Access to Fluoroalkylated Azoles and 2-Acylaminoketones via Anhydride-Mediated Cleavage of NH-1,2,3-Triazoles

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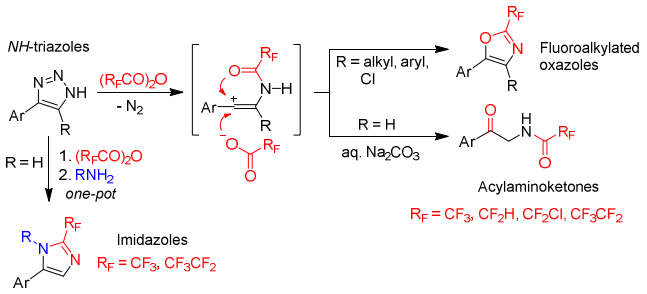
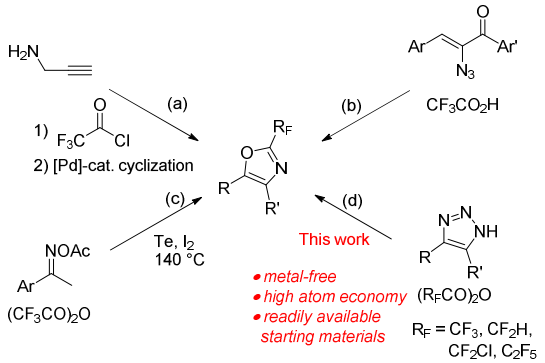
Supporting Information Placeholder



ABSTRACT: NH-1,2,3-Triazoles undergo a ring cleavage in reactions with fluorinated acid anhydrides (trifluoroacetic, difluoroacetic chlorodifluoroacetic and pentafluoropropionic anhydrides) by nitrogen acylation and acid-mediated triazole ring opening. Structurally diverse fluoroalkylated oxazoles were prepared from 4,5-disubstituted-1,2,3-triazoles. Efficient synthesis of 2-acylaminoketones was achieved from 4-substituted-1,2,3-triazoles. Finally, easy access to fluoroalkylated imidazoles and 1,2,4-tetrazines was developed by one-pot two step routes from fluorinated anhydrides and NH-triazoles.

Oxazoles and imidazoles are highly important heterocycles, widely represented in natural alkaloids and pharmaceutical drugs.[1-2] Fluoroalkylated 1,3-azoles are attractive in medicinal chemistry as potential drug candidates with anti-inflammatory,[3-4] anticancer[5] and other[6] biological activities. Moreover, incorporation of a fluoroalkyl moiety is known to significantly enhance the metabolic stability, lipophilicity and bioavailability of azoles.[7-8] Therefore, 2-fluoroalkyloxazoles are attractive targets in synthetic organic chemistry. The most efficient synthetic approaches developed recently are based on Pd-catalyzed cyclization of alkynyl trifluoroacetamides (Scheme 1a),[9-11] reaction of azidochalcones with trifluoroacetic acid (Scheme 1b)[12] and tellurium-mediated annulation of oxime acetates with trifluoroacetic anhydride (TFAA) (Scheme 1c).[13] However, these methods suffer from drawbacks, such as the necessity of using expensive metal catalysts or multistep synthesis of starting substrates. Herein, we report an efficient synthesis of 2-fluoroalkyloxazoles from readily available NH-1,2,3-triazoles and fluorinated acid anhydrides, together with novel approaches to fluorinated 2-acylaminoketones, imidazoles and 1,2,4-triazines.

1,2,3-Triazoles bearing an electron-withdrawing group at N1 have been explored for the last two decades as versatile building blocks for the synthesis of functionalized heterocycles, as well as bioactive molecules.[14-15] In particular, transannulation of N-sulfonyl triazoles catalyzed by Rh(II) is a well-known transformation of triazoles into different nitrogen-containing heterocycles. We have recently reported that transannulation efficiently proceeds for N-fluoroalkylated triazoles,[16-19] which allowed to overcome the limitation of the presence of sulfonyl group. Moreover, a ring cleavage of electron-deficient triazoles in the presence of Brønsted and Lewis acids, proceeding via a vinyl cation intermediate, was reported by our[20-22] and other[23] groups. However, the preparation of N-sulfonyl and N-fluoroalkyl triazoles requires multiple synthetic steps. From this point of view, the utilization of NH-triazoles as building blocks appears highly promising. They are easily available from commercial aldehydes via a one-pot cascade Henry reaction/[3+2]-cycloaddition[24-25] or from terminal alkynes via a click reaction with $TMSN_3$.[26] Last year, the first example of triazole ring transformation starting from NH-triazoles to prepare β-halogenated enamides was reported.[27] N-acyltriazoles[28] are suspected intermediates in this transformation. Inspired by these results, we investigated the possibility of vinyl cation generation from



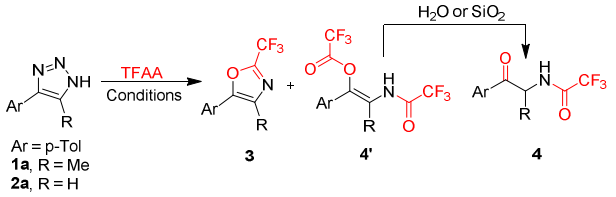
Scheme 1. Approaches to 2-fluoroalkylated oxazoles.

NH-triazoles using fluorinated electrophilic agents. In particular, TFAA is among the strongest acylating agents, which could be potentially applied for the direct synthesis of 2-fluoroalkylated oxazoles from NH-triazoles via the intermediacy of vinyl cation. To the best of our knowledge, the only known synthesis of oxazoles from triazoles involves Rh(II)-catalyzed transannulation of N-perfluoroalkylated 1,2,3-triazoles reported by us.[18] However, synthesis of the initial triazoles requires the use of fluoroalkyl azides[29-31] and the substrate scope of the method is rather limited.

We initiated our studies by the reaction of NH-triazoles **1a** and **2a** with TFAA. To our delight, 2-trifluoromethyloxazole **3** was observed as the main product in the case of 4,5-disubstituted triazole **1a**. For monosubstituted triazole **2a**, β-acyloxyenamide **4'** was mainly observed by NMR of the reaction mixture. It underwent partial hydrolysis upon the treatment with water or on column chromatography with silica gel leading to the formation of 2-acylaminoketone **4**.

Screening of the reaction conditions to determine the optimal triazole/TFAA ratio, solvent and temperature was performed (Table 1). At room temperature full conversion of **3** could not be achieved (entry 1). A slight heating of the reaction mixture, together with an increase of the amount of TFAA led to a complete conversion to **3** (entry 3) and **4´** (entry 6). 1,2-Dichloroethane (DCE) was found to be the optimal solvent for this transformation. Whereas a high yield of **4'** was also obtained in other non-polar solvents (entries 7 and 8), the reaction in acetonitrile gave inferior results (entry 9). The use of roughly equimolar amount of TFAA called for the prolonged reaction time at 50 °C (entry 10), while heating to 80 °C resulted in low product yield (entry 11).

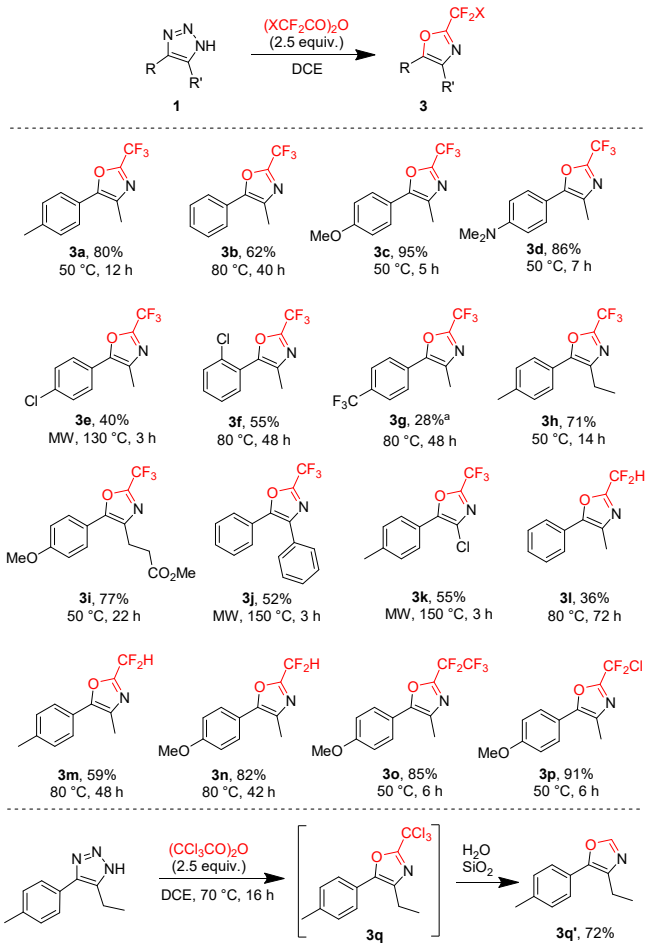
Table 1. Optimization of the reaction conditions.[a]



Entry	R	TFAA (equiv.)	Solvent	Temp. (°C)	Yield **3** (%)	Yield **4'** (%)
1	Me	2.0	DCE	rt	29	<5
2	Me	2.0	DCE	50	45	19
3	Me	2.5	DCE	50	82 (80)[b]	16
4	Me	3.0	DCE	50	79	12
5	H	2.0	DCE	50	<5	83
6	H	2.5	DCE	50	<5	97 (95)[b]
7	H	2.5	$CHCl_3$	50	<5	87
8	H	2.5	$PhCH_3$	50	<5	85
9	H	2.5	MeCN	50	7	<5
10[c]	H	1.1	DCE	50	<5	78
11	H	1.1	DCE	80	<5	35

[a] Reaction conditions: **1a** or **2a** (0.1 mmol), solvent (0.5 ml) and TFAA (1.1-3.0 equiv.) stirred in a 10 mL sealed vial for 6 h. Yields were determined by ^{19}F NMR with $PhCF_3$ as an internal standard. [b] Isolated yield. [c] Reaction time 18 h.

With optimized conditions in hand, the scope of fluoroalkylated oxazoles available from 4,5-disubstituted triazoles was investigated (Scheme 2). Trifluoromethylated oxazoles were prepared in good yields from triazoles containing neutral aryl substituents (products **3a**, **3b**). Excellent yields were obtained from electron-rich triazoles (**3c**, **3d**). Chlorophenyl-substituted triazoles were less reactive, thus more drastic conditions were necessary and products **3e** and **3f** were obtained in moderate yields. Triazole with an electron-acceptor-substituted phenyl ring reacted very sluggishly (product **3g**). The method is perfectly applicable to 5-ethyl-substituted triazole (product **3h**), as well as in the case of longer chain at position five bearing an additional ester function (product **3i**). For 4,5-diaryltriazole and 4-chloro-5-aryltriazole, the ring cleavage did not take place under conventional heating. Therefore, microwave heating was applied in these cases to prepare the corresponding trifluoromethylated oxazoles **3j** and **3k**.



Scheme 2. The scope of 2-fluoroalkylated oxazoles ([a] ^{19}F NMR yield).

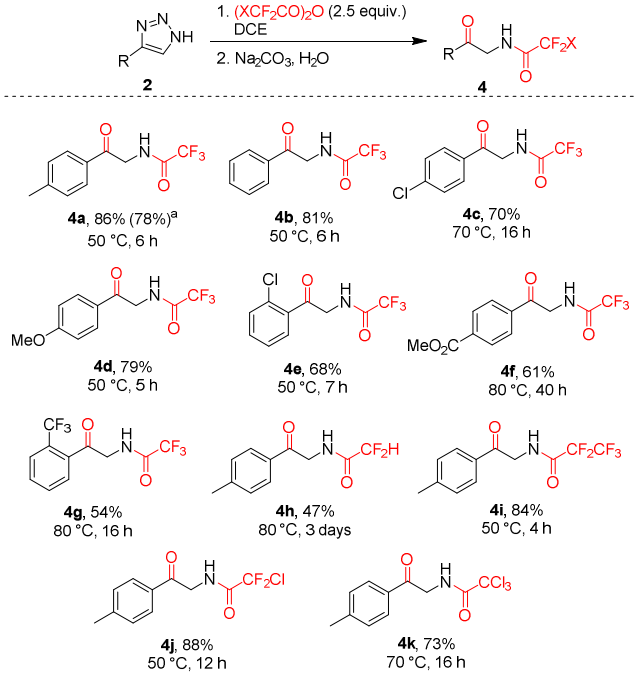
In addition to trifluoromethylated oxazoles, other fluoroalkyl oxazole derivatives were prepared from fluorinated acid anhydrides. Difluoroacetic anhydride exhibited significantly weaker reactivity in comparison to TFAA. Thus, the preparation of difluoromethylated oxazoles **3l-n** required longer reaction times at 80 °C. On the other hand, oxazoles bearing perfluoroethyl and chlorodifluoromethyl substituents (**3o**, **3p**) were smoothly obtained from the corresponding anhydrides in mild conditions with excellent yields. Using trichloroacetic anhydride resulted in the formation of 2-unsubstituted oxazole **3q'**, which was

isolated in 72% yield. In fact, the expected oxazole **3q** was the only product detected in the crude reaction mixture by NMR and GC-MS analyses; however, the cleavage of the CCl_3 group (hydrolysis and decarboxylation) readily took place upon isolation using silica gel column chromatography.

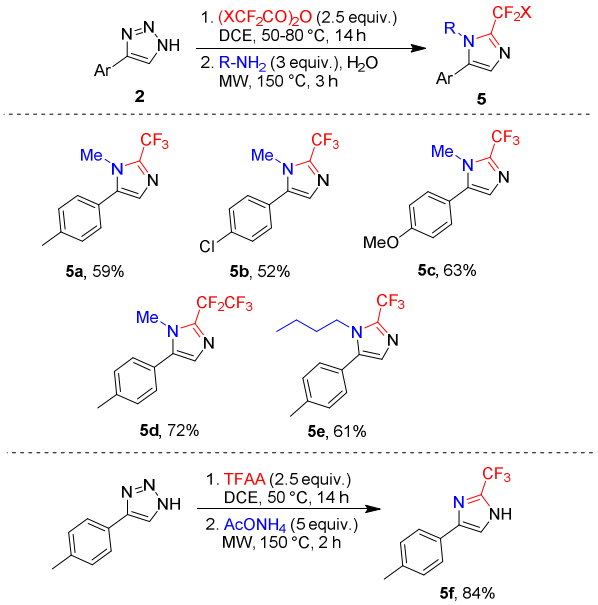
Next, we explored the scope of 2-acylaminoketones **4** available from 4-substituted 1,2,3-NH-triazoles (Scheme 3). Trifluoroacetylated aminoketones themselves exhibit biological activities, such as antibacterial, anti-inflammatory, antihistamine, and others.[32-33] Moreover, these compounds are attractive precursors of nitrogen heterocycles,[18,34] therefore, developing new routes of their synthesis is an important task. The literature methods to access these compounds are based on the trifluoroacetylation of silyl enol ethers, with TFAA in the presence of an Mn(V) catalyst[35] or with trifluoroacetylated iminoiodinane.[36] Very recently, a novel method of 2-acylaminoketone synthesis by the treatment of azirines with carboxylic acids was reported.[37] However, our synthesis of acylaminoketones from 1,2,3-triazoles has a significant advantage of simple metal-free reaction conditions and more readily available starting materials.

To access 2-acylaminoketones 4-substituted triazoles were treated with fluorinated acid anhydride, followed by hydrolysis of the formed β-acyloxyenamides **4'** to the target acylaminoketones **4** using aqueous Na_2CO_3 solution. The method was found to be universal for the preparation of these compounds from triazoles containing neutral aryl substituents, as well as halogen-substituted, electron-rich (OMe) and electron-deficient (CO_2Me, CF_3) examples, affording compounds **4a-h** in good yields (Scheme 3). The process is easily scalable and provided a high yield of **4a** on a 2 mmol scale. Generally, the reaction was significantly faster for electron-rich triazoles, which corresponds to our recently explored observation on N-fluoroalkyl-1,2,3-triazole cleavage reactions.[20] For the synthesis of product with the difluoromethyl group (**4h**) extensive heating at 80 °C was necessary to achieve a complete conversion. Perfluoroethyl- and chlorodifluoromethyl-substituted acylaminoketones (**4i, 4j**) were obtained in excellent yields after heating at 50 °C. The trichloromethylated product **4k** was isolated in 73% yield after an overnight heating at 70 °C. Importantly, halogen substituents on the aryl ring or on acetyl moiety were compatible with the treatment with sodium carbonate solution, and no side-products were detected.

We have additionally explored a possibility of a one-pot preparation of fluorinated heterocycles starting from NH-triazoles and TFAA. The synthesis of N-substituted 2-trifluoromethylimidazoles is especially attractive for medicinal chemistry as these structures exhibit high anti-inflammatory activities[38] and were explored as HMG-CoA reductase (HMGR) inhibitors.[39] However, known approaches to these fluoroalkylated heterocycles are limited,[40-42] and 1,2,5-trisubstituted 2-fluoroalkylimidazoles are still unknown. To our delight, the synthesis of compounds **5** was achieved via *in situ* cyclization of the formed 2-acylaminoketones **4** with primary amines under microwave heating. Trifluoroacetic acid formed after the first step of the reaction between triazoles and TFA is highly beneficial for the cyclization step, as related cyclization reactions are usually acid-mediated.[25, 43] Simply adding aqueous methylamine solution or butylamine and water to the reaction mixture after the first step, followed by microwave heating without changing the solvent was sufficient to obtain N-alkyl 2-trifluoromethyl- or 2-pentafluoroethylimidazoles **5** in good yields. With ammonium acetate instead of primary amine in the cyclization step, the synthesis of 2-trifluoromethyl-NH-imidazole **5f** was successfully realized.



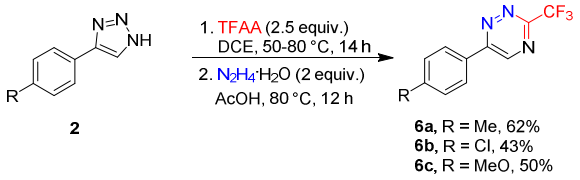
Scheme 3. Synthesis of 2-acylaminoketones from 4-substituted 1,2,3-triazoles ([a] Yield on 2 mmol scale).



Scheme 5. One-pot synthesis of 2-fluoroalkylimidazoles from 1,2,3-triazoles.

Moreover, a one-pot synthesis of trifluoromethylated six-membered aromatic heterocycles – 1,2,4-triazines **6** – was achieved by *in situ* cyclization of acylaminoketone with hydrazine hydrate in acetic acid (Scheme 6). Triazines are medicinally attractive compounds represented in several recent publications[44-45] and fused analogues of obtained trifluoromethylated triazines have been shown to exhibit antifungal activities.[46]

Thus, compounds **6** are of interest as new lead structures in medicinal chemistry.

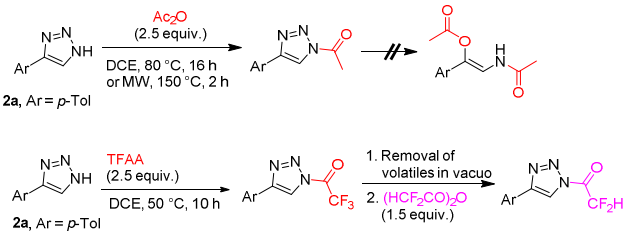


Scheme 6. One-pot synthesis of 2-trifluoromethyl-1,2,4-triazines **6** from NH-1,2,3-triazoles.

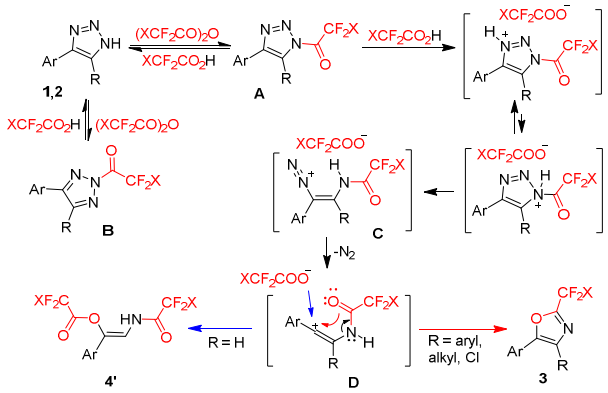
To unravel the mechanism of triazole cleavage process, several control experiments were performed (Scheme 7). Triazole **2a** underwent acylation when treated with acetic anhydride without base; however, no ring cleavage took place even under microwave heating at 150 °C. This result underlines the importance of strongly electron-withdrawing character of trifluoroacetylated triazole intermediate and much higher acidity of trifluoroacetic acid compared to acetic acid for the successful triazole ring cleavage.

Due to high lability N-acylated triazoles, they could not be isolated and characterized. However, monitoring trifluoroacetylation of **2a** by ^{19}F NMR revealed the appearance of a new signal at -70 ppm. This matched the literature data for N1-trifluoroacetyl-benzotriazole.[47] We noticed that N-trifluoroacetyl triazole underwent acyl exchange by addition of difluoroacetic anhydride to the reaction mixture after removal of volatile trifluoroacetic acid and anhydride. Interestingly, only a trace amount of difluoromethyl oxazole was detected by ^{19}F NMR, which supported the hypothesis that acid, and not anhydride was responsible for the triazole ring cleavage. However, as mentioned in the optimization table, the presence of an excess of anhydride was necessary to affect efficient triazole ring cleavage. Presumably excess anhydride increases acid acidity to facilitate ring opening.

To summarize the above-mentioned observations, we propose the following reaction mechanism (Scheme 8). First, acylation of NH-triazole takes place to give N1-acyl- as well as N2-acyltriazoles (**A** and **B**, respectively). It is known that 4-substituted NH-1,2,3-triazoles undergo reactions with electrophiles via both N1 and N2 centres.[28] The regioselectivity of acylation of triazoles was not thoroughly studied due to the instability of acyltriazoles and their propensity to deacylation. However, in several examples of N-carbamoyl triazole synthesis N1-acylation was reported.[48-50] In the presence of bulky aryl substituent or a halogen atom at the position five N2-functionalization is known to be more favored.[51-54] However, we believe that in the case of reversible acylation, a rapid interconversion between N1 and N2-acyltriazoles takes place. Next, protonation of the most basic N3 nitrogen of acylated triazole takes place;[20] however, the proton is labile and can coordinate to any basic site of the molecule. When the proton is attached to N1, the triazole ring opens to form diazonium **C** and eliminates nitrogen molecule to vinyl cation **D**. **D** can further undergo intramolecular cyclization with amide oxygen to form oxazole **3** or react intermolecularly with trifluoroacetate anion to form β-acyloxyenamide **4'**. The latter undergoes deacylation upon the treatment with a base giving 2-acylaminoketones **4**. Vinyl cation is stabilized by groups in the position five, exhibiting M+ effect (Cl, aryl) or hyperconjugation (alkyl). Therefore, in the case of 4,5-disubstituted triazoles, intramolecular cyclization is favored and oxazoles **3** (not β-acyloxyenamides **4'**) are formed as major products.



Scheme 7. Control mechanistic experiments.



Scheme 8. Proposed reaction mechanism.

In conclusion, a versatile transformation of NH-1,2,3-triazoles, mediated by fluoroalkylated acid anhydrides afforded a general route to 2-fluoroalkyloxazoles and acylated aminoketones. A broad substrate scope and high functional group tolerance of the reaction was demonstrated. One-pot routes to fluoroalkylated imidazoles or 1,2,4-triazines directly from 4-substituted NH-1,2,3-triazoles were developed. Further synthetic applications of NH-triazoles in reaction with TFAA are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at ….
Experimental methods and copies of NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of both authors. Both authors have given approval to the final version of the manuscript.

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