



## A convenient and practical method for the selective preparation of deuterofluorocarbons



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### ABSTRACT

A detailed study of the development of efficient and practical conditions for the selective synthesis of 1-deuteriononafluorobutane from 1-iodononafluorobutane is reported. The optimal conditions involve treatment of the iodo-precursor in D<sub>2</sub>O at ~170 °C in the presence of metallic zinc in a sealed Schlenk tube to give a 59% yield of 1-deutero-1,1,2,2,3,3,4,4,4-nonafluorobutane. The same method was applied successfully to two higher homologues to produce 1-deutero-1,1,2,2,3,3,4,4,5,5,5-undecafluoropentane and 1-deutero-1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane in yields of 64% and 56%, respectively. Surprisingly, even the non-perfluorinated product 6-deutero-1,1,1,2,2,3,3,4,4-nonafluorohexane could be synthesized in 69% yield with this method.

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### 1. Introduction

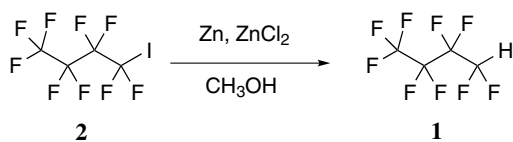
As part of a research program directed at the study of vibrational overtone dynamics in polyfluorinated hydrocarbons [1], we required a source of highly isotopically enriched mono-deuterofluorocarbons (DFCs). These compounds are generally not commercially available and literature reports of their synthesis, and of their hydroisotopomers, are limited. For example, Hudlicky et al. reported in 1992, in a study of potentially anesthetic mono- and di-hydrofluorocarbons (HFCs), that 1,1,1,2,2,3,3,4,4-nonafluorobutane **1** (“4H-nFB”) could be prepared by addition of 4-iodononafluorobutane **2** (“4I-nFB”) to a warm mixture of zinc metal, catalytic zinc chloride, and methanol, followed by reflux (Scheme 1) [2]. This approach was based on seminal studies of the preparation and reactivity of perfluoroorganozinc iodides by Miller et al. [3] and by Haszeldine [4,5].

In related subsequent work, Howell et al. reported that primary iodoperfluoroalkanes also can be converted efficiently to the corresponding primary hydroperfluoroalkanes by treatment with sodium methoxide in methanol [6]. Howell, et al. conducted mechanistic studies (including deuterium transfer experiments

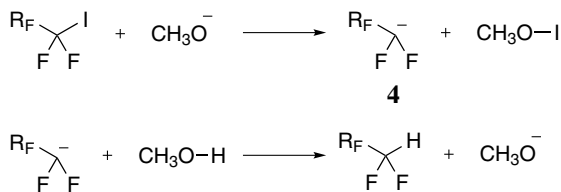
with CH<sub>3</sub>OD, CD<sub>3</sub>OH, or CD<sub>3</sub>OD) that demonstrated this conversion proceeds through either an anion-mediated mechanism (high temperature, methanol solution, no radical initiators present; Scheme 2) or a radical-mediated mechanism (low temperature, methanol solution, elemental iodine present as radical initiator; Scheme 3).

We reasoned that simple extension of Hudlicky et al.'s method for zinc-mediated transformation of iodofluorocarbons to include a suitable deuterium source would provide access to our desired mono-deuterofluorocarbons, and might also provide a general route to selectively deuterated synthetic targets. Selective deuterium incorporation plays a critical role in a broad range of experimental applications, from mechanistic studies employing kinetic isotope effects to spectroscopic work in which deuterium substitution provides easier spectral analysis and peak assignment. Moreover, recent pharmaceutical research has focused on the preparation and study of selectively deuterated drugs in order to increase overall drug efficacy by decreasing toxicity and slowing excretion rates, and to accomplish patent lifetime stretching [7]. Examples include deuterium-enriched *N*-pyrrolidinyl arylamides for treatment of urinary stress incontinence [8] and deuterium-enriched montelukast for treatment of asthma and allergies [9]. Deuterated organic compounds are also useful in the construction of light-emitting devices and photodiodes [10]. The research described herein details our attempts to maximize the efficiency of

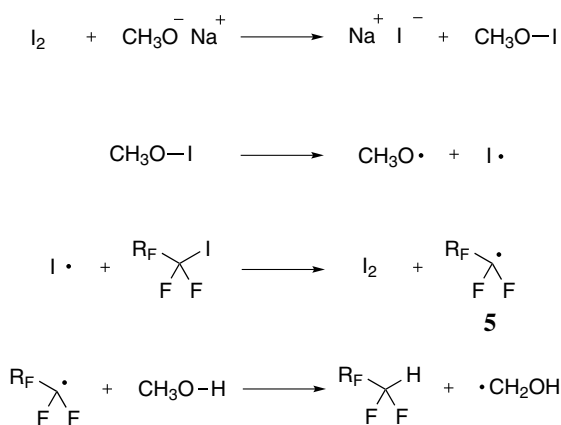
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**Scheme 1.** Zinc-mediated synthesis of 4H-nonafluorobutane **1**.



**Scheme 2.** Proposed [6] anion-mediated mechanism for transformation of primary iodoperfluoroalkanes.



**Scheme 3.** Proposed [6] radical-mediated mechanism for transformation of primary iodoperfluoroalkanes.

the synthesis of singly deuterated fluorocarbons by the simplest, mildest, and cheapest method possible through the use of  $D_2O$  as deuterium source.

## 2. Results and discussion

### 2.1. General aims and preliminary results

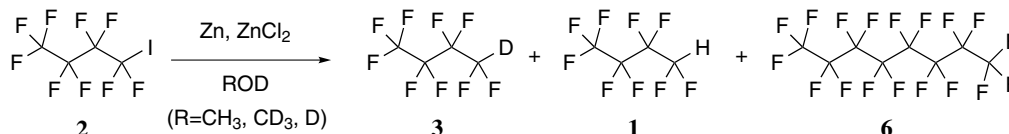
Our primary goal was to develop a convenient, efficient and economical method to synthesize 1-deutero-1,1,2,2,3,3,4,4,4-nonafluorobutane **3** (1-deuterononafluorobutane, “1D-nFB”). Hudlicky et al.’s preparation of the hydroisotopomer of **3** (**1**, Scheme 1) from **2** demonstrated that a readily protonated reactive intermediate was accessible from primary iodoperfluoroalkanes under very mild conditions ( $Zn^0$ /catalytic  $ZnCl_2$ /refluxing methanol). On the downside, isolating the highly volatile **1** (b.p. = 14 °C) in reasonable yield (72%) using this approach required conducting the reaction on large scale (100 g), the use of a dry ice trap and product purification by spinning-band distillation. Hence, our initial aims were to demonstrate that the Hudlicky et al. approach

could be extended to produce **3** using a suitably deuterated form of methanol as solvent, and to develop a method that could conveniently provide highly pure product on a relatively modest scale (1–20 g).

We found that conducting the reaction in a 50 mL Schlenk tube was the easiest way to decrease its scale. Subsequent transfer to a second Schlenk tube, using standard vacuum line transfer techniques, then accomplished product isolation. In a preliminary trial, we found that simply shaking **2** in a sealed Schlenk tube containing zinc dust (1.4 eq.), a catalytic amount of anhydrous  $ZnCl_2$  and  $CH_3OD$  ([**2**] ~0.8 M) gave an exothermic reaction and produced a mixture of **3** (1D-nFB) contaminated with unreacted **2**, the hydroisotopomer **1** (4H-nFB), perfluorooctane **6** (“dimer”), and traces of methanol, following product isolation and  $^{19}F$  NMR analysis (Scheme 4,  $R = CH_3$ ) [11]. Because reaction was so spontaneous and vigorous under these conditions, we took pains to temporarily isolate the  $ZnCl_2$  catalyst by placing it in a small test tube that was carefully positioned in the bottom of the Schlenk tube. After being sealed, the Schlenk tube was carefully tipped, allowing the reaction solvent to enter the test tube. Gentle shaking then allowed the catalyst to mix with the other reactants leading to vigorous bubbling and heat release.

We observed low levels of the dimeric side product **6** throughout our studies of zinc-mediated transformation of **2**.  $^{19}F$  NMR and GC-MS data analyses of product mixtures were consistent with a molecular formula of  $C_8F_{18}$  for **6**, clearly suggesting that two nonafluorobutane fragments combined during its formation. Howell et al.’s work [6] indicated that either anionic (**4**, Scheme 2) or radical (**5**, Scheme 3) intermediates can be produced during transformation of primary iodoperfluoroalkanes. Hence, formation of **6** in our experiments could result from  $S_N2$  reaction between an anionic intermediate (**2i**) and a molecule of **2**, or from coupling of a pair of radical intermediates (**2r**), as shown in Scheme 5.

Our initial study sought to maximize conversion to and yield of 1D-nFB **3** while minimizing contamination with unreacted **2**, isotopomer **1**, “dimer” **6**, and solvent. Parameters varied included reaction time, reaction temperature, concentration, and deuterium source (i.e.  $CH_3OD$  and  $CD_3OD$ ). Results for these experiments are summarized in Table 1. In this Table, and all that follow, we include data that we measured in an effort to determine both the conversion of starting iodide to the desired deuterated product and the isolated yield of the product. Due to the extremely volatile nature of the deuterated products, and the necessarily small reaction scales involved, however, it was only possible in our experiments to *estimate* conversion and yield based on NMR analysis of products that could be only incompletely purified by a single stage of low-temperature/low-pressure bulb-to-bulb distillation. Thus, Trials 1–3 explored the use of  $CH_3OD$  as deuterium source (Scheme 4,  $R = CH_3$ ). Trial 1 examined the effect of conducting the reaction at an elevated temperature: the reactants were mixed briefly at room temperature and then the Schlenk tube was immediately placed in a heating bath (60 °C). Under these conditions, crude yield of **3** appeared moderate (43%) and the very low level (<1%) of unreacted **2** contaminating the isolated product indicated conversion was high. However, contamination with the undesired hydroisotopomer **1** (7%) and reaction solvent (~45%) were far from ideal. Contamination with solvent was essentially



**Scheme 4.** Zinc-mediated synthesis of 1D-nonafluorobutane **3**.

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