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Synthesis of new α,α,β,β-tetrafluoroesters

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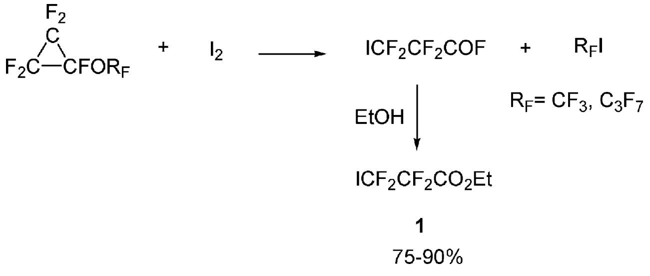
Abstract

Substituted phenyl iodides or diiodides reacted with ethyl iodotetrafluoroproponylate $ICF_2CF_2CO_2Et$, **1** in the presence of copper powder to give the coupled products **2** or **3** in good yields. Addition of **1** to ethylene and allyl acetate proceeded smoothly under thermal and radical conditions to give the corresponding adducts, which underwent elimination reaction to give β-vinyl and β-allyl α,α,β,β-tetrafluoroesters, $CH_2{=}CHCF_2CF_2CO_2Et$, **4** and $CH_2{=}CHCH_2CF_2CF_2CO_2Et$, **5**, respectively. **1** also readily reacted with 1,5-hexadiene and 1-hexene with copper or palladium complex, followed by reduction to remove iodine to produce ω-alkenyl-α,α,β,β-tetrafluoroester $CH_2{=}CH(CH_2)_4CF_2CF_2CO_2Et$ **6** and α,α,β,β-tetrafluoroester $C_4H_9CH_2CHICF_2CF_2CO_2Et$.

Keywords: Iodotetrafluoroproponylate; α,α,β,β-Tetrafluoroesters; Coupling reaction

Partially fluorinated compounds have been widely utilized in the areas of agrochemicals and pharmaceuticals or as probes for investigating biochemical processes, since the introduction of fluorine into organic molecules leads to significant changes in biological activities [1]. Recently, the introduction of the difluoromethylene functionality into organic compounds has been growing attentions since it was discovered that selected difluoromethylene containing molecules have inhibited one or more enzymes or been partially metabolized into a more active substance [2]. It has been argued that the difluoromethylene group could be regarded as an isopolar-isosteric replacement for oxygen [3]. Among many building blocks, α-halo-α,α-difluoroacetates have been most widely used as synthones for making α,α-difluoromethylene containing compounds [4]. However, α,α,β,β-tetrafluoroesters are difficult to prepare and their properties are virtually unknown since the suitable precursors for the preparation are not available previously. We now report the preparations of various types of α,α,β,β-tetrafluoroesters.

We previously discovered ring-opening reaction of highly fluorinated cyclopropanes with halogenes to give the corresponding 1,3-dihalofluoropropane derivatives [5]. When reaction of perfluoromethoxylcyclopropane with iodine at 240 °C, iodotetrafluoroproponyl fluoride was obtained in high yield along with perfluoroalkyl iodides [6]. The iodotetrafluoroproponyl fluoride can be quenched with ethanol in the presence of sodium or potassium fluoride to give the ethyl iodotetrafluoroproponylate **1** in 75–90% yields from fluorinated cyclopropane derivatives.



With **1** in hand, we tried to prepare various aryl substituted α,α,β,β-tetrafluoroesters from **1**. It was reported that perfluoroalkyl iodides coupled with aryl iodides in the presence of copper to give perfluoroalkylated aromatics via a perfluoroalkylcopper intermediate [7]. Kobayashi extend the reaction to iododdifluoroacetate and aryl iodies to give aryldifluoroesters. Although the reaction worked well in DMSO at room temperature, the only decomposition products were obtained when the reaction was carried out at

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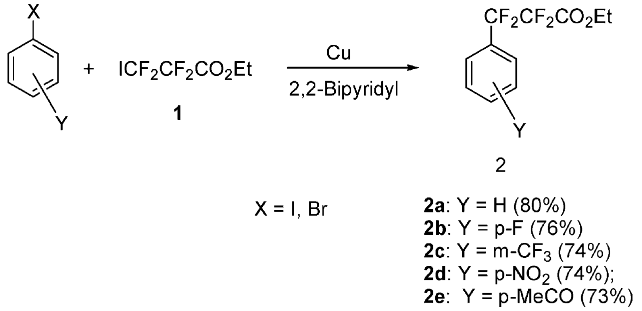
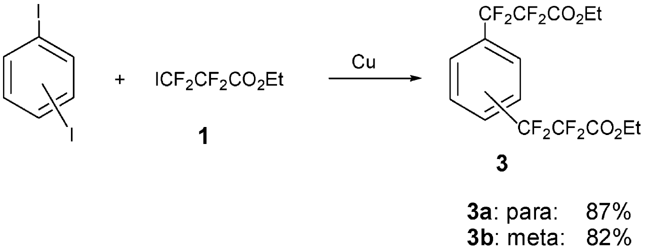
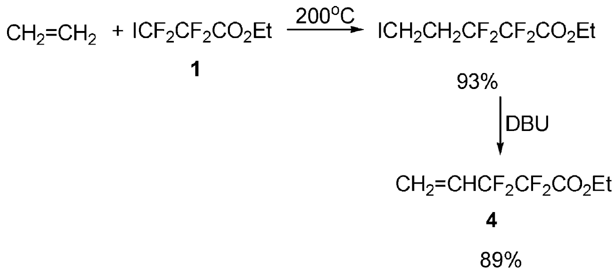
above 60 °C [8]. I found that **1** coupled with aryl iodides and copper powder in DMF at 80–110 °C to give the corresponding α,α,β,β-tetrafluoroesters **2**.



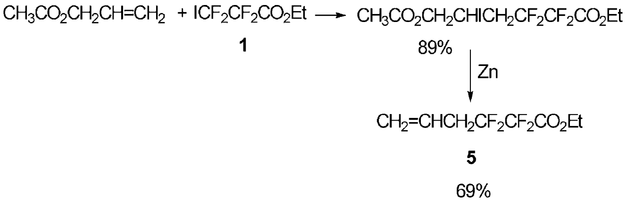
Although phenyl iodides gave the products in good yields, phenyl bromide containing an electron-withdrawing also worked well in the coupling reaction. For example phenyl bromide substituted with acyl group formed the coupled product **2e** in 80%. The coupling reaction also worked well with phenylene diiodide. Upon the reaction of $ICF_2CF_2CO_2Et$ with 1,3-diiodobenzene or 1,4-diiodobenzene and copper powder in the presence of 2,2′-dipridyl in DMF, the corresponding bis-coupled products **3** were isolated in 82–87% yields. However, with 1,4-diiodobiphenyl ($IC_6H_4C_6H_4I$), only 48% yield of product $(EtO_2CCF_2CF_2C_6H_4)_2$ **3c** was formed under similar conditions and substantial starting material was recovered.



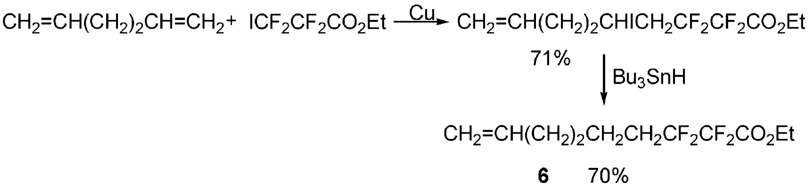
β-Vinyl-α,α,β,β-tetrafluoroesters also can be prepared from **1**. Although a coupling reaction of vinyl iodides and **1** in the presence of copper powder could produce β-vinyl-α,α,β,β-tetrafluoroesters, an addition–elimination method is more cost effective and easy to scale up. **1** was readily added to ethylene at 200 °C in an autoclave to give the corresponding adduct. The high temperature addition is believed to be a radical reaction. To prevent polymerization of ethylene, a small amount of polymerization inhibitor such as D-limonene is usually added to the reaction mixture. The formation of product in high yield indicated the absence of side reactions such as thermal elimination of ethylene from **1** or the adduct. When elimination of HI from the adduct, a suitable base in an aprotic solvent should be selected to prevent the hydrolysis of the ester. DBU has been demonstrated to be an effective base in the elimination reaction. The reaction was carried in dry ether or CH_2Cl_2 at room temperature to afford β-vinyl-α,α,β,β-tetrafluoroester **4** in high yield.



Preparation of β-allyl-α,α,β,β-tetrafluoroesters is also achieved from **1**. Addition of **1** to allyl acetate can be initiated with copper powder or radical initiators, but the radical initiator such as benzoyl peroxide gave better yields of product. When copper used as an initiator, one to two adduct was also formed although one to one adduct was major product. One to one adduct was obtained in 89% yield when benzoyl peroxide was added to the reaction mixture portion by portion in the absence of solvent. The adduct was treated with zinc powder in DMF to produce allyl substituted α,α,β,β-tetrafluoroester **5** [9].



1 can be used to prepare ω-alkenyl-α,α,β,β-tetrafluoroesters. A general method for the preparation of these compounds is selective addition of **1** to appropriate dienes, followed by reduction to remove iodine. To minimize the formation of a bis adduct, large excesses diene are required. For example, upon the reaction of **1** to 2 mole excess1,5-hexadiene and copper powder, the corresponding mono-adduct was isolated in 71% yield. Reduction of the adduct was achieved with Bu_3SnH to produce the ω-alkenyl-α,α,β,β-tetrafluoroester **6** [9]. Although a small amount of bis-adduct was also formed, no five membered ring adduct was detected. In contrast, reaction of perfluoroalkyl iodides with 1,6-heptadiene or its derivatives gives a cyclic adduct as a major product [10]. It would be expected that **1** reacts with 1,6-heptadiene to produce the corresponding cyclic adduct.



The addition–reduction strategy can be applied to the synthesis of saturated α,α,β,β-tetrafluoroesters. There are numerous initiators to initiate the addition of perfluoroalkyl iodides or functional fluorinated iodides to olefins and various functional groups can be tolerated in the addition as reported in our previous papers [11,12]. I anticipated that these initiators could initiate the addition of **1** to olefins. I have demonstrated an example of addition of **1** to 1-hexene with $Pd(PPh_3)_4$ as an initiator to give the corresponding adduct $C_4H_6CHICH_2CF_2CF_2CO_2Et$ in 89% yield.

In conclusion, I have developed efficient methods for the synthesis of various aryl-, vinyl-, allyl-, ω-alkenyl-, and alkyl α,α,β,β-tetrafluoroesters that previously were not readily accessible from now available precursor **1**. These new fluorinated esters may have interesting properties themselves or are important and useful compounds for making other more complex materials.

Typical procedure for ***2a***: A mixture of 5.7 g (28 mmol) of iodobenzene, 9.0 g of (30 mmol) of $ICF_2CF_2CO_2Et$, 4.8 g (75 mmol) of Cu powder and 0.3 g of 2,2′-bipyridyl in 25 ml of DMF was stirred at 100 °C for 6 h under N_2. After being cooled to room temperature, the mixture was diluted with 100 ml of ether. Solids were removed by filtration and washed with ether. The filtrate was poured to water and the ether lay was separated, and then washed with diluted HCl, water, NaCl solution and dried over $MgSO_4$. After removal of the ether, residue was distilled to give 5.6 g (80%) of product, b.p. 95–96 °C/5 mmHg. ^{1}H NMR: 7.58–7.25 (m, 5H), 4.37 (q, $J = 7.5$ Hz, 2H), 1.35 (t, $J = 7.5$ Hz, 3H), ^{19}F NMR: −112.0 (t, $J = 6.0$ Hz, 2F), −119.3 (t, $J = 6.0$ Hz, 2F). HRMS: calcd for $C_{11}H_{10}F_4O_2$: 250.0617. Found: 250.0596.

Typical procedure for **5**: To a stirred mixture of 110 g (1.1 mol) of allyl acetate and 300 g (0.99 mol) of $ICF_2CF_2CO_2Et$ Et was added 0.8 g of benzoyl peroxide at 100 °C in N_2. Exothermic reaction occurred and the temperature raised to 165 °C. After cooling to 110 °C, additional 0.6 g of benzoyl peroxide was added and the reaction mixture was stirred for 30 min. Three grams of benzoyl peroxide was added in a fraction of 1.0 g for every 30 min. GC indicated the formation of 95% of adduct, and the mixture was distilled to give 350.6 g (89%) of adduct, bp 104–105 °C/0.8 mmHg. ^{19}F NMR: −113.6 (ddd, $J = 266.8$ Hz, $J = 27$ Hz, $J = 10.7$ Hz, 1F), −115.2 (ddd, $J = 266.8$ Hz, $J = 24.5$ Hz, $J = 14.2$ Hz, 1F), −120.6 (s, 2F). Anal: calcd for $C_{10}H_{13}F_4IO_4$: C, 30.02; H, 3.27; F, 18.99; I, 31.72. Found: C, 30.12; H, 3.25; F, 19.83; I, 30.57. To a stirred mixture of 75 g (1.15 mol) of Zn and 500 ml of DMF was dropwise added 344 g (0.85 mol) of $AcOCH_2CHICH_2CF_2CF_2CO_2Et$ at 100 °C under N_2. After the addition was complete, the reaction mixture was stirred for 40 min. Excess Zn was removed by filtration and washed with CH_2Cl_2. The filtrate was poured into acidic water. Lower layer was separated and washed with water aqueous NaCl solution and dried over $MgSO_4$. After removal of CH_2Cl_2, residue was distilled to give 125.6 g (69%) of the desired product, bp 77–78 °C/40 mmHg. ^{19}F NMR: −114.3 (t, $J = 18.3$ Hz, 2F), −120.3 (s, 2F). IR: 1775 (vs), 1648 (w), 1246 (vs), 1167 (s). Anal: calcd for $C_8H_{10}F_4O_2$: C, 44.87; H, 4.71; F, 35.48. Found: C, 44.78; H, 4.66; F, 35.79.

Acknowledgements

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