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Facile synthesis of 4-vinyl- and 4-fluorovinyl-1,2,3-triazoles via bifunctional “click-olefination” reagents

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Abstract

Modular synthesis of vinyl and fluorovinyl triazoles can be achieved from bifunctional propargyl and fluoropropargyl sulfones by Cu-catalyzed azide-alkyne ligation and Julia-Kocienski olefination. Competitive click reactions of the protio and fluoropropargyl sulfones show higher reactivity of the latter, and a preliminary DFT analysis was performed.

Formation of triazoles *via* the Huisgen ligation of azides and alkynes is an efficient, atom-economical process.¹ Furthermore, the Cu-catalyzed azide-alkyne *click* ligation has yielded facile and efficient access to triazoles, often with high regioselectivity.^{2,3} Using the fluorinated building block approach,⁴ we^{5,6} and others⁷ have been developing syntheses of regiospecifically fluorinated molecules *via* the Julia-Kocienski olefination.^{5–7} Since both the triazole moiety⁸ and the fluorine atom⁹ are widely prevalent in pharmacological agents, a modular methodology allowing facile assembly of triazole rings as well as the fluorovinyl moiety, would be of high interest. This communication describes such an approach.

We hypothesized that a bifunctionalizable building block containing a “clickable” unit and an olefination handle, would offer great flexibility in accessing regioselectively difunctionalized triazoles, wherein both the *N*1 and vinyl substituents can be readily varied. Although conversion of enynes to 4-vinyl-1,2,3-triazoles has been reported,¹⁰ to the best of our knowledge, the combination of click chemistry and Julia-Kocienski reaction has not been used for synthesis of either unfluorinated or fluorinated vinyl triazoles. Hence, we decided to explore such a route for the synthesis of *N*-substituted 4-vinyl and 4-(α -fluorovinyl)-1,2,3-triazoles.

For this approach, appropriate propargyl and α -fluoropropargyl heteroaryl (benzothiazole or phenyltetrazole)¹¹ sulfones were required. Benzothiazol-2-yl (BT) propargyl sulfone **1** was prepared by reaction of TMS-protected propargyl bromide and sodium salt of BT-thiol, followed by *m*-CPBA oxidation of the sulfide (Scheme 1).¹² Metalation-fluorination of **1** yielded the unknown fluoro derivative **2** (63%). Although deprotection of the TMS group in **2** proceeded cleanly, chromatographic purification of **2** gave a mixture of alkyne and the corresponding rearranged allene. An *in situ* alkyne deprotection-click reaction route was therefore investigated.

Conditions for the deprotection-click reaction were evaluated using *p*-methoxyphenyl azide and fluoropropargyl sulfone **2** (Table 1). Use of AgBF₄, CuSO₄ and Na ascorbate in the biphasic CH₂Cl₂/H₂O led to low conversion to desired triazole after 72 h, at room temperature (Table 1, entry 1). Conditions recently reported for one-pot synthesis of triazoles from TMS-protected alkynes were then evaluated.¹³ Reaction in the presence of AgBF₄, CuSO₄/Na ascorbate in *t*BuOH/H₂O at 35 °C resulted in an incomplete reaction even after 72 hours, with 16% conversion to triazole **4** (entry 2). On the other hand, fast, efficient alkyne deprotection and azide ligation could be achieved with AgBF₄ and Cu(CH₃CN)₄PF₆ in CH₂Cl₂/MeOH (entry 3).¹³ No further optimizations were performed.

With AgBF₄/Cu(CH₃CN)₄PF₆, reactions of sulfones **1** and **2** with alkyl and aryl azides in CH₂Cl₂/MeOH yielded the corresponding triazoles (Scheme 1). Both BT-sulfones **1** and **2** gave high yields of the triazole sulfones **3-8** (74%-84% in reactions of **1** and 68%-93% in reactions of **2**, Fig. 1).

To assess whether the fluorine atom exerted any influence on the click reactions of propargyl sulfone **2**, competitive reactions of **1** and **2** with *p*-methoxyphenyl, 3-phenylpropyl and decyl azides were performed (Table 2).

α -Fluoro-substituted propargyl sulfone **2** was more reactive in the azide-alkyne ligation reactions, than the unfluorinated propargyl sulfone **1**. This is consistent with results from uncatalyzed and catalyzed azide ligation reactions with fluoro-substituted cyclooctyne¹⁴⁻¹⁵ and diynes,¹⁶ respectively. The ratio of fluoro/protio substituted triazole products in the competitive reactions of **1** and **2** with 3-phenylpropyl and *n*-decyl azide was 4.9 and 2.6, respectively. A higher difference in reactivity between **1** and **2** was observed in the reaction with *p*-methoxyphenyl azide, where the ratio of fluoro/protio substituted triazole derivatives was 11.5 (Table 2).

In order to obtain insight into the difference in reactivity between **1** and **2** in click reactions, preliminary DFT calculations were performed at the B3LYP/6-311++G(2d,2p) level on BT fluoropropargyl sulfone **2a** (shown in the Scheme above Table 1) and on BT propargyl sulfone **1a** (the protio analogue of **2a**). These calculations showed little difference between the HOMO energies of **2a** and **1a**, whereas the LUMO energy of **2a** is lower than that of **1a** by 3.7 kcal/mol (Table 2 in the Supporting Information). The NBO bond order of the triple bond was similar in **1a** and **2a** (1.932 and 1.926, respectively). Interesting differences emerged upon comparing the NBO analyzed natural charges at the triple bond (Table 3 in the Supporting Information). In **1a** there is higher electron density at the terminal alkynyl carbon atom as compared to **2a**. On the other hand, electron density at the internal alkynyl carbon in fluoro analogue **2a** is higher as compared to protio **1a**. The alkynyl proton is slightly more electropositive in **2a** than in **1a**. The ability of the fluorine atom to stabilize accumulating negative charge at the terminal alkynyl carbon in the course of the ligation reaction may be an important contributor to the enhanced reactivity of **2a** compared to **1a**. In this context, a stepwise mechanism for the azide-alkyne ligation has been proposed,^{2b} and has been supported by computation^{17a,c} and kinetic studies.^{17b} In this mechanism, formation of a copper metallacycle is described as the rate-limiting step, with an increase in electron density at the terminal alkynyl carbon. A second copper atom in close proximity to the terminal alkynyl carbon has been proposed to stabilize the transition state.^{17b,c} In our case, the fluorine atom in **2a** may additionally contribute to such charge stabilization, which is absent in protio analogue **1a**. These reactions are complex and clearly additional studies will be needed in order to fully understand the reactivity differences.

The protio Julia-Kocienski reagents **3** and **5**, as well as the fluoro analogues **4** and **6** were next tested in olefination reactions (Table 3). These olefinations were performed under

reaction conditions that were previously shown to favor a trans disposition of aryl and alkyl substituents, i.e. *E*-isomer in reactions of the unfluorinated Julia-Kocienski reagents **18** and *Z*-isomer with α -fluorobenzyl BT-sulfones. **6a**

Yields and stereoselectivities in olefinations with the protio reagents **3** and **5** depended on both the carbonyl compound as well as the R group on the triazolyl moiety (entries 1-8). Yields were lowest in condensations of *N*-(3-phenylpropyl) substituted triazole **5** with alkanals (entries 6, 8). Olefinations with fluoro analogues **4** and **6** were *Z*-selective in every case tested (entries 10-17). Product yields in reactions with the fluorinated building blocks **4** and **6** were generally higher in comparison to those with protio derivatives **3** and **5**. Reactions of the ketone, *N*-benzylpiperidone with protio reagent **5** and fluoro reagent **4** gave the corresponding vinyl triazoles in 59% and 87% yield, respectively (entries 9, 18).

In summary, facile and previously unprecedented access to vinyl and fluorovinyl triazoles is possible from the bifunctional propargyl and fluoropropargyl benzothiazolyl sulfones. The fluoropropargyl derivative is readily obtained *via* metalation-fluorination of propargyl benzothiazolyl sulfone. Synthesis of triazoles from TMS-protected propargyl and fluoropropargyl sulfones can be accomplished in a single step by *in situ* TMS deprotection and Cu-catalyzed azide-alkyne ligation (68-93% yields). In competitive experiments a higher reactivity of the fluoropropargyl sulfone **2** was observed, compared to the protio analogue. DFT calculations show lower electron density at the terminal alkynyl carbon atom in **2a** compared to the protio analogue. This may be a contributor to the higher reactivity of the fluoropropargyl sulfone in the azide-alkyne ligation. This highly modular approach offers rapid access to diversely functionalized *N*-substituted vinyl and fluorovinyl triazoles, and can potentially find broad applicability in organic synthesis as well as in high-throughput methodology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.
Structures of the triazolyl Julia reagents.

Scheme 1.

Synthesis and click reactions of BT-propargyl and fluoropropargyl sulfones.

Table 1Conditions tested for deprotection-click reaction of **2**

Entry	Click catalyst (molar equiv)	AgBF ₄ (molar equiv)	Solvent; T (°C); t (h)	%Ratio of 4:2:2a ^a or yield
1	CuSO ₄ ·5H ₂ O (0.05); Na ascorbate (0.1)	0.2	CH ₂ Cl ₂ –H ₂ O 1.7:1; rt; 72	5:77:18
2	CuSO ₄ ·5H ₂ O (0.1); Na ascorbate (0.2)	0.2	<i>t</i> -BuOH–H ₂ O 9.5:0.5; 35 °C; 72	16:0:84
3	Cu(CH ₃ CN) ₄ ·PF ₆ (0.2)	0.2	CH ₂ Cl ₂ –CH ₃ OH 4:1; rt; 2	93 ^b

^aIn case of incomplete conversion, product was not isolated. Relative ratio of **4:2:2a** determined by ¹⁹F NMR. The ratio takes into consideration the molar excess of **2**.

^bYield of isolated, purified **4**.

Table 2Competitive click reactions of **1** and **2** with various azides

Entry	<i>R</i> =	%Ratio of products ^a	
		<i>X</i> = H	<i>X</i> = F
1	<i>p</i> -MeO-C ₆ H ₄ -	3 : 8	4 : 92
2	Ph(CH ₂) ₃ -	5 : 17	6 : 83
3	CH ₃ (CH ₂) ₉ -	7 : 28	8 : 72

^aRelative ratio of products determined by ¹H NMR.

Table 3

Synthesis of vinyl and fluorovinyl triazoles

$R = p\text{-MeO-C}_6\text{H}_4\text{-: 3, 4}$
 $R = \text{Ph}(\text{CH}_2)_3\text{-: 5, 6}$
 $X = \text{H: 9-17}$
 $X = \text{F: 18-26}$

Entry	Carbonyl	X =	BT-sulfone	Yield, ^a E/Z ratio ^b
1		H	3	9 : 73%, 33/67
2		H	5	10 : 85%, 15/85
3		H	5	11 : 65%, 72/28
4		H	5	12 : 44%, 83/17
5		H	3	13 : 67%, 86/14
6		H	5	14 : 41%, 77/23
7		H	3	15 : 71%, 72/28
8		H	5	16 : 31%, 7/93
9 ^c		H	5	17 : 59%
10		F	6	16 : 47%, 26/74
11		F	4	19 : 72%, 14/86
12		F	6	20 : 90%, 7/93
13		F	6	21 : 76%, 38/62
14		F	4	22 : 60%, 15/85
15		F	6	23 : 57%, 19/81
16		F	4	24 : 68%, 34/66

^aYields of isolated, purified products.

^bRelative ratio of diastereomers determined in the crude reaction mixture either by ¹H or by ¹⁹F NMR.

^cConditions: LHMDS, THF, 0 °C.