

The First General and Efficient Method for the Synthesis of Tertiary Alkyl Fluorides

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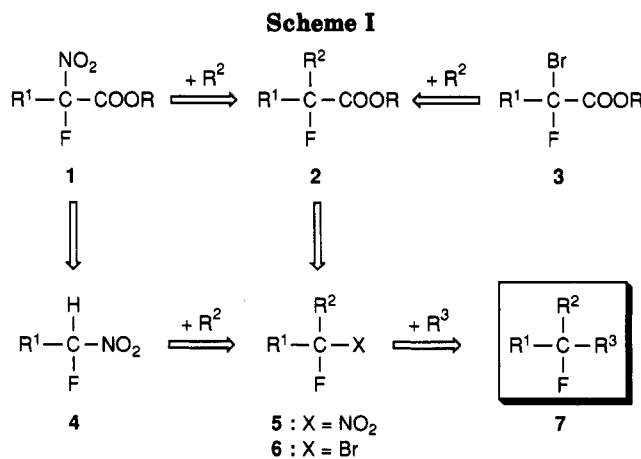
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Summary: The first general and regioselective method for the synthesis of a wide variety of tertiary alkyl fluorides $[R^1(R^2)C(F)R^3]$ has been developed. This novel method involves the successive introduction of three different alkyl groups onto fluorine-bearing prototertiary carbon fragments.

Many attempts have been reported for the introduction of fluorine atoms into bioactive molecules in anticipation of pronounced enhancement and/or drastic alteration of their biological activities.¹ Of the various fluorinated structures, nonlabile hydrocarbon molecules having a single fluorine atom on a specific site have been the most difficult to obtain because of extremely poor selectivity in the fluorination of hydrocarbon skeletons² and because of a lack of available building blocks for preparing them.³ Regioselective construction of tertiary alkyl fluorides has been particularly difficult, and no general synthetic routes to the monofluoro hydrocarbon structure have as yet appeared.⁴ Herein, we report the development of regioselective synthetic pathways to a wide variety of deliberately-designed tertiary alkyl fluorides $[R^1(R^2)C(F)R^3]$. The pathways involve the use of monofluoro building blocks having multifunctional carbon structures.⁵ This approach seems of potential significance for both basic⁶ and applied¹ fluorine chemistry.

Our basic strategy involves the sequential introduction of different alkyl chains (R^1 , R^2 , and R^3) onto a fluorine-bearing carbon fragment. This methodology is entirely new to fluorine chemistry. Trifunctional compounds **1** and **3** bearing both the first alkyl chain (R^1) and a single fluorine atom were chosen as potentially versatile building blocks for tertiary alkyl fluorides **7** because of the ease of their preparation and the ability of their functional groups to undergo subsequent alkylation. Our preliminary investigation led us to believe that it would be possible to introduce the second alkyl group (R^2) onto **1** or **3** to produce precursors **2** and variants **5** and **6**, which would be transformed into **7** by the third alkylation (R^3) (Scheme I).



Since the route involving the utilization of α -fluoronitroalkanes **5** did not give satisfactory results,⁷ we focused on structures that we thought would be more receptive to radical alkylation at the fluorine-bearing carbon atom, i.e., α -bromofluoroalkanes **6**. Compounds **1a,b** were treated with $\text{Bu}_3\text{SnH/AIBN}$ in the presence of a large excess of the Michael acceptor $\text{CH}_2=\text{CHCN}$ to produce alkylated products **2j,k**, although in low yields (ca. 18%).⁹ We also used tin reagents Bu_3SnR^2 ($R^2 = \text{allyl, methyl}$) that carried the functional groups necessary for both denitration and alkylation. Thus, the reactions of **1a-d** with these tin reagents (AIBN/PhH , reflux, 3 h) successfully gave **2l-p** in 73–98% yields.

Key compounds **2** could also be prepared from α -bromo α -fluoro esters **3**, which were obtained either by diazotization¹⁴ of α -amino esters followed by bromofluorination¹⁵ or by monoalkylation¹⁶ of dibromofluoroacetates with certain tin reagents. For example, compounds **2q** and **2r** were obtained either by treatment of **3g** with $\text{Bu}_3\text{SnH/}$

(7) We first investigated the route involving direct alkylation (R^3) of the α -fluoronitroalkanes **5e,f** which can be readily obtained from **4a**.⁸ Michael alkylation of **5e,f** with $\text{Bu}_3\text{SnH/AIBN/excess CH}_2=\text{CHCN}$ produced tertiary alkyl fluorides **7s,t**, although in very poor yields (ca. 5%).⁹ Analogous reactions employing Bu_3GeH ,¹⁰ $(\text{Me}_3\text{Si})_3\text{SiH}$,¹¹ and $(\text{Me}_3\text{Si})_2\text{SiH}$,¹² which have less hydrogen-donating ability¹³ than Bu_3SnH , failed. However, the reaction of **5f** with $\text{Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2$ afforded **7u** in 14% yield. These unsatisfactory results are presumably caused by the difficulty of generating α -fluoro carbon radicals on inert hydrocarbon chains.

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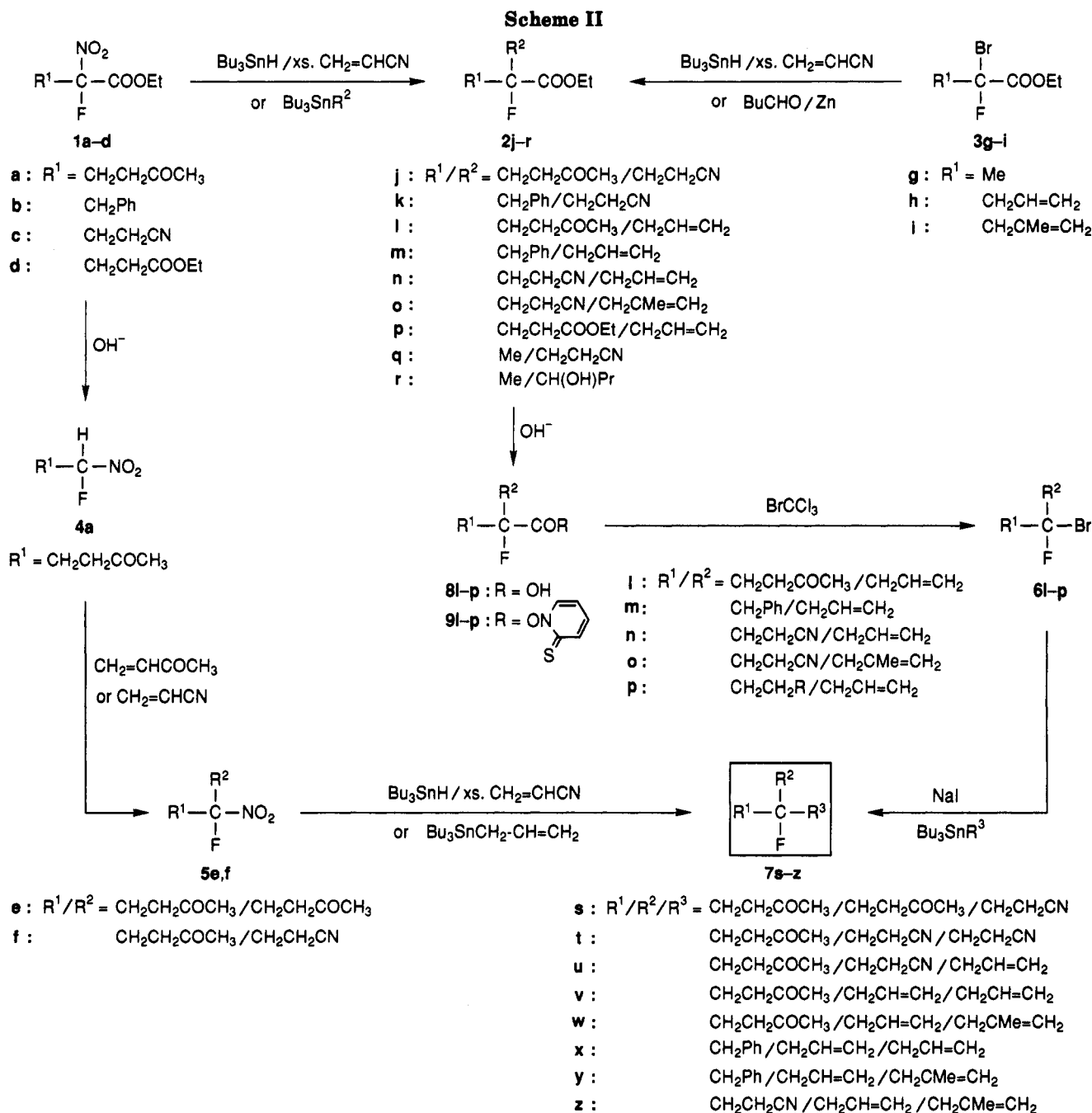
(2) Conventional monofluorination procedures are not applicable to aliphatic compounds, especially to those having no labile functional groups. See: German, L.; Zernakov, S. *New Fluorinating Agents in Organic Synthesis*; Springer-Verlag: Berlin, 1989.

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excess CH₂=CHCN (AIBN/PhH, reflux, 3 h) or by condensation of 3g with Zn/BuCHO via a Reformatsky reaction in 68% or 76% yield, respectively.

Esters 2 obtained by means of these routes^{17,18} were converted to variant equivalents 6, which had favorable structures for subsequent alkylation. Thus, the reactions of 2l-p with aqueous 1 N NaOH (rt, 4 h) gave acids 8l-p in 91-99% yields without the anticipated defluorination. Condensation of 8l-p with *N*-hydroxy-2-thiopyridone to give activated esters 9l-p was achieved either directly with

(16) This new reaction was carried out as follows: A benzene solution of dibromofluoroacetate, 1 molar equiv of Bu₃SnCHR³ (R³ = allyl, methallyl), and a catalytic amount of AIBN was heated at reflux for 3 h.

(17) The olefin part of 2l-p was readily converted (OsO₄/NaIO₄, 62-78%) into the aldehyde functionality, which is then available for further extension of the side chain (R²).

(18) Various α-alkylated α-fluoroalkanoates 2 can also be obtained by the DAS¹ fluorination of α-alkylated α-hydroxyalkanoates; see: Takeuchi, Y.; Ogura, H.; Ishii, Y.; Koizumi, T. *Chem. Pharm. Bull.* 1990, 38, 2404.

DCC or via the corresponding acid chlorides, according to the procedure¹⁹ of Barton. Attempted direct introduction of the third alkyl groups into 9l,m with Bu₃SnR³ did not produce the desired compounds 7v-y. We then investigated the bromination of 9l-p with BrCCl₃ (reflux, 1 h). Bromination produced the very versatile α-bromo-α-fluoroalkanes 6l-p in 83-92% yields (R = Br in 6p).

Debrominative alkylation was achieved by treatment of 6l-n with Bu₃SnR³ (R³ = allyl, methallyl) to give the target tertiary alkyl fluorides 7v-z, although in unsatisfactory yields (ca. 45%). This step was improved, however, by treatment of 6l-n with NaI/MeCN and subsequent reaction of the unstable iodide intermediates with Bu₃SnR³ (AIBN/PhH or PhMe, reflux, 2-4 h) to afford 7v-z in 67-73% yields (Scheme II).

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In summary, we have succeeded in developing new and general pathways to nonlabile tertiary alkyl fluorides, which are among the most difficult to obtain of the various organofluorine compounds. This novel methodology features the sequential introduction of different alkyl groups onto a fluorine-bearing one carbon fragment. We have also developed some new methods involving direct alkylation at the fluorine-bearing prototertiary carbon atom.

We believe that this approach can be used in the synthesis of new bioactive compounds from known active compounds.

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Supplementary Material Available: General experimental procedures and compound characterization data (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.