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

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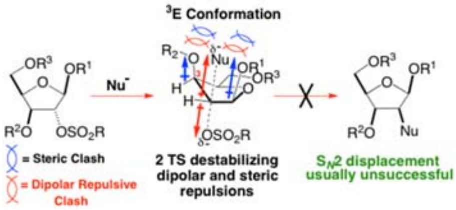
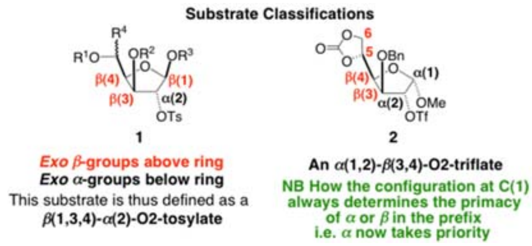
Supporting Information Placeholder



ABSTRACT: Rules for predicting anionic S$_N$2 displacement viability in furanose and furanoside sulfonates are presented.

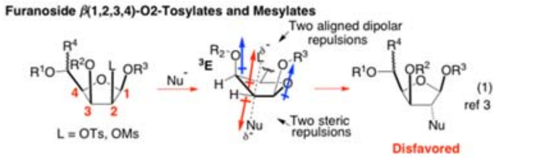
Recently, we published an update[1] of the Richardson-Hough rules[2] for predicting S$_N$2 displacement viability in pyranoside sulfonates with charged nucleophiles. Here, we present a second set of rules for the rapid assessment of anionic S$_N$2 displacement viability in furanose and furanoside O-sulfonates,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

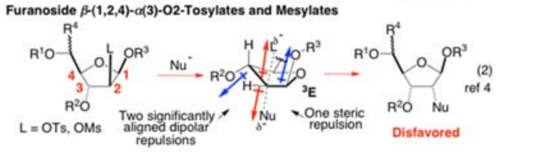
Central to the successful development and future application of these rules is the new system we have devised for categorizing the different types of furanoside/furanose O-sulfonate. For this we employ the long established descriptors, β and α, to define upward- and downward-pointing *exo*-heteroatom stereochemistry on a furanose/furanoside ring. Standard monosaccharide ring numbering is additionally employed to depict *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

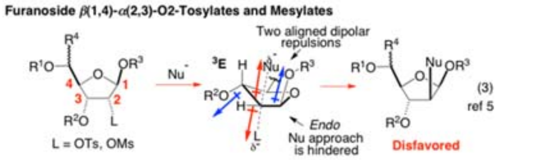


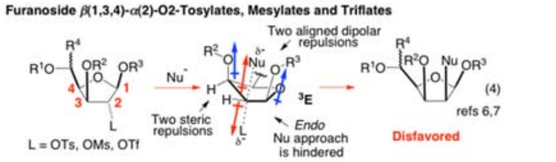
furanoside ring. Accordingly, structure **1** can be designated as a β(1,3,4)-α(2)-O2-tosylate, and glycoside **2** as an α(1,2)-β(3,4)-O2-triflate. By structurally classifying all of the main types of furanoside/furanose O-sulfonate in like fashion, and comparing their differing S$_N$2 reactivity profiles, it is possible to formulate a general set of S$_N$2 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 Supporting Information).

Rule 1. *β-Furanoside 2-O-sulfonates*: (a) S$_N$2 reactions are disfavored[3-7] on the following β-furanoside 2-O-sulfonates:

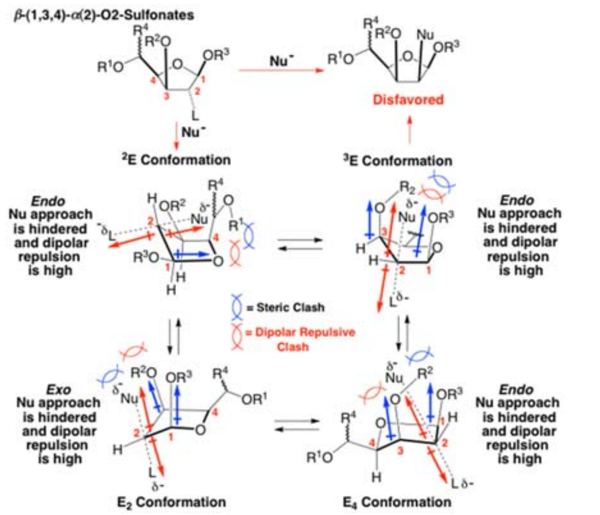




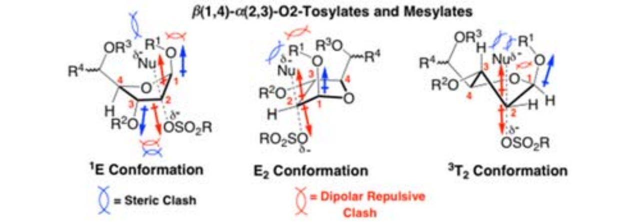




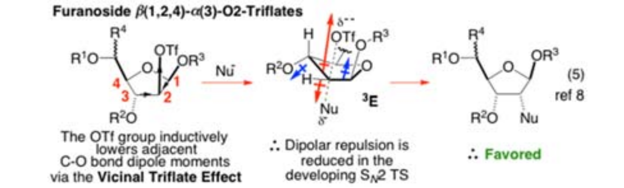
The great reluctance with which these four classes of furanoside O-sulfonate engage in S$_N$2 displacement reactions can be ascribed to adverse steric and dipolar repulsions being encountered in the advancing S$_N$2 transition states (TSs) as they attempt to proceed towards product. While eqs 1-4 illustrate just a few of the vicinal repulsions encountered in the different S$_N$2 TSs, when in the ^{3}E conformation, similar opposing forces can be identified in the S$_N$2 TSs of many other readily accessed starting conformers. The situation can perhaps be most readily visualized by examining several different S$_N$2 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:



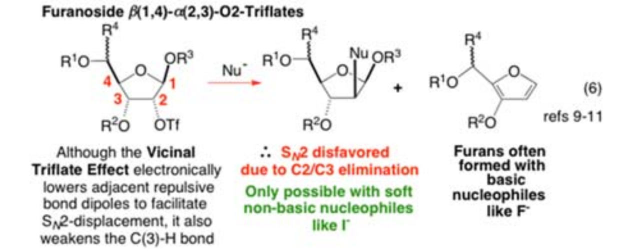
In all cases, the combined depicted repulsions conspire to strongly disfavor or thwart successful S$_N$2 displacement, and the Vicinal Triflate Effect[1] can only help to a limited extent. Likewise, for furanoside *β*(1,4)-*α*(2,3)-O2-tosylate and mesylate displacements, strong steric hindrance and unfavorable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



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

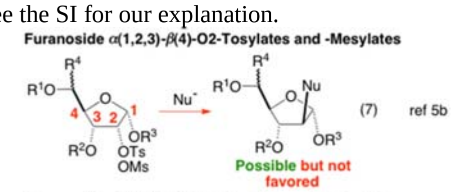


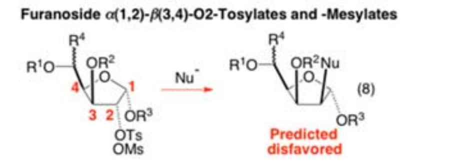
(ii) Although S$_N$2 displacements are disfavored with *β*(1,4)-*α*(2,3)-O2-triflates[9-11], they are not prohibited, with greatest success coming when soft nucleophiles are used (e.g. I^- in C_6H_6) (eq 6). With basic, hard, nucleophiles (e.g. F^-), or with good nucleophiles of intermediate basicity (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$_N$2 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.

Rule 2. *α-Furanoside 2-O-sulfonates*: (a) S$_N$2 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.

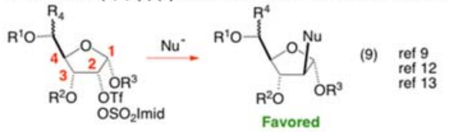




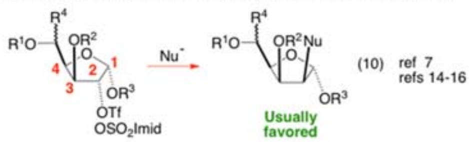
(b) By way of contrast, S$_N$2 reactions are usually successful when conducted on the corresponding *α*(1,2,3)-*β*(4)-O2-triflates and -O2-imidazolesulfonates (eq 9),[9,12,13] *α*(1,2)-*β*(3,4)-O2-triflates and -O2-imidazolesulfonates (eq 10), [7,14-16] and

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.

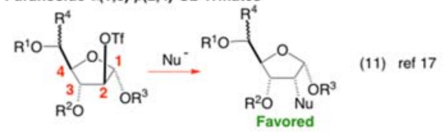
Furanoside α(1,2,3)-β(4)-O2-Triflates and -Imidazolesulfonates



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



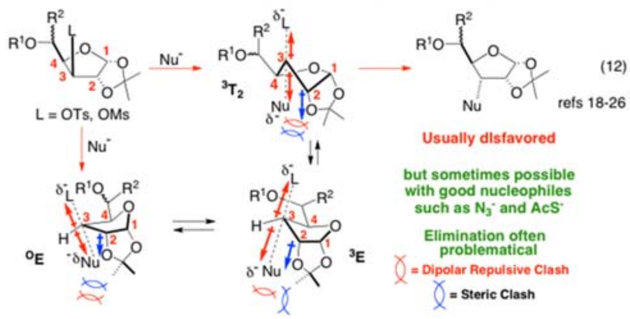
Furanoside α(1,3)-β(2,4)-O2-Triflates



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:

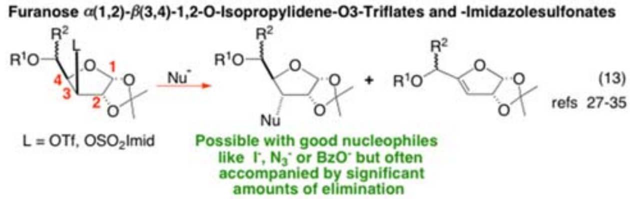
(a) (i) S$_N$2 displacements on α(1,2)-β(3,4)-1,2-O-isopropyl-

Furanose α(1,2)-β(3,4)-1,2-O-Isopropylidene-O3-Tosylates and -Mesylates



idene-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$_N$2 TSs (eq 12). Despite this, such substitutions can occasionally be effected with good nucleophiles such as N_3^- or AcS$^-$, but frequently they are accompanied by E2 elimination.[18-26] In many cases, as well, such alkene by-products are difficult to separate from the desired S$_N$2 products. **(ii)** While S$_N$2 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.

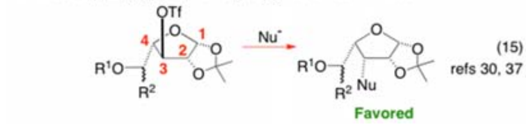
Furanose α(1,2)-β(3,4)-1,2-O-Isopropylidene-O3-Triflates and -Imidazolesulfonates



(b) For α(1,2,4)-β(3)-1,2-O-isopropylidene-O3-tosylates and mesylates, anionic S$_N$2 displacements (eq 14) are frequently disfavored.[20,25,36] However, the limited data that exists on the corresponding O-triflates suggests 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.

Furanose α(1,2,4)-β(3)-1,2-O-Isopropylidene-O3-Tosylates and -Mesylates

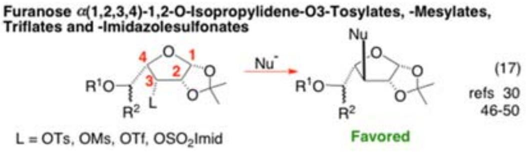
Furanose α(1,2,4)-β(3)-1,2-O-Isopropylidene O3-Triflates



(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$_N$2 displacements with charged nucleophiles, but elimination is sometimes problematical for the latter type of substrate, particularly when the nucleophile has significant basicity. This is due to H(4) being *anti* with respect to the C(3)-OSO$_2$R group and the latter acidifying these H-atoms by electron-withdrawal.

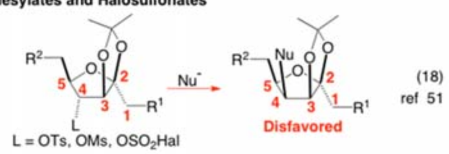
Furanose α(1,2,3)-β(4)-1,2-O-Isopropylidene O3-Tosylates, -Mesylates, Triflates and -Imidazolesulfonates

Furanose α(1,2,3,4)-1,2-O-Isopropylidene-O3-Tosylates, -Mesylates, Triflates and -Imidazolesulfonates

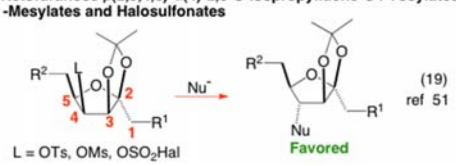


Rule 4. ***2,3-O-Isopropylidene Ketofuranose 4-O-Sulfonates*.** Current evidence suggests that S$_N$2 displacements on ketofuranoside β(2,3,5)-α(4)-2,3-isopropylidene O4-halosulfonates, tosylates and mesylates are strongly disfavored stereoelectronically (eq 18).[51] Displacements on their β(2,3,4,5)-O4-sulfonate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

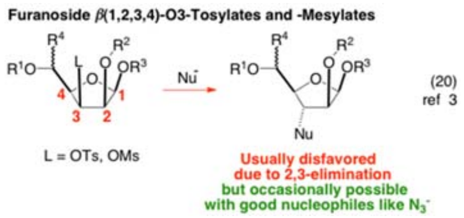
Ketofuranose β(2,3,5)-α(4)-2,3-O-Isopropylidene-O4-Tosylates, -Mesylates and Halosulfonates



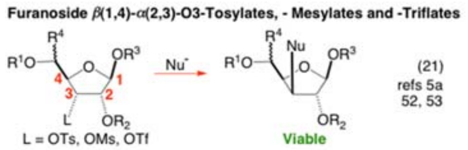
Ketofuranose β(2,3,4,5)-α(4)-2,3-O-Isopropylidene-O4-Tosylates, -Mesylates and Halosulfonates

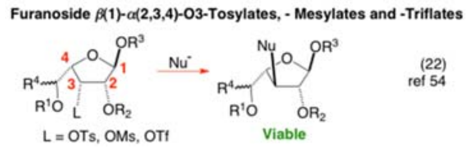


Rule 5. ***Furanoside 3-O-sulfonates*. (a)** While S$_N$2 processes are usually difficult to effect on β(1,2,3,4)-O3-tosylates and mesylates, they can occasionally be performed in modest yield with very good nucleophiles (eq 20),[3] but once more, C(2)-C(3)-elimination can interfere detrimentally.



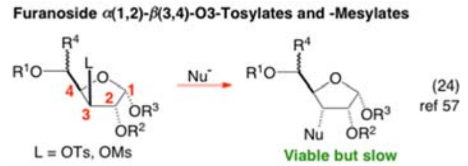
(b) S$_N$2 displacements on β(1,4)-α(2,3)-O3-tosylates and mesylates[5a,52,53] and β(1)-α(2,3,4)-O3-tosylates and mesylates generally proceed in acceptable yield (eqs 21, 22).[54]





(c) β(1,3,4)-α(2)-O3-sulfonates (eq 23) will usually undergo S$_N$2 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$_N$2 substrates,[57] they generally react slowly (eq 24).



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$_N$2 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$_N$2 displacements on C(1)-OTs and -OMs derivatives are usually difficult due to the TSs encountering adverse dipolar repulsions from the two C(2)-O atoms, and steric hindrance from the neopentylic center. Even so, the Vicinal Triflate Effect[1] can allow these S$_N$2 displacements to proceed with 1-OTf derivatives.

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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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