JOC*Note*

New and Efficient Syntheses of α-Iodo-α,α-Difluoro- and *β*-Iodo-α,α,*β*,*β*-Tetrafluorocarboxylic Acid Derivatives as Useful Building Blocks for Making Functional Fluoro Compounds†

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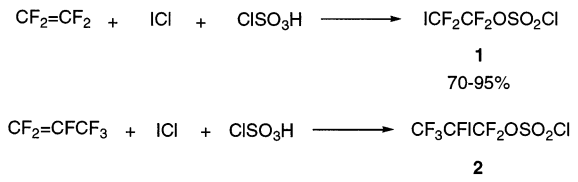
Abstract: Perfluoroolefins reacted with I−Cl and $ClSO_3H$ under mild conditions to give $R_FCFICF_2OSO_2Cl$, which could be readily converted into various α-iodo-perfluorocarboxylic acid derivatives or telomerized with tetrafluoroethylene to $I(CF_2CF_2)_nOSO_2Cl$. Ring-opening reaction of perfluoroalkoxypentafluorocyclopropane with iodine at 240 °C produced ICF_2CF_2COF, which was quenched by alcohol, water, or NH_3 to give *β*-iodo-α,α,*β*,*β*-tetrafluorocarboxylic acid derivatives. These functional fluorinated iodides can be used as building blocks for making selectively fluorinated compounds.

Partially fluorinated functional compounds have gained attention since it was found that the introduction of fluorine into organic molecules can lead to significant changes in biological activities.[1] Fluorinated alkyl iodides are one of the most important starting materials for the introduction of F-alkyl groups into organic molecules.[2] The introduction of the difluoromethylene functionality into organic compounds has been a very active field.[3] Difluoromethylene-containing molecules have been found to inhibit various enzymes, and some can be partially metabolized into more active substances.[4] It has been argued that the difluoromethylene group is regarded as an isopolar−isosteric replacement for oxygen.[5] α-Halo-α,α-difluoroacetates have been most widely used as a synthon for making α,α-difluoromethylene-containing compounds.[3] The Reformatsky reaction of α-halo-α,α-difluoroacetate[6] and the Lewis-acid-catalyzed reaction of difluoroketene silyl acetates[7] with carbonyl substrates have been applied to synthesize compounds bearing the carboalkoxydifluoromethyl group. The coupling reaction of selected organic iodides with (carbomethoxydifluoro)-methylcopper, prepared from methyl iododifluoroacetate and copper, produces α,α-difluoroesters.[8] The atom transfer reactions of methyl iododifluoroacetate with alkenes to make α,α-difluoroesters have been reported by Kiseleva,[9] Burton,[10] Taguchi, and others.[11] However, iododifluoroacetate and its derivatives are difficult and expensive to make. α,α,*β*,*β*-Tetrafluoro functional compounds have been found to be almost inaccessible previously, and their chemistry and properties are virtually unknown. In this note, we report facile and cost-effective preparations of various types of α-iodo-α,α-difluoro- and α,α,*β*,*β*-tetrafluorocarboxylic acid derivatives that are expected to be useful building blocks for making selectively fluorinated compounds.

α-Iodo-α,α-difluoroacetates were previously made from costly bromodifluoroacetates through iodination of difluoro Reformatsky agents[10] or from hydrolysis of highly toxic ICF_2CF_2I with oleum.[12] We used tetrafluoroethylene (TFE) as a starting material and directly reacted it with $ClSO_3H$ and I−Cl under mild conditions to give $ICF_2CF_2OSO_2Cl$ in high yields. Although a similar reaction was reported previously, it required use of the expensive FSO_3H and only moderate yields were obtained.[13] This reaction could be extended to other fluoroolefins such as hexafluoropropylene (HFP), and the corresponding sulfate **2** was formed in high yield.



In these reactions, temperature control was found to be critical to obtain high yields. The initial stage of the

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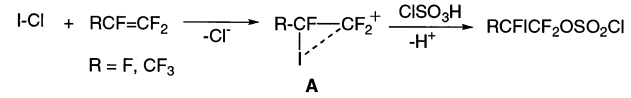
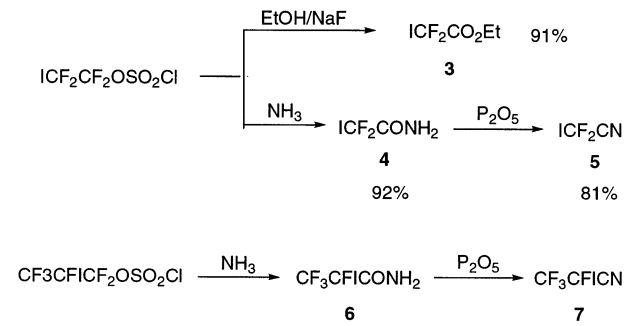
reaction is exothermic, and temperature must be controlled by the addition rate of TFE (*caution: TFE is explosive and extremely hazardous; the reaction needs to be done in a barricade*). We found the optimal temperature to be around 0−10 °C, and the yields of product isolated were between 70 and 95%. As a typical example, into a 1 L pressure reactor was charged a mixture of iodine monochloride (390 g, 2.4 mol) and chlorosulfonic acid (490 g, 4.206 mol). The reactor was cooled and kept at 0−10 °C while 300 g of tetrafluoroethylene (3.0 mol) were added. After the addition of TFE was complete, the reaction mixture was held at 0−10 °C for 6 h, at 25 °C for 2 h, and at 50 °C for 2 h. The reaction mixture was then slowly poured into a large amount of ice water with stirring. The lower layer was separated, washed with dilute aqueous $NaHSO_3$ and water, and dried over $MgSO_4$. Distillation afforded 610 g (74% yield) of **1** as a clear, colorless liquid.

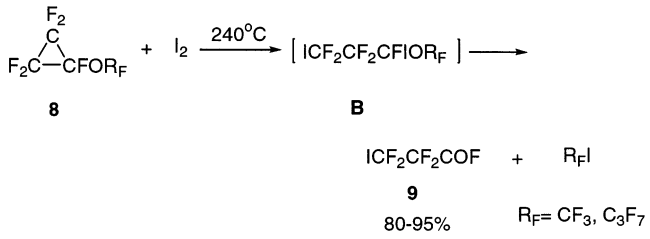
Although the exact mechanism for this useful conversion is still unclear, we propose that an iodinium of I−Cl first electrophilically adds to the double bond of TFE to form intermediate **A**, which is trapped by chlorosulfonic acid. The regiochemistry of the addition also supports this mechanism. When I−Cl and $ClSO_3H$ react with HFP, only isomer **2** is obtained; the iodinium adds favorably to the central carbon of HFP due to electronic effects. Fluorine atoms are well-known to stabilize the carbon cation, whereas CF_3 groups destabilize the adjacent carbocation.[14]



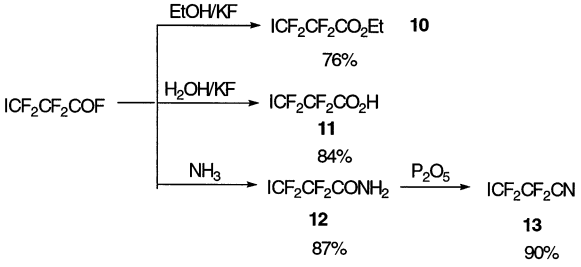
1 and **2** are versatile compounds and can be readily converted into other α-iodo-difluoro functional compounds. **1** can be quenched with alcohols such as ethanol in the presence of NaF to give α-iodo-α,α-difluoroacetate **3** in 90% yield. When reacted with aqueous ammonium hydroxide in ether, the corresponding α-iododifluoroacetamide **4** was formed in high yield. Similarly, **2** could be readily converted into the corresponding amide **6**. When the amides, **4** and **6**, were treated with P_2O_5, the corresponding α-iodofluoronitriles, **5** and **7**, were obtained, respectively.



β-Iodo-α,α,*β*,*β*-tetrafluorocarboxylic acid derivatives were obtained by ring-opening reaction of fluorinated cyclopropanes with iodine.[15] When perfluoroalkoxylcyclopropane was treated with iodine neat at 240 °C, the ring-opening product **B** decomposed to iodotetrafluoropropionyl fluoride **8** in quantitative yield along with formation of the perfluoroalkyl iodides.[15b]



The ring-opening reaction can be quenched without purification of the corrosive ICF_2CF_2COF since the byproduct R_FI does not react with the quenching reagents. The reaction mixture was added to ethanol to form the ester **10** in 76% yield from **8**. KF is usually used to trap the HF formed. Hydrolysis of **9** produced the acid **11** in high yields. When NH_3 gas was bubbled into the reaction mixture, the corresponding amide **12** was obtained. The use of ether or other inert solvents is recommended to control the rate of the highly exothermic reaction. After the amide **12** was ground into a fine powder and mixed with finely powdered P_2O_5, the solid mixture was heated directly to 180−200 °C to give a clear liquid ICF_2CF_2CN in 90% yield.[16]



Longer chain iodofluorocarboxylic acid derivatives $I(CF_2)_{2n}CO_2R$ ($n > 1$) can be obtained by telomerization of TFE and $ICF_2CF_2OSO_2X$ (X = Cl, F), prepared by reaction of TFE, I−Cl, and XSO_3H (X = Cl, F). The telomerizations are usually carried out in sealed stainless steel tubes. When a 1−1.25 molar ratio of $ICF_2CF_2OSO_2F$ and TFE was heated at 250 °C for 4 h, oligomers $I(CF_2CF_2)_nOSO_2F$ were formed in 60% yields and 38% of $ICF_2CF_2OSO_2F$ was recovered. The major oligomers were $I(CF_2CF_2)_2OSO_2F$ and $I(CF_2CF_2)_3OSO_2F$ along with higher homologues. These oligomers can be readily converted into longer chain $I(CF_2)_{2n}CO_2R$ ($n > 1$) by treatment of $I(CF_2CF_2)_nOSO_2F$ with alcohols and NaF or KF.

In summary, we have developed new and cost-effective methods for the preparation of various iodofluorocar-

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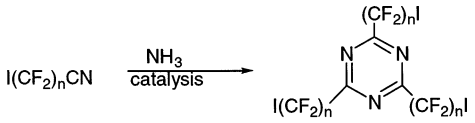
boxylic acid derivatives, which are versatile reagents and can participate in numerous reactions. These compounds are useful building blocks for making other interesting compounds such as bioactive molecules or specialty materials. For example, we have demonstrated that $I(CF_2)_nCN$ may be used to make iododifluorinated triazines **14** by catalysis with NH_3 gas at 40−130 °C. The triazine **14**, containing an extremely thermally stable triazine core and multiple reactive sites (C−I bond), is useful in building networks for highly thermally stable specialty materials. Other applications of the iodofluorocarboxylic acid derivatives will be reported in the future.



14

14a: n = 1: 33%
14b: n = 2: 51%

Experimental Section

Compound 8 was prepared according to the literature.[15b]

Preparation of 2-iodo-1,1,2,2-tetrafluoroethyl chlorosulfate (1). Into a 1 L pressure reactor was charged a mixture of iodine monochloride (390 g, 2.4 mol) and chlorosulfonic acid (490 g, 4.206 mol). The reactor was cooled and kept at 0−10 °C until 300 g of tetrafluoroethylene (3.0 mol) was added. After the addition of TFE was complete, the reaction mixture was held at 0−10 °C for 6 h, at 25 °C for 2 h, and at 50 °C for 2 h. The reaction mixture was then slowly poured into a large amount of ice with stirring and worked up as described above, affording 610 g of the desired product (74%), bp 62−64 °C/50 mmHg. ^{19}F NMR ($CDCl_3$): δ −85.6 (t, J = 4.5 Hz, 2F), −65.3 (t, J = 4.5 Hz, 2F). Anal. Calcd for $C_2F_4ICISO_3$: C: 7.02, F: 22.19. Found: C: 7.19, F: 22.73.

Preparation of Ethyl Iododifluoroacetate (3). A 500 mL flask was charged with sodium fluoride (18.9 g, 0.45 mol) and ethanol (200 mL) and cooled in an ice−water bath. 2-Iodo-1,1,2,2-tetrafluoro-ethyl chlorosulfate (103 g, 0.3 mol) was added slowly. The reaction was exothermic, and the reaction temperature was controlled at 20−30 °C. After addition, the reaction mixture was stirred at room temperature for 10 h and then poured into cold water. Ether was added to extract the product. The organic layer was washed with saturated NaCl solution and dried over $MgSO_4$. Evaporation of the solvent in vacuo followed by distillation gave 68.1 g (91%) of ethyl iododifluoroacetate, bp 57−58 °C/30 mmHg. ^{1}H NMR ($CDCl_3$): δ 1.35 (t, J = 7.0 Hz, 3H), 4.37 (q, J = 7.0 Hz, 2H).^{19}F NMR ($CDCl_3$): δ −57.9 (s, 2F).

Preparation of Iododifluoroacetamide (4). Into the stirred solution of ammonium hydroxide (150 mL, 28−30% in aqueous) and ether (150 mL) was added dropwise $ICF_2CF_2OSO_2Cl$ (102.8 g, 0.3 mol) with external cooling. The temperature was maintained at 10−20 °C during the addition. After that, the mixture was warmed to room temperature and stirred for 30 min. The ethereal layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent followed by recrystallization from hexane/ether gave 61.5 g, (92%) of ICF_2CONH_2 as a white solid, mp. 96−98 °C. ^{1}H NMR (300 MHz, acetone-d_6): δ 7.35 (br, 1H), 7.81 (br, 1H). ^{19}F NMR (acetone-d_6): δ −57.5.

Preparation of Iododifluoroacetonitrile (5). Iododifluoroacetamide (155 g, 0.7 mol) was well mixed with P_2O_5 (100 g, 0.704 mol) and heated at 150 °C in vacuo (about 150 mmHg). The volatile was collected in a cold trap (dry ice−acetone bath). The heating oil bath temperature was increased slowly to 200 °C, and the reaction was stopped until no more product was distilled off. Redistillation gave pure ICF_2CN (115 g, 81% yield), bp 52−54 °C. ^{19}F NMR ($CDCl_3$): δ −46.5. MS: calcd for [M^+], 202.9116; found, 202.9116.

Preparation of 2-Iodo-hexafluoropropyl Fluorosulfate (2). Into a 1.3 L stainless steel tube was charged a mixture of iodine monochloride (130 g, 0.80 mol) and fluorosulfonic acid (88 g, 0.88 mol). The tube was sealed and cooled, and then hexafluoropropylene (144 g, 0.96 mol) was transferred into the tube. The reaction mixture was kept at 25 °C for 2 h, 50 °C for 2 h, and 80 °C for 4 h. The product unloaded from the shaker tube was poured into ice−water, and the bottom organic layer separated was washed with water and distilled to afford the title product (120 g, 40% yield) as a clear liquid, bp 47 °C/50 mm. ^{19}F NMR ($CDCl_3$): δ −74.5 (m, 3F), −77.0 (m, AB-pattern, 2F), −148.2 (m, 1F), +49.7 (m, 1F).

Preparation of Ethyl 2-Iodo-tetrafluoropropionate. The starting material (112.8 g, 0.30 mol) was added dropwise into a mixture solution of potassium fluoride (17.5 g, 0.31 mol) and absolute ethanol (110 mL). The pot temperature was controlled at 20−25 °C with external cold water cooling during the addition process. After the addition was completed, the reaction mixture was heated at 70 °C for 4 h. The mixture was then dumped into ice−water. The bottom organic layer was separated, and the top layer was extracted with ether. The ether phase was combined with the bottom layer material, washed with brine, and dried over magnesium sulfate. The ether was removed in vacuo, and the residue was distilled to afford the title product (50 g, 55.6% yield) as a clear, light-pink-colored liquid, bp 50−54 °C at 25 mmHg. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.40 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H). ^{19}F NMR (188.235 MHz, $CDCl_3$): δ −76.2 (d, J = 12.4 Hz, 3F); −140.5 (q, J = 12.8 Hz, 1F). IR (KBr): 1761 cm^{-1}. Mass [M] for $C_5H_5F_4IO_2$: calcd, 299.9270; found, 299.9285. Anal. Calcd for $C_5H_5F_4IO_2$: C, 20.02; H, 1.68; F, 25.33. Found: C, 20.24; H, 1.75; F, 24.68.

Preparation of 2-Iodo-tetrafluoropropionamide (6). Into a glass flask was placed a mixture of aqueous ammonium hydroxide (28 wt %, 40.5 mL, 0.6 mol) and methylene chloride (80 mL), and the mixture was cooled at 10−15 °C. 2-Iodohexafluoropropyl fluorosulfate (37.6 g, 0.1 mol) was added slowly with vigorous stirring, while the reaction temperature was controlled at <15 °C. After the addition was completed, the mixture was warmed to ambient temperature, and the bottom organic layer was separated, washed with aqueous sodium bisulfite solution, and dried over $MgSO_4$. The solvent was removed in vacuo to give the title product as a white solid (18.5 g, 68.3% yield), mp 75−77 °C. ^{1}H NMR ($CDCl_3$): δ 6.98, 6.53 (2 broad singlets). ^{19}F NMR ($CDCl_3$): δ −76.3 (2 singlets, 3F), −138.5 (m, 1F). IR: 1690 cm^{-1} (C═O). Anal. Calcd for $C_3H_2F_4INO$: C, 13.30; H, 0.74; F, 28.05; N, 5.17. Found: C, 13.68; H, 0.83; F, 28.43; N, 5.21. Mass: calcd for [M^+], 270.9117; found, 270.9093.

Preparation of 2-Iodo-tetrafluoropropionitrile (7). 2-Iodotetrafluoropropionamide prepared from experiment 7 (16.3 g, 0.06 mol) was thoroughly mixed with P_2O_5 (16.3 g, 0.115 mol) in a flask under a nitrogen atmosphere. The mixture was heated slowly to 95−100 °C, the volatile product started to form and was collected in a cold trap (dry ice−acetone bath). The title product was obtained as a slightly pink liquid after purified by distillation, yield 12.5 g (82.5%), bp 68−70 °C. ^{19}F NMR (188.24 MHz, $CDCl_3$): δ −78.7 (2 singlets, 3F), −137.9 (q, J = 16 Hz, 1F). IR: 2288 cm^{-1}. Mass: calcd for [M^+], 252.9382; found, 252.9012.

Preparation of I-$(CF_2CF_2)_n$-OSO_2F Oligomer. 2-Iodo-1,1,2,2-tetrafluoroethyl fluorosulfate (65.2 g, 0.2 mol) was mixed with TFE (25 g, 0.25 mol) in a sealed stainless tube. The mixture was heated at 250 °C for 4 h. The product unloaded was subjected to fractional distillation. About 25 g (38.3%) of the starting was recovered. Other oligomer products (ca. 50 g) obtained were I-$(CF_2CF_2)_2$-OSO_2F (bp 42 °C/25 mm), I-$(CF_2CF_2)_3$-OSO_2F (bp 54 °C/5 mm), and higher boiling I-$(CF_2CF_2)_n$-OSO_2F (n > 3). **I-$(CF_2CF_2)_2$-OSO_2F.** ^{19}F NMR (188.24 MHz, $CDCl_3$): δ −60.3 (t, J = 13.8 Hz, 2F), −83.7 (d, J = 7.2 Hz, 2F), −113.7 (s, 2F), −124.1 (t, J = 12.4 Hz, 2F), +50 9 (m, br, 1F). Mass: calcd for [M^+], 425.8471; found, 425.8381. I-$(CF_2CF_2)_3$-OSO_2F: ^{19}F

NMR (188.24 MHz, $CDCl_3$): δ −59.7 (m, 2F), −83.5 (m, 2F), −113.5 (m, 2F), −121.4 (m, 2F), −122.3 (m, 2F), −125.0 (m, 2F), +50 6 (t, J = 8.2 Hz, 1F). Mass: calcd for [M^+], 525.8407; found, 525.8345.

Preparation of Ethyl 2-Iodotetrafluoropropanoate (10). A 300 mL shaker tube was charged with 50.8 g of iodine and 50 g of trifluoromethoxylpentafluorocyclopropane and heated at 150 °C for 4 h and 240 °C for 8 h. After the tube was cooled to room temperature, 57.6 g of crude products was obtained, which was treated with 75 mL of EtOH and 11.g of KF at 10 °C for 4 h. The reaction mixture was poured into water. The lower layer was separated, washed with Na_2SO_3 solution, and dried over molecular sieves to give 51.2 g of crude ester. Distillation gave 45.3 g of pure product, bp 72−73 °C/30 mmHg. ^{1}H NMR: δ 4.43 (q, J = 7.0 Hz, 2H), 1.39 (t, J = 7.2 Hz, 3H). ^{19}F NMR: δ −60.6 (t, J = 7.0 Hz, 2F), −111.9 (t, J = 7.0 Hz, 2F). IR (neat): 2995 (w), 1778 (s), 1374 (m), 1709 (s), 1185 (s), 1141 (s), 1076 (s). Anal. Calcd for $C_5H_5F_4IO_2$: C, 20.02; H, 1.68; F, 25.33; I, 42.30. Found: C, 19.83; H, 1.52; F, 27.74; I, 43.46.

Preparation of $ICF_2CF_2CO_2H$ (11). To a stirred solution of 11.6 g of KF and 40 mL of H_2O was added 67.3 g of ICF_2CF_2-COF at 5 °C. After the addition was complete, the mixture was stirred for 2 h, then neutralized with HCl, and extracted with ether. The ether layer was dried over $MgSO_4$. After removal of the ether, residue was distilled to give 52.0 g (84%) of ICF_2CF_2-CO_2H as an ether complex, bp 80−81 °C/15 mmHg. ^{1}HNMR: δ 10.85 (s). ^{19}F NMR: δ −61.0 (t, J = 7.7 Hz, 2F), −112.1 (t, J = 7.7 Hz, 2F). IR: 3200 (br), 1769 (s), 1187 (s), 1151 (s), 1077 (s).

Preparation of 2-Iodotetrafluoropropanoamide (12). A 1 L autoclave was charged with 353 g of iodine and 285 g of trifluoromethoxylpentafluorocyclopropane and heated at 150 °C for 3 h and 240 °C for 12 h. After the autoclave was cooled to room temperature, the reaction mixture was diluted with 1 L of ether and cooled to −78 °C. NH_3 gas was added until the solution was basic. The reaction mixture was warmed to room temperature over 1.5 h. The mixture was poured into 1 L of ether, washed with water, and dried over $MgSO_4$. After removal of the ether, 203.5 g of product was obtained. An analytic sample was obtained by recrystallization from hexane and ether, mp 136−137 °C. ^{19}F NMR: δ −62.3 (t, J = 5 Hz, 2F), −112.1 (t, J = 5 Hz, 2F). ^{1}H NMR (acetone-d_6): δ 7.99 (br, 1H), 7.69 (br, 1H). IR (neat): 3375, 3267 (m), 3193 (m), 1708 (s), 1416 (s), 1180 (s), 1080 (s), 647 (s). Anal. Calcd for $C_3H_2F_4NOI$: C, 13.30; H, 0.74; F, 28.05; N, 5.17; I, 46.84. Found: C, 13.35; H, 0.78; F, 27.10; N, 4.81; I, 46.87.

Preparation of Iodotetrafluoropropanonitrile (13). A mixture of 150 g of fine powder of $ICF_2CF_2CONH_2$ and 235 g of P_2O_5 was heated at 130 to 150 °C, during which volatiles were distilled out. Final volatiles were collected in a −78 °C trap at 200 mmHg. A total 125.3 g of crude product was obtained, 95% GC pure. Redistillation gave pure product, bp 60−61 °C. ^{19}F NMR: δ −63.3 (t, J = 10.4 Hz, 2F), −100.5 (t, J = 10.4 Hz, 2F). IR (neat): 2264 (w), 1235 (s), 1196 (s), 1172 (s), 1146 (s), 1089 (s), 1065 (s), 893 (s). (See ref 16.)

Preparation of 2,4,6-Iododifluoromethyl-1,3,5-triazine (14a). A mixture of ICF_2CN (8.1 g, 40 mmol) and ammonia (ca. 0.1 g) was stirred in a sealed tube at 40 °C for 40 h and then purified on a silica gel column using hexane and ethyl acetate as an eluant to give the triazine (2.7 g, 33% yield), bp 100 °C/0.5 mmHg. ^{19}F NMR (acetone-d_6): δ −57.9. IR (KBr): 1540 cm^{-1}. Mass: calcd for [M^+], 608.7131; found, 608.7123.

Preparation of 2,4,6-Iodotetrafluoroethyl-1,3,5-triazine (14b). A mixture of ICF_2CF_2CN (13.3 g, 52.6 mmol) and ammonia (0.15 g) was stirred in a sealed tube at 130 °C for 12 h and then purified on silica gel column using hexane and ethyl acetate (9:1) as an eluant to give the triazine (6.8 g, 51% yield). ^{19}F NMR (acetone-d_6): δ −62.8 (t, J = 6 Hz, 6F), −109.3 (t, J = 6 Hz, 6F). IR (KBr): 1540 cm^{-1}. Anal. Calcd for $C_9F_{12}N_3I_3$: C, 14.25; F, 30.04; N, 5.54. Found: C, 14.33; F, 29.94; N, 5.33.

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