Metal-Free Click Synthesis of Functional 1-Substituted-1,2,3-Triazoles

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Abstract: The 1,2,3-triazole group is one of the most important connective linkers and functional aromatic heterocycles in modern chemistry. The boom in growth of, in particular, 1,4-disubstituted triazole products since the early 2000's, can be largely attributed to the birth of click chemistry and the discovery of the Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC). Yet the synthesis of relatively simple, albeit important, 1-substituted-1,2,3-triazoles, has been surprisingly more challenging. We report a straightforward and scalable click-protocol for the synthesis of 1-substituted-1,2,3-triazoles from organic azides and the bench stable acetylene-surrogate, ethenesulfonyl fluoride (ESF). The transformation proceeds through a thermal 1,3-dipolar cycloaddition of the azide and ESF to give a sulfonyl fluoride substituted triazoline, that itself spontaneously aromatizes through formal loss of HF/SO_2 to give the stable triazole products with excellent fidelity. The new click reaction tolerates a wide selection of substrates and proceeds smoothly under metal-free conditions to give the products in excellent yield, and without need for additives or chromatographic purification. Further, under controlled conditions, the 1-substituted-1,2,3-triazole products undergo Michael reaction with a second equivalent of ESF to give the unprecedented 1-substituted triazolium sulfonyl fluoride salts, demonstrating the versatility and orthogonal reactivity of ESF. The importance of this novel method is evidenced through the late-stage modification of several drugs and drug fragments, including the synthesis of a new improved derivative of the famous antibiotic, chloramphenicol.

The 1,2,3-triazole group is an important aromatic heterocycle system with a long history.[1] First reported by Pechmann in 1888,[1a] it has evolved to become one of the most successful connective linkers and functional heterocyclic cores in modern organic chemistry[2] — not least due to the pioneering work of Huisgen,[1g,3] and subsequent discovery of the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) click[4] reaction.[1n,1o] The weakly basic 1,2,3-triazole products (pKa = 9.3, pKb = 1.2)[5] function as stable linkers that are resistant to metabolic degradation, but moreover, through hydrogen bonding and dipole interactions, 1,2,3-triazoles can associate

effectively with biological targets and may function as pharmacophores,[6,7] sharing both topological and electronic features of amides.[8] Of particular importance are the 1-substituted-1,2,3-triazoles — prevalent in several drugs and clinical candidates,[9,10] including: PH-027 (**1**), a potent derivative of the antimicrobial linezolid;[11,12] the ß-lactamase inhibitor tazobactam(**2**);[13] the quinazolinamine based VEGF receptor kinase inhibitor **3**;[14] the antiretroviral 7-(5-methyl-3-(1*H*-1,2,3-triazol-1-yl)imidazo[1,5-*b*]pyridazin-7-yl)-1-phenylheptan-1-one, **4**[15] and the HER-2 protein kinase inhibitor, mubritinib (**5**)[16] among others (Figure 1A). Despite their significance, few direct methods are available for their synthesis and, of those, a majority involve the 1,3-dipolar cycloaddition between organic azides and acetylenic materials.[1h,1y]

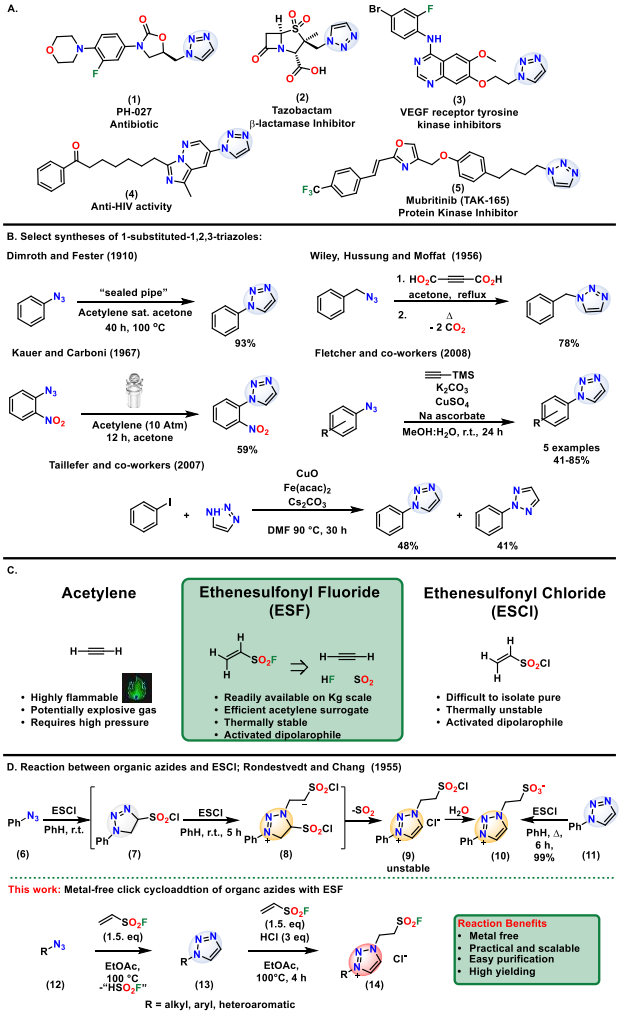


Figure 1. A) Representative examples of drugs comprising a 1-substituted-1,2,3-triazole group; B) Representative examples of methods for the synthesis of 1-substituted-1,2,3-triazoles; C) Comparison between acetylene, ESF and ESCl; D) The reaction between organic azides and ESCl, and the development this work with ESF.

Dimroth and Fester first reported (1910) that when heated in a sealed pipe, phenyl azide and acetylene-saturated acetone react to give 1-phenyl-1,2,3-triazole.[1c] Several analogous protocols have since emerged,[1h,1x,1z] each requiring high pressure and specialized apparatus to handle the potentially dangerous acetylene gas.[17] Representative methods circumventing the direct use of acetylene include the reaction of organic azides with: sodium acetylide;[1y] norbornadiene;[1m] a phase-vanishing fluorous system for *in situ* generation of acetylene from calcium carbide,[1aa] and a copper catalyzed approach using trimethylsilylacetylene (TMS-acetylene).[1k,1v] The direct

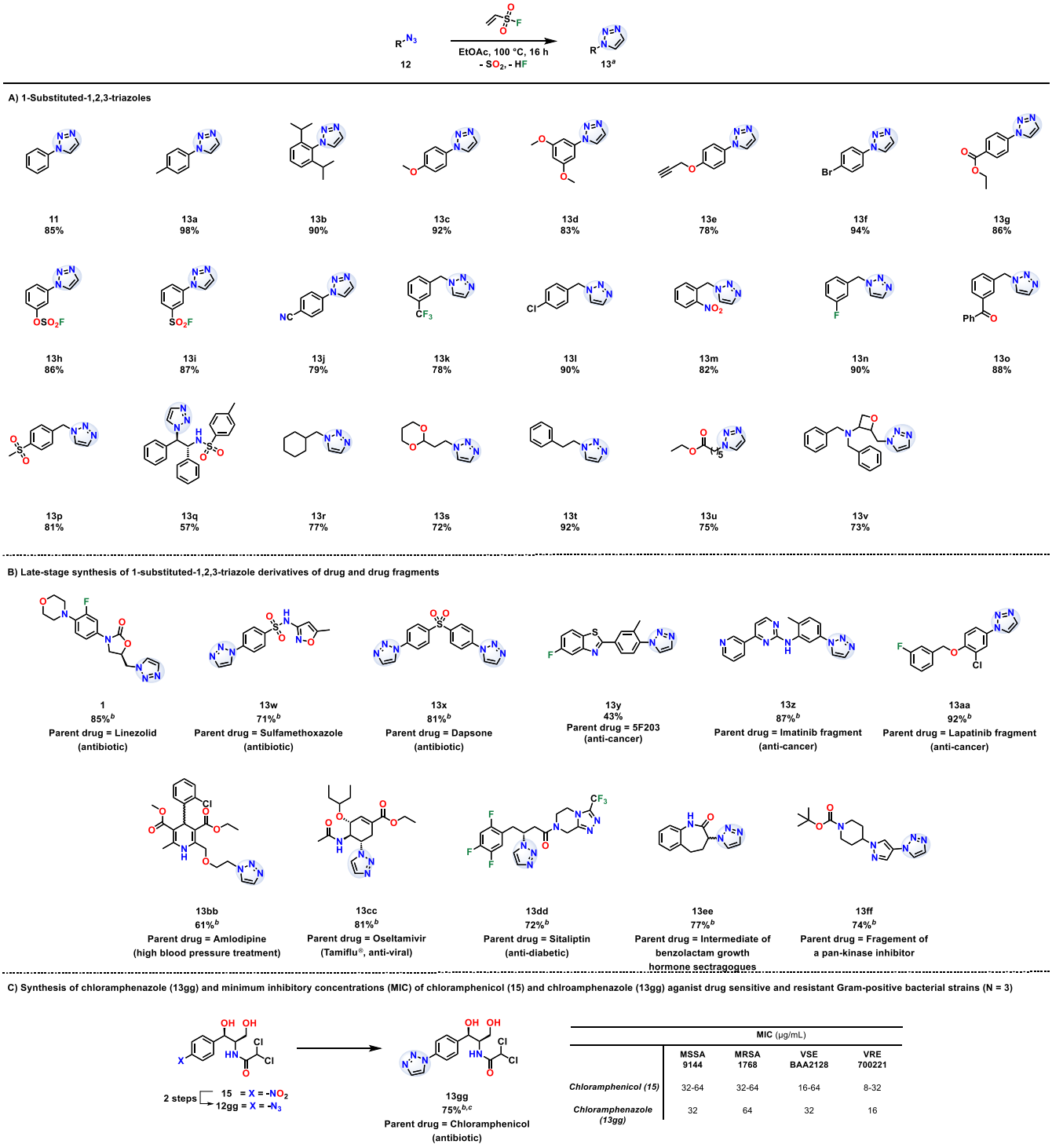
substitution of organic halides with 1*H*-1,2,3-triazole is possible, although is disadvantaged by the tendency of 1*H*-1,2,3-triazole to tautomerize to the 2*H*-1,2,3-triazole (Figure 1B).[1u,1w]

We report herein a straightforward click-protocol for the synthesis of 1-substituted-1,2,3-triazoles from organic azides and ethenesulfonyl fluoride (ESF). We demonstrate for the first time ESF as a bench stable, safe and efficient acetylene surrogate for cycloaddition chemistry (Figure 1C). The transformation fulfils all of the strict selection criteria to attain click-status, being[4]: *modular; wide in scope; high yielding; simple to perform; generate only inoffensive byproducts that can be removed by nonchromatographic methods, and uses solvents that are easily removed*.[18]

The inspiration behind the new method can be traced to a 1955 report by Rondestvedt and Chang describing the reaction between ethenesulfonyl chloride (ESCl) and phenyl azide (**6**) to give the [2:1]; [ESCl:azide] adduct product (**9**). The product was unstable and hydrolyzed upon standing to the corresponding sulfonate (**10**) (Figure 1D).[19] Even with an excess of phenyl azide, the same product was consistently obtained. The reaction was suggested to occur through a 1,3-dipolar cycloaddition of **6** and ESCl to give triazoline (**7**), followed by *N*-alkylation with a second equivalent of ESCl to **8** — proton abstraction and elimination of SO_2 lead to the triazole salt **9**. It was also noted that **10** could be synthesized by heating 1-phenyl-1,2,3-triazole (**11**) with ESCl; presumably *via* a direct Michael reaction pathway (Figure 1D). While the reported method is not practical for the synthesis of 1-substituted-1,2,3-triazoles due to the unavoidable ring alkylation, we were intrigued by the potential role of ESCl as surrogate for acetylene.[20]

In related studies, we[21] and Fokin[22] independently reported the 1,3-dipolar cycloaddition reaction between 1-bromoethene-1-sulfonyl fluoride and organic azides to give the corresponding 1-substitutued-1*H*-1,2,3-triazole-4-sulfonyl fluorides. No alkylation of the triazole ring by 1-bromoethene-1-sulfonyl fluoride was observed, leading us to question whether ESF could itself function as a practical acetylene surrogate in the reaction with organic azides, without the interfering side reactions (*cf.* ESCl). [23, 24] ESF offers many other advantages over ESCl in terms of stability and properties (Figure 1C),[25] and has even been described as *"the most perfect Michael acceptor ever found*".[23, 26]

Studies commenced by performing a reaction between ESF and phenyl azide (**6**) following the method of Rondestvedt and Chang (*cf.* ESCl)[19]: stirring in benzene at ambient temp for 5 hours in a sealed tube. Under these conditions, no products were observed and starting materials fully recovered.



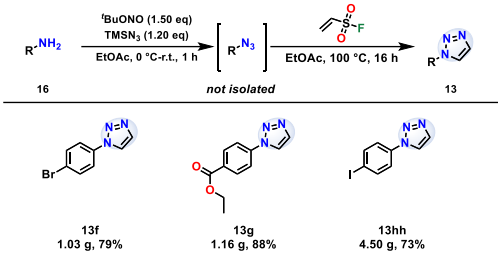
Scheme 1. A) Metal-free click-protocol for the synthesis of 1-substituted-1,2,3-triazoles from ESF and organic azides; B) Metal-free late-stage click functionalization of a selection of azide functionalized drugs and drug fragments with ESF to give the 1,2,3-triazole groups; C) Synthesis of chloramphenazole (**13gg**). [a] Isolated yields; reactions performed on 0.50 mmol scale of the azide and 0.75 mmol of ESF. [b] Reactions performed on 0.25 mmol scale of the organic azide and 0.38 mmol of ESF. [c] Compound **12gg** was synthesized directly from chloramphenicol (**15**) using Pd/C (10 mol%) under an atmosphere of H_2 then using ^{t}BuONO (1.50 eq) and $TMSN_3$ (1.20 eq). The minimum inhibitory concentration (MIC) was determined using a broth microdilution method according to guidelines defined by the Clinical Laboratory Standards Institute (See SI).

However, raising the reaction temperature to 100 °C and stirring for a further 5 h, the 1-phenyl-1,2,3-triazole (**11**) was isolated in 47% yield along with unreacted starting materials (See SI). Significantly, no alkylated triazole product was detected. Further optimization revealed the following protocol: 1.0 equivalent of azide with 1.5 equivalents of ESF in EtOAc; stirring at 100 °C for 16 h in a sealed tube (Table 1, SI).[18] The method performs well with a wide range of aromatic azides, including electron-rich (**12a-e**), electron-poor (**12f-j**), and the sterically hindered aromatic azide (**12b**), and equally well with benzyl and alkyl azides (**12k-v**) to give the corresponding 1-substituted-1,2,3-triazole products in excellent yields (Scheme 1).[27] The chemoselective transformation tolerates multiple functional groups, including alkynes (**13e**), esters (**13g**, **13u**), ketones (**13o**), acetals (**13s**), sulfones (**13p**), sulfonamides (**13q**), oxetanes (**13v**) and nitriles (**13j**), to name a few.

The potential of the new click-method was demonstrated in the late-stage functionalization (LSF) of a selection of important biologically active compounds.[28] The azide derivatives of a selection of drug and drug-fragments were prepared[29] and reacted with ESF following the new click-protocol. The 1-substituted-1,2,3-triazoles (**1, 13w,** and **13x**) from the azides of linezolid,[12] sulfamethoxazole[30] and dapsone,[31] were accomplished with excellent yields (up to 85%). The azide derivative of 5F203 (**12y**); a benzothiazole anti-cancer agent,[32] also gave the corresponding triazole (**13y**, 43%) — the lower yield attributed to the instability of the parent azide. Further, the azido modified fragments of the anti-cancer tyrosine kinase inhibitor drugs imatinib[33] and lapatinib[34] gave the corresponding 1-substituted-1,2,3-triazoles **13z** and **13aa** in 87% and 92% respective yields. The azides of amlodipine (**12bb**), a 1,4-dihydropyridine calcium antagonist used for the treatment of high blood pressure,[35] oseltamivir (**12cc**), an acetamido cyclohexene anti-viral neuraminidase inhibitor used to treat and prevent influenza A and B[36] and sitagliptin (**12dd**) an inhibitor of dipeptidyl peptidase-IV used in the treatment for diabetes mellitus type 2,[37] were successfully subjected to the reaction conditions to give the corresponding triazole products **13bb**, **13cc** and **13dd** with respective yields of 61%, 81%, and 72%. The triazoles **13ee** (77%) and **13ff** (74%) were synthesized from the azide fragments of key intermediates in the synthesis of a growth hormone secretagogues (**12ee**)[38] and a pan-kinase inhibitor, respectively (**12ff**).[39] Of particular note is chloramphenazole (**13gg**); itself prepared in 75% yield from the unstable azide derivative **12gg** of chloramphenicol (**15**) (Scheme 1C). Chloramphenicol inhibits the peptidyl transferase activity of the bacterial ribosome and has been used extensively with great effect in the treatment of severe bacterial infections.[40] However, the occurrence of adverse side effects resulting from the use of **15**, including sometimes fatal aplastic anemia and bone marrow suppression, have been linked to the metabolism of the aromatic nitro-group and formation of reactive nitroso and *N*-hydroxy- species.[41,42] When tested against a panel of pathogenic Gram-positive bacteria, including: methicillin sensitive and resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) and vancomycin susceptible and resistant *enterococci* (VSE and VRE, receptively), the observed minimum inhibitory concentrations (MICs) for chloramphenazole (**13gg**) were comparable to those for chloramphenicol (**15**). This impressive retention of activity suggests that replacement of the nitro-group with a metabolically stable triazole group is a valid strategy with much potential (Figure 1C). Collectivity,

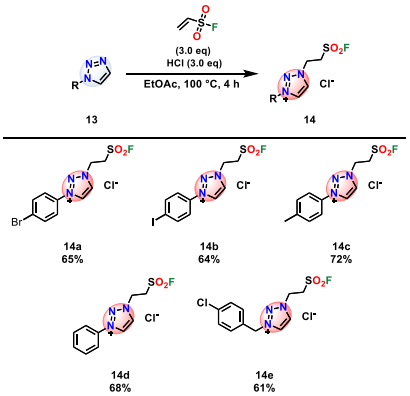
the results demonstrate the power of the new click-reaction as a valuable tool for the late-stage introduction of 1-substituted-1,2,3-triazoles for drug discovery and development.

The click-protocol is also scalable and can be performed in one-pot directly from anilines through *in situ* generation of the azide — hence avoiding the need to handle potentially hazardous intermediates.[27] The 1,2,3-triazole products **13f** (1g, 79%), **13g** (1g, 88%) and **13hh** (5g, 73%) were each isolated as single products on gram scale without need for additional purification (Scheme 2).



Scheme 2. One-pot gram scale synthesis of 1,2,3-triazoles directly from anilines.

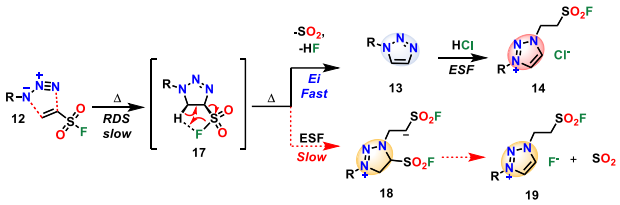
Rondestvedt and Chang demonstrated that 1-phenyl-1,2,3-triazole (**11**) undergoes direct Michael addition to ESCl (reflux in benzene, 6h) to give the sulfonate adduct (**10**) in 99% yield [presumed to arise through hydrolysis of the unstable sulfonyl chloride (**9**)].[43] Under the equivalent conditions with ESF, we observe no such reaction. However, upon heating at 100 °C in EtOAc with 3 equivalents of HCl for 4 hours (see SI), the triazole addition products (**14a-e**) could indeed be obtained in good yield. The controlled synthesis of these unprecedented 1-substituted triazolium sulfonyl fluoride salts, enabled only through reaction with ESF, highlights the incredible versatility and duality of this reagent as an acetylene surrogate and electrophile (Scheme 3).



Scheme 3. Synthesis of the triazole derived salts **14a-e** from ESF and 1-substituted-1,2,3-triazoles.

To rationalize the mechanism of the new click-protocol several features were taken into account: that no additives or base are required, and that solvent polarity does not appear to affect the yield or reaction rate to any significant degree, ruling out large build-up of charge in the transition state.[44] Collectively, these observations support a concerted pathway proceeding through a 1,3-dipolar cycloaddition ESF

and the azide (**12**) to the 1,4-disubstituted triazoline (**18**) (Scheme 4). The suggested *anti*-regiochemistry of the initial cycloaddition product **17** is supported by related 1,3-dipolar cycloaddition products between organic azides and 1-bromoethene-1-sulfonyl fluoride,[21,22] and 1-bromoethene-1-sulfonyl chloride,[19] and rationalized by the lower energy transition state for the *anti*-addition pathway, which avoids unfavorable steric clashes (*cf. syn*-addition).[45] However, this regiochemical assignment could not be corroborated — under the reaction conditions no evidence for the formation of **17** was observed. We posit that in the case of ESF, the cycloaddition step is rate limiting and that subsequent elimination of SO_2 and HF occurs rapidly through an E_i thermal *syn*-elimination mechanism. This may explain the absence of any alkylated triazolium product **19**, since under the high reaction temperature (*cf.* ESCl at r.t.), the elimination of SO_2/HF may be significantly faster than the Michael reaction between ESF (*cf*. ESCl) and the triazoline intermediate (**17)** (Figure 1C).[46, 47]



Scheme 4. Plausible concerted reaction pathway for the thermal reaction between ESF and organic azides.

In conclusion, a new click synthesis of 1-substituted-1,2,3-triazoles has been established through a 1,3-dipolar cycloaddition-elimination reaction between ethenesulfonyl fluoride and organic azides. The straightforward and practical method is wide in scope, demonstrating broad functional group tolerance. The metal-free reaction yields the 1-substituted-1,2,3-triazoles in good to excellent yields (up to 98%) and without the need for chromatographic purification in most cases. The reliable protocol was successfully applied to the late-stage functionalization of a selection of drugs and fragments, including the synthesis of the stable chloramphenicol derivative, chloramphenazole (**13gg**), which demonstrated excellent activity against MSSA, MRSA, VSE and VRE. Under acidic conditions, we demonstrate that the 1-substituted-1,2,3-triazoles undergo Michael addition to ESF to give the unprecedented addition products, demonstrating that ESF is a more practical and superior reagent to ESCl.

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Keywords: Metal-Free Click Chemistry • 1,2,3-triazole • Acetylene • Ethenesulfonyl Fluoride • Late-stage Functionalization

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