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Rules and Stereoelectronic Guidelines for the Anionic Nucleophilic Displacement of Furanoside and Furanose O-Sulfonates

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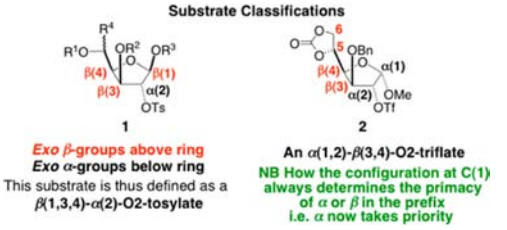
Ⓢ *Supporting Information*

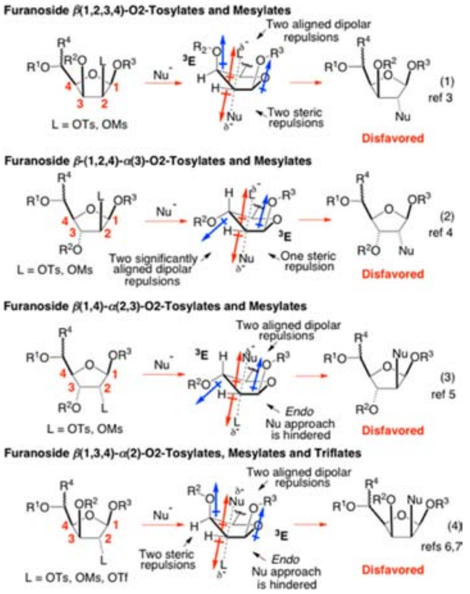
ABSTRACT: Rules for predicting anionic S_N2 displacement viability in furanose and furanoside sulfonates are presented.

Recently, we published an update[1] of the Richardson–Hough rules[2] for predicting S_N2 displacement viability in pyranoside sulfonates with charged nucleophiles. Here, we present a second set of rules for the rapid assessment of anionic S_N2 displacement viability in furanose and furanoside O-sulfonates, and although the guidelines that we proffer do not cover every reaction possibility, they do allow the confident prediction of many outcomes, particularly when used with the detailed reaction survey that we have provided in the Supporting Information (SI). The latter gives examples of the various types of furanoside/furanose secondary O-sulfonate that have so far been examined in the S_N2 process.



Central to the successful development and future application of these rules is the new system we have devised for categorizing the different types of furanoside/furanose O-sulfonate. For this we employ the long established descriptors, β and α, to define upward- and downward-pointing *exo*-heteroatom stereochemistry on a furanose/furanoside ring. Standard monosaccharide ring numbering is additionally employed to depict the *exo* substituent position. For the hypothetical furanoside **1**, where three heteroatom groups are located on the top-side of the ring at carbons 1, 3, and 4, and a single substituent is present on the underside of the ring at C(2), the prefix β(1,3,4)-α(2)- unambiguously defines its substitution pattern, while the configuration at C(1) determines α/β primacy within the prefix. A suffix is also used to specify the type of O-sulfonate that is being displaced. It too is numbered to identify its position on the furanoside ring. Accordingly, structure **1** can be designated as a β(1,3,4)-α(2)-O2-tosylate, and glycoside **2** as an α(1,2)-β(3,4)-O2-triflate.

By structurally classifying all of the main types of furanoside/furanose O-sulfonate in like fashion, and comparing their differing S_N2 reactivity profiles, it is possible to formulate a general set of S_N2 viability rules for the various classes of O-sulfonate that exist. These guidelines are adumbrated below, with the proviso that many other electronegative substituents, such as an N_3 or F, will exert a similar electronic effect to a ring OR group when they are stationed in an identical position (see the SI).



Rule 1. *β*-Furanoside 2-O-Sulfonates. (a) S_N2 reactions are disfavored[3−7] on the β-furanoside 2-O-sulfonates shown in eqs 1−4.

The great reluctance with which these four classes of furanoside O-sulfonate engage in S_N2 displacement reactions

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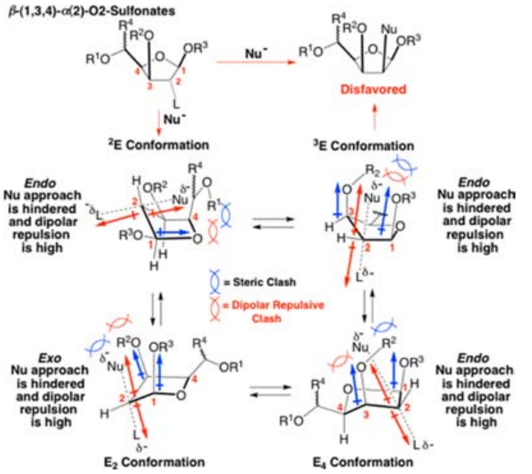
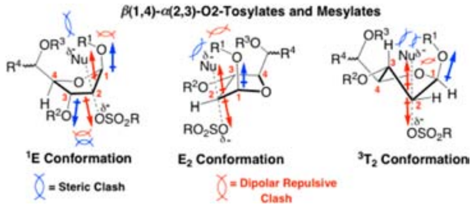
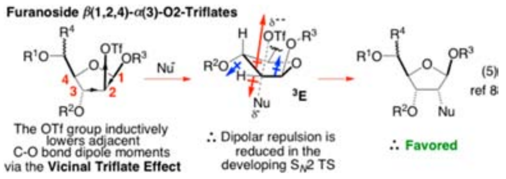
can be ascribed to adverse steric and dipolar repulsions being encountered in the advancing S_N2 transition states (TSs) as they attempt to proceed toward product. While eqs 1−4 illustrate just a few of the vicinal repulsions encountered in the different S_N2 TSs, when in the ^3E conformation, similar opposing forces can be identified in the S_N2 TSs of many other readily accessed starting conformers. The situation can perhaps be most readily visualized by examining several different S_N2 TSs for β(1,3,4)-α(2)-furanoside O2-sulfonates, and considering these as representative of the many possible for each of the four classes of O-sulfonate:


β-(1,3,4)-α(2)-O2-Sulfonates

In all cases, the combined depicted repulsions conspire to strongly disfavor or thwart successful S_N2 displacement, and the Vicinal Triflate Effect[1] can only help to a limited extent. Likewise, for furanoside β(1,4)-α(2,3)-O2-tosylate and mesylate displacements, strong steric hindrance and unfavorable dipolar repulsions are both apparent in many prospective S_N2 TSs in a wide range of conformers. For example:


β(1,4)-α(2,3)-O2-Tosylates and Mesylates

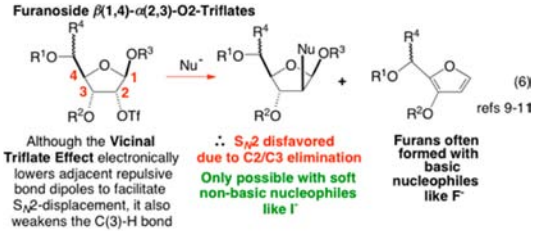
(b) **(i)** β(1,2,4)-α(3)-O2-triflates normally undergo anionic S_N2 displacement successfully (eq 5)[8] due to the beneficial workings of the Vicinal Triflate Effect[1] and limited opposing steric hindrance.


Furanoside β(1,2,4)-α(3)-O2-Triflates

The OTf group inductively lowers adjacent C-O bond dipole moments via the **Vicinal Triflate Effect**
∴ Dipolar repulsion is reduced in the developing S_N2 TS
∴ Favored

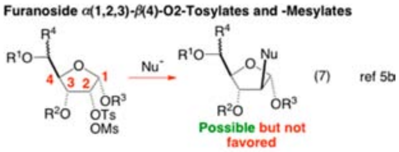
(ii) Although S_N2 displacements are disfavored with β(1,4)-α(2,3)-O2-triflates,[9−11] they are not prohibited, with greatest success coming when soft nucleophiles are used (e.g., I^- in C_6H_6) (eq 6). With basic, hard, nucleophiles (e.g., F^-), or with good nucleophiles of intermediate basicity (e.g N_3^-), invertive substitution and elimination often occur in direct competition.

Despite the Vicinal Triflate Effect[1] lowering adjacent fixed opposing C−O dipoles in β(1,4)-α(2,3)-O2-triflates, to render the S_N2 process electronically viable for all nucleophiles, the *anti*-relationship between H(3) and the C(2)−OTf makes the latter highly susceptible to undergoing E2 elimination even with moderately basic nucleophiles.

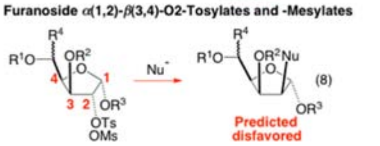

Furanoside β(1,4)-α(2,3)-O2-Triflates

Although the **Vicinal Triflate Effect** electronically lowers adjacent repulsive bond dipoles to facilitate S_N2-displacement, it also weakens the C(3)-H bond
∴ S_N2 disfavored due to C2/C3 elimination
Only possible with soft non-basic nucleophiles like I⁻
Furans often formed with basic nucleophiles like F⁻

Rule 2. *α*-Furanoside 2-*O*-Sulfonates. **(a)** S_N2 displacements on α(1,2,3)-β(4)-O2-tosylates and mesylates are possible, but are generally disfavored and fairly low yielding when attempted (eq 7).[5b] Displacements on their α(1,2)-β(3,4)-O2-tosylate and mesylate cousins are also *likely* to be problematical (eq 8); see the SI for our explanation.

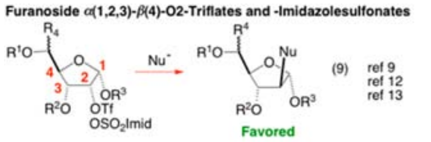

Furanoside α(1,2,3)-β(4)-O2-Tosylates and -Mesylates

Possible but not favored

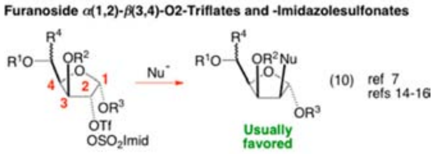

Furanoside α(1,2)-β(3,4)-O2-Tosylates and -Mesylates

Predicted disfavored

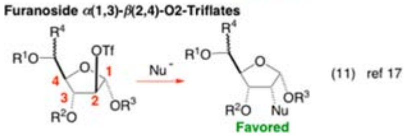
(b) By way of contrast, S_N2 reactions are usually successful when conducted on the corresponding α(1,2,3)-β(4)-O2-triflates and -O2-imidazolesulfonates (eq 9),[9,12,13] α(1,2)-β(3,4)-O2-triflates and -O2-imidazolesulfonates (eq 10),[7,14−16] and α(1,3)-β(2,4)-O2-triflates (eq 11)[17] due the dipole-lowering effects of these two leaving groups on adjacent OR or other electronegative groups.


Furanoside α(1,2,3)-β(4)-O2-Triflates and -Imidazolesulfonates

Favored


Furanoside α(1,2)-β(3,4)-O2-Triflates and -Imidazolesulfonates

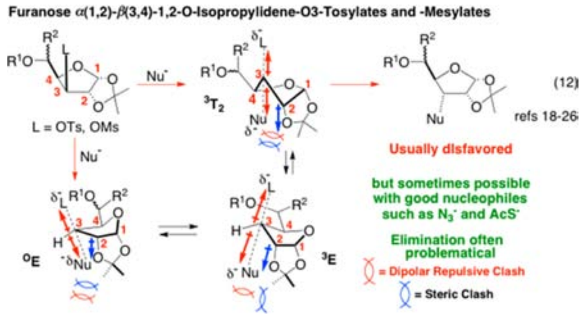
Usually favored


Furanoside α(1,3)-β(2,4)-O2-Triflates

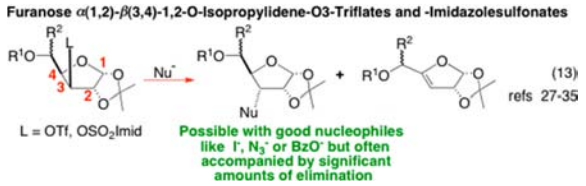
Favored

Rule 3. 1,2-O-Isopropylidenated *α*-Furanose 3-O-Sulfonates. For 1,2-O-isopropylidenated furanose 3-O-sulfonates, the descriptor "1,2-O-isopropylidene" is also introduced into the O-sulfonate classification system. Accordingly:

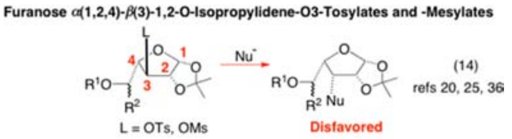
(a) **(i)** S_N2 displacements on α(1,2)-β(3,4)-1,2-O-isopropylidene-O3-tosylates and mesylates are usually counteracted sterically by the 1,2-O-acetal and electronically by the opposing repulsive C(2)−O(2) fixed dipole, which collectively hamper



attainment of many S_N2 TSs (eq 12). Despite this, such substitutions can occasionally be effected with good nucleophiles such as N_3^- or AcS^-, but frequently they are accompanied by E2 elimination.[18−26] In many cases, as well, such alkene byproducts are difficult to separate from the desired S_N2 products. **(ii)** While S_N2 displacements on the analogous 3-O-triflates do typically proceed with much greater facility,[27−34] due to the Vicinal Triflate Effect[1] (eq 13), and likewise 3-O-imidazolesulfonates[35] (due to analogous vicinal dipole-lowering effects associated with imidazolesulfonates and their imidazole-displaced sulfonate intermediates), still, C(3)/C(4)-elimination is a common problem for more basic nucleophiles.

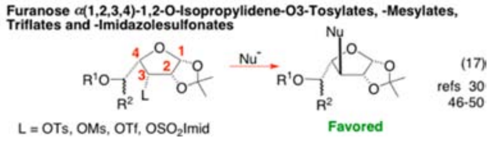


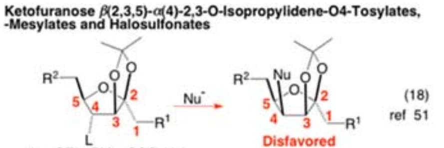
(b) For α(1,2,4)-β(3)-1,2-O-isopropylidene-O3-tosylates and mesylates, anionic S_N2 displacements (eq 14) are frequently disfavored.[20,25,36] However, the limited data that exist on the corresponding O-triflates suggest that these will undergo displacement due to a beneficial Vicinal Triflate Effect (eq 15),[30,37] but far less successfully than α(1,2,3,4)-1,2-O-isopropylidene-O3-triflates (eq 17), due to adverse steric influences.

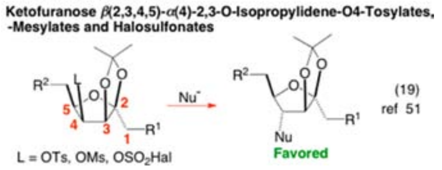


(c) α(1,2,3)-β(4)-1,2-O-Isopropylidene-O3-sulfonates (eq 16)[21,30−32,38−45] and their α(1,2,3,4)-1,2-O-isopropylidene-O3-sulfonate counterparts (eq 17)[30,46−50] both readily engage in S_N2 displacements with charged nucleophiles, but elimination is sometimes problematical for the latter type of substrate, particularly when the nucleophile has significant basicity. This is due to H(4) being *anti* with respect to the C(3)−OSO$_2$R group and the latter acidifying these H atoms by electron withdrawal.

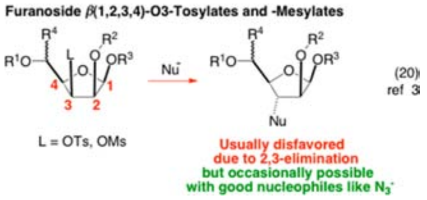
Rule 4. 2,3-O-Isopropylidene Ketofuranose 4-*O*-Sulfonates. Current evidence suggests that S_N2 displacements on ketofuranoside β(2,3,5)-α(4)-2,3-isopropylidene O4-halosulfonates, tosylates, and mesylates are strongly disfavored stereoelectronically (eq 18).[51] Displacements on their β(2,3,4,5)-O4-sulfonate counterparts are viable however (eq 19).[51]



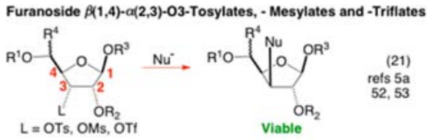


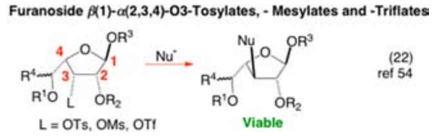


Rule 5. Furanoside 3-O-Sulfonates. **(a)** While S_N2 processes are usually difficult to effect on β(1,2,3,4)-O3-tosylates and mesylates, they can occasionally be performed in modest yield with very good nucleophiles (eq 20),[3] but once more, C(2)−C(3)-elimination can interfere detrimentally.



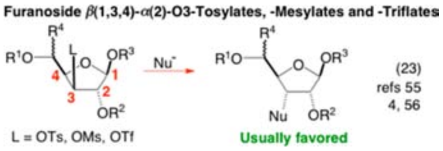
(b) S_N2 displacements on β(1,4)-α(2,3)-O3-tosylates and mesylates[5a,52,53] and β(1)-α(2,3,4)-O3-tosylates and mesylates generally proceed in acceptable yield (eqs 21, 22).[54]





(c) β(1,3,4)-α(2)-O3-sulfonates (eq 23) will usually undergo S_N2 displacement readily,[55,4] but if the anomeric group is a participatory O-benzoate ester, failures can occur (see SI).[56]

(d) Although α(1,2)-β(3,4)-O3-tosylates and mesylates are viable S_N2 substrates,[57] they generally react slowly (eq 24).



(23)
refs 55
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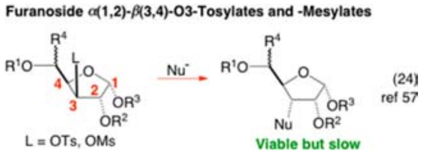

(24)
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Rule 6. Furanoside 5-Sulfonates. When primary, these always displace readily. However, *when secondary*, as in hexofuranosides, often more forcing conditions are required to effect S_N2 displacement, and such reactions usually proceed *without neighboring-group participation* if an O-ester group is present at O(6).

Rule 7. Hexofuranoside 6-O-Sulfonates. Being primary, these generally occur in good yield for all 6-O-sulfonates.

Rule 8. Hexulofuranoside 1-O-Sulfonates. S_N2 displacements are best performed with 1-OTf derivatives.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The experimental data that underpins these rules can be found tabulated in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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