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Review

Chemistry of fluoroalkyl-substituted 1,2,3-triazoles

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ABSTRACT

This review is devoted to the chemistry of fluoroalkyl-substituted 1,2,3-triazoles: their synthesis and chemical properties. Synthesis of *C*-fluoroalkyl-substituted 1,2,3-triazoles and *N*-fluoroalkyl-substituted 1,2,3-triazoles is considered. *C*-Fluoroalkyl-substituted 1,2,3-triazoles can be prepared via 1,3-dipolar cycloaddition, cyclizations of R^F-vinyl azides, deoxyfluorination of alcohols, transformation of CO into CF_2H, transformation of CO_2H into CF_3, electrophilic α-fluorination of 4/5-alkyl-1,2,3-triazoles, and using other methods. *N*-Fluoroalkyl-substituted 1,2,3-triazoles can be prepared via *N*-difluoromethylation of 1,2,3-triazoles, their *N*-trifluoromethylation with Togni's reagent, *N*-fluoroalkylation with haloethylenes, using 1,3-dipolar cycloaddition and other methods. Fluoroalkyl-substituted 1,2,3-triazoles are chemically reactive substances, and they can be used as building-blocks for the preparation of medicinally and biologically beneficial compounds.

1. Introduction

Fluorine-containing organic compounds have attracted much interest because of their unique physicochemical properties and biological activities [1–13], often distinct from their corresponding nonfluorinated analogues, and besides pharmaceuticals, are the widely used components of agrochemicals and advanced materials [13]. Chemistry of fluoroalkyl-containing heterocyclic compounds encompasses a large part of organofluorine chemistry: the collected data on the preparation of R^F-heterocycles, their chemical properties, significance and potential applications allow systematization of these data within the framework of separate branches of fluorine chemistry, affecting advanced synthetic methods and medicinal chemistry. Thus, recently, it was shown that fluoroalkyl-substituted 2- and 4-pyrones are versatile building-blocks for the regioselective syntheses of trifluoromethylated organic compounds [14,15], whereas 1-/2-/3-fluoroalkyl-substituted indoles are promising medicinally and biologically beneficial substances [16].

This review describes the chemistry of fluoroalkyl-substituted 1,2,3-triazoles (R^F-1,2,3-triazoles), which can be prepared using a wide variety of synthetic methods, and many of which have important bioactive properties. All R^F-1,2,3-triazoles can be divided into two groups: *C*-fluoroalkyl-substituted 1,2,3-triazoles and *N*-fluoroalkyl-substituted 1,2,3-triazoles. *C*-Fluoroalkyl-substituted 1,2,3-triazoles (*C*-R^F-1,2,3-triazoles), designated by core structure **A**, can belong to one of three isomeric structures, **1A** (4-R^F-1*H*-1,2,3-triazoles), **2A** (4-R^F-2*H*-1,2,3-triazoles) or **3A** (5-R^F-1*H*-1,2,3-triazoles) (Fig. 1).

In the case of *N*-unsubstituted *C*-fluoroalkyl-substituted 1,2,3-triazoles, due to a facile tautomeric equilibrium (TM) involving a shift of the proton on a nearest-neighbor nitrogen atom, these compounds can be designated by any of the structures below (**1–3A**) (Scheme 1). However, if spectral data (e.g. NMR or X-Ray) allow the determination of the preferable tautomer, the corresponding structure for the designation can be selected on the basis of these data.

The other group, *N*-fluoroalkyl-substituted 1,2,3-triazoles, (*N*-R^F-1,2,3-triazoles), designated by core structure **B**, can belong to one of two isomeric structures, **1B** (1-R^F-1*H*-1,2,3-triazoles) or **2B** (2-R^F-2*H*-1,2,3-triazoles) (Fig. 2).

The presence of the relatively unstable N—N—N moiety and highly

Abbreviations: Bub1, budding uninhibited by benzimidazoles 1; Cbz, benzyloxycarbonyl; CD69, a human transmembrane C-Type lectin protein; DAST, diethylaminosulfur trifluoride; dba, dibenzylideneacetone; DIPEA, *N*,*N*-diisopropylethylamine; DMAD, dimethyl acetylenedicarboxylate; DMF, dimethylformamide; DMSO, dimethylsulfoxide; dppf, 1,1′-bis(diphenylphosphino)ferrocene; FACS, fluorescence-activated cell sorting; HATU, (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate); HFTA, hexafluorothioacetone; LCRF-0004, a potent and selective RON receptor tyrosine kinase inhibitor; LiHMDS, lithium bis(trimethylsilyl)amide; Ms, mesyl; MS-GLC, gas-liquid chromatography and mass spectrometry; NCS, *N*-chlorosuccinimide; NFSI, *N*-fluorobenzenesulfonimide; P_2-Et, phosphazene base; P_2-*t*-Bu, phosphazene base; PDE10, phosphodiesterase type 10; PDE10A, phosphodiesterase 10A; PSEQUAD, a comprehensive program for the evaluation of potentiometric and/or spectrophotometric equilibrium data using analytical derivatives; PTC, phase-transfer catalyst (benzyltriethylammonium chloride); R^F, fluoroalkyl; SET, single-electron transfer; TBAF, tetrabutylammonium fluoride; TBDMS, *tert*-butyldimethylsilyl; TDAE, tetrakis(dimethylamino)ethylene; TFA, trifluoroacetic acid; TFE, tetrafluoroethylene; THF, tetrahydrofuran; TLC, thin-layer chromatography; TM, tautomerism; TMS, trimethylsilyl; Ts, tosyl

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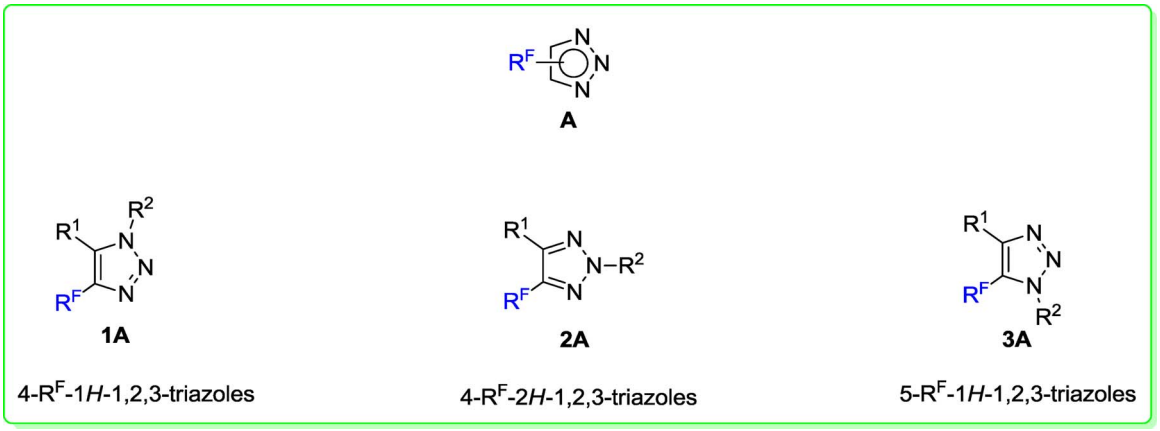
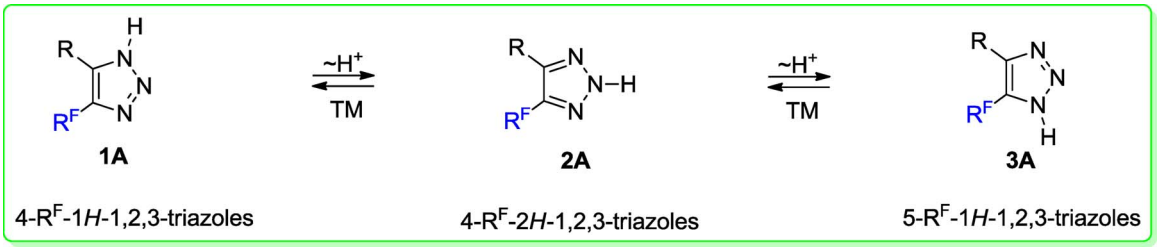


Fig. 1. *C*-Fluoroalkyl-substituted 1,2,3-triazoles: Core structure **A** and isomers **1A**, **2A** and **3A**.



Scheme 1. *N*-unsubstituted *C*-fluoroalkyl-substituted 1,2,3-triazoles: tautomers **1A**, **2A** and **3A**.

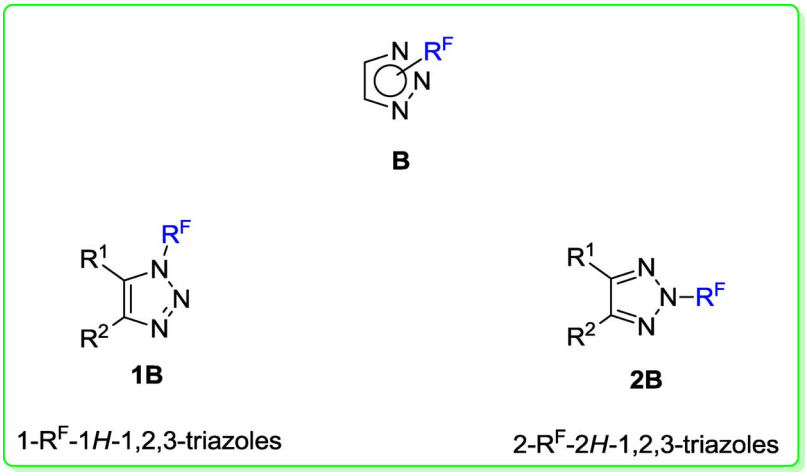


Fig. 2. *N*-Fluoroalkyl-substituted 1,2,3-triazoles: Core structure **B** and isomers **1B** and **2B**.

electron-withdrawing R^F group in molecules of R^F-1,2,3-triazoles, generally makes these compounds thermodynamically less stable and more reactive than many nonfluorinated 1,2,3-triazoles or such analogues as R^F-imidazoles, R^F-pyrazoles and R^F-1,2,4-triazoles. Thus, it was shown that Bu- and Ph-substituted 1-R^F-1*H*-1,2,3-triazoles decompose with nitrogen elimination at 160–170 °C [17], while 1-CF_3-imidazole and 1-CF_3-pyrazole (as well as 1-CF_2H-pyrazole) were prepared at 170–180 °C, and 1-$CF_3(CF_2H)$-1,2,4-triazoles were prepared at 200 °C [18]. The high availability of R^F-1,2,3-triazoles, a wide variety of synthetic methods, that can be used for the synthesis of these R^F-compounds, and their interesting chemical and bioactive properties, make the chemistry of fluoroalkyl-substituted 1,2,3-triazoles a convenient tool for the construction of various 1,2,3-triazolyl-containing molecules.

2. Synthesis of *C*-fluoroalkyl-substituted 1,2,3-triazoles

2.1. Synthesis of N-unsubstituted C-R^F-1,2,3-triazoles

2.1.1. 1,3-Dipolar cycloaddition

2.1.1.1. Reactions of diazo compounds with trifluoroacetonitrile. It was shown in 1973 that diazomethyltrimethylsilane **1** reacts with trifluoroacetonitrile to give *N*-trimethylsilyl-4-trifluoromethyl-1,2,3-triazole, probably the 2-trimethylsilyl isomer **2A1** [19]. Cycloadduct **2A1** was readily hydrolyzed by aqueous ethanol or even by atmospheric moisture to give 4-trifluoromethyl-l,2,3-triazole **1A1** (Scheme 2) [19].

Some later, in 1976, it was reported that trifluoroacetonitrile was used in the reaction with diazo compounds **2** that resulted in the