A Rapid and Efficient Method for the Fluoroalkylation of Amines and Amides. Development of a Method Suitable for Incorporation of the Short-Lived Positron Emitting Radionuclide Fluorine-18

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We have described a two-step method for the preparation of fluoroalkyl-substituted amines and amides. The sequence involves fluoride ion displacement of a haloalkyl trifluoromethanesulfonate (triflate), followed by fluoroalkylation of the heteroatom system (amine or amide) by the fluoroalkyl halide. Alternatively, the fluoroalkyl halide can be prepared by halofluorination of a terminal olefin. These reactions have been used to prepare various fluoroalkyl derivatives of *N*-phenylpiperazine and *N*-fluoroalkyl derivatives of the neuroleptic agent spiperone (7). The sequence is rapid, convenient, and efficient, even when fluoride ion is the limiting reagent. Therefore, it is readily adaptable to the preparation of a variety of compounds labeled with the short half-life ($t_{1/2}$ = 110 min) positron-emitting radionuclide fluorine-18.

Introduction

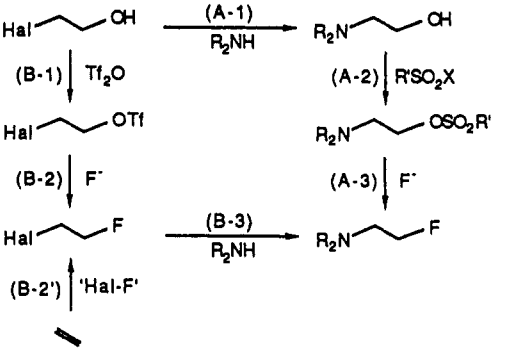
With the increased use of positron emission tomography as a method for determining the distribution of substances labeled with positron-emitting radionuclides,[1] there has been great interest in the development of methods suitable for the synthesis of pharmaceuticals labeled with positron emitters,[2] as these can be used as tracers for physiological and pharmacological phenomena. Fluorine-18 is a positron emitter with excellent characteristics for tomographic imaging, as it is readily prepared and has a low positron energy; its half-life (110 min) is sufficiently long to pemit imaging to be extended out to 4–6 h, yet short enough to ensure high specific activity and minimize radiation exposure to the subject. The short half-life of fluorine-18, however, places constraints on chemical approaches and methods used to prepare fluorine-18-labeled compounds, since all the operations involving the introduction of the label, further chemical transformations, and the isolation and purification of intermediates and final products need to be performed within a period of 2–4 h. In addition, for the preparation of receptor-binding radiopharmaceuticals, methods that do not require the addition of substantial amounts of carrier (fluorine-19) are needed.[3]

We have described methods for introducing fluorine-18 by [^{18}F]fluoride ion displacement of highly reactive trifluoromethanesulfonates (triflates) and have used this approach to prepare fluorine-18-labeled steroidal and nonsteroidal estrogens.[4] In this report, we present an approach to the synthesis of fluoroalkyl amines and amides, based on a two-step sequence involving fluoride ion displacement on a haloalkyl triflate precursor, followed by a fluoroalkylation reaction with the resulting fluoroalkyl halide. An alternative preparation of the fluoroalkyl halide involves olefin halofluorination. This sequence is rapid and efficient,[5] and in work described elsewhere has been adapted to the preparation of a series of [^{18}F]fluoroalkyl derivatives of the dopamine antagonist spiperone (7).[6]

Results

General Strategy. As illustrated in Scheme I, one can imagine two approaches to the preparation of a fluoroalkyl-substituted amine or amide. By the first (arrows marked with A), the amine or amide is alkylated with a hydroxylalkyl group (A-1); the hydroxyl group is subsequently derivatized as, for example, a reactive sulfonate ester (A-2), which then undergoes displacement by fluoride ion (A-3). Such an approach has been used by Kiesewetter et al. for the preparation of 3-*N*-(2-fluoroethyl)spiperone,[7] and by Jerabek et al. for the preparation of the fluorinated analogue of misonidazole (1-*N*-(2-fluoroethyl)-2-nitroimidazole).[8] The alternative approach (arrows marked with B), involves the same reactions, but in a different sequence. First, the haloalcohol is derivatized as a highly reactive sulfonate ester (e.g., triflate) (B-1); fluoride ion displaces the triflate (B-2), and then the resulting fluoroalkyl halide is used to alkylate the heteroatom system R_2NH (B-3). A variant of the second approach involves olefin halofluorination to produce the fluoroalkylation

Scheme I. Two Approaches to Fluoroalkyl Derivatives



(1) Raichle, M. E. *Annu. Rev. Neurosci.* **1983**, *6*, 249.
(2) (a) Fowler, J. S.; Wolf, A. P. *The Synthesis of Carbon-11, Fluorine-18, and Nitrogen-13 Labeled Radiotracers for Biomedical Applications*; U.S. Department of Energy, Technical Information Center: Springfield, VA, 1982. (b) Palmer, A. J.; Clark, J. C.; Goulding, R. W. *Int. J. Appl. Radiat. Isot.* **1977**, *28*, 53.
(3) *Receptor-Binding Radiotraces*; Eckelman, W. C., Ed.; CRC: Boca Raton, FL, 1982; Vol. I, Chapter 6.
(4) (a) Landvatter, S. W.; Kiesewetter, D. O.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Welch, M. J. *Life Sci.* **1983**, *33*, 1933. (b) Kiesewetter, D. O.; Kilbourn, M. R.; Landvatter, S. W.; Heiman, D. F.; Katzenellenbogen, J. A.; Welch, M. J. *J. Nucl. Med.* **1984**, *25*, 1212.
(5) Chi, D. Y.; Kiesewetter, D. O.; Katzenellenbogen, J. A.; Kilbourn, M. R.; Welch, M. J. *J. Fluorine Chem.* **1986**, *31*, 99.
(6) Chi, D. Y.; Kilbourn, M. R.; Katzenellenbogen, J. A.; Brodack, J. W.; Welch, M. J. *Appl. Radiat. Isot.*, in press.
(7) Kiesewetter, D. O.; Eckelman, W. C.; Cohen, R. M.; Larson, S. M. *Abstracts of Papers*, 190th National Meeting of the American Chemical Society, Chicago, IL; American Chemical Society: Washington, DC, 1985; MEDI 40.
(8) Jerabek, P. A.; Patrick, T. B.; Kilbourn, M. R.; Dischino, D. D.; Welch, M. J. *Appl. Radiat. Isot.*, in press.

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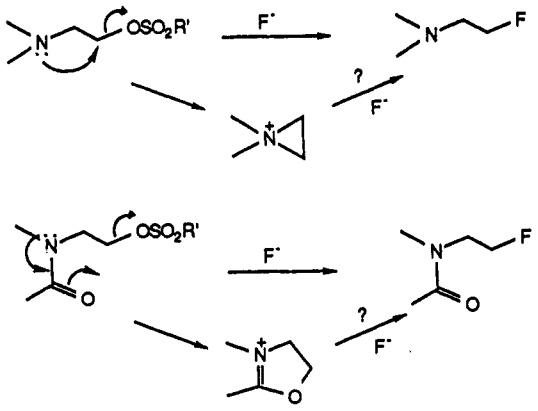
Scheme II. Potential Side Reactions of Trifloxyalkyl Amines and Amides



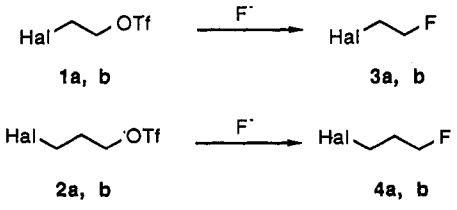
agent (B-2′). It is evident that the displacement–N-alkylation route (B-2,3) is readily adaptable to the preparation of ω-fluoroalkylated systems, whereas the halofluorination–N-alkylation sequence (B-2′,3) leads most directly to 2-fluoroalkylated systems.

In principle, one can imagine advantages and disadvantages with both approaches. With approach A, fluorine is introduced in the final step (A-3) of the sequence, a significant advantage in keeping reaction times with [^{18}F]fluoride ion to a minimum. However, there are potential side reactions in this final step that involve intramolecular attack by nucleophiles; these might be particularly troublesome with the amines and amides, as illustrated in Scheme II. Attempts to reduce this alternative pathway by adjusting the reactivity of the sulfonate leaving group ($R'SO_3^-$) would probably simply have a parallel effect of the facility of the fluoride ion displacement.

In contrast, with Approach B, the most reactive sulfonate esters (triflates) can be used in the fluoride displacement step (B-2). However, one additional step is then required (B-3), and potential side reactions between the amine or amide with excess haloalkyl triflate must be considered.

In this paper, we have described methods that permit the rapid and efficient synthesis of 2-fluoroethyl and 3-fluoropropyl amines and amides, using the two-step process: (1) fluoride ion displacement of a haloalkyl triflate (step B-2) or olefin halofluorination (step B-2′), followed by (2) N-alkylation by the fluoroalkyl halide (step B-3). In some cases, these two reactions can be conducted in a "one-pot" mode.

Preparation of Fluoroalkyl Halides. Fluoride Ion–Triflate Displacements. 2-Fluoroethyl and 3-fluoropropyl halides **3** and **4** can be synthesized rapidly and efficiently by fluoride ion displacement on the corresponding triflates **1** and **2**, as illustrated below.



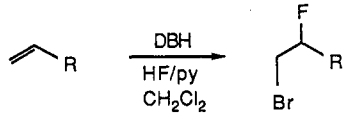
a, Hal = Br
b, Hal = I

As a matter of convenience, we have used the bromoalkyl triflates (**1a** and **2a**). These can be prepared as colorless oils; they are quite stable to water and silica gel, and they can be stored indefinitely at −20 °C. The iodopropyl triflate **2b** is of comparable stability, but must be stored over a copper wire to prevent discoloration. The iodoethyl triflate **1b**, however, is unstable to storage at −20 °C and is rapidly decomposed on contact with silica gel or neutral alumina.

The displacement reactions proceed within a matter of seconds when equimolar quantities of triflate and an appropriate soluble form of fluoride ion are mixed at room temperature in a variety of solvents. (Yields were determined by gas–liquid chromatography (GLC) and by NMR.) Various sources of fluoride ion were investigated: The reaction failed with pyridine poly(hydrogen fluoride) (0% in *o*-dichlorobenzene (*o*-DCB)), and was variable with $Bu_4NF{\cdot}2HF$ (30% in *o*-DCB) and $Et_4NF{\cdot}3H_2O$ (25% in *o*-DCB, 100% in acetonitrile), but with *n*-$Bu_4NF{\cdot}3H_2O$, quantitative yields were obtained within seconds in *o*-DCB, acetonitrile, and tetrahydrofuran (THF). The finding that the displacement reaction with *n*-Bu_4NF consistently gives a good yield even on a 10 μmol scale and is quite water tolerant, is encouraging for the prospects of F-18 labeling, since reasonably dry and reactive *n*-Bu_4NF can be produced from [^{18}F]fluoride ion generated by proton bombardment of an [^{18}O]water target.[9] Also, as is critical for the no-carrier-added fluorine-18 radiochemical syntheses, the reaction also proceeds efficiently when fluoride ion is the limiting reagent (≤1.0 equiv).

Olefin Halofluorination. Precursors for fluoroalkylation can also be prepared by the halofluorination of terminal olefins (reaction B-2′).[5] The procedure involves the exposure of the olefin to a source of electrophilic halogen in the presence of fluoride ion under acidic conditions. Elsewhere, we have reported a detailed study of this reaction with regard to its applicability for labeling with fluorine-18.[6] It operates rapidly and efficiently, even with a deficiency of fluoride ion. For the use intended here—preparation of a fluorine-substituted alkylating agent—we have restricted ourselves to bromofluorination of four terminal olefins (**5a–d**). Since the addition proceeds in a Markownikow sense, the major product is the 2-fluoroalkyl bromides (**6a–d**), a suitable precursor for alkylation on nitrogen.

Shown below are the bromofluorination reactions of four olefins, propene, 1-butene, 1-pentene, and 1-hexene, with 1,3-dibromo-5,5-dimethylhydantoin (DBH), to produce the 2-fluoroalkyl bromides (**6a–d**) that are later used in the

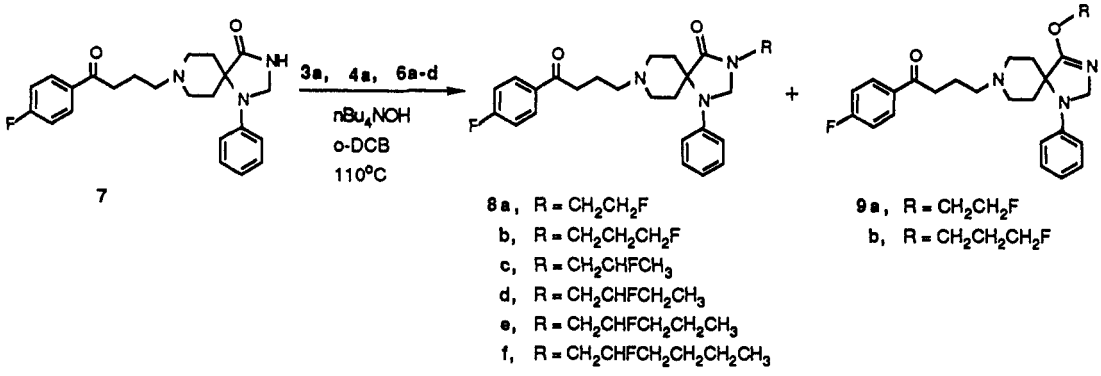


5a, R = CH_3	**6a**, R = CH_3
b, R = CH_2CH_3	**b**, R = CH_2CH_3
c, R = $CH_2CH_2CH_3$	**c**, R = $CH_2CH_2CH_3$
d, R = $CH_2CH_2CH_2CH_3$	**d**, R = $CH_2CH_2CH_2CH_3$

alkylation reactions. The isolated yields of these halofluorinations are good (45–50% for **6a–d**); while **6c** and **6d** were prepared by reaction in a solvent (CH_2Cl_2), **6a** and **6b** were prepared using an excess of olefin (**5a** and **5b**) as solvent. The yield of halofluorination products measured by GLC are high (80–90%); isolated yields are lower, however, particularly with the lower molecular weight halofluorination products because of their high volatility. Because of this volatility problem, where it was possible, the halofluorination products were not isolated, but were used directly in the subsequent heteroatom alkylation

(9) Kilbourn, M. R.; Jerabek, P. A.; Welch, M. J. *Int. J. Appl. Radiat. Isot.* **1985**, *36*, 327.

Scheme III



reaction in a one-pot reaction (see below).

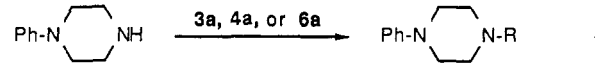
Fluoroalkylation Reactions. To exemplify the fluoroalkylation reactions, an amide (the neuroleptic agent spiperone **7**) and an amine (1-phenylpiperazine **10**) were selected for reaction with the fluoroalkyl halides **3**, **4**, and **6**. Because the half-life of fluorine-18 is so short, it is advantageous to perform the fluoride ion incorporation reaction and the alkylation step with minimum delay. Ideally, this would involve omission of product isolation at the fluoroalkyl halide stage, giving a "one-pot" reaction. Therefore, in the fluoroalkylation sequences involving fluoride ion–triflate displacement followed by alkylation, we have performed these transformations under one-pot conditions. It was not possible to perform one pot reactions with the halofluorination alkylation sequence, for the reasons noted below.

Spiperone. There is great interest in developing spiperone analogues labeled with fluorine-18 as potential imaging agents for the dopamine receptor -rich areas of the brain,[10] and elsewhere, we have described the preparation of the 3-*N*-(fluoroalkyl)spiperone derivatives, reported here, in fluorine-18-labeled form.[6] The *N*-(fluoroalkyl)-spiperone derivatives that we have prepared are shown in Scheme III below.

The two fluoroalkyl halides prepared by the fluoride ion displacement of triflate route (**3** and **4**) can be used to alkylate spiperone. A strong base (tetrabutylammonium hyroxide (*n*-Bu_4NOH) or tetraethylammonium hydroxide (Et_4NOH)) is required, and optimal reaction conditions are at 110 °C in *o*-DCB for 30 min. The reactions are conducted in tightly sealed heavy-walled glass reaction vials (Reacti-Vials; Pierce) to minimize evaporative loss of the fluoroalkyl halide. Yields, for the two-step fluoride ion displacement–alkylation sequence, done in one pot, are 75–80% (determined by HPLC) or 60–70% (after chromatographic isolation). About 10–17% of the O-alkylated product, the fluoroalkyl iminoester **9**, is produced together with the desired *N*-fluoroalkylation product. The overall yields for the formation of the two *N*-fluoroalkylspiperone derivatives by this two-step/one-pot sequence are summarized in Table I (entries 1 and 2).

The four 2-fluoroalkyl bromides (**6a–d**) produced by the olefin halofluorination reaction could also be used to N-alkylate spiperone (*o*-DCB and *n*-Bu_4NOH) (Table I, entries 5–8). However, it was important to remove carefully most of the dichloromethane used as solvent in the halofluorination reactions of 1-pentene and 1-hexene, as this solvent reacts with spiperone under the *N*-alkylation conditions.[6] Although we examined a number of other solvents such as 1,2-dichloroethane, 1,1-dichloroethane, 2,2-dichloropropane, 2,3-dichlorobutane, 1,1,2-trichloroethene, and dichlorodifluoromethane, none proved satisfactory for both the halofluorination and the spiperone N-alkylation reaction. Therefore, the halofluorination–N-alkylation sequence to prepare 3-*N*-(2-fluoroalkyl)spiperone derivatives **8c–f** was performed as two separate steps.

Phenylpiperazine. 1-Phenylpiperazine (**10**) was used as a model for the amine fluoroalkylation (reactions shown below). In contrast to spiperone, no exogenous base was required for this alkylation, simply an excess of 1-phenylpiperazine. The reaction proceeded quickly, with moderate to good efficiency in several solvents. The overall yields for the two-step/one-pot procedure are summarized in Table I (entries 10 and 11). Also, the *n*-alkylation reaction of **10** with the purified bromofluorination product



10

11a, R = CH_2CH_2F
b, R = $CH_2CH_2CH_2F$
c, R = CH_2CHFCH_3

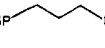
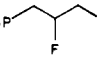
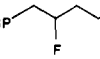
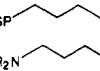
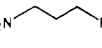
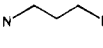
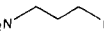
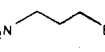
was carried out in the presence of K_2CO_3 and KI with an equivalent of amine and alkylating agent, providing a 78% yield. Although the fluoroalkylation reactions proceed satisfactorily, it is of note that the two attempts to effect a bromoalkylation, by reaction with 1,3-dibromopropane (entry 16) or 3-bromopropyl triflate (entry 17), gave none of the expected product (1-(3-bromopropyl)-4-phenylpiperazine). In addition, the use of an excess of triflate destroyed (entry 13) the desired product **11b**, presumably by formation of the quaternary ammonium salt. However, this problem can be solved by performing the N-alkylation reaction of amine in a heterogeneous phase in the presence of aqueous *n*-Bu_4NOH which destroys the excess of triflate[6] (entries 14 and 15).

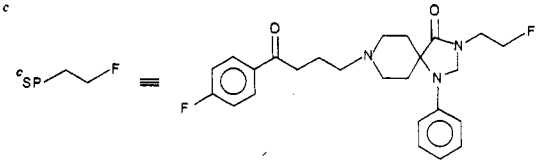
Discussion

We have described a simple reaction sequence that permits the rapid and efficient synthesis of fluoroalkyl-substituted amines and amides. The motivation for this study was the need to develop a versatile method for the synthesis of fluorine-substituted compounds that might be applicable to labeling with the short-lived positron-emitting radionuclide fluorine-18. The two sequences we have described—fluoride ion displacement of haloalkyl triflates followed by N-fluoroalkylation and bromo-

(10) (a) Burns, H. D.; Dannals, R. F.; Langström, B.; Ravert, H. T.; Zemyan, S. E.; Duelfer, T.; Wong, D. F.; Frost, J. J.; Kuhar, M. J.; Wagner, H. N. *J. Nucl. Med.* **1984**, *25*, 1222. (b) Kilbourn, M. R.; Welch, M. J.; Dence, C. S.; Tweson, T. J.; Saji, H.; Meada, M. *Int. J. Appl. Radiat. Isot.* **1984**, *35*, 591. (c) Moerlein, S. M.; Laufer, P.; Stöcklin, G. *J. Labelled Compd. Radiopharm.* **1985**, *22*, 1007. (d) Shiue, C.-Y.; Fowler, J. S.; Wolf, A. P.; McPherson, D. W.; Arnett, C. D.; Zecca, L. *J. Nucl. Med.* **1986**, *27*, 226.

Table I. Reactions of Fluoride Ion Displacement–N-Alkylation and Halofluorination–N-Alkylation to Selected Amide (7) and Amine (10)

reactant	entry	method[a]	precursor	fluorination agent	alkylating agent	solvent	product	overall yield, %
spiperone (7)	1	A		*n*-Bu_4NF[b]		*o*-DCB		74–90
	2	A						80–90
	3	A						80–90
	4	A		$Et_4NF·3H_2O$				25
	5	B		HF/py, DBH		CH_3CN		70[d]
	6	B						55[d]
	7	B						68[d]
	8	B						70[d]
	9	B		--	--	*o*-DCB		0
1-phenylpiperazine (10)	10	A		*n*-Bu_4NF		*e*		53–64
	11	A	--	--	--	DMF		40
	12	B		HF/py, DBH		CH_3CN		78[d]
	13	A		*n*-Bu_4NF		THF		trace
	14	A				*o*-DCB[g]		49
	15	A				*o*-DCB[g]		48
	16	B	--	--		THF		0
	17	B		--	--	THF		0

[a] Method A = two-step/one-pot reaction, Method B = N-alkylation reaction with purified alkylating agent. [b] Either *n*-$Bu_4NF·3H_2O$ or 1M solution of *n*-Bu_4NF in THF (Aldrich). [c] 

[d] Yield of N-alkylation step only; halofluorination isolated yields are 45–50%. [e] *o*-DCB, CH_3CN, or THF. [f] [g] At the end of the displacement reaction, *n*-Bu_4NOH/H_2O were added to destroy excess triflate.

fluorination of a terminal olefin followed by fluoroalkylation—both satisfy the criteria of speed and efficiency required for adaptation to fluorine-18 labeling. We have described elsewhere the application of these two methods for the preparation of six 3-*N*-([^{18}F]fluoroalkyl)spiperone derivatives.[6]

The alternative approach to the synthesis of fluoroalkyl-substituted amines and amides by direct fluoride ion displacement on a preformed alkyl derivative (outlined in Scheme I, arrows labeled A) has been utilized in certain instances[7,8] and has the advantages and disadvantages outlined in the results section. The second approach that we have selected operates very well—it is rapid, and in the case of the displacement-alkylation sequence, is also efficient and convenient.

We believe that it is particularly fortuitous to utilize as displacement–alkylation precursors, "unsymmetrical" compounds such as the haloalkyl triflates, in which the sites for fluoride ion displacement (triflate) and N-alkylation (halide) differ in reactivity by five (triflate vs. bromide)[11] and six (bromide vs. fluoride)[12] orders of magnitude. The high reactivity of the fluoride ion displacement site (triflate) ensures that this reaction will proceed rapidly. This high reactivity may provide an additional bonus: Since in the reaction with [^{18}F]fluoride ion, an excess of haloalkyl triflate will be used, it is important that the remaining haloalkyl triflate not compromise the subsequent N-alkylation reaction.

We have looked carefully for the formation of haloalkylation products that might result from nitrogen displacement of the triflate, but have found little (cf. Table I, entries 9, 15, and 17). In the case of spiperone alkylation, we believe that the excess triflate is hydrolyzed by the excess base (*n*-Bu_4NOH) present during the N-alkylation step, leaving only the fluoroalkyl halide for N-alkylation. The fate of the haloalcohol that would result from hydrolysis of excess haloalkyl triflate has not been determined. If it were to react with the nitrogen, it would produce more polar hydroxylalkyl products that could easily be separated from the fluoroalkyl products. The case with 1-phenylpiperazine is less clear; reaction with the excess haloalkyl triflate might give a haloalkyl amine which, under the basic reaction conditions, would cyclize to the spiro ammonium salt and might react further to give an alkyl diamine. None of these reactions interfere with the formation of the N-fluoroalkyl amine. As was the case

(11) Streitwieser, A., Jr.; Wilkins, C. L.; Kiehlmann, E. *J. Am. Chem. Soc.* **1968**, *90*, 1598.
(12) Noyce, D. S.; Virgilio, J. A. *J. Org. Chem.* **1972**, *37*, 2643.

in the N-alkylation of spiperone, the excess of triflate in the 1-phenylpiperazine alkylation could be hydrolyzed by adding aqueous n-Bu_4NOH, so that the two-step/one-pot reactions of amine **10** with either equivalent (Table I, entry 14) or excess (entry 15) of triflate gave yields comparable to a homogenous reaction (entry 10).

One might imagine that the use of displacement–alkylation precursors with "symmetrical" reactivity such as dihalides or disulfonate esters might result in larger amounts of undesired heteroatom alkylated side products than those which are formed from the unsymmetrical precursors we have used. Furthermore, because these side products would have a polarity similar to those of the fluoroalkyl products, they might cause problems during separations.

The methods we have described for the preparation of fluoroalkyl substituted amines and amides should enable the facile preparation of a number of compounds bearing fluoroalkyl substituents of varying structure. In addition, because of the favorable characteristics of this reaction (rapid, efficient), it will be of use for the preparation of compounds labeled with the positron-emitting radionuclide fluorine-18.

Experimental Section

Materials and Methods. Spiperone was a generous gift of Janssen Pharmaceutical, Inc., New Brunswick, NJ. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. n-$Bu_4NF{\cdot}3H_2O$, n-Bu_4NF in THF (1 M), and $Et_4NF{\cdot}xH_2O$ were purchased from Aldrich. The extent of hydration of $Et_4NF{\cdot}xH_2O$ was determined by microanalysis (C, H, N, F) to be three. Analytical gas–liquid chromatography was performed in a Hewlett-Packard 5750B gas–liquid chromatograph (GLC) equipped with a flame ionization detector using hydrogen as the carrier gas and bonded fused silica open tubular (FSOT) capillary columns: (1) 30 meter × 0.25 mm, coated with methyl silicone, RSL-150, Alltech, and (2) 30 meter × 0.25 mm, coated with superox BP, Alltech. The chromatograms were recorded with Hewlett-Packard 3390A integrator. Column chromatography was done by Flash chromatography with Woelm 32-63 micron silica gel.[13]

^1H NMR spectra were obtained on Varian XL-200, General Electric QE-300, and Nicolet NIC-360 spectrometers and are reported in parts per million downfield from internal tetramethylsilane. ^{19}F NMR spectra were obtained on Varian EM-390 spectrometer at 84.6 MHz and Nicolet NIC-360 at 338 MHz and are reported in parts per million from internal $CFCl_3$. Mass spectra were obtained on Finnigan MAT CH5 and MAT 731 spectrometers for low- and high-resolution spectra, respectively. Elemental analyses were performed by the Microanalytical Service, School of Chemical Sciences, University of Illinois. High-performance liquid chromatography (HPLC) was performed with Varian Model 5060 and Spectra-Physics Model 8700 liquid chromatographs, using a 5 um analytical silica gel column (4.6 mm × 25 cm, IBM, or 4.6 mm × 30 cm, Varian Si-5 Micro Pak), 10 μm preparative silica gel column (10 mm × 50 cm, Alltech), or a 10 μm C_{18} column (4.6 mm × 30 cm, Varian MCH-10 Micro Pak).

2-Bromo-1-[((trifluoromethyl)sulfonyl)oxy]ethane (1a). 2-Bromoethanol (1 g, 8.0 mmol) was dissolved in 2.05 mL of 2,6-lutidine (17.6 mmol) diluted with 10 mL of CH_2Cl_2, and cooled to 0 °C. Trifluoromethanesulfonic anhydride (2.83 mL, 16.8 mmol) was added dropwise. After being stirred for 30 min, the reaction mixture was quenched with 10% EtOAc in hexane and passed through a short silica gel column. Removal of solvent in vacuo and bulb-to-bulb distillation (50 °C at 0.5 mmHg) gave 1.5 g (53%) of colorless liquid of triflate **1a**: GLC chromatogram, one peak, t_R = 3.92 min (column 1, carrier gas H_2, 0.95 mL/min, programming 60 °C (2-min hold, then 10 °C/min)); NMR (200 MHz, $CDCl_3$) δ 3.62 (t, 2, J = 6.35 Hz, CH_2Br), 4.75 (t, 2, J = 6.35 Hz, CH_2O); mass spectrum (70 eV), m/z (relative intensity) 177 (M^+ – Br, 1), 163 (2), 109 (45), 108 (85), 107 (50), 106 (85), 69 (100). Anal. Calcd for $C_3H_4BrF_3O_3S$: C, 14.02; H, 1.57; Br, 31.09; F, 22.17; S, 12.47. Found: C, 14.25; H, 1.61; Br, 31.15; F, 22.22; S, 12.38.

3-Bromo-1-[((trifluoromethyl)sulfonyl)oxy]propane (2a). The same procedure as for **1a** was followed: 3-bromo-1-propanol (2.24 g, 16 mmol), 2,6-lutidine (4.12 mL, 35.4 mmol), CH_2Cl_2 (25 mL), trifluoromethanesulfonic anhydride (10 gm, 35.4 mmol), bulb-to-bulb distillation (120 °C, at 5 mmHg), colorless liquid **2a** (4.0 g, 92%); GLC chromatogram, one peak, t_R = 5.98 min (column 1, carrier gas H_2, 0.95 mL/min, programming 60 °C (2 min hold, then 10 °C/min)); NMR (200 MHz, $CDCl_3$) δ 2.37 (quin, 2, J = 6.4 Hz, CH_2CH_2Br), 3.52 (t, 2, J = 6.4 Hz, CH_2Br), 4.72 (t, 2, J = 6.0 Hz, CH_2O); mass spectrum (70 eV), m/z (relative intensity) 123 (9), 122 (22), 121 (9), 120 (24), 69 (34), 41 (100).

3-Iodo-1-[((trifluoromethyl)sulfonyl)oxy]propane (2b). 3-Iodo-1-propanol was prepared from 3-bromo-1-propanol and NaI in refluxing acetone by the Finkelstein exchange reaction (yield 75%). 3-Iodo-1-propanol (0.5 g, 2.68 mmol) was dissolved in 2,6-lutidine (0.63 mL, 5.38 mmol) diluted with 5 mL CH_2Cl_2, and the solution was cooled to 0 °C. Trifluoromethanesulfonic anhydride (0.91 mL, 5.38 mmol) was added dropwise. After being stirred for 30 min, the reaction mixture was quenched with 10% EtOAc in hexane and passed through a short silica gel column. Removal of the solvent in vacuo, and bulb-to-bulb distillation (80 °C at 0.5 mm Hg) provided 0.64 g (75%) of colorless liquid triflate **2b**: GLC chromatogram, one peak, t_R = 7.39 min (column 1, carrier gas H_2, 0.95 mL/min, programming 60 °C (2-min hold, then 10 °C/min); NMR (200 MHz, $CDCl_3$) δ 2.31 (quintet, 2, J = 6.4 Hz, CH_2CH_2I), 3.26 (t, 2, J = 6.4 Hz, CH_2I), 4.64 (t, 2, J = 5.9 Hz, CH_2O); mass spectrum (70 eV), m/z (relative intensity) 318 (M^+, 2), 191 (65), 99 (26), 69 (85), 41 (100).

1-Bromo-2-fluoroethane (3a). Method A. 2-Bromoethyl triflate (**1a**) (2.63 mg, 10 μmol) was added to 50 μL of a 0.2 M solution of tetrabutylammonium fluoride trihydrate ($nBu_4NF{\cdot}3H_2O$, 10 μmol) in o-DCB in a sample vial (3 mL). After the reaction had been stirred for 2 min, an aliquot was removed, passed through a tiny silica gel column and washed with 50 μL of o-DCB. The GLC chromatogram of this solution gave two peaks (column 1, carrier gas H_2, 0.95 mL/min, programming 30 °C (2 min hold, then 10 °C/min); t_R = 1.81 min (**3a**), t_R = 8.99 min (o-DCB)). The authentic sample of **3a** made by bromofluorination of ethylene had the same retention time. Because of the low boiling point (lit. 71.5 °C at 754 torr),[14] **3a** could not be isolated on this reaction scale; it was used directly as a solution in the one-pot alkylation reaction.

Method B. 2-Bromoethyl triflate (**1a**) (5.7 mg, 20 μmol) was added to 0.5 mL of a 0.02 M solution of tetrabutylammonium fluoride trihydrate ($nBu_4NF{\cdot}3H_2O$, 20 μmol) in CD_3CN in a 5-mm NMR tube. The tube was shaken, and the NMR spectrum was obtained within 2 min. All peaks of CH_2OTf had disappeared, and two new doublet–triplet peaks for CH_2Br and CH_2F appeared at δ 3.64 (dt, 2, J = 26.0, 4.9 Hz, CH_2Br), 4.67 (dt, 2, J = 52.0, 5.1 Hz, CH_2F).

1-Bromo-3-fluoropropane (4a). **4a** was prepared by the same method as for **3a**: GLC chromatogram, t_R = 2.14 min, column 1, carrier gas H_2, 0.95 mL/min, programming 60 °C (2 min hold, then 10 °C/min; NMR (200 MHz, CD_3CN) δ 3.55 (t, 2, J = 6.7 Hz, CH_2Br), 4.56 (dt, 2, J = 47.4, 5.8 Hz, CH_2F).

1-Fluoro-3-iodopropane (4b). **4b** was prepared by the same method as for **3a**: GLC chromatogram, t_R = 4.10 min (column 1, carrier gas H_2, 0.95 mL/min, programming 30 °C (2 min hold, then 10 °C/min); NMR (200 MHz, CD_3CN) δ 3.32 (t, 2, J = 6.7 Hz, CH_2I) 4.49 (dt, 2, J = 47.4, 5.5 Hz, CH_2F).

1-Bromo-2-fluoroalkanes 6a–d. The procedures for the preparation and characterizations of **6a** and **6d** were described in a previous paper.[5] 1-Bromo-2-fluorobutane (**6b**) was prepared according to the same procedure as **6a**: colorless oil (yield, 45%); NMR (200 MHz, $CDCl_3$) δ 1.01 (t, 3, J = 7.5 Hz, CH_3), 1.69–1.87 (m, 2, CH_2CH_3), 3.48 (dd, 2, J = 19.8, 5.7 Hz, CH_2Br), 4.63 (dquin, 1, J = 47.2, 5.7 Hz, CHF); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ –179.25 (dtt, 1, J = 47.4, 22.6, 19.7 Hz); mass spectrum (70 eV), m/z (rel intensity) 156 (M^+, 16), 154 (M^+, 16), 75 (69), 61 (59), 55 (100). Anal. Calcd for C_4H_8BrF: C, 30.99; H, 5.20; Br, 51.55. Found:

(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(14) Pattison, F. L. M.; Peters, D. A. V.; Dean, F. H. *Can. J. Chem.* **1965**, *43*, 1689.

C, 31.27; H, 5.15; Br, 41.70. 1-Bromo-2-fluoropentane (**6c**) was prepared by the same procedure as **6d**: colorless oil (yield, 50%); NMR (200 MHz, $CDCl_3$) δ 0.97 (t, 3, J = 7.1 Hz, CH_3), 1.39–1.80 (m, 4, $CH_2CH_2CH_3$), 3.48 (dd, 2, J = 19.9, 5.7 Hz, CH_2Br), 4.66 (dquin, 1, J = 47.5, 5.7 Hz, CHF); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ −178.54 (dtt, 1, J = 47, 23, 20 Hz); mass spectrum (70 eV), m/z (rel intensity) 170 (M^+, 6), 168 (M^+, 6) 155 (2), 153 (2), 69 (100). Anal. Calcd for $C_5H_{10}BrF$: C, 35.53; H, 5.96; Br, 47.27. Found: C, 35.48; H, 5.97; Br, 47.31.

General Procedure for the Two-Step/One-Pot Reaction: Fluoride Ion Displacement–N-Fluoroalkylation of Spiperone. A Reacti-Vial (1 mL) was charged with 100 μL of 0.2 M solution of $nBu_4NF{\cdot}3H_2O$ (20 μmol) in *o*-DCB or THF. To this solution, ω-haloalkyl triflate **1** or **2** (20 μmol) was added. After the solution was stirred at 25 °C for 2 min, spiperone (**7**, 10 mg, 20 μmol) and an aqueous solution of nBu_4NOH (150 μL, 0.4 M solution, 60 μmol) were added; the vial was closed tightly, and was placed in an oil bath at 110 °C. After 30 min, the reaction was quenched with CH_2Cl_2 and then passed through a Na_2SO_4 column. The solvent was removed in vacuo, and the residue was subjected to flash chromatography (silica gel, EtOH (1% NH_4OH)/benzene 1:10), preparative TLC (silica gel, 20 cm × 20 cm, EtOH (1% NH_4OH)/benzene 1:10), or preparative HPLC (CH_2Cl_2/MeOH (1% NH_4OH) 97:3, 10 mm × 50 cm, Alltech), to yield the N-alkylated products **8a** or **8b** (70–80%) and O-alkylated products **9a** or **9b** (10–17%) as very viscous pale yellow oils.

3-*N*-(2-Fluoroethyl)spiperone (8a). **8a** was prepared according to the general procedure of N-alkylation of spiperone for the two-step/one-pot reaction, and was formed together with the O-alkylated product **9a** (8-[4-(4-Fluorophenyl)-4-oxobutyl]-1-phenyl-4-(2-fluoroethoxy)-1,3,8-triazaspiro[4.5]dec-3-ene) (**8a**:**9a** = 10:1). **8a**: HPLC chromatogram, t_R = 16.0 min (column; 10 mm × 50 cm, Partisil M9 Whatman, CH_2Cl_2/MeOH (1% NH_4OH) 97:3 (0–10 min, 3 mL/min; 10–20 min, 4 mL/min)); NMR (360 MHz, $CDCl_3$) δ 1.68 (bd, 2, J = 13.5 Hz); 1.96 (quin, 2, J = 7.2 Hz, $COCH_2CH_2$), 2.50 (t, 2, J = 7.0 Hz, $COCH_2$), 2.55–2.61 (m, 2), 2.76–2.81 (m, 4), 3.02 (t, 2, J = 7.2 Hz, $COCH_2CH_2CH_2N$), 3.74 (dt, 2, J = 4.5, 28.9 Hz, NCH_2CH_2F), 4.65 (dt, 2, J = 4.6, 47.2 Hz, CH_2F), 4.79 (s, 2, NCH_2N), 6.86–6.93 (m, 3), 7.13 (t, 2, J = 8.6 Hz), 7.25 (t, 2, J = 8.7 Hz), 8.03 (dd, 2, J = 5.5, 8.7 Hz); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ −220.89 (tt, 1, J = 46.4, 29.0 Hz, CH_2F), −106.26 (m, 1, aromatic F); mass spectrum (70 eV), m/z (relative intensity) 441 (M^+, 2), 423 (22), 303 (30), 290 (100), 221 (38), 206 (25), 165 (35); exact mass (HR-EIMS) calcd for $C_{25}H_{29}F_3N_3O_2$ 441.2234, found 441.2231. **9a** was characterized as the same as **9b** and had expected ^1H, ^{19}F NMR, and mass spectra.

3-*N*-(3-Fluoropropyl)spiperone (8b). **8b** was prepared according to the general procedure of N-alkylation of spiperone for the two-step/one-pot reaction and was formed together with the O-alkylated product **9b** (8-[4-(4-Fluorophenyl)-4-oxobutyl]-1-phenyl-4-(3-fluoropropoxy)-1,3,8-triazaspiro[4.5]dec-3-ene). (**8b**:**9b** = 10:1). **8b**: HPLC chromatogram, t_R = 16.0 min (column, 10 mm × 50 cm, Partisil M9 Whatman, CH_2Cl_2/MeOH (1% NH_4OH) 97:3 (0–10 min, 3 mL/min; 10–20 min, 4 mL/min)); NMR (360 MHz, $CDCl_3$) δ 1.68 (m, 2), 1.93–2.09 (m, 4), 2.50 (t, 2, J = 7 Hz, $COCH_2$), 2.57–2.62 (m, 2), 2.79–2.83 (m, 4), 3.00 (t, 2, J = 7.0 Hz, $COCH_2CH_2CH_2N$), 3.55 (t, 2, J = 7.0 Hz, $NCH_2CH_2CH_2F$), 4.5 (dt, 2, J = 5.6, 47.0 Hz, CH_2F), 4.69 (s, 2, NCH_2N), 6.83–6.88 (m, 3), 7.12 (t, 2, J = 8.5 Hz), 7.25 (m, 2), 8.01 (dd, 2, J = 5.5, 8.8 Hz); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ −221.43 (tt, 1, J = 47.1, 27.3 Hz, CH_2F), −106.20 (m, 1, aromatic F); mass spectrum (70 eV), m/z (relative intensity) 455 (M^+, 1), 437 (33), 317 (27), 304 (100), 235 (19), 221 (29), 165 (45); exact mass (HR-EIMS) calcd for $C_{26}H_{31}F_2N_3O_2$ 455.2356, found 455.2370. **9b**: HPLc chromatogram, t_R = 12.5 min (same condition as for **8a**); NMR (360 MHz, $CDCl_3$) δ 1.58 (bd, 2, J = 14.4 Hz), 1.96 (quin, 2, J = 7.1 Hz), 2.17 (dt, 2, J = 6.0, 25.6 Hz, OCH_2CH_2F), 2.4–2.6 (m, 4), 2.75–2.95 (m, 6), 3.04 (t, 2, J = 7.1 Hz, $COCH_2$), 4.40 (t, 2, J = 6.1, $OCH_2CH_2CH_2F$), 4.62 (dt, 2, J = 5.8, 47.0 Hz, $OCH_2CH_2CH_2F$), 4.79 (s, 2, NCH_2N), 6.75–6.82 (m, 3), 7.14 (t, 2, J = 5.4, 8.8 Hz); ^{19}F (338 MHz, $CDCl_3$) ϕ −228.18 (tt, 1, J = 47.1, 25.6 Hz, CH_2F); mass spectrum (70 eV), m/z (relative intensity) 455 (M^+, 5), 437 (15), 362 (29), 304 (45), 301 (50), 247 (17), 222 (48), 206 (18), 165 (100), 149 (28), 123 (89); exact mass (HR-EIMS) calcd for $C_{26}H_{31}F_2N_3O_2$ 455.2384, found 455.2392.

3-*N*-(2-Fluoropropyl)spiperone (8c). Spiperone (**7**, 20 mg, 50 μmol), 2-fluoro-1-iodopropane (**6e**, 14.3 mg, 75 μmol) in *o*-DCB (200 μL) and *n*-Bu_4NOH (0.4 M soln, 200 μL, 80 μmol) were placed into Reacti-Vial. The vial was heated to 110 °C for 30 min with vigorous stirring. The reaction was worked up as in the general procedure for the displacement–N-alkylation of spiperone, yielding **8c** as a very viscous pale yellow oil (16 mg, 70% with O-alkylated side product). **8c**: t_R = 14.8 min (10 mm × 50 cm, Partisil M9 Whatman, CH_2Cl_2/MeOH (1% NH_4OH) 97:3 (0–10 min, 3 mL/min; 10–20 min, 4 mL/min)); NMR (360 MHz, $CDCl_3$) δ 1.38 (dd, 3, J = 23.8, 7.1 Hz, CH_3), 1.67 (bd, 2, J = 13 Hz), 1.96 (quin, 2, J = 7.1 Hz), 2.5 (t, 2, J = 7.1 Hz, $COCH_2$), 2.50–2.64 (m, 2), 2.73–2.90 (m, 4), 3.01 (t, 2, J = 7.2 Hz, $COCH_2CH_2CH_2N$), 3.4–3.8 (m, 2, NCH_2CHF), 4.79 (dd, 2, J = 19.2, 4.7 Hz, NCH_2N), 4.8–5.0 (dm, 1, J = 48.9 Hz CHF), 6.85–6.92 (m, 3), 7.13 (t, 2, J = 8.6 Hz), 7.25 (t, 2, J = 7.9 Hz), 8.02 (dd, 2, J = 5.4, 8.8 Hz); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ −175.34 (m, 1, CH_2F), −106.17 (m, 1, aromatic F); mass spectrum (70 eV), m/z (relative intensity) 455 (M^+, 2), 437 (28), 317 (26), 304 (100), 206 (33), 165 (54), 123 (80), 42 (99); exact mass (HR-EIMS) calcd for $C_{26}H_{31}F_2N_3O_2$ 455.2384, found 455.2392.

3-*N*-(2-Fluorobutyl)spiperone (8d). **8d** was prepared by the same method as **8c**. **8d**: HPLC chromatogram, t_R = 14.7 min (same conditions as for **8a**); NMR (360 MHz, $CDCl_3$) δ 1.04 (t, 3, J = 7.5 Hz, CH_3), 1.62–1.76 (m, 4), 1.96 (quin, 2, J = 7.1 Hz), 2.50 (t, 2, J = 7.1 Hz, $COCH_2$), 2.54–2.64 (m, 2), 2.76–2.82 (m, 4), 3.01 (t, 2, J = 7.2 Hz, $COCH_2CH_2CH_2N$), 3.43–3.79 (m, 2, NCH_2CHF), 4.57–4.75 (dm, 1, J = 49.5 Hz, CHF), 4.78 (dd, 2, J = 24.3, 4.5 Hz, HCH_2N), 6.85–6.91 (m, 3), 7.13 (t, 2, J = 8.6 Hz), 7.25 (t, 2, J = 8.0 Hz), 8.02 (dd, 2, J = 5.4, 8.8 Hz); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ −182.85 (m, 1, CHF), −106.24 (m, 1, aromatic F); mass spectrum (70 eV), m/z (relative intensity) 469 (M^+, 2), 451 (41), 331 (28), 318 (100), 273 (11), 261 (16), 249 (15), 221 (33), 206 (38), 165 (46), 149 (18), 135 (28), 123 (63), 98 (57); exact mass (HR-EIMS) calcd for $C_{27}H_{33}F_2N_3O_2$ 469.2541, found 469.2535.

3-*N*-(2-Fluoropentyl)spiperone (8e). **8e** was prepared by the same method as **8c**. **8e**: HPLC chromatogram, t_R = 14.5 min (same conditions as for **8a**); NMR (300 MHz, $CDCl_3$) δ 0.96 (t, 3, J = 7.1 Hz, CH_3), 1.40–1.73 (m, 6), 1.96 (quin, 2, J = 7.0 Hz), 2.49 (t, 2, J = 7.1 Hz, $COCH_2$), 2.56–2.59 (m, 2), 2.81 (m, 4), 3.01 (t, 2, J = 7.2 Hz, $COCH_2CH_2CH_2N$), 3.41–3.80 (m, 2), 4.62–4.84 (m, 3), 6.84–6.96 (m, 3), 7.13 (t, 2, J = 8.6 Hz), 7.25 (t, 2, J = 8.0 Hz), 8.03 (dd, 2, J = 8.8, 5.6 Hz); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ −182.18 (m, 1, CHF), −106.24 (m, 1, aromatic F); mass spectrum (70 eV), m/z (relative intensity) 483 (M^+, 1), 465 (43), 345 (29), 332 (100), 275 (19), 273 (13), 263 (19), 221 (37), 206 (48), 203 (10), 165 (53), 135 (35), 123 (91); exact mass (HR-EIMS) calcd for $C_{28}H_{35}F_2N_3O_2$ 483.2698, found 483.2690.

3-*N*-(2-Fluorohexyl)spiperone (8f). **8f** was prepared by the same method as **8c**. **8f**: HPLC chromatogram, t_R = 14.5 min (same conditions as for **8a**); NMR (360 MHz, $CDCl_3$) δ 0.92 (t, 3, J = 7.1 Hz, CH_3), 1.1–1.8 (m, 8), 2.02 (quin, 2, J = 7.2 Hz), 2.3–3.1 (m, 10), 3.55–3.85 (m, 2), 4.55–4.90 (m, 3), 6.8–7.0 (m, 3), 7.13 (t, 2, J = 8.5 Hz), 7.27 (t, 2, J = 8.1 Hz), 8.03 (dd, 2, J = 5.4, 8.8 Hz); ^{19}F NMR (338 MHz, $CDCl_3$) ϕ −181,68 (m, 1, CHF), −106.19 (m, 1, aromatic F); mass spectrum (70 eV), m/z (relative intensity) 497 (M^+, 1), 479 (42), 359 (27), 346 (100), 289 (15), 221 (41), 206 (47); exact mass (HR-EIMS) calcd for $C_{29}H_{37}F_2N_3O_2$ 497.2854, found 497.2846.

General Procedure for the Two-Step/One-Pot Reaction: Displacement–N-Alkylation of 1-Phenylpiperazine. To a 0.2 M solution of *n*-$Bu_4NF{\cdot}3H_2O$ (20 μmol) in CH_3CN, *o*-DCB, or THF (50 μL) in a Reacti-Vial (1 mL) was added ω-haloalkyl triflate **1** or **2** (20 μmol). The reaction was stirred at 25 °C for 2 min. To this solution, 1-phenylpiperazine (**10**, 3.2 mg, 40 μmol) was added, and the reaction was heated at 120 °C for 30 min. The reaction mixture was either analyzed by GLC and NMR with internal standards (added at the end of the reaction, 1-pentyl-4-phenylpiperazine for GLC and *p*-chloroacetophenone for NMR) or, it was processed to isolate the products (diluted with Et_2O and dried (Na_2SO_4), then subjected to flash chromatography (silica gel, EtOAc/benzene/Et_3N 80:19:1)) yielding 1-(ω-fluoroalkyl)-4-phenylpiperazine **11a** or **11b** (50–60%).

1-(2-Fluoroethyl)-4-phenylpiperazine (11a). The reaction was performed same as the general procedure for the N-alkylation

of 1-phenylpiperazine from **1a** (129 mg, 500 μmol), n-$Bu_4NF{\cdot}3H_2O$ (158 mg, 500 μmol), and **10** (178.5 mg, 1.1 mmol). The reaction was diluted with Et_2O and dried (Na_2SO_4), and then the residue was subjected to flash chromatography (silica gel, EtOAc/benzene/Et_3N 80:19:1), yielding **11a** as a light yellow oil (56 mg, 54%): NMR (360 MHz, $CDCl_3$) δ 2.68–2.73 (m, 5, 4 H; $(CH_2)_2$-NCH_2 + 1 H; NCH_2CH_2F), 2.79 (t, 1, J = 4.9 Hz, NCH_2CH_2F), 3.22 (t, 4, J = 5.0 Hz, $(CH_2)_2NPh$), 4.57 (dt, 2, J = 4.8, 47.7 Hz, CH_2F), 6.83–6.95 (m, 3, aromatic), 7.23–7.28 (m, 2, aromatic); ^{19}F NMR (338 MHz, $CDCl_3$) φ −218.52 (tt, 1, J = 47.7, 28.6 Hz); mass spectrum (70 eV), m/z (relative intensity) 222 (M^+, 50), 202 (27), 175 (92), 160 (17), 132 (76), 105 (58), 42 (100). Anal. Calcd for $C_{12}H_{17}FN_2$: C, 69.20; H, 8.23; F, 9.12; N, 13.45. Found: C, 68.98; H, 8.33; F, 8.96; N, 13.34.

1-(3-Fluoropropyl)-4-phenylpiperazine (11b). The reaction was performed according to the same procedure as **11a** from **10** and **2a** (136 mg, 500 μmol), yielding **11b** as a light brown yellow oil (60 mg, 54%): GLC chromatogram, t_R = 9.54 min (column 2, carrier gas H_2, 0.95mL/min, isothermal 180 °C); NMR (350 MHz, $CDCl_3$) δ 1.83–2.00 (dm, 2, J = 25.6 Hz, $NCH_2CH_2CH_2F$), 2.52 (t, 2, J = 7.4 Hz, $NCH_2CH_2CH_2F$), 2.60 (t, 4, J = 5.0 Hz, $(CH_2)_2NCH_2$), 3.19 (t, 4, J = 5.0 Hz, $(CH_2)_2NPh$), 4.57 (dt, 2, J = 6.0, 47.2 Hz, CH_2F), 6.82–6.93 (m, 3), 7.23–7.27 (m, 2); ^{19}F NMR (338 MHz, $CDCl_3$), φ −220.52 (tt, 1, J =47.3, 25.4 Hz); mass spectrum (70 eV), m/z (relative intensity) 222 (M^+, 95), 175 (100), 147 (16), 132 (44), 105 (51), 70 (63). Anal. Calcd for $C_{13}H_{19}FN_2$: C, 70.24; H, 8.61; F, 8.54; N, 12.60. Found: C, 70.30; H, 8.58; F, 8.35; N, 12.56.

1-(2-Fluoropropyl)-4-phenylpiperazine (11c). A mixture of finely powdered KI (498 mg, 3 mmol) and K_2CO_3 (414 mg, 3 mmol) was placed into a Reacti-Vial. 1-Phenylpiperazine (487 mg, 3 mmol) and a solution of 1-bromo-2-fluoropropane (423 mg, 3 mmol) in 1 mL of acetonitrile were added. The mixture was stirred at 120 °C for 25 min. The reaction was quenched with water and extracted with ether. The organic extract was washed with water and dried (Na_2SO_4). The GLC chromatogram of this solution gave two peaks (Column 2, carrier gas H_2, 0.95 mL/min, isothermal 180 °C, t_R = 5.05 min (**10**, trace), t_R = 7.55 min (**11c**, 99%)). Removal of the solvent and flash chromatography (40% EtOAc in hexane) yielded **11c** as a pale yellow oil (520 mg, 78.1%): NMR (200 MHz, $CDCl_3$) δ 1.35 (dd, 3, J = 23.6, 6 Hz, CH_3), 2.37–2.72 (m, 6, $(CH_2)_3N$), 3.19–3.24 (m, 4, $(CH_2)_2N$), 4.90 (dm, 1, J = 50 Hz, CHF), 6.81–6.95 (m, 3, aromatic), 7.22–7.30 (m, 2, aromatic); ^{19}F NMR (338 MHz, $CDCl_3$) φ −174.15 (dtq, 1, J = 49, 25, 18 Hz); mass spectrum (70 eV), m/z (relative intensity) 222 (M^+, 50), 202 (27), 175 (92), 160 (17), 132 (76), 105 (58), 42 (100). Anal. Calcd for $C_{13}H_{19}FN_2$: C, 70.24; H, 8.61; F, 8.55; N, 12.60. Found: C, 70.00; H, 8.47; F, 8.58; N, 12.71.

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Registry No. **1a**, 103935-47-3; **2a**, 103935-48-4; **2b**, 106114-40-3; **3a**, 762-49-2; **4a**, 352-91-0; **4b**, 462-40-8; **5b**, 106-98-9; **5c**, 109-67-1; **6a**, 1871-72-3; **6b**, 1871-73-4; **6c**, 106114-41-4; **6d**, 1871-74-5; **7**, 749-02-0; **8a**, 106114-42-5; **8b**, 106114-44-7; **8c**, 106114-46-9; **8d**, 106114-47-0; **8e**, 106114-48-1; **8f**, 106114-49-2; **9a**, 106114-43-6; **9b**, 106114-45-8; **10**, 92-54-6; **11a**, 106114-50-5; **11b**, 106114-51-6; **11c**, 106114-52-7; $HO(CH_2)_3I$, 627-32-7; $BrCH_2CHFCH_3$, 1871-72-3; $HO(CH_2)_2Br$, 540-51-2; $Br(CH_2)_3OH$, 627-18-9; ICH_2CHFCH_3, 20174-93-0.

Notes

Use of Aryltrimethylgermanium Substrates for Facile Aromatic Chlorination, Bromination, and Iodination

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The prevalence of halogenated compounds in medicinal chemistry[1] and radiopharmaceutical chemistry[2,3] has generated a need for synthetic methods that yield a single halogenated product and avoid the necessity of separating isomeric mixtures. Silicon[4,5] and tin[6,7] have been used for many years in organic syntheses to direct the specificity of electrophilic reactions, and ipso substitution of aromatic carbon–silicon and –tin bonds has been used to regiospecifically introduce halogens onto aromatic rings. Although both silylated and stannylated arenes have been successfully applied for this purpose, these fourth-group organometallics suffer from various synthetic disadvantages. When silylated arenes are used as halogenation substrates, electron-donating substituents are generally required for high halogenodesilylation yields,[8-11] and in those aromatic rings that are relatively activated toward electrophiles, halogenodeprotonation products predominate.[10,12] Halogenation of stannylated arenes, on the other hand, results in regiospecific substitution of the tin group on aromatic rings that are activated or deactivated toward electrophiles,[13-15] but the great sensitivity of the carbon–tin bond to protolysis[16] or alkaline hydrolysis[17] limits the synthetic utility of this technique.

The intermediate group IVB (group 14)[32] element germanium has a greater covalent radius[18] and a lower car-

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