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A novel synthesis of 1,5-disubstituted fluorinated tetrazoles from 1,1-difluoroazides

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ABSTRACT

A new one-step reaction between 1,1-difluoroazides and primary amines is reported as an efficient synthetic approach for tetrazole formation. Examples include the syntheses of fluorine-containing 1,5-substituted tetrazoles from three fluorinated azide precursors and various amines. Greater substituent diversity in comparison with conventional methods is achieved.

In pioneering studies in 1946[1] several alkyl-substituted 1,5-tetrazoles were investigated for their anticonvulsant and analeptic activities. Further studies revealed their similarity with the *cis*-amide bond in peptides.[2] A brief review of the pharmacological activity of 1,5-substituted tetrazole compounds has been published.[3] They were shown to be potential $P2X_7$-antagonists,[4] TNF-alpha inhibitors,[5] and inhibitors of anandamide cellular uptake.[6] 1,5-Disubstituted tetrazoles are used as intermediates for the synthesis of substituted dihydropyrimidinones,[7] vinyl silanes,[8] indolizidinones,[9] and other valuable compounds.[10]

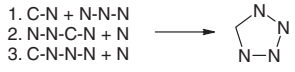
Known methods for the synthesis of 1,5-disubstituted tetrazoles are mostly based on reactions of azides with substituted nitriles, suitable imidoyl derivatives, or on diazotization of amidrazones;[10] these correspond to reaction types 1 and 2 in Scheme 1.

Recently reported approaches have led to an increase in selectivity and easier syntheses of the target compound, and these also correspond to reaction types 1 and 2 in Scheme 1. These approaches include ambient temperature reactions of imidoylbenzotriazoles with NaN_3,[11] a catalyzed, one-pot, trimethylsilyl azide reaction with a nitrile and an alkene,[12] and a catalyzed Passerini-type reaction involving an aldehyde, an isocyanide, and an HN_3.[13] The introduction of a substituent using an amine group was developed for the preparation of 1*H*,5-substituted tetrazoles, for example, via reaction of primary amines with NaN_3 and triethyl orthoformate.[14]

Only a few examples of the synthesis of fluorinated 1,5-disubstituted tetrazoles exist, and all are based on general tetrazole ring construction reactions: azide anion cycloaddition with fluorinated nitriles[15] and imidoyl halogenides.[16] Difluoromethylenetetrazoles are known as potent inhibitors of protein tyrosine phosphatases[17] and estrone sulfate analogs,[18] and their activity exceeds that of non-fluorinated compounds. It should be mentioned that the introduction of fluorine atoms often alters the biological activity of organic compounds significantly, sometimes resulting in the discovery of important drugs.[19]

Here we report a novel method for the synthesis of fluorinated 1,5-disubstituted tetrazoles based on a reaction between 1,1-difluoroazides (R^1-CF_2–N_3) and primary aliphatic amines allowing the direct introduction of a fluorine-containing 1C-substituent from the 1,1-difluoroazide (reaction type 3 in Scheme 1, and Scheme 2).

This reaction proceeds under mild conditions and often at ambient temperature in dry EtOH or THF. It is sensitive to steric hindrance, but even adamantyl-containing and *tert*-alkyl amines can be converted into the corresponding tetrazoles. The ratio of products **1**:**2** is not solvent dependent. In the case of azide **A-2**, an



Scheme 1. Different types of 1,5-disubstituted tetrazole ring construction methods.

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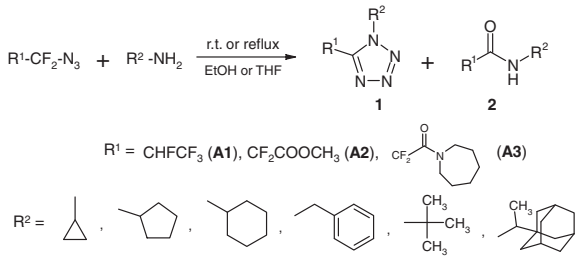


Scheme 2. Reaction of 1,1-difluoroazides with various amines.

excess of amine reacts with the ester group to afford the corresponding amides (the sterically hindered *tert*-butyl amine provides both the ester and amide forms of **1** together with the amide and ester forms of **2**). The results are summarized in Table 1.

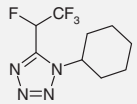
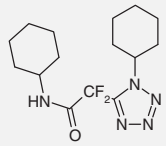
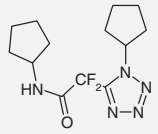
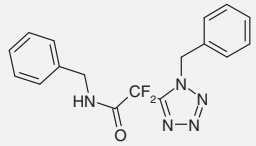
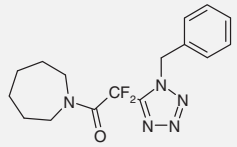
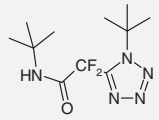
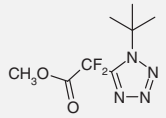
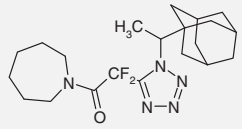
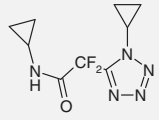
1,1-Difluoroazides are stable and safe compounds which are easily prepared from fluoroolefins and possess a wide range of R^1 groups;[20] these include alkyl, aryl, keto, ester, or hydroxy. They have been reported as precursors for fluoroazirines and fluoromonomers,[21] oxidative fluorinating reagents,[20f] and fluorinated triazole precursors.[22]

Compounds **1** and **2** are probably the products of competitive nucleophilic substitution of the fluorine atoms, or of an azide group, by the primary amine (Scheme 3).

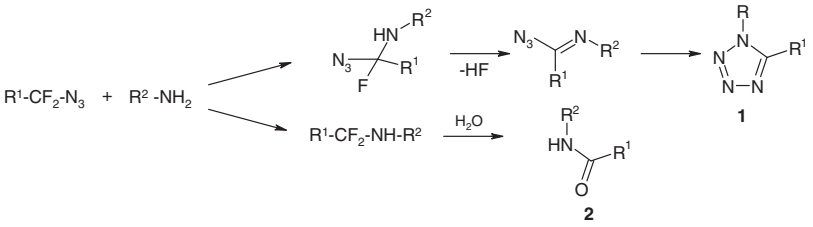
The amide structure was attributed to by-product **2** according to LC–MS data and by isolation of compound **3** during the preparation of azide **A-3** (Scheme 4).

It is necessary to mention that the reaction of a CF_2–N_3 moiety with primary amines could not be predicted a priori from literature data. 1,1-Difluoroazides are quite stable in alcohols and a standard procedure for their preparation implies the presence of a very basic and nucleophilic alkoxide anion which does not react with the

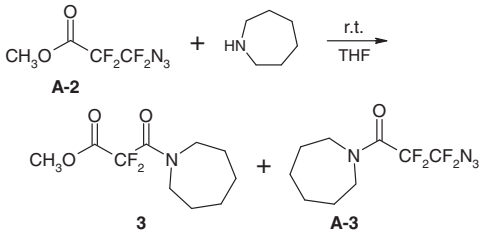
Table 1
Reaction conditions and yields of fluorinated tetrazoles

Product		R^2	Azide	Reaction conditions	Isolated yield (%) of **1**	Molar ratio **1**:**2** (LC–MS)
1a[a]		*c*-C_6H_{11}	**A-1**	rt, 8 h, EtOH rt, 12 h, THF	60 45	3:2 3:2
1b[a]		*c*-C_6H_{11}	**A-2**	rt, 2.5 h, EtOH rt, 4 h, THF	85 70	6:1 6:1
1c[a]		*c*-C_5H_9	**A-2**	rt, 2.5 h, EtOH rt, 4 h, THF	83 75	6:1 6:1
1d[a]		$PhCH_2$	**A-2**	rt, 2.5 h, EtOH rt, 4 h, THF	70 60	5:2 5:2
1e		$PhCH_2$	**A-3**	rt, 10 h, EtOH rt, 16 h, THF	70 60	7:3 7:3
1fa[a,b]		*t*-Bu	**A-2**	Reflux, 15 h, THF	10	1:3
1fb[b]		*t*-Bu	**A-2**	Reflux, 15 h, THF	50	5:1
1g		1-AdCHCH$_3$	**A-3**	Reflux, 15 h, THF	40	2:3
1h[a]		*c*-C_3H_5	**A-2**	rt, 2.5 h, EtOH rt, 4 h, THF	80 70	6:1 6:1

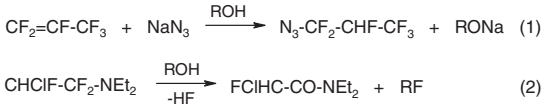
[a] Structure confirmed by X-ray analysis.
[b] Compounds **1fa** (amide) and **1fb** (ester) were isolated from the reaction mixture together with compounds **2**.



Scheme 3. Probable reaction pathways leading to the formation of **1** and **2**.



Scheme 4. Products of the reaction of azepane with **A-2** (**A-2** to azepane ratio = 1:3, ratio of **A-3**:**3** = 3:1).



Scheme 5. Behaviour of 1,1-difluoroazides and Yarovenko–Ishikawa reagents in alcohols.

resulting azide molecule (Eq. 1, Scheme 5).[20f] The reactivity of difluoroazides differs greatly from that of other N–CF_2-containing compounds (Yarovenko–Ishikawa reagents) which react vigorously with alcohols (Eq. 2, Scheme 5).[23]

In conclusion, the reported results describe a novel reaction pattern for tetrazole ring synthesis (Scheme 1, Eq. 3). This method should be suitable for the insertion of diverse substituents into a tetrazole ring.

A typical experimental procedure is as follows: azide **A-1** (0.95 g, 5 mmol) and cyclohexylamine (2 g, 20 mmol) were stirred in 50 mL of dry EtOH for 8 h. The reaction was quenched with 100 mL of 5% aqueous $NaHCO_3$ and the reaction mixture was extracted with EtOAc (2 × 20 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated. LC–MS analysis of the resulting oil revealed the presence of two products in a 3:2 ratio. The target 1-cyclohexyl-5-(1,2,2,2-tetrafluoroethyl)tetrazole was separated by column chromatography (SiO_2, hexane/EtOAc = 10:1), crystallized from EtOH, and then dried in vacuo. Compound **1a** was isolated as a white crystalline powder (0.75 g, 60%), mp 54–55 °C. In almost all the experiments the oily products **2** had very low R_f values and decomposed during purification.

Supplementary data

Characterization data for all new compounds as well as X-ray studies results are available. CCDC 762986–762991 contain the supplementary data for compounds **1a**, **1e**, **1b**, **1c**, **1h**, and **1fa**, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.016.

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