principle favoured by intramolecular quenching of triflic acid by the amino group.

In qualitative agreement with the above, the combination of primary alcohol and monoalkylamine in alaninol **4a** has produced a measurable degree of reaction at oxygen, ca 1:10 for **6a** vs.**5a**.



Scheme 2

In summary, we have reported that trifluoroethyl(phenyl)iodonium triflate can be produced from commonly available reagents. We have also investigated its reaction with aminoalcohols. The experimental results indicate that the O-trifluoroethylated isomers **6** are formed in minor amounts, which become negligible with the less reactive secondary alcohols.

Acknowledgement: Thanks are due to Ms. D. DalPioLuogo for the NMR spectra and to Mr. W.Panzeri for mass spectra.

References and Notes

1. (a) Umemoto, T.; Gotoh, Y. *J. Fluorine Chem.* **1986**, *31*, 231-236 (b) Umemoto, T.; Gotoh,Y. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3307-3313; 3823-3825. (c) Fuchigami, T.; Ichikawa, S. *J. Org. Chem.* **1994**, *59*, 607-615. These papers discuss trifluoroethylation reactions with the relevant literature references. Ref. 1c also gives examples of the reduction of trifluoroacetamides to trifluoroethylamines with borane-dimethylsulfide.
2. Yagupol'skii, L.M.; Maletina, I.I.; Kondratenko, N.V.; Orda, V.V. *Synthesis*, **1978**, 835 with refs. to their earlier papers.
3. a) Bravo, P.F.; Montanari, V.; Resnati, G.; DesMarteau, D.D. submitted *J. Org. Chem.* b) Lucas, H. J.; Kennedy, E. R. *Org. Synth.* **1942**, *22*, 69-70; Collective Vol. 3, 482 (1955). This preparation of (dichloroiodo)benzene is followed for $CF_3CH_2ICl_2$ (**1**): the preferred solvent is CCl_4; passing chlorine through drying traps is inessential in our experience. **1** (yellow crystals, mp 108-111 °C when powdered) does not require protection from light or moisture during handling, but should be refrigerated (+ 5 °C) for storage. c) Montanari, V.; Quici, S.; Resnati, G. *Tetrahedron Lett.* **1994**, *35*, 1941-1944 (preparation of polyfluoroalkyl iodides).
4. Since **5b** was found to be quite volatile, **5a** as the free alcohol was anticipated to be too volatile for proper isolation. After the first step (cfr. **5d**, text) one more equivalent of collidine, one of Ph_3SiCl

and a cat. amt of DMAP were added, the mixture was stirred 1 hr, concentrated, and the salts precipitated with ether. Filtration and flash chromatography (hex./acetate = 95/5) gave pure **5a**. The yield of **6a** is calcd from NMR including cross cuts. The calcd yield of **5a** is 85%.

5. NMR shifts in $CDCl_3$ (250 MHz) are relative to TMS and $CFCl_3$. The signals not indicated otherwise are multiplets. The MS spectra of the triphenylsilyl ethers (cfr. Note 4) are reported for **5a-c**. **5a**: ^1H NMR 7.3-7.6 (15 H); 3.6-3.8 (2H); 3.1 (q, 2H, J=10 Hz); 2.9 (1H); 1.8-2-0 (br, 1H); 1.0 (d, 3h, J=5 Hz). ^{19}F NMR: -73.1(t, J=10Hz). MS (EI): 416(M); 259(Ph_3Si); 338; 126($CF_3CH_2NC_2H_5$).
   5b: ^1H NMR 3.4 and 3.6 (2H); 3.2-3.4 and 3.0-3.1 (2H); 2.8 (1H, unres.); 2.5 (q, 1H, J=7 Hz); 2.1-2.4 (br, 1H); 1.7-1.9 (5 H). ^{19}F NMR: -72.1(t, J=9Hz). MS (EI): 181(M-Ph_3Si); 152($CF_3CH_2NC_4H_7$); 83.
   5c: ^1H NMR 7.2-7.4 (5H); 4.9 (d, J=7Hz); 3.0-3.25 (2H); 2.9 (1H); 2.5-2.7 (br, 1H); 2.5 (s, 3H); 1.0 (d, 3H, J=4 Hz). ^{19}F NMR: -71.5(t, J=10 Hz). MS(EI): 506(M); 259; 140($CF_3CH_2N(Me)C_2H_4$).
   5d: ^1H NMR7.3-7.4 (5H); 3.5-4.0 (2H + 1H); 3.0-3.2 (2H); 1.8-2.5 (br, 2H), split in DMSO: 2.8 (m, 1H) and 5.0 (t, 1H, J=5Hz). ^{19}F NMR: -72.9 (t, J=10Hz): MS(EI): 218(M); 186($PhCH_2NCH_2CF_3$); 109($CH_2NCH_2CF_3$).
6. (a) Cady, G.H.; Hara, R. *J. Am. Chem. Soc.* **1954**, *76*, 4285-4287. (b) Poyer, L.; Fielder, M.; Harrison, H.; Bryant, B.E. *Inorg. Synth.* **1957**, *5*, 19; through *Gmelins Handbuch d. Anorg. Chemie*, Silber B3 (1973) p. 274. A new commercial sample of silver trifluoroacetate gave poor results. Possibly it was coated with some foreign matter, e.g. paraffin, to the benefit of its appearance but to the detriment of our reaction. A good material was obtained (a) from commercial Ag_2CO_3 and CF_3CO_2H. Pure, pale yellow silver carbonate can be prepared from silver nitrate and sodium carbonate in water (b).
7. Intermolecular substitution at CH_2 is unlikely[1a,b,c]. See also Kubota, T.; Miyashita, S.; Kitazume, T. Ishikawa, N. *J. Org. Chem.* **1980**, *45*, 5052-5057. c) Oae has proposed that this reaction may pertain to his general scheme of ligand coupling in hypervalent species: Oae, S.; Uchida, Y. *Acc. Chem. Res.* **1991**, *24*, 202-208, page 207.

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