Recent Advancement in Synthesis of Isothiocyanates

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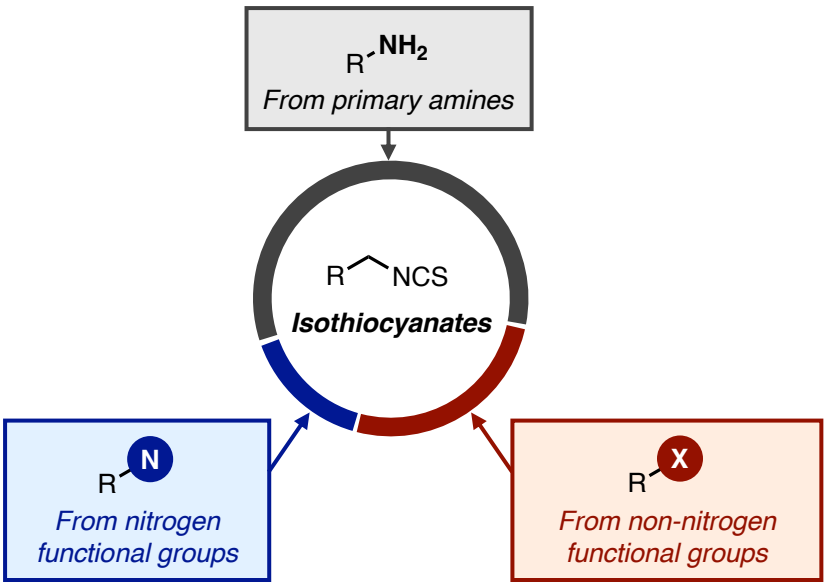


ABSTRACT. Isothiocyanates exhibit various biological characteristics, including antimicrobial, anti-inflammatory, and anticancer properties. Their significance extends to synthetic chemistry, where they serve as valuable platforms for versatile transformations. Consequently, they have attracted the attention of biologists and chemists. This review summarizes recent advancements in the synthesis of isothiocyanates. Access to a variety of starting materials is important to prepare isothiocyanates with diverse structures. This review categorizes synthetic methods into three types based on the starting materials and functional groups: (i) Type A, derived from primary amines; (ii) Type B, derived from other nitrogen functional groups; and (iii) Type C, derived from non-nitrogen groups. Recent trends in synthetic methods have revealed the prevalence of type-A reactions derived from primary amines. However, Type B reactions have rarely been reported. Notably, over the past four years, there has been a notable increase in Type C reactions, indicating a growing interest in non-nitrogen-derived isothiocyanates. Overall, this review not only outlines the advancements in the synthesis of isothiocyanates but also highlights trends in the methodology.

Keywords: Isothiocyanate • Synthetic methods • Bioactive compounds• Synthetic intermediates • C–N bond formation

1. Introduction

Isothiocyanates are abundantly present in natural products and bioactive compounds, with a general structure of R–N=C=S. (Figure 1). Isothiocyanate-containing compounds have been reported to exhibit a wide range of pharmacological properties, including antioxidant[1,2], antimicrobial[3,4], antibacterial[5], anti-inflammatory[6–10], antifeedant[11], anticancer[12–16], antiproliferative[17], and enzyme-inhibitory effects against HIV[18,19]. Notably, isothiocyanates are generated by members of the Brassica family and act as defense chemicals against herbivorous insects[20], bacteria[21], and fungi[22]. Therefore, isothiocyanates can be used as agrochemicals[23]. They are also important reagents in biochemistry such as fluorescein isothiocyanate (FITC), which is used in biological assays of DNA and proteins[24–26]. Phenyl isothiocyanate is useful for sequencing amino acids in peptides (Edman degradation).[27] During this process, it reacts with the *N*-terminal amino group, and the amino-terminal residue is labeled and cleaved from the peptide as phenylthiohydantoin. In synthetic chemistry, isothiocyanate has emerged as a valuable building block in the synthesis of thiourea[28,29], *N*-trifluoromethyl amine[30,31], and various heterocyclic compounds[32]. Therefore, isothiocyanates are promising platforms in medicinal chemistry.[33–40]

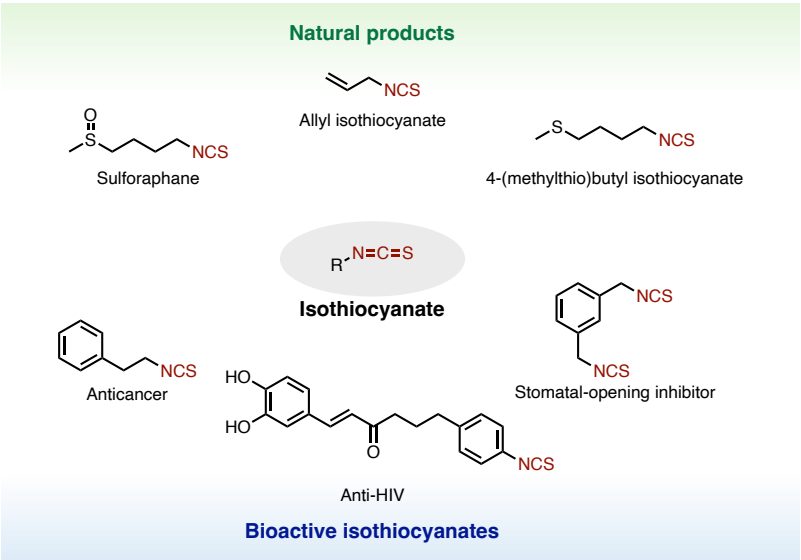


Figure 1. Examples of isothiocyanate-containing natural products and bioactive compounds.

As isothiocyanate is an important functional group in both biochemistry and synthetic chemistry, numerous synthetic methods have been developed.[41,42] This review provides a comprehensive summary of recent progress in isothiocyanate synthesis, with a focus on substrate categorization. Figure 2 illustrates the recent trends in isothiocyanate synthesis, showing three main substrates based on their functional groups: (i) Type A, derived from primary amines; (ii) Type B, derived from other nitrogen functional groups; and (iii) Type C, derived from non-nitrogen functional groups.

The abundance and structural variability of commercially available primary amines of Type A make them versatile starting materials. Despite having a single Type A starting material, Figure 2B indicates that reports on Type A have been the most frequent in this decade (29 reports). Type B includes isothiocyanates derived from other nitrogen-containing functional groups, such as azido, nitrile oxide, chloroxime, and isocyanide. These substrates, prepared from compounds other than primary amines, have contributed to the expansion of resources for isothiocyanates. However, since 2013, the number of Type B examples has been comparatively lower, with seven methods.

The isothiocyanation of non-nitrogen-containing substrates (Type C) is challenging and often competes with thiocyanation. Generally, thermodynamically controlled conditions are required to selectively obtain isothiocyanates that are more stable than thiocyanates. Over the past decade, 13 Type C reactions have been reported, and noteworthy advancements have been made since 2020. Several methods have enabled the one-step synthesis of isothiocyanates from olefins and C–H bonds. These methods have significantly increased their utility in biochemical and medicinal chemistry.

The review structure is organized as follows: Section 2 discusses the methods of isothiocyanate synthesis from primary amines (Type A). Section 3 reviews the synthetic methods involving nitrogen functional groups other than primary amines (Type B). Finally, the isothiocyanation of other functional groups and C–H bonds (Type C) is discussed in Section 4.

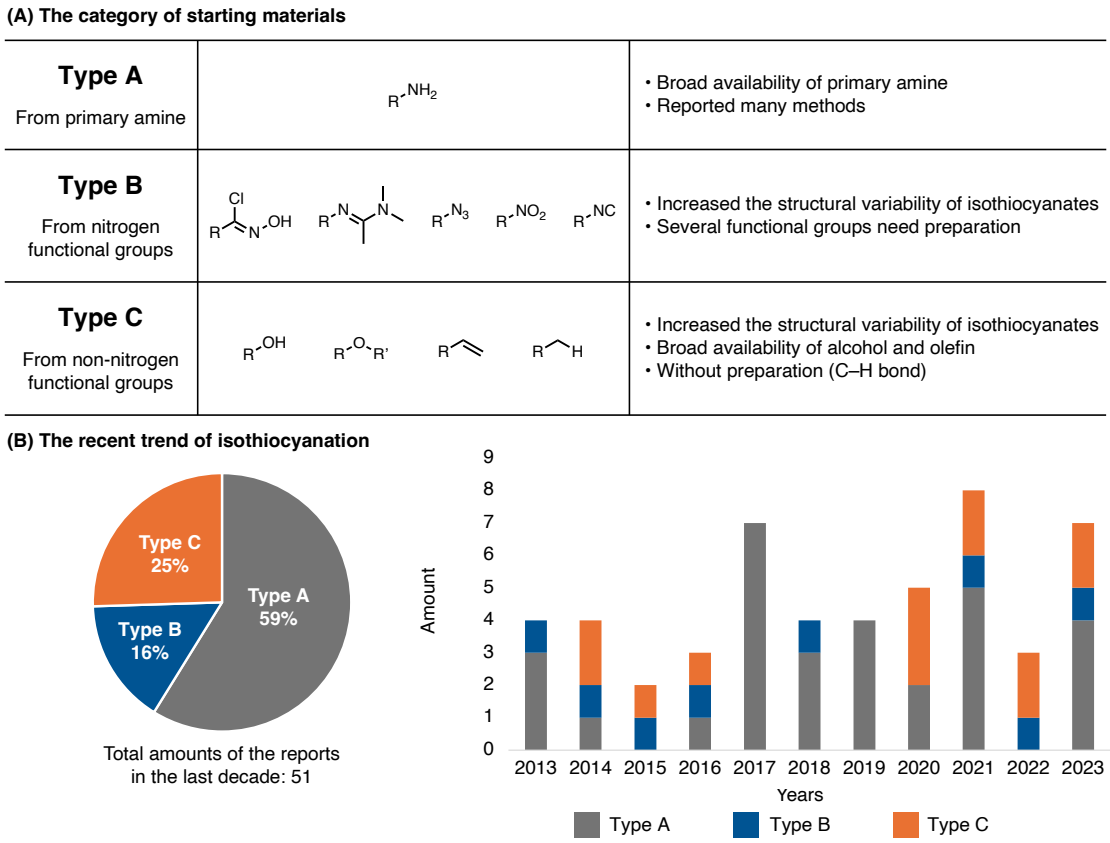
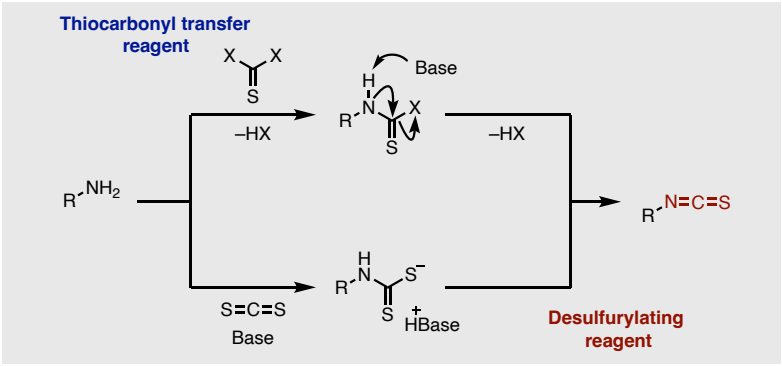


Figure 2. (A) The list of the starting materials and notes in each category. (B) The ratio of each starting material type in the last decade and the trend of the starting material type in each year.

2. Synthesis of isothiocyanates with primary amines (Type A)

As discussed earlier, primary amines have emerged as ideal substrates for the synthesis of a diverse range of isothiocyanates, owing to the ready availability of structurally diverse primary amines. Traditional synthetic methods using thiophosgene are challenging because of their high toxicity. To overcome these issues, alternative compounds such as thiocarbonyldiimidazole[43], di-2-pyridyl thiocarbonate[44], and thiocarbonylditriazole[45] have been developed. Unfortunately, these alternatives, while addressing toxicity concerns, are either non-commercialized or expensive reagents, or they require a preparation process. In contrast, a two-step approach utilizing the CS_2

has made remarkable progress. Indeed, many types of Type A methods discussed in this review employ CS_2. In this process, primary amines, the CS_2, and a base react to form dithiocarbamate salts. The subsequent decomposition of these salts using a desulfurylating reagent yields the corresponding isothiocyanates (Figure 3). Although various methods and desulfurylating reagents have been developed, such as *p*-toluenesulfonyl chloride[46], bis(trichloromethyl)carbonate (BTC)[47], claycop (clay-supported copper nitrate)[48], hydrogen peroxide[49], iodine[50], lead nitrate[51], and di-*tert*-butyl decarbonate (Boc_2O)[52], noteworthy progress has been made over the past decade.



Thiocarbonyl transfer reagent	X =	Cl					
Desulfurylating reagent	TsCl	BTC	claycop	H_2O_2	I_2	$Pb(NO_3)_2$	Boc_2O

Figure 3. The two mechanisms with a thiocarbonyl transfer reagent or a desulfurylating reagent and the examples of thiocarbonyl transfer reagent and desulfurylating reagent.

2-1. Synthesis of isothiocyanate with thiocarbonyl transfer reagents

In 2013, Sun and Chen reported a new method for the synthesis of isothiocyanates using chlorothionoformate (**1-1**) (Figure 4).[53] Previously, they established a one-pot synthesis of

isothiocyanates from primary amines using chlorothionoformate. However, this protocol exhibits limitations for a broad range of amines, particularly those with highly electron-deficient groups.[54] Through optimization, chlorothionoformate was found to be an efficient thiocarbonyl-transfer reagent when used in combination with NaOH in dichloromethane. In Method A, the one-step protocol provided electron-rich isothiocyanates in high yield (**1-2**). Meanwhile, a two-step process (Method B) for the synthesis of isothiocyanates from electron-deficient amines such as 4-nitroaniline afforded the corresponding isothiocyanates with high efficiency (**1-3** and **1-4**).

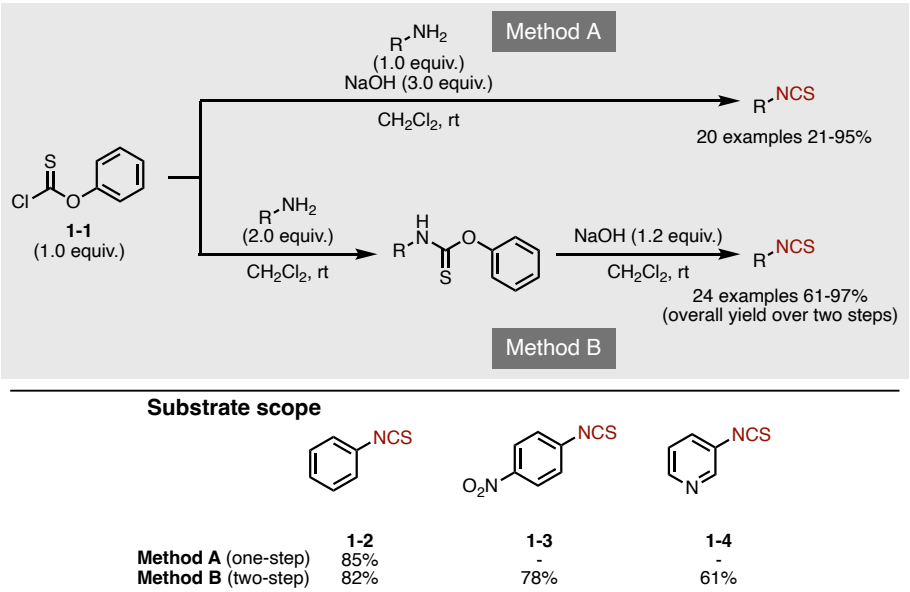


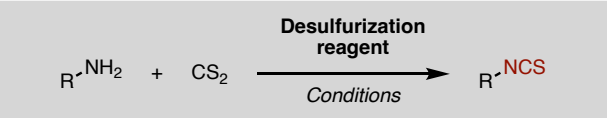
Figure 4. Synthesis of isothiocyanates with chlorothionoformate.

2-2. Synthesis of isothiocyanates via dithiocarbamate salt

Nearly all methods that use thiocarbonyl transfer reagents such as thiophosgenes encounter challenges with thiourea byproducts. Therefore, an alternative approach involving the desulfurization of dithiocarbamate salts generated by the treatment of primary amines with CS_2 in the presence of a base was developed. Desulfurization is crucial for the decomposition of

dithiocarbamate salts.[41,42] Most desulfurization reagents are not universally applicable to electron-deficient aryl isothiocyanates. Numerous methods using CS_2 have been reported to overcome these limitations.[55–75] Several methods have been explored to broaden the substrate scope of electron-deficient anilines and aminopyridines.[55,57–61,67,71,72,74,75] Moreover, employing a strong base[69], ball milling[56], a photoredox catalyst[72], an electrolytic reaction[73], or an appropriate desulfurylating reagent[60,61,68,71] enables the one-step synthesis of isothiocyanates. Table 1 provides a comprehensive review of the progress in dithiocarbamate salt protocols over the past decade. The table summarizes the years of reporting, desulfurylating reagents, reaction conditions, substrate scope, and key tips for each method. The work of Srivastava is particularly noteworthy for the straightforward synthesis of isothiocyanates from primary amines.[71] The reaction rapidly provides various isothiocyanates, including electron-deficient anilines, utilizing commercially available reagents such as CS_2, iodine, and TBAI.

Table 1. The list of the synthesis of isothiocyanates from primary amines with CS_2.



Year	Desulfurization reagents	Conditions	Substrates	tips	ref
2013	BTC	1st DABCO, CS_2/Acetone, rt 2nd BTC, $CHCl_3$, rt	· alkyl amine · aryl amine	Electron-deficient anilines are applicable	55
	None	CS_2, KOH, ball milling	· aryl amine	Without desulfurization reagent	56
2014	$FeCl_3 \cdot 6H_2O$	1st CS_2, DABCO, THF, rt 2nd $FeCl_3 \cdot 6H_2O$, H_2O	· aryl amine	Pyridyl amines and electron-deficient aniline are applicable	57
2016	$CoCl_2 \cdot 6H_2O$	1st CS_2, $NaHCO_3$, EtOAc, rt 2nd $CoCl_2 \cdot 6H_2O$, rt	· alkyl amine · aryl amine	Electron-deficient anilines were unsuccessful Heterogeneous solvent (EtOAc/H_2O) afforded ITCs	58
2017	$Fe_2(SO_4)_3 \cdot H_2O$	1st CS_2, NaOAc, DMSO, rt 2nd $Fe_2(SO_4)_3 \cdot H_2O$, NaOAc, rt	· aryl amine	2-halo anilines are the mainly substrates	59
	$CuSO_4 \cdot 5H_2O$	CS_2, NEt_3, $CuSO_4 \cdot 5H_2O$ EtOAc/H_2O or EtOH/H_2O, rt	· alkyl amine · aryl amine	The reaction proceeds in one-step in clean conditions	60
	TPATB	TPATB, $NaHCO_3$, EtOAc/H_2O	· alkyl amine · aryl amine	The substrate is dithiocarbamate salt	61
2018	DEAD	1st CS_2, DEAD, THF, -40 °C 2nd AcOH, THF, -40 °C to 35 °C	· alkyl amine	Isothiocyanates were obtained from xanthates	62
	$Na_2S_2O_8$	1st CS_2, K_2CO_3, H_2O, rt 2nd $Na_2S_2O_8$, K_2CO_3, H_2O, rt	· alkyl amine · aryl amine	The one-pot procedure achieved the synthesis chiral ITCs from a chiral amine	63
	T3P®	1st CS_2, NEt_3, CH_2Cl_2, rt 2nd T3P®, 4 °C to rt 3rd H_2O	· alkyl amine · aryl amine	Strong electron-deficient anilines were unsuccessful	64
2019	None	1st CS_2, NEt_3 or DBU, CH_2Cl_2, rt 2nd M.W., 90 °C	· alkyl amine · aryl amine	Without desulfurization reagent	65
	None	1st CS_2, DMSO, rt 2nd Triton-B, rt	· alkyl amine · aryl amine	Phase-transfer catalyst enabled one-pot ITCs synthesis	66
2020	$FeCl_3$	1st CS_2, NEt_3, Acetone, rt 2nd $FeCl_3$, NaOAc, Acetone, rt	· alkyl amine · aryl amine	Heating and K_2CO_3 afforded electron-deficient ITCs	67
2021	TBHP	CS_2, TBAI, DMAP, TBHP, MeOH, 0 °C	· alkyl amine · aryl amine	ITCs were obtained in one-step	68
	None	CS_2, NaOH, MeCN, rt	· alkyl amine · aryl amine	Strong electron-deficient anilines were unsuccessful	69
	DMT/NMM/TsO^-	1st CS_2, NEt_3 or DBU or NMM, CH_2Cl_2 or H_2O, rt 2nd DMT/NMM/TsO^-, M.W., 90 °C	· alkyl amine · aryl amine	ITCs were obtained in short time Without racemization	70
	I_2	CS_2, I_2, TBAI, DMSO, rt	· alkyl amine · aryl amine	ITCs were obtained in one-step Iodine is inexpensive and green desulfurization reagent	71
2023	None	CS_2, DBU, RB, MeCN, rt, Green LED	· alkyl amine · aryl amine	RB performed as a desulfurization catalyst	72
	None	CS_2, or/not DBU, CH_2Cl_2 or MeOH C_{gr}(+)||Ni(-) 5 mA, 2.2 F/mol	· alkyl amine · aryl amine	Electron performed as a desulfurization reagent	73
	PIDA	1st CS_2, NaOH, TPGS-750-M/H_2O, rt 2nd PIDA, NaOH, rt	· alkyl amine · aryl amine	The surfactant and hypervalent iodine enable Isothiocyanation in H_2O	74
	CBr_4	1st CS_2, DBU, MeCN, rt 2nd CBr_4, rt	· alkyl amine · aryl amine	Electron-deficient anilines are applicable Mild condition, simple operation, and metal-free process	75

2-3. Synthesis of isothiocyanates without thiocarbonyl transfer reagent and carbon disulfide

Numerous methods for isothiocyanate synthesis from primary amines without the use of thiocarbonyl transfer reagents or CS_2 have been developed. Notably, several approaches have been reported that involve the *in situ* generation of thiocarbonyl fluoride, which serves as a thiocarbonyl transfer reagent.

In 2017, Zheng and Tang reported copper-catalyzed isothiocyanation using the Langlois reagent (F_3CSO_2Na) and diethyl phosphonate (Figure 5).[76] Notably, steric effects did not significantly affect the yield (**2-1** and **2-2**). Moreover, alkyl isothiocyanates were obtained in moderate yields. The proposed mechanism is illustrated in Figure 5. Two plausible pathways are suggested, as evidenced by the detection of the desired isothiocyanate using either CuI or $HPO(OEt)_2$ alone. In the initial step, the Langlois reagent reacts with $HPO(OEt)_2$, affording **2-A** without the involvement of CuI. In contrast, the reaction can also be initiated by the reaction with CuI and the Langlois reagent to afford **2-B**. Intermediates **2-A** and **2-B** react with $HPO(OEt)_2$ to form intermediate **2-C**. Upon treatment with **2-C** at 110 °C, thiocarbonyl fluoride (**2-E**) was slowly generated in the transition state **2-D**.[77] In addition, **2-B** may undergo direct defluorination to furnish thiocarbonyl fluoride. Finally, the generated thiocarbonyl fluoride reacts with the primary amine to produce the corresponding isothiocyanates.

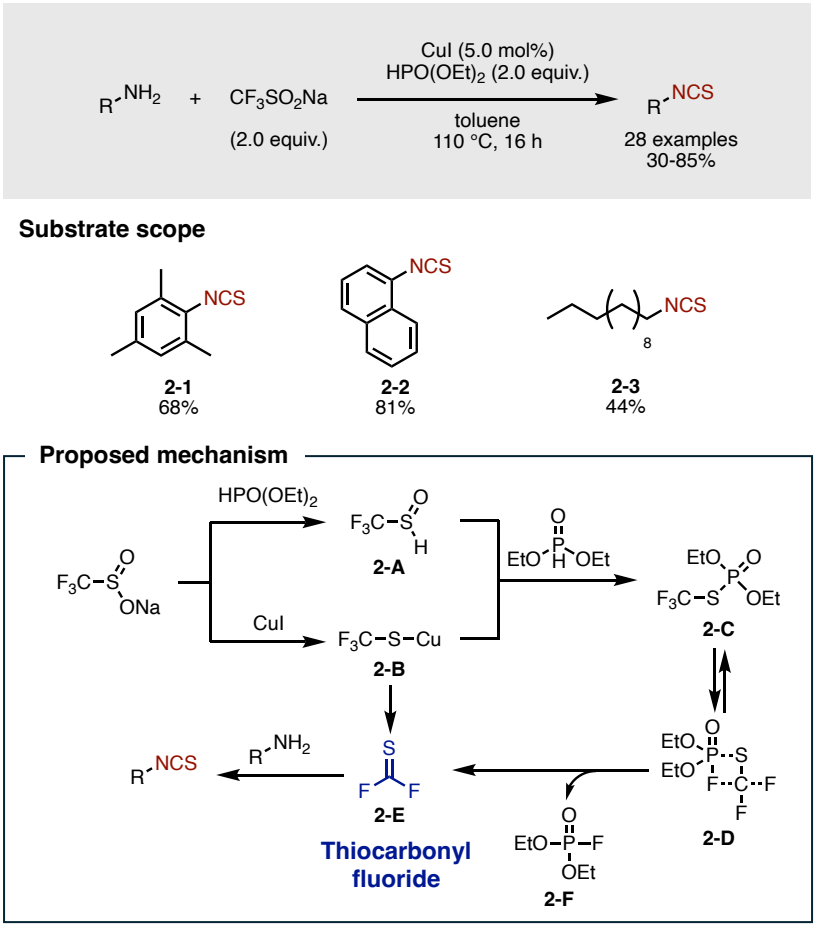


Figure 5. Copper-catalyzed isothiocyanation with the Langlois reagent.

The use of thiocarbonyl fluoride as an important intermediate has also been reported by Xiao et al. (Figure 6).[78] Thiocarbonyl fluoride was generated via difluorocarbene (**3-A**) provided by PDFA and S_8. This approach enables the rapid conversion of various primary amines into their corresponding isothiocyanates using thiocarbonyl fluoride. Bulky and electron-deficient anilines are applicable in this reaction (**3-1** and **3-2**). Although 1-adamantanamine is applicable to give **3-3**, the synthesis of a more sterically hindered alkyl isothiocyanate (**3-4**) is challenging. They observed direct evidence of thiocarbonyl fluoride formation, confirming the formation of CF_2=S using HRMS(EI) spectroscopy under simple heating conditions for a mixture of PDFA/S_8 in DME.

Furthermore, these conditions led to the formation of a bridged compound **3-5** through a Diels–Alder reaction, providing additional evidence for the generation of **3-B**.

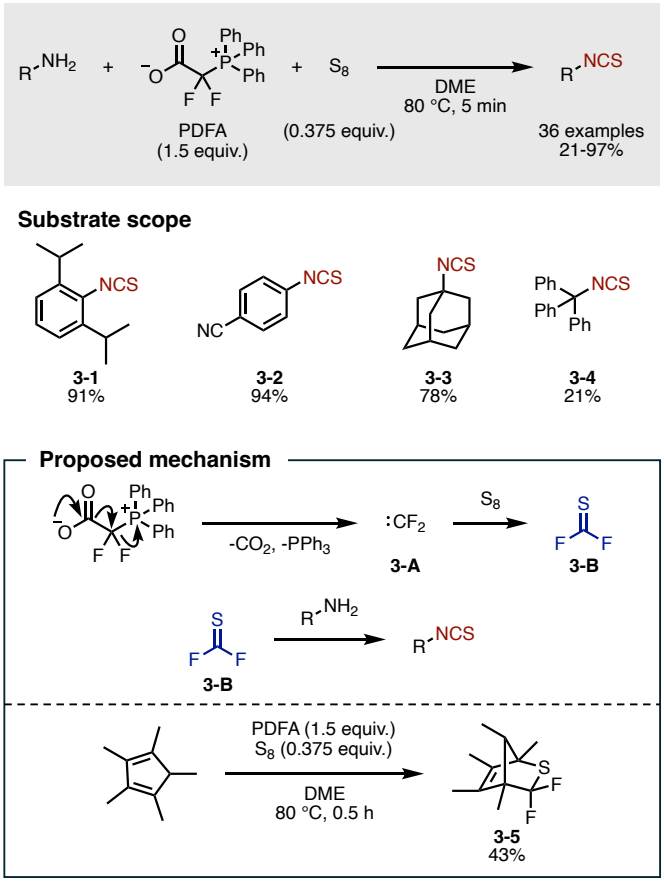


Figure 6. Isothiocyanation with PDFA and S_8.

In 2019, Zhang et al. reported a Cu-catalyzed isothiocyanation without the use of an organophosphine reagent (Figure 7).[79] They effectively employed sodium bromodifluoroacetate as the difluorocarbene source. Many aryl and alkyl isothiocyanates bearing terminal alkynes or strong electron-withdrawing groups were successfully obtained in moderate-to-high yields. Sodium bromodifluoroacetate has been proposed to provide difluorocarbenes directly in the presence of a copper catalyst and base. Two methods for the synthesis of isothiocyanates from

difluorocarbenes have been proposed. In Path a, the combination of the generated difluorocarbene, stabilized by a copper catalyst (**4-A**), and elemental sulfur resulted in thiocarbonyl fluoride (**4-B**). Subsequently, the corresponding isothiocyanate is generated through the reaction of thiocarbonyl fluoride with the primary amine. Alternatively, in path b, difluorocarbenes react directly with amines to produce isocyanide (**4-C**). The intermediate is then trapped by elemental sulfur to provide the target isothiocyanates.

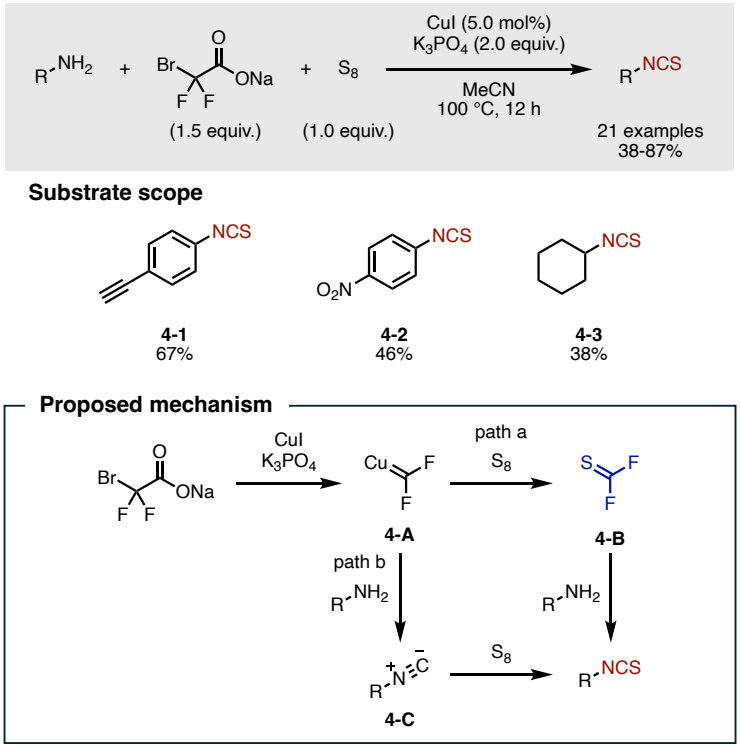


Figure 7. Copper-catalyzed isothiocyanation without organophosphine reagent.

Jiang et al. achieved a facile and mild isothiocyanation of primary amines (Figure 8).[80] In contrast to the thiocarbonyl fluoride precursors used in previous isothiocyanations[76,78,79], the Ruppert–Prakash reagent ($TMSCF_3$) is stable, readily available, easy to handle, and relatively inexpensive (Method A). In addition, they developed an alternative isothiocyanation protocol using $AgSCF_3$/KBr (Method B). These reactions proceed via $KSCF_3$, as outlined in the proposed mechanism in Figure 8. The use of $TMSCF_3$, S_8, and KF generates $KSCF_3$ (**5-A**). Similarly, the

$AgSCF_3$/KBr system generates $KSCF_3$ along with a KBr precipitate. $KSCF_3$ was in equilibrium with thiocarbonyl fluoride and KF (**5-B**), and thiocarbonyl fluoride efficiently afforded isothiocyanates. Various aryl amines bearing electron-donating or electron-withdrawing substituents and alkyl amines afforded the corresponding isothiocyanates through this reaction. Notably, the $AgSCF_3$/KBr system proved suitable for late-stage pharmaceutical modification, and sulfamethoxazole was smoothly transformed into the desired isothiocyanate derivative **5-3** in quantitative yield. The reaction proceeded at room temperature using commercially available reagents to establish a broad substrate scope (**5-1**–**5-3**). Therefore, this reaction is preferred for the synthesis of isothiocyanates without the use of CS_2.

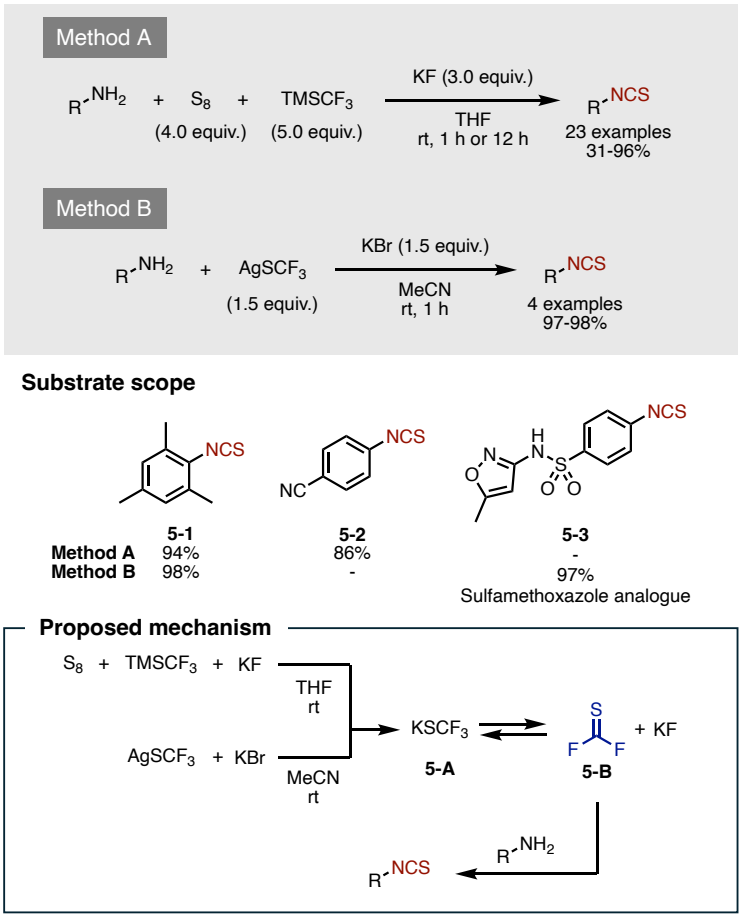


Figure 8. Isothiocyanation via thiocarbonyl fluoride from $TMSCF_3$ or $AgSCF_3$.

Isothiocyanation using trifluoromethanesulfonyl chloride (CF_3SO_2Cl) was first reported by Yi in 2020 (Figure 9).[81] Although Tang and Zheng previously used the Langlois reagent as a precursor of thiocarbonyl fluoride, their method required high temperatures and long reaction times.[76] Yi et al. discovered that PPh_3 and NaI serve as efficient additives for releasing thiocarbonyl fluoride from the Langlois reagent. The proposed mechanism is illustrated in Figure 9. According to their mechanistic investigation, sulfenyl chloride initially reacted with PPh_3 to form a chlorophosphonium salt via halogen bonding. The generated chlorophosphonium sulfinate (**6-A**) was converted into *O*–sulfinatophosphonium chloride (**6-B**). Subsequently, the Arbuzov collapse occurred, generating CF_3SOCl (**6-C**) and triphenylphosphine oxide. CF_3SOCl was further reduced by PPh_3 via a similar process, leading to the formation of CF_3SCl (**6-D**) *in situ*. In the next step, sulfenyl chloride reacted with PPh_3 to form CF_3S^- and a chlorophosphonium salt (**6-E**), which was then attacked by NaI to produce CF_3SNa (**6-F**) and $PPh_3{}^+I\ Cl^-$. CF_3SNa decomposes to thiocarbonyl fluoride(**6-G**) and NaF due to its instability. Finally, thiocarbonyl fluoride reacted with the primary amines to afford the corresponding isothiocyanates.

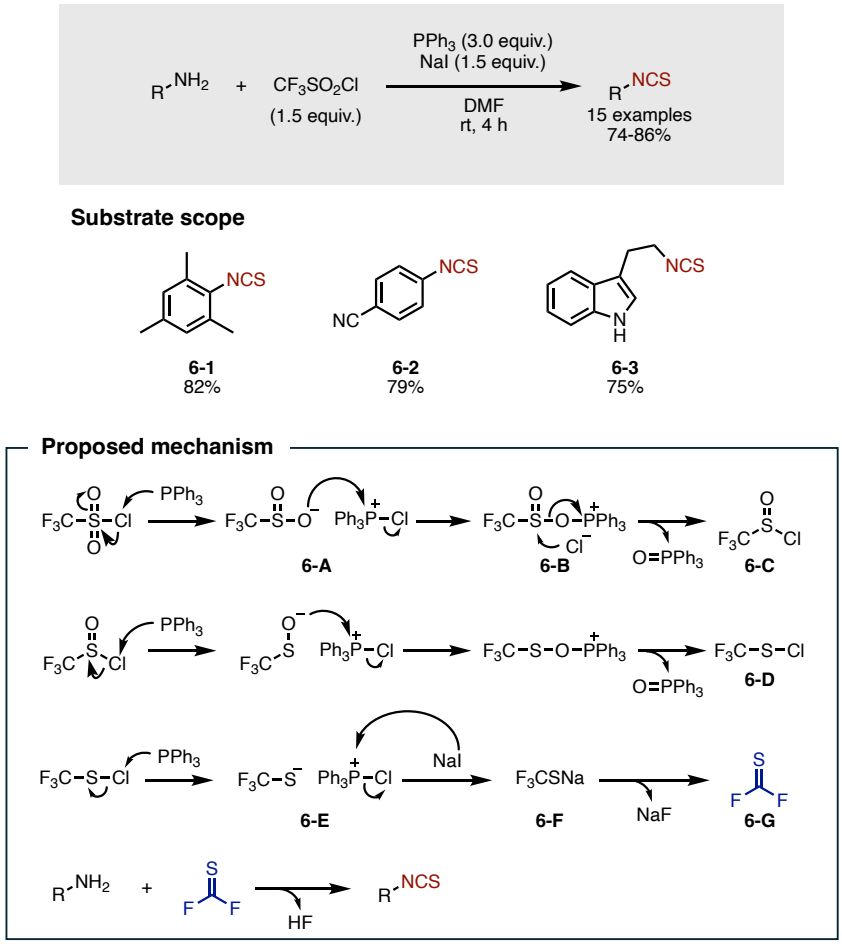


Figure 9. Isothiocyanation with utilizing CF_3SO_2Cl.

Schonebeck et al. reported a procedure for the synthesis of isothiocyanates via the reaction of $(Me_4N)SCF_3$ with primary amines (Figure 10).[82] Notably, this reaction suggests that thiocarbonyl fluoride was not an intermediate. $(Me_4N)SCF_3$, an easy-to-handle reagent, remained completely stable as a solid and in solution, eliminating the need for cooling and slow addition during the reaction. Through *in situ* NMR spectroscopy, they revealed that $(Me_4N)SCF_3$ remained unchanged in solution until the addition of reactive primary amines. Consequently, direct and rapid formation of isothiocyanates occurred upon the addition of primary amines in the reaction. This

reaction proceeds at room temperature, is tolerant to various functional groups, and produces numerous pharmaceutical isothiocyanate analogs. Notably, $(Me_4N)SCF_3$ discriminated between primary and secondary amines, providing asymmetric cyclic thioureas **7-3** in high yield from *N*-methyl-1,3-diaminopropane. In contrast, thiophosgenes generate complex mixtures of polymeric materials under analogous conditions.

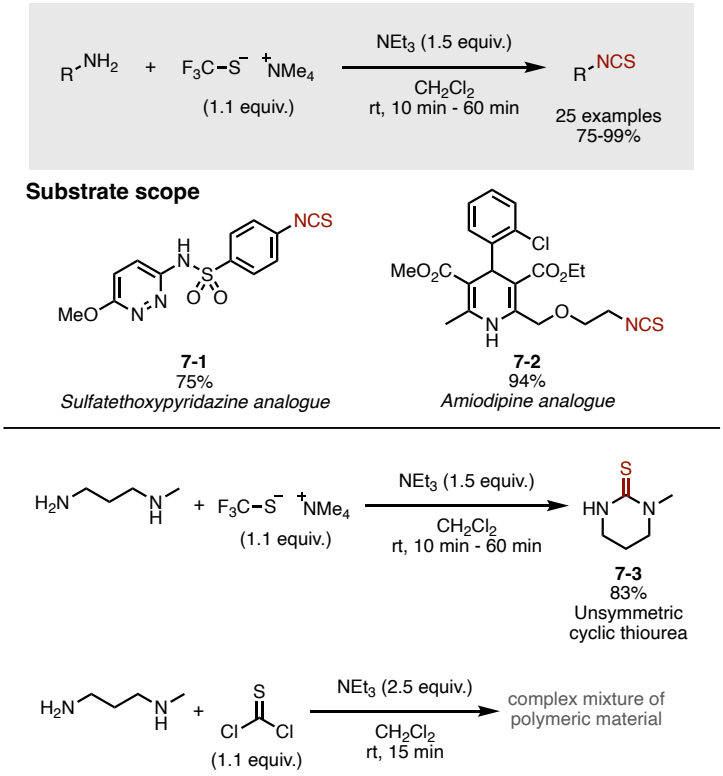


Figure 10. Isothiocyanation with $(Me_4N)SCF_3$.

In another isothiocyanation approach, protocols utilizing phenyl isothiocyanates were developed. The reaction proceeds with primary amines and phenyl isothiocyanate, leading to thiourea formation. Subsequently, thiourea decomposes at high temperatures into the

corresponding isothiocyanates and aniline. This method offers several advantages, including the use of inexpensive and commercially available materials, mild conditions, reduced byproducts, and a simple workup procedure.

In 2017, Butov et al. developed a novel method for the synthesis of adamantyl isothiocyanates (Figure 11).[83] Although adamantyl isothiocyanates are promising precursors for the synthesis of various bioactive compounds, a simple and effective method for preparing 1-adamantyl isothiocyanate and its analogs is currently lacking. Phenyl isothiocyanate facilitates group metathesis with various adamantyl amine analogs. The reaction proceeds via a trimolecular mechanism, in which thiourea **8-A** is generated from adamantyl amine. Subsequently, adamantyl thiourea reacts with another phenyl isothiocyanate, and the thermal decomposition of compound **8-B** produces adamantyl isothiocyanates.

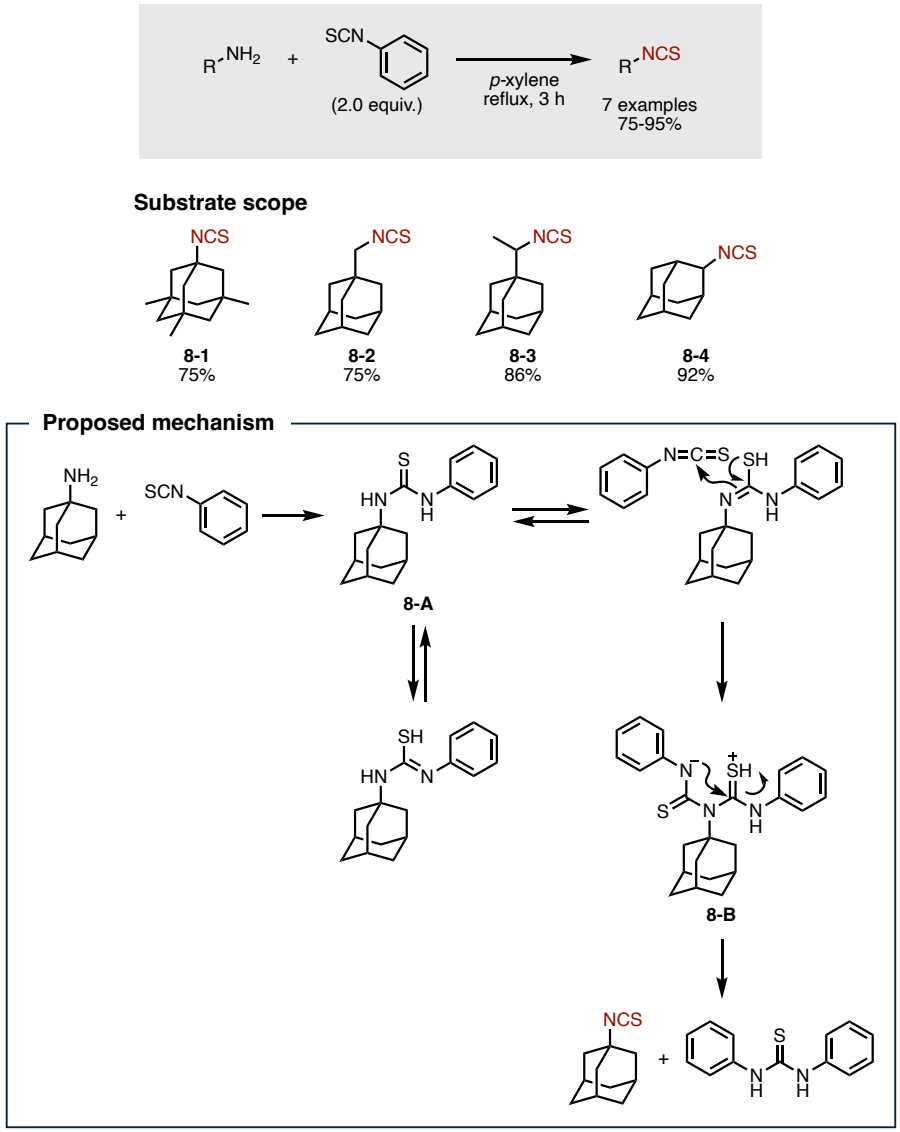


Figure 11. Synthesis of adamantyl isothiocyanate via a group metathesis.

In 2021, Zhu and Li reported the replacement reaction between phenyl isothiocyanate and primary amines (Figure 12).[84] Aliphatic amines readily underwent reaction with phenyl isothiocyanate (**9-1** and **9-2**). However, electron-deficient aromatic amines yield the corresponding

thioureas instead of the desired isothiocyanates, making them unsuitable for this reaction. In contrast to Butov's methodology, which uses a trimolecular mechanism[83], the reaction between primary amines and phenyl isothiocyanate in Zhu's and Li's methods proceeds via a group metathesis reaction with a bimolecular mechanism.

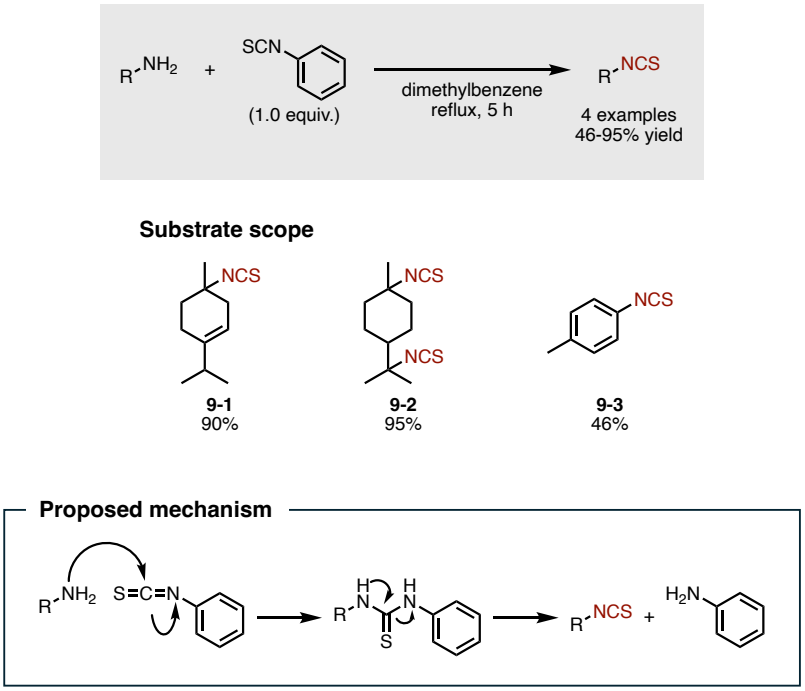


Figure 12. Isothiocyanation with phenyl isothiocyanate.

3. Synthesis of isothiocyanates with nitrogen-containing functional groups (Type B)

Isothiocyanation using nitrogen-containing functional groups other than amines has several advantages. First, it enhances the tolerance of electrophilic functional groups because these reactions are performed without nucleophilic moieties such as amines. In addition, these reactions exhibit high chemoselectivity. The detailed discussions in the next section shed light on the

frequent observations of thiocyanation competition in Type C. In contrast, Type B reactions yield isothiocyanates as the sole product. Moreover, the Type B reaction plays a pivotal role in broadening the substrate scope for accessing isothiocyanates to expand their structural variety. Thus, type-B reactions of Type B stand important for diversifying isothiocyanate structures. One of the best-known Type B reactions is the biosynthesis of isothiocyanates from glucosinolates (Figure 13). In *Brassica* vegetables, the myrosinase enzyme cleaves the glucose group from glucosinolates.[85] Subsequently, a Lossen-like rearrangement occurred, yielding the corresponding isothiocyanates. Several Type B reactions proceeding via similar rearrangements have been reported.

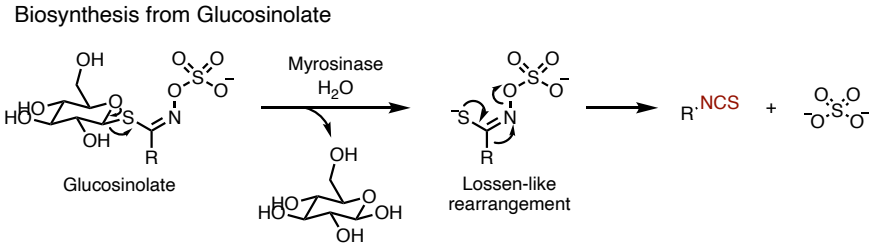


Figure 13. The mechanism of biosynthesis from glucosinolate.

3-1. Recent advances in isothiocyanate synthesis with Type B

In 2013, Baxendale reported the effectiveness of immobilized reagents and flow chemistry for the synthesis of isothiocyanates via a 1,3-dipolar cycloaddition reaction between nitrile oxide **10-A** and thiourea (Figure 14).[86] The 1,3-dipolar cycloaddition of nitrile oxides is typically hindered by the formation of the furoxan byproduct **10-C,** which is generated by the dimerization of nitrile oxides. In their strategy, the use of two immobilized reagents, a weak base ($Pyr{\cdot}SiO_2$) and a functionalized thiourea (QP-TU or QS-MTU), minimizes the formation of the furoxan byproduct by creating a scenario of pseudo-high dilution of the nitrile oxide. The immobilized base generates a reactive nitrile oxide from chloroxime, which is then immediately captured by a

locally tethered thiocarbonyl dipolarophile (QP-TU or QS-MTU). Finally, the generated 1,4,2-oxathiozoline intermediate **10-B** underwent rearrangement into the desired isothiocyanates and urea. This reaction provided not only simple isothiocyanates (**10-1** or **10-2**) but also complex substrates, with complete retention of the stereo configuration observed (**10-3**).

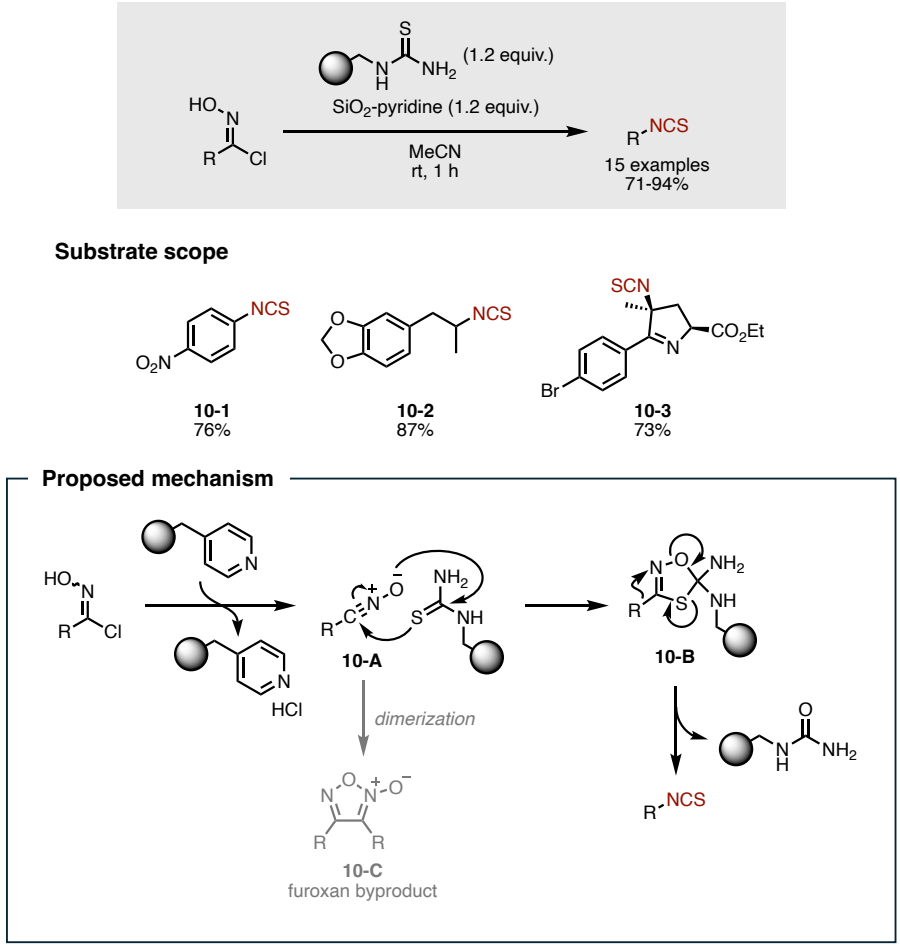


Figure 14. Isothiocyanation with an immobilized reagent.

Burkett reported purification-free isothiocyanation via the fragmentation of polymer-supported 1,4,2-oxathiazoles (Figure 15).[87] Previously, they had introduced a polymer-supported catch-and-release method using polymer-supported thiobenzophenone; however, the involvement

of a Lewis acid in the "release" step led to contamination of the final products.[88] To address this issue, their focus was shifted to the donor heteroatom at the 5-position of 1,4,2-oxathiazoles, promoting facile fragmentation. Consequently, the combination of polymer-supported thiocarbonates and chloroximes enables purification-free isothiocyanation. In this study, a polymer-supported thiocarbonate served as a dipolarophile. The thiocarbonate "catches" the nitrile oxide **11-A** through a 1,3-dipolar cycloaddition reaction, which affords the corresponding polymer-supported 1,4,2-oxathiazole **11-B**. The polymer supports were then washed with various solvents. The "release" of the isothiocyanate form **11-B** is achieved through a fragmentation reaction with microwave-assisted heating. As a result, a wide range of functional groups was tolerated by this reaction, and the purification steps were circumvented.

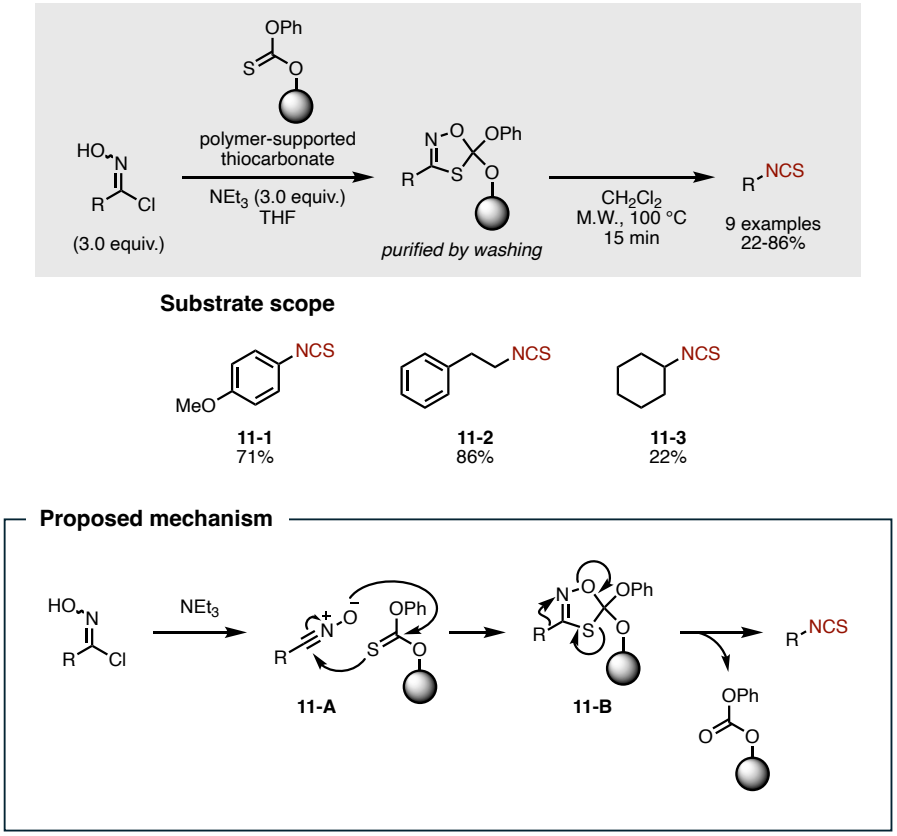


Figure 15. Purification-free isothiocyanation via fragmentation from polymer-supported 1,4,2-oxathiazoles.

In 2015, Jessop and Mosey investigated the reactivity of CS_2 with amidines (Figure 16).[89] The reaction of the cyclic amidine with CS_2 afforded cyclic carbamic carboxylic trithioanhydride **12-1**. In contrast, acyclic amidines afforded the corresponding isothiocyanates (**12-2**–**12-4**) and dimethylthioacetamides (**12-C**). The calculations indicated that the difference in the reactivity of the cyclic and acyclic amidines can be attributed to the entropic change and significant distortion in the formation of the four-membered ring transition state **12-B**. Intermediate **12-A** was generated from both acyclic and cyclic amidines. In the case of the acyclic amidine, intermediate **12-A** forms a four-membered ring through the internal rotation of the C–N single bond at the carbamodithioate. Finally, the reverse [2+2] cycloaddition afforded the desired isothiocyanates. For cyclic amidines, path A converts the two starting materials into two product molecules, whereas path B converts the four reactant molecules into two product species. The thermodynamic preference for path A in reactions with acyclic reagents can be understood in terms of the entropic contribution to the free energy of the reaction. In contrast, for cyclic amidines with DBU, the six-membered ring in the reagent restricts the formation of the four-membered ring transition state **12-B**. Consequently, carbamic carboxylic trithioanhydride and hydrogen sulfide salts were obtained via path B.

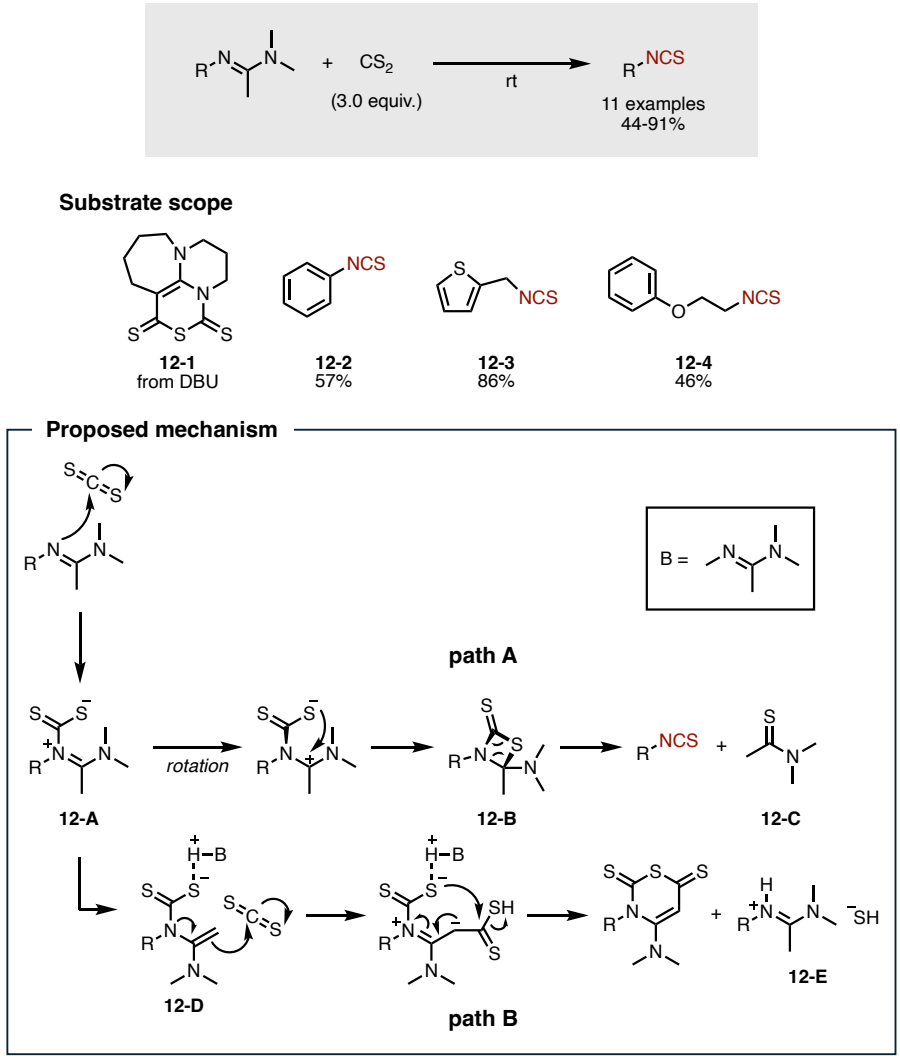


Figure 16. Isothiocyanation from acyclic amidines.

In 2016, Kim developed an efficient synthetic method for α-isothiocyanato-α,β-unsaturated esters (Figure 17).[90] These esters possess diverse reactivities that are useful for the synthesis of various heterocyclic compounds. Traditional approaches for synthesizing α-isothiocyanato-α,β-unsaturated esters involved the Staudinger reaction with PPh_3 to form iminophosphorane and *aza*-Wittig reaction with CS_2. However, these methods often result in low to moderate yields.

Previously, a one-pot procedure for the isothiocyanation of primary nitroalkanes was reported.[91] This reaction shares a similar mechanism in which an aryl isocyanate and a catalytic base generate nitrile oxide **13-A**. Subsequent [3+2] cycloaddition between the nitrile oxide and thiourea afforded 1,4,2-oxathiazole **13-B**. They considered that α-isothiocyanato-α,β-unsaturated esters could be obtained from α,β-unsaturated ester acetate **13-1**, which was prepared by Morita-Baylis-Hillman (MBH) reaction through 1,4,2-oxathiazole **13-B**. The reaction afforded various α-isothiocyanato-α,β-unsaturated esters including alkyl and styryl derivatives (**13-3** and **13-4**).

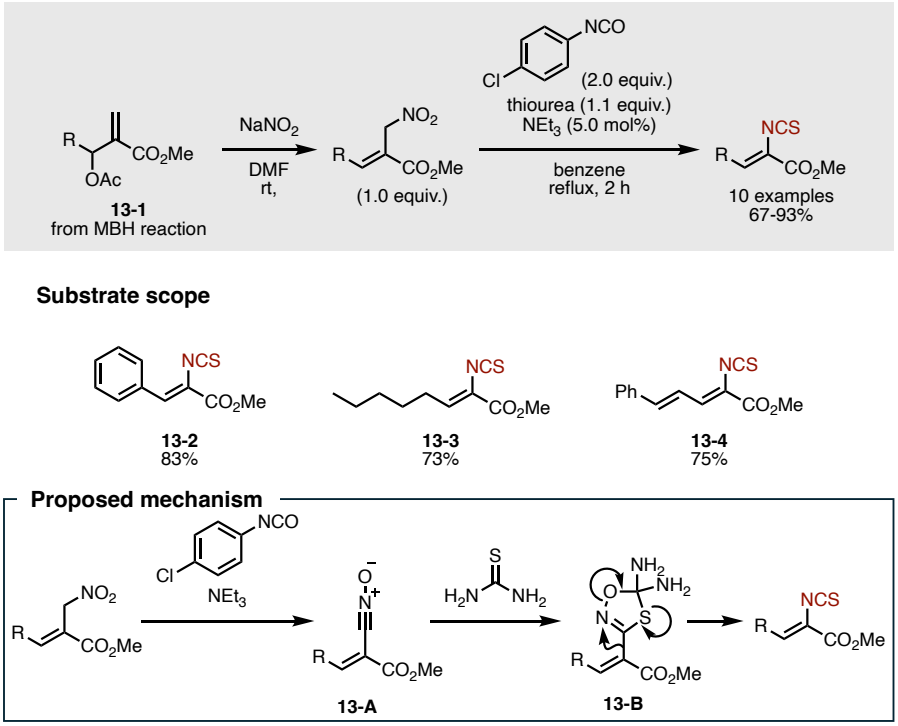


Figure 17. Synthesis of α-isothiocyanato-α,β-unsaturated esters.

Isothiocyanates are derived from amino acids and are important because of their stereochemistry. Despite their significance, literature on the synthesis of amino acid isothiocyanates is limited, with very few reports on isothiocyanation at the C-terminus (N^{β}-

protected amino alkyl isothiocyanate **14**). Previously, Sureshbabu's group reported two synthetic methods for N^{β}-protected amino alkyl isothiocyanates,[92] with each protocol tailored to the *N*-terminal protecting group. In 2018, they developed a new synthetic method applicable to various functional groups (Figure 18).[93] This approach involves obtaining isothiocyanates from azide compounds via the Staudinger reaction, followed by the aza-Wittig reaction. Initially, C-terminal azide compounds were prepared from *N*-protected amino acids. Subsequently, the Staudinger/aza-Wittig reaction successfully provided N^{β}-protected amino alkyl isothiocyanates. The use of neutral reaction conditions enabled the synthesis of racemization-free isothiocyanates from various amino acids, including natural amino acids (**14-1** and **14-2**) and side-chain-protected amino acids (**14-3** and **14-4**).

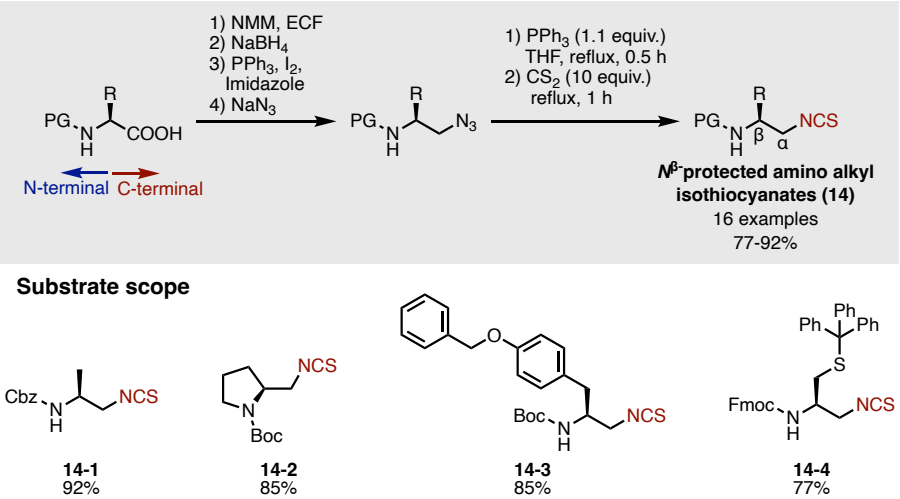


Figure 18. Synthesis of N^{β}-protected amino alkyl isothiocyanates.

In 2021, Meier et al. reported sustainable isothiocyanation through amine-catalyzed sulfurization of isocyanides (Figure 19).[94] To address the noxious and harsh conditions associated with conventional isothiocyanate synthesis, a more environmentally friendly method was

developed. Isocyanides, known for their low toxicity,[95] were chosen for isothiocyanation. The focus was on amine bases capable of efficiently catalyzing the formation of isothiocyanates during sulfurization. The reaction conditions were optimized to reduce the toxicological impact of the synthetic reagents and to minimize waste generation, as indicated by the E-factor. Through careful optimization, DBU was employed as the amine base and S_8, a waste product from the petroleum industry, served as the sulfur source. The E-factor for this method was notably lower (0.129) than those for other isothiocyanation methods. As shown in Figure 19, the reaction was initiated by the reaction between the tertiary amine and S_8, producing the polysulfur chain **15-A**. Subsequently, the thiolate attacks isocyanide, leading to the generation of isothiocyanates through the decomposition of intermediate **15-B**. Using a secondary or primary amine as a base resulted in the formation of corresponding thioureas as byproducts.

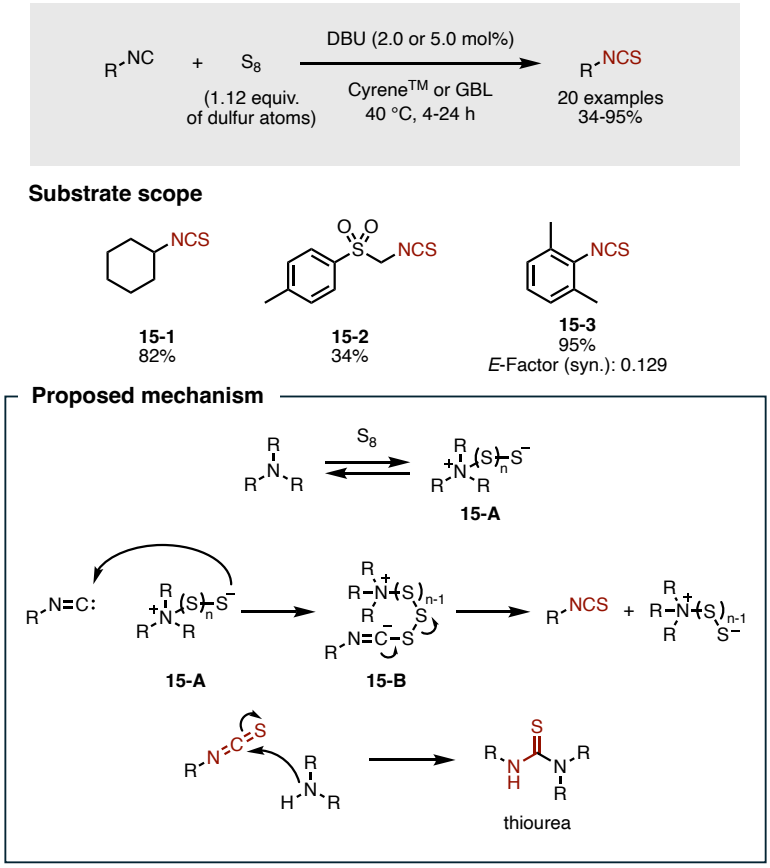


Figure 19. Sustainable isothiocyanation by amine-catalyzed sulfurization of isocyanide.

Tang et al. reported the synthesis of diverse trifluoromethylthiolated isothiocyanates and amines from *N*-Ts aziridines in 2022 (Figure 20).[96] They found that the products were switchable by the choice of the iodide counter cation. When KI was used as the iodide source, isothiocyanates were obtained in high-to-moderate yields. However, the use of TBAI resulted in the formation of the corresponding amines. The combination of $AgSCF_3$ and KI produced trifluoromethylthiolated isothiocyanates, demonstrating tolerance to various functional groups. Camphanic acid derivatives have been successfully used as substrate (**16-4**). The proposed mechanism is illustrated in Figure 20. Aziridines undergo nucleophilic attack by trifluoromethylthiolated anions to generate the

intermediate **16-A**. This intermediate could be trapped by thiocarbonyl fluoride produced *in situ* from the SCF_3 anion, generating the intermediate carbamothioic fluoride **16-B**. The product of this reaction was determined to be the counter cation. The activation of the tosyl group and carbamothioic fluoride in intermediate **16-B** by potassium cations results in the generation of intermediate **16-C**. Subsequently, the fluoride anion attacks the tosyl group to afford the corresponding trifluoromethylthiolated isothiocyanate.

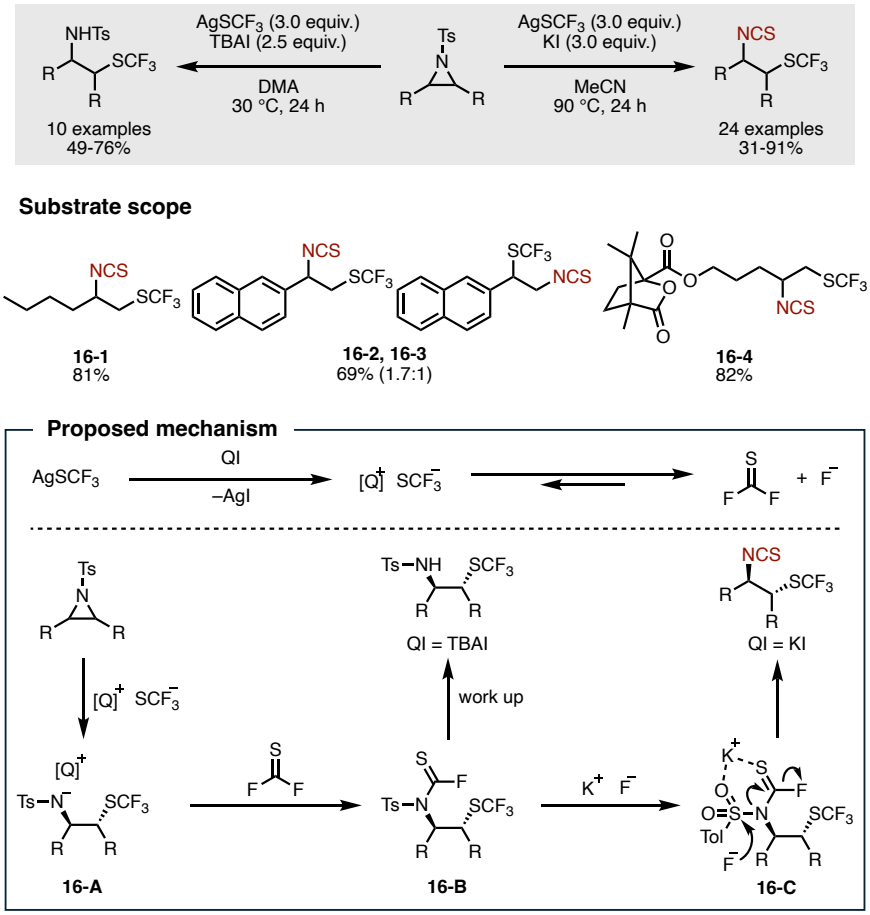


Figure 20. Synthesis of trifluoromethylthiolated isothiocyanates from aziridines.

In 2023, Beier et al. reported the synthesis of vinyl isothiocyanates from NH-1,2,3-triazoles.[97] Although transformations involving the cleavage of *N*-substituted 1,2,3-triazoles are well established, much less attention has been paid to the ring-cleavage chemistry of NH-1,2,3-triazoles. They transformed NH-1,2,3-triazoles via ring cleavage, using thiophosgenes or triphosgenes and nucleophiles. This reaction was applicable to electron-rich arenes, heterocycle-substituted triazoles (**17-1–17-3**), and the 4,5-disubstituted triazole (**17-4**). The proposed reaction mechanism is illustrated in Figure 21. Thioacylation of NH-1,2,3-triazole with thiophosgene afforded N1- or N2-thioacyl triazoles (**17-A** and **17-B**). In the presence of an acid, intermediate **17-A** undergoes ring cleavage to form a diazo compound, followed by nitrogen elimination and recombination with chloride anions to generate thiocarbonyl chloride **17-C**. Elimination of HCl provided the *Z*-isomer of vinyl isothiocyanate **17-D**. However, protonation and deprotonation of the double bond lead to an isomeric mixture of vinyl isothiocyanate with poor stereoselectivity.

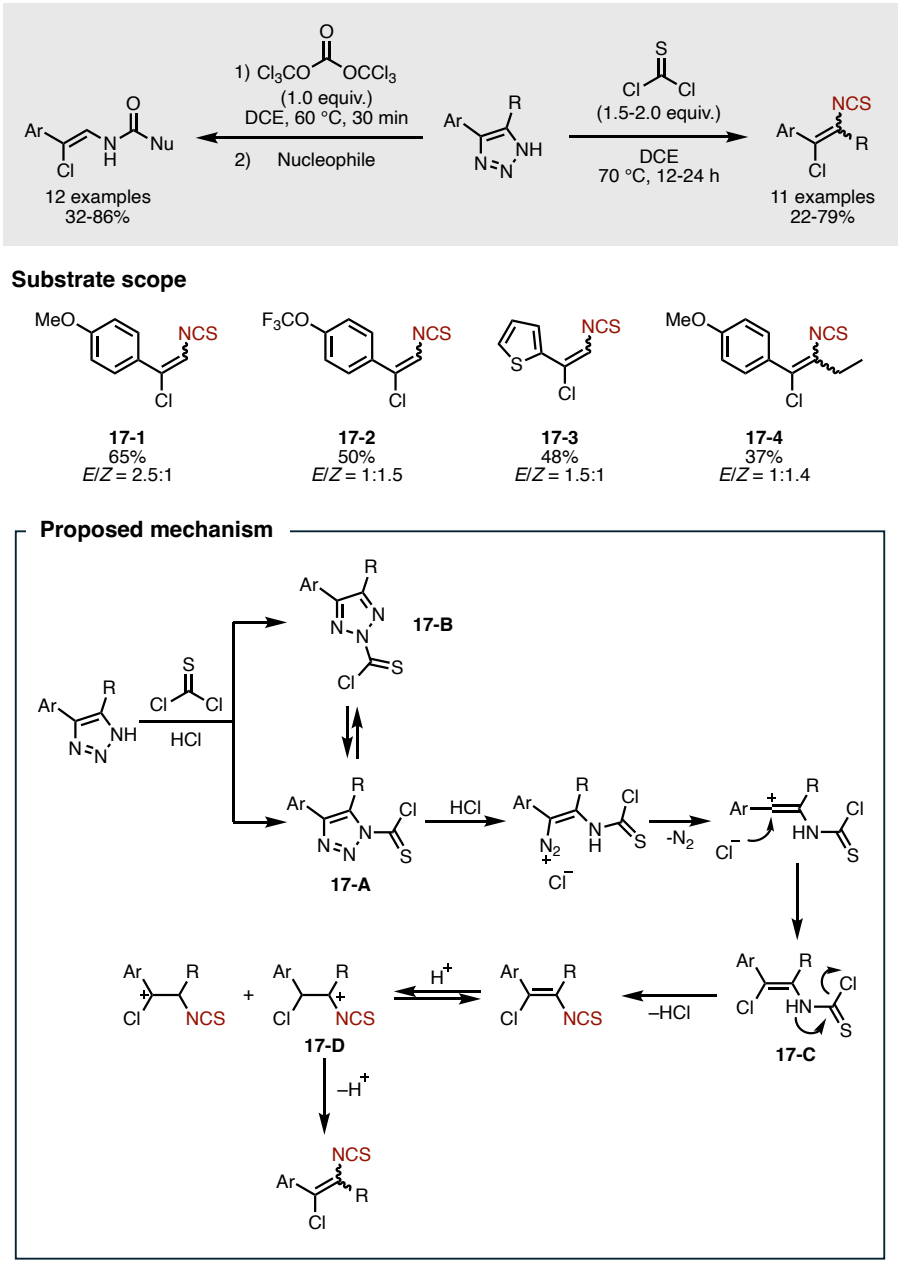


Figure 21. Synthesis of *N*-vinyl isothiocyanates from NH-1,2,3-triazoles.

4. Isothiocyanation with non-nitrogen functional groups (Type C)

The isothiocyanation of substrates devoid of nitrogen functional groups fundamentally differs from the previously illustrated isothiocyanation involving a nitrogen-containing starting material. While the isothiocyanation of nitrogen functional groups entails the installation of a C=S moiety or S atom into amine or isonitrile compounds, the isothiocyanation of non-nitrogen-compounds necessitates the introduction of an N=C=S moiety. Generally, three patterns of isothiocyanation have been reported in this decade: (i) substitution reaction for a substrate with a leaving group, (ii) isothiocyanate addition reaction to unsaturated bonds, such as alkenes, and (iii) isothiocyanation via C–H bond cleavage. In many cases, isothiocyanation is thermodynamically favored, whereas thiocyanate is kinetically favored. Therefore, selectivity between isothiocyanate and thiocyanate must be carefully considered when isothiocyanation involves substrates lacking nitrogen.

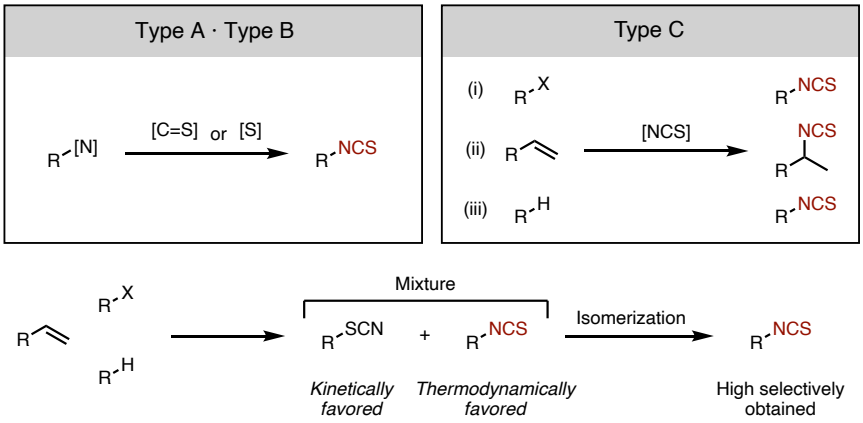


Figure 22. Examples of the starting materials in Type C.

4-1. Recent advances in isothiocyanation Type C with substitution reaction

Isothiocyanation via substitution reactions has been performed for a considerable time, mainly using Br and Cl as leaving groups. Recently, alcohols and ethers with lower leaving-group

abilities have been used as starting materials. In addition, aryl isothiocyanates can be obtained via S_NAr reactions. In these reactions, elevated temperatures are inevitable for selectively obtaining the thermodynamically favored isothiocyanates.

In 2014, Asgharzadeh found that chlorodiphenylphosphine and ammonium thiocyanate can convert alcohols, tetrahydropyranyl ethers, and silyl ethers to thiocyanate and isothiocyanate (Figure 23).[98] The order of reactivity of these substrates was as follows: silyl ether > alcohol > tetrahydropyranyl ether. In this reaction, primary alcohols or ethers afford only thiocyanates, whereas secondary substrates produce isomeric products. Tertiary compounds afforded isothiocyanate as the sole product. Although the reaction mechanism is unclear, the authors proposed a plausible mechanism, in which the thiocyanate anion produces diphenylthiocyanatophosphine (**18-A**) from chlorodiphenylphosphine. The substrates react with the generated phosphine to form intermediate **18-B**. Finally, substitution with the thiocyanate anion affords alkyl thiocyanates and isothiocyanates.

Furthermore, Staver reported the nucleophilic substitution reaction of alcohols with catalytic *N*-halosuccinimides in 2020.[99] The reaction provided isothiocyanates, including those derived from benzyl alcohol, as part of the substrate scope.

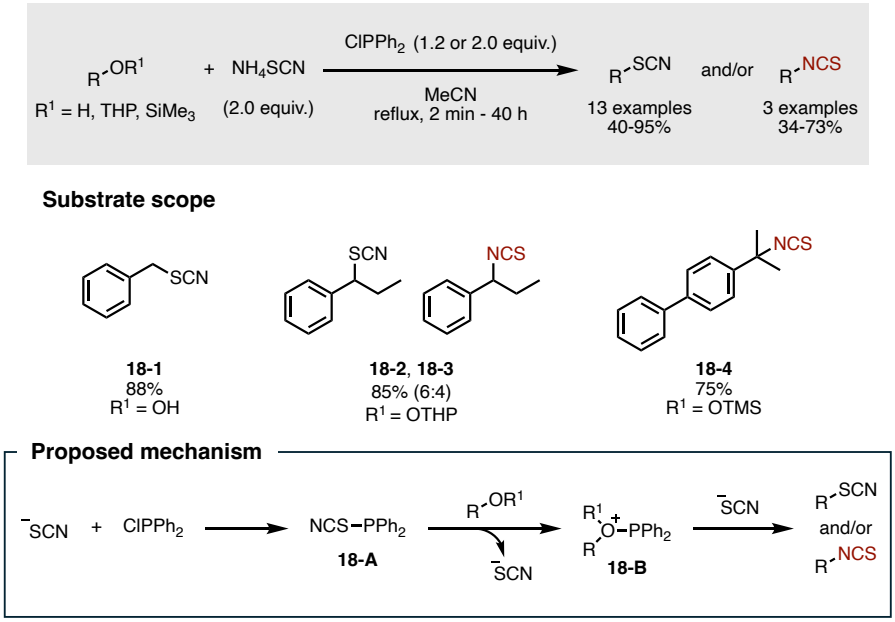


Figure 23. Isothiocyanation via substitution reaction.

Crimmin et al. reported an organocatalyzed fluoride metathesis between fluoroarenes and carbonyl compounds (Figure 24).[100] In this reaction, the fluoride anion was exchanged as an alternating nucleophile in the presence of a catalytic organic base (DMAP or DBU). When benzoyl isothiocyanate was used as the nucleophilic source, 4-isothiocyanato-tetrafluoropyridine (**19**) was obtained. In the proposed mechanism, DMAP first activates both pentafluoropyridine and benzoyl isothiocyanate, generating intermediates **19-A** and **19-B**. These intermediates are more susceptible to nucleophilic attack by isothiocyanate and fluoride anions. Finally, the desired isothiocyanate was generated via an S_NAr reaction. Compound **19** served as the substrate, and they successfully obtained various functionalized fluoroarenes with diverse nucleophiles (OAc^-, OCO_2R^-, SR^-, Cl^-, CN^-).

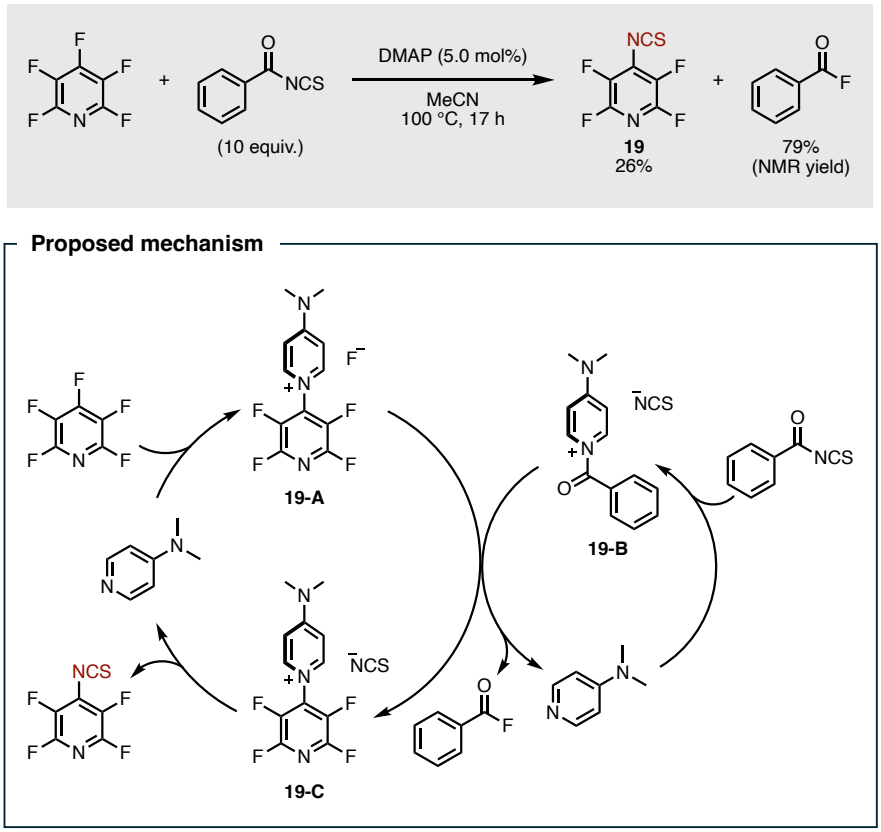


Figure 24. Synthesis of 4-isothiocyanato-tetrafluoropyridine by S_NAr.

4-2. Recent advances in isothiocyanation Type C with alkenes

The thiocyanation of olefins is kinetically favored over isothiocyanation, which generally proceeds via thiocyanation and isomerization. Consequently, it is challenging to selectively produce isothiocyanates, often resulting in a mixture of thiocyanates and isothiocyanates. Recently, efficient isomerization methods have been developed for highly selective isothiocyanation.

In 2014, Bunge et al. reported the selective oxidative halogenation and thiocyanation of 1-arylallenes (Figure 25).[101] In this study, we investigated the reactivity of 1-arylallenes with electrophilic equivalents of Cl^+, Br^+, I^+, and SCN^+ generated from TMSX (X = Cl, Br, I, and SCN)

using Selectfluor. Simultaneous isothiocyanation and thiocyanation occurred via the oxidation of 1-arylallene with TMSNCS/Selectfluor. As a result, dithiocyanate derivatives were obtained as the major isomer (**20-1** and **20-3**), whereas isothiocyanate- and thiocyanate-substituted compounds were obtained as minor isomers (**20-2** and **20-4**). According to the mechanism proposed in a previous study[102], the nucleophilic attack by the central carbon of the allenyl moiety on an equivalent of SCN^+ affords thiocyanate or isothiocyanate allyl cations (**20-A** and **20-B**). Nucleophilic trapping by the thiocyanate anion at the terminal carbon afforded the corresponding compounds.

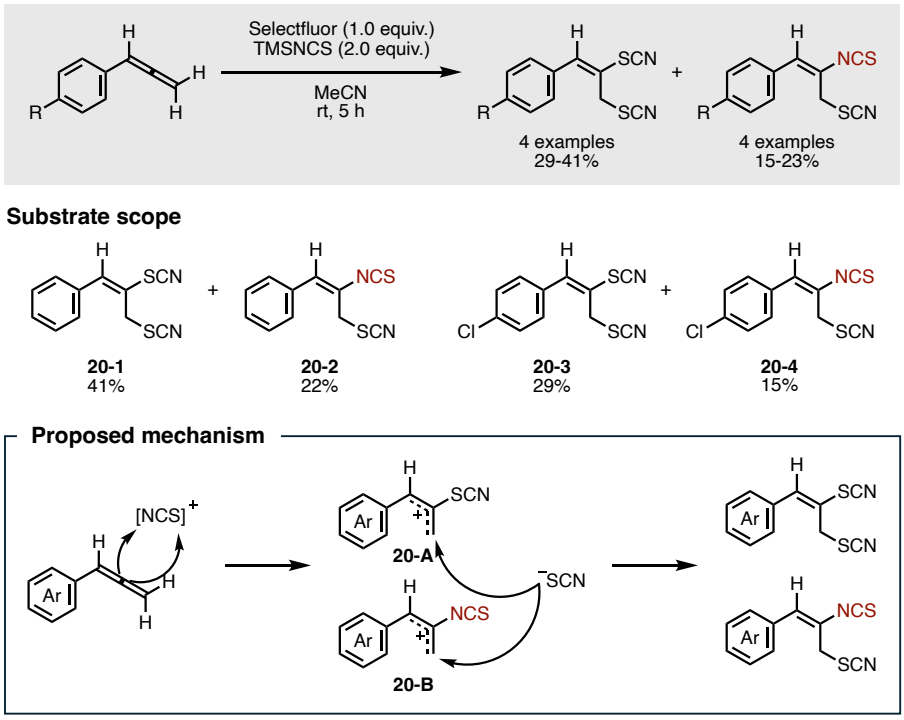


Figure 25. Difunctionalization of allenes by Selectfluor and TMSNCS.

In 2015, Becker et al. investigated one-pot anodic thiocyanation and isothiocyanation of alkenes in both acidic two-phase and homogeneous single-phase solvents (Figure 26).[103] These electrochemical thiocyanation and isothiocyanation reactions are environmentally friendly and

avoid the use of toxic oxidizing reagents. This reaction affords several products as mixtures, including (SCN/NCS), (SCN/SCN), and (OH/SCN). The selectivity and substrate scope were determined using the solvent. In the two-phase reaction (CH_2Cl_2-water), the substrates were limited to aliphatic-substituted alkenes. Moreover, the aromatic conjugated alkenes reacted only under homogeneous solvent conditions (MeCN-H_2O).

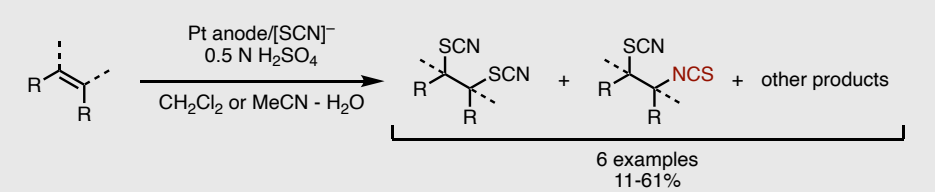


Figure 26. Electrochemical thiocyanation and isothiocyanation of alkenes.

In 2016, catalyst-free isothiocyanatoalkylthiation of styrenes was achieved by Fu et al. (Figure 27).[104] Thiopyrrolidine-2,5-diones and trimethylsilyl isothiocyanate rapidly reacted with terminal and internal styrenes at 90 °C. Under these conditions, various thiophenol and alkylthio moieties were applicable (**21-1**, **21-2**, and **21-3**). According to the mechanistic investigation, although the reaction occurred at room temperature, product **21-4** conjugating with sulfide and thiocyanates, were obtained as the main products. Subsequent heating led to the isomerization of **21-4** to the desired isothiocyanate **21-1**. Fu et al. proposed a possible reaction mechanism. Thiiranium ion intermediate **21-A** was generated from the reaction of styrene and thiopyrrolidine-2,5-dione. Electrophilic attack by nitrogen or sulfur from trimethylsilyl isothiocyanate to **21-A** affords **21-B** or the desired isothiocyanate. The thiocyanate compound **21-B** easily undergoes isomerization to the corresponding isothiocyanate upon heating.

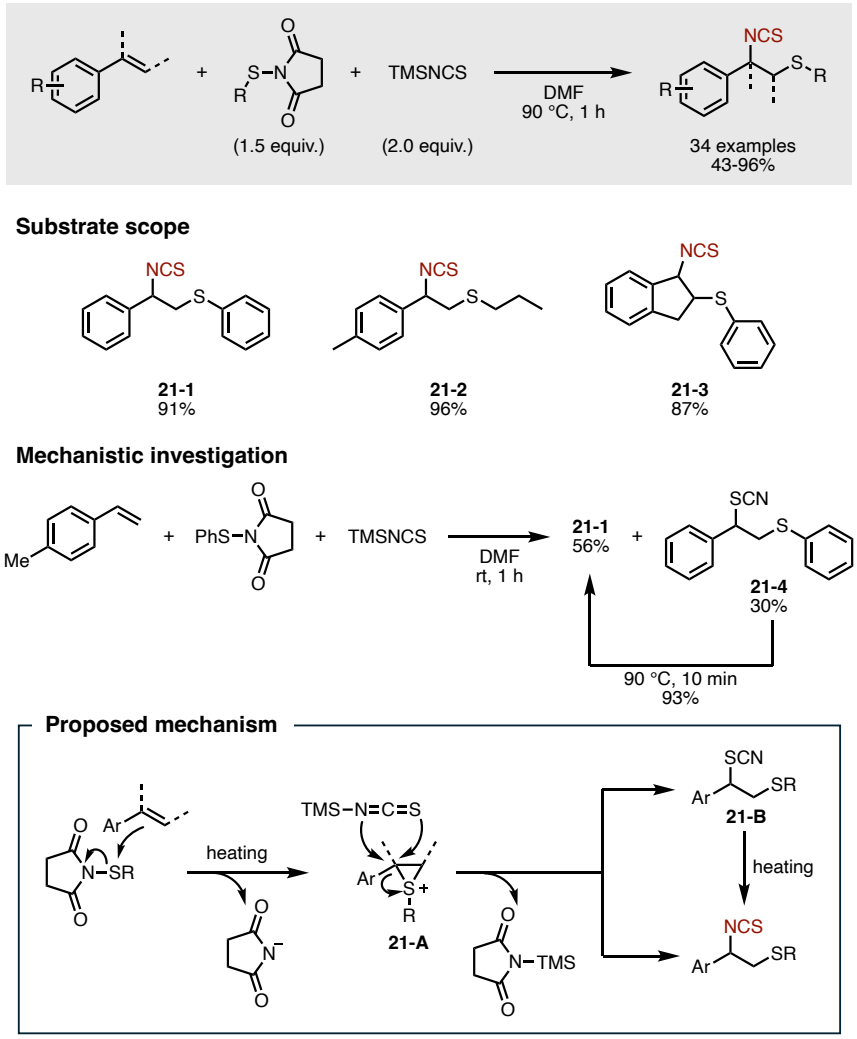


Figure 27. Catalyst-free isothiocyanatoalkylthiation of styrenes.

The selective 1,2-aminoisothiocyanation of 1,3-dienes with a photoredox catalyst was reported by Zhu et al. in 2021 (Figure 28).[105] By irradiating blue light onto a 1,3-diene in the presence of *N*-aminopyridinium salt TMSNCS and $Ir(ppy)_3$, the desired 1,2-aminoisothiocyanato products were obtained in moderate to good yields. When alkyl-substituted dienes were used as substrates, the target product **22-2** was provided in moderate yield along with the concurrent

formation of the 1,4-aminoisothiocyanato product. Various pyridinium salts provide a variety of amide moieties, including NHBoc, which affords the primary amine following the removal of the protecting group (**22-3**). Additionally, internal 1,3-dienes are also applicable (**22-4**). The proposed mechanism is illustrated in Figure 28. Initially, amidyl radical **22-B** is generated by reduction by excited $Ir(ppy)_3$ and regioselective radical addition of the amidyl radical to 1,3-diene provides allylic radical **22-C**. Subsequent oxidation of the allyl radical by $Ir(ppy)_3^+$ affords allyl cation **22-D** with the concurrent regeneration of $Ir(ppy)_3$. Finally, the nucleophilic addition of TMSNCS to the allylic cation provided the desired isothiocyanate or 1,2-aminothiocyanato product **22-E**. Photocatalyzed isomerization affords highly chemoselective 1,2-aminoisothiocyanation.

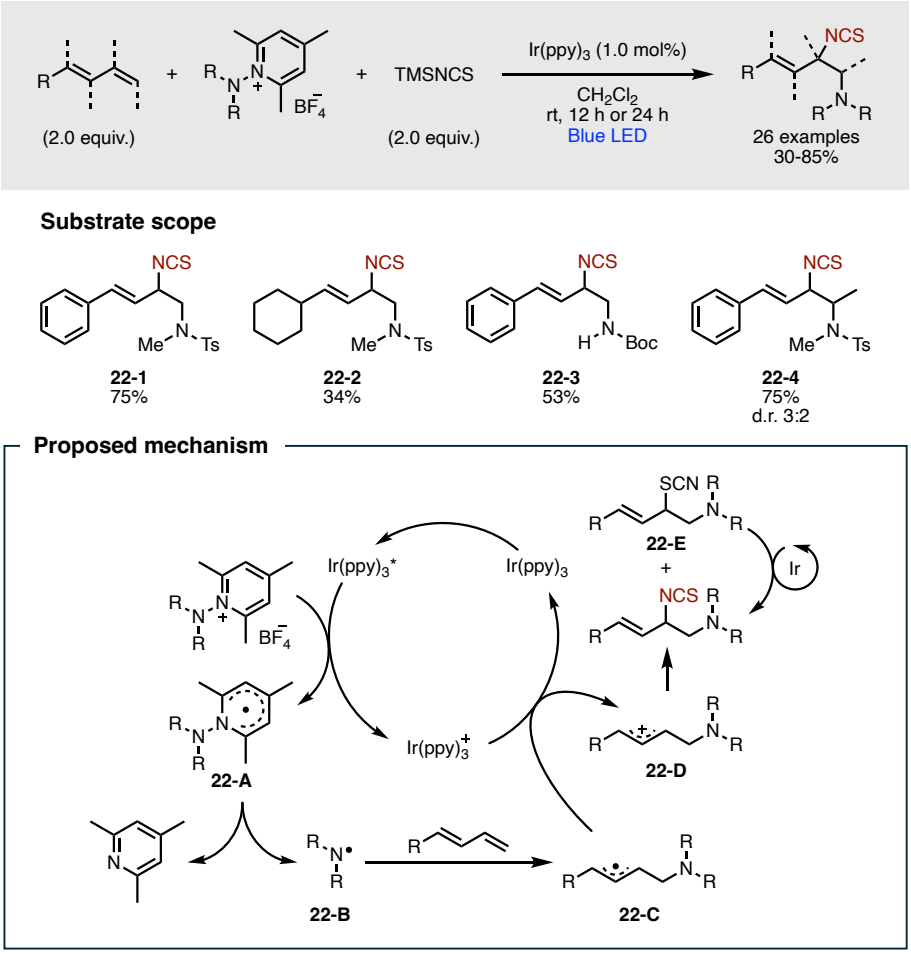


Figure 28. Photocatalyzed 1,2-aminoisothiocyanation of 1,3-dienes.

Zeng et al. reported the green *cis*-selective isothiocyanato-chalcogenization of alkenes in water (Figure 29).[106] This reaction does not require the use of highly toxic reagents. In this reaction, KI and $K_2S_2O_8$ were effective additives for producing the target isothiocyanates. Diselenides and disulfides have been used as chalcogens, resulting in the formation of various isothiocyanatoselenes and isothiocyanatosulfides. Notably, this three-component reaction with cyclohexene provided *cis*-isothiocyanatoselene compound. They proposed a plausible mechanism for the isothiocatanoselenization based on several mechanistic investigations. Initially, the sulfate radical anion is generated by homolytic cleavage of the persulfate anion, affording molecular iodine. Next, molecular iodine and diphenyl diselenide provide benzeneselenyl iodine **23-A**, which reacts with styrene to afford benzyl radical intermediate **23-B**. Mechanistic experiments showed that intermediate **23-B** was trapped by TEMPO, as confirmed by high-resolution mass spectrometry (ESI). Additionally, sulfate radical anions oxidize thiocyanate anions to isothiocyanate radical **23-C**. Finally, intermediate **23-B** is coupled with an isothiocyanate radical to yield the desired isothiocyanate.

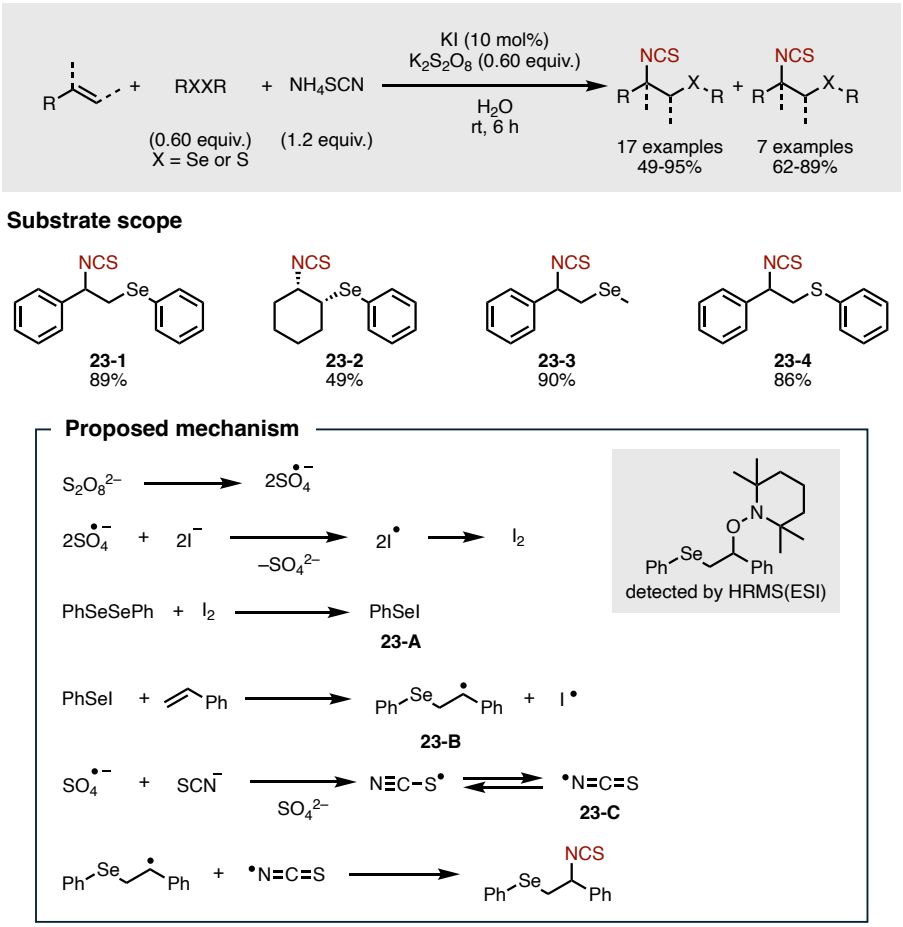


Figure 29. Green *cis*-selective isothiocyanato-chalcogenization of alkenes.

In 2023, Taniguchi developed a hydroisothiocyanation of alkenes using ammonium thiocyanate (Figure 30).[107] In this reaction, zinc iodide, *n*Bu_4NI, and TsOH•H_2O effectively provided the desired isothiocyanate products. Hydroisothiocyanation can be applied to both the terminal and internal olefins. Moreover, compounds bearing electron-withdrawing and electron-donating groups were tolerated in this reaction. Mechanistic experiments indicated that the reaction proceeded via a radical pathway, and the corresponding thiocyanate **24-C** was observed as an intermediate. The proposed reaction mechanism is illustrated in Figure 30. The thiocyanate anion

is in equilibrium with the isothiocyanate anion and it forms the zinc complexes **24-A** and **24-B** from ZnI_2. The reaction of **24-B** with an alkene in the presence of 4-toluenesulfonic acid produced an isothiocyanate. Additionally, radical isomerization has been proposed as the main process. Zinc complex **24-A** reacts with the alkene to generate thiocyanate **24-C**; finally, intramolecular radical isomerization provides the corresponding isothiocyanate.

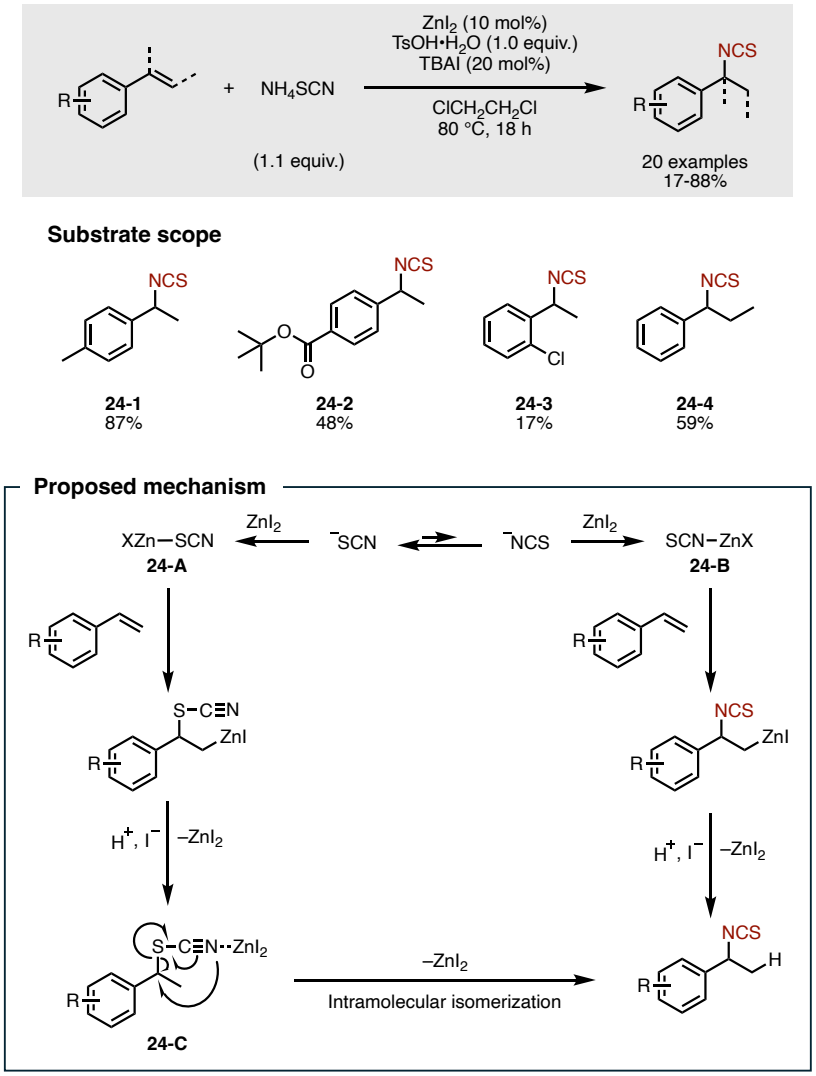


Figure 30. Hydroisothiocyanation of alkenes with ammonium thiocyanate.

1,2-Carboisothiocyanation of dienes was first developed by Tripathi et al. in 2023 (Figure 31).[108] The difunctionalization and isothiocyanation of dienes present several potential challenges: (i) 1,4-functionalization competes with 1,2-functionalization. (ii) The possibility of competing hydroisothiocyanations is also a concern. (iii) The chemoselective installation of isothiocyanate without concurrent thiocyanation was difficult. Tripathi et al. overcame these problems and achieved carboisothiocyanation with a Hantzsch ester, benzoic acid, and TMSNCS under blue light irradiation. Since allyl isothiocyanates are unstable, they were purified as thiourea following the reaction with aniline (**25-1**–**25-3**). They proposed that the reaction proceeds via an electron donor-acceptor (EDA) complex mechanism with a diene and TMSNCS. Photoirradiation and subsequent single-electron transfer provided radical ion pair **25-A**. The trimethylsilyl radical then abstracts hydrogen from the Hantzsch ester activated by benzoic acid, generating an alkyl radical. Radical addition of the alkyl radical and the radical cation affords carbocation **25-B**. Finally, the isothiocyanate anion furnishes the desired isothiocyanate.

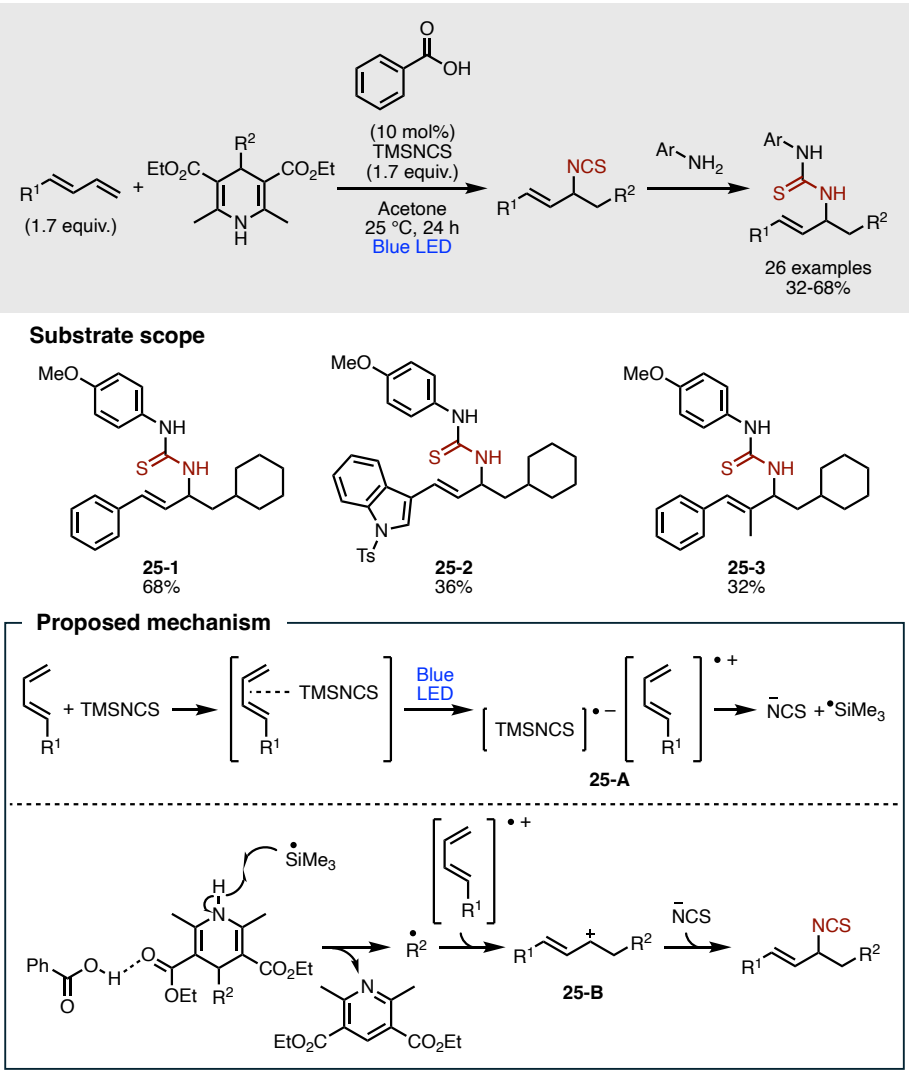


Figure 31. Photo-induced 1,2-carboisothiocyanation of dienes.

4-3. Recent advances in isothiocyanation Type C with C–H bonds

C–H functionalization is one of the most useful and frequently employed methods for the late-stage functionalization of pharmaceuticals.[109–114] Therefore, direct C–H functionalization is an important methodology for the synthesis of isothiocyanates, which exhibit various biological

activities. However, C–H isothiocyanation is difficult because strong C–H bond scission is required. To address this issue, recent examples of C–H isothiocyanations involving radical reactions have been reported. In these reactions, thiocyanation is favored over isothiocyanation, and the corresponding thiocyanates are obtained as intermediates. Subsequent isomerization to isothiocyanate in one-pot or *in situ* enabled C–H isothiocyanation.

In 2020, Cu-catalyzed C–H bond thiocyanation and one-pot isothiocyanation were reported by Liu et al. (Figure 32).[115] Thiocyanation proceeded with a copper catalyst, TMSNCS, and NFSI as oxidants, followed by treatment of the thiocyanates with $ZnCl_2$, enabling formal C–H isothiocyanation. Various thiocyanates were successfully obtained; however, when 4-ethylanisole and isopropylbenzene were used as substrates, the corresponding isothiocyanates were obtained without zinc chloride (**26-1** and **26-2**). In addition, the one-pot isothiocyanation can be applied to several complex isothiocyanates in good yields. The proposed mechanism is illustrated in Figure 32. Initially, LCu(I) reduced NFSI, generating an amidyl radical. The amidyl radical then abstracts the benzylic C–H bond, forming a benzyl radical. The benzyl radical reacts with LCu(II)SCN to obtain the corresponding thiocyanates. Finally, adding $ZnCl_2$ causes isomerization of the isothiocyanates.

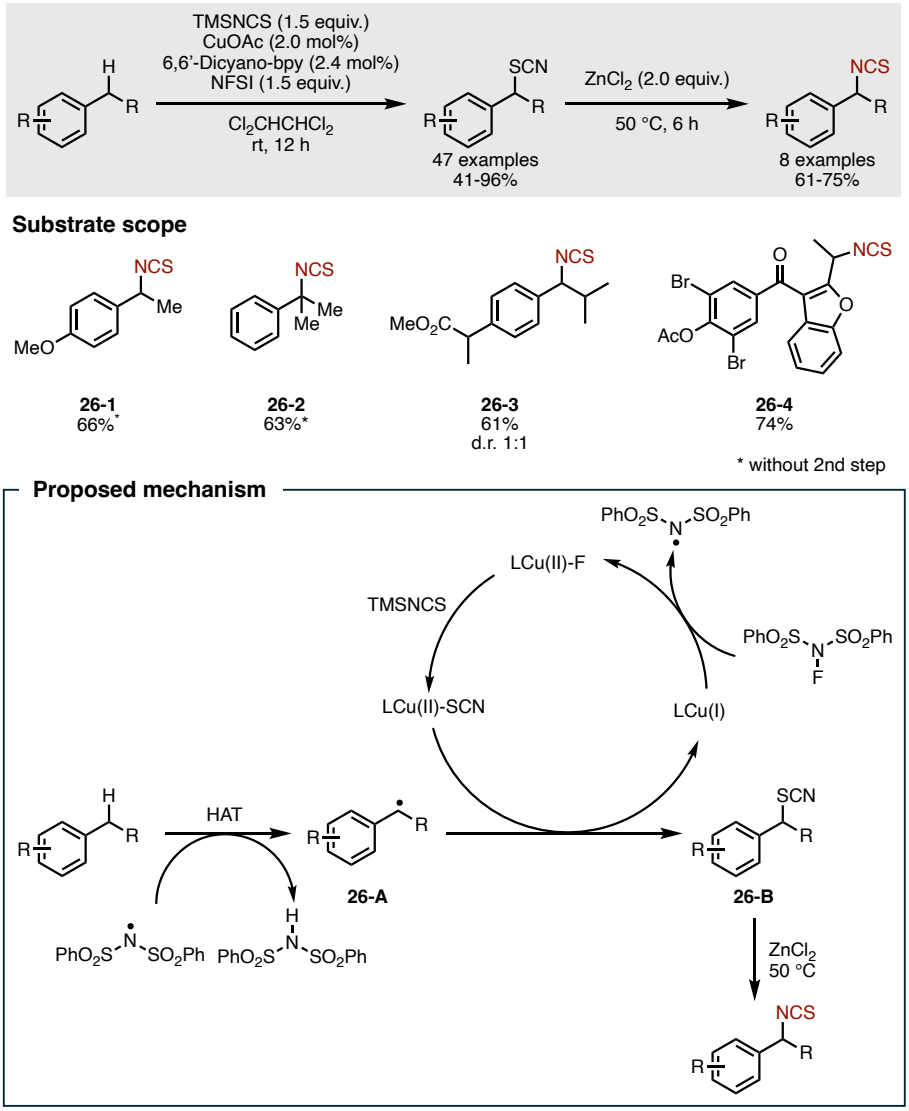


Figure 32. Copper-catalyzed C–H thiocyanation and one-pot isothiocyanation.

We previously reported C–H thiocyanation and one-pot isothiocyanation (Figure 33).[116] Photoirradiation was essential for obtaining the products. Irradiation of the substrate with a blue LED in the presence of TMSNCS and Selectfluor provided thiocyanates in moderate-to-high yields. Additionally, unstable thiocyanates such as tertiary thiocyanate **27-1**, which easily

isomerizes into isothiocyanate by heating or Lewis acids, can be obtained by tuning the reaction temperature. Furthermore, following photoinduced C–H thiocyanation, one-pot isomerization with molecular iodine and oxalic acid provided various isothiocyanates in low-to-moderate yields (**27-2**–**27-4**). We propose a reaction mechanism driven by thiocyanogens. Thiocyanogen (**27-A**) is generated by the oxidation of TMSNCS by Selectfluor and is in equilibrium with thiocyanate radicals (**27-B**) under blue light irradiation. Hydrogen atom transfer (HAT) occurs via the generated thiocyanate radical, subsequently producing the benzyl alkyl radical **27-C**. The alkyl radical reacts with thiocyanogen to produce thiocyanate. Finally, molecular iodine and oxalic acid isomerize the thiocyanate in nitromethane.

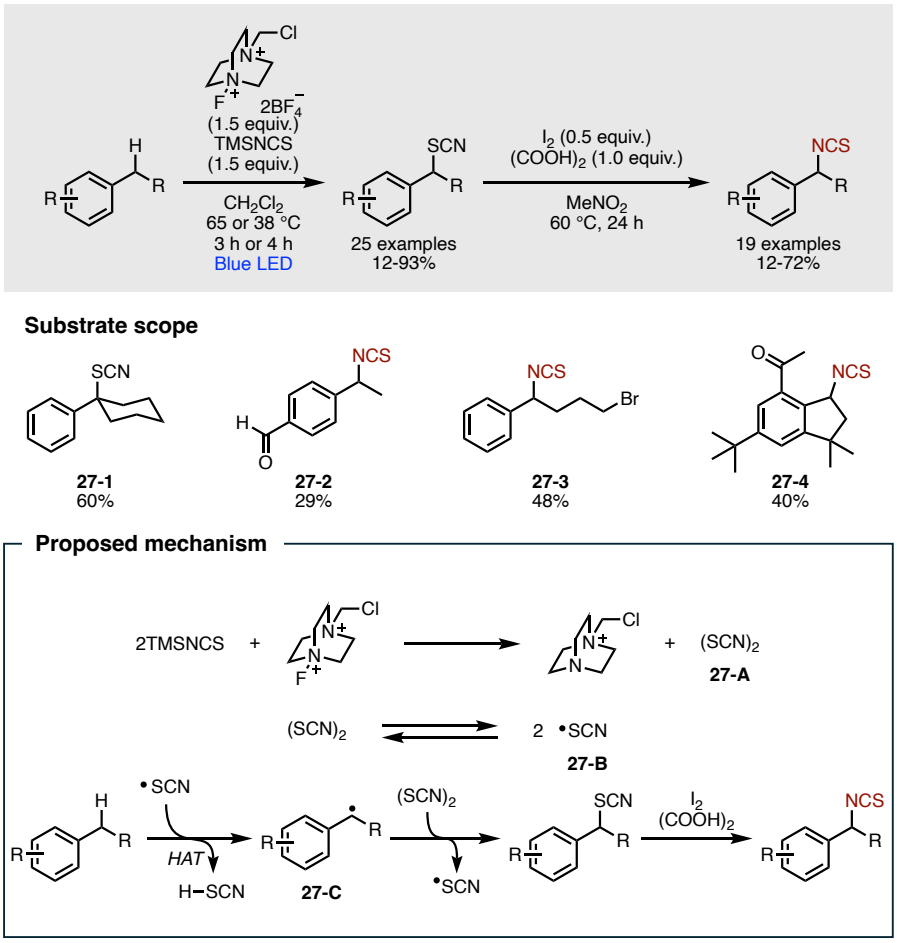


Figure 33. Photo-induced C–H thiocyanation and one-pot isothiocyanation.

Organic electrosynthesis is a powerful and sustainable method for benzyl functionalization. In 2022, an electrochemical benzylic C–H isothiocyanation using a green and efficient protocol was reported by Guo et al. (Figure 34).[117] They used TMSNCS, and nBu$_4$NBF$_4$, the corresponding isothiocyanates were obtained from benzyl compounds using a constant current (7 mA) with a graphite felt (GF) anode and a nickel (Ni) cathode in a DCE/HFIP mixed solvent. To the best of our knowledge, this is the first example of a general method for the direct C–H isothiocyanation. The reaction afforded a wide substrate scope, mainly electron-rich compounds including pharmaceutical analogs, in moderate-to-good yield (**28-2** and **28-3**). Based on several control experiments, the authors proposed a plausible reaction mechanism. Initially, the benzyl substrate was oxidized to furnish a radical cation, followed by the release of a proton to produce the benzylic radical **28-A**. Additionally, anodic oxidation of the benzylic radical afforded the benzyl cation **28-B**. The desired isothiocyanate was obtained by trapping the benzyl cation with an isothiocyanate anion. A thiocyanate compound was also generated and *in situ* isomerization to the corresponding isothiocyanate was performed.

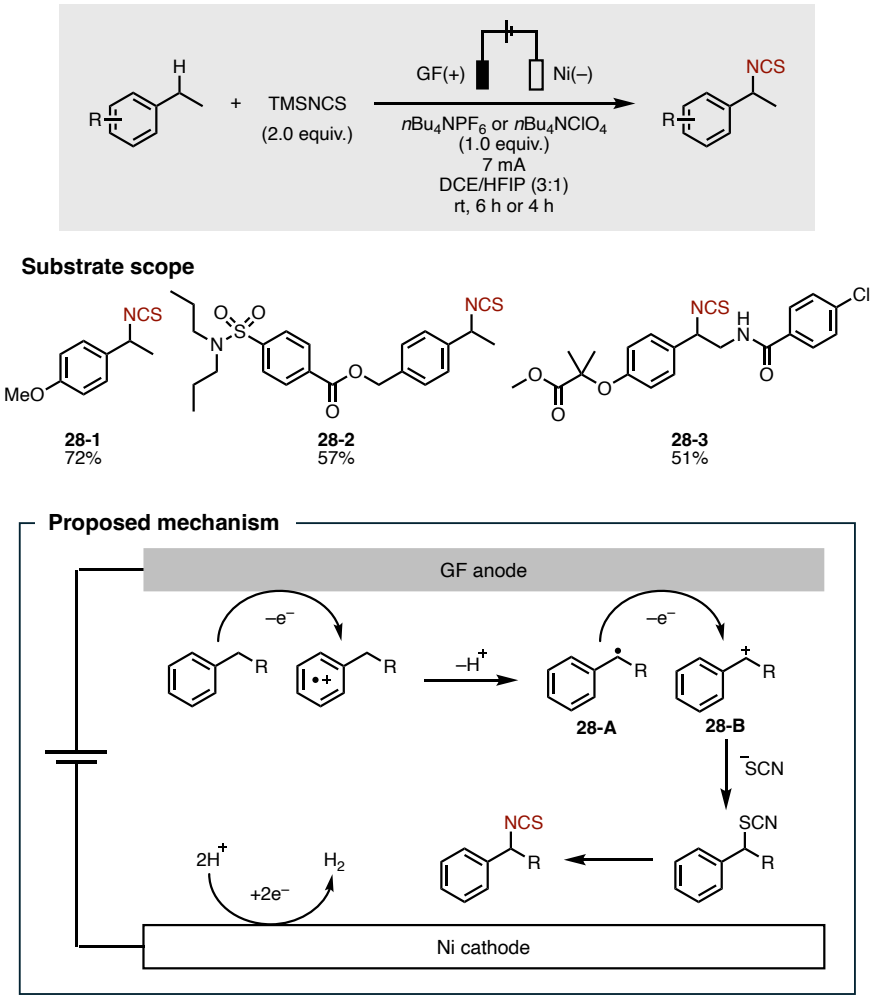


Figure 34. Electrochemical C–H isothiocyanation.

5. Conclusion

Isothiocyanates are versatile compounds, demonstrating a variety of bioactivities including anti-inflammatory, anticancer, antibacterial, and antimicrobial properties. They are also used as bioprobes and for sequencing amino acids in peptides. Moreover, isothiocyanates serve as valuable intermediates due to the various transformations that have been developed. The remarkable versatility of isothiocyanates has encouraged chemists to explore new synthetic methods, resulting in numerous novel approaches being reported over the past decade. Some methods have

successfully produced isothiocyanates from primary amines without the need for desulfurylating reagents by utilizing strong bases or single-electron oxidation. Notably, isothiocyanation using thiocarbonyl fluoride efficiently produces a wide range of isothiocyanates. In addition, isothiocyanation via rearrangement or the Staudinger reaction, followed by the aza-Wittig reaction, plays a crucial role in the synthesis of complex isothiocyanates. Furthermore, significant progress has been made in synthetic chemistry, enabling the selective synthesis of isothiocyanates from olefins and C–H bonds. These methods have greatly expanded the structural diversity of isothiocyanates. However, it is essential to acknowledge that the substrate scope of C–H isothiocyanation is currently limited to benzyl compounds. Therefore, further development of isothiocyanation methodologies is required to enable the synthesis of more valuable isothiocyanates.

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Keywords: Isothiocyanate • synthetic methods • bioactive compounds• synthetic intermediates • C–N bond formation.

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