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Metal-Free Synthesis of Functional 1-Substituted-1,2,3-Triazoles from Ethenesulfonyl Fluoride and Organic Azides

Marie-Claire Giel,[a] Christopher J. Smedley,[a] Emily R. R. Mackie,[a] Taijie Guo,[b] Jiajia Dong,[b] Tatiana P. Soares da Costa,[a] and John E. Moses*[a]

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 1,4-disubstituted triazole products, in particular, 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-inspired protocol for the synthesis of 1-substituted-1,2,3-triazoles from organic azides and the bench stable acetylene-surrogate, ethenesulfonyl fluoride (ESF). The new transformation tolerates a wide selection of substrates and proceeds smoothly under metal-free conditions to give the products in excellent yield. Under controlled acidic conditions, the 1-substituted-1,2,3-triazole products undergo a Michael addition reaction with a second equivalent of ESF to give the unprecedented 1-substituted triazolium sulfonyl fluoride salts.

The 1,2,3-triazole group is an important aromatic heterocycle system with a long history.[1] First reported by Pechmann in 1888,[1a] triazoles have evolved to become one of the most successful connective linkers[1m] and functional heterocyclic cores in modern organic chemistry[2] — not least due to the pioneering work of Huisgen,[1g] and subsequent discovery of the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) click[3] reaction.[1k,1l] The weakly basic 1,2,3-triazole products (pKa = 9.3, pKb = 1.2)[4] 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,[5,6] sharing both topological and electronic features of amides.[7] Of particular importance are the 1-substituted-1,2,3-triazoles — prevalent in several drugs and clinical candidates,[8,9] including: PH-027 (**1**), a potent derivative of the antimicrobial linezolid;[10,11] the ß-lactamase inhibitor tazobactam (**2**);[12] the quinazolinamine based VEGF receptor kinase inhibitor

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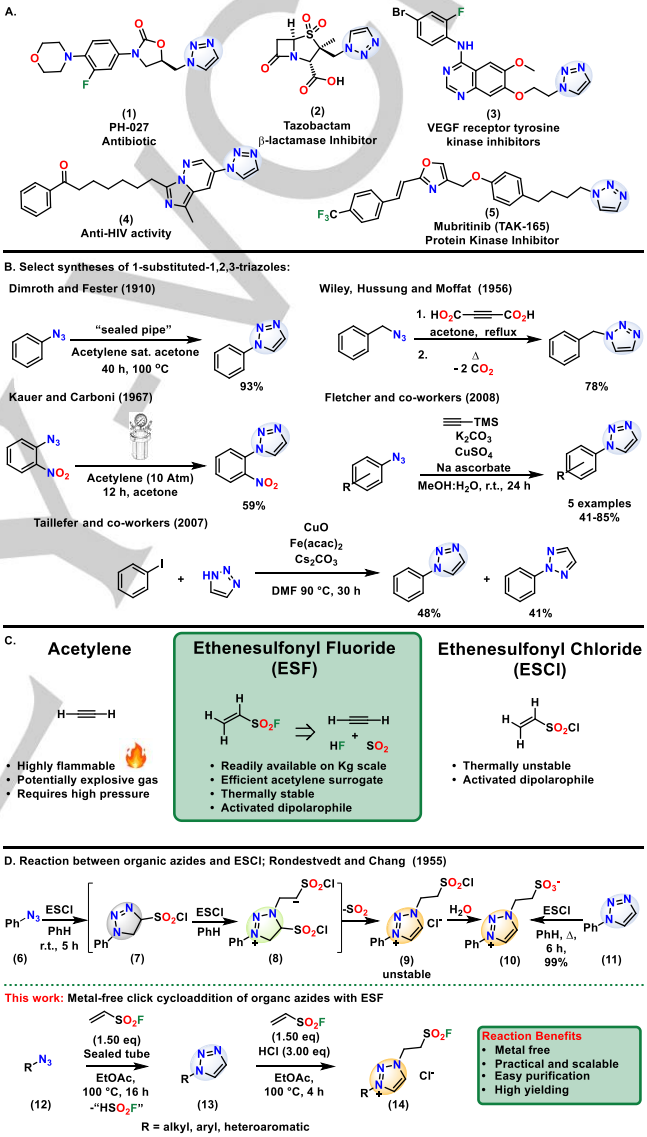

Figure 1. A) Representative examples of drugs comprising a 1-substituted-1,2,3-triazole group; B) Representative examples of methods for the synthesis of 1-substituted-1,2,3-triazoles; C) Comparison between acetylene, ESF and ESCl; D) The reaction between organic azides and ESCl, and the development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

3;[13] 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**[14] and the HER-2 protein kinase inhibitor, mubritinib (**5**)[15] among others (Figure 1A). Despite their significance, few direct methods are available for their synthesis and, of those, a majority involve

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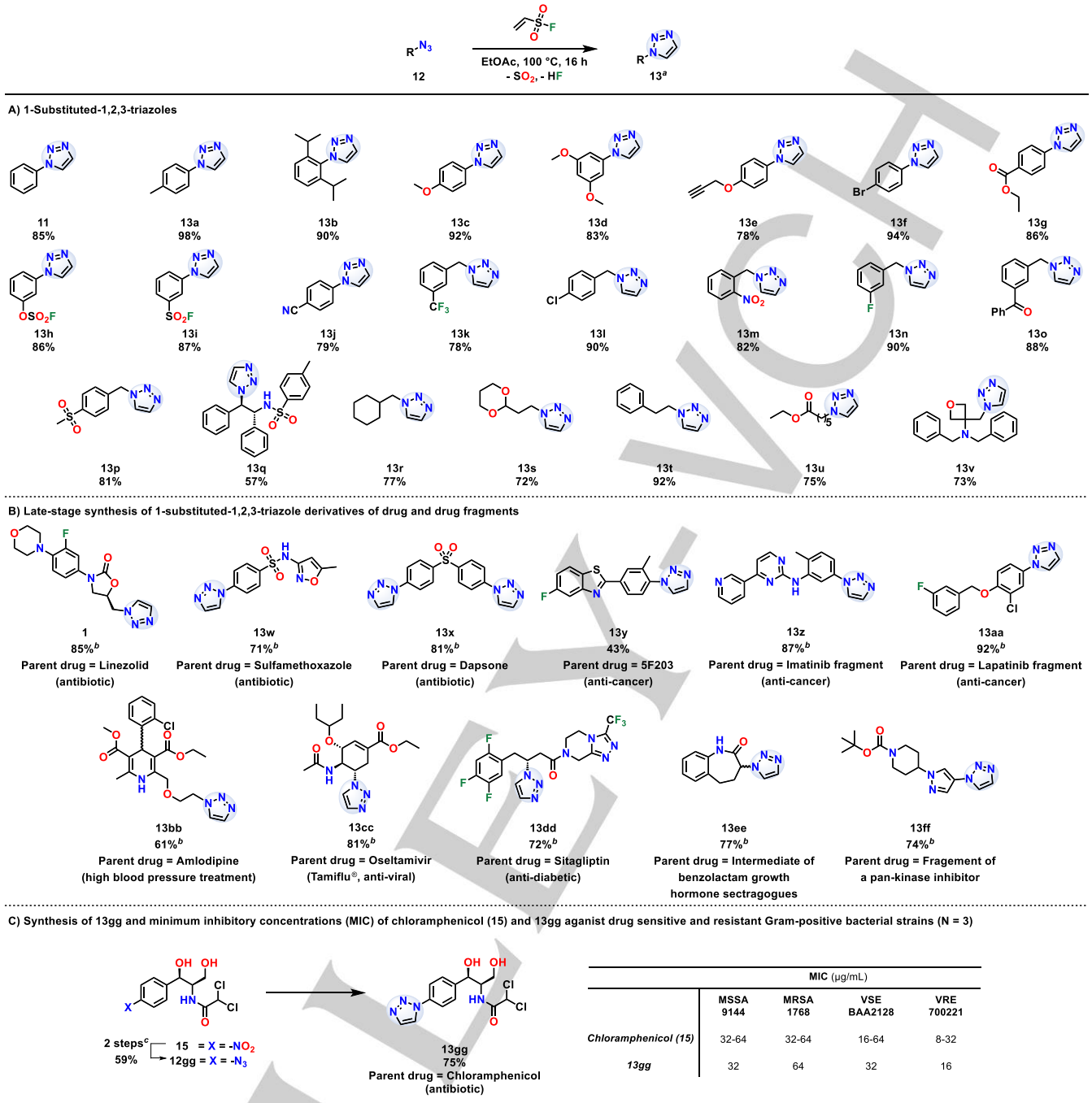

Scheme 1. A) Metal-free protocol for the synthesis of 1-substituted-1,2,3-triazoles from ESF and organic azides; B) Metal-free late-stage functionalization of a selection of azide functionalized drugs and drug fragments with ESF to give the 1,2,3-triazole groups. C) Synthesis of **13gg**. [a] Isolated 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] The compound **12gg** was synthesized from chloramphenicol (**15**) following a modified literature procedure,[16,17] 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).

the 1,3-dipolar cycloaddition between organic azides and acetylenic materials.[1h,1t]

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,1s,1u] each requiring high pressure and specialized apparatus to handle the potentially dangerous acetylene gas.[18] Representative methods circumventing the direct use of acetylene include the reaction of organic azides with: sodium acetylide;[1t] norbornadiene;[1j] a phase-vanishing fluorous system for *in situ* generation of acetylene from calcium carbide,[1v] and a copper catalyzed

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approach using trimethylsilylacetylene (TMS-acetylene).[1i,1q] 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).[1p,1r]

We report herein a straightforward click-inspired protocol for the synthesis of 1-substituted-1,2,3-triazoles from organic azides and ethenesulfonyl fluoride (ESF).[19] In contrast to earlier methods, the new metal-free transformation eliminates the need for potentially dangerous gases and specialized apparatus, delivering the 1-substituted-1,2,3-triazole products exclusively. The protocol also demonstrates a broader substrate scope to reported literature which is often displayed with simple aromatic and alkyl substrates.[1i, 1s-v] We demonstrate, for the first time, ESF as a bench stable, safe and efficient acetylene surrogate for application in 1,3-dipolar cycloaddition chemistry (Figure 1C). The transformation meets many of the criteria of a click reaction,[3] being: *modular; wide in scope; high yielding; simple to perform and using solvents that are easily removed*.

The inspiration for 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).[20] 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 led 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.[21]

In related studies, we[22] and Fokin[23] independently reported the 1,3-dipolar cycloaddition reaction between 1-bromoethene-1-sulfonyl fluoride and organic azides to give the corresponding 1-substituted-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).[24, 25] ESF offers many other advantages over ESCl in terms of stability and properties (Figure 1C),[26] and has been described as *"the most perfect Michael acceptor ever found*" [24, 27]

Studies commenced by performing a reaction between ESF and phenyl azide (**6**) following the method of Rondestvedt and Chang (*cf.* ESCl)[20]: 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. 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 (Table 1, SI): 1.00 equivalent of azide with 1.50 equivalents of ESF in EtOAc; stirring at 100 °C for 16 h in a sealed tube (for safety precautions see footnote 28).[28] The method performs well with a wide range of aromatic azides,[17] 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 good to excellent yields (Scheme 1). 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 method was demonstrated in the late-stage functionalization (LSF) of a selection of important biologically active compounds.[29] The azide derivatives of a selection of drug and drug-fragments were prepared[30] and reacted with ESF following the new protocol (Scheme 1B and C). The 1-substituted-1,2,3-triazoles (**1**, **13w** – **13gg**) were synthesized in mostly good yields (up to 92%) from a wide range of azido modified drug and drug-fragments including antibiotics and anti-cancer agents.[30]

Of particular note is **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.[31] 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.[32,33] 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, respectively), the observed minimum inhibitory concentrations (MICs) for **13gg** were comparable to those for chloramphenicol (**15**). This impressive retention of activity suggests that replacement of the nitro-group with a metabolically stable 1,2,3-triazole group is a valid strategy with much potential (Figure 1C). Collectivity, the results demonstrate the power of the new click-inspired reaction as a valuable tool for the late-stage introduction of 1-substituted-1,2,3-triazoles for drug discovery and development.

The metal-free protocol is also scalable and can be performed in a one-pot synthesis directly from anilines through *in situ* generation of the azide — hence avoiding the need to handle potentially hazardous intermediates.[17] The 1,2,3-triazole products **13f** (79%), **13g** (88%) and **13hh** (73%) were each isolated as single products on gram scale without need for additional purification. While a lower yield (56%) of the triazole product **13ii** was observed from the alkyl amine (**16ii**) *via in situ* diazotransfer to the azide starting material,[34, 35] the one-pot synthesis from alkyl halides or alcohols (*via* the corresponding azides) gave good yields of the 1,2,3-triazole products **13l** (78%), **13u** (61%) and **13jj** (67%) (Scheme 2, See SI).

Rondestvedt and Chang demonstrated that 1-phenyl-1,2,3-triazole (**11**) undergoes direct Michael addition to ESCl (reflux in benzene, 6 h) to give the sulfonate adduct (**10**) in 99% yield [presumed to arise through hydrolysis of the unstable sulfonyl chloride (**9**).[20, 36] Under the equivalent conditions with ESF, we observe no such reaction. However, upon heating at 100 °C in EtOAc with 3.00 equivalents of HCl for 4 hours, the triazole

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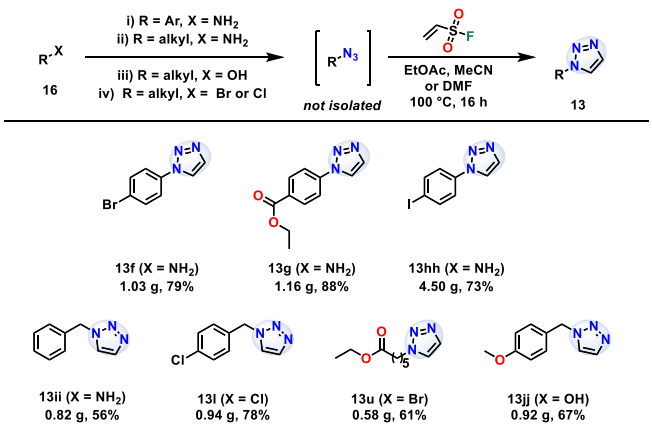
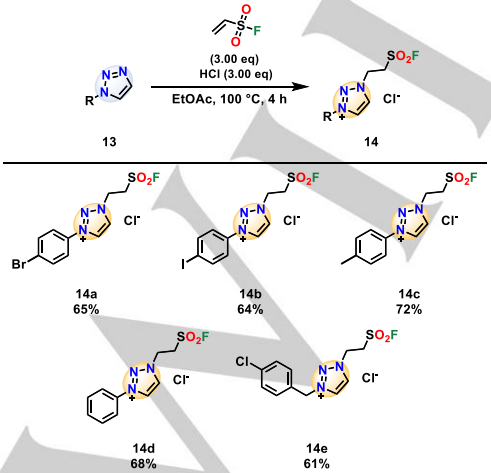


Scheme 2. One-pot gram scale synthesis of 1,2,3-triazoles directly from anilines (i), alkyl amines (ii), halides (iii) and alcohols (iv). See SI for conditions i, ii, iii and iv.

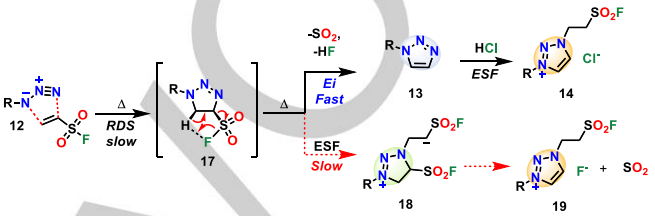
addition products (**14a-e**) could indeed be obtained in good yield. The controlled synthesis of these unprecedented 1-substituted triazolium sulfonyl fluoride salts, enabled only through the reaction with ESF, highlights the incredible versatility and duality of this reagent as an acetylene surrogate and electrophile (Scheme 3).

To rationalize the mechanism of the new reaction 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.[37] Collectively, these observations support a concerted pathway proceeding through a 1,3-dipolar cycloaddition of ESF and the azide (**12**) to the 1,4-disubstituted triazoline (**17**) (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,[22,23] and 1-bromoethene-1-sulfonyl chloride,[20] and rationalized by the lower energy transition state for the *anti*-addition pathway, which avoids



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

unfavorable steric clashes (*cf. syn*-addition).[38] 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 (**18**) (Figure 1C).[39, 40]



Scheme 4. Plausible concerted reaction pathway for the 1,3-dipolar thermal cycloaddition reaction between ESF and organic azides.

In conclusion, a new metal-free click-inspired 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 metal-free method is wide in scope, has broad functional group tolerance, good to excellent yielding (up to 98%) and often requires no chromatographic purification. 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, **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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[1] For a selection of 1,2,3-triazole syntheses and reviews see and references there in: a) H. Pechmann, *Ber. Dtsch. Chem. Ges.* **1888**, *21*, 2751-2756; b) A. Michael, *J. Prakt. Chem* **1893**, *2*, 94–95; c) O. Dimroth, G. Fester, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2219–2230; d) T. Curtius, K. Raschig, *J. Prakt. Chem* **1930**, *125*, 466–497; e) F. R. Benson, W. L. Savell, *Chem. Rev.* **1950**, *46*, 1–68; f) R. H. Wiley, K. F. Hussung, J. Moffat, *J. Org. Chem.* **1956**, *21*, 190–192; g) R. Huisgen, *Angew. Chem. Int. Ed.* **1963**, *2*, 565–632; h) J. C. Kauer, R. A. Carboni, *J. Am. Chem. Soc.* **1967**, *89*, 2633–2637; i) V. Melai, A. Brillante, P. Zanirato, *J. Chem. Soc., Perkin Trans 2* **1998**, 2447–2449; j) M. Gardiner, R. Grigg, M. Kordes, V. Sridharan, N. Vicker, *Tetrahedron* **2001**, *57*, 7729–7735; k) C. W. Tornøe, C. Christensen, M. Meldel, *J. Org. Chem.* **2002**, *67*, 3057-3064; l) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599; m) N. J. Agard, J. A. Prescher, C. R. Bertozzi, *J. Am. Chem. Soc.* **2004**, *126*, 15046-15047; n) V. P. Krivopalov, O. P. Shkurko, *Russ. Chem. Rev.* **2005**, *74*, 339–379; o) L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin, G. Jia, *J. Am. Chem. Soc.* **2005**, *127*, 15998–15999; p) M. Taillefer, N. Xia, A. Ouali, *Angew. Chem. Int. Ed.* **2007**, *46*, 934–936; q) J. T. Fletcher, S. E. Walz, M. E. Keeney, *Tetrahedron Lett.* **2008**, *49*, 7030–7032; r) S. W. Kwok, J. E. Hein, V. V. Fokin, K. B. Sharpless, *Heterocycles* **2008**, *76*, 1141–1154; s) L. Y. Wu, Y. X. Xie, Z. S. Chen, Y. N. Niu, Y. M. Liang, *Synlett* **2009**, 1453–1456; t) Y. Jiang, C. Kuang, Q. Yang, *Tetrahedron* **2011**, *67*, 289–292; u) L. Wu, B. Yan, G. Yang, Y. Chen, *Heterocycl. Commun.* **2013**, *19*, 397–400; v) R. Matake, Y. Niwa, H. Matsubara, *Org. Lett.* **2015**, *17*, 2354–2357

[2] H. Wamhoff, *Comprenesive Heterocyclic Chemistry*, Edited by A. R. Katrizky, C. W. Rees, Oxford: Pergamon Press, **1984**.

[3] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

[4] J. Catalan, J. L.M. Abboud, J. Elguero, *Adv. Heterocycl. Chem*. **1987**, *41*, 187–274.

[5] H. C. Kolb, K. B. Sharpless, *Drug Discov. Today* **2003**, *8*, 1128–1137.

[6] A. D. Moorhouse, A. M. Santos, M. Gunaratnam, M. Moore, S. Neidle, J. E. Moses, *J. Am. Chem. Soc.* **2006**, *128*, 15972–15973.

[7] D. S. Pedersen, A. Abell, *Eur. J. Org. Chem.* **2011**, 2399–2411.

[8] S. Haider, M. S. Alam, H. Hamid, *Inflamm. Cell Signal.* **2014**, 1–10.

[9] a) S. G. Agalave, S. R. Maujan, V. S. Pore, *Chem. Asian J.* **2011**, *6*, 2696–2718; b) A. Jain, P. Piplani, *Mini-Reviews in Medicinal Chemistry,* **2019**, *19*, 1298–1368.

[10] O. A. Phillips, V. O. Rotimi, W. Y. Jamal, M. Shahin, T. L. Verghese, *J. Chemother.* **2003**, *15*, 113–117.

[11] O. A. Phillips, E. E. Udo, A. A. M. Ali, N. Al-Hassawi, *Bioorganic Med. Chem.* **2003**, *11*, 35–41.

[12] A. Gin, L. Dilay, J. A. Karlowsky, A. Walkty, E. Rubinstein, G. G. Zhanel, *Expert Rev. Anti. Infect. Ther.* **2007**, *5*, 365–383.

[13] L. F. Hennequin, A. P. Thomas, C. Johnstone, E. S. E. Stokes, P. A. Plé, J.-J. M. Lohnmann, D. J. Ogilvie, M. Dukes, S. R. Wedge, J. O. Curwen, *et al., J. Med. Chem.* **1999**, *42*, 5369–5389.

[14] D. G. H. Livermore, R. C. Bethell, N. Cammack, A. P. Hancock, M. M. Hann, D. V. S. Greene, R. B. Lamont, S. A. Noble, D. C. Orr, J. J. Payne, *et al.*, *J. Med. Chem.* **1993**, *36*, 3784–3794.

[15] D. Lednicer, L. A. Mitscher, The *Organic Chemistry of Drug Synthesis*, Wiley, New York, **1977**.

[16] P. E. Nielsen, V. Leick, O. Buchardt, *Acta Chem. Scand., Ser B* **1975**, *29B*, 662-666.

[17] K. Barral, A. D. Moorhouse, J. E. Moses, *Org. Lett.* **2007**, *9*, 1809-1811.

[18] R. J. Lewis, N. I. Sax, *Sax's Dangerous Properties of Industrial Materials*, Van Nostrand Reinhold: New York, **1992**.

[19] For the synthesis of ESF, see: Q. Zheng, J. Dong, K. B. Sharpless, *J. Org. Chem.* **2016**, *81*, 11360-11362.

[20] C. S. Rondestvedt, P. K. Chang, *J. Am. Chem. Soc.* **1955**, *77*, 6532–6540.

[21] The analogous reaction between phenyl azide and 1-bromoethene-1-sulfonyl chloride revealed no alkylation product.

[22] C. J. Smedley, M.-C. Giel, A. Molino, A. S. Barrow, D. J. D. Wilson, J. E. Moses, *Chem. Commun.* **2018**, *54*, 6020–6023.

[23] J. Thomas, V. V. Fokin, *Org Lett.* **2018**, *20*, 3749-3752.

[24] J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430–9448.

[25] A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong, J. E. Moses, *Chem. Soc. Rev.* **2019**, *48*, 4731–4758.

[26] The homolytic bond dissociation energy of the S-F bond in SO_2F_2 (90.5 ± 4.3 kcal mol^{-1}) is far larger than the S–Cl bond in SO_2Cl_2 (46 ± 4 kcal mol^{-1}),[24] hence sulfonyl chlorides are more prone to thermolysis.

[27] ESF is known to function as an effective dienophile and dipolarophile: a) H. U. Daeniker, J. Druey, *Helv. Chim. Acta* **1962**, *604145*, 1972–1981; b) J. J. Krutak, R. D. Burpitt, W. H. Moore, J. A. Hyatt, *J. Org. Chem.* **1979**, *44*, 3847–3858; c) Q. Chen, P. Mayer, H. Mayr, *Angew. Chem. Int. Ed.* **2016**, *55*, 12664–12667.

[28] **Note:** Unless otherwise stated, all reactions were performed in a sealed Biotage Microwave Reaction vial designed to withstand pressures of up to 30 bar using 0.50 mL (0.25 mmol scale) or 1.00 mL of solvent (0.50 mmol scale) in a vial with a solvent capacity between 0.50-2.00 mL. The 1 g scale reactions were performed in a vial with a capacity between 10.0-20.0 mL. No damage of the glassware from HF was observed. The reactions may also be performed in an open system at reflux, and the SO_2 and HF by-products (b.p. -10 °C and 19.5 °C respectively) removed by passing through a solution of aqueous NaOH. The reactions must be vented in a well ventilated hood and all glassware soaked in a solution of aqueous NaOH for 16 h to quench remaining ESF and HF.

[29] C. J. Smedley, Q. Zheng, B. Gao, S. Li, A. Molino, H. M. Duivenvoorden, B. S. Parker, D. J. D. Wilson, K. B. Sharpless, J. E. Moses, *Angew. Chem. Int. Ed.* **2019**, *58*, 4552-4556.

[30] G. Meng, T. Guo, T. Ma, J. Zhang, Y. Shen, K. B. Sharpless, J. Dong, *Nature* **2019**, *574*, 86-89.

[31] T. D. Brock, *Bacteriol. Rev* **1961**, *25*, 32–48.

[32] A. A. Yunis, G. K. Arimura, M. Isildar, *Am. J. Hematol.* **1987**, *24*, 77–84.

[33] H. M. Feder, C. Osier, E. G. Maderazo, *Rev. Infect. Dis.* **1981**, *3*, 479–491.

[34] A. S. Barrow, J. E. Moses, *Synlett*, **2016**, *27*, 1840-1843.

[35] J. Dong., K. B. Sharpless, J. W. Kelly, W. Chen. *US Pat.,* 10117840, 2018.

[36] Details about the formation of the sulfonate were not provided.[20] The S–Cl bonds of sulfonyl chloride are prone to homolysis at higher

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temperatures,[39] and under the reported reaction conditions, we cannot discount the possibility of an alternative pathway.

[37] a) R. B. Woodward, R. Hoffmann, *J. Am. Chem. Soc.* **1965**, *87,* 395-397; b) R. B. Woodward, R. Hoffmann, *Angew. Chem. Int. Ed.* **1969**, *11*, 781-853; c) T. L. Gilchrist, R. C. Storr, *Organic Reactions and Orbital Symmetry*, Cambridge University Press, **1979**.

[38] Computational studies performed on the reaction of nitrile oxides and 1-bromo-ethene-1-sulfonyl fluoride support this hypothesis see ref. 22. For additional literature examples of 1,3-dipolar cycloaddition reactions of alkenes see a) F. Schoenebeck, D. H. Ess, G. O. Jones, K. N. Houk, *J. Am. Chem. Soc.* **2009**, *131*, 8121-8133; b) H. Jangra, Q. Chen, E. Fuks, I. Zenz, P. Mayer, A. R. Ofial, H. Zipse, H. Mayr, *J. Am. Chem. Soc.* **2018**, *140*, 16758-16772.

[39] The importance of temperature in the cycloaddition reaction of sulfonic acid derivatives has been described: C. S. Rondestvedt, J. C. Wygant, *J. Org. Chem.* **1952**, *17*, 975-979.

[40] W. E. Truce, F. D. Hoerger, *J. Am. Chem. Soc.* **1954**, *76*, 3230-3232.

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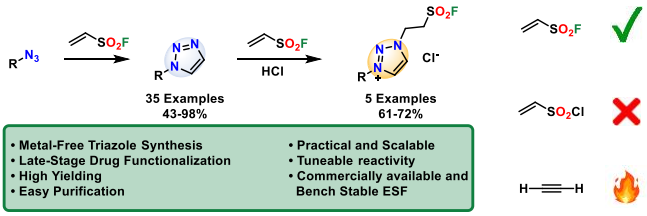

A metal-free click-protocol for the synthesis of 1-substituted-1,2,3-triazoles from organic azides and ethenesulfonyl fluoride (ESF) is described. The synthetic value of the concerted reaction is reflected in the simplicity of the protocol and demonstrated by the one-pot preparation of the triazole from the corresponding amine, alkyl halide or alkyl alcohol performed on gram scale. The utility of this method is shown in the late-stage modification of several drugs, including the famous antibiotic chloramphenicol to give the new active antibiotic derivative.

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