Streamlining SuFEx Inhibitor Development: A Unified Approach Using Orthogonal Sulfinate Protecting Groups

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Abstract: Sulfonyl fluorides have gained significant importance due to their classification as a click reaction and therefore have seen increased use in drug discovery and biochemistry. Their use, however, is complicated by the methods by which they are synthesized and their general synthetic instability. This results in sulfonyl fluorides being introduced late in a synthetic route with minimal structural diversity. Masking the reactivity of a sulfonyl fluoride by protecting the parent sulfinate is one method to ameliorate these issues. This study outlines discovery and selection of sulfinate protecting groups (SPGs) based on their overall stability, ease of synthesis, and simple deprotection conditions. This includes the discovery of two novel, photolabile sulfinate protecting groups (SPGs), *para*-methoxybenzyl Rongalite and *ortho*-nitrobenzyl Rongalite that can be directly converted to the sulfonyl fluoride using light and selectfluor. Along with known SPG, 2-trimethylsilylethyl sulfone (SES), all three SPGs were found to possess broad stability when exposed to numerous common synthetic conditions and are easily coupled to aryl halides from their sulfinate salt precursor. Overall, having access to a wide range of stable, easily functionalized SPGs will aid in increasing the structural diversity of sulfonyl fluorides.

Introduction

Over the past decade, sulfonyl fluoride exchange (SuFEx) chemistry has seen an increase in popularity owing to its use as a biocompatible "click" reaction.[1-4] First introduced in 2014, SuFEx chemistry relies upon the exchange of an incoming nucleophile with fluoride on a hexavalent sulfur forming an irreversible, covalent bond.[3] This exchange, however, must occur under catalytic conditions whereby both the sulfonyl group and departing fluoride group are stabilized by hydrogen bonding. This imparts a degree of stability and selectivity on sulfonyl fluorides (SFs) not seen with other electrophilic groups such as sulfonyl chlorides, epoxides, and acrylamides. When placed in the context of an enzyme active site, this catalytic condition is the hydrogen bonding associated with donor residues surrounding the nucleophilic residue of interest. This quiescent affinity model requires that the sulfonyl fluoride first establishes noncovalent interactions before undergoing nucleophilic attack. This selectivity and click-like reactivity of SFs has led to their incorporation into pharmaceutically active drug molecules and biochemical probes.[4, 5, 6]

Although SFs contain enhanced stability under physiological conditions,[7] their use is often complicated by their incompatibility to various common synthetic conditions such as nucleophiles, base, and high temperature. This results in SFs being incorporated onto a core scaffold late in the synthetic route. There are two main approaches for introducing sulfonyl fluorides in a synthetic route: first, a premade aryl SF is often coupled to a pendant group (such as an amine) through amide bond formation or amine alkylation (Figure 1a). Examples of this approach is evident in the synthesis of inhibitors for xIAP, MCL-1, BCL-1, and HSP27.[6, 8] Although this approach offers high yields, it relies on the commercial availability of the aryl sulfonyl fluoride, thus restricting the functional diversity possible. Furthermore, this

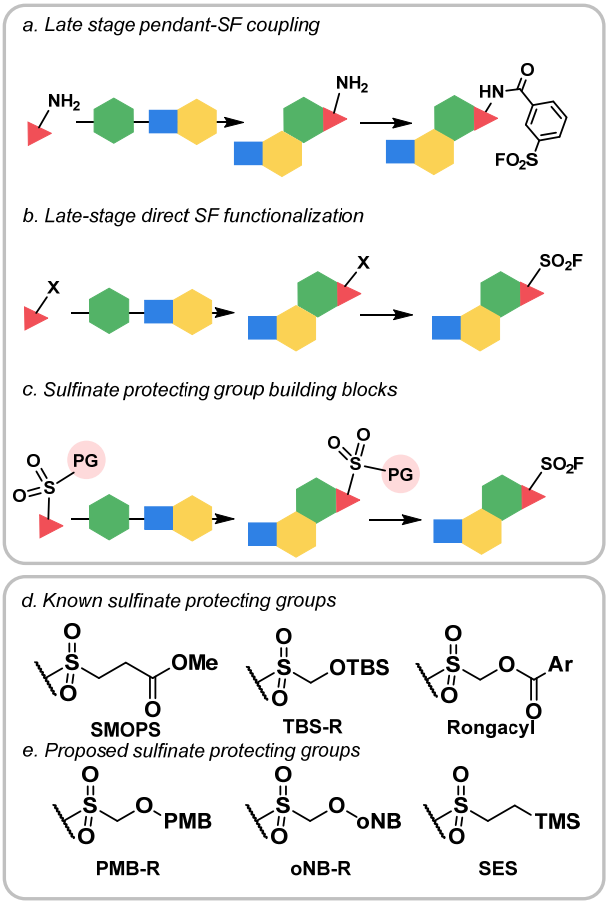


Figure 1. Current paradigms in SF incorporation and sulfinate late protecting group use

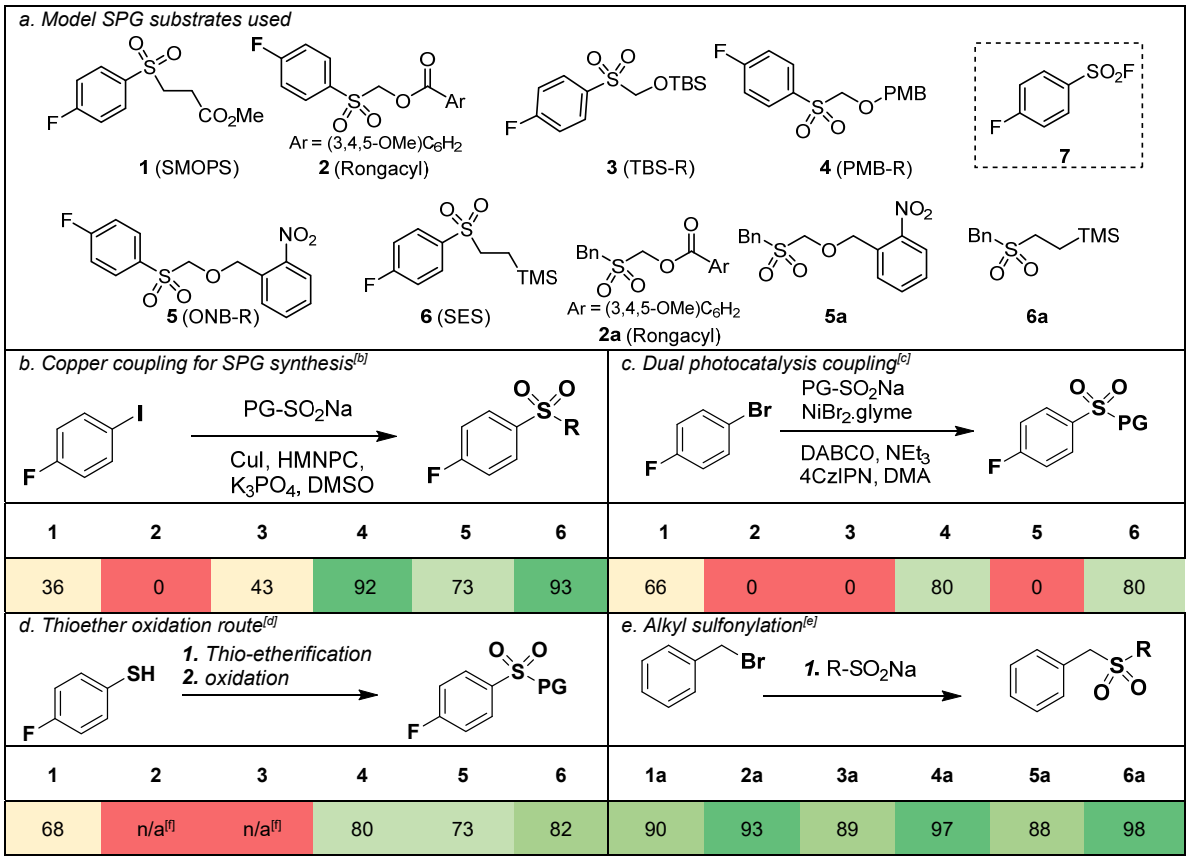


Figure 2. (a) model SPG substrates used in SPG synthesis and stability studies; (b) isolated yield of copper coupling conditions, conditions: 4-fluoroiodobenzene (0.23 mmol, 1 equiv), NaO_2S-PG (1.5-3 equiv), CuI (6-10 mol %), (2*S*,4*R*)-4-hydroxy-*N*-(2-methylnaphthalen-1-yl)pyrrolidine-2-carboxamide (HMNPC, 6-10 mol %), K_3PO_4 (1 equiv), DMSO, 50 °C, 24 h; (c) isolated yields of dual photocatalysis, conditions: 4-fluoroiodobenzene (0.1 mmol, 1 equiv), NaO_2S-PG (2 equiv), $NiBr_2$DME (5 mol %), 4CzIPN (0.2 mol %), DABCO (2.2 equiv), Et_3N (0.5 equiv), DMA, blue LED, 24 h; (d) isolated yields of two-step oxidation sequence, conditions: (1) see Supporting Information for alkylation (2) *m*-CPBA (3 equiv), CH_2Cl_2, 23 °C, 12 h, or Na_2WO_4 (0.5 equiv), H_2O_2 (5 equiv), MeOH, 23 °C, 24 h; (e) isolated yields of alkylation, conditions: BnBr (0.29 mmol, 1 equiv), NaO_2S-PG (1.5 equiv), DMSO, 23 °C, 24 h. [f] not applicable due to lack of access to corresponding alkyl halide.

approach leads to a pendant SF that is exposed, and therefore susceptible to off-target reactivity. The second option is direct late-stage SF functionalization (Figure 1b). Many efforts have been made to advance this area including the direct coupling of aryl halides and diazonium salts to sulfur dioxide surrogate, DABSO and various photocatalytic methods.[9] These efforts usually result in sulfinate salts that can then be oxidized to the SF using selectfluor or N-fluorobenzenesulfonimide (NFSI). In these cases, although the late-stage installation is elegant, the parent starting material (for example an aryl bromide) must be introduced late stage and/or be compatible with previous synthetic steps. Aryl sulfonyl fluorides can also be obtained from the corresponding sulfonic acid, sulfonamide, sulfonyl chloride, or thiol.[1]

Sulfinate protecting groups (SPGs) represent a promising approach to overcome the limitations associated SF synthetic instability (Figure 1c). The protected sulfinate can be carried through the necessary synthetic transformations and then subsequently deprotected. This would allow for not only greater structural diversity, but also permit a more combinatorial approach to developing varied SF-containing structures. Currently, three common SPGs are used (Figure 1d). Most common is 3-methoxy-3-oxopropane-1-sulfone (SMOPS),[10] which undergoes deprotection to the sulfinate in basic conditions. More recently, TBS-Rongalite (TBS-R),[11] and Rongacyl[12] have also been introduced and undergo deprotection with fluoride and hydroxide, respectively (Figure 1d). As with any protecting group, high stability and orthogonal deprotection conditions are required. In the course of our laboratory's efforts towards the synthesis of SF-containing small molecule inhibitors, we found that all three known SPGs had low stability in many common synthetic transformations. Thus, in this study, a comprehensive analysis of SPG synthesis and stability was undertaken. This ultimately resulted in the discovery of three additional SPGs with broad stability and unique, selective deprotection conditions.

Results and Discussion

Synthesis of aryl SFs

In addition to SMOPS, TBS-R, and Rongacyl, three additional SPGs were envisioned. *Para*-methoxybenzyl-

Table 1. SPG stability study

Reaction	Conditions[a]	Percent protected sulfinate compound recovered[b]								
		1	**3**	**4**	**5**	**6**	**2a**	**5a**	**6a**	**7**
		SMOPS	TBS-R	PMB-R	oNB-R	SES	Rong.	oNB-R	SES	SF
Amide Coupling	RCOOH, RNH_2, HATU, DIPEA, DMF, 23 °C, 24 h	100	100	100	100	100	88	100	100	73
S_NAr	Het-X, R-NH_2, DIPEA, 110 °C, 16 h	11	0	57	48	100	3	52	100	0
Boc Deprotection	BocNHR, TFA, DCM, 23 °C, 12 h	100	94	0	100	100	100	100	100	68
Ester hydrolysis	RCO_2Me, NaOH, H_2O:dioxane (1:1) 23 °C, 12h	0	0	100	100	100	0	92	100	0
Suzuki-Miyaura	ArI, $ArB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, dioxane:H_2O (5:1) 110 °C, 12 h	0	41	51	82	100	33	76	100	0
Amine S_N2	R_2NH, Alk-Br, K_2CO_3, MeCN, 23 °C, 2 h	100	100	100	100	100	100	100	100	100
Reductive Amination	R-CHO, R-NH_2, $Na(CN)BH_4$, MeOH, 23 °C 18 h	82	100	100	100	100	0	54	100	0
Hydrogenation	Olefin, H_2, Pd/C, MeOH, 23 °C 12 h	100	100[c]	100[c]	52	100	90	50	100	100
Buchwald-Hartwig	ArI, R_2NH, $Pd_2(dba)_3$, P(o-tolyl)$_3$, NaO^{t}Bu, Dioxane, 100 °C 24 h	0	0	35	10	100	0	9	100	0

[a] See supporting information for full conditions; reaction yield was greater than 70% unless otherwise noted; [b] Yields refer to percent protected sulfinate recovered as calculated from ^{19}F NMR or ^1H with an internal standard; [c] Parent reaction did not yield product.

Rongalite (PMB-R) and *ortho*-nitrobenzyl Rongalite (oNB-R) were intended to be deprotected under oxidizing conditions and light, respectively, while 2-trimethylsilylethylsulfone (SES) would be deprotected with fluoride (Figure 1e). SES is a common protecting group for sulfonamides; however, its use as a sulfinate protecting group is much rarer with only a single report showing its use in forming sulfinates.[13] Combined with the already known protecting groups of TBS-R, Rongacyl, and SMOPS, PMB-R, oNB-R and SES should provide orthogonal deprotection conditions and stability profiles.

The use of a copper catalyst and the proline-derived ligand, (2*S*,4*R*)-4-hydroxy-*N*-(2-methylnaphthalen-1-yl)pyrrolidine-2-carboxamide (HMNPC) has been used in the S-arylation of sulfinates with aryl iodides under mild conditions.[14] The sulfinate salts of SMOPS, TBS-R, and Rongacyl are all known.[10-12] PMB-R and oNB-R sulfinate salts were made from the corresponding chloromethyl ether in a facile manner on gram scale (see Supporting Information). The resulting solids were shelf stable (2+ months), non-hygroscopic powders. SES sulfinate was made from vinyltrimethylsilane according to a modified literature procedure (See Supporting Information).[13, 15] All reactions proceeded in high yield. PMB-R, oNB-R, and SES sulfinates coupled with aryl iodides in high yields at 50 °C in the presence of CuI/HMNPC (Figure 2b). In contrast, SMOPS, TBS-R, and Rongacyl sulfinate resulted in either low yields or no product. It is worth noting that higher yields for the coupling of TBS-R sulfinate were obtainable when the aryl iodide was held in excess (3 equiv) as per the original literature report.[16] Only SES sulfinate coupled with aryl bromides albeit at elevated (100 °C) temperatures.

Recently, König reported universal conditions for the coupling of aryl bromides and various nucleophiles, including sulfinates, using nickel and the photocatalyst 4CzIPN.[17] SMOPS, PMB-R, and SES sulfinate were effectively coupled with aryl bromides using $NiBr_2$(DME), 4CzIPN, and DABCO in 80%, 80%, and 75% yield, respectively (Figure 2c). The PMB-R sulfinate coupling required air-free conditions while both SMOPS and SES required the presence of oxygen (air). oNB-R sulfinate failed to engage and Rongacyl degraded. This photocatalytic method provides a straightforward method to access protected sulfinates from the much more readily accessible aryl bromide. Efforts are ongoing to further the utility of this reaction.

It is also possible to access the aryl SPG from the thiol via alkylation and subsequent oxidation with sodium tungstate (Figure 2d). PMB-R and oNB-R can all be made via this route in high yield. SES and SMOPS are made via the addition of the thiol to the vinyl trimethylsilane and methyl acrylate with AIBN, respectively (See Supporting Information). TBS-R and Rongacyl cannot be accessed via this method due to the inability to obtain the corresponding alkyl halide. To access alkyl SPGs, benzyl bromide was reacted with the corresponding sulfinate in high yield (Figure 2e).

As with any protecting group, broad stability is required. To provide insight for their use in any synthetic endeavor, the stability of SPGs was investigated in a variety of synthetic conditions. The top ten most used synthetic transformations in medicinal chemistry were chosen for SPG stability testing (Table 1).[18] These conditions included: amide coupling (HATU), S_NAr (Et_2N^iPr, 110 °C), acidic Boc deprotection (4 M HCl), ester hydrolysis (NaOH), Suzuki coupling ($Pd(PPh_3)_4$, K_3PO_4, 110 °C), amine S_N2 (K_2CO_3), reductive amination ($Na(CN)BH_3$), hydrogenation (Pd/C, H_2), and Buchwald-Hartwig amination ($Pd_2(dba)_3$, P(o-tolyl)$_3$, NaO^{t}Bu, 100 °C). Model aryl protected sulfinates **1**-**6** and benzyl protected sulfinates **2a**, **5a**, and **6a**, were added to the reaction mixture for a certain transformation, and upon completion of the reaction, the percentage of recovered SPG was calculated. Sulfonyl fluoride **7** was also subjected to these same conditions. The conditions chosen were the most common conditions found for each transformation. It is possible that in optimizing a reaction, one may find specific conditions that are less harsh and therefore result in greater retention of the SPG. In each

transformation, the reaction itself proceeded in greater than 70% yield unless otherwise noted (see Supporting Information).

Overall, all SPGs were stable under mild reaction conditions such as amide coupling, amine S_N2, and acidic Boc deprotection. Similarly, under reductive amination and hydrogenation conditions, most SPGs demonstrated high stability. The oNB-R protecting group (**5** and **5a**) was partially reduced to the aniline under hydrogenation conditions and did not deprotect. It is worth noting that under hydrogenation conditions the PMB-R (**4**) protecting group was stable. In reactions with harsher conditions, such as SN_{Ar}, Suzuki coupling, and ester hydrolysis, PMB-R, oNB-R and SES (**4**, **5**, and **6**) were superior to known SPGs, which degraded under these conditions. Only the SES protecting group was stable under Buchwald-Hartwig coupling conditions with potassium tert-butoxide as base. Switching the base, however, to cesium carbonate and Xantphos as ligand, resulted in a higher retention of oNB-R, **5** (see Supporting Information). As a point of comparison, the parent sulfonyl fluoride (**7**) only survived S_N2, acidic deprotection, and amide coupling, highlighting the need for SPGs.

Deprotection

Deprotection of TBS-R (**3**) and Rongacyl (**7**) were accomplished according to their literature methods.[11, 12] TBS-R (**3**) has the benefit of being a one-pot deprotection (CsF, Selectfluor). SMOPS **(1**) and Rongacyl (**7**) requires a two-step procedure with deprotection via sodium hydride (SMOPS) and sodium hydroxide (Rongacyl) followed by workup and selectfluor addition (Table 2). Given that PMB groups are generally deprotected under oxidizing conditions, we first looked for methods that would allow for selectfluor to act as the oxidant. This led to the photocatalytic deprotection of the PMB group following conditions first reported by Stephenson.[19] Using either iridium or acridinium photocatalysis in the presence of blue light and selectfluor led directly to sulfonyl fluoride (Table 3, entry 2 and 3). Interestingly, however, deprotection and fluorination was able to occur (89% yield) in the absence of photocatalyst provided that three equivalents of selectfluor were present (entry 1). These conditions provide a direct, metal-free method to mildly deprotect and fluorinate PMB-R-protected aryl sulfones. Lower yields were obtained when 1 or 2 equivalents of selectfluor was used (entry 4 and 5). The presence of water is essential for the successful removal of the protecting group (entry 6).

Switching to NFSI or addition of TEMPO resulted in little to no product confirming a radical-based mechanism involving the 1,4-diazoniabicyclo[2.2.2]octane (TEDA) radical cation (See Supporting Information for a plausible mechanism).[20] No reaction occurred in the absence of selectfluor and light (entry 8 and 12, respectively).

A small scope was investigated for this deprotection (Table 4). The deprotection of the PMB was tolerable to both electron deficient (**11b**, **13b**, and **15b**) ring systems as well as electron rich (**12b**), ring systems. Amides were tolerable, as well as pyridine and thiophene heterocycles (**17b** and **18b**). Alcohols were also well tolerated (**14b**). Alkyl benzyl sulfinates were also deprotected cleanly (**19b**).

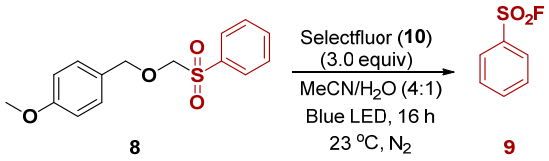
Turning to the oNB-R protecting group, deprotection and fluorination can occur cleanly under irradiation with blue light in the presence of selectfluor via a Norrish-type II deprotection mechanism. The scope of this reaction was similarly wide with high yields for electron rich, electron poor, and heterocyclic ring systems (Table 3**, 11a-19a**). Finally, the SES protecting group was deprotected using TBAF at 70 °C followed by cooling and addition of selectfluor. The yield, although slightly lower than the deprotection for oNB-R and PMB-R groups, was still high across all substrates tested (**11c-19c**).

Table 2. Overview of stability and deprotection/ fluorination of SPGs

	1	**3**	**4**	**5**	**6**	**2b**
Stability Ranking[a]	5	4	3	2	1	6
Deprotection Conditions[b]	1. NaH 2. **10**	**10** CsF	**10** hn	**10** hn	TBAF 70 °C then **10**	1. NaOH 2. NFSI
One-pot	×	✔	✔	✔	✔	×
Yield[c]	44%	91%	84%	86%	89%	76%

[a] based off average yield of all 10 reactions from Table 2. [b] See Supporting Information for detailed conditions; temperature of the reaction is 23 °C unless otherwise noted. [c] yields refer to isolated yield.

Table 3. Optimization of PMB-R deprotection / fluorination[a]



8 **9**

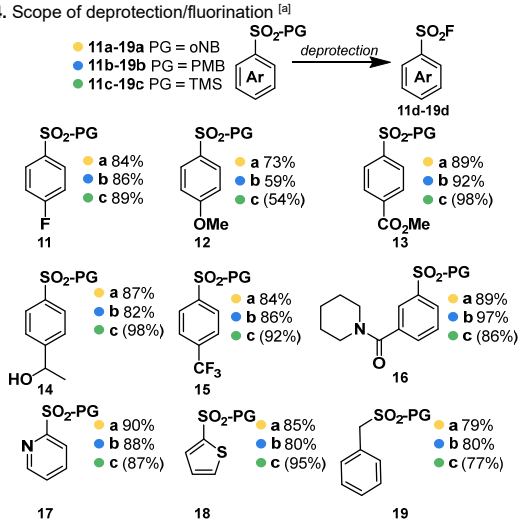
Entry	Variation from standard conditions	Yield (%)[b]
1	As above	97 (89%)[c]
2	2 mol% $(Ir[dF(CF_3)ppy]_2(dtbpy))PF_6$	85
3	2 mol% Mes-Acr catalyst	52
4	1.0 equiv of **10** instead of 3.0 equiv	10
5	2.0 equiv of **10** instead of 3.0 equiv	22
6	MeCN only, no H_2O	0
7	NFSI instead of **10**	17
8	No selectfluor	0
9	Open atmosphere	25
10	60 °C	trace
11	4.0 equiv TEMPO	0
12	No Light	0

[a] Conditions: **8** (0.2 mmol), **10** (3.0 equiv), (MeCN:H_2O (0.2 M), 23 °C, 16 h, N_2. [b] yields determined by ^1H NMR analysis with 4-fluoroacetophenone as an internal standard. [c] isolated yields are in parentheses, Mes-Acr = 9-Mesityl-3,6-di-tert-butyl-10-phenylacridinium tetrafluoroborate TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, NFSI = N-fluorobenzenesulfonimide

Summary

Overall, considering the synthesis, stability, and deprotection, SES and oNB-R proved to be the most useful SPGs. SES was the most stable across all conditions tested and could be synthesized from the aryl bromide via copper coupling or nickel dual photocatalysis. SES was amenable to most sulfinate coupling chemistry, further demonstrating its utility. SES, however, had harsher deprotection conditions with TBAF at elevated temperatures. oNB-R on the other hand, had stability across most conditions and had extremely mild and orthogonal deprotection conditions. PMB-R was a useful SPG in basic conditions but showed instability under harsher conditions. PMB-R, however, has a selective and unique deprotection method. SMOPS, the most common SPG used, had limited stability across numerous reaction conditions. It also cannot be excluded the ease of synthesis and availability of the corresponding SPG and its precursors. SMOPS benefits from being derived from inexpensive methyl 3-mercaptopropionate. For this reason, SMOPS is also used in making some of the other SPG sulfinates. oNB-R and PMB-R are more cost intensive to make and

Table 4. Scope of deprotection/fluorination [a]



[a] yields refer to isolated yields; yields in brackets refer to NMR yields with 4-fluoroacetophenone as an internal standard. Conditions for deprotection of **11a-19a:** **11** (0.2 mmol), selectfluor (5.0 equiv), (MeCN:H_2O (0.2 M), 40 °C, 16 h, N_2; for deprotection of **11b-19b**: **11b** (0.2 mmol), selectfluor (3.0 equiv), (MeCN:H_2O (0.2 M), 40 °C, 16 h, N_2; for deprotection of **11c-19c**: **11c** (0.2 mmol), TBAF (1.1 equiv, 1M in THF), THF 70 °C 16 h, then selectfluor (1.2 equiv), MeCN, 23 °C, 1 h.

employ (yet can still be made on multigram scale). SES, once again, is not overly cost and time intensive to synthesize and when combined with its favorable stability, proves to be a useful SPG.

Conclusions

In conclusion, we have undertaken a comprehensive study of sulfinate protecting group stability by subjecting six different sulfinate protecting groups to a variety of common synthetic transformations. Additionally, methods to synthesize aryl containing SPGs were also assessed. From these studies, it was found that 2-trimethylsilylsulfone (SES) and the newly disclosed *ortho*-nitrobenzyl Rongalite sulfone (oNB-R) possessed a broad stability profile, a facile method of synthesis, and a selective and orthogonal deprotection/fluorination procedure. An additional SPG, *para*-methoxybenzyl Rongalite was also found to have broad stability and an intriguing deprotection/fluorination condition of selectfluor and light. Ultimately, the SPG chosen in a synthetic endeavor should be tailored to the synthetic conditions used and the functionality present. The studies above outline the benefits and drawbacks of each SPG while providing additional groups with novel, orthogonal deprotection conditions. Overall, these groups should allow for more structural diversity in the synthesis of SF containing small molecule inhibitors or probes.

Acknowledgements

This work was supported by funding from Rutgers University and from the New Jersey Health Foundation (to M.J.M).

Conflicts of interest

A provisional patent application has been filed by Rutgers University, which covers the synthesis and use of benzyloxy sulfinate protecting groups.

Author Contributions

T.I.P, R.L., and M.J.M conceived the program. T.I.P performed synthesis, stability, deprotection studies. Y.C aided in sulfinate synthesis. T.I.P and M.J.M. wrote and contributed to the manuscript.

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