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Preparation of *o*-Fluorophenols from Nonaromatic Precursors: Mechanistic Considerations for Adaptation to Fluorine-18 Radiolabeling

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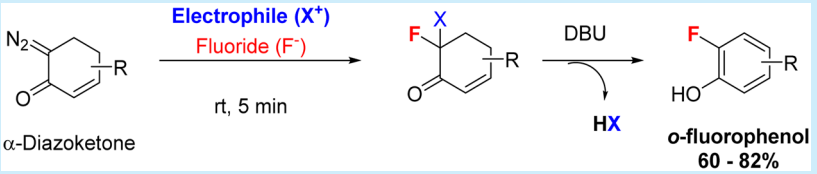
Supporting Information



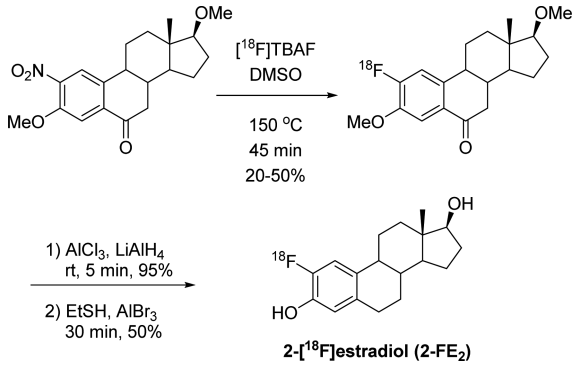
ABSTRACT: The preparation of fluorine-18 labeled *o*-fluorophenols at high specific activity is challenging and requires use of [^{18}F]fluoride ion as the radioisotope source. As a novel, alternative approach, we found that treatment of α-diazocyclohexenones with Selectfluor and $Et_3N{\cdot}3HF$ followed by HF elimination and tautomerization afforded *o*-fluorophenols regioselectively and rapidly. To adapt this chemistry to ^{18}F radiolabeling, using bromine electrophiles in place of Selectfluor gave the *o*-fluorophenol via an α-bromo-α-fluoroketone intermediate in lower but still reasonable yields.

Many phenolic functions in drugs are substituted with fluorine, particularly at the *ortho* position, because this often enhances in vivo potency by increasing receptor target binding affinity and/or retarding metabolism.[1] An interesting example is 2-fluoroestradiol, whose fluorine-18 radiolabeled version has the potential to be a better radiotracer for positron emission tomographic (PET) imaging than widely used 16α-[^{18}F]fluoroestradiol (FES) due to its enhanced binding to a serum steroid carrier protein. In any case, fluorine substitution is either beneficial to bioactivity or, in the worst case, is generally well tolerated and thus potentially suitable for radiolabeling with ^{18}F.

Curiously, conventional fluorination methods of phenols have limited efficiency and selectivity. Common electrophilic fluorinating agents, such as *N*-fluoropyridinium and *N*-fluoroammonium compounds, provide poor regioselectivity and require harsh conditions. For instance, electrophilic fluorination of estradiol produces a mixture of 2- and 4-estradiol, and Selectfluor affords *ipso*-fluoroestradiol as the major product.[2−4]

Nucleophilic substitution on aromatic rings has been studied extensively for ^{18}F radiolabeling of PET radiotracers. There are many methods for labeling small molecules with ^{18}F on electron-deficient aromatic rings, but until recently, there were no reliable and practical methods to label electron-rich aromatic rings, such as phenols, with ^{18}F at high specific activity (SA, i.e., radioactivity per molar mass). Most approaches for ^{18}F labeling of phenols involve labeling electron-poor precursor arenes by nucleophilic aromatic substitution, followed by conversion to phenols; these indirect routes are often inefficient and time-consuming (see Scheme 1).[5] Direct fluorination of phenols with electrophilic fluorinating agents is not optimal for ^{18}F labeling because, when labeled with ^{18}F, such reagents can only be produced using ^{19}F as the carrier, which results in greatly lowered SA.

Scheme 1. 2-Fluoroestradiol and Its Indirect Radiosynthesis



Recently, transition-metal-mediated fluorination of arenes used Pd^{II}-mediated aromatic fluorination by reductive elimination from Ar−Pd^{II}-F intermediates.[6] Subsequently, Ar−F bond formation methods using highly oxidized palladium complexes were reported;[7,8] this was followed by a Ni-mediated

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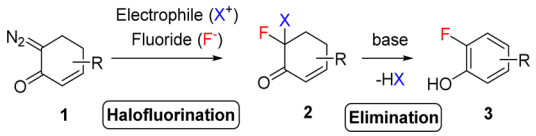
aryl fluorination method.[9] The preparation of the precursors for these methods, however, is troublesome. Recent work has focused on hypervalent iodine compounds (Ar–I^+-Ar′) as precursors for ^{18}F radiolabeling of arenes, but directing [^{18}F]fluoride attack on the proper arene ring is often problematic, although Cu-mediated regioselective fluorination using Mes-I^+-Ar as precursor gives minimum formation of the Mes-F byproduct.[10,11]

Rotstein and co-workers' discovery of spirocyclic iodonium ylides as stable precursors appears to be a more practical approach for ^{18}F radiolabeling on aromatic rings.[12] However, this method still requires prior phenol protection and then deprotection to obtain the *o*-fluorophenol; acid-sensitive functional groups are not stable under most deprotection conditions. Thus, novel approaches to produce fluorophenols efficiently, rapidly, conveniently, and adaptable to ^{18}F labeling, are still needed.

Herein, we report a novel and rapid method to prepare *o*-fluorophenols regioselectively with minimum transformation after fluorine incorporation using α-diazocyclohexenones as precursors. Diazo compounds are known to react with various electrophiles, including *N*-bromosuccinimide (NBS) and HF-pyridine,[13,14] PhSeX[15] and $PhIX_2$,[14,16] forming C–F bonds α to the carbonyl group. Therefore, by starting from α-diazocyclohexenone, we thought that halofluorination would afford an α-halo-α-fluoroketone that would undergo hydrohalide elimination followed by tautomerization to produce the fluorinated electron-rich arene *o*-fluorophenol (Scheme 2). Notably, even

Scheme 2. Strategy for *o*-Fluorophenol Preparation from an α-Diazoketone

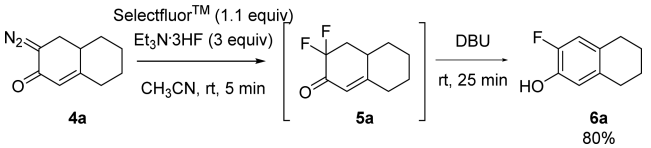


though the starting material is a nonaromatic precursor, the oxidation state of the α-diazocyclohexenone is the same as *o*-fluorophenol, so these transformations involve no oxidation or reduction. Thus, the overall reaction conditions are potentially mild with a likelihood of good functional group tolerance.

We chose α-diazocyclohexenone **4a** as a model substrate because it mimics the AB ring system of estradiol and can be readily prepared by Robinson annulation of cyclohexanone with methyl vinyl ketone, followed by α-activation with a trifluoroacetyl group and diazo transfer from methanesulfonyl azide (see the Supporting Information).[17] This substrate turned out to be stable for at least 6 months at low temperature in the dark.

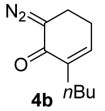
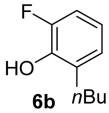
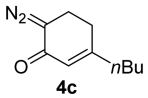
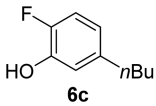
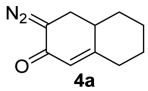
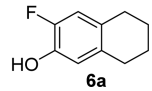
Diazoketone **4a** reacted with Selectfluor in the presence of $Et_3N{\cdot}3HF$, producing α,α-difluoroketone **5a** followed by HF elimination promoted by DBU to produce *o*-fluorotetralol **6a** in a good yield (Scheme 3). This sequence of two reactions proceeded rapidly (5 and 25 min, respectively) and efficiently

Scheme 3. *o*-Fluorophenol from an α-Diazoketone



(80% overall yield). The substrate scope is shown in Table 1. *o*- and *m*-butyl-α-diazocyclohexenone also produced the corresponding *o*-fluorophenols as well.

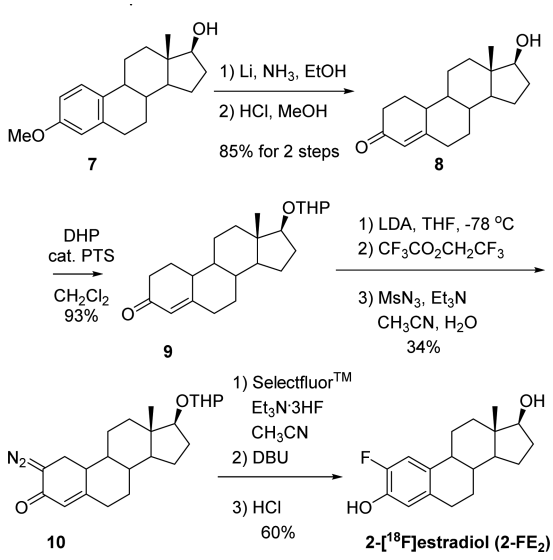
Table 1. Substrate Scope for *o*-Fluorophenol Synthesis from α-Diazoketones Using Selectfluor[a]

entry	substrate	product	yield (%)[b]
1	 **4b**	 **6b**	82 (75)
2	 **4c**	 **6c**	72 (63)
3[c]	 **4a**	 **6a**	60 (58)

[a]Conditions: Selectfluor (1.2 equiv), $Et_3N{\cdot}3HF$ (2 equiv), CH_3CN (0.1 M), rt, 5 min; DBU (1.5 equiv), rt, 25 min. [b]Yields determined by ^{1}H and ^{19}F NMR; isolated yields are in parentheses. [c]Without $Et_3N{\cdot}3HF$.

2-Fluoroestradiol could also be prepared from the corresponding diazoketone efficiently and selectively (Scheme 4). 3-

Scheme 4. Synthesis of 2-Fluoroestradiol



Methylestradiol **7** underwent Birch reduction to 1,4-diene, and acid hydrolysis/isomerization gave α,β-unsaturated ketone **8**. After protection of the C-17 OH as the THP ether the diazo function was introduced as previously described.

The resulting diazoketone precursor **10** was readily converted by Selectfluor to the corresponding α,α-difluoroketone, and following DBU treatment and a rapid acidic deprotection of the THP group, 2-fluoroestradiol was obtained in a good yield. It is notable that because the diazo function directs the site of reaction, this method produces no other isomers whereas conventional electrophilic fluorination methods give in many cases mixtures of regioisomers that are troublesome to separate.

Our ultimate application is to develop an ^{18}F-labeling method suitable for the preparation of *o*-[^{18}F]fluorophenols at high SA,

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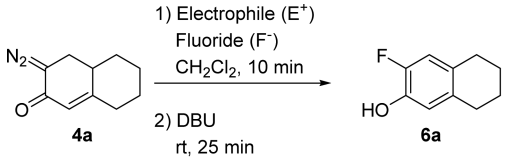
and for this purpose, it is not suitable to use fluorine electrophiles due to their low SA, mentioned previously. Thus, in our search for nonfluorine-containing electrophiles that could ultimately be partnered with [^{18}F]fluoride ion, we investigated the electrophile scope of this reaction, focusing on those containing bromine, chlorine, and iodine (Table 2; see also Table S1). For these studies, the halofluorination and elimination reactions were done in one pot.

Table 2. *o*-Fluorophenol Synthesis from an *α*-Diazoketone Precursor



11: R_1 = X, R_2 = H
12: R_1, R_2 = X

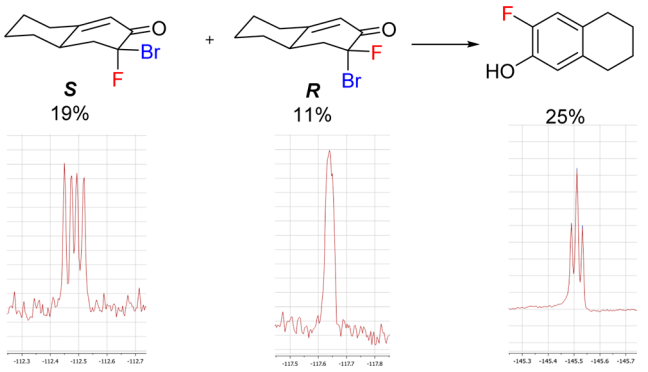
			yield[a] (%)		
entry	E^+ (X)	fluoride	**6a**	**11**	**12**
1	NBA	$Et_3N{\cdot}3HF$	17	4	59
2	DBDMH	$Et_3N{\cdot}3HF$	14	5	66
3	NCS	$Et_3N{\cdot}3HF$	0	100	0
4	NIS	$Et_3N{\cdot}3HF$	0	43	11
5	I_2	$Et_3N{\cdot}3HF$	0	100	0
6[b]	NBA	Pyr·9HF	14	20	68
7[b]	DBDMH	Pyr·9HF	27	5	68
8[b]	DBDMH	Pyr·9HF[c]	18	0	82
9[d]	NBA	$Et_3N{\cdot}3HF$	29	42	15
10	DBDMH	TBAF[e]	0	trace	trace
11	DBDMH	TBAF[f]	6	nd	nd

[a]Yields were determined by ^{1}H and ^{19}F NMR. [b]Electrophile and fluoride source were mixed before substrate addition. [c]0.9 equiv of fluoride was used. [d]Electrophile was added portionwise at 0 °C. [e]Trihydrate was used without drying. [f]TBAF was dried azeotropically with CH_3CN and *t*-BuOH. nd = not determined.

Bromine electrophiles, such as 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) and *N*-bromoacetamide (NBA) (entries 1 and 2), gave moderate yields of the desired *o*-fluorophenol, using $Et_3N{\cdot}3HF$ as fluoride source. Chlorine or iodine electrophiles did not produce the fluorophenol, giving only other undesired *o*-halophenols byproducts (entries 3–5). As a fluoride source, Pyr·9HF gave similar product yields (entries 6 and 7). However, other fluoride sources typically used in ^{18}F radiolabeling, such as CsF or KF/Kryptofix 222, did not produce any fluoride-containing products (see the SI). Although $TBAF{\cdot}3H_2O$ interfered with reaction of the diazoketone with the electrophile (no N_2 release observed, unreacted starting material recovered) (entry 10), after azeotropic drying, fluorine incorporation was observed. Among the solvents tested, best yields were obtained in CH_2Cl_2 or Et_2O; polar solvents were unsuitable for the formation of the *o*-fluorophenol (see also Table S1). The highest yield was obtained by lowering the reaction temperature and/or portionwise addition of electrophile. Substoichiometric levels of fluoride ion still produced *o*-fluorophenol in comparable yields, which bodes favorably for the effectiveness of this reaction in ^{18}F radiolabeling in which only a trace amount of radiofluoride ion is used together with a large excess amount of substrate and reagents (entry 8). (It is of note that entry 3 of Table 1 shows that *o*-fluorophenol was formed even without added fluoride, $Et_3N{\cdot}3HF$. In this case, the *o*-fluorophenol was formed directly, not via the *α*,*α*-difluoroketone, as is discussed in detail later in this paper (Scheme 6, path B).)

Formation of the bromophenol side product was thought to arise from elimination of HF instead of HBr. To investigate this, we tried to isolate the bromofluorination *α*-bromo-*α*-fluoroketone intermediates; however, they proved to be very unstable. Nevertheless, we could quantify the formation of two presumed epimeric intermediates, *R* and *S*, indirectly by ^{19}F NMR using an internal standard. (We are illustrating only one enantiomeric series of the racemic epimers.) These are shown in half-chair conformations, and based on their H–F coupling constants, the one with the larger coupling (*S*, having F axially disposed) is more abundant (19%), and the one with the smaller coupling (*R*, having F disposed equatorially) is less abundant (11%) (Scheme 5).

Scheme 5. Proposed Stereochemistry of Bromofluoroketone Epimers, *S* and *R*, Revealed by ^{19}F NMR



We expected that elimination of hydrogen halide from these epimeric bromofluoroketones would proceed by an E2 process, following strict antiperiplanar geometry, with *R* losing HBr and *S* losing HF. Consequently, we anticipated that the yield of the fluorophenol could not exceed that of epimer *R* having bromine axially disposed (namely 11%). The fact that the fluorophenol is obtained in 25% yield, which is 14% greater than the amount of epimer *R* present, indicates, surprisingly, that a substantial amount of product is coming from the *S* epimer. Thus, it appears that the more abundant epimer (*S*) is able to access an alternate, half-twist chair conformer in which H and Br approach an antiperiplanar geometry.

We explored this possibility through careful energy calculations of both the half-chair and half-twist chair conformations of both the *R* and *S* epimers (see details in SI). Indeed, the energies of the half-chair and twist-chair conformers of the *S* epimer differ by less than 1 kcal/mol and are separated by a conformational energy barrier of ca. 9 kcal/mol, suggesting that elimination of HBr from this epimer is indeed feasible. By contrast, the twist-chair conformer of the *R* epimer (which would lose HF by an E2 elimination) is ca. 3 kcal/mol higher in energy than the half-chair conformer, making it an unlikely participant in the elimination.

These findings also indicate that HF elimination from the bromofluoroketone intermediates is not the major route for

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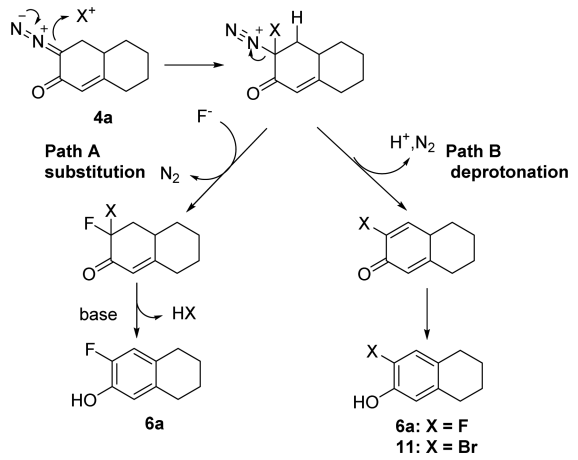
forming the *o*-bromophenol (Scheme 6). In fact, the *o*-bromophenol had already been formed at the bromofluorination

Scheme 6. Proposed Mechanism for Halofluorination/Elimination



step, though no *o*-fluorophenol had yet been produced (see the SI). Thus, the sequence of reactions appears to be somewhat complex: The first step is the attack of Br^+ on the diazo group, giving a highly reactive *α*-bromo-*α*-diazonium intermediate that then rapidly partitions, either with fluoride displacing the diazonium group, giving the epimeric bromofluoroketone intermediates *S* and *R*, or alternatively, by deprotonation at the *β* position, leading directly to the bromophenol. Further bromination forms dibromophenol **12**, presumably by a conventional electrophilic aromatic bromination. This sequence of events also explains why no bromofluorophenol was observed, and in the reactions with Selectfluor, the *o*-fluorophenol was formed without added fluoride ion, as noted earlier (entry 3, Table 1).

In summary, *α*-diazoketones are of considerable interest as direct precursors of *o*-fluorophenols for two reasons: (a) the *o*-fluorophenols can be obtained efficiently, regioselectively, and under mild conditions by using Selectfluor, and (b) the *o*-fluorophenols can also be obtained using bromine electrophiles and fluoride ion, conditions that are potentially suitable for the preparation of high SA *o*-[^{18}F]fluorophenols. Rapid reactions, in particular, are important for ^{18}F labeling because of the 110 min half-life of fluorine-18. With the diazoketones we have examined, release of N_2 gas is observed immediately after the addition of electrophile, and the subsequent hydrobromide elimination was complete within 25 min, with reactions conducted in a one-pot manner. Most ^{18}F-labeling methods require an elevated reaction temperature, which is not suitable for "late stage fluorination" of complex molecules. Thus, it is fortuitous that our halofluorination from diazoketone reactions can be conducted at as low as 0 °C (Table 2, entry 10). Furthermore, this method is the first example of fluorine incorporation into an electron-rich arene synthesis starting from a nonaromatic precursor. Therefore, it holds potential for expanding the synthesis of PET tracers of interest in biological studies and drug development. Our efforts are underway to apply this halofluorination/elimination strategy for ^{18}F radiolabeling of biologically important radiotracers, such as 2-[^{18}F]fluoroestradiol. Irrespective of its ultimate utility for ^{18}F labeling, however, this method for producing *o*-fluorophenols from *α*-diazocyclohexanones is valuable for introducing ^{19}F into phenols where regioselectivity and mild conditions are required.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02640.

Complete experimental details and relevant spectra for all important compounds (PDF)

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Notes

The authors declare no competing financial interest.

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