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Uracil Nucleosides with Reactive Group at C5 Position: 5-(1-Halo-2-sulfonylvinyl)uridine Analogues

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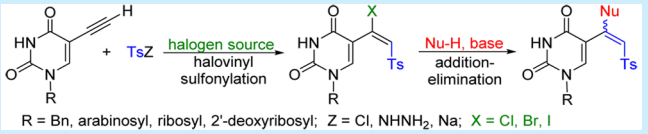
Supporting Information

ABSTRACT: The transition-metal-catalyzed or radical-mediated halosulfonylation of 5-ethynyluridine provided (*E*)-(1-halo-2-tosylvinyl)uridines. These (*β*-halo)vinyl sulfones undergo efficient stereoselective addition−elimination with amines or thiols to provide *Z*-*β*-aminovinyl or *E*-*β*-thiovinyl sulfones tethered to the C5 position of the uracil ring.



Vinyl sulfones are widely used intermediates in organic and medicinal chemistry.[1] They serve efficiently as Michael acceptors, 2*π*-partners in cycloaddition reactions, and chiral building blocks. Vinyl sulfones are potent irreversible inhibitors of cysteine proteases through the conjugate Michael addition of the thiol group of the active site cysteine residues.[1b,d]

Pyrimidine nucleosides with C5 modified bases have been extensively studied, and many analogues serve as potent antiviral and anitancer agents.[2] Introduction of reactive groups at the C5 position of pyrimidine nucleobases such as an alkyne[3] or azide[4] (for [2 + 3]-dipolar cycloadditions), aldehyde[5] for reductive aminations,[6] or ene/diene for Diels−Alder reaction,[7] among others,[8] have been explored. Rieder and Luedke reported 5-vinyl-2′-deoxyuridine−tetrazine ligation for imaging cellular DNA.[9] Recently, Hocek's laboratory developed a vinyl sulfonamide probe attached to the C5 position of the cytosine ring via the propargyl linker to study its bioconjugation with the protein by Michael addition and their applications in bioanalysis[10] (Figure 1). The triphosphates of these vinylsulfone probes were incorporated into deoxyoligonucleotides by DNA polymerases and were coupled with cysteine-containing proteins under physiological conditions.[10]

We were interested in developing an *alternative* probe based also on the vinyl sulfone scaffold but whose reactivity could be attained via conjugated addition−elimination processes rather than Michael additions. One alternative we explored was (*β*-halo)vinyl sulfones in which the *electrophilic* vinylic *β*-carbon functionalized with a halogen should be prone to substitution by nucleophiles. Surprisingly, much less is known about the chemistry of (*β*-halo)vinyl sulfones[11,12] than the (*α*-halo)vinyl sulfones, whose application to organic chemistry as well as nucleoside and medicinal chemistry is well documented.[13] Following our interest in the chemistry of vinyl sulfones,[14] (*α*-halo)vinyl sulfones,[15] and the chemistry of C5-modified uracil nucleosides,[16] we explored the synthesis of C5 pyrimidine nucleosides modified with a (*β*-halo)vinyl sulfone scaffold. Taking advantage of the recently developed transition-metal-catalyzed halosulfonylation of alkynes, which provide access to the (*β*-halo)vinyl sulfones,[17] we intended to explore their chemistry in nucleosides. Our rationale was that cross-linking of these reactive probes attached to nucleobases (of oligonucleotides) might offer a convenient method for a specific bioconjugation of DNA/RNA fragments to an active protein or other residues. Herein we report the design and synthesis of the (*β*-halo)vinyl sulfone probes attached to the C5 position of pyrimidine nucleobases and their capability to react efficiently with nucleophiles, including amino acid thiols, via the addition−elimination pathway.

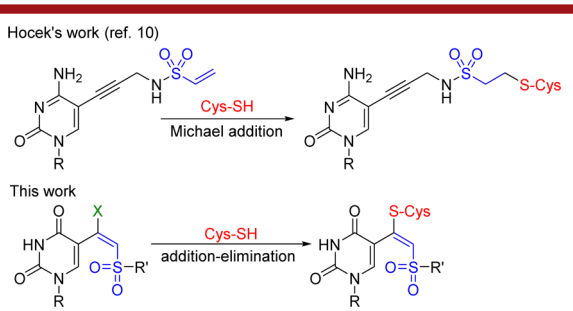


Figure 1. Bioconjugation of uracil-based vinyl sulfones with thiolates via the Michael addition[10] or conjugated addition−elimination.

The pyrimidine nucleosides with the (*β*-halo)vinyl sulfone modification at the C5 position were synthesized by halosulfonylations of the 5-alkyne precursors. Initially, we tested this approach with 1-*N*-benzyl-5-ethynyluracil **1** substrate. Thus, treatment of **1** with tosyl chloride **2** in the presence of $Fe(acac)_3$ and Ph_3P[17a] gave 5-(1-chloro-2-tosylvinyl)uracil **3** as a single *E* isomer (*vide infra*) in 60% isolated yield (Scheme 1).

Sulfones of type **3** were also prepared using FeX_3 (X = Cl or Br) as halogen sources[17b] and tosyl hydrazide **4**. Thus, treatment of **1** with **4** in the presence of $FeCl_3 \cdot 6H_2O$ and *tert*-butyl hydroperoxide (TBHP) also gave **3** (85%) as a single isomer

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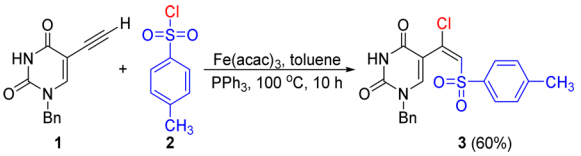
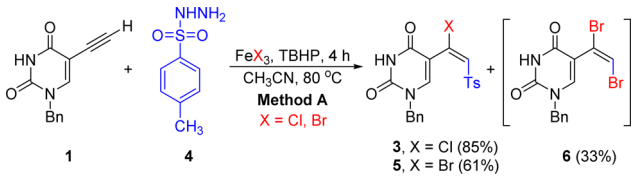
Scheme 1. Iron-Catalyzed Chlorosulfonylation of 1-*N*-Benzyl-5-ethynyluracil 1 with TsCl



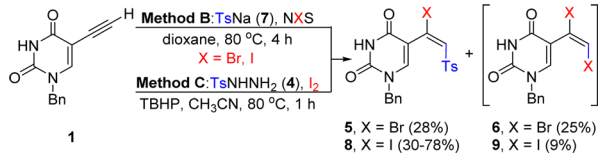
Scheme 2. Synthesis of (*E*)-(*β*-Halo)vinyl Sulfones *via* FeX_3-Mediated Halosulfonylation of 1 with Tosyl Hydrazide



(Method A, Scheme 2). Analogous bromosulfonylation of **1** in the presence of $FeBr_3$ provided the 5-(*β*-bromo)vinyl sulfone **5** (61%). The 5-*α*,*β*-dibromovinyl uracil derivative **6** was also formed (33%). It is noteworthy that the analogous dichlorovinyl byproduct was not isolated from the $FeCl_3$-mediated reaction with **1**.

The 5-(*β*-iodo)vinyl sulfone **8** was prepared[18] by either NIS-promoted[19] or I_2/TBHP-mediated[20] iodosulfonylation of **1** with sodium *p*-toluenesulfinate **7** or hydrazide **4**. Thus, treatment of **1** with **7** (1.5 equiv) in the presence of NIS (3.0 equiv) in 1,4-dioxane (80 °C/4 h) gave 5-(*β*-iodo)vinyl sulfone **8** (10%) in addition to the 5-(*α*,*β*-diiodo)vinyl byproduct **9** (30%; Method B, Scheme 3). Increasing the ratio of **7** to NIS (from 1:2 to 2:1)

Scheme 3. Synthesis of 5-(*β*-Halo)vinyl Sulfones via NXS-Catalyzed Halosulfonylation of 1 with 7 or TBHP-Promoted Halosulfonylation of 1 with 4

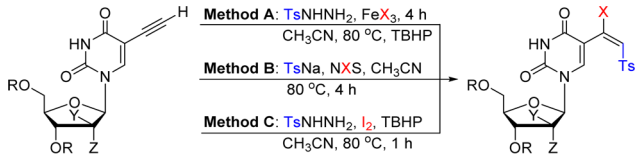


produced **8** in a slightly higher yield (30%). We found, however, that treatment of **1** with hydrazide **4** in the presence of I_2/TBHP provided **8** in 78% yield (Method C). The bromosulfonylation of **1** with **7** in the presence of NBS also yielded sulfone **5** (28%).

The halovinylsulfonylation protocols were successfully applied to the uracil nucleosides. Thus, treatment of 2′,3′,5′-tri-*O*-acetyl-5-ethynyluridine **10** with $TsNHNH_2$ **4** in the presence of $FeCl_3$/TBHP in MeCN provided protected (*E*)-5-(1-chloro-2-tosylvinyl)uridine **16a** (68%; Table 1, entry 1). Analogous treatment of **10** with **4**/$FeBr_3$ gave the 5-(*β*-bromovinylsulfone) **16b** (entry 2). Alternatively, **16b** was synthesized by the reaction of **10** with sulfinate **7** in the presence of NBS in MeCN, though in lower yield (entry 3). The $FeCl_3$/TBHP-mediated chlorosulfonylation of the protected 5-ethynyl arabinouridine **11** and 2′-deoxyuridine **12** gave *β*-chlorovinyl sulfones **17a** and **18a**, respectively (entries 4 and 5), showing stability of the glycosidic bond in the labile 2′-deoxy substrates under conditions required for *β*-halosulfonylations.

The unprotected 5-ethynyl nucleosides **13**–**15** were also efficiently converted to 5-(*β*-halovinylsulfones) **19**–**21**. Thus, treatment of uridine **13** with **4** in the presence of $FeCl_3$ or $FeBr_3$

Table 1. Synthesis of 5-(1-Halo-2-tosylvinyl)pyrimidine Nucleoside *via* Regio- and Stereoselective Halosulfonylation of 5-Ethynylpyrimidine Nucleosides[a]



Compounds: 10, **16** Z = OAc, Y = H, R = Ac
11, **17** Z = H, Y = OAc, R = Ac
12, **18** Z = H, Y = H, R = Ac
13, **19** Z = OH, Y = H, R = H
14, **20** Z = H, Y = OH, R = H
15, **21** Z = H, Y = H, R = H

Compounds: 16-21, Series: **a** X = Cl, **b** X = Br, **c** X = I

entry	substrate	method	halogen	product	yield[b]/%
1	**10**	A	$FeCl_3$	**16a**	68
2	**10**	A	$FeBr_3$	**16b**	53
3	**10**	B	NBS	**16b**	31
4	**11**	A	$FeCl_3$	**17a**	66
5	**12**	A	$FeCl_3$	**18a**	76
6	**13**	A	$FeCl_3$	**19a**	59
7	**13**	A	$FeBr_3$	**19b**	41
8	**13**	B	NIS	**19c**	42
9	**13**	C	I_2	**19c**	20
10	**14**	A	$FeCl_3$	**20a**	61
11	**15**	A	$FeCl_3$	**21a**	90
12	**15**	A	$FeBr_3$	**21b**	44
13	**15**	B	NIS	**21c**	30

[a]Reaction conditions: 5-Ethynyluracil nucleosides **10**–**15** (0.2 mmol), TsNa or $TsNHNH_2$ (0.4 mmol), halogen source (0.1–04 mmol), TBHP (0.4 mmol), MeCN, 80 °C. [b]Isolated yields.

gave *β*-chloro(or bromo)vinylsulfones **19a** and **19b** (entries 6 and 7), whereas reactions of **13** with **7**/NIS or **4**/I_2 provided *β*-iodovinylsulfone **19c** (entries 8 and 9). The generality of the method was further demonstrated by conversion of the 5-ethynyl-1-(*β*,D-arabinofuranosyl)uracil **14** or 5-ethynyl-2′-deoxyuridine **15** into the *β*-chloro **20a** and *β*-halo **21a**–**c** derivatives, respectively (entries 10–13).

The *E* stereochemistry[21] for the halovinylsulfones was established by (a) the lack of correlation between H6 and the vinylic proton in the NOESY spectra of **3** (which should be observed in the case of the *Z* isomer) and (b) the X-ray structure of **19a**. The molecular structure of **19a** is shown in Figure 2 and Figure S2 in the Supporting Information (SI). The glycosyl torsion angle C6–N1–C1′–O4′ is 43.9°, and the furanose

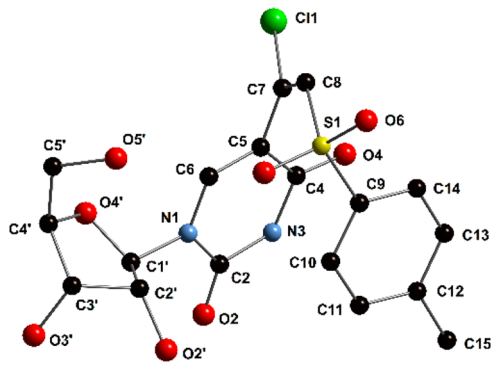


Figure 2. X-ray crystal structure of *E*-**19a**. H atoms and interstitial H_2O molecules are omitted for clarity.

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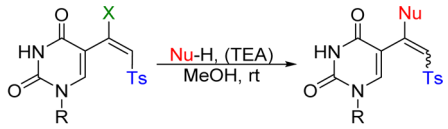
pseudorotation angle is 164.9° ($^2T_3$ conformation). The C3′−C4′−C5′−O5′ torsion angle is 53.6° and is in the g+/gg range. Nearly parallel uracil and benzene ring orientation would allow favorable $\pi-\pi$ interactions.

We were gratified to find that treatment of 1-*N*-benzyl-5-(1-chloro-2-tosylvinyl)uracil **3** with methanolic ammonia (rt/2 h) indeed led to the efficient nucleophilic substitution of chloride by an amine to yield the β-aminovinyl sulfone **22** as a single *Z* isomer in high yield (Table 2, entry 1). The *Z* stereochemistry of **22** was confirmed by the correlation between H6 and the vinylic proton in its NOESY spectra. The existence of β-sulfonylvinylamines as *Z* isomers has been recently proven by X-ray analysis and explained by stabilizing intramolecular H-bonding between the amine and the sulfone group.[22]

The generality of this substitution reaction has been demonstrated by the reactions of various (β-halo)vinyl sulfones with different nucleophiles (Table 2, entries 2−13). Thus, treatment of **3** with *n*-butylamine in MeOH gave an *E*/*Z* mixture of β-(alkylamino)vinyl sulfones **23** (entry 2). Reaction of **3** with propanethiol in the presence of TEA in MeOH led to vinylic substitution with retention of configuration to give β-thiovinyl sulfone *E*-**24** (entry 3). It is noteworthy that addition of a base (TEA) to the reaction of **3** with PrSH was necessary; otherwise, no substitution was observed even after 24 h. The *E*-configuration of **24** was established by X-ray analysis of **24** (Figure S3) and is in agreement with the analogous vinylic substitution reactions of (β-halo)vinyl sulfones with thiols.[11]

Table 2. Nucleophilic Substitution of 5-(1-Halo-2-tosylvinyl)uracil Nucleosides via Conjugated Addition−Elimination[a]



R: **3** = Bn
16a = Tri-*O*-acetylribos-1-yl
19a-d = Ribos-1-yl
21a = 2′-Deoxyribos-1-yl

entry	substrate	X	Nu−H	product	yield[b]/%
1	**3**	Cl	NH_3[c]	*Z*-**22**	71 (95)
2	**3**	Cl	*n*-$BuNH_2$	**23**[d]	71
3	**3**	Cl	*n*-PrSH[e]	*E*-**24**	62
4	**16a**	Cl	NH_3[c]	*Z*-**25**	60
5	**19a**	Cl	NH_3[c]	*Z*-**25**	84
6	**19a**	Cl	Cys-OEt[e]	**26**[f]	56
7	**19a**	Cl	*n*-PrSH[e]	*E*-**27**	75 (95)
8	**19b**	Br	*n*-PrSH[e]	*E*-**27**	91 (96)
9	**19c**	I	*n*-PrSH[e]	*E*-**27**	85 (97)
10	**19d**	H	*n*-PrSH[e]	–[g]	–
11	**19d**	H	NH_3[c]	–[g]	–
12	**21a**	Cl	*n*-PrSH[e]	*E*-**28**	68
13	**21a**	Cl	Cys-OEt[e]	**29**[h]	70[i]

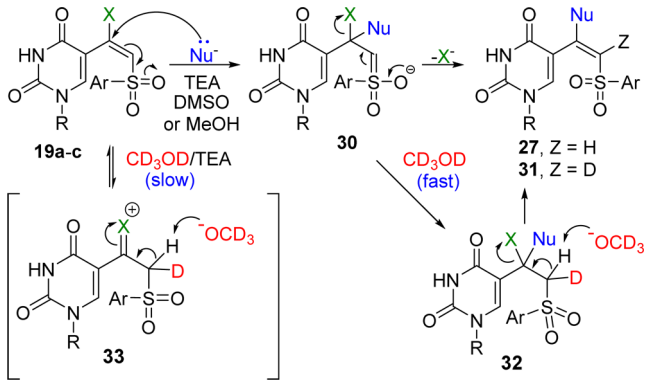
[a]Reaction conditions: β-halovinylsulfones **3**−**21** (0.1 mmol), nucleophiles (0.12 mmol), TEA (0.12 mmol; if needed), MeOH (2 mL), rt, 1−2 h. [b]Isolated yields. Yields for crude products (^{1}H NMR) in parentheses. [c]NH_3/MeOH. [d]*E*/*Z*, 15:85. [e]With the addition of TEA (0.12 mmol). [f]*E*/*Z*, 85:15. [g]No reaction. [h]*E*/*Z*, 80:20. [i]Single *E* isomer was isolated in 50% yield.

Treatment of the protected uridine (β-chloro)vinyl sulfone **16a** with methanolic ammonia (24 h) resulted in a concomitant deacetylation and vinylic substitution to give the β-sulfonylvinylamine (enamine) **25** as a single *Z* isomer (60%, entry 4). Reaction of the unprotected **19a** with NH_3/MeOH also yielded **25** but in a shorter time (2 h) and higher yield (84%, entry 5).

Reaction of (β-chloro)vinylsulfone **19a** with cysteine ethyl ester in TEA (1.2 equiv)/MeOH resulted in efficient addition−elimination to give the vinyl product **26** (entry 6) illustrating the possibility for bioconjugation of proteins to nucleos(t)ides bearing the (β-halo)vinylsulfone moiety. Treatment of **19a** with *n*-PrSH in MeOH/TEA (1−2 h) provided the vinyl thioether **27** as a single *E* isomer without formation of any byproducts (entry 7). Analogous treatment of (β-bromo)vinylsulfone **19b** and (β-iodo)vinylsulfone **19c** with PrSH afforded **27** in high yields (entries 8 and 9). It is noteworthy that analogous treatment of the nonhalogenated 5-(2-tosyl)vinyl uridine **19d** (prepared by hydrosulfonylation[23] of **10**; see SI) with NH_3/MeOH or PrSH resulted in recovery of **19d** (entries 10 and 11). Reaction of the 2′-deoxyuridine sulfone **21a** with PrSH or Cys-OEt in MeOH/TEA also yielded vinyl thioethers **28** and **29** (entries 12 and 13).

Kinetic analysis of the reactions between (β-halovinyl)sulfones **19a**−**c** (c = 9.93 mM in DMSO-d_6) and *n*-PrSH (1 equiv) in the presence of TEA (1 equiv) showed that these reactions display a second-order rate constant of 0.0096, 0.0192, and 0.0228 M^{-1} s^{-1} for the chloro **19a**, bromo **19b**, and iodo **19c** vinylsulfones, respectively (Figure S1). In general, the iodo and bromo vinylsulfones were more reactive toward substitution compared to the chloro analogues (I ≥ Br > Cl). The nucleophilic substitution is believed to proceed via the conjugative addition−elimination mechanism (Scheme 4). Thus, the nucleophile attacks the β-carbon of the halovinylsulfone **19a**−**c**, which is partially positive due to a combination of the electron-withdrawing properties of the sulfonyl moiety and the inductive effect of the halogen atom, giving **27** by elimination of the halide from the intermediate **30**. We also noted that when reactions were carried out in MeOH-d_4, the vinylic proton underwent exchange with deuterium to give the observed product **31** under these nucleophilic conditions (PrSH/MeOH-d_4/TEA). Perhaps intermediate **30** (with enolate-like basicity) is quenched by MeOH-d_4 to give intermediate **32**. The subsequent deprotonation of the more acidic C−H bond, compared to C−D bond, in **32** leads to **31**.

Scheme 4. Plausible Mechanism for the Nucleophilic Substitution of Halides from Uracil 5-(β-Halo)vinylsulfones



We also noticed that the vinylic proton undergoes exchange with deuterium when the aminovinylsulfone (e.g., **22** or **25**) is

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dissolved in DMSO-d_6/D_2O or MeOH-d_4 (^{1}H NMR). Such exchange does not occur when the vinyl thioether (e.g., **24** or **27**) is dissolved in MeOH-d_4 even in the presence of TEA. However, the exchange of the vinylic proton for deuterium also occurred for the chlorovinyl sulfone (e.g., **3** or **19**) in MeOH-d_4/TEA, although it is *slower* than that of aminovinylsulfones. Moreover, parallel experiments show that chlorovinyl substrates (e.g., **19a**) are converted *faster* to products **31** (Nu = PrS) under nucleophilic conditions (PrSH/MeOH-d_4/TEA) than the deuterium exchange occurred in chloro substrates **19a** dissolved in MeOH-d_4/TEA in the absence of thiol. Faster inclusion of deuterium under the nucleophilic conditions can be explained by the greater basicity of intermediate **30**, which leads to rapid deuterium acquisition, compared to *direct* vinylic deuteration of substrate **19a** via intermediate of type **33**.

In summary, we have developed a synthetic route to (*β*-halo)vinyl sulfone probes tethered to the C5 position of the pyrimidine nucleosides by transition-metal-catalyzed or radical-mediated halovinylsulfonylation of the 5-acetylenic precursors. The 5-*E*-(1-halo-2-tosyl)vinyl pyrimidine nucleosides undergo efficient nucleophilic substitution of halogens with the retention of configuration (with thiols) or inversion of configuration (with amines). The iodo and bromo substituents are replaced by a thiol group faster than the corresponding chloro counterpart.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00346.

Synthetic procedure for the preparation and characterization of compounds (PDF)

X-ray data for compounds **19a** and **24** (CCDC Nos. 1419905, 1447952) (CIF)

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Notes

The authors declare no competing financial interest.

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