# Heterocycles

Halogen Exchange (Halex) Reaction of 5-Iodo-1,2,3-triazoles: Synthesis and Applications of 5-Fluorotriazoles**

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Fluorinated molecules are omnipresent in pharmaceuticals and agrochemicals,[1] materials,[2] and as imaging agents for positron emission tomography (PET) scanning.[3] PET imaging has become a widely used technique in medical diagnostics in recent years. This method requires the use of a fluorine-containing agent enriched with the ^{18}F nucleus. This fluorine isotope has a notoriously short half-life of 109 minutes, thus imposing strict requirements for the speed and operational simplicity of reactions used for its introduction into imaging probes. Considerations of cost and practicality demand that the fluorine is derived from simple fluoride salts (such as KF and NaF). While methods for the late-stage introduction of fluorine into complex molecules have been reported,[4] a new robust process would be a useful addition to the developing field of medical imaging, especially in light of the growing use of the CuAAC (see below).

The copper(I)-catalyzed azide–alkyne cycloaddition reaction[5] (CuAAC; Scheme 1a) has emerged as a powerful method for the creation of covalent links between diverse
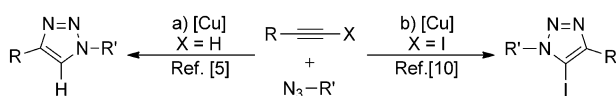

Scheme 1. Routes to various substituted 1,2,3-triazoles.

building blocks. The experimental simplicity and robust nature of 1,2,3-triazole products have enabled numerous applications of this process in synthetic and medicinal chemistry,[6] bioconjugations,[7] materials science,[8] and polymer chemistry.[9] Medical imaging has also benefited from this process, and a number of probes containing 1,2,3-triazoles have been described.[10] However, none of them rely on the introduction of the fluorine atom directly appended to the triazole heterocycle.

Recently, our group has reported the use of 1-iodoalkynes as active cycloaddition partners with organic azides for the regiospecific synthesis of 5-iodo-1,2,3-triazoles (Scheme 1 b).[11] With a simple route to these halogenated heterocycles in hand, we were interested in expanding the repertoire

of methods for their postsynthetic functionalization (Scheme 2),[12] specifically the introduction of other halides by a halogen exchange (Halex) reaction.[13] To this end, when
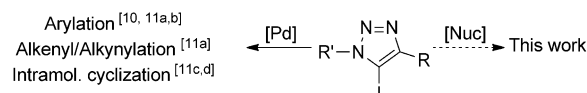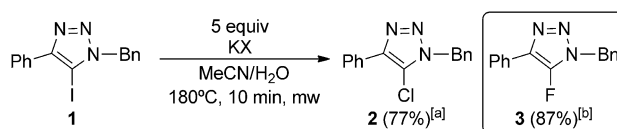

Scheme 2. Postsynthetic functionalization of 5-iodotriazoles.

the iodotriazole 1 was heated in a brine solution at 100 °C over a two-day period, the complete conversion of the starting material into a mixture of the chlorotriazole 2 and the 5-H-1,2,3-triazole (ca. 1:3) was observed. Encouraged by this result, we examined the exchange of different halides under microwave-assisted conditions. We were pleased to discover that 5-chloro- (2) and, most interestingly, 5-fluorotriazoles (3) could be obtained in synthetically useful yields by this method. While several other syntheses of 5-chloro-substituted triazoles exist,[14] we found no reports describing fluorinated (neither 4- nor 5- substituted) triazoles.[15] As a result of their conspicuous absence in the chemical literature and the distinct value of sp²-hybridized fluorine compounds (see below), we focused our studies on this process. Reported herein is a general, rapid, and operationally simple approach for the synthesis of 5-fluoro-1,4,5-trisubstituted-1,2,3-triazoles from the corresponding 5-iodotriazoles and the synthetic application of this unique scaffold to regiospecifically generate previously inaccessible fully substituted triazoles.

Initial survey of the reaction conditions proved that both basic potassium fluoride (KF) and the acidic potassium bifluoride (KHF₂) were effective as the nucleophilic fluoride source (Scheme 3). We were pleased to discover that only 5 equivalents of KF and 7 equivalents of KHF₂ were necessary for this reaction to reach completion. In consideration of both cost and practicality, other fluoride sources were omitted from this study and we instead concentrated on these inexpensive and commercial salts.

The temperature required for this reaction was found to be less forgiving, requiring a minimum of 140 °C for the reaction to be initiated and 180 °C to drive it to completion. A
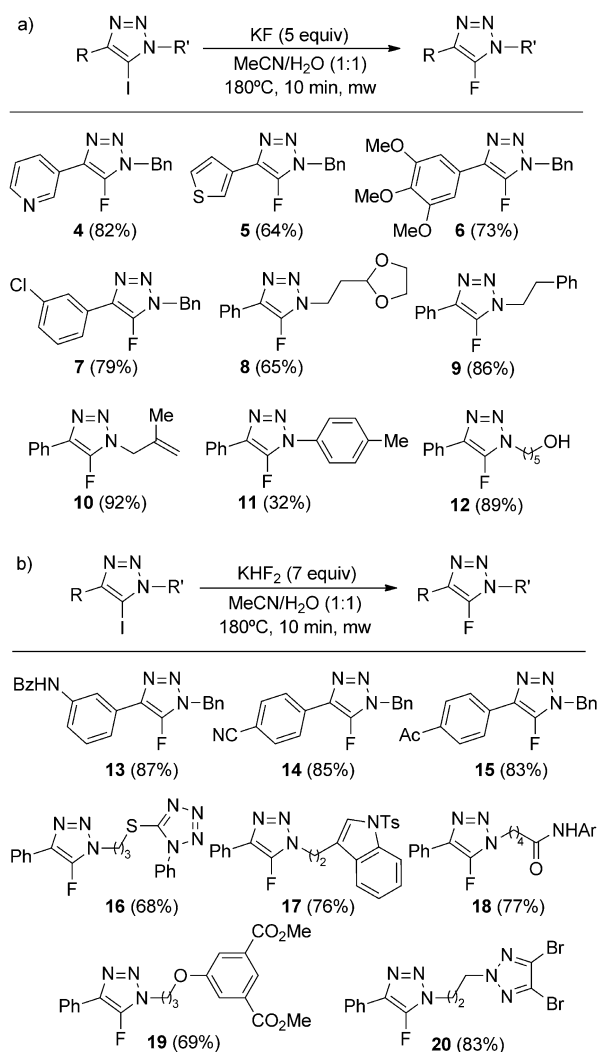
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Scheme 3. Halogen exchange reaction of 1 to give various halogenated 1,2,3-triazoles. [a] Used KCl. [b] Used KF. Values in parentheses represent yields of isolated products. Bn = benzyl.

biphasic solvent mixture of water/acetonitrile (1:1, v/v) was effective and did not require further optimization. The use of various cryptands, crown ethers, and polar aprotic solvents did not accelerate or affect the efficiency of this reaction; the best results were observed utilizing the above biphasic conditions.[16] Short reaction times, only 10 minutes to reach complete conversion, were most effective, while prolonged heating led to decomposition of the product.
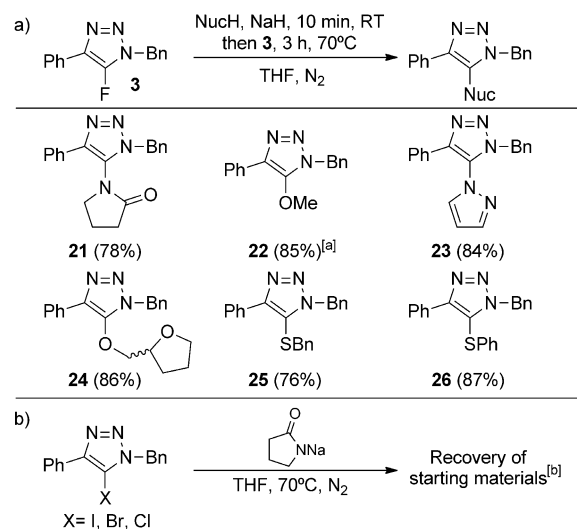
Under these optimized reaction conditions, we screened a large variety of 5-iodo-1,2,3-triazoles for substitution with the fluoride anion. The basic fluoride nucleophile (KF) demonstrated good functional group compatibility: 5-iodotriazoles containing heterocycles (**4** and **5**), chloride (**7**), acetal (**8**), N1-aryl (**11**) and alcohol (**12**) groups were smoothly converted into the corresponding fluorinated products in

excellent yield (Scheme 4a). Utilization of the acidic fluoride salt (KHF$_2$) further expanded compatibility with other functional groups: free amides (**13** and **18**), nitrile (**14**), ketone (**15**), *N*-toluenesulfonyl (**17**), and bis(bromo)triazole (**20**) moieties readily underwent this substitution reaction (Scheme 4b). Both of these complementary procedures produced 5-fluorotriazoles in moderate to excellent yields, and in all cases the starting material was completely consumed. It should be noted that an aromatic group at the 4-position of the triazole is required for an effective transformation to the 5-fluorotriazole product, as aliphatic substituents resulted in complex mixtures of products.[17] Alternatively, triazoles with an aromatic substituent at N1 gave the corresponding 5-fluorotriazole products, albeit in lower yields (e.g., **11**).[18]

With a general method for the synthesis of 5-fluorotriazoles in hand, we examined their reactivity in S$_N$Ar-type reactions to yield fully substituted 1,2,3-triazoles. Indeed, we found that the sodium salts of the amide **20**, alcohols **21** and **23**, azole **22**, and thiols **24** and **25** gave good yields of the 5-substituted triazoles under mild reaction conditions (70 °C) in THF (Scheme 5a). Although S$_N$Ar reactions of S, O, and

Scheme 4. a) Substrate scope for the halogen exchange reaction of 5-iodotriazoles with KF. General reaction conditions with KF: 5-iodotriazole (1 equiv), KF (5 equiv), MeCN/H$_2$O, 180 °C, 10 min. Values in parentheses represent yields of isolated products. b) Substrate scope for the halogen exchange reaction of 5-iodotriazoles with KHF$_2$. General reaction conditions with KHF$_2$: 5-iodotriazole (1 equiv), KHF$_2$ (7 equiv), MeCN/H$_2$O, 180 °C, 10 min. Values in parentheses represent yields of isolated products. Ac = acetyl, Ar = 3,5-bistrifluoromethyl benzene, Bz = benzoyl, Ts = tosyl.

Scheme 5. a) S$_N$Ar reactions of 5-fluorotriazoles. [a] General reaction conditions with NaH: **3** (1 equiv), NuH (1.5 equiv), NaH (1.5 equiv), THF, RT to 70 °C, 15 h. [a] Commercial NaOMe (1.5 equiv) was used instead. b) Unsuccessful S$_N$Ar reactions of 5-iodo-, 5-bromo-, and 5-chlorotriazole analogues of fluorotriazole **3**. [b] No reaction under the general reaction conditions was observed (see the Supporting Information for details). Values in parentheses represent yields of isolated products.

N nucleophiles with 5-chlorotriazoles have been described, they require electron-withdrawing substituents at the 4-position (esters, amides, etc.) and do not proceed with non-activated triazoles (e.g. **1**, **2**).[19] Indeed, when 5-iodo- (**1**), 5-bromo- (**26**), and 5-chlorotriazole (**2**) analogues of the fluorotriazole **3** were reacted under the general S$_N$Ar conditions, only starting materials were recovered (Scheme 5b).

To demonstrate the generality of this method, we used it for the moderate scale synthesis of a complex molecule
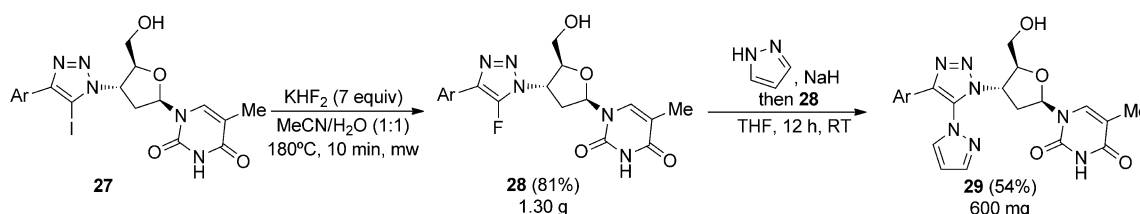
Scheme 6. Large-scale synthesis of the 5-fluorotriazole **28** and the subsequent S_NAr reaction to produce the fully substituted triazole **29**. Values in parentheses represent yields of isolated products. Ar = 4-tBuC$_6$H$_4$.

containing multiple functional groups and several stereogenic centers. To this end, we synthesized the 5-iodotriazole **27**, in high yield and submitted it to the newly developed fluorination reaction with KHF$_2$ (Scheme 6). The fluorinated product **28** was formed in 81% yield on a gram scale. Furthermore, when the flurotriazole **28** was reacted under our reaction conditions for S_NAr with the sodium salt of pyrazole, the fully substituted triazole **29** was obtained in acceptable yield. Thus, this fluorination/substitution sequence could be employed not only as a method for the synthesis of PET tracer molecules, but also as a general route to various previously inaccessible fully substituted triazoles with absolute control of regioisomeric purity.[20]

Interestingly, when different isomers of the triazole **1** (**30** and **31**) were submitted to our general halogen exchange conditions, no fluorinated products were obtained; only starting materials were fully recovered (Scheme 7a). We hypothesize that the observed reactivity of only the 1,4-substituted-5-iodotriazoles (**32**) in this process is its ability to undergo ring-chain isomerization, thus resulting in the formation of a diazo/imidoyl halide tautomer at elevated temperature (**33**). Indeed, imidoyl halides (i.e. **33**) are well known to undergo halogen exchange reactions under similar experimental conditions, specifically for the formation of imidoyl fluorides.[21] Therefore, we postulate that the open diazo form **33** is the intermediate reacting with the fluoride

anion. Thus, the reaction proceeds by the reversible opening of the triazole **32** to the diazo/imidoyl iodide tautomer **33**, reversible addition of the nucleophile (F$^-$) to give putative intermediate **34**, extrusion of the iodide anion giving the intermediate **35**, and final ring closure yielding the 5-fluorotriazole product **36** (Scheme 7b). Similar to other reactions of 1-sulfonyl-1,2,3-triazoles,[22] an aromatic group at C4 of the triazole is necessary for the stabilization of the open diazo form of the heterocycle (**33–35**). An alternative, more familiar S_NAr mechanism, proceeding through an intermediate such as **37** (Scheme 7c), cannot be discounted as a viable pathway at this time.

This work demonstrates that 5-iodotriazoles (e.g., **1**) efficiently engage in the halogen exchange reaction with simple fluoride salts to produce 5-fluorotriazoles (e.g., **3**). This reaction proceeds quickly (10 min), gives bench-stable fluorinated products, and exhibits excellent functional-group tolerance. This previously unreported fluorinated heterocycle is reactive in S_NAr-type transformations under mild reaction conditions and gives the corresponding fully substituted products in excellent yields. In addition to the synthetic utility of these heterocycles, fluorination of iodotriazoles with hot fluoride sources (^{18}F salts) should prove useful in the synthesis of PET imaging probes.
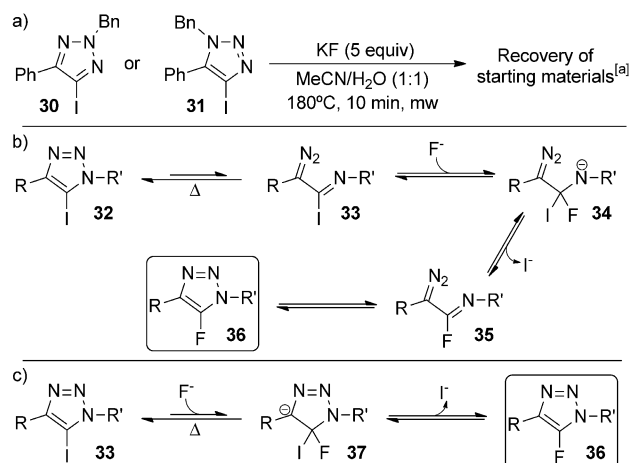
Scheme 7. a) Unsuccessful halogen excahnge reactions of triazole isomers **30** and **31**. [a] No reaction under general reaction conditions was observed (see the Supporting Information for details). b) Proposed mechanism for the halogen exchange reaction of 5-iodotriazoles. c) Alternative proposed mechanism.

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[16] In polar/protic solvents higher concentrations of the open diazo/imine form of the triazole has been observed. This solvent mixture (acetonitrile/water) could likely promote opening of the iodotriazole and further stabilize these intermediates. Even highly solubilized fluoride anions are evidently efficient enough nucleophilies to undergo this substitution reaction. Solvent effects for the reversible opening of triazoles: M. Regitz, G. Himbert, *Tetrahedron Lett.* **1970**, *11*, 2823.

[17] When 5-iodotriazoles bearing ester, amide, perfluoroalkane or other electronically withdrawing groups attached directly to the 4-position were submitted to our general halogen exchange conditions (either KF or KHF_2) intractable reaction mixtures were obtained. When the reaction temperature was lowered, only starting materials were recovered.

[18] The proto-dehalogenated triazole was observed as the main by-product with *N*-1-aryl-5-iodotriaozles.

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