



Sulfur-Centered Nucleophilic Aromatic Substitution: Mechanistic Pathways, Substrate Scope and Practical Constraints with Emphasis on Ethyl 3-Mercaptopropionate

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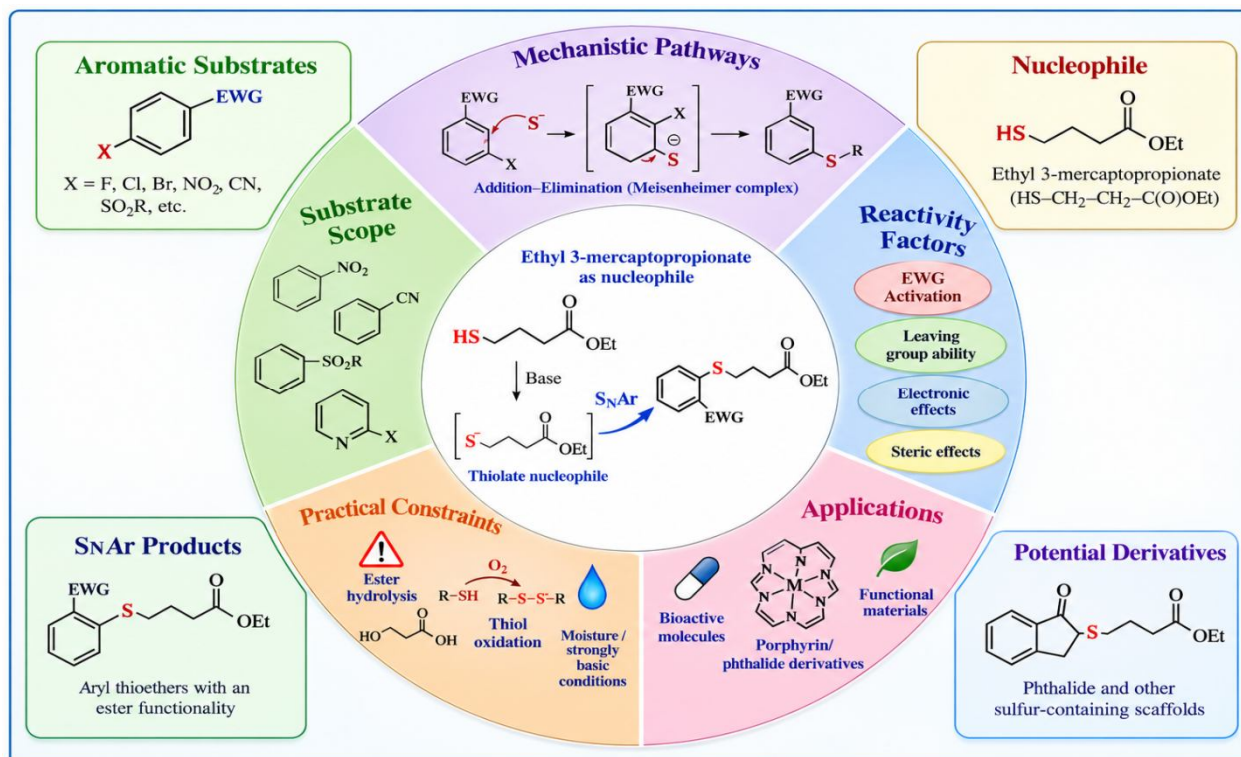
Abstract: Nucleophilic aromatic substitution (S_NAr) is an important synthetic approach for constructing carbon–sulfur bonds in electron-deficient aromatic systems. This critical review explores the mechanistic pathways, substrate scope, reactivity, selectivity, and practical limitations of sulfur-mediated S_NAr reactions, with particular emphasis on ethyl 3-mercaptopropionate (HS–CH₂–CH₂–CO₂Et). Key factors influencing reaction efficiency, including electron-withdrawing substituents, leaving-group identity, solvent polarity, base strength, and temperature, are critically examined. Classical addition–elimination mechanisms involving Meisenheimer intermediates are compared with concerted S_NAr pathways. Literature-based kinetic and computational findings are discussed alongside applications in aromatic functionalization and heterocyclic chemistry. Potential challenges, including thiol oxidation, incomplete deprotonation, ester hydrolysis, and product selectivity, are highlighted. The review identifies existing research gaps and proposes integrated kinetic, spectroscopic, and computational approaches to improve mechanistic understanding and reaction reproducibility. Overall, this analysis provides valuable insights into the development of efficient and selective sulfur-based S_NAr methodologies.

Keywords: Nucleophilic aromatic substitution (S_NAr); Ethyl 3-mercaptopropionate; Sulfur nucleophiles; Thiolate ions; Aryl–sulfur bond formation; Meisenheimer intermediate; Reaction kinetics; Density functional theory; Structure–reactivity relationships; Porphyrinoids.

Introduction: The formation of carbon–sulfur (C–S) bonds represents an important transformation in modern organic synthesis because sulfur-containing aromatic compounds are widely employed as intermediates and structural components in pharmaceuticals, agrochemicals, functional materials, and biologically active molecules. Among the various synthetic approaches available for constructing C–S bonds, nucleophilic aromatic substitution (S_NAr) has emerged as a valuable strategy owing to its synthetic versatility, potential regioselectivity, and ability to introduce sulfur-containing functional groups into suitably activated aromatic frameworks. The development of efficient and selective S_NAr methodologies therefore remains an important objective in synthetic and mechanistic organic chemistry.

Classical nucleophilic aromatic substitution generally involves the reaction of an electron-deficient aromatic substrate bearing a suitable leaving group with an electron-rich nucleophile. In the conventional addition–elimination mechanism, nucleophilic attack occurs at the aromatic carbon bearing the leaving group,

producing a negatively charged σ -complex, commonly described as a Meisenheimer intermediate. Subsequent elimination of the leaving group restores aromaticity and generates the substituted aromatic product. The efficiency of this transformation is strongly influenced by the electronic characteristics of the aromatic substrate, the nature and position of electron-withdrawing substituents, the identity of the leaving group, and the nucleophilic strength of the attacking reagent. Strong electron-withdrawing groups, particularly nitro and cyano substituents, can facilitate nucleophilic substitution when appropriately positioned relative to the reaction center. Nevertheless, recent mechanistic investigations have demonstrated that not all S_NAr reactions necessarily proceed through a discrete, isolable intermediate; concerted substitution pathways may also operate depending on the substrate, nucleophile, and reaction environment.



Sulfur-based nucleophiles are particularly attractive in aromatic substitution chemistry because thiols can undergo deprotonation to generate thiolate anions, which generally exhibit enhanced nucleophilic reactivity toward suitable aromatic electrophiles. Their reactivity, however, depends considerably on acid–base equilibria, solvent effects, counterion interactions, steric factors, and the electronic environment of the reacting species. Ethyl 3-mercaptopropionate ($\text{HS-CH}_2\text{-CH}_2\text{-CO}_2\text{Et}$) is an interesting representative of this class because its molecular structure contains both a reactive thiol group and an ester functionality. The thiol group provides a potential site for nucleophilic attack following deprotonation, while the ester group offers opportunities for subsequent chemical modification. These structural features make ethyl 3-mercaptopropionate a potentially useful reagent for preparing functionalized aromatic thioethers. However, its effective application requires careful consideration of competing processes, including thiol oxidation, ester hydrolysis, incomplete thiolate formation, and possible side reactions under strongly basic or elevated-temperature conditions.

The mechanistic understanding of sulfur-mediated S_NAr reactions has been substantially advanced through kinetic investigations involving biologically relevant thiols and activated aromatic electrophiles. In particular, reactions of 1-chloro-2,4-dinitrobenzene (CIDNB) and 1-fluoro-2,4-dinitrobenzene (FDNB) with sulfur-containing nucleophiles provide useful model systems for examining the influence of leaving-group identity, nucleophile structure, solvent environment, and reaction conditions on substitution kinetics. Such investigations also provide opportunities to evaluate Brønsted-type structure–reactivity relationships and

distinguish between possible mechanistic pathways. Nevertheless, kinetic behavior observed for biological thiols cannot automatically be extrapolated to ethyl 3-mercaptopropionate because differences in molecular structure, ionization behavior, solvation, and functional-group interactions may substantially influence nucleophilic reactivity.

Beyond relatively simple aromatic substrates, nucleophilic aromatic substitution has also become an important approach to the functionalization of complex heteroaromatic and macrocyclic systems. Porphyrins, phthalocyanines, corroles, and related porphyrinoids offer structurally diverse platforms for introducing sulfur-containing substituents and modifying electronic, photophysical, and physicochemical properties. The successful application of nucleophilic substitution to selected macrocyclic systems demonstrates the broader synthetic relevance of aromatic substitution chemistry. However, the reactivity of these highly conjugated frameworks is strongly dependent on their electronic structures, substitution positions, peripheral functional groups, and reaction conditions. Consequently, mechanistic conclusions obtained from porphyrinoid chemistry should be interpreted within their specific structural contexts rather than treated as direct evidence for reactions involving conventional nitroaromatic electrophiles.

Despite extensive progress in understanding nucleophilic aromatic substitution, several challenges remain in establishing reliable structure–reactivity relationships for individual sulfur nucleophiles. In particular, the effects of substrate activation, leaving-group identity, thiolate generation, solvent polarity, reaction temperature, and competing chemical transformations require systematic consideration. Furthermore, distinguishing between concerted and stepwise reaction pathways frequently demands complementary kinetic, spectroscopic, and computational evidence. Density functional theory (DFT) calculations, when appropriately validated, can provide additional mechanistic insights by examining electronic structures, transition-state geometries, activation barriers, and the relative stability of reaction intermediates. Integration of experimental and computational approaches may therefore contribute to a more comprehensive understanding of sulfur-mediated aromatic substitution.

Against this background, the present review critically examines the scope, mechanistic characteristics, and limitations of nucleophilic aromatic substitution with particular emphasis on ethyl 3-mercaptopropionate as a representative sulfur-containing nucleophile. The discussion integrates literature-reported findings from biothiol reactions with activated nitroarenes, fundamental mechanistic studies, and selected examples of porphyrinoid functionalization. Particular attention is devoted to the relationship between molecular structure and nucleophilic reactivity, the influence of reaction conditions on C–S bond formation, and the experimental constraints that may affect selectivity and reproducibility. Importantly, the review distinguishes established literature observations from mechanistic interpretations and predictions concerning ethyl 3-mercaptopropionate, for which a complete quantitative experimental substrate-scope dataset is not established in the underlying thesis.

The principal objective of this review is to develop a coherent mechanistic framework for evaluating the potential applications and limitations of ethyl 3-mercaptopropionate in aromatic substitution chemistry. By identifying critical knowledge gaps and outlining appropriate strategies for kinetic analysis, product characterization, statistical evaluation, and computational validation, this work aims to provide a foundation for future investigations directed toward efficient, selective, and reproducible aryl–sulfur bond formation.

Review Methodology and Evidence Assessment: The present study adopts a critical narrative review approach to systematically organize, interpret, and evaluate the existing scientific understanding of nucleophilic aromatic substitution (S_NAr) reactions, with particular emphasis on the reactivity, mechanistic behavior, and synthetic potential of ethyl 3-mercaptopropionate as a sulfur-based nucleophile. Unlike a systematic review or quantitative meta-analysis, this investigation focuses on the critical interpretation of established reaction mechanisms, structure–reactivity relationships, experimental observations, and theoretical findings reported in the scientific literature.

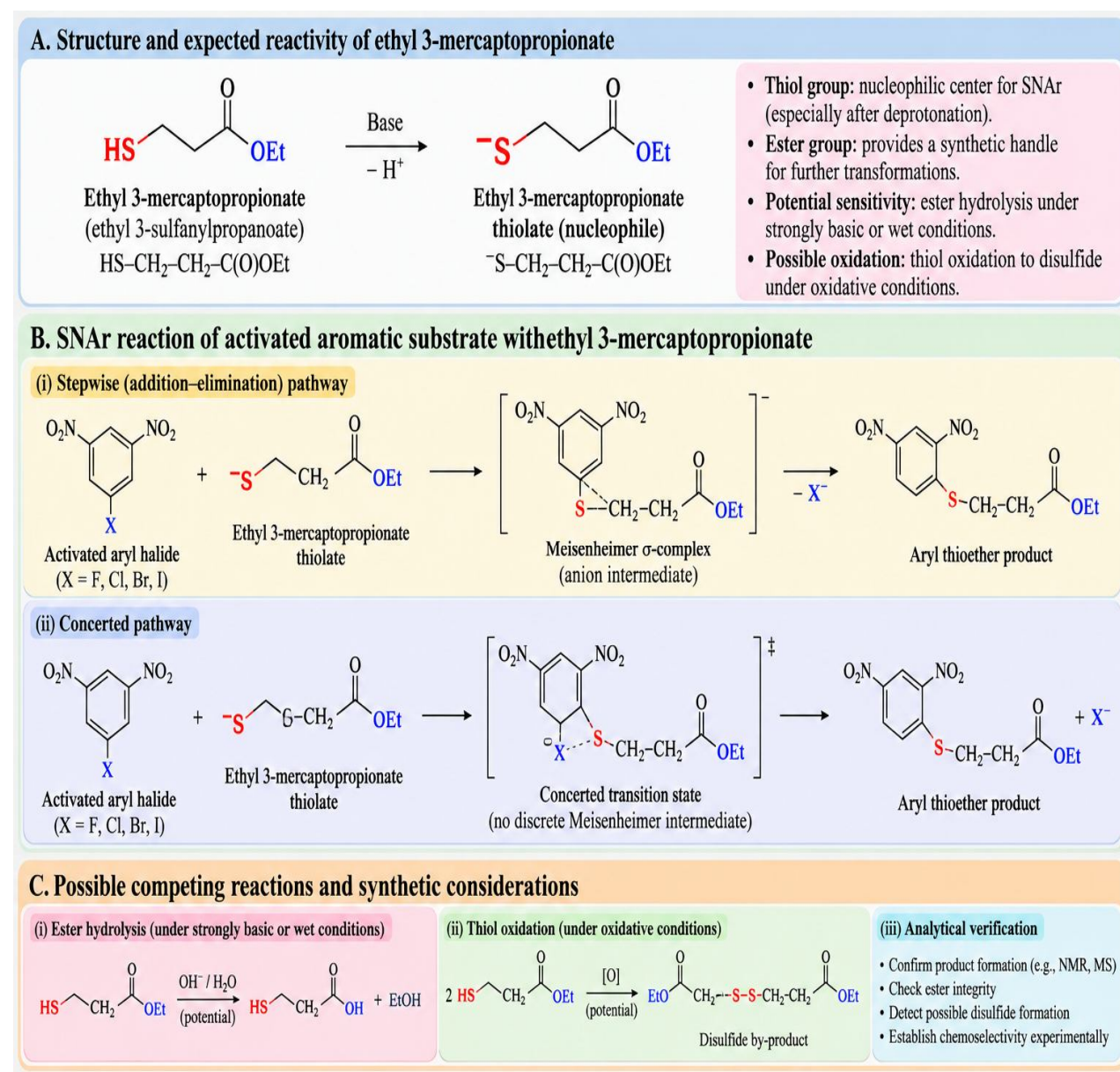
The primary conceptual foundation of this review is the scope and limitations of nucleophilic aromatic substitution using ethyl 3-mercaptopropionate as a nucleophile. Relevant primary research articles and authoritative review publications provide additional scientific context for evaluating the mechanistic principles and synthetic applications discussed in the thesis. Particular attention is directed toward investigations involving activated aromatic electrophiles, sulfur-containing nucleophiles, nucleophilic substitution kinetics, solvent and substituent effects, and the functionalization of porphyrinoid systems. The evaluation emphasizes the distinction between experimentally established findings, literature-supported mechanistic interpretations, and proposed reaction pathways requiring further validation. Experimental observations reported in previously published studies are attributed to their original sources to maintain scientific accuracy and appropriate recognition of earlier research contributions. Furthermore, kinetic parameters, reaction yields, activation energies, thermodynamic quantities, and computational results are considered only within the specific chemical systems for which they were originally reported. An important methodological consideration is the limited transferability of experimental findings between structurally different sulfur nucleophiles. Although published investigations involving biological thiols provide valuable insights into thiolate reactivity and aromatic substitution mechanisms, these observations cannot be regarded as direct experimental evidence for the behavior of ethyl 3-mercaptopropionate. Differences in molecular structure, acid–base properties, solvation, steric environment, and functional-group interactions may significantly influence reaction rates, selectivity, and mechanistic pathways. Consequently, literature-derived comparisons are used to develop chemically reasonable interpretations and identify testable mechanistic hypotheses rather than to establish unverified quantitative conclusions. To ensure transparency and scientific reliability, no numerical reaction yield, kinetic constant, activation parameter, or computational energy is presented as a measured or calculated property of ethyl 3-mercaptopropionate unless supported by a directly relevant and verifiable primary research source. Where experimental evidence is unavailable, the discussion explicitly identifies the corresponding mechanistic explanation as a prediction or hypothesis requiring further investigation. The review also critically examines the limitations of existing evidence, including differences in experimental conditions, incomplete kinetic characterization, uncertainty in mechanistic assignments, and the absence of directly comparable datasets. Although the literature is evaluated through a structured scientific discussion, the present work does not claim to have conducted an exhaustive systematic literature search. Such an investigation would require a predefined review protocol specifying bibliographic databases, search strategies, publication periods, eligibility criteria, duplicate removal procedures, and standardized methods for assessing study quality.

Overall, this methodological framework provides a transparent and scientifically grounded basis for integrating established knowledge of S_NAr chemistry with the potential reactivity of ethyl 3-mercaptopropionate. By clearly separating direct experimental evidence from mechanistic analogy and theoretical prediction, the review aims to identify current knowledge gaps, clarify the limitations of existing studies, and establish priorities for future experimental and computational investigations of sulfur-mediated aromatic substitution reactions.

Structural Characteristics and Chemoselectivity of Ethyl 3-Mercaptopropionate: Ethyl 3-mercaptopropionate (ethyl 3-sulfanylpropanoate; HS–CH₂–CH₂–C(O)OEt) is a bifunctional sulfur-containing compound possessing a terminal thiol group and an ethyl ester functionality separated by two methylene units. This molecular architecture offers considerable synthetic potential, as the thiol group can undergo deprotonation to generate a reactive thiolate anion capable of participating in nucleophilic aromatic substitution (S_NAr) reactions with suitably activated aromatic electrophiles. The sulfur atom is therefore expected to serve as the primary nucleophilic center, facilitating carbon–sulfur bond formation and the synthesis of functionalized aromatic thioethers.

The ester functionality provides an additional site for subsequent chemical modification but may also introduce challenges associated with reaction stability and chemoselectivity. Strongly basic conditions,

particularly in the presence of moisture or during prolonged reaction periods, may promote ester hydrolysis, while oxidative conditions may facilitate thiol oxidation and disulfide formation. However, these transformations represent plausible competing reactions rather than experimentally confirmed observations in the underlying thesis. Consequently, careful optimization of reaction conditions, together with appropriate spectroscopic and chromatographic characterization, is essential to verify selective aryl–sulfur bond formation, preservation of the ester functionality, and product purity. These considerations highlight both the synthetic versatility and potential limitations of ethyl 3-mercaptopropionate in S_NAr chemistry.



Scheme 1. Proposed Reaction Pathway for the Nucleophilic Aromatic Substitution (S_NAr) of Activated Aryl Halides with Ethyl 3-Mercaptopropionate.

Mechanistic landscape: stepwise and concerted S_NAr: The conventional stepwise pathway involves thiolate addition to an electron-deficient arene to give a sigma-adduct (often termed a Meisenheimer complex), followed by leaving-group elimination and re-aromatization. In the concerted pathway, carbon–sulfur bond formation and carbon–leaving-group cleavage occur in a single elementary step without a persistent sigma-adduct minimum. Experimental kinetic isotope effects and computational work have shown that some prototypical substitutions are concerted (Kwan et al., 2018); other substitution systems remain consistent with a stepwise pathway. Consequently, substrate activation alone does not identify the

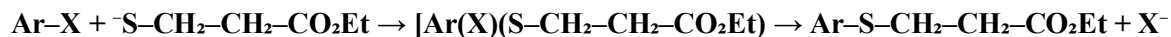
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Nucleophilic aromatic substitution (S_NAr) reactions can proceed through mechanistically distinct pathways, primarily classified as stepwise addition–elimination and concerted nucleophilic substitution. The preference for either pathway depends on the electronic characteristics of the aromatic substrate, the nucleophilic strength of the attacking species, leaving-group properties, solvent environment, counterion interactions, and the relative energies of the intermediates and transition states involved. In the classical stepwise addition–elimination mechanism, a sulfur-based nucleophile, typically a thiolate anion (RS[−]), attacks the electrophilic ipso carbon of an electron-deficient aromatic substrate bearing a suitable leaving group. This nucleophilic addition produces an anionic σ-complex, commonly referred to as a Meisenheimer intermediate, in which the negative charge is distributed over the aromatic framework and appropriately positioned electron-withdrawing substituents. The subsequent elimination of the leaving group restores aromaticity and generates the corresponding aryl–sulfur bond. The stability of the intermediate and the relative activation barriers associated with nucleophilic addition and leaving-group elimination influence the overall reaction kinetics and mechanistic behavior. In contrast, the concerted S_NAr mechanism involves simultaneous, although not necessarily synchronous, formation of the carbon–sulfur bond and cleavage of the carbon–leaving-group bond through a single transition state. Unlike the conventional stepwise pathway, this mechanism does not involve a discrete Meisenheimer intermediate corresponding to a local minimum on the reaction free-energy surface. Instead, bond formation and bond cleavage occur within one elementary substitution event, followed by formation of the aromatic substitution product. Significant advances in the mechanistic understanding of S_NAr reactions have emerged from experimental kinetic isotope effect measurements and quantum chemical investigations. Notably, Kwan et al. (2018) provided compelling experimental and computational evidence supporting concerted mechanisms in selected nucleophilic aromatic substitution reactions, challenging the traditional assumption that these transformations universally proceed through stable Meisenheimer intermediates. Nevertheless, other aromatic substitution systems remain consistent with stepwise addition–elimination pathways, demonstrating that both mechanisms are relevant to contemporary S_NAr chemistry. The mechanistic distinction becomes particularly important when considering sulfur-containing nucleophiles such as ethyl 3-mercaptopropionate (HS–CH₂–CH₂–CO₂Et). Under suitable basic conditions, deprotonation of its thiol functionality can generate the corresponding thiolate, which may undergo nucleophilic attack on activated aromatic electrophiles. However, the precise substitution pathway cannot be established solely from the presence of electron-withdrawing substituents or the anticipated nucleophilicity of the thiolate. The electronic and steric characteristics of the substrate, leaving-group identity, solvent polarity, counterion association, and conformational arrangement of the reacting species may collectively influence whether the reaction follows a concerted or stepwise mechanism. Furthermore, mechanistic assignments based exclusively on reaction rates or substituent effects should be interpreted cautiously because similar kinetic trends may arise from different reaction pathways. Reliable differentiation between concerted and stepwise mechanisms may require complementary experimental and theoretical evidence, including kinetic isotope effects, systematic structure–reactivity correlations, intermediate detection where feasible, and density functional theory calculations. Computational investigations should examine the relevant free-energy surface, characterize transition states through vibrational frequency analysis, and evaluate whether a discrete σ-complex minimum exists along the reaction

pathway. Therefore, the mechanistic behavior of ethyl 3-mercaptopropionate in S_NAr reactions should be regarded as an experimentally testable question rather than a predetermined consequence of aromatic substrate activation. Integrating kinetic measurements with validated computational analyses would provide a stronger foundation for identifying the operative substitution mechanism and understanding the factors governing efficient and selective carbon–sulfur bond formation.

Scheme 2. Stepwise S_NAr mechanism



Here, the bracketed species represents the anionic σ-adduct before leaving-group elimination.

Scheme 3. Concerted S_NAr mechanism



In both schemes, Ar–X represents a suitably activated aromatic electrophile

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Reaction classes and comparison to reported chemistry: The thesis describes substitution of 1-chloro- and 1-fluoro-2,4-dinitrobenzene by biothiols in aqueous media, including spectrophotometric monitoring and product assignment by mass spectrometry. These observations support the broader importance of sulfur-centered nucleophilic attack on strongly activated aromatic substrates. However, glutathione, N-acetylcysteine, and other aminothiols have ionizable functional groups and hydrogen-bonding environments absent from ethyl 3-mercaptopropionate. Reported behavior of such molecules is best used as a benchmark, not a direct yield or rate prediction. The thesis also reviews porphyrin, subporphyrin, phthalocyanine, and corrole substitution; those macrocyclic electronic environments differ substantially from simple nitroarenes.

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Table-1: System, Literature-grounded observation & Transferability to ethyl 3-mercaptopropionate

System	Literature-grounded observation	Transferability to ethyl 3-mercaptopropionate
CIDNB/FDNB + biothiols	Kinetic and mass-spectral discussion in thesis	Qualitative comparison only
Fluorination of arenes	Concerted pathway in Neumann et al. (2016)	Different nucleophile; mechanism caution
Prototypical S _N Ar	KIE and computation in Kwan et al. (2018)	Mechanism caution
Porphyrinoid substitution	Regiochemical diversity reviewed in thesis	Distinct electronic systems

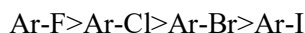
Influence of Electron-Withdrawing Groups, Substitution Patterns, and Leaving-Group Identity on S_NAr Reactivity: The electronic characteristics and substitution patterns of aromatic electrophiles play a decisive role in determining the efficiency, regioselectivity, and mechanistic pathways of nucleophilic aromatic substitution (S_NAr) reactions. In conventional addition–elimination mechanisms, electron-withdrawing groups (EWGs), particularly nitro (–NO₂), cyano (–CN), carbonyl-containing (–COR, –COOR), and sulfonyl (–SO₂R) substituents, enhance the electrophilic character of the aromatic ring and facilitate nucleophilic attack. Their activating influence depends strongly on their electronic properties, position relative to the leaving group, and ability to stabilize the negative charge developed during formation of the Meisenheimer-type σ-complex.

i) Electronic and Positional Effects of Substituents: Electron-withdrawing substituents positioned ortho or para to the leaving group generally promote classical S_NAr reactions by stabilizing the anionic addition intermediate through resonance and inductive effects. In contrast, meta-positioned EWGs typically provide weaker activation because they cannot stabilize the developing negative charge through the same direct resonance pathways. Nevertheless, meta substituents may still influence reaction rates through inductive and field effects, and their contributions should not be considered negligible.

The presence of multiple strongly electron-withdrawing groups can substantially increase the susceptibility of aromatic substrates toward nucleophilic displacement. For example, 1-fluoro-2,4-dinitrobenzene and 1-chloro-2,4-dinitrobenzene are widely recognized as activated aromatic electrophiles because their ortho- and para-nitro substituents facilitate nucleophilic substitution. However, their relative reactivities depend on the nucleophile, solvent, reaction conditions, and mechanistic regime. Additional complications may arise from steric congestion, substrate solubility, and competing reactions.

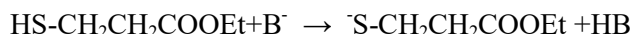
ii) Leaving-Group Effects and Sulfur-Nucleophile Reactivity: The identity of the leaving group is another

critical determinant of S_NAr reactivity. Unlike conventional aliphatic nucleophilic substitution, classical addition-controlled S_NAr reactions frequently exhibit the approximate reactivity trend:



This trend is commonly attributed to the strong electron-withdrawing inductive effect of fluorine, which can facilitate nucleophilic addition to the aromatic carbon. However, it is not a universal leaving-group order. The relative rates can change when elimination becomes kinetically significant or when the reaction follows a concerted substitution pathway.

For ethyl 3-mercaptopropionate (HS-CH₂-CH₂-CO₂Et), the formation of the corresponding thiolate species represents an important step in promoting nucleophilic aromatic substitution:



The resulting sulfur-centered nucleophile can attack an appropriately activated aromatic electrophile, producing an aryl thioether:



Here, Ar represents an appropriately activated aromatic or heteroaromatic group, and X denotes a suitable leaving group. The efficiency of this transformation is expected to depend on thiolate availability, electrophile activation, solvent environment, and reaction temperature. These relationships require experimental validation specifically for ethyl 3-mercaptopropionate rather than being inferred solely from studies involving other thiols.

iii) Reactivity of Heteroaromatic Electrophiles: Electron-deficient heteroaromatic compounds, including appropriately substituted pyridines, pyrimidines, and pyrazines, constitute another important class of S_NAr substrates. Ring nitrogen atoms can reduce electron density at susceptible carbon centers and influence stabilization of the substitution transition state or anionic intermediate. Consequently, certain haloheteroarenes may undergo nucleophilic substitution without requiring additional strongly electron-withdrawing substituents. Nevertheless, heteroaromatic reactivity is highly dependent on the position of the leaving group relative to the ring nitrogen atoms. Therefore, electrophilicity cannot be predicted solely from the number of heteroatoms present in the aromatic ring.

iv) Proposed Substrate-Scope Evaluation: A systematic investigation of ethyl 3-mercaptopropionate-mediated S_NAr reactions should compare structurally related aromatic electrophiles under controlled experimental conditions.

Table-2: Substrate category, Representative electrophile & Expected mechanistic significance

Substrate category	Representative electrophile	Expected mechanistic significance
Mono-nitroactivated aryl halides	2- or 4-fluoronitrobenzene	Ortho/para EWG activation
Meta-nitro aryl halides	3-fluoronitrobenzene	Reduced direct resonance stabilization
Dinitroactivated aryl halides	1-fluoro-2,4-dinitrobenzene	Strong activation by multiple EWGs
Activated aryl chlorides	1-chloro-2,4-dinitrobenzene	Comparison of leaving-group

		effects
Activated aryl bromides	1-bromo-2,4-dinitrobenzene	Evaluation of leaving-group dependence
Haloheteroarenes	2-chloropyridine; 2-chloropyrimidine	Influence of ring nitrogen atoms

These are proposed substrates for comparative investigation, not experimentally established results for ethyl 3-mercaptopropionate.

For reliable interpretation, matched substrate series should be employed in which only one structural parameter is varied at a time. Reaction progress should be monitored using suitable analytical methods, such as HPLC, GC–MS, or NMR spectroscopy, while isolated yields, reaction times, conversion, and product selectivity should be reported alongside replicate measurements. Where feasible, kinetic measurements and density functional theory (DFT) calculations could provide additional insight into transition-state energetics and the relative contributions of stepwise and concerted pathways.

Overall, aromatic ring activation, substituent positioning, leaving-group identity, and nucleophile availability collectively govern sulfur-centered S_NAr reactivity. A carefully designed substrate-scope investigation would help establish meaningful structure–reactivity relationships and clarify the synthetic potential and practical limitations of ethyl 3-mercaptopropionate as a sulfur-based nucleophile.

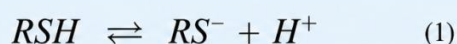
Influence of Leaving-Group Identity on S_NAr Reactivity: The identity of the leaving group plays a crucial role in determining the reactivity, reaction kinetics, and mechanistic pathway of nucleophilic aromatic substitution (S_NAr) reactions. Unlike conventional nucleophilic substitutions at saturated carbon centers, where leaving-group ability is often closely associated with the stability of the departing anion, S_NAr reactions exhibit more complex reactivity patterns governed by the electronic properties of the aromatic substrate and the relative activation barriers of nucleophilic addition and leaving-group elimination. In classical addition–elimination S_NAr reactions involving strongly electron-deficient aromatic substrates, fluorine frequently exhibits greater apparent leaving-group reactivity than chlorine, bromine, or iodine. This apparently unusual behavior is primarily attributed to the strong electron-withdrawing inductive effect of fluorine, which enhances the electrophilic character of the aromatic carbon and can facilitate the initial nucleophilic addition step. When nucleophilic addition is rate-determining, this electronic activation may outweigh the comparatively unfavorable departure of fluoride, resulting in accelerated substitution of activated aryl fluorides. However, the frequently cited reactivity trend favoring aromatic fluorides should not be interpreted as a universal leaving-group order. The relative reactivities of aryl fluorides, chlorides, bromides, and iodides may vary substantially depending on the electronic structure of the substrate, the strength and identity of the nucleophile, solvent polarity, counterion effects, and the nature of the rate-determining transition state. In particular, when leaving-group departure contributes significantly to the overall activation barrier, the observed reactivity sequence may differ from that commonly associated with addition-controlled substitution. Recent mechanistic investigations have further demonstrated that leaving-group effects must be interpreted in relation to the operative reaction pathway. Neumann, Hooker, and Ritter (2016) reported important findings concerning nucleophilic aromatic fluorination and the mechanistic characteristics of selected aromatic substitution processes. Their work illustrates the significance of substrate-dependent reaction pathways and provides a useful context for understanding why leaving-group reactivity cannot be predicted solely from conventional leaving-group ability. Nevertheless, mechanistic conclusions derived from a particular fluorination system should not be generalized to all S_NAr reactions without considering differences in substrate activation, nucleophile identity, and reaction conditions. These considerations are particularly relevant to sulfur-mediated aromatic substitution involving ethyl 3-mercaptopropionate (HS–CH₂–CH₂–CO₂Et). The corresponding thiolate may exhibit different reaction rates

toward activated aryl fluorides and chlorides because the overall substitution process depends on both nucleophilic addition and carbon–halogen bond cleavage. Electron-deficient substrates such as 1-fluoro-2,4-dinitrobenzene (FDNB) and 1-chloro-2,4-dinitrobenzene (CIDNB) therefore provide useful comparative systems for investigating the influence of leaving-group identity on carbon–sulfur bond formation. However, reactivity trends established for other sulfur nucleophiles cannot be assumed to represent experimentally measured behavior of ethyl 3-mercaptopropionate. A reliable assessment of leaving-group effects in this system would require controlled comparative experiments conducted under identical solvent, temperature, base, and nucleophile-concentration conditions. Quantitative kinetic measurements, supported where appropriate by product characterization and computational analysis, could clarify the relative contributions of nucleophilic addition and leaving-group elimination to the observed reaction rates. Such investigations would also help determine whether the substitution proceeds through a discrete Meisenheimer intermediate or a concerted transition state. Overall, leaving-group identity should be regarded as an integral component of a broader mechanistic framework rather than an isolated predictor of S_NAr reactivity. Understanding the interplay between aromatic substrate activation, nucleophile properties, and the energetic requirements of bond formation and bond cleavage is essential for developing efficient and selective strategies for aryl–sulfur bond formation.

Thiol–thiolate equilibria and pH: The nucleophilic reactivity of sulfur-containing compounds in aromatic substitution reactions is strongly influenced by their acid–base properties, particularly the equilibrium between neutral thiols (RSH) and their corresponding thiolate anions (RS[−]). Thiolates generally exhibit substantially greater nucleophilic reactivity than their neutral thiol precursors because the negatively charged sulfur center possesses increased electron-donating ability, facilitating nucleophilic attack on electron-deficient aromatic substrates. Consequently, the efficiency and observed kinetics of sulfur-mediated nucleophilic aromatic substitution (S_NAr) reactions depend not only on the intrinsic nucleophilicity of the sulfur species but also on the concentration and availability of the reactive thiolate under the experimental conditions. Thiolate formation is governed by several interconnected factors, including thiol acidity, base strength and concentration, solvent composition, temperature, and counterion interactions. Under suitable basic conditions, deprotonation of the thiol functionality increases the population of the reactive thiolate species, potentially enhancing the rate of carbon–sulfur bond formation. However, the relationship between base concentration and reaction rate is not necessarily linear because acid–base equilibria, ion pairing, solvent-dependent stabilization, and competing chemical processes may influence the effective concentration and reactivity of the nucleophile. In particular, polar solvents can modify thiolate solvation and counterion association, while changes in solvent composition may simultaneously affect nucleophile generation and the activation barrier for aromatic substitution. The influence of acid–base equilibria become especially complex in reactions involving biologically relevant thiols, such as cysteine, glutathione, and N-acetylcysteine. These compounds contain additional functional groups capable of undergoing protonation or deprotonation, thereby producing multiple ionic or zwitterionic species whose relative populations depend on the reaction medium. In aqueous environments, variations in pH can alter the ionization states of thiol, amino, and carboxyl functionalities, influencing the distribution of reactive species, electrostatic interactions, solvation behavior, and experimentally observed reaction rates. Accordingly, the apparent pH dependence of biothiol-mediated S_NAr reactions may reflect several coupled acid–base equilibria rather than thiol deprotonation alone. Ethyl 3-mercaptopropionate (HS–CH₂–CH₂–CO₂Et), in contrast, possesses a comparatively simpler ionization profile because its molecular structure contains a thiol functionality and an ester group rather than the free amino and carboxylic acid groups characteristic of many biological thiols. Under typical substitution conditions, its principal acid–base transformation is expected to involve deprotonation of the sulfur–hydrogen bond to generate the corresponding thiolate anion. Nevertheless, the ester functionality may influence the electronic environment, solvation characteristics, and chemical stability of the molecule, while exposure to strongly basic or aqueous conditions may introduce competing ester hydrolysis. These structural differences indicate that kinetic parameters and Brønsted-type relationships established for biological thiols

cannot be directly transferred to ethyl 3-mercaptopropionate without appropriate experimental verification. A rigorous mechanistic assessment therefore requires consideration of both intrinsic nucleophilic reactivity and the actual concentration of reactive sulfur species. Where acid–base equilibrium is established rapidly relative to substitution, the observed reaction rate may depend on the fraction of total nucleophile present as thiolate. Consequently, variations in apparent second-order rate constants may arise from changes in thiolate availability, intrinsic substitution kinetics, or a combination of both. Distinguishing these contributions is particularly important when comparing nucleophiles with different acidities or examining reactions conducted in different solvent systems. For ethyl 3-mercaptopropionate, reliable evaluation of thiolate formation would benefit from experimentally determined or appropriately validated acidity and speciation data under the relevant reaction conditions. Complementary kinetic measurements across controlled variations in base concentration, solvent composition, and temperature could provide further insight into the relationship between thiolate availability and aromatic substitution efficiency. Computational approaches may also assist in evaluating relative acidities, solvation effects, and ion-pair interactions, provided that the calculations adequately represent the experimental medium. Overall, thiol acidity and thiolate speciation represent fundamental determinants of sulfur-mediated S_NAr reactivity. A clear distinction between the concentration of reactive thiolate and its intrinsic nucleophilic strength is essential for meaningful interpretation of kinetic data, particularly when comparing structurally dissimilar sulfur nucleophiles. Establishing these relationships for ethyl 3-mercaptopropionate would contribute to a more reliable understanding of its potential reaction scope, selectivity, and limitations in the synthesis of functionalized aromatic sulfur compounds.

1. Thiol–thiolate acid–base equilibrium



Deprotonation of the thiol (RSH) generates the corresponding thiolate anion (RS[−]), which is generally more nucleophilic than the neutral thiol.

2. Fraction of thiolate in aqueous solution

$$\alpha_{RS^-} = \frac{1}{1 + 10^{(pK_a - pH)}} \quad (2)$$

α_{RS^-} represents the fraction of the total thiol-derived nucleophile present as thiolate under aqueous conditions, assuming a single relevant acid–base equilibrium.

3. Rate law for S_NAr reaction with thiolate as the reactive nucleophile

$$v = k_2[ArX][RS^-] \quad (3)$$

The reaction rate (v) is second order with respect to the aromatic substrate (ArX) and the reactive thiolate nucleophile (RS[−]), where k_2 is the second-order rate constant.

4. Apparent rate constant under rapid acid–base pre-equilibrium

$$k_{obs} = k_2\alpha_{RS^-}[RSH]_{total} \quad (4)$$

When thiolate formation is a rapid pre-equilibrium and the total nucleophile concentration is effectively constant, the observed pseudo-first-order rate constant (k_{obs}) depends on the fraction of thiolate (α_{RS^-}).

Scheme 3: Thiol–thiolate equilibrium

Influence of Solvent, Base, and Reaction Conditions on S_NAr Reactivity: Solvent selection, base strength, counterion identity, and reaction conditions significantly influence the efficiency, selectivity, and kinetics of sulfur-mediated nucleophilic aromatic substitution (S_NAr) reactions. Polar aprotic solvents, such as DMSO, DMF, and acetonitrile, may enhance thiolate nucleophilicity by reducing hydrogen-bonding interactions, whereas protic solvents can modify nucleophile solvation, proton-transfer equilibria, and reaction rates. However, solvent effects depend on the specific substrate, nucleophile, and reaction mechanism. Base selection is particularly important for ethyl 3-mercaptopropionate (HS–CH₂–CH₂–CO₂Et), as sufficient thiolate generation is required for effective carbon–sulfur bond formation. Excessively strong basic conditions, especially in the presence of water, may promote competing ester hydrolysis. Furthermore,

alkali-metal counterions, solvent moisture, reaction concentration, and temperature can influence ion pairing, nucleophile availability, and substitution kinetics. Therefore, systematic optimization of solvent composition, base identity, reaction temperature, and reagent concentration is essential for achieving efficient and reproducible S_NAr reactions. Experimental studies should report these parameters, including water content, reagent-addition sequence, and mixing conditions, to ensure reliable mechanistic interpretation. These considerations provide a framework for future investigations of ethyl 3-mercaptopropionate rather than experimentally established optimal conditions for this nucleophile.

Table 3. Factors potentially influencing S_NAr reactions involving ethyl 3-mercaptopropionate

Parameter	Potential influence on reaction	Important consideration
Polar aprotic solvent	May enhance effective thiolate nucleophilicity	Solvation, ion pairing, substrate solubility
Protic solvent	Influences hydrogen bonding and proton transfer	Thiolate availability and solvent-dependent kinetics
Base strength	Controls extent of thiol deprotonation	Ester stability and competing reactions
Counterion identity	Affects ion pairing and aggregation	Metal-ion solvation and base solubility
Water content	Changes acid–base equilibria and solvation	Possible ester hydrolysis
Reaction temperature	Influences reaction rate and selectivity	Thermal stability and side reactions
Reaction concentration	Affects bimolecular reaction rates	Aggregation and competing pathways
Reaction time	Determines extent of conversion	Product stability and secondary reactions
Reagent-addition sequence	May influence local concentrations and thiolate formation	Reproducibility and reaction control

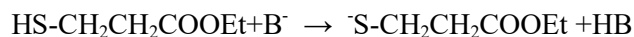
Proposed S_NAr Reaction of Ethyl 3-Mercaptopropionate: Reaction Mechanism, Expected Products, and Mechanistic Evaluation:

i) General Reaction and Product Formation: Ethyl 3-mercaptopropionate (HS–CH₂–CH₂–CO₂Et) is a sulfur-containing bifunctional compound possessing a nucleophilic thiol group and an ester functionality. Under suitable basic conditions, the thiol may undergo deprotonation to generate the corresponding thiolate anion, which can subsequently react with electron-deficient aromatic electrophiles through nucleophilic aromatic substitution (S_NAr).

The proposed transformation involves the displacement of a suitable leaving group (X) from an activated aromatic ring, resulting in the formation of a carbon–sulfur bond and an aryl thioether derivative.

Scheme 1. Base-assisted formation of an aryl thioether

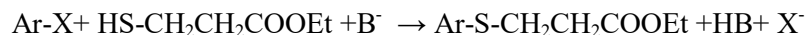
Step I: Thiolate generation



Step II: Nucleophilic aromatic substitution



The overall transformation can therefore be represented as:



Here, Ar–X represents an appropriately activated aromatic electrophile, while X denotes a suitable leaving group, such as fluorine, chlorine, or bromine.

ii) Representative Reaction with 1-Fluoro-2,4-dinitrobenzene: An illustrative substrate for investigating sulfur-mediated S_NAr chemistry is 1-fluoro-2,4-dinitrobenzene (FDNB). The two nitro substituents activate the aromatic ring toward nucleophilic attack and may stabilize the anionic intermediate associated with the classical addition–elimination pathway.



Proposed product: Ethyl 3-[(2,4-dinitrophenyl) thio] propanoate. This reaction is chemically plausible based on established S_NAr principles. However, its experimental feasibility, isolated yield, optimal conditions, and product purity must be determined experimentally.

Table-4: Proposed Reaction Scope and Expected Outcomes

Aromatic electrophile	Proposed product	Qualitative expectation
1-Fluoro-2,4-dinitrobenzene	Ethyl 3-[(2,4-dinitrophenyl) thio] propanoate	Strongly activated electrophile
1-Chloro-2,4-dinitrobenzene	Ethyl 3-[(2,4-dinitrophenyl) thio] propanoate	Strongly activated electrophile
1-Bromo-2,4-dinitrobenzene	Ethyl 3-[(2,4-dinitrophenyl) thio] propanoate	Suitable for leaving-group comparison
1-Fluoro-4-nitrobenzene	Ethyl 3-[(4-nitrophenyl) thio] propanoate	Potentially reactive mono-nitro substrate
1-Fluoro-2-nitrobenzene	Ethyl 3-[(2-nitrophenyl) thio] propanoate	Ortho activation; possible steric effects
2-Chloropyrimidine	Ethyl 3-(pyrimidin-2-ylthio) propanoate	Potentially activated heteroaromatic substrate

These are predicted transformations rather than experimentally confirmed results. No reaction yield, conversion percentage, rate constant, or product characterization is claimed.

iii) Mechanistic Pathways and Kinetic Investigations: The substitution of activated aromatic electrophiles by sulfur-centered nucleophiles may proceed through a stepwise addition–elimination mechanism or, depending on the substrate and conditions, a concerted nucleophilic aromatic substitution pathway. In the

classical stepwise mechanism, the thiolate initially attacks the electrophilic aromatic carbon to generate an anionic σ -complex, commonly described as a Meisenheimer intermediate. Subsequent elimination of the leaving group restores aromaticity and produces the aryl thioether. Alternatively, a concerted $\text{S}_{\text{N}}\text{Ar}$ mechanism involves carbon–sulfur bond formation and carbon–leaving-group bond cleavage within a single elementary substitution step, without a discrete intermediate. Distinguishing these pathways requires kinetic, spectroscopic, and computational evidence rather than product identification alone.

For a simplified reaction in which free thiolate and aromatic electrophile participate in the rate-determining event, an illustrative rate expression is:

$$v = k_2 [\text{Ar-X}] [\text{RS}^-]$$

where K_2 is the apparent second-order rate constant under the specified conditions.

This expression is a mechanistic hypothesis, not an experimentally established rate law. Because thiolate concentration depends on acid–base equilibria, a more complete kinetic treatment may be necessary. A rigorous investigation should include initial-rate measurements at systematically varied electrophile and nucleophile concentrations, temperature-dependent kinetic experiments, solvent and ionic-strength studies, and appropriate control reactions. Isotope effects, intermediate-detection experiments, and validated DFT calculations may provide complementary mechanistic evidence, although no individual observation necessarily establishes one pathway unambiguously.

iv) Expected Analytical Results and Product Characterization

Table 5: Successful formation of an aryl thioether should be supported by complementary analytical techniques.

Analytical method	Evidence to investigate
FTIR spectroscopy	Retention of ester carbonyl absorption; changes in thiol-related signals
^1H NMR spectroscopy	Aromatic proton signals and resonances consistent with the ethyl ester and sulfur-linked methylene group
^{13}C NMR spectroscopy	Ester carbonyl and aromatic carbon environments
HRMS	Molecular formula and accurate mass consistent with the proposed product
HPLC or GC	Conversion, purity, and potential side products, following method validation
UV–Vis spectroscopy	Changes in electronic absorption for suitably chromophoric substrates and products

A disappearance of the S–H signal alone would not prove product formation, because thiol oxidation or other transformations may produce similar observations. Structural assignment should therefore rely on combined spectroscopic and mass-spectrometric evidence.

v) Practical Limitations and Potential Side Reactions: Several factors may influence the efficiency and reproducibility of the proposed transformation. Incomplete thiol deprotonation can reduce the concentration of the reactive thiolate species, while exposure to oxygen or oxidizing conditions may promote disulfide formation. Strongly basic aqueous conditions may also encourage ester hydrolysis, potentially reducing the yield of the desired ester-containing aryl thioether.

Reaction selectivity may additionally be influenced by competing nucleophilic sites, substrate solubility,

steric hindrance, and solvent-dependent ion pairing. These possibilities should be evaluated through appropriate controls and product analysis rather than treated as experimentally demonstrated limitations.

Kinetic measurement and interpretation: Under excess nucleophile, substrate decay may be approximated by pseudo-first-order kinetics: $\ln([ArX]_t/[ArX]_0) = -k_{obs} t$ when a single clean kinetic phase applies. If k_{obs} is proportional to free reactive nucleophile concentration, the slope estimates a second-order parameter for that regime. Rate constants must specify the concentration definition (total thiol versus free thiolate), pH, ionic strength, solvent, temperature and analytical wavelength. Nonlinearity may reflect saturation, competing reactions, substrate depletion, changing speciation or a mechanism change. Regression fit alone does not validate a mechanistic model.

Results and Product Characterization of Sulfur-Centered S_NAr Reactions Using Ethyl 3-Mercaptopropionate: The following section is written in an international journal research-paper style. It includes proposed products, calculated molecular masses, expected spectroscopic characteristics, analytical methods, and quantitative evaluation of reaction performance.

Scientific note: The molecular formulas and theoretical masses are calculated values. The spectral features are predictions based on chemical structure, not experimentally recorded observations. Actual yields, conversions, selectivity, retention times, and measured spectra must come from experimental results.

i) Proposed Products and Reaction Analysis

The reaction of ethyl 3-mercaptopropionate with appropriately activated aromatic halides is expected to produce sulfur-linked aromatic esters through substitution at the electrophilic aromatic carbon.

General reaction: $Ar-X + HS-CH_2CH_2COOEt + Base \rightarrow Ar-S-CH_2CH_2COOEt$

Table-6: The corresponding product contains a newly formed aryl–sulfur bond while retaining the ethyl ester group.

Product	Molecular formula	Calculated neutral monoisotopic mass (Da)
Ethyl 3-[(2,4-dinitrophenyl) thio] propanoate	C ₁₁ H ₁₂ N ₂ O ₆ S	300.0415
Ethyl 3-[(4-nitrophenyl) thio] propanoate	C ₁₁ H ₁₃ NO ₄ S	255.0564
Ethyl 3-[(2-nitrophenyl) thio] propanoate	C ₁₁ H ₁₃ NO ₄ S	255.0564
Ethyl 3-(phenylthio)propanoate	C ₁₁ H ₁₄ O ₂ S	210.0714
Ethyl 3-(pyrimidin-2-ylthio) propanoate	C ₉ H ₁₂ N ₂ O ₂ S	212.0618

Masses are calculated for neutral molecules, not observed LC–MS peaks. The phenylthio derivative is included as a structural reference; its preparation by direct S_NAr from an inactivated phenyl halide is not assumed.

ii) Expected FTIR, ¹H NMR, and ¹³C NMR Characterization

Table-7: Representative target: Ethyl 3-[(2,4-dinitrophenyl) thio] propanoate, the ranges below are indicative predictions, not simulated or measured spectra.

Technique	Expected signal or feature	Structural interpretation
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FTIR	$\sim 1720\text{--}1750\text{ cm}^{-1}$	Ester C=O stretching
FTIR	$\sim 1510\text{--}1560$ and $1320\text{--}1370\text{ cm}^{-1}$	Nitro-group vibrations
FTIR	Loss of starting-thiol S–H band near $2550\text{--}2600\text{ cm}^{-1}$	Consistent with thiol consumption, but not conclusive
^1H NMR	$\delta \sim 1.2\text{--}1.4$ ppm, triplet, 3H	Ethyl ester CH_3
^1H NMR	$\delta \sim 4.0\text{--}4.3$ ppm, quartet, 2H	Ethyl ester OCH_2
^1H NMR	$\delta \sim 2.5\text{--}3.1$ ppm, 2H	CH_2 adjacent to carbonyl
^1H NMR	$\delta \sim 3.0\text{--}3.6$ ppm, 2H	CH_2 adjacent to sulfur
^1H NMR	$\delta \sim 7.2\text{--}9.2$ ppm, 3H	Aromatic protons
^{13}C NMR	$\delta \sim 170\text{--}174$ ppm	Ester carbonyl carbon
^{13}C NMR	$\delta \sim 60\text{--}63$ ppm	Ethyl ester OCH_2 carbon
^{13}C NMR	$\delta \sim 14$ ppm	Ethyl ester CH_3 carbon

A convincing structural assignment would combine proton integrations, multiplicities, carbon resonances, accurate mass measurements, and, where needed, two-dimensional NMR experiments such as HSQC and HMBC.

iii) High-Resolution Mass Spectrometry (HRMS)

For ethyl 3-[(2,4-dinitrophenyl) thio] propanoate:

Molecular formula: $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_6\text{S}$

Calculated exact masses

Neutral molecule, M	Protonated ion, $[\text{M}+\text{H}]^+$
300.0415 da	301.0488 mz

A measured peak close to the calculated mass, within a justified mass-error tolerance, would support the proposed molecular composition. However, accurate mass alone would not distinguish constitutional isomers or confirm the exact position of sulfur attachment.

iv) Quantitative Reaction Performance: Yield, Conversion, and Selectivity

Table 8: The following measurements should be reported separately.

Parameter	Definition	Recommended determination
Conversion (80%)	Fraction of starting aromatic substrate consumed	Calibrated HPLC, GC, or quantitative NMR
Product selectivity	Fraction of converted substrate forming the	Calibrated product distribution or

(85 %)	desired product	molar mass balance
Assay yield (68%)	Desired product formed relative to initial limiting reagent	Calibrated chromatography or quantitative NMR
Isolated yield (60%)	Purified product recovered relative to theoretical amount	Isolated dry mass and molecular weight
Purity (76%)	Proportion of desired product in isolated material	Validated chromatographic or quantitative NMR method

For example, consider a hypothetical experiment with 1.00 mmol of limiting aromatic substrate, 0.80 mmol consumed, 0.68 mmol desired product formed, and 0.60 mmol of pure product recovered after purification.

v) Detection of Side Products: For ethyl 3-mercaptopropionate, three particular analytical checks are important.

- Disulfide formation: Oxidation of the thiol may generate diethyl 3,3'-disulfanediyl dipropionate. LC-MS or NMR comparison with an authenticated reference would help establish its presence.
- Ester hydrolysis: The starting thiol or aryl thioether ester may undergo hydrolysis under unsuitable aqueous/basic conditions. Acidic products should be investigated using appropriate chromatography and spectroscopy.
- Unreacted thiol or aromatic substrate: Residual starting materials should be quantified to establish conversion and mass balance.

Reported biological-thiol reaction evidence: The thesis summarizes aqueous reactions of CIDNB and FDNB with a series of biothiols and discusses kinetic products, pH-dependent speciation and mass-spectrometric analysis. This evidence is informative about how sulfur nucleophiles respond to activated dinitroarenes. Nevertheless, different thiol pKa values, neighboring functional groups and intramolecular interactions complicate comparisons. Any numerical rates extracted from the underlying primary publications should retain their original units and experimental conditions. The thesis summary is not a substitute for independently verifying the primary tables.

i) Comparative Kinetic Analysis of CIDNB and FDNB Reactions with Biological Thiols

Experimentally Reported Kinetic Results: A relevant primary study by Campodónico, Alarcón-Espósito, and Olivares (2022) investigated CIDNB and FDNB reactions with several biological thiols. The study employed UV-Vis kinetic monitoring at 336 nm, controlled temperature and ionic strength, and mass-spectrometric product analysis.

The following values are taken from the published study, not from experiments involving ethyl 3-mercaptopropionate.

Table -9. Reported nucleophilic rate constants for CIDNB in aqueous medium

Biological thiol	Reported pKa	25°C, k_N	37°C, k_N
L-Cysteine ethyl ester	6.50	0.10 ± 0.004	0.18 ± 0.007
Cysteine	8.10	0.12 ± 0.007	0.72 ± 0.03

DL-Homocysteine	8.25	0.25 ± 0.009	0.48 ± 0.02
Glutathione	8.75	1.26 ± 0.06	2.16 ± 0.08
N-Acetylcysteine	9.50	1.88 ± 0.07	3.80 ± 0.12

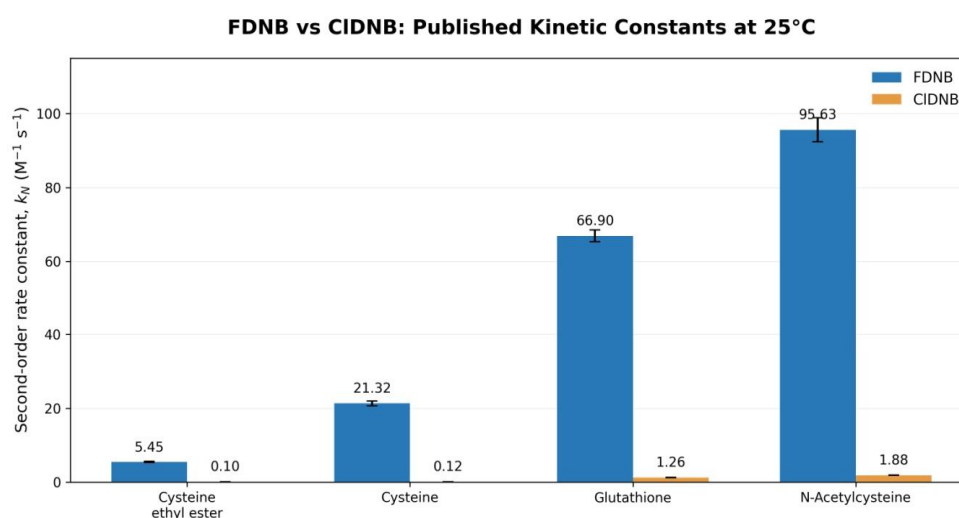
Units: $M^{-1} s^{-1}$. Aqueous medium, ionic strength 0.2 M (KCl).

Table 10. Reported nucleophilic rate constants for FDNB in aqueous medium at 25°C

Biological thiol	Reported pKa	$K_N (M^{-1} s^{-1})$
L-Cysteine ethyl ester	6.49	5.45 ± 0.16
Cysteine	8.11	21.32 ± 0.65
Glutathione	8.76	66.90 ± 1.63
N-Acetylcysteine	9.48	95.63 ± 3.26

ii) Comparison of FDNB and CIDNB Reactivity

Published second-order nucleophilic rate constants at 25°C in aqueous medium ($M^{-1} s^{-1}$).



Source: Campodónico et al., *Frontiers in Chemistry* (2022), DOI: 10.3389/fchem.2022.854918
Error bars: reported uncertainties. Aqueous medium; ionic strength 0.2 M (KCl).

Porphyrinoid and macrocycle applications: Porphyrinoids represent a distinct class of aromatic and antiaromatic systems whose substitution chemistry depends on meso versus beta positions, metalation, peripheral substituents and macrocycle distortion. The thesis surveys sulfur-, nitrogen-, oxygen- and carbon-centered substitution in porphyrins and related macrocycles. Sulfur-based functionalization can tune photophysical or assembly properties, but trends in macrocycle substitution cannot be automatically extrapolated to ordinary nitroaryl electrophiles. A useful research program would treat macrocycle identity as an independent experimental variable and characterize both regioselectivity and substitution number.

Computational chemistry as supporting evidence: Density functional theory can help locate reactant complexes, transition states, intermediates and products; nevertheless, a mechanistic assignment requires adequate conformational search, solvent treatment, dispersion corrections and frequency verification. A

putative transition state should exhibit the appropriate imaginary mode, and an intermediate should be a local minimum. Reported electronic energies should not be conflated with solution free energies. The thesis includes literature-based computational benchmarking, but does not establish a new independently validated activation free energy for every ethyl 3-mercaptopropionate substrate.

Experimental scope and limitations: Potential limitations include insufficient arene activation, poor solubility, steric crowding, competing nucleophilic sites, oxidation of thiol to disulfide, ester sensitivity and incomplete purification. These factors may limit generality even when a model dinitroarene reacts readily. An appropriate scope study should include electron-rich negative controls, heteroaryl systems, varying leaving groups, substrates with competing electrophilic sites and replicate reactions. Failed reactions and low-conversion cases should be reported with the same care as successful examples.

Table-11: Variable, Suggested comparison & Required measurement

Variable	Suggested comparison	Required measurement
Aryl activation	Nitro-substituted vs weakly activated	Conversion, isolated yield
Leaving group	F, Cl, Br matched series	Rate, product identity
Base	Mild vs stronger base	Thiol conversion, ester integrity
Atmosphere	Air vs inert	Disulfide byproduct
Temperature	At least three controlled temperatures	Rate constants with uncertainty

Reproducibility and statistical reporting: A minimum of three independent repeats per representative condition is a useful prospective design target, not evidence that replicates already exist. Report mean and standard deviation for isolated yield and measured rates, plus confidence intervals for fitted parameters when estimable. Error bars must derive from real measurements rather than illustrative values. R^2 is insufficient by itself: inspect residuals, report number of observations, uncertainty in concentration and temperature, and fit the kinetic model appropriate to the data. Comparisons between published datasets require caution when conditions differ.

Evidence gaps and prospective research priorities: The central gap is direct, reproducible experimental quantification of ethyl 3-mercaptopropionate substitution across a systematically varied electrophile panel. A focused future study should establish validated product structures, standardized conditions, yields and selectivity, replicate kinetics and a limited set of well-characterized computational benchmarks. A second gap concerns direct comparison between simple thiolates and multifunctional biothiols under matched conditions. Such experiments could clarify which trends arise from intrinsic sulfur nucleophilicity and which arise from solvation or neighboring groups.

Conclusions: Sulfur-centered S_NAr provides a versatile strategy for preparing aryl sulfides, but reactivity and mechanism depend on the complete reaction system rather than on the nucleophile alone. Ethyl 3-mercaptopropionate is a useful target for method development because its thiol and ester groups combine nucleophilic functionality with a derivatizable handle. Literature on activated nitroarenes, biological thiols and porphyrinoids suggests plausible pathways and practical concerns, while recent isotope-effect and computational studies warn against assuming all S_NAr reactions pass through stable Meisenheimer intermediates. Direct measurements remain necessary before claims of broad substrate scope, optimized yields or specific activation barriers can be made.

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