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


Published in:
Organic Letters

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
Link to publication record in Queen's University Belfast Research Portal

Publisher rights
Copyright © 2015 American Chemical Society

This document is the Accepted Manuscript version of a Published Work that appeared in final form in Organic Letters, © American Chemical Society after peer review and technical editing by the publisher.
To access the final edited and published work see http://pubs.acs.org/doi/abs/10.1021/acs.orglett.5b00511

General rights
Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.
Rules and Stereoelectronic Guidelines for the Anionic Nucleophilic Displacement of Furanoside and Furanose O-Sulfonates

Karl J Hale,* Leslie Hough, Soraya Manaviazar and Andrew Calabrese

The School of Chemistry & Chemical Engineering and the Centre for Cancer Research and Cell Biology (CCRCB), the Queen’s University Belfast, Stranmillis Road, Belfast BT9 5AG, Northern Ireland, United Kingdom

Supporting Information Placeholder

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

Recently, we published an update1 of the Richardson-Hough rules2 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. 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 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 N3 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_N2 reactions are disfavored4-7 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 $E_4$ 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 $\beta$-$\alpha$-$\alpha$-$\alpha$-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\textsuperscript{1} can only help to a limited extent. Likewise, for furanoside $\beta$-$\alpha$-$\alpha$-$\alpha$-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) $\beta$-$\alpha$-$\beta$-$\alpha$-O2-triflates normally undergo anionic S$_{N}$2 displacement successfully (eq 5)\textsuperscript{8} due to the beneficial workings of the Vicinal Triflate Effect\textsuperscript{1} and limited opposing steric hindrance.

(ii) Although S$_{N}$2 displacements are disfavored with $\beta$-$\alpha$-$\alpha$-$\alpha$-O2-triflates\textsuperscript{9-11}, they are not prohibited, with greatest success coming when soft nucleophiles are used (e.g. I$^-$ in C$_6$H$_6$ (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.

Rule 2. $\alpha$-Furanoside 2-O-sulfonates: (a) S$_{N}$2 displacements on $\alpha$-$\alpha$-$\alpha$-$\alpha$-O2-tosylates and mesylates are possible, but are generally disfavored and fairly low yielding when attempted (eq 7).\textsuperscript{5b} Displacements on their $\alpha$-$\alpha$-$\alpha$-$\alpha$-O2-triflates and -O2-imidazolesulfonates (eq 9),\textsuperscript{9,12,13} $\alpha$-$\alpha$-$\alpha$-$\alpha$-O2-triflates and -O2-imidazolesulfonates (eq 10),\textsuperscript{7,14-16} and

Despite the Vicinal Triflate Effect\textsuperscript{1} lowering adjacent fixed opposing C-O dipoles in $\beta$-$\alpha$-$\alpha$-$\alpha$-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.

(b) By way of contrast, S$_{N}$2 reactions are usually successful when conducted on the corresponding $\alpha$-$\alpha$-$\alpha$-$\alpha$-O2-tosylates and -O2-imidazolesulfonates (eq 9),\textsuperscript{9,12,13} $\alpha$-$\alpha$-$\alpha$-$\alpha$-O2-triflates and -O2-imidazolesulfonates (eq 10),\textsuperscript{7,14-16} and
α(1,3)-β(2,4)-O2-triflates (eq 11) due to the dipole-lowering effects of these two leaving groups on adjacent OR or other electron-negative groups.

**Rule 3. 1,2-O-Isopropylidened α-Furanose 3-O-sulfonates.** For 1,2-O-isopropylidened 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 by-products 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 (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. 20,25,26 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.

(c) α(1,2,3)-β(4)-1,2-O-Isopropylidene-O3-sulfonates (eq 16) 1,2,10-32,33,45 and their α(1,2,3,4)-1,2-O-isopropylidene-O3-sulfonate counterparts (eq 17) 10,46-50 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_2R 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 processes are usually difficult to effect 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.
Furanoside (1,2,3,4)-O3-Tosylates and -Mesylates

L = OTs, OMs

(b) $S_2$ displacements on $\beta(1,4)\rightarrow(2,3)$-O3-tosylates and mesylates$^{5,2,53}$ and $\beta(1)\rightarrow(2,3,4)$-O3-tosylates and mesylates generally proceed in acceptable yield (eqs 21, 22).$^{54}$

(c) $\beta(1,3,4)$-$\alpha(2)$-O3-sulfonates (eq 23) will usually undergo $S_2$ displacement readily,$^{55,4}$ but if the anomeric group is a participatory O-benzoate ester, failures can occur (see SI).$^{56}$

(d) Although $\alpha(1,2)$-$\beta(3,4)$-O3-tosylates and mesylates are viable $S_2$ substrates,$^{57}$ they generally react slowly (eq 24).

Rule 6. Furanoside 5-sulfonates. When primary, these always displace readily. However, when secondary, as in hexasulfonides, often more forcing conditions are required to effect $S_2$ displacement, and such reactions usually proceed without neighboring-group participation if an O-ester group is present at O(6).

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

Rule 8. Hexulosfuranoside 1-O-sulfonates. $S_2$ 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 neopentyl center. Even so, the Vicinal Triflate Effect can allow these $S_2$ displacements to proceed with 1-OTT derivatives.

AUTHOR INFORMATION

Corresponding Author
*k.j.hale@qub.ac.uk

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

REFERENCES

Authors are required to submit a graphic entry for the Table of Contents (TOC) that, in conjunction with the manuscript title, should give the reader a representative idea of one of the following: A key structure, reaction, equation, concept, or theorem, etc., that is discussed in the manuscript. Consult the journal’s Instructions for Authors for TOC graphic specifications.