Benefits of Using PSC in Various Applications

Background

Propanesulfonyl chloride (PSC; CAS# 10147-36-1) is a liquid with hue ranging from colorless to light-yellow. Pictured in Figure 1, this structural homologue of methanesulfonyl chloride (MSC) has an α-carbon with protons that are, in accordance with the electron-donating effect of the rest of the propyl chain[1,2], less acidic ($pK_a \approx 7.9$)[3,4,5]. Thus, in the presence of Et_3N (conjugate acid $pK_a \approx 10.8$) or DIPEA, the ensuing E1cB[6] or E2-like[5] elimination of PSC's chloride would yield lower amounts of a highly-reactive sulfene electrophile at some given time, enabling[7] PSC to more-selectively sulfonylate, e.g., a substrate's primary (1°) hydroxy or amino groups without[8] the need for prior protecting group installation at less-nucleophilic 2° –OH sites[9]. The greater flexibility afforded to organic synthesis route design by considering PSC for sulfonylation would also, given the greater steric hindrance[5] at PSC's sulfur compared to MSC's, come from a substrate nucleophile's more-hindered displacement[7] of the positively-charged catalyst (e.g., pyridinium) substituent formed from, e.g., pyridine's S_N2-like chloride displacement[10]. When foregoing isolation and/or purification (e.g., column chromatography), as for instance in "single-pot" synthesis, the lesser[11] leaving group (L.G.) lability of –OPs compared to mesylate could then be advantageous—like with isolated but *non*-purified sulfonate ester subsequently being reacted in a pressure bottle at 115 °C with NaI and co-added DIPEA (replaces the iodide L.G. substituent)—due to yielding fewer, and lower amounts of, side products[12].

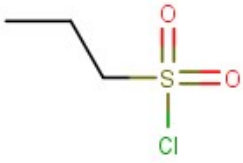

Figure 1. Structure of PSC.

Compared to *p*-toluenesulfonyl chloride (TsCl), the lighter[i] steric hindrance at PSC's sulfur may advantage a higher reaction rate—as shown with pyridine in 2° –OH activation[13]—and be especially preferable if TsCl use would make an already-lengthy sulfonylation too long. With Et_3N, one could expect any PSC-TsCl reactivity difference to shift more in PSC's favor given TsCl's lack of α-hydrogens along with the PSC-Et_3N acid-base reaction proceeding faster[2] than Et_3N's S_N2 attack on PSC's sulfur. Meanwhile, PSC-based[14] (i.e., via oxime sulfonylation) oxime sulfonates (e.g., Irgacure PAG 103) which generate propanesulfonic acid in the presence of light or heat to assist coating formation continue to find uniquely-preferential[15,16,17,18,19] applications (e.g., self-assembly of mesoporous heteroatom molecular sieves)[20] in the patent literature. PSC's utility with regard to sulfonamides and sulfonate esters, along with a separate consideration of selective activation, is briefly presented below.

Representative Cases of PSC as a Value-added Differentiator

Usage 1: Sulfonamide and Sulfonate Ester Synthesis

PSC has found considerable use in, via amino group sulfonylation, generating propyl sulfonamide moieties for such "sulfa drug" APIs as Abrocitinib and BI 882370 (i.e., XP-102). Although the latter API is a pan-RAF inhibitor uniquely binding to the DFG-out conformation[21] of protein targets[22], its 1° propyl sulfonamide sidechain, also possessed by Vemurafenib (and PLX-4720), has been a key feature[23] for stabilizing the protein DFG-in/αC-helix shift modes of binding with other exploratory RAF (i.e., B-RAF) inhibitors. This group is also known to be optimal[24,25] for fitting a RAF-selective pocket—into which the propyl chain[26] may be directed[27,28,29] by the sulfonamide-DFG-motif (e.g., H-bonding[30] with the backbone amide of Asp594) binding interactions—that is largely[31] unique to RAF-protein kinases[32].

[i] As evaluated in MarvinSketch, and reinforced by picturing PSC as being essentially a bisected TsCl—having only the latter compound's, from a 2-D visual perspective, "top" three C-atoms (i.e., without the bottom "half" of the *p*-tolyl group) minus the aromaticity.

When sulfonylating less-reactive 1° amines, particularly[33,34] those that are sterically hindered and have nearby EWGs, prudent addition of PSC and sufficiently-non-acidic base (i.e., and not just in catalytic amounts)[35] could[36] permit the removal of a hydrolysis (i.e., mono-desulfonylation) process step while still obtaining high product yields under, compared with pyridine, milder conditions (e.g., temperature, time)[37]. With PSC-based sulfonamidation (i.e., without bis-sulfonamidation) of deactivated anilines having been achieved via 3.0 eq. Et_3N elsewhere[37], consider the aniline-based substrates and reaction conditions presented in Figure 2; though drop-wise PSC addition at 0 °C for typical exothermicity control primarily led to bis-sulfonylation (75% yield)[38], a kilogram-scale procedure involving drop-wise addition of Et_3N over 80 minutes with stirring at 0 °C followed by PSC helped give in 97% yield[39] the mono-sulfonamide with[40] 95% purity. Rather than ortho F-Cl reactivity effect differences, the importance of chemical addition mode (e.g., speed, method) for mono-sulfonamidation of less-nucleophilic anilines when utilizing Et_3N or DIPEA may be reinforced by, with pyridine and DCM being nearly equal polarity-wise[41], the identical 89% yields achieved for mono-propanesulfonylated methyl 3-amino-2-fluorobenzoate (pyridine, 1.1 eq., in DCM) and methyl 3-amino-2-chlorobenzoate (pyridine as base *and* solvent, 2.6 eq.)[42].

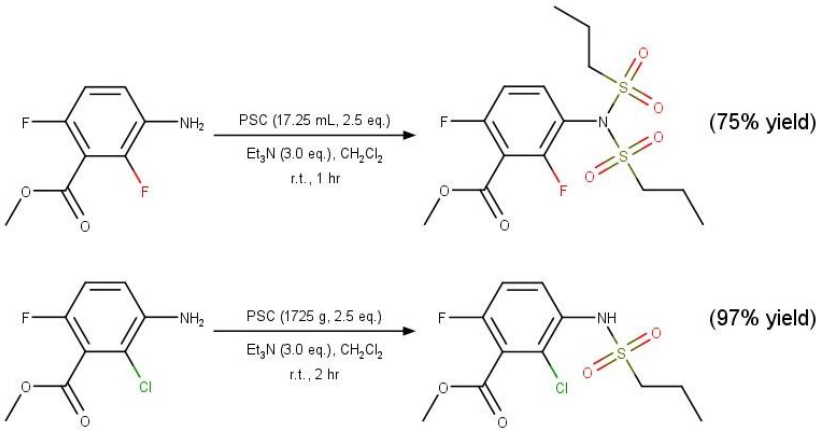

Figure 2. Example aniline-substrate bis-sulfonamidation (top) and kilogram-scale mono-sulfonamidation (bottom) procedures utilizing identical molar amounts of PSC (2.5 eq.) and Et_3N (3.0 eq.)[38,39,40].

In the literature, PSC-based sulfonate esters have found (ca. 2020) prominent use as additives, with PSC being used on a 100-g scale in preparation, to $LiPF_6$ and $LiSO_3CF_3$ solutions for high-voltage $LiCoO_2$-based rechargeable LIBs[43]. Propanesulfonate esters from PSC have also served[44,45] as low-melting-point (< -90 °C) solvents giving lower viscosity for higher Li^+ mobility than ESC-derived solvents. An acid amplifier obtained by reacting PSC with a substrate's 2° –OH was prominently featured (ca. 2017) in a patent's chemically-amplified photoresist compositions for exemplary, after thick-film exposure and development, pattern formation without inclusion of a light absorber in said compositions[46].

Usage 2: Selective Activating Agent

For PSC-based selective activation, 2,4,6-collidine (conj. acid $pK_a \approx 7.4$)[47] could be a particularly useful catalytic base due to, besides the activating effect of its three methyl EDGs outweighing the ortho-located sterics for enhanced reactivity over pyridine, its methyl groups sterically screening-out S-atom attack and consequent catalyst L.G. (i.e., collidinium) displacement by 2° –OH nucleophiles[7]. In particular, collidine and PSC were used together, and were the most-preferred base and reagent, for kilogram-scale activation (e.g., 20–25 °C) of a simple cyclohexanol's meta- and para-substituted hydroxymethyl groups without, by limiting reaction time to 4–6 h (by which point no starting material and < 2.5% of the intermediate mono-sulfonates remained), activating this triol's 2° –OH[48]. In contrast to the prior art's route for this Serlopitant API intermediate utilizing[49] MSC for merely, given the 2° –OH had already been etherified, non-selective 1° –OH activation, the propanesulfonate group's potential as an –OH protecting

group of sorts[50] is illustrated by a subsequent reduced-temperature 2° –OH etherification with imidate, after which allylamine (5 eq.) in polar *protic* solvent at 80 °C gave in 95% yield a double-sulfonate-displaced, allyl-protected pyrrolidine[48]. In slowing down S_N2 reaction[51] and thereby nicely complementing the aforementioned lower lability of –OPs, the solvent could have helped ensure that only one of the two 1° –OPs groups would be displaced to form a 2° amine that subsequently clearly[48] outpaced allylamine under the elevated temperature to S_N2-displace, intramolecularly, the other –OPs. Alternatively using PSC with 2,6-lutidine, this chloride-L.G. scavenger's non-nucleophilicity[51] instead perhaps[52,53] resulting in the S_N2-like attack of a substrate triol's 1° alcohols on PSC's sulfur, represents a successful selective activation method involving non-rigorous control of reaction time given the 100% yield achieved[54] for a similar triol-reactant's di-propanesulfonate after ≤ 41 h—even if $T > 25$ °C would have driven a faster reaction without loss of yield. Non-purified[12] product addition along with benzylamine and EtOH solvent to a tube sealed for reaction (140 °C, 3 h) subsequently gave pyrrolidine ring formation in ≥ 18% higher yield than from the aforementioned prior-route di-methanesulfonate[49] under quite similar conditions (150 °C, 3 h)[54,55].

For vicinal diols with one 2° –OH, PSC enabled epoxide formation in high combined yield (76–87%) from the sulfonate equivalent of a halohydrin[56] via methanolic[57] sodium methoxide[58]. Propanesulfonylation with 2.1 eq. Et_3N, notably *without* a separate and metallic catalyst like dibutyltin oxide (DBTO)[59,60], was run for 20 minutes from ⁻10 °C prior to adding the methoxide (with stirring subsequently carried out below 0 °C) base for 2° –OH deprotonation[58]. A more-advanced-structure diol substrate with –OH sites further apart as pictured in Figure 3 was selectively, on a 100-g scale, sulfonylated (0 °C, 2 h) by PSC with DIPEA base (1.3 eq.) in THF—with subsequent NaI addition at 0 °C to the non-purified[12] product in acetone for S_N2 iodation (25 °C, 2 h) giving a combined product yield of 91%[61]. As such, while a separate and/or metallic catalyst may not be necessary given the above reactivity and selectivity, DBTO could[62] still be added to further boost PSC's selective activating power besides reactivity.

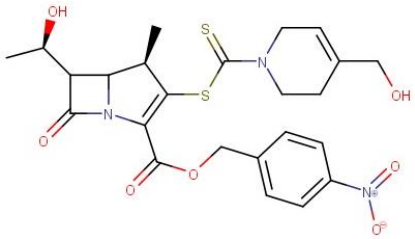

Figure 3. Structure of the diol whose 1° –OH site was selectively activated by PSC, prior to iodide's S_N2 displacement of the –OPs[61].

Varsal Advantage

Varsal is a leading producer of extremely-high-purity PSC, which is important considering the limited[37] commercial availability of MSC derivatives. We are differentiated from the competition as Varsal's proprietary manufacturing logistics processes allows us to produce consistent, stable, extremely-high-purity material—leading to maximal yield and product quality for Varsal's customers.

Extremely high purity for PSC is important for producing high yields of sulfa drug API intermediates in acceptable purity, such as when reacting PSC with "expensive" heterocyclic amines[63]. A literature source[40] with numerous synthesis examples only specified the reagent purities for the steps of the example featuring the aforementioned kilogram-scale mono-sulfonamidation—underscoring highly-pure-PSC's importance in scale-up reactions. Meanwhile, a low moisture content for PSC is important given that, even with a slow hydrolysis below at least[64] 70 °C, PSC's moisture sensitivity[65] nonetheless makes this chemical more subject to hydrolytic degradation in the presence of greater moisture[63]. Limiting the

moisture content introduced by reagents and/or precursors like PSC is also crucial for anhydrous and inert-atmosphere (e.g., N_2) conditions, which have been applied to an assortment of PSC-involved reactions including selective activation of vicinal diols[57], Ar-atmosphere preparation of –OPs solvents for LIB electrolytes[44,45], and 100-g-scale aniline-substrate propanesulfonylation[35].

Varsal is able to serve a wide variety of end-markets and applications, as our intimate knowledge of the manufacturing process allows us to custom-manufacture various grades of PSC tailored to our customers' requirements. Please contact us at info@varsal.com to learn more about how Varsal can help you solve your complex chemical and specialty intermediates challenges!

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