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# Stereoselective Synthesis of (*Z*)- $\beta$ -Enamido Triflates and Fluorosulfonates from *N*-Fluoroalkylated Triazoles

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**Abstract:** *N*-Fluoroalkylated 1,2,3-triazoles in the presence of triflic acid or fluorosulfonic acid underwent a cascade reaction consisting of triazole protonation, ring opening, nitrogen elimination, sulfonate addition, HF elimination, and hydrolysis to furnish novel trifluoromethanesulfonyl- or fluorosulfonyl-substituted enamides, respectively, in a highly stereoselective fashion. The vinyl triflates underwent cross-coupling reactions to a variety of substituted enamides and serve as sources of the aminovinyl cations. In reactions with triflic acid, electron-rich triazoles afforded 2-fluoroalkylated oxazoles.

Since 1960's.[1],[2] the first the late report in trifluoromethanesulfonates (triflates) have become the subject of numerous studies not only as precursors of vinyl cations<sup>[3-6]</sup> but also as substrates in transition metal-catalyzed C-C bondforming reactions.<sup>[7-11]</sup> Recently, the synthetic community has been witnessing a renewed interest in tranformations involving vinyl cations.<sup>[12,13]</sup> Despite valuable synthetic applications of vinyl triflates, they possess some drawbacks which limit their industrial application. For instance, they are commonly liquids, sensitive to hydrolysis and their preparation requires expensive reagents.<sup>[14]</sup> Vinyl triflates are usually prepared from carbonyl compounds either by trapping the respective enolate with a triflating agent<sup>[15,16]</sup> or by treating the carbonyl compound with triflic anhydride in the presence of a bulky base.[11],[17-20] Other synthetic approaches are based on the introduction of triflate moiety into alkynes.<sup>[21-23]</sup> Recently, Gaunt and Studer described regio- and stereoselective electrophile-induced triflation of alkynes via hypervalent iodine reagents. This methodology enabled the introduction of highly functionalized alkenes,[24] acrylonitriles,<sup>[25]</sup> and vinyl perfluoroalkanes<sup>[26]</sup> into organic molecules (Figure 1A).

*N*-Sulfonyl triazoles, precursors of azavinyl carbenes, are known to undergo a variety of rhodium-catalyzed reactions. They have been used for the preparation of different types of heterocycles, *N*-sulfonyl-containing compounds,<sup>[27]</sup> and for stereoselective synthesis of 2,2-diaryl or 2-alkyl-2-aryl- substituted *N*-sulfonyl enamides (Figure 1B).<sup>[28–33]</sup> We have recently shown that *N*fluoroalkyl triazoles prepared by a [3+2] cycloaddition of stable and safe azido(per)fluoroalkanes and alkynes<sup>[34–36]</sup> are efficiently transformed to new *N*-fluoroalkyl heterocycles *via* rhodium

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Chemical Technology of Russia Miusskaya sq. 9, Moscow 125047 (Russia) carbenoids.<sup>[37,38]</sup> However, the reactivity profiles of *N*-fluoroalkyl triazoles and *N*-sulfonyl triazoles are markedly different.

Herein, we report a conceptually unprecedented, stereoselective and metal-free transformation of *N*-fluoroalkyl-substituted 1,2,3triazoles to  $\beta$ -fluorosulfonyl or  $\beta$ -trifluoromethanesulfonyl enamides in presence of fluorosulfonic or triflic acids. These enamido triflates and fluorosulfonates are a new class of compounds. Enamido triflates cannot be prepared by triflatation of  $\alpha$ -aminoketones due to their self-condensation. Mechanistically, the reaction proceeds through the formation of relatively stable triazolium salts *via* aminovinyl cation intermediate (Figure 1C). Unlike other vinyl triflates, (*Z*)- $\beta$ enamido triflates and fluorosulfonates are stable solids.



**Figure 1.** Recent synthetic approaches from alkynes to vinyl triflates or substituted alkenes. **A** - Alkyne functionalizations using hypervalent iodine compounds, **B** - Rh(II)-catalyzed reactions of *N*-sulfonyl triazoles and **C** - superacid-mediated approach to (Z)- $\beta$ -enamido triflates and fluorosulfonates.

Furthermore, the triflate group can be substituted for a variety of carbon functions in cross-coupling reactions to provide medicinally and synthetically attractive enamides,<sup>[39–41]</sup> which are difficult to prepare using other methods. Triazoles with electronrich groups attached on the aryl ring in position 4 behaved differently and they provided 2-fluoroalkyl oxazoles.

Considering the high stability of carbon-nitrogen bond of *N*-fluoroalkyl triazoles in comparison with sulfur-nitrogen bond of *N*-sulfonyl triazoles<sup>[42]</sup> and good hydrolytic stability of 1,2,3-triazoles and their salts,<sup>[43–46]</sup> we assumed that the addition of a strong Brønsted acid would yield a triazolium salt that might lead to ring opening, nitrogen elimination and ultimately afford an enamine (Scheme 1A).

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Scheme 1. Initial hypothesis and findings.

To test this hypothesis, we treated triazole 1a with triflic acid. A precipitate quickly formed from the 1,2-dichloroethane (DCE) solution at ambient temperature, which was followed by a slow dissolution accompanied by gas evolution and the formation of vinyl triflate 2a. NMR spectroscopy revealed a high efficiency of the reaction without side-products and the presence of only (Z)stereoisomer of the product. However, aqueous workup resulted in decomposition due to hydrolytic instability of the NHCF3 moiety.<sup>[47]</sup> This outcome led us to use a longer chain perfluoroalkyl group and to stabilize the product in the form of enamide. Thus, triazole 3a with triflic acid provided enamine 4a which upon HF elimination and hydrolysis, afforded enamide 6a (Scheme 1B). Optimization experiments revealed that if the substrate 3 containined an electron-rich aryl group, the reactions proceeded at ambient temperature, whereas for electron-poor aryl groups, the temperature needed to be increased to 40-60 °C. The hydrolysis of unstable intermediates 4 to final enamides 6 was accomplished by elevating the temperature in moisturecontaining DCE or by hydrolysis on silica gel.

The scope of this new transformation was then studied on 4substituted-N-fluoroalkyl triazoles (Table 1). 4-Aryl-substituted triazoles with the pentafluoroethyl, ArOCF<sub>2</sub>CF<sub>2</sub>, or difluoromethyl groups were found to be relevant substrates and afforded products 6 in good to high yields even on a multigram scale in the case of 6b. A high functional group tolerance on the aryl ring was found (6a-i) where alkyl, CF<sub>3</sub>, nitro, halogen and even hydroxy group-containing triazoles furnish vinyl triflates 6 in good yields and Z selectivities. In Rh<sup>II</sup>-catalyzed transformations of 1,2,3-triazoles the presence of a free OH group interfered with rhodium-carbenoids.<sup>[48,49]</sup> With alkene or nitrile additives (MeCN or 2-methyl-2-butene, 10 equiv.) our reaction was not affected, while in Rh-catalyzed reactions transannulations took place. Additionally, N-sulfonyl 1,2,3-triazoles did not react with triflic acid in an analogous way to N-perfluoroalkyl triazoles but the main observed reaction in the former case was desulfonylation. The stereochemistry of products 6 as determined by 2D NMR and X-ray analyses was excellent (>20:1, Z:E) in all cases except for 6g and 6n where lower Z:E ratios were observed. N-Difluoromethyl triazoles 3k and 3l showed lower reactivity compared to other N-fluoroalkyl triazoles; nevertheless, formamides 6k and 6l were isolated in good yields. On the other hand, 4-alkyl-substituted triazole 3j afforded the product 6j in rather low yield, indicating a limitation which is related to the relatively lower stability of the vinyl cation intermediate as discussed later. In some cases (6a-e), small amounts (<10%) of side-products 9 were observed. Although the starting Ntrifluoromethyl triazole 1a afforded hydrolytically unstable enamine 2a, which prevented the isolation of a stable product,



[a] Isolated yields. [b] 2D ROESY NMR was measured. [c] After heating at 50 °C for 16 h, additional TfOH (0.45 equiv.) was added and the reaction continued at 50 °C for 2 h. [d] NMR yield, product was not isolated. [e] (*Z*)-isomer isolated in 70% yield. See Supporting Information for experimental details.

the addition of various alcohols in the presence of a base led to the formation of new carbamates **7a-c**.

Keeping in mind the attractivity of fluorosulfonates in sulfur(VI) fluoride exchange (SuFEx) chemistry,<sup>[50]</sup> we focused on the preparation of vinyl fluorosulfonates (Table 1). The reaction of triazoles **3** with fluorosulfonic acid (DCE, 40 °C) afforded vinyl fluorosulfonates **8** in moderate to good yields and with the exclusive formation of (*Z*)-isomers. This time, the amount of side-products **9** increased (up to 20%). The fluoro-enamides **9** resulted from fluorodesulfonylation of **6** and **8**. The formation of **9** is in line with the recent Sandford's reports of nucleophilic deoxyfluorination of aryl triflates and fluorosulfonates where the latter underwent a more facile deoxofluorination than triflates.<sup>[51,52]</sup> Triazoles **1** and **3** were unreactive in reactions with other strong acids such as nitric or chlorosulfonic acids.

Concerning the mechanism of triazole ring opening and formation of **2**, we propose the formation of a protonated triazole in the presence of triflic acid (triazolium triflate **10** was isolated and fully characterized), followed by ring opening to the diazonium compound, nitrogen elimination to the vinyl cation,

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and reaction with the triflate anion tethered through a hydrogen bonding with the oxygen of the triflate delivering the triflate in a Zconfiguration (Pathway A). Alternatively, a carbocation which reacts with the triflate anion can be formed, followed by a C-H bond cleavage, ring opening and nitrogen elimination to afford product **2** (Pathway B). The pathway B was ruled out based on an isotope labelling experiment which showed that there was no C-H/D bond cleavage during the course of the reaction (Scheme 2).



**Scheme 2.** Proposed mechanisms: Pathway A via vinyl cation, Pathway B via carbocation: The D/H ratio was determined by <sup>1</sup>H NMR (for **1aD**, **2aD** R = p-Tol, R<sub>F</sub> = CF<sub>3</sub>).

Unexpected results were observed in the case of triazoles with electron-rich aromatic rings (such as *p*-methoxyphenyl or naphthyl). Although vinyl triflates **6** were observed by NMR and in the case of naphthyl-substituted vinyl triflate **6f** fully characterized, they were found to be highly reactive and 2-fluoroalkyl oxazoles were isolated as final products in moderate (**11a**) or good (**11b-d**) yields (Table 2).

Table 2. Transformation to 2-fluoroalkyl oxazoles.[a]



#### [a] Isolated yields.

This reactivity may be explained by the formation of vinyl cation stabilized by electron-rich aryl groups.  $S_N$ 1-like cyclization with amide oxygen followed by deprotonation afforded oxazoles **11**. Therefore, the superacid-mediated approach provides a route to the rare C-2-fluorinated oxazoles directly from electron-rich *N*-fluoroalkyltriazoles. In contrast to *p*-methoxyphenyl and naphthyl-substituted triflates, the phenyl derivative **6b** was stable, even after prolonged heating in DCE.

To demonstrate the synthetic value of the method, we investigated futher transformations of vinyl sulfonates to synthetically versatile enamides (Table 3). Pd-Catalyzed cross-coupling reactions including Suzuki (**12a-e**), Sonogashira (**13a,b**) and Pd-catalyzed alkylation with diethyl zinc (**14a**) proceeded with good to excellent yields and full retention of configuration on the double bond. The cross-coupling reactions





[a] Isolated yields. [b] Prepared by one-pot two-steps procedure from 3f. [c] 2D ROESY NMR was measured. See Supporting Information for experimental details.

can be performed in a one-pot two-step modification starting from *N*-fluoroalkyl triazole **3**: the dinaphthyl derivative **12d** was obtained in good yield from electron-rich triazole **3f** *via* metastable **6f**.

In conclusion, a practical, metal-free method for the synthesis of novel  $\beta$ -enamido-sulfonates starting from *N*-fluoroalkyl-1,2,3-triazoles is presented. The method has a high functional group tolerance and uses readily available triflic or fluorosulfonic acids. A mechanism involving the formation of a triazolium salt and aminovinyl cation intermediate was proposed. Synthetic transformations of vinyl triflates in cross-coupling reactions afforded functionalized enamides. 2-Fluoroalkyl oxazoles were prepared by a one-pot procedure from electron-rich triazoles by the cyclization of vinyl triflate intermediates.

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**Keywords:** 1,2,3-triazoles • triazolium salt • vinyl cation • enamide • vinyl triflate

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	Page No. – Page No. Stereoselective Synthesis of
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A new transformation of *N*-fluoroalkylated 1,2,3-triazoles is presented. In the presence of triflic or fluorosulfonic acids they are converted to novel trifluoromethanesulfonyl- or fluorosulfonyl-substituted enamides, respectively, in a highly stereoselective fashion. The trifluoromethanesulfonyl enamides are competent partners for cross-coupling reactions to stereodefined enamides.