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Sulfur Nucleophile-Mediated SNAr as a Complementary Strategy for C–S Bond Construction: Mechanistic Principles, Substrate Scope and Prospects for Sulfur-Containing Systems

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Abstract: *Nucleophilic aromatic substitution (SNAr) is a powerful platform for constructing aryl–heteroatom bonds without obligatory transition-metal catalysis. Among the available nucleophiles, sulfur-centered reagents are particularly attractive because sulfur combines high polarizability with substantial nucleophilicity and can therefore engage efficiently with activated aryl and heteroaryl electrophiles. This review-style manuscript examines sulfur-nucleophile-mediated SNAr as a complementary strategy for C–S bond construction, with emphasis on mechanistic requirements, substrate electronics, leaving-group effects, solvent and base effects, sulfur-nucleophile scope, polyfluoroarene substitution, heteroaryl SNAr, sequential substitution, and reversible sulfur exchange. Recent literature demonstrates that activated aryl fluorides, chlorides, and bromides can undergo metal-free substitution with thiophenols and selected alkyl thiols under basic conditions, while electron-deficient heteroaryl halides can react with thiols under similarly practical conditions. Polyfluoroarenes provide an additional class of highly electrophilic substrates in which the fluorination pattern controls regioselectivity. More unusual reversible sulfur-exchange processes further demonstrate that SNAr can operate as a dynamic rather than strictly irreversible transformation. The literature is evaluated here with particular attention to its relevance to sulfur-containing synthetic systems and to the prospective functionalization of 3-sulfonyl phthalide-related frameworks. Importantly, the literature surveyed does not establish conventional sulfur-nucleophile SNAr of 3-sulfonylphthalides themselves. Accordingly, direct reactions involving 3-sulfonylphthalides are treated as prospective design hypotheses rather than reported precedents. This distinction preserves a clear boundary between established chemistry and future synthetic opportunities while identifying experimentally testable directions for C–S bond construction, annulation, rearrangement, and sulfur-centered diversification.*

Keywords: *Nucleophilic Aromatic Substitution; SNAr; Sulfur Nucleophile; Thiophenol; Thiolate; C–S Bond Formation; Polyfluoroarene; Heteroaryl Halide; Sulfur Exchange; 3-Sulfonylphthalide.*

1. Introduction: Nucleophilic aromatic substitution has evolved from a classical reaction of strongly activated nitro arenes into a broad family of bond-forming processes applicable to medicinal chemistry, heterocycle synthesis, materials chemistry, and molecular diversification. The central synthetic attraction is straightforward: an aromatic or heteroaromatic carbon bearing a leaving group can be replaced by a

nucleophile, often under conditions that avoid transition-metal catalysts. The reaction is especially useful when the electrophilic carbon is electronically activated by one or more electron-withdrawing substituents or is embedded in an intrinsically electron-deficient heteroaromatic ring.

Sulfur nucleophiles occupy a distinctive position within this chemistry. Thiophenols, thiolates, primary alkyl thiols, and related sulfur-centered reagents can provide direct access to aryl and heteroaryl thioethers. The sulfur atom is highly polarizable, and its nucleophilicity can be increased substantially by deprotonation. At the same time, sulfur-containing products are versatile intermediates: aryl sulfides can be oxidized, selectively functionalized, incorporated into medicinal scaffolds, or used as handles for subsequent transformations. These characteristics make sulfur-mediated SNAr relevant not only as an isolated substitution reaction but also as a strategic C–S bond-forming operation within multistep synthesis.

The mechanistic framework of SNAr is well established. Classical addition–elimination reactions involve nucleophilic attack at the ipso carbon to form an anionic σ-complex, followed by expulsion of the leaving group and restoration of aromaticity. However, the field also recognizes concerted substitution pathways and mechanistic continua between fully stepwise and effectively concerted processes. Substrate activation, leaving-group identity, nucleophile structure, solvent, and reaction medium collectively determine which pathway is accessible. Terrier's comprehensive treatment emphasizes precisely these variables and provides a useful foundation for interpreting modern sulfur-mediated substitutions.

The present manuscript focuses on sulfur nucleophile-mediated SNAr as a complementary framework for C–S bond construction. It does not claim that every sulfur-containing aromatic system undergoes SNAr, nor does it assign conventional SNAr reactivity to 3-sulfonylphthalides without direct experimental evidence.

Instead, reported sulfur-mediated substitutions are organized according to mechanistic and structural principles and then used to identify experimentally testable opportunities for sulfur-containing systems. This distinction is important for a review article because it separates established literature from prospective chemistry and prevents mechanistic analogy from being presented as experimental precedent. [1–4]

2. Mechanistic Foundation of Sulfur-Mediated SNAr: The conventional representation of an ipso-SNAr reaction is Ar–X + RS^- → Ar–SR + X^-. The elementary steps can be represented as nucleophilic addition to the aromatic carbon bearing X, formation of an anionicσ-complex, and elimination of X^-. The first step is favored when the aromatic substrate is sufficiently electrophilic, while the second step benefits from restoration of aromaticity and favorable leaving-group departure. In strongly activated systems, the distinction between the two steps may become blurred, and concerted substitution can become mechanistically competitive.

Electron-withdrawing substituents are particularly important because they lower the energy of the σ-complex formed after nucleophilic attack. Nitro groups are classical activators, but cyano, carbonyl, ester, and related substituents can also increase susceptibility to substitution. In heteroarenes, ring nitrogen atoms can provide substantial intrinsic activation. Consequently, a heteroaryl chloride or bromide may undergo SNAr even in the absence of a conventional nitro substituent if the hetero aromatic ring is sufficiently electron deficient.

Sulfur nucleophiles illustrate the importance of polarizability. Thiophenol itself is neutral and comparatively less nucleophilic than its conjugate base, whereas thiophenolate formation produces a strongly nucleophilic sulfur center. In practical reactions, a mild inorganic base such as K2CO3 can simultaneously generate the reactive sulfur species and avoid some of the complications associated with very strong bases. The choice of base is therefore not simply a proton-transfer detail; it influences sulfur speciation, ion pairing, solubility, and the effective nucleophile concentration.

The role of the leaving group in SNAr differs from that in a conventional aliphatic SN2 reaction. Aryl fluoride is frequently an excellent SNAr substrate because the C–F bond is strongly polarized and fluorine

exerts a powerful inductive effect that facilitates nucleophilic addition to the ipso carbon. The subsequent fluoride departure from an anionic σ-complex can also be favorable. Thus, activated aryl fluorides can be more reactive than corresponding chlorides or bromides, despite fluoride being a relatively poor leaving group in many aliphatic substitution contexts.

Solvent effects are equally important. Polar aprotic solvents such as DMSO and DMAc can enhance the effective nucleophilicity of anionic sulfur species by providing solvation without strongly hydrogen-bonding to the nucleophile. They can also improve dissolution of inorganic bases and facilitate contact between the sulfur reagent and the activated aromatic substrate. The practical literature therefore repeatedly identifies polar aprotic media as useful environments for sulfur-mediated SNAr.

Mechanistic interpretation should nevertheless remain substrate-specific. A high yield in one activated aryl fluoride does not establish that all aryl fluorides will react similarly, and an observed Ar–F >Ar–Cl >Ar–Br trend should be understood as a substrate-dependent experimental result rather than a universal law. Likewise, a reaction that appears stepwise from analogy may be concerted under different electronic conditions. For review purposes, the safest formulation is that sulfur-mediated SNAr can access both stepwise and concerted regimes, with the balance governed by the complete reaction system. [1–4, 12, 13]

3. Thiophenol and Thiolate-Mediated C(sp^2)–S Bond Formation: A recent study by Kumar and co-workers provides a particularly useful modern benchmark for metal-free sulfur-mediated SNAr. The authors reported C(sp^2)–S bond formation through ipso substitution of activated aryl fluorides, chlorides, and bromides with aryl and alkyl thiols. The method is notable because it avoids transition-metal catalysts, ligands, phase-transfer catalysts, crown ethers, and fluoride additives, while delivering good-to-excellent yields across a range of activated substrates.

In the reported optimization, thiophenol and 4-fluorobenzaldehyde were combined with K2CO3 in DMSO. The optimized conditions used K2CO3 (1.5 equiv), DMSO, and 90 °C for 10 h and afforded 4-(phenylthio) benzaldehyde in 95% NMR yield. Other bases displayed substantially different performance:

Cs_2CO_3 gave a lower yield, KOH was less effective, NaOAc gave only a minor amount of product, and pyridine or triethylamine did not provide detectable product under the reported conditions. DMSO was also markedly superior to several alternative solvents. At room temperature, the same general system remained productive, although a longer reaction time was required.

The substrate scope supports a strong connection between electrophilicity and reaction efficiency. Para-nitro-substituted aryl fluorides, chlorides, and bromides underwent thiophenol substitution in high yield, while other electron-withdrawing substituents such as cyano, aldehyde, acetyl, and benzoyl groups were compatible. Heteroaryl electrophiles, including 4-halopyridines, also furnished sulfur-substituted products. These results reinforce the central SNAr principle that the electronic activation of the aromatic carbon is often more decisive than the nominal identity of the halogen.

The sulfur-nucleophile scope was informative as well. Primary alkyl thiols such as 1-dodecanethiol and benzylthiol participated, and a dithiol substrate could also react. In contrast, cyclohexane thiol was not productive under the optimized conditions. This difference is consistent with the influence of the steric environment on the approach of sulfur to the activated aromatic carbon and on the efficiency of the resulting substitution pathway. The observation also cautions against treating “thiol” as a single reactivity class: aryl and primary alkyl thiols may behave differently from more hindered secondary or cyclic thiols.

Mechanistic monitoring by 19F NMR provided direct evidence for fluoride departure. In the reaction of 4-fluoronitrobenzene with thiophenol, the starting aryl fluoride displayed a signal near −104 ppm. Following addition of base and thiophenol, a new signal near −165 ppm appeared, consistent with fluoride ion, while the substrate signal disappeared on the reaction timescale. This observation supports consumption of the

activated aryl fluoride and is valuable because it connects the macroscopic reaction outcome with direct spectroscopic evidence for leaving-group release.

Taken together, the study establishes a practical reference point for sulfur-mediated SNAr: substrate activation, a suitable inorganic base, a polar aprotic solvent, and an accessible sulfur nucleophile can be sufficient to achieve direct C–S bond formation without transition-metal catalysis. The work is particularly relevant to contemporary synthetic planning because it demonstrates that aryl fluoride, chloride, and bromide Electrophiles can be evaluated within a common reaction platform rather than being restricted to One privileged leaving group.[5]

Table1: Representative literature examples

Electrophile class	Sulfur nucleophile	Representative conditions	Representative outcome	Principal feature
Activated aryl fluoride	Thiophenol	K_2CO_3/, DMSO, heat	High yield reported	Strong EWG-assisted SNAr
Activated aryl chloride/ bromide	Thiophenol	K_2CO_3/ DMSO	High yields for activated examples	Electronic activation dominates
Activated aryl halides	Primary alkyl thiols	K_2CO_3DMSO	Moderate-to-good, substrate dependent	Steric/nucleophile effects
4-Halopyridines	Thiophenol	K_2CO_3/ DMSO	High yields in reported examples	Heteroaryl activation
Penta fluorobenzene	Thiophenol	K_2CO_3, DME, reflux	88% reported	Polyfluoroarene activation
Polyfluoroarenes	Substituted thiophenols	Basic conditions	ca.40–71%in reported examples	Regioselective C–F substitution
Dibromothiadiazolopyridazine	Thiophenol	CHC_{13}/ THF/DMF	45–80% depending on conditions	Rapid sequential substitution
Electron-deficient heteroaryl halides	Thiols /selected S nucleophiles	K_2CO_3, DMAc, rt–100 °C	Good yields across scope	Ring electronics and halogen orientation

4. Polyfluoroarenes as Electrophilic Platforms for C–S Bond Construction: Polyfluoroarenes provide an important extension of the sulfur-SNAr concept because multiple fluorine substituents can create highly electrophilic aromatic systems even in the absence of a classical nitro group. Zhou and co-workers examined substitution of pentafluorobenzene, methyl 2, 3, 4, 5-tetrafluorobenzoate, and 1, 2, 4, 5-tetrafluorobenzene with substituted thiophenols. The reported products showed useful regioselectivity, demonstrating that the position of sulfur substitution is controlled by the electronic distribution of the fluorinated ring.

Pentafluorobenzene reacted with thiophenol under basic conditions to give a C–S-substituted product in high

yield. Other polyfluoroarenes displayed more variable yields, illustrating that increasing fluorine content does not automatically make every C–F bond equivalent. Instead, fluorination redistributes electron density throughout the aromatic system, and individual C–F bonds can have different susceptibilities toward nucleophilic displacement.

Computational analysis in the Zhou study linked the observed regioselectivity to local electronic descriptors. This point is important for reaction design: polyfluoroarene SNAr should not be described simply as "fluorine substitution." The fluorine pattern, neighboring substituents, and heteroatom effects collectively determine which carbon is most electrophilic and therefore which C–F bond is preferentially displaced.

A complementary approach was reported for perfluoroarenes using copper-catalyzed C–F substitution with aryl thioacetates or benzyl thioacetate. Although mechanistically distinct from strictly metal-free SNAr, this chemistry is relevant to the same strategic problem: exploiting the high electrophilicity of fluorinated aromatic systems to build aryl–sulfur bonds. The thioacetate approach can also address practical limitations of direct thiol use, including odor, oxidation, and disulfide formation. The comparison illustrates how substrate activation can be combined with either nucleophilic or metal-assisted pathways depending on the desired operational profile. [6, 7]

5. Sulfur Nucleophiles in Heteroaryl SNAr: Heteroaryl substitution broadens the synthetic value of sulfur-mediated SNAr because heteroaromatic scaffolds are common in pharmaceutical and functional-molecule synthesis. Liu, Jin, and Ma reported in 2024 that heteroaryl chlorides and bromides undergo substitution with thiols in DMAc in the presence of K2CO3 over a range extending from room temperature to 100 °C. The study provides a useful modern demonstration that chlorine and bromine can serve as practical SNAr leaving groups when the hetero aromatic system is sufficiently electron deficient.

For most electron-deficient heteroarenes examined, no additional electron-withdrawing group was required. By contrast, more electron-rich heteroarenes generally required an ester, keto, cyano, or nitro substituent to promote complete substitution. The authors also found that the reactivity of heteroaryl halides depended strongly on the electronic character of the ring and on the orientation of the halogen. This is consistent with the broader mechanistic picture: the leaving group is only one part of the activation problem, and the ring must stabilize the developing negative charge during substitution.

The sulfur-nucleophile scope extended beyond simple thiols. Selected functionalized thioureas and thioamides were compatible with the conditions and produced heteroaryl sulfur-containing products. This observation is significant for complex-molecule synthesis because it suggests that sulfur-mediated SNAr can be incorporated into multifunctional substrates without requiring the sulfur reagent to be a simple low-molecular-weight thiophenol. The 2024 JOC study therefore complements the aryl-halide work of Kumar and co-workers. Together, the studies support a general framework in which activated aromatic fluorides, chlorides, and bromides and electron-deficient heteroaryl halides can all participate in sulfur-centered substitution, but the optimal conditions depend on substrate electronics, nucleophile structure, and the ability of the ring to stabilize the substitution intermediate.[8]

6. Polyhalogenated Hetero arenes and Sequential Sulfur Substitution: Polyhalogenated heteroarenes provide a particularly informative test of SNAr because multiple electrophilic sites can be available in the same molecule. A study of 4, 7-dibromo [1, 2, 5] thiadiazolo[3, 4-d] pyridazine showed that thiophenol reacted readily at room temperature in several organic solvents to produce the corresponding disulfur-substituted product. The reaction was accelerated in polar aprotic media such as DMF, and isolation of the monosubstituted intermediate proved difficult because the first substitution was followed rapidly by the second.

The observed behavior illustrates an important design principle: substitution at one position can alter the

electronics of the remaining ring and thereby change the rate of subsequent substitution. In highly activated heteroarenes, the first C–S bond may not simply terminate the reaction; it can be part of a cascade toward multiple functionalization. Consequently, control over mono- versus di substitution may require careful adjustment of stoichiometry, concentration, solvent, temperature, and addition order.

For synthetic planning, sequential sulfur substitution can be either an advantage or a liability. If a multifunctional sulfur-rich heteroarene is desired, rapid double substitution is useful. If a selectively monosubstituted intermediate is required, the same reactivity can create a chemoselectivity problem. This distinction should be incorporated into any attempt to translate sulfur-SNAr conditions to new multifunctional substrates. [10]

7. Reversible SNAr and Dynamic Sulfur Exchange: The sulfur-dance chemistry reported by Gahlot and co-workers provides a conceptual extension of ordinary SNAr. Their 2024 Chemistry—A European Journal study demonstrated reversible nucleophilic aromatic substitutions involving exchange of sulfur components around activated arenes and heteroarenes. The authors showed that sulfur exchange could occur at room temperature in appropriate systems and that product distributions could converge through reversible substitution pathways.

This behavior challenges the simplistic view of SNAr as a one-way reaction from electrophile plus nucleophile to substituted product. When both forward and reverse substitutions are accessible, the system can become dynamically reorganized. Product distributions may then reflect kinetic accessibility, thermodynamic stability, and the relative concentrations of sulfur components rather than a single irreversible elementary sequence.

For sulfur-containing synthesis, reversible SNAr is relevant in two ways. First, it demonstrates that aryl–sulfur bonds can participate in dynamic exchange under conditions that preserve aromaticity. Second, it suggests that sulfur substitution could be used not only to install a fixed substituent but also to reorganize sulfur-containing aromatic architectures. Such chemistry is conceptually distinct from ordinary thioether formation but belongs in the same broader discussion because both rely on nucleophilic attack at activated aromatic carbon and leaving-group exchange.

The sulfur-dance literature also provides a caution for reaction development. If a proposed sulfur-SNAr substrate contains multiple activated positions or multiple exchangeable sulfur substituents, the isolated product may not necessarily be the kinetic product expected from the initial substitution event. Time, temperature, sulfur stoichiometry, and the identity of the thiolate promoter may influence the final distribution. These considerations become especially important for densely functionalized heteroaromatic systems. [9]

8. Comparative Reactivity and Practical Variables: Across the literature, several variables repeatedly control sulfur-mediated SNAr. The first is electrophile activation. Nitro, cyano, aldehyde, ketone, ester, polyfluoro, and electron-deficient heteroaromatic motifs can all increase susceptibility to substitution. The second is sulfur nucleophile structure. Thiophenol and primary alkyl thiols can be highly effective, whereas sterically hindered thiols may be less productive. The third is base selection, which determines the concentration and identity of the reactive sulfur species.

Solvent is a fourth major variable. DMSO and DMAc are repeatedly useful because they combine high polarity with relatively weak hydrogen-bond donation. DMF can also accelerate reactions in highly activated heteroarenes. Less polar solvents may still work when the substrate is exceptionally activated, but they should not be assumed to be interchangeable with polar aprotic media.

Temperature and time provide additional control. Strongly activated aryl fluorides can react at or near room temperature, whereas less activated aryl halides may require heating. Higher temperature can improve

conversion but may also increase side reactions, sulfur oxidation, decomposition, or multiple substitution. A rational optimization sequence should therefore vary base, solvent, temperature, nucleophile loading, and concentration systematically rather than changing several variables simultaneously.

The practical literature also highlights an important distinction between direct thiol chemistry and protected or activated sulfur reagents. Direct thiols are inexpensive and simple, but odor, oxidation, and disulfide formation can complicate handling. Thioacetates and other sulfur derivatives may provide operational advantages, although their reactivity can require metal catalysis or additional activation. The appropriate sulfur reagent should therefore be chosen according to both mechanistic compatibility and practical constraints. [3–5, 8]

Table2. Practical variables in sulfur-mediated SNAr

Variable	Favorable feature	Potential complication	Design implication
Aromatic activation	NO_2, CN, CHO, COR, CO_2R, polyfluoro, electron-deficient heteroarene	Poor conversion on non-activated rings	Select or introduce a genuinely electrophilic ipso carbon
Leaving group	Aryl often effective in activated SNAr; Cl/Br viable in hetero arenes	Leaving-group behavior is substrate dependent	Do not extrapolate a universal F>Cl>Br rule
Sulfur nucleophile	Thiophenol; primary alkyl thiols	Steric hindrance; oxidation; disulfide formation	Compare sulfur reagents explicitly
Base	K2CO3 frequently practical	Too-strong base can cause side reactions	Optimize sulfur deprotonation and substrate stability together
Solvent	DMSO, DMAc, DMF	Work-up and high-boiling solvent handling	Use polar aprotic medium when ionic SNAr is limiting
Temperature	Heating can accelerate less reactive substrates	Decomposition/over-substitution	Increase temperature only after confirming clean conversion
Stoichiometry	Controlled thiol loading enables selective substitution	Polyhalogenated systems may over-substitute	Use equivalents and concentration as selectivity variables

9. Literature Summary: The principal literature can be summarized by electrophile class, sulfur reagent, and dominant reactivity feature. Activated aryl fluorides provide the clearest examples of metal-free C–S

bond formation. Polyfluoro arenes add a region selectivity dimension because multiple C–F bonds can have different electronic environments. Heteroaryl chlorides and bromides demonstrate that ring activation can compensate for the weaker intrinsic electrophilicity of some C–Cl or C–Br substrates. Poly halogenated heteroarene scan undergo sequential substitution, while reversible sulfur exchange demonstrates that some activated aromatic systems can support dynamic rather than strictly irreversible substitution.

The comparative trends are not universal rules. Reported yields depend on the precise substrate, sulfur reagent, base, solvent, temperature, and stoichiometry. Accordingly, numerical yields should be used as literature benchmarks rather than as guaranteed outcomes for new substrates. The most transferable conclusion is qualitative: sulfur-mediated SNAr is favored when the electrophilic carbon is sufficiently activated, the sulfur reagent can generate a competent nucleophile, and the reaction medium supports the relevant ionic species [5–10].

10. Relevance to 3-Sulfonyl phthalide Chemistry: Within a review focused on 3-sulfonylphthalide chemistry, sulfur-nucleophile-mediated SNAr should be positioned as a complementary reactivity framework rather than as a directly established reaction class of 3-sulfonylphthalides. The literature surveyed here demonstrates how sulfur-centered nucleophilicity and aromatic electrophilicity can be combined to achieve C–S bond construction, but it does not establish that 3-sulfonylphthalides themselves undergo conventional SNAr with sulfur nucleophiles.

This distinction is especially important because the structural features of a 3-sulfonylphthalide are not equivalent to those of a classical nitro-activated aryl halide. A sulfone substituent may strongly influence local electronics, but its presence alone does not establish the existence of an SNAr leaving group or a sufficiently activated ipso carbon. A review should therefore avoid wording such as “3-sulfonylphthalides undergo sulfur-nucleophile SNAr” unless a primary study directly demonstrates the transformation.

Instead, the literature provides a useful conceptual bridge. First, it establishes that sulfur nucleophiles can form aryl and heteroaryl C–S bonds under mild or moderate basic conditions. Second, it identifies the structural motifs that promote substitution: electron-deficient aromatic carbons, suitable leaving groups, and accessible sulfur nucleophiles. Third, it shows that sulfur substitution can be coupled to sequential substitution, dynamic exchange, or subsequent functional-group manipulation. These principles can guide the design of experiments involving phthalide-derived electrophiles or sulfur-containing partners without being presented as established precedent.

Several prospective directions follow naturally. Appropriately activated aryl or heteroaryl partners bearing nitro, cyano, carbonyl, ester, or polyfluoro substituents could be paired with sulfur-containing fragments that are structurally related to phthalide chemistry. Alternatively, a phthalide framework could be incorporated on the electrophile side if an activated aryl leaving group is available. The resulting thioether could then be examined for downstream oxidation, annulation, rearrangement, desulfonylation, or cyclization. Each proposal is a reaction-design hypothesis and requires experimental validation.

A particularly useful strategy for future work would be to establish a small mechanistic matrix rather than screen a large substrate library immediately. Representative activated aryl fluoride, chloride, and heteroaryl halide controls could first be compared with the proposed phthalide-derived substrate under K_2CO_3/DMSO or K_2CO_3/DMAc conditions. Conversion, sulfur oxidation, multiple substitution, and decomposition should be monitored by LC–MS, NMR, and, where appropriate, 19F NMR. Only after confirming that the sulfur reagent remains nucleophilic under the reaction conditions should more elaborate phthalide substrates be evaluated.

Such an approach would preserve the central editorial logic of the review: reported sulfur-nucleophile SNAr establishes the mechanistic and synthetic foundation; 3-sulfonylphthalide chemistry represents the

prospective extension. This structure allows the manuscript to discuss emerging opportunities without conflating literature evidence with hypothesis. [5–10]

11. Prospective Reaction-Design Framework: A rational experimental program can be organized around four variables: electrophile activation, sulfur-nucleophile identity, reaction medium, and downstream reactivity. Electrophile activation should be tested first because it defines whether an SNAr pathway is plausible. Nitro- and polyfluoro-activated systems provide useful positive controls, while non-activated halobenzenes provide negative controls. Heteroaryl substrates can then be introduced to determine whether ring nitrogen activation changes the required conditions.

The sulfur-nucleophile series should ideally include thiophenol, a primary alkyl thiol, and a sterically hindered thiol. These substrates probe the effects of sulfur polarizability, steric accessibility, and the balance between nucleophilicity and solubility. Where direct thiols are problematic, thioacetate or related sulfur reagents can be evaluated as operational alternatives. Oxidation to disulfides should be monitored because it can consume the effective nucleophile and lower apparent SNAr efficiency.

Condition screening should prioritize K_2CO_3 in a polar aprotic solvent because this combination is directly supported by recent literature. DMSO and DMAc provide useful complementary media. Temperature can then be varied from room temperature upward, with the objective of distinguishing slow but clean conversion from conditions that induce decomposition. Stoichiometric control is particularly important in polyhalogenated systems where sequential substitution can be rapid.

Finally, downstream chemistry should be treated as part of reaction design rather than as an afterthought. An aryl thioether can be oxidized to a sulfoxide or sulfone, subjected to further cross-coupling or substitution chemistry, or incorporated into a cyclization sequence. If a sulfur substituent is positioned appropriately relative to a phthalide carbonyl or other electrophilic center, intramolecular reactions may provide a route to fused or spirocyclic products. These possibilities are prospective and should be tested only after the initial C–S bond-forming step is established. [5, 8, 10]

12. Limitations and Editorial Considerations: The literature base discussed here is sufficiently strong to establish sulfur-mediated SNAr as a general complementary strategy, but it is not sufficiently specific to support a claim that this chemistry is already developed for 3-sulfonylphthalides. The manuscript should therefore distinguish three levels of evidence: established general SNAr principles; experimentally demonstrated sulfur-mediated examples; and proposed applications to 3-sulfonylphthalide-related systems.

Another limitation is that literature yields are highly substrate dependent. A 95% yield for one activated aryl fluoride cannot be extrapolated to a structurally different electrophile. Likewise, a successful reaction with a primary thiol does not establish that a hindered secondary thiol will react. Comparative tables should therefore report representative conditions and outcomes while avoiding language that implies universal reactivity orders.

Mechanistic statements should also be phrased cautiously. The presence of an anionic σ-complex is a classical and well-supported model for many SNAr reactions, but not every sulfur-mediated substitution has been demonstrated experimentally to proceed through a discrete intermediate. Where the literature supports only a mechanistic proposal, the manuscript should use terms such as “consistent with, “ “compatible with, “ or “plausibly proceeds through, “ rather than presenting the pathway as directly observed.

For journal submission, the final version should be adapted to the target journal’s reference style, graphical-abstract requirements, word limit, and formatting instructions. Chemical structures, reaction schemes, and a graphical abstract should be prepared from the primary literature rather than recreated from secondary

descriptions. The present manuscript deliberately avoids inventing structures or experimental data that were not verified. [1–5, 8, 9]

Table3. Evidence hierarchy for manuscript wording

Evidence level	What can be stated	What should not be stated without further evidence
Established SNAr principle	Electron-deficient aryl/heteroaryl systems can undergo nucleophilic substitution	A new substrate will necessarily react
Reported sulfur SNAr	Specific literature substrates react with thiols/thiolates under defined conditions	The same yield or mechanism applies universally
3-Sulfonyl phthalide prospect	SNAr literature provides a rational design framework	3-Sulfonylphthalidesarealready established SNAr substrates
Mechanistic proposal	Data may be consistent with addition–elimination or concerted pathways	A discrete σ-complex was experimentally observed unless directly demonstrated

13. Conclusions: Sulfur nucleophile-mediated SNAr is a versatile complementary strategy for C–S bond construction. The literature demonstrates that activated aryl fluorides, chlorides, and bromides, polyfluoroarenes, electron-deficient heteroaryl halides, and polyhalogenated heteroarenes can participate in sulfur-centered substitution under appropriately basic and often metal-free conditions. Reaction efficiency is governed by the combined effects of aromatic electrophilicity, leaving-group environment, sulfur-nucleophile structure, base, solvent, temperature, and stoichiometry.

Recent studies further expand the conceptual scope of this chemistry. Direct metal-free thiol substitution provides a practical route to aryl thioethers, polyfluoroarene substitution reveals strong region electronic control, hetero aryl SNAr demonstrates the importance of intrinsic ring activation, and reversible sulfur exchange shows that aromatic substitution can become dynamically reorganizing under appropriate conditions.

For 3-sulfonylphthalide research, the most defensible conclusion is therefore prospective. Sulfur-mediated SNAr supplies a literature-supported framework for understanding and designing C–S bond-forming reactions, but direct SNAr of 3-sulfonylphthalides with sulfur nucleophiles should not be described as established without primary experimental evidence. Presented in this way, the chemistry provides a coherent bridge from known sulfur reactivity to testable future transformations involving phthalide-containing systems. [5–10]

Comparative Literature Summary

The following condensed table can be used as a manuscript overview or converted into a graphical summary for a target journal.

Electrophile class	Sulfur nucleophile	Representative conditions	Representative outcome	Principal feature

Activated arylfluoride	Thiophenol	K_2CO_3, DMSO, heat	High yield reported	Strong EWG-assisted SNAr
Activated aryl chloride/bromide	Thiophenol	K_2CO_3/ DMSO	High yields for activated examples	Electronic activation dominates
Activated aryl halides	Primary alkyl thiols	K_2CO_3/ DMSO	Moderate-to-good, substrate dependent	Steric/nucleophile effects
4-Halopyridines	Thiophenol	K_2CO_3/ DMSO	High yields in reported examples	Heteroaryl activation
Pentafluorobenzene	Thiophenol	K2CO3, DME, reflux	88% reported	Polyfluoroarene activation
Polyfluoroarenes	Substituted thiophenols	Basic conditions	ca.40–71%in reported examples	Regioselective C–F substitution
Dibromothiadiazolopyridazine	Thiophenol	$CHCl_3$/ THF/ DMF	45–80% depending on conditions	Rapid sequential substitution
Electron-deficient heteroaryl halides	Thiols/selected S nucleophiles	K_2CO_3, DMAc, rt–100 °C	Good yields across scope	Ring electronics and halogen orientation

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