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Reactivities and mechanisms in organic reactions involving activation of elemental sulfur under basic conditions

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A B S T R A C T

As a readily available and benign waste product of the petrochemical industry, elemental sulfur displays desirable characteristics as a raw material for new processes. Accordingly, the use of elemental sulfur as a reactant or reagent in synthetic organic chemistry receives continuous interest. The implementation of sulfur in synthetic procedures often necessitates the presence of basic or nucleophilic compounds, which are known to serve as activators, enabling a diverse range of transformations. However, the underlying mechanisms are still poorly understood, even for synthetically useful and well-established reactions that have been known for decades. While numerous reviews focus on the various types of products accessible via organic reactions involving elemental sulfur, this manuscript will put its emphasis on common mechanistic steps of these transformations, highlighting and discussing mechanistic studies and postulated pathways.

1. Introduction

The global production of elemental sulfur steadily increased during the past decades, with the annual market volume consistently exceeding 80 million tons since 2020, making it one of the most produced chemicals worldwide [1]. The vast majority of elemental sulfur is, in contrast to other products of the chemical industry, not the result of targeted production, but is instead generated as a byproduct of the refining of natural oil and gas [2,3]. The removal of sulfur species from petroleum is critical, since their presence is associated with several issues such as sulfur dioxide emissions upon their combustion, as well as the poisoning of catalysts employed in downstream processes [4,5]. The ongoing depletion of fossil resources will presumably necessitate the utilization of feedstocks with an even higher sulfur content, hence sulfur production is projected to further increase in the future [6].

By far the largest industrial use of elemental sulfur is sulfuric acid production, accounting for more than 85% of sulfur usage, with other applications being rubber and gunpowder production or, in terms of materials use, smaller applications such as alkali metal-sulfur batteries [2,7,8]. Still, these applications have not been able to counterbalance the large sulfur input from the petrochemical industry. Excess sulfur thus accumulates every year, with the currently most feasible solution being indefinite storage in designated sulfur deposits in the form of large blocks. This presents several risk factors, such as the high flammability of sulfur along with the associated release of sulfur oxides into the atmosphere, as well as groundwater pollution due to microbial oxidation into sulfuric acid [2,9–11].

Numerous chemical processes involving elemental sulfur have been known for a long time, such as the vulcanization of rubber discovered by Charles Goodyear in 1839, as well as several well-known organic reactions such as the Willgerodt-Kindler reaction, first described in 1887 [12,13]. The above described circumstances, in combination with the knowledge that sulfur containing materials show promising application possibilities, have recently served as new inspiration for scientists to explore novel potential applications for elemental sulfur. As a cheaply available waste material and a non-toxic, non-odorous and storage-stable solid at ambient conditions, sulfur exhibits highly desirable properties as a raw material for novel processes. In addition to these convenient characteristics, sulfur possesses great potential as a versatile reagent in chemical synthesis.

Nowadays, a great number of synthetic procedures involving the direct use of elemental sulfur have been described and reviewed, demonstrating an exceptional variety of valuable products for numerous applications [14].

Generally, in order to take advantage of the versatile reactivities that elemental sulfur is capable of, the conditions of these transformations need to be adapted in order to achieve activation of the relatively inert and poorly soluble S_8 rings by converting them into more reactive species. Besides the use of high reaction temperatures, the activation of elemental sulfur with nucleophilic bases has long been successfully

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employed.

The common consensus is that the latter activation is effected by an initial nucleophilic attack of the base to the cyclic S_8 molecule, leading to a ring opening via heterolytic S–S-bond cleavage. However, the exact mechanistic steps between the initial activation and the generation of the final product are still not fully understood and can be expected to be heavily dependent on the nature of the base, the substrates and the external conditions.

The high reactivity of the activated sulfur species often makes it very difficult to impossible to detect and characterize the formed intermediates. Furthermore, the large number of different species involved also hampers *in situ* monitoring [13,15]. Mechanistic insights into reactions with elemental sulfur can often only be gained via control experiments using slightly modified conditions, on the basis of postulated pathways. Furthermore, the amount of computational studies regarding the behavior of elemental sulfur under base-activation is still scarce.

In recent years, several reviews have summarized applications of elemental sulfur in organic synthesis, often laying their focus on a certain type of transformation or substrate [13,14,16–19]. Mechanistic studies on the other hand are seldomly critically discussed. Other recent reviews centering on specific sulfur species, for instance the trisulfide radical anion $S_3^{\bullet-}$ (*vide infra*), have highlighted its potential importance in organic reactions with elemental sulfur [20,21]. Particularly, Chivers, Wang et al. reviewed several organic transformations, in which the trisulfide radical anion was detected, and critically discussed the mechanistic postulates provided by these reports [21]. In this review, we thus aim to complement the existing discussion by summarizing typical recurring reactivities that have been observed in reactions involving elemental sulfur in the presence of activating bases, as well as critically evaluating the mechanistic postulates provided for the discussed transformations.

Despite the considerable advances already made in utilizing elemental sulfur for new chemical processes, we hope that this review will incentivize further studies in the future in order to allow for more targeted approaches towards unlocking the full potential of this highly versatile material.

2. Elemental sulfur and its interaction with bases

2.1. Basic physical and chemical properties of sulfur

Since the chemistry of sulfur is versatile enough to fill entire textbooks, the following section will provide only a brief overview of the basic physical and chemical properties of elemental sulfur [22–24]. Sulfur chemistry is characterized by the high variety of possible oxidation states, ranging from –II to + VI. As the heavier homologue of oxygen in Group 16 of the periodic table, sulfur-based equivalents of many oxygen-containing functional groups are well described [22,25]. In contrast to oxygen, however, sulfur more readily forms stable bonds with itself. The average S–S-bond dissociation energy is 265 kJ/mol, making it the third most stable homoatomic single bond, only surpassed, on average, by H–H and C–C bonds [15,26]. In accordance with the double-bond-rule, the tendency of sulfur to form double bonds is significantly lower than that of oxygen [23]. Instead, sulfur is known for its tendency to form long chains and cycles. In fact, elemental sulfur has the largest known number of solid allotropes, comprising cyclic modifications with 6–20 S-atoms, as well as phases consisting of polymeric sulfur chains. Additionally, a great number of polysulfur cations, anions and radicals have been described [23].

The only thermodynamically stable modification at standard ambient temperature and pressure is α-sulfur, consisting of cyclic, crown-shaped S_8 molecules of D_{4d} symmetry, which crystallize in an orthorhombic lattice, forming the characteristic yellow crystals that are commonly associated with elemental sulfur [27]. Above 96 °C, a phase transition to β-sulfur occurs, which is a monoclinic modification also consisting of S_8 cycles. The melting point of β-sulfur is reached at roughly 120 °C. In liquid sulfur, S_8 rings are still the predominant species, however an equilibrium with other S_x ring sizes is established. Upon further heating to 159 °C, the entropy gain of homolytic S_8-ring opening starts to outweigh the enthalpy required for the bond scission, rendering this temperature the floor temperature for the homopolymerization of the sulfur cycles. Consequently, starting at this temperature, the formation of biradical polymeric sulfur chains comprising up to 10^5 S-atoms is observed, which is accompanied by a color change from yellow to deep red, as well as a drastic viscosity increase of the melt [23,28]. Clearly, up to the homopolymerization floor temperature of 159 °C, it can hence be expected that the S_8 molecule is the defining species for the physical and chemical properties of elemental sulfur.

The solubility of S_8 is generally very poor, especially at low temperatures. The very notable exception is carbon disulfide, which dissolves roughly 25 wt% of elemental sulfur even at ambient temperature and pressure [29]. Moderate solubility of elemental sulfur has been reported in toluene, *p*-xylene, chlorobenzene and cyclohexane, with toluene being the most effective solvent among them, dissolving approximately 2.8 wt% sulfur at 30 °C. Generally, sulfur solubility increases with rising temperature. The presence of ions drastically decreases the solubility [30,31]. It has been reported that in solutions of elemental sulfur in polar solvents, like methanol or acetone, an equilibrium is established in which ~1 % of the dissolved sulfur is present as smaller S_7 and S_6 cycles. The solubility of S_8 can be drastically enhanced by the addition of surfactants. While pure water dissolves merely 5 μg/L of α-sulfur, the addition of cetyltrimethylammonium bromide was shown to significantly enhance the solubility of S_8 to up to 26.5 mg/L at room temperature, corresponding to a factor of 5300 [32].

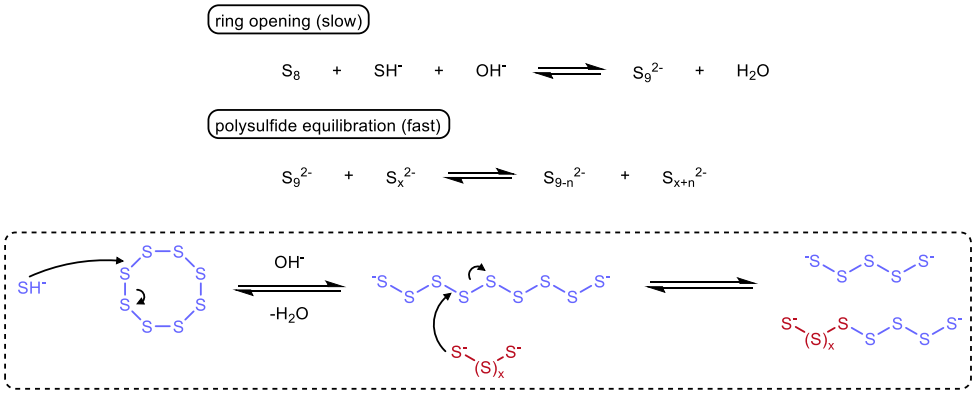
2.2. Fundamental interactions of elemental sulfur with bases

While the S_8 molecule is chemically inert towards most reagents and mostly insoluble in pure solvents at standard conditions, it shows much higher reactivity towards basic compounds. The interaction of sulfur with bases is accompanied by a chemical transformation of S_8, typically associated with the formation of polysulfide anions and/or sulfur-centered radicals.

As a very classic example, elemental sulfur rapidly dissolves in aqueous solutions of ammonium sulfide and other inorganic sulfides (Scheme 1). The resulting yellowish-brown solutions comprise polysulfide dianions $[S_n]^{2-}$ of variable chain lengths, with their ratio depending on the pH, the pentasulfide anion S_5^{2-} typically being the most dominant species [33,34]. Mechanistically, it has been suggested that the sulfur dissolution initiates with the nucleophilic attack of the bisulfide ion on the S_8 ring, resulting in the formation of the nonasulfide dianion S_9^{2-}, followed by the rapid establishment of an equilibrium with polysulfide dianions of variable chain lengths via continuous nucleophilic substitution of sulfur atoms within the polysulfide chains (Scheme 1).

Nucleophilic substitution reactions on sulfur centers in the open-chain species are reported to be significantly faster than the initial S_8 ring opening [24,35,36]. The high rate of the exchange reactions was underlined by a radiotracer experiment. Adding ^{35}S-enriched elemental sulfur to an aqueous polysulfide solution revealed an almost instantaneous incorporation of the radioactive isotope into the polysulfide species [37].

In addition to their equilibrium with each other and with S_8, polysulfide dianions also exist in an equilibrium with the corresponding radical monoanions, resulting from the homolytic scission of a central S–S-bond [15,24]. The most notable and well-described is the deep-blue trisulfide radical anion $S_3^{\bullet-}$, which is today well known as the species responsible for the blue color of several minerals such as lapis lazuli or ultramarines [38]. Although the formation of a blue color associated with the interaction of sulfur and bases or solutions of polysulfide salts had been observed numerous times before, the nature of the $S_3^{\bullet-}$ as the



Scheme 1. Reported mechanism of derivatizing elemental sulfur dissolution in aqueous sulfide solutions, resulting in the formation of a transient nonasulfide anion, followed by its rapid equilibration to other polysulfide species.

underlying species was first characterized by Chivers et al. in 1972 in a solution of alkali polysulfides in hexamethylphosphoramide (HMPA) [20,39–42]. Other important polysulfide radical anions are the disulfide and tetrasulfide radical anions $S_2^{\bullet-}$ and $S_4^{\bullet-}$. However, these species are observed significantly less frequently than $S_3^{\bullet-}$ [15].

The equilibrium between the dianions and the radical monoanions depends on the characteristics of the solvent and other factors. Generally, in solvents of high polarity such as water, the dianions seem to be more stable towards dissociation, making them the predominant species in comparison to the radicals. The nature and solvation of the cations are also reported to influence the ratio of dianions and radical monoanions, with poorly solubilized, strongly interacting cations stabilizing short-chain dianionic species. Higher temperatures favor the formation of the radicals due to the increased influence of entropy [15,43,44].

These tendencies are underlined by computational studies for the dissociation of polysulfide anions S_n^{2-} with n = 4–8, revealing negative Gibbs free energies for the dissociation of pentasulfide and hexasulfide in solvents with a low dielectric constant at 298 K, explaining the observation of $S_3^{\bullet-}$ and $S_2^{\bullet-}$. For water, all calculated Gibbs free energies were positive, confirming the observation of negligible radical anion formation in aqueous polysulfide solutions at room temperature [45].

As briefly mentioned previously, the $S_3^{\bullet-}$ radical anion has been detected using its characteristic UV/Vis absorption between 590 and 620 nm as well as its electron paramagnetic resonance (EPR) and Raman signals in numerous organic reactions with elemental sulfur and bases, particularly those involving oxygen-centered bases such as hydroxides, alkoxides or carbonates, and in polar aprotic solvents like dimethyl sulfoxide (DMSO) or *N,N*-dimethylformamide (DMF) [15,21,46–48]. Clearly, polysulfide anions are thus also formed from the interaction of such bases with sulfur, presumably via similar mechanisms as depicted in Scheme 1 [20,46].

Nitrogen-centered bases such as ammonia and amines similarly display characteristic interactions with elemental sulfur. Solutions of elemental sulfur in liquid ammonia are highly complex systems that have been controversially discussed and thoroughly investigated using Raman, UV/Vis, EPR and nuclear magnetic resonance (NMR) spectroscopies by various groups [49–52]. The main sulfur species detected within these solutions are the hexasulfide dianion S_6^{2-}, in temperature- and concentration-dependent equilibrium with its corresponding radical monoanion $S_3^{\bullet-}$, as well as several sulfur-nitrogen anions, namely the cyclic S_7N^-, and the open-chain species S_4N^- and S_3N^- [51]. The presence of shorter-chain aminopolysulfides, such as NH_2S^- and $NH_2S_2^-$, has also been suggested [53]. Physically dissolved S_8 was not detected [50]. A tentative mechanism for the main steps of this derivatizing dissolution has been suggested by Chivers et al. entailing initial ring-opening of S_8 by amide anions, followed by extrusion of H_2S to form the cyclic heptasulfurimide anion S_7N^-, which is known to further decompose into S_4N^- (Scheme 2) [50,54]. The initial step of the nucleophilic ring opening could similarly involve ammonia instead of amide [35]. The generation of H_2S results in the subsequent formation of polysulfide anions in analogy to the mechanism presented in Scheme 1.

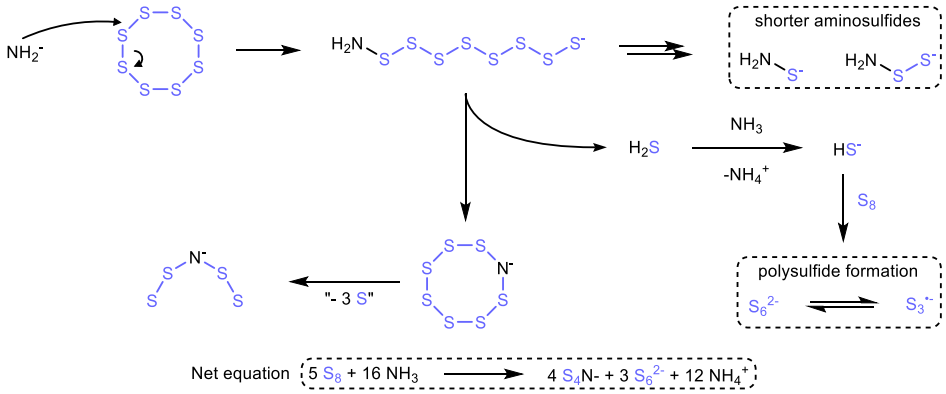
In a similar fashion to ammonia, amines also react with elemental sulfur to form complex systems involving polysulfides and nitrogen-sulfur species. Several studies concerning sulfur-amine systems allow to draw some general conclusions about the formed species, depending on basicity, steric hindrance and the degree of N-substitution of the amines.

Davis et al. investigated several physical properties of solutions of sulfur in various amines, which they reported to be strongly colored, and detected a strong rise in electrical conductivity as compared to the pure amine for primary and secondary amines, with primary amines showing a stronger increase. They further noted that the extent of the conductivity and color intensity enhancements generally correlated well with the basicity of the amine, and was impeded with increasing steric hindrance. The observations were explained by the formation of ionic polysulfides by nucleophilic attack of the amine on the cyclooctasulfur ring, followed by deprotonation of the resulting zwitterion (Scheme 3) [55]. These results were soon after complemented by Hodgson et al. who confirmed the presence of radicals in sulfur solutions of primary and secondary amines, which they attributed to the formation and subsequent homolysis of polythiobisamines from the aminopolysulfides (Scheme 3). Notably, such a reaction would also entail the formation of polysulfide dianions and their corresponding radicals [56]. Raman spectroscopy studies further reinforced the presence of polysulfide anions as well as the radical anions [57,58].

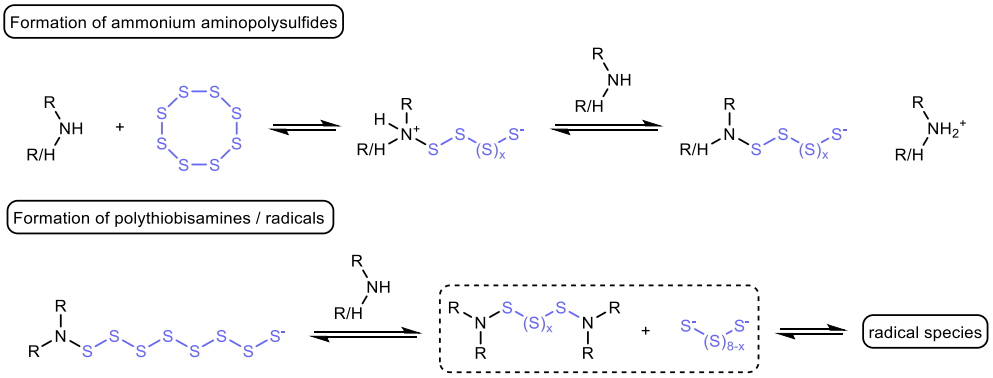
From fresh solutions, sulfur could in most cases be quantitatively recovered by evaporation, indicating the reversibility of all steps. Upon aging of the solutions however, the conductivity and color intensity of the solutions of sulfur in amines was observed to decrease, accompanied by a release of H_2S, which was attributed to the irreversible formation of thioamides by slow oxidation of the amine-α-methylene groups [55].

In a report by Nicolaou et al., the presence of polythiobisamines in sulfur solutions of strong nitrogen bases was confirmed. A mixture of polythiobisamines of different chain lengths, mainly the tetrasulfide, could be detected via mass spectrometry (MS) and isolated from a solution of sulfur and sodium hexamethyldisilazide (NaHMDS) in tetrahydrofuran (THF) [59].

All of these observations were underlined by NMR studies reported by Ozin et al. [60] Upon examining solutions of elemental sulfur in *n*-octylamine, they found that the resonance of the amine protons was shifted downfield as a function of the sulfur content, which is consistent with an increasing positive charge on the nitrogen atom due to ammonium formation. Although not detected via NMR, the formation of a small amount of polythiobisamine at room temperature was assumed,



Scheme 2. Proposed mechanism for the derivatizing dissolution of elemental sulfur in liquid ammonia.



Scheme 3. Formation of ammonium aminopolysulfides and subsequent formation of polythiobisamines and polysulfides and their equilibrium with radicals, as postulated by Davis (see Ref. [55]) and Hodgson (see Ref. [56]).

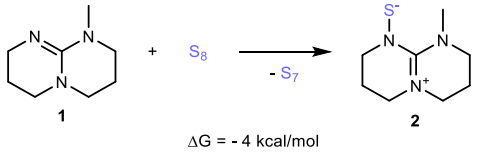
since the formation of H_2S was observed. Furthermore, a study of the system at 130 °C confirmed the formation of a thioamide under H_2S development.

Overall, it can be expected that the reversible formation of polysulfide species and also the corresponding radical anions define the chemistry of primary/secondary amine-elemental sulfur systems. The irreversible formation of products from primary amines and sulfur at low temperatures only occurs in special cases, which will be discussed later in this manuscript [61,62].

Tris(alkylamines) did however not show any significant increase in electrical conductivity upon sulfur addition, nor were radicals detected [55,56]. It was suggested by Davis et al. that the initial ring opening of S_8 cannot take place, but instead a formation of a charge-transfer complex between amine and S_8 was postulated [55]. This was based on observations made earlier by Bartlett et al., who investigated catalytic effects on the reaction of triphenylphosphine with sulfur to triphenylphosphine sulfide (*vide infra*). They reported that triethylamine only catalyzed the reaction in the simultaneous presence of hydrogen sulfide or sulfur dioxide, which would result in the formation of polysulfide anions and radicals via the mechanism described in Scheme 1 [63]. In accordance with this, Hodgson et al. observed radical formation only upon addition of hydrogen sulfide to triethylamine/sulfur [56].

While to our knowledge there have been no further fundamental studies on the interaction of sulfur with tris(alkylamines) like NEt_3, a recent DFT study has confirmed the exergonic formation of a stable zwitterion **2** from the strong guanidine-base 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) **1** and sulfur (Scheme 4). The sulfur-centered nucleophilic reactivity of the zwitterion **2** was also confirmed in the same study [64].

As will become apparent later in this manuscript, catalytic effects of



Scheme 4. Formation of a stable zwitterion from the guanidine base MTBD and elemental sulfur.

tris(alkylamines) have however often been observed in sulfur-organic reactions. The assumption that triethylamine does not activate elemental sulfur is hence at odds with most of the suggested mechanisms. Notably, even if the interaction of tris(alkylamines) and sulfur is merely the formation of a charge-transfer complex, this would still entail the weakening of the S–S bonds in elemental sulfur to some degree. The lack of an observed catalytic effect of NEt_3 on the phosphine/sulfur reaction could also be due to a stronger interaction of phosphines with sulfur, which is likely given regarding their high nucleophilicity. Still, the presented results potentially indicate that activation by tertiary amines may in fact not be caused by the amine, but by hydrogen sulfide impurities. This is illustrative of the poor understanding of sulfur-activation remaining to this day, and reinforces our view that further fundamental studies are required in order to fully understand the behavior of sulfur with the amines that are commonly used for its activation.

2.3. *Irreversible transfer of sulfur to activating nucleophiles*

While the interactions of elemental sulfur and the bases described in

section 2.2 are generally reversible, other nucleophiles form thermodynamically stable products via the incorporation of sulfur atoms, driving the reaction by being removed from the equilibria. Both the cyanide ion, as well as phosphines react with elemental sulfur to form stable monosulfurized products, namely the thiocyanate anion and phosphine sulfides, respectively (Scheme 5). The former reaction has been used as an analytical probe for the quantitative analysis of S^0 in aqueous samples [65]. Both reactions have been very extensively studied and will be discussed together, as the same methods have been used for their investigation.

Bartlett et al. performed kinetic investigations on both systems in homogeneous solution [66,67]. The reaction of triphenylphosphine **3** with elemental sulfur in benzene solution at ambient temperature was found to follow second-order kinetics, dependent both on sulfur and phosphine concentrations. Increasing basicity of the phosphine was found to increase the reaction rate. Tris(*p*-tolyl)phosphine reacted significantly faster, while replacement of the phenyl substituents with *p*-chlorophenyl successively lowered the reaction rate. Alkyl-substituted phosphines were reported to react too fast to be measured.

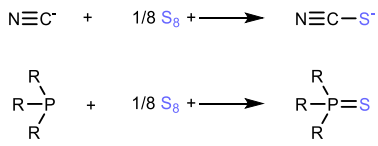
Based on these observations, the nucleophilic attack of the phosphine on the S_8 ring was proposed as the initial, rate-determining step. The resulting triphenylphosphine octasulfide **4** was suggested to be degraded in a cascade of seven nucleophilic attacks by other PPh_3 molecules upon the sulfur chain, each forming triphenylphosphine sulfide **5** and a phosphine polysulfide shortened by one sulfur atom (Scheme 6). The nucleophilic attack was proposed to occur at the S^2 position, *i.e.* the sulfur atom furthest from the negative terminus not bonded to a heteroatom. The same corresponding mechanism was suggested for the reaction of cyanide with sulfur, since the same overall kinetics were observed in this case.

Recently, extensive computational studies have been performed by Champagne et al. on the reactions of cyanide, PPh_3 and PMe_3 with sulfur, revealing a significantly greater degree of complexity in the pathways of the reactions [68].

The calculations confirmed that for all polysulfide chain lengths, the S^2 position is the most electrophilic position. The activation barriers for the nucleophilic attack were found to increase with decreasing polysulfide chain length due to increasing Coulomb repulsion, caused by the increasing vicinity of the negatively charged chain terminus to the electrophilic site. This effect is accordingly stronger for the anionic cyanide as compared to the neutral phosphines.

Interestingly however, it was found that for both cyanide and PMe_3, the Gibbs free energy of activation for the nucleophilic attack at the S^2 position of the trisulfide stage exceeds that of the initial opening of the S_8 ring, which is inconsistent with the observed overall second-order kinetics. Hence, two other possible pathways for the degradation of the polysulfides were investigated.

Unimolecular cyclization of a polysulfide NuS_x^- results in the formation of the monosulfurized product NuS^- and a cyclic elemental sulfur allotrope *cyclo*-S_{x-1} (Scheme 7). For polysulfides between 6 and 8 S-atoms, this reaction has significantly lower Gibbs free energy of activation than the bimolecular nucleophilic decomposition pathways, making it a highly favored process in comparison. For shorter chain lengths, the results become ambiguous between the formation of open-chain and cyclic sulfur species, and also transitions states could not be located in some cases. It was expected by the authors that for shorter-chain species, unimolecular decomposition becomes less relevant.



Scheme 5. Reactions of Cyanide and Phosphine with elemental sulfur.

Furthermore, all possible sulfur allotropes formed via unimolecular decomposition were found to have lower activation barriers for their reaction with the reactant nucleophile compared to S_8.

Polysulfide scrambling was suggested as another bimolecular decomposition pathway, involving the nucleophilic attack of a polysulfide NuS_y^- upon the S^2 position of another polysulfide NuS_x^- (Scheme 8). This results in the formation of the monosulfurized product NuS, and a longer polysulfide NuS_{x+y-1}^-. Scrambling was found to be the most favorable decomposition pathway for shorter polysulfides, where the other pathways are increasingly disfavored. Still, nucleophilic decomposition of polysulfides by the reactant nucleophile Nu is expected to play a significant role due to the initial high concentration of Nu [68].

These possible pathways allowed the authors to suggest complete reaction mechanisms for each investigated system, with the initial S_8 ring opening step possessing the highest activation barrier, in accordance with the observed kinetics. Overall, the combination of all possible modes of product generation adds up to a highly complicated mechanism for these seemingly simple reactions.

It can be expected that the reactions of other nucleophiles with S_8 also involve the described pathways, however the exact influence of each is expected to be highly individual with regard to the nucleophile.

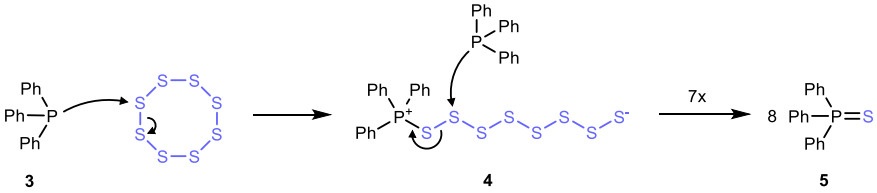
2.4. The nucleophilic reactivity of anionic polysulfide species

Sulfur-centered anions, such as thiolates, are widely known to be excellent nucleophiles. This nucleophilic character is also observed for anionic polysulfides, as also evidenced in the nucleophilic scrambling mechanisms described in section 2.3, which define the chemistry of polysulfide dianions.

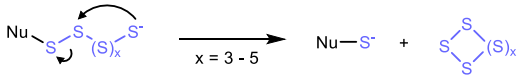
Numerous studies have demonstrated that anionic polysulfides can also undergo nucleophilic reactions with electrophiles. Indeed, polysulfide anions exhibit an enhanced nucleophilic character due to an α-effect exhibited by the sulfur atom bonded to the negatively charged terminus. This effect was demonstrated by Paris et al. when comparing the kinetics of the alkylation of aromatic thiolates and the corresponding disulfides with alkyl halides. For the *p*-nitrophenyl substrates **6a** and **6b**, the S_N2 reaction with ethyl iodide **7** was approximately 9 times faster for disulfide **6b** than for thiolate **6a** (Scheme 9). This general trend was observed for all other examined substrates [69]. Furthermore, studies on the degradation of chlorazines and phosphorothionate esters via nucleophilic substitution reactions (S_NAr and S_N2, respectively) demonstrated a higher reactivity of polysulfide dianions S_n^{2-} compared to the hydrosulfide anion HS^- [70,71].

Paris et al. reported on nucleophilic reactions of polysulfide dianions, generated via electrolysis of elemental sulfur, with various electrophiles. Specifically, nucleophilic reactions involving S_6^{2-} and the corresponding radical monoanion $S_3^{\bullet-}$ in *N,N*-dimethylacetamide (DMAc) solution were investigated. It was found that aromatic halides bearing *o*- and/or *p*-nitro substituents undergo nucleophilic aromatic substitution reactions with the polysulfide species, yielding the corresponding thiolate and disulfide anions as the products. The S_NAr character of the reaction was further reinforced by the observation that non-S_NAr-active aromatic substrates, such as bromobenzene, did not react, indicating that a radical-nucleophilic aromatic substitution ($S_{RN}Ar$) mechanism is not operative under the examined conditions despite the presence of $S_3^{\bullet-}$ radical anions. The substitution reaction was found to follow second-order kinetics in $S_3^{\bullet-}$, leading the authors to the conclusion that the dimer S_6^{2-} is the active species in the S_NAr [72]. These findings were further reinforced by studies investigating nucleophilic addition-elimination reactions of carbonyl compounds, as well as S_N2 reactions of alkyl halides under the same conditions, also identifying the dianion as the active species instead of the radical monoanion [73–75].

Polysulfide dianions, as well as other species containing negatively charged sulfur termini bonded to π-donor heteroatoms, are readily formed in reactions of elemental sulfur with bases. Based on the described observations, these species are often attributed strong



Scheme 6. Mechanism for the reaction of phosphines and sulfur, involving bimolecular nucleophilic decomposition of polysulfide **4**, proposed by Bartlett et al. in Ref. [66].



Scheme 7. Unimolecular decomposition of a polysulfide into a monosulfide and a cyclic sulfur allotrope.

nucleophilic character, which is in many cases proposed to be the key reactivity in organic reactions involving elemental sulfur and bases (*vide infra*).

3. Typical reactivities of base-activated elemental sulfur in organic reactions

3.1. Oxidation of thiols

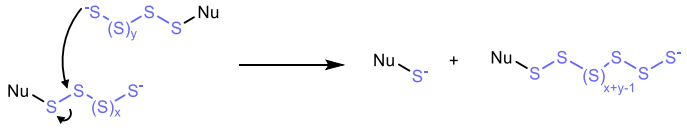
Thiols (R–SH) are known to react with elemental sulfur in the presence of bases, being oxidized to bis(organyl)polysulfides RS_xR, accompanied by formation of hydrogen sulfide H_2S. MacMillan et al. reported spontaneous formation of the corresponding bis(alkyl)disulfides from several primary, aliphatic thiols in the presence of traces of amines (*n*-butylamine or morpholine) or NaOH at room temperature [76]. In the absence of base, no reaction was observed. Furthermore, excess sulfur was reported to result in the formation of polysulfides RS_xR with $x > 2$.

Further studies were performed by Vineyard, who investigated the products of *n*-propylamine-catalyzed oxidation of the isomeric butanethiols with different stoichiometries at room temperature (Table 1) [77]. The primary *n*-butanethiol and *iso*-butanethiol form the trisulfide as the clear main product when reacted with one atomic equivalent of sulfur (corresponding to a twofold excess according to the reaction stoichiometry), with small amounts of disulfide and tetrasulfide also being detected. Using a stoichiometric amount of sulfur (0.5 equivalents), the disulfide was predominantly formed from *n*-butanethiol (Table 1, entries 1–3). *sec*-Butanethiol almost exclusively formed the trisulfide with both stoichiometries, while *tert*-butanethiol formed predominantly the tetrasulfide (Table 1, entries 4–7). Clearly, increasing steric hindrance at the thiol center favors the formation of polysulfides with increasing sulfur content.

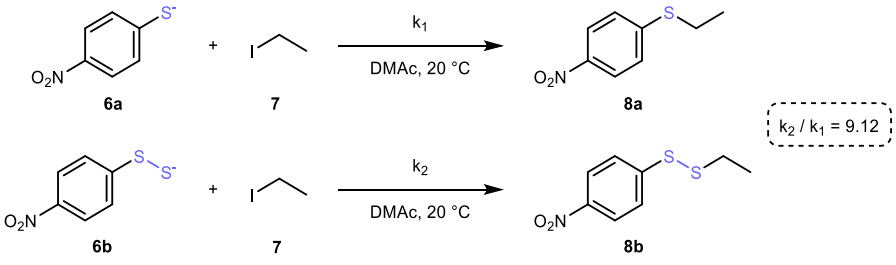
In a consecutive study, Vineyard found that increasing the reaction temperature and using an excess of thiol (0.4 atomic equivalents of sulfur) increased the selectivity for the disulfide formation (Table 1, entries 8–10) [78]. A mechanism was suggested, entailing an initial formation of the thiolate anion via deprotonation of the thiol by the basic catalyst and subsequent nucleophilic S_8 ring opening, forming an alkyl nonasulfide **9**. The product is formed by subsequent attack of another thiolate ion at the sulfur chain, forming the bis(alkyl)polysulfide **10** along with a polysulfide dianion. The latter is expected to eventually be converted into hydrogen sulfide, which is removed from the equilibrium (Scheme 10).

Recently, Zhang et al. investigated the influence of different organobase catalysts on the oxidation of *n*-octanethiol **11** [79]. With an increasing base strength, it was found that not only the reaction time until full conversion decreased, but also the selectivity of the formation of disulfide **12a** increased. Accordingly, the same trend was observed with increasing thiol acidity. Common organic guanidine- and amidine-based superbases, such as *tert*-butyltetramethylguanidine (BTMG) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were identified as highly effective catalysts, achieving fast reaction times even at extremely low catalyst loadings of 0.001 mol%. Lower catalyst loading of the same base resulted however in an increased formation of trisulfide **12b** (Table 2).

Based on their results, they expanded upon the mechanistic postulate of Vineyard by suggesting that the trisulfide **12b** can be further converted to the disulfide **12a** by reaction with a thiolate anion. Hence, a high concentration of thiolate, *i.e.* an effective deprotonation, is the key to ensuring high selectivity for disulfide formation, explaining the high selectivity for disulfides when excesses of thiol are used [79].

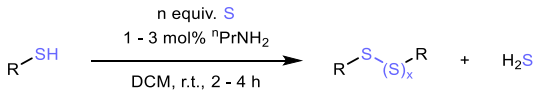


Scheme 8. Scrambling between two polysulfides.



Scheme 9. Relative rate constants of the *S*-alkylations of *p*-nitrophenylthiolate **6a** and -disulfide **6b** with ethyl iodide **7**, reported by Paris et al. in Ref. [69].

Table 1
Product distributions of the oxidation of isomeric butanethiols with elemental sulfur, obtained by Vineyard (see Ref. [77]). The main products are highlighted in bold.



Entry	R	n (equiv. S)	Composition of products [%]		
			Disulfide (x = 0)	Trisulfide (x = 1)	Tetrasulfide (x = 2)
1	*n*-butyl[a]	1	15.4	**75**	<5
2	*n*-butyl[a]	0.5	**71**	29	n.a.
3	*iso*-butyl[a]	1	5	**87**	5
4	*sec*-butyl[b]	1	<3	**>95**	trace
5	*sec*-butyl[b]	0.5	<3	**>95**	trace
6	*tert*-butyl[b]	1	n.a	12.5	**87.5**
7	*tert*-butyl[b]	0.5	n.a	10.6	**89.4**
8	*n*-butyl[c]	0.4	**97.5**	2.5	n.a
9	*iso*-butyl[c]	0.4	**95.0**	5.0	n.a
10	*sec*-butyl[c]	0.4	**92.3**	7.7	n.a

[a] Percentages indicate the relative yield of the isolated products compared to the thiol.
[b] Percentages indicate the product composition determined via ^{1}H NMR, not the isolated product.
[c] Reaction carried out at 62 °C in MeOH, product distribution analyzed via gas chromatography.

Notably, assuming that in analogy to the reactivity of the polysulfides formed from cyanides and phosphines, the S^2 position is the most electrophilic, the trisulfide could be expected to be the most easily formed product. Steric factors could contribute to an increased activation barrier for the attack on S^2, making the attack on S^3 and subsequent formation of tetrasulfide more feasible for bulky substrates. An attack on S^1, which would result in the disulfide, showed a higher activation barrier, which is consistent with the higher temperatures required for the formation of the disulfide.

Shaw et al. further observed a selectivity towards the disulfide formation for the oxidation of *n*-propanethiol in aqueous NaOH when using several poly(ethylene glycol) based cocatalysts. However, no suggestions or investigations have been made on how the co-catalysts mediate this selectivity on a mechanistic level [80].

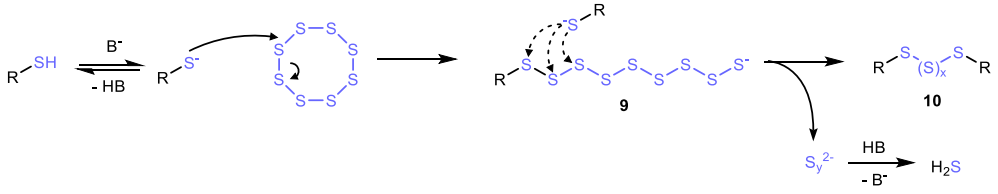
The oxidation of dithiols often yields cyclic polysulfides, with the thermodynamic stability of the resulting ring being the determining factor. As such, *o*-benzenedithiol **13** reacts with elemental sulfur and base, forming the corresponding trithiolane **14a**, pentathiepin **14b** and heptathionane **14c** (Scheme 11). The even-numbered heterocycles were reported to have decreased thermodynamic stability and have not been observed [81–83].

Paris et al. found that for sufficiently deactivated aromatic thiolates, such as *p*-nitrophenylthiolate **6a**, the oxidation to bis(arylpolysulfides) **15** is hindered, leading to the observation of a stable aryl disulfide anion **6b** (Scheme 12) [84].

In several instances, the polysulfide anion species formed upon reaction of thiolate and sulfur were reacted with other electrophiles.

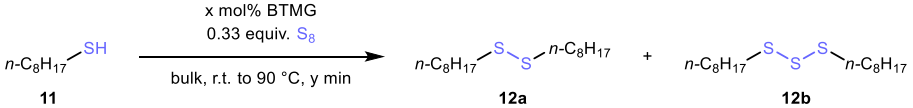
Mutlu et al. reported the synthesis of polydithiocarbonates in a DBU-mediated polycondensation of dithiols with carbonyldiimidazole (CDI) **16** [85]. When conducting the polymerization of 1,6-hexanedithiol **17** in the presence of elemental sulfur, polymers with a higher sulfur content were obtained, as confirmed by ^{1}H and ^{13}C NMR and elemental analysis (Scheme 13), where sulfur was incorporated via its interaction with the thiolate anions. The high electrophilicity of CDI, which is enhanced by the presence of DBU due to the formation of a stable ionic liquid from DBU and imidazole, presumably favors the reaction of the polysulfides with CDI in comparison to the formation of bis(organyl) polysulfides. Still, the number average molecular weights of the polymers obtained by copolymerization with sulfur are lower than those of the polymers obtained in the absence of sulfur, possibly indicating a small degree of monomer deactivation by oxidation to linear or cyclic polysulfides.

Penczek et al. investigated the anionic polymerization of thiiranes in

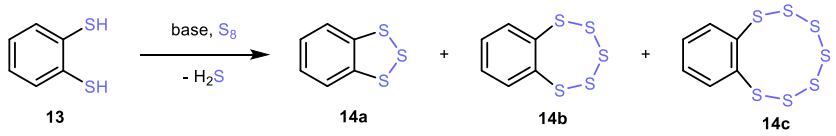


Scheme 10. Proposed mechanism of the oxidation of thiols with elemental sulfur, proposed by Vineyard in Ref. [78].

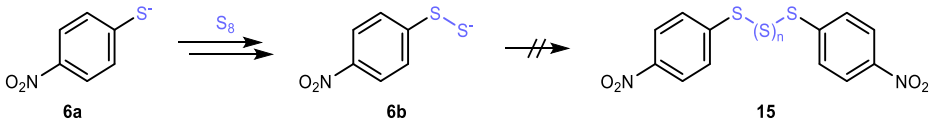
Table 2
Product composition of the BTMG-catalyzed oxidation of n-octanethiol **11** with sulfur, as reported by Zhang et al. in Ref. [79]. Reactions were conducted until hydrogen sulfide development ceased. The product composition was determined via gas chromatography.



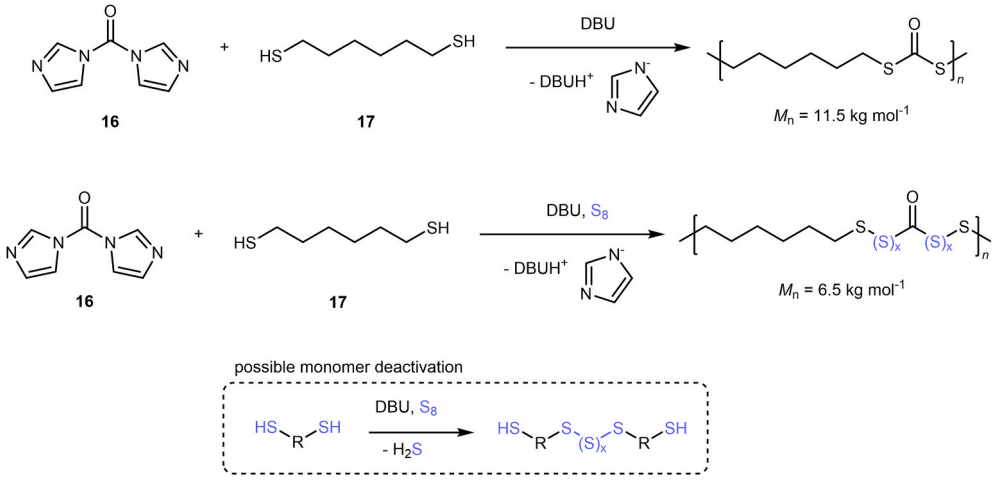
Entry	mol% BTMG	t/min	Composition of products [%]	
			Disulfide	Trisulfide
1	0.1	23	100	0
2	0.01	24	99.0	1.0
3	0.001	471	97.2	2.8



Scheme 11. Oxidation of *o*-benzenedithiol **13** to a mixture of cyclic polysulfides **14**.



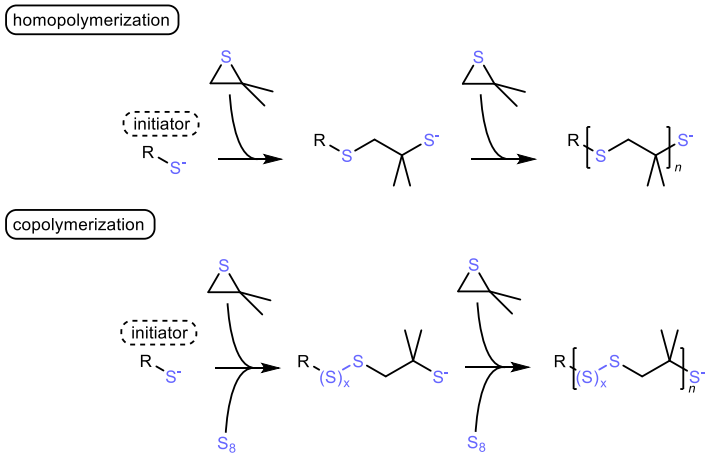
Scheme 12. Formation of a stable disulfide anion **6b** from *p*-nitrophenylthiolate **6a**.



Scheme 13. Synthesis of polydithiocarbonates from CDI **16** and hexanedithiol **17**, with and without sulfur (top and bottom, respectively), reported by Mutlu et al. in Ref. [85].

the presence of elemental sulfur in benzene solution at 60–80 °C [86–88]. It was found that elemental sulfur could be efficiently copolymerized with the thiiranes, yielding polysulfide linkages in the final polymer in addition to the thioether groups resulting from the thiirane homopolymerization (Scheme 14). Extensive characterization by Raman and NMR spectroscopies confirmed the successful copolymerization. In the case of isobutylene sulfide, it was possible to completely suppress thioether formation by using a 2.5-fold excess of atomic sulfur in comparison to the thiirane monomer. In this case, the polysulfide linkage chain length is distributed between 2 and 4, with an average chain length of 2.6. Kinetic studies revealed that the copolymerization proceeded with pseudo-first-order kinetics in thiirane due to the low concentration of the active species, indicating that the propagation by nucleophilic addition to the thiirane is the rate-determining step, and thus slower than the incorporation of elemental sulfur [86–88].

The suggested mechanism involves the reaction of the thiolate end



Scheme 14. Schematic representation of the anionic homo- and copolymerization of isobutylene sulfide with elemental sulfur.

group of the active species with S_8 to form a nonasulfide, which then adds to another thiirane monomer, forming a nonasulfide linkage. The authors proposed that the reason for the observation of only di-, tri- and tetrasulfide linkages are scrambling reactions by attack of a thiolate on already formed nonasulfide linkages, *i.e.* chain transfer or backbiting processes, in later stages of the polymerization (Scheme 15) [86–88].

The occurrence of inter- and intramolecular chain transfer processes would lead to the formation of shorter rings or chains, hence likely leading to an increase in the dispersity of the polymers, which was unfortunately not reported by the authors.

Recently, Ren et al. reported the selective synthesis of polydisulfides via the anionic copolymerization of propylene sulfide with elemental sulfur [64]. The selectivity was mediated by a cocatalyst system comprising the organic base MTBD, as well as a quaternary ammonium salt. The MTBD catalyst significantly accelerated the reaction, allowing the copolymerization to proceed at 25 °C, however the formation of polysulfides larger than disulfide linkages was still observed, even with a stoichiometric amount of atomic sulfur (1 atom of S per monomer). It was found that the presence of the quaternary ammonium ion bis(triphenylphosphine)iminium (PPN) almost completely inhibited the formation of polysulfide linkages larger than the disulfide.

The optimized conditions for the copolymerization employ thiirane and atomic sulfur in a 1:1 ratio, along with 0.25 mol% each of MTBD, PPN hexafluoroantimonate and the initiator BnSH, for 2 h at 25 °C in toluene. These conditions were applied to 7 different thiirane monomers **18**. The obtained polydisulfides **19** showed high number average molecular weights ranging between 22 and 77 kDa, and dispersities around 1.3. The relatively narrow dispersities indicate that the polysulfide scrambling postulated by Penczek et al. only seems to have minor influence under these conditions (Scheme 16).

However, DFT studies indicate that this copolymerization presumably proceeds via a different mechanism than those described by Penczek et al. As previously mentioned, the exergonic formation of a stable zwitterion **2** from the interaction of MTBD **1** and elemental sulfur was confirmed, serving as an important indicator that tertiary nitrogen bases can indeed activate elemental sulfur. Interestingly, in the presence of a quaternary ammonium ion (NMe_4^+ was used in the calculations), the formation of the monosulfide zwitterion is favored. It was found that the nucleophilic attack of this zwitterion on the thiirane, forming intermediate **20**, is kinetically favored over the nucleophilic attack of a thiolate. It was proposed that subsequently the thiolate chain end of the already formed polymer (or the initiator) attacks the S-atom bonded to the MTBD, propagating the chain by forming a disulfide linkage and reforming the MTBD catalyst (Scheme 17).

How exactly the presence of the ammonium ion induces the selectivity for the monosulfide zwitterion mechanistically remains unclarified. Still, this study is a rare instance of a thorough computational investigation of an amine-catalyzed reaction of elemental sulfur, not only demonstrating that a tertiary nitrogen-base can react with elemental sulfur, leading to ring-opening, but also demonstrating the often assumed nucleophilic reactivity of the resulting zwitterionic polysulfide [64].

3.2. Oxidative reactions of imines and enamines

Imines are readily formed from carbonyl compounds and amines, and exist in tautomeric equilibrium with their corresponding enamines. The oxidation of terminal imines/enamines to thioamides are a very common step, postulated in the pathways of many transformations.

The Willgerodt-Kindler (WK) reaction is an important example for the synthesis of thioamides. It is perhaps the oldest organic reaction involving the use of base-activated elemental sulfur, first reported by Kindler in 1923, based on an earlier report by Willgerodt in 1889. The "classic" Willgerodt-Kindler reaction entails the synthesis of a terminal thioamide from an araliphatic ketone, a primary or secondary amine and elemental sulfur (Scheme 18). However, the synthesis of thioamides is known for a much wider range of substrates such as aldehydes, alkynes, alkenes, among others, which are sometimes also classified as Willgerodt-Kindler reactions [13,89,90].

3.2.1. The Willgerodt-Kindler reaction of ketones and aldehydes

The most peculiar feature of the classic Willgerodt-Kindler reaction of ketones is the migration of the functional group towards the end of the alkyl chain. For instance, it was noted by Asinger et al. that the isomeric phenylbutanones **21a-c** all yield the same terminal γ-phenylbutanethioamide **23** when reacted with morpholine **22** and sulfur at 130 °C, albeit with decreasing yields with increasing distance of the carbonyl group from the chain end (Scheme 19) [91].

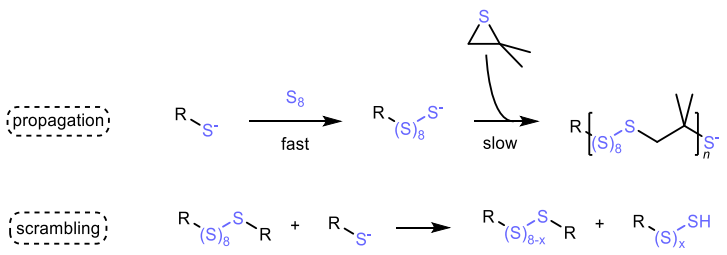
Carmack et al. performed extensive mechanistic studies and postulated a pathway for the Willgerodt-Kindler reaction in 1989 [92,93]. According to a review from 2013, this pathway is the still most widely accepted and to our knowledge, no further studies have since been performed to change this perspective [13]. Still, slightly different mechanisms have been suggested in some instances.

The Carmack pathway involves the formation of the enamine **25a** from ketone **24** and amine as the key intermediate for the subsequent isomerization along the alkyl chain (Scheme 20). The terminal enamine **25b** is irreversibly oxidized to the thioamide **26**, thereby removing itself from the equilibrium.

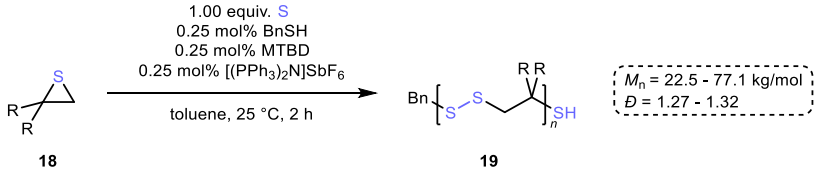
Carmack et al. investigated the isomerizations of 1,3-diphenylacetone **27** and cyclohexanones, which are unable to form terminal enamines, as model reactions (Scheme 21). Most of the studies were carried out at temperatures of 100 °C, using the cyclic secondary amines morpholine **22**, piperidine **29** and pyrrolidine **30** [92,93].

The results provide evidence that the enamines, formed by reversible condensation of amine and ketone, undergo the isomerization reaction, since substitution of amine for other bases such as NaOH did not result in isomerization. Furthermore, the presence of water slowed down the reaction, which was attributed to the shifting of the ketone/enamine equilibrium to the starting materials.

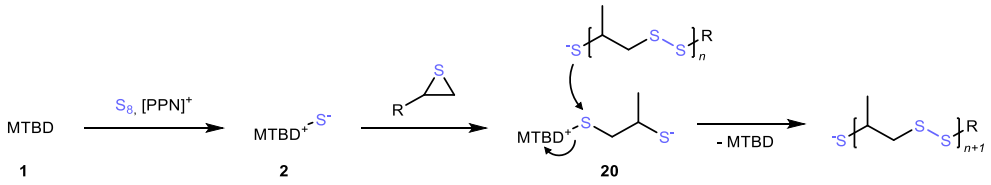
The tertiary *N*-methylmorpholine, unable to form an enamine, did not result in isomerization of the ketone. It was further observed that a presynthesized enamine underwent isomerization when sulfur was added, the authors noted however that the presence of additional free amine accelerated the isomerization.



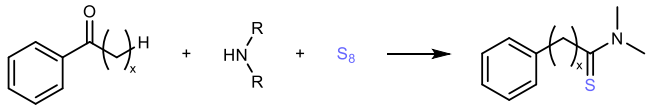
Scheme 15. Proposed mechanism for the copolymerization of isobutylene sulfide with elemental sulfur, involving propagation by fast nonasulfide formation, and formation of other polysulfide chain lengths via scrambling.



Scheme 16. Selective synthesis of poly(disulfides) via MTBD- and PPN-catalyzed copolymerization of sulfur and thiiranes, reported by Ren et al. in Ref. [64].

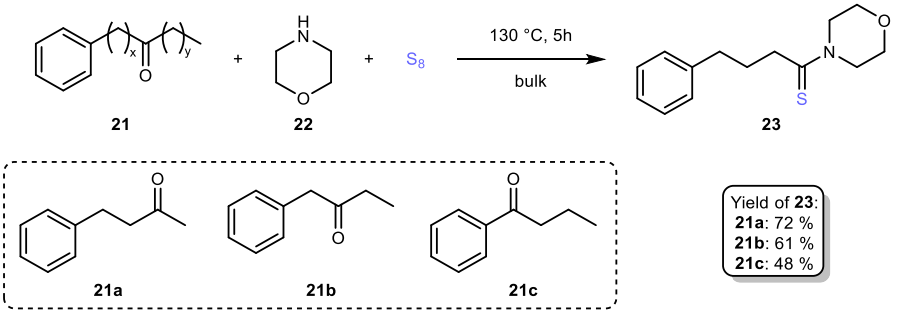


Scheme 17. Suggested mechanism of the MTBD- and PPN-catalyzed copolymerization of propylene sulfide and elemental sulfur (see Ref. [64]).

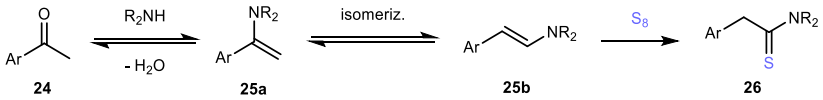


Scheme 18. Willgerodt-Kindler reaction of an araliphatic ketone with a secondary amine and sulfur, yielding a terminal thioamide.

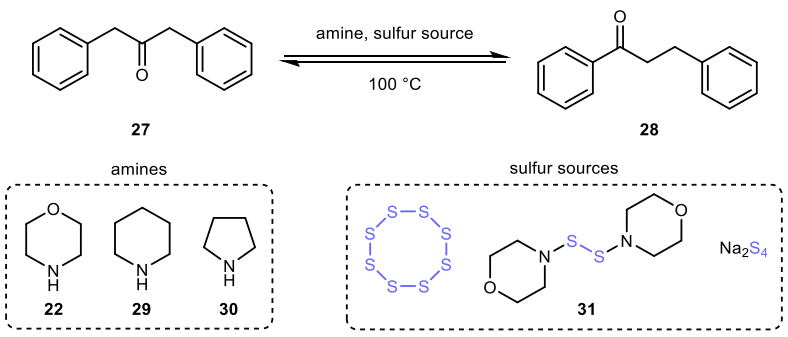
The isomerization was shown to proceed when other sources of sulfur, such as sodium tetrasulfide or dithiobis(morpholine) **31**, were added. Both the bisamine **31** and the tetrasulfide dianion can be formed by the interaction of morpholine with sulfur according to the general mechanism presented in Scheme 3. The rate of the isomerization reaction was demonstrated to increase with an increasing sulfur loading. However, it was noted that no sulfur is consumed during the isomerization process, it assumes a purely catalytic role. Further studies using heptanal **32a** as the substrate indicated that the isomerization proceeds



Scheme 19. Willgerodt-Kindler reaction of isomeric phenylbutanones **21a-c** with morpholine and sulfur, reported by Asinger et al. in Ref. [91].



Scheme 20. Schematic representation of the Carmack mechanism of the Willgerodt-Kindler reaction.



Scheme 21. Isomerization of 1,3-diphenylacetone **27** under Willgerodt-Kindler conditions, reported in Ref. [93].

at comparable rates to the oxidation to the thioamide **33**, since both the corresponding thioamide **33** and isomeric heptanones **32b-c** could be observed after short reaction times (Scheme 22).

Based on their observations, Carmack et al. proposed the following mechanism for the isomerization of a ketone **24**, mediated by morpholine and sulfur (Scheme 23). Initially, the enamine **25a** formed upon condensation of ketone and amine reacts with a morpholine-sulfur species, forming intermediate **34a**. As the active sulfur-amine species, both morpholine octasulfide, as well as dithiobis(morpholine) **31**, were proposed. Clearly, elemental sulfur itself can also be attacked by the enamine, as evidenced by the successful isomerization of an enamine with sulfur without the presence of additional base.

Intermediate **34a** is proposed to be in equilibrium with a thiirenium species **35**, formed after elimination of morpholine. It was proposed that the elimination of morpholine is facilitated by the presence of free base, which mediates proton transfer. Subsequent attack of morpholine on either of the two thiirenium carbon atoms either regenerates intermediate **34a** or generates its isomeric form **34b**. Another important implication of this postulated pathway is the reversibility of the α-thiolation, since the enamines **25** can be regenerated from the intermediates **34** (*vide infra*).

It was noted by the authors that the nature of the *S*-substituent of the thiirenium species was speculative, and that other substituents such as longer polysulfides are equally possible. However, the high reactivity of the intermediates did not allow for any further insights to be gained.

Recently, a synthetic application for the Willgerodt-Kindler isomerization was reported by Bhawal and Morandi et al. who employed catalytic amounts of sulfur and pyrrolidine to isomerize cyclic steroidal ketones (Scheme 24) [94].

As mechanism for the oxidation of the terminal enamine, Carmack et al. postulated a nucleophilic attack of an anionic polysulfide on the electrophilic iminium carbon atom. Subsequently, a proton shift to the α-position, which is only possible for the terminal species, followed by extrusion of a shortened polysulfide, generates the thioamide **26** (Scheme 23) [92,93].

Poupaert et al. proposed a slightly different mechanism for the thioamide formation from acetophenones **24**, entailing the α-thiolation of the enamine, followed by migration of the amine to the terminal carbon via an intermediate zwitterionic aziridinium species **37**. While this mechanism is conceivable for acetophenones, no suggestion was provided for the isomerization of ketones with longer alkyl chains (Scheme 25) [95].

Although Carmack et al. observed that tertiary amines alone do not lead to ketone isomerization, there is indication that tertiary amines can still mediate the isomerization and oxidation, as long as other enamine-forming amines are present. Poupaert et al. found that tertiary amines, such as triethylamine or *N*-methylmorpholine, have a catalytic effect on the Willgerodt-Kindler reaction of ketones with morpholine. It was further noted that the Willgerodt-Kindler reaction proceeds in a large variety of different solvents, with polar solvents such as DMF or ethanol leading to the best results, which was attributed to the high polarity of the postulated mechanistic intermediates [96].

Nguyen et al. synthesized benzoxazoles **39** from *o*-aminophenols **38** and acetophenones **24**, using a stoichiometric amount of *N*-methylpiperidine (NMPip) (Scheme 26). Less basic additives than NMPip, such as pyridine, resulted in significantly lower yields. Mechanistically, the involvement of the enamine in the isomerization was however not suggested by the authors. Instead, it was proposed that an NMPip-polysulfide species forms an enethiol **40**, which is further thiolated in α-position, forming a thiirenium species **41** via intramolecular nucleophilic attack. The amine is incorporated only via nucleophilic attack on the thiirenium species **41**. In the final step of the reaction, the formed thioamide derivative **42** undergoes cyclization with the *o*-phenolic substituent, yielding a benzoxazole **39** [97].

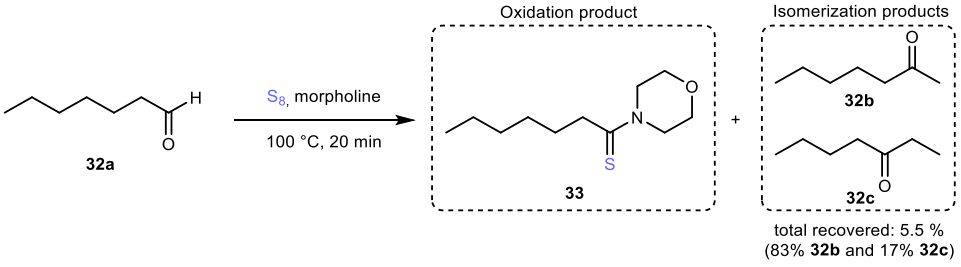
Willgerodt-Kindler reactions of ketones generally require elevated temperatures. In contrast, several reports of Willgerodt-Kindler reactions of aldehydes at room temperature have recently been made. Dalal et al. were able to conduct the thioamide synthesis from aromatic aldehydes at room temperature in polar aprotic solvents. Interestingly, they found that their reaction protocol only works for cyclic, secondary amines such as piperidine or morpholine. The open-chain diethylamine did not undergo a reaction at room temperature in DMSO [98]. However, in a subsequent report using bulk conditions, diethylamine was also effective at room temperature. The less basic primary amines required higher temperatures [99]. As a general trend, it was found that benzaldehydes bearing electron-withdrawing substituents react faster. Hence, a nucleophilic pathway for the oxidation in accordance with Carmack's pathway was suggested [98,99].

In contrast to the observations made by Dalal, Gururaja et al. successfully employed aqueous dimethylamine in a Willgerodt-Kindler reaction with aromatic and aliphatic aldehydes. It was suggested by the authors that the presence of water is essential for the reaction, reporting the formation of a complex mixture from the reaction of dimethylamine with sulfur and benzaldehyde in THF in the absence of water [100]. Water had previously been identified by Aghapoor et al. as an effective solvent for the thioamidation of aldehydes with sulfur and amines at higher temperatures. Ketones did not react under these conditions, which was attributed to the interference of water with the enamine formation required for their isomerization. This effect however seems to be inconsequential for the oxidation to the thioamide. It was suggested that the high efficacy of water is due to effectively dissolving ionic intermediates. Consequently, in all cases, the mechanism for the oxidation was suggested to involve a nucleophilic attack of an anionic polysulfide on the iminium carbon, in accordance with the mechanism proposed by Carmack (compare Scheme 23).

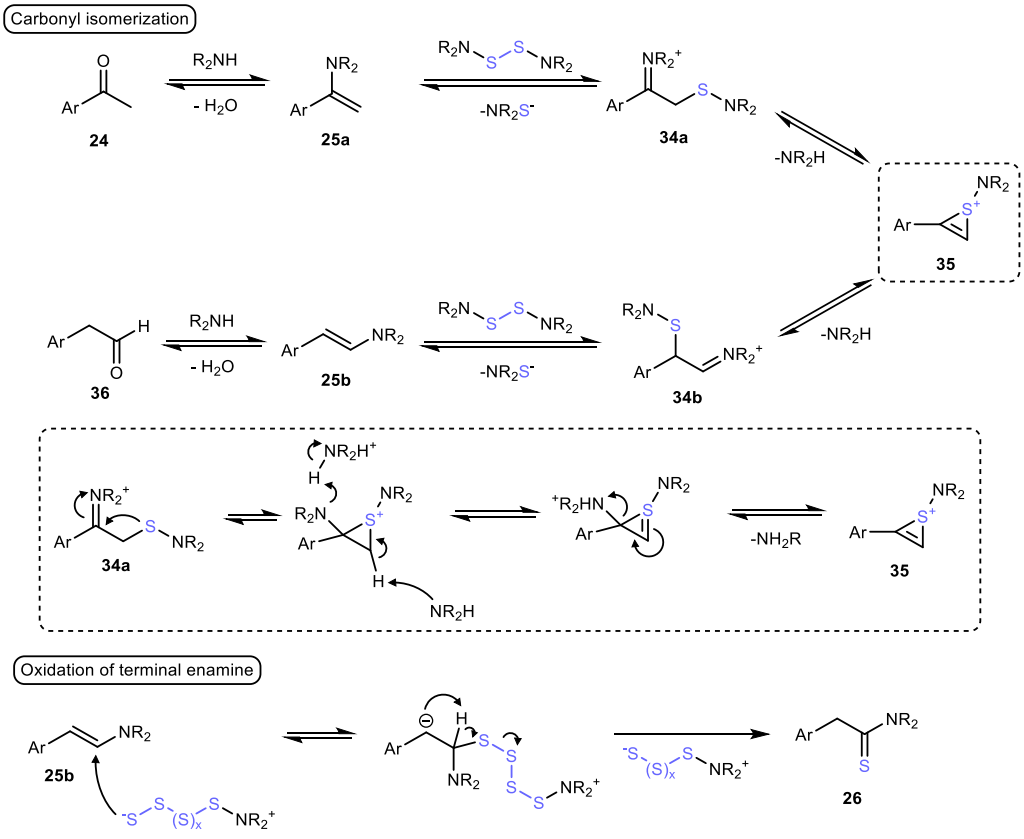
A recent review on the chemistry of the trisulfide radical anion has noted that radical pathways for the Willgerodt-Kindler reaction have not been sufficiently considered, and has suggested a possible involvement of radicals in the pathways, referring to the detection of such species in sulfur solutions of amines [21]. Due to its uniqueness and the ambiguity that clearly still exists in the mechanistic proposals for transformations involving Willgerodt-Kindler-type transformations, all aspects of this interesting reaction merit further investigation.

3.2.2. *Competing reactions to the Willgerodt-Kindler reaction*

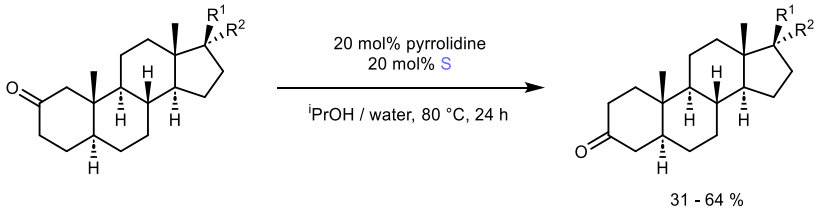
In 2007, Neckers et al. reported a one-pot synthesis of 2-



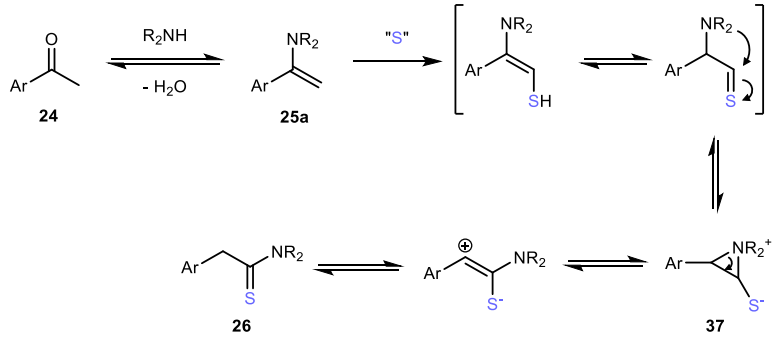
Scheme 22. Willgerodt-Kindler reaction of heptanal **32a**, leading to the recovery of both thioamide **33** and isomeric heptanones **32b-c** (see Ref. [93]).



Scheme 23. The Carmack mechanism of the Willgerodt-Kindler isomerization (see Ref. [92]).



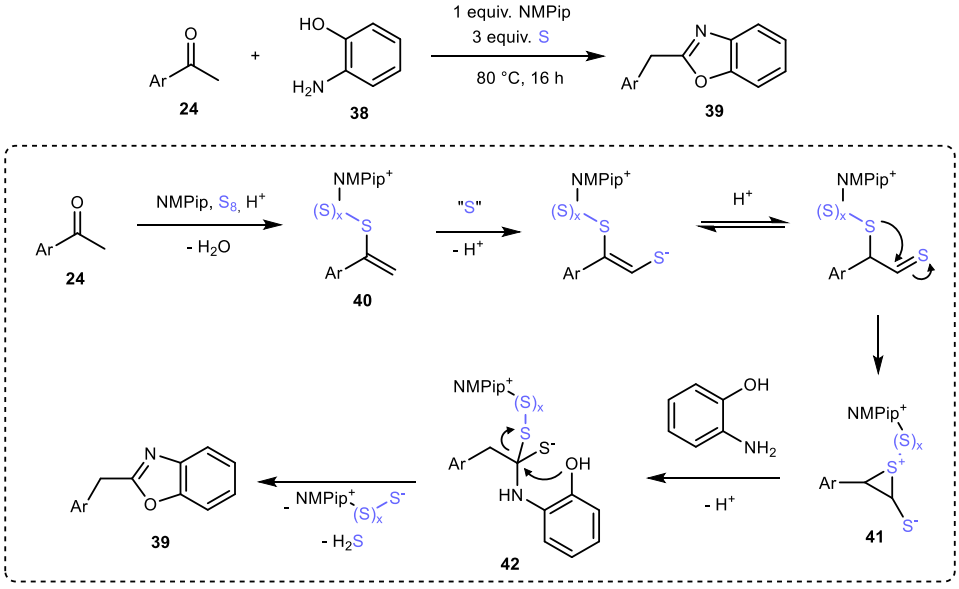
Scheme 24. Isomerization of steroidal ketones conducted by Bhawal, Morandi et al. reported in Ref. [94].



Scheme 25. Willgerodt-Kindler mechanism proposed by Poupaert et al. involving an aziridinium intermediate **37** (see Ref. [95]).

aminobenzothiophenes **44a** from 2-chloro-5-nitroacetophenone **43**, sulfur and amines in DMF at temperatures ranging between 35 °C and 100 °C, using several different bases such as sodium acetate or excess amine [101].

Biehl et al. performed the same reaction under microwave conditions and suggested a mechanism for the transformation, involving Willgerodt-Kindler-type formation of a terminal thioamide **47** from the acetophenone, followed by ring closure via nucleophilic aromatic substitution of the chloride substituent by the thiocarbonyl sulfur (Scheme 27). This is supported by the occurrence of direct S_NAr of amine and



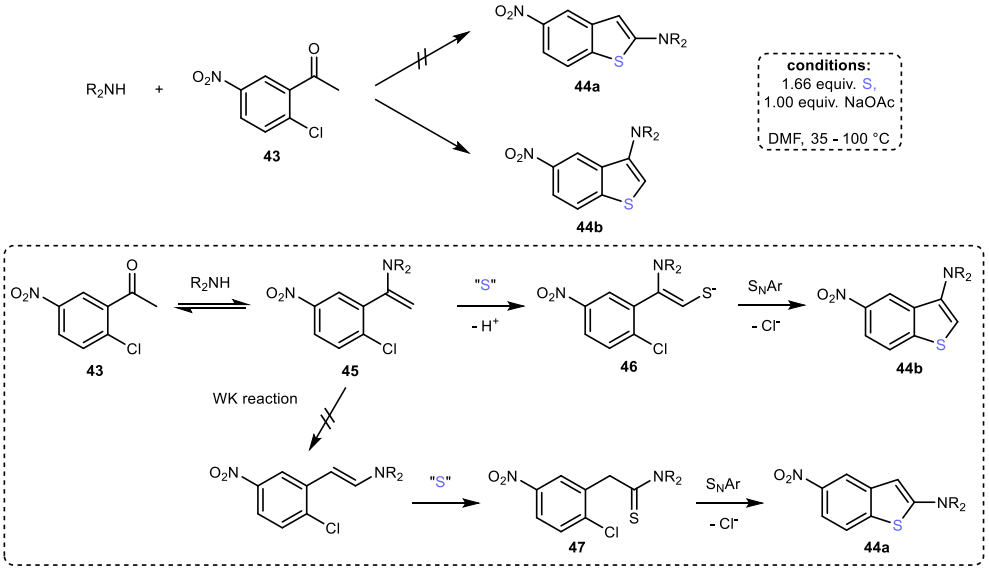
Scheme 26. Benzoxazole (**39**) synthesis from *o*-aminophenol **38**, sulfur and acetophenones **24**, reported by Nguyen et al. along with the proposed mechanism for the transformation (see Ref. [97]).

acetophenone as a side reaction [101,102]. However, in 2010, Androsov et al. reported that the products of the reaction had been incorrectly characterized, stating that the synthesis had yielded the corresponding 3-aminobenzothiophenes **44b** instead [103]. Accordingly, the postulated mechanism was adapted (Scheme 27). It was suggested that enamine **45** reacts with sulfur to form a thiolate in α-position **46** by reaction with elemental sulfur, which quickly undergoes intramolecular S_NAr in favor of the Willgerodt-Kindler isomerization, yielding **44b**.

It is not clear if the Willgerodt-Kindler reaction can occur under the conditions reported by the authors. Neckers reported that using acetophenones lacking the 5-nitro substituent resulted in the formation of a complex product mixture. Biehl reported that under their conditions, such substrates did not react at all. Notably however, their test reactions were performed with primary amines, which reportedly require higher temperatures for the Willgerodt-Kindler reaction [101,102].

A frequently observed side reaction of the Willgerodt-Kindler reaction of methylketones is the competing formation of an α-ketothioamide. In 2004, Darabi et al. reported an investigation on the reactivity of acetone under Willgerodt-Kindler conditions and found that both the terminal thioamide **52** and bis(thioamide), as well as the corresponding ketothioamide **51**, could be generated under certain conditions. Using DMF as solvent, only thioamides were obtained, while in water only ketothioamides were obtained. Notably, under solventless conditions, both thioamides and ketothioamides were observed, which is attributable to formation of water due to enamine condensation [104].

Hence, it was proposed that in the presence of water, the enamine **48** is thiolated in α -position, yielding **49**, followed by nucleophilic attack of amine, forming a thiosemiaminal, which is oxidized to thioamide **50**. The keto group is regenerated by hydrolysis of the iminium function at the central carbon, yielding **51**. Interestingly, the formation of the terminal thioamide **52** without the keto group was proposed to occur via reduction with hydrogen sulfide, instead of a Carmack pathway. However, no studies were performed to support this claim (Scheme 28) [104].



Scheme 27. Synthesis of aminobenzothiophenes **44**, first reported by Neckers et al. in Ref. [101].

In 2012, Valdez-Rojas et al. investigated the use of alternative heating modes for the Willgerodt-Kindler reaction of acetophenone **53**. It was found that using infrared irradiation in addition to heating to 100 °C increased the selectivity towards the ketothioamide **55** compared to the thioamide **54**. Without the additional irradiation, the regular Willgerodt-Kindler products were observed. The observation was attributed to local overheating caused by the IR radiation (Scheme 29) [105].

Very recently, Bolm et al. also observed an unexpected increased selectivity for ketothioamide formation when using ball-milling techniques for the Willgerodt-Kindler reaction of acetophenones. Several mechanistic control experiments were performed, ruling out that ketothioamide is formed from thioamide. Furthermore, the involvement of radicals was ruled out via the use of radical scavengers. Using propiophenone instead of acetophenone resulted in an inseparable product mixture, indicating that the ketothioamide formation proceeds via competing pathways. It was proposed that the enol form **53'** of the ketone is oxidized to an α-thione **56**, which condenses with the amine, yielding an iminium species **57** and hydrogen sulfide. The iminium compound is then postulated to undergo oxidation via nucleophilic polysulfide attack in analogy to the postulated pathways for the regular Willgerodt-Kindler reaction (Scheme 30) [106].

The exact conditions for the preference of this side reaction deserve further investigation. It is known that water hinders the isomerization of the ketone by impeding the formation of enamine. It appears that ketothioamide formation is preferred when using alternative heating modes.

Another reaction involving α-thiolation of an enamine was reported by Nguyen et al. involving the synthesis of quinoxalinethiones **60** and quinoxalines **61** from *o*-phenylenediamine **59**, acetophenones **24** and elemental sulfur, catalyzed by amine bases [107]. It was suggested that an intermediate enamine **62** attacks elemental sulfur, forming an α-aminothione **63** after elimination of a shortened polysulfide, which then undergoes intramolecular attack by the other amino group, forming thiol **64**. The oxidation of **64** to the product thione **60** was suggested to be mediated either by sulfur or the solvent DMSO (Scheme 31). Interestingly, the most effective catalysts for the reaction were amines, such as piperidine, which could theoretically undergo Willgerodt-Kindler reactions themselves with the acetophenone. The authors noted however that no Willgerodt-Kindler product was observed, indicating that the cyclization is favored in comparison.

Notably, quinoxaline **61** was detected as a side product of the reaction, formed via elimination of hydrogen sulfide preceding the final oxidation. It was found that **61** can be generated selectively when employing acid catalysis instead of a base, as well as a smaller amount of sulfur. It was assumed that the acid catalyst promotes the elimination of hydrogen sulfide from intermediate **64**, preventing the final oxidation to the thione **60** [108].

3.2.3. *Other reactions involving imines and enamines*

The Asinger reaction is a four-component reaction between two ketones **65** or aldehydes, ammonia and elemental sulfur, yielding a thiazolines **66**. The reaction was first reported by Asinger et al. in 1957 and proceeds already at room temperature [109]. Asinger found that hydrolysis of the produced thiazoline yielded the reactant ketone in addition to the corresponding α-sulfhydrylketone **67**. Based on this, it was observed that the direct use of sulfhydrylketones **67** instead of sulfur also yielded thiazolines from the reaction with ketones and ammonia.

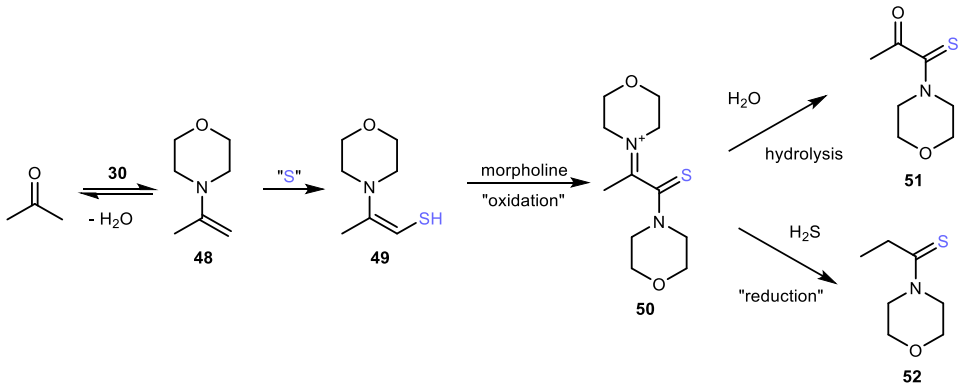
Therefore, Asinger proposed the generation of **67** as the first step of the reaction via thiolation of the enol form. The cyclization was then proposed to occur via condensation of **67** with semiaminal **68**, formed from ketone and ammonia (Scheme 32).

A recent review proposed that the corresponding imine **69** is the active component for the thiolation, yielding an α-sulfhydrylenamine **70**, which condenses with another molecule of imine to form the final product (Scheme 32) [19]. To our knowledge, there have been no further studies on the Asinger reaction to clarify the exact mechanism of the reaction.

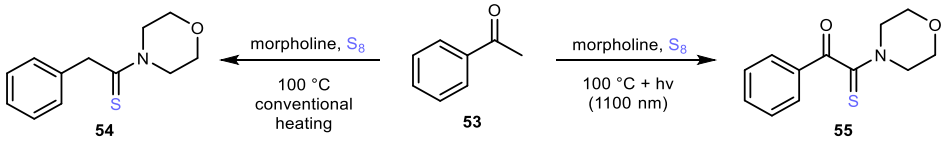
A very interesting observation made by Asinger et al. in their original report is the desulfurization of α-sulfhydrylketones **67** back to their ketones **65** with reformation of elemental sulfur when treated with primary amines or ammonia (Scheme 33) [109]. Secondary amines and tertiary amines were merely commented to result in other reactions of "unknown mechanism". To our knowledge, these transformations have not received any meaningful attention since, and no mechanism was suggested by Asinger.

A series of sulfur-mediated oxidative aromatization reactions involving imine/enamine intermediates was reported by the groups of Nguyen and Deng. In 2017, Nguyen et al. published the synthesis of quinoxalines **72** from cyclohexanones **71** and *o*-phenylenediamines **59** (Scheme 34) [110]. Although no mechanistic study was performed, it was proposed that the C–N bond formation proceeds via thiolation of the intermediate enamine **76**, followed by condensation of the thiolated α-position with another amino group (schematic representation of the mechanism in Scheme 34). As a side product, quinazines **73** were observed, resulting from full aromatization of the cyclohexane ring. A follow-up investigation from 2018 suggests sulfur as the oxidizing agent for the aromatization [111].

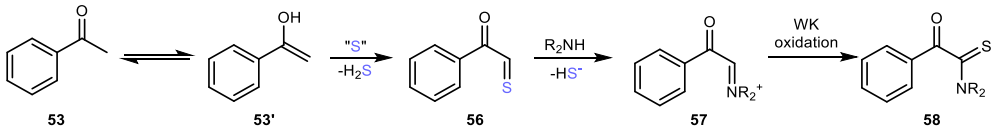
Deng et al. reported similar reactions involving the oxidative aromatization of cyclohexanones **71** with aromatic amines and sulfur, yielding *o*-phenylenediamines **74**, suggesting similar mechanisms (Scheme 34) [112]. A later, separate report features the same reaction under similar conditions, using primary amines with non-primary aliphatic substituents instead [113]. Deng et al. found that an oxygen atmosphere is essential for the oxidative aromatization of the cyclohexane ring to occur, suggesting that elemental sulfur does not



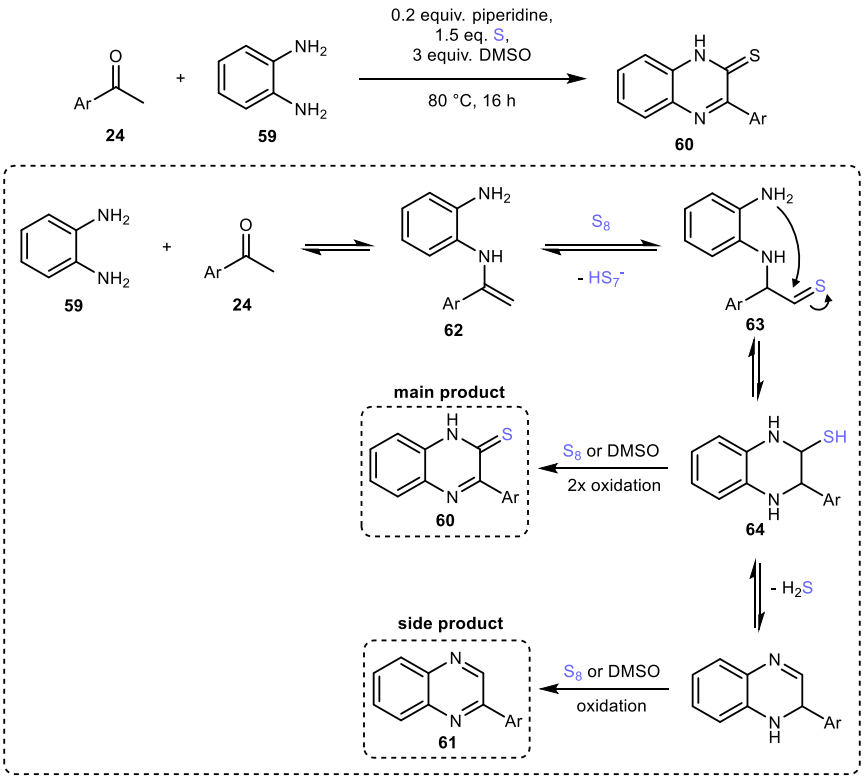
Scheme 28. Pathways proposed by Darabi et al. for the formation of thioamides **52** and ketothioamides **51** from acetone and morpholine/sulfur (see Ref. [104]).



Scheme 29. Preferred formation of ketothioamide **55**, observed by Valdez-Rojas et al., when using IR irradiation as additional heating mode for the WK reaction of acetophenone **53** (see Ref. [105]).



Scheme 30. Mechanism for the α-ketothioamide (**58**) formation proposed by Bolm et al. in Ref. [106].



Scheme 31. Synthesis and proposed mechanism of the synthesis of quinoxaline-2-thiones **60**, reported by Nguyen et al. in Ref. [107].

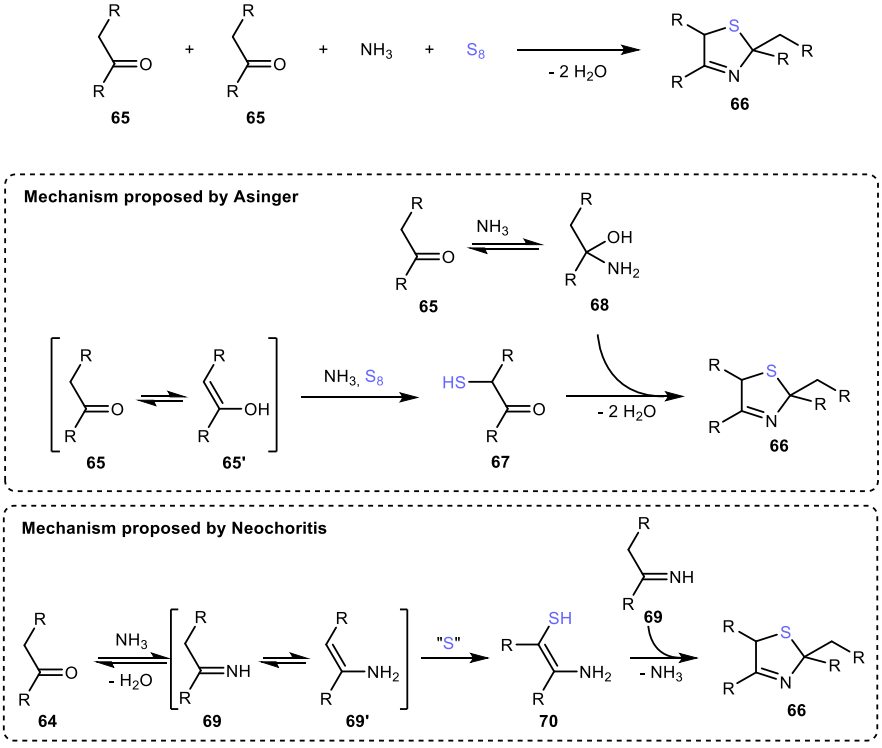
participate in this reaction step. The authors ruled out radical involvement in control experiments with radical scavengers.

Interestingly, the use of amines with primary aliphatic substituents under similar conditions yields imidazoles **75** instead, without any aromatization of the cyclohexane ring (Scheme 34) [114].

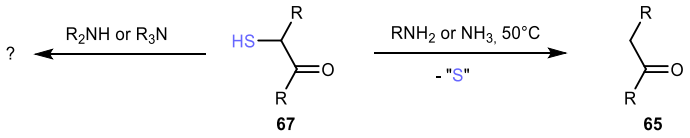
Clearly, the reactions of elemental sulfur with imines and enamines formed from amines and carbonyl compounds can give rise to a variety of different products, even under similar conditions. Mechanistically, it is generally proposed that the enamines act as carbon-centered nucleophiles, which interact with elemental sulfur or other sulfur species formed via the interaction of sulfur with the present amines, forming C–S bonds. We believe that the interesting reactivities observed under these conditions, such as the Willgerodt-Kindler rearrangement or the desulfurization of α-sulfhydrylketones, deserve further investigation.

3.3. Oxidative transformations in activated C–H positions

In many organic transformations involving base-activated elemental sulfur, oxidative transformations at carbon atoms in α-position of electron withdrawing groups are observed. In most cases, this entails the effective replacement of an H-substituent with a thiol function. If the β-position bears H-atoms, the formation of α,β-unsaturated compounds by elimination of hydrogen sulfide are also frequently reported. In some cases, further conversion of the α-thiol to an α-thione is suggested as well (Scheme 35). The substrates for such reactions include for instance the α- and vinylogous positions of carbonyl or cyano functions, as well as benzylic positions. In the following section, we will present several pathways comprising such transformations and discuss the mechanisms suggested by the authors.



Scheme 32. Schematic representation and proposed mechanisms of the Asinger-four component reaction, see Refs. [19,109].



Scheme 33. Desulfurization of α-sulfhydrylketones **67**, observed by Asinger et al. in Ref. [109].

3.3.1. *The Gewald reaction*

The Gewald reaction was first reported in 1966 and is one of the most well-known organic reactions involving elemental sulfur. In its most prevalent form, it is a base-catalyzed three-component reaction between an enolizable carbonyl component **65**, an α-acidic nitrile **77** and elemental sulfur, yielding a 2-aminothiophene **78** (Scheme 36). The Gewald reaction proceeds already at room temperature. The scope of the nitrile component of the Gewald three-component reaction includes highly C–H acidic nitriles such as dicyanomethane, α-cyanoesters, α-cyanoketones or α-cyanoamides [115]. Furthermore, 1,3-diketones have been successfully employed, although higher temperatures were required [116].

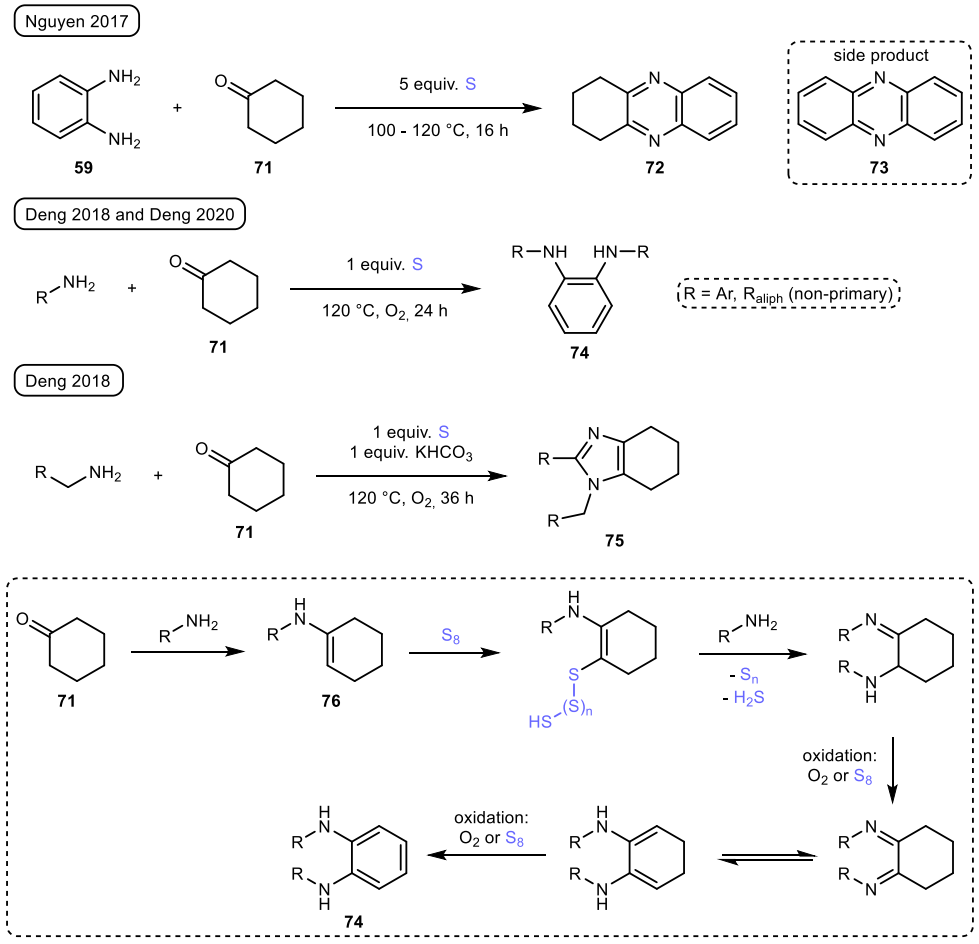
Already in the original manuscript, Gewald reported that the same reaction was possible using α-sulfhydrylketones **67** instead of a ketone and sulfur, indicating that in the multicomponent approach, the α-thiolation of the ketone could be part of the mechanistic pathway. It was also found that the product **79** obtained from the Knoevenagel condensation of the nitrile, more specifically a cyanoacetate, and the carbonyl component, could be reacted with sulfur and base, likewise yielding the aminothiophene product **78** (Scheme 36). In this case, the thiolation occurs at the vinylogous γ-position of the Knoevenagel product. Clearly, the mechanism of the reaction is a combination of both the Knoevenagel condensation and the thiolation, followed by cyclization of the product of these steps, although the order of these transformations remains unclarified to this day (Scheme 37). Gewald proposed that the Knoevenagel condensation occurs first, since higher yields of thiophene were obtained when using presynthesized Knoevenagel products, as opposed to presynthesized α-sulfhydrylketones. Regarding the incorporation of sulfur into the product, no particular pathway was proposed [117].

A review from 2011 suggests that the incorporation of elemental sulfur occurs via γ-deprotonation of the Knoevenagel product, followed by nucleophilic attack of the resulting carbanion on the cyclooctasulfur ring, leading to an octasulfide. Nucleophilic attack of the S_1 position of the octasulfide on the nitrile carbon, followed by extrusion of S_7 was proposed to lead to the final aminothiophene product [115]. Another report employs cyanocyclopropanes **80** as substitutes for the Knoevenagel product, which generates the equivalent γ-carbanion **81** via ring-opening, indicating a possible involvement of this species in the mechanism (Scheme 38) [118].

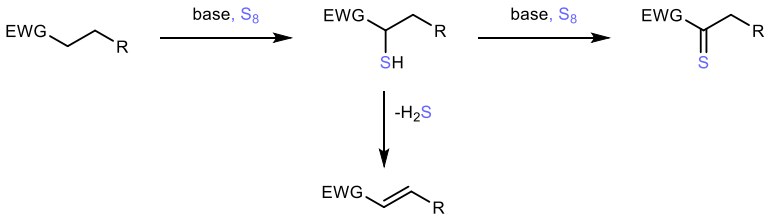
Feroci et al. reported an interesting variation of the Gewald reaction, where the use of amine base was omitted in favor of a cyanomethyl anion, electrochemically generated from acetonitrile prior to the reaction. The Gewald reaction was conducted by first adding sulfur to the cyanomethyl solution, where characteristic color changes for activated sulfur were observed, followed by addition of a presynthesized Knoevenagel adduct **82**. Assuming that the strongly basic cyanomethyl anion completely reacts with sulfur, forming weakly basic polysulfides, it is reasonable to assume that this variation of the Gewald reaction is presumed to initiate via the nucleophilic attack of cyanomethyl polysulfide species on the nitrile carbon, followed by cyclization (Scheme 39) [119].

3.3.2. *Enolates*

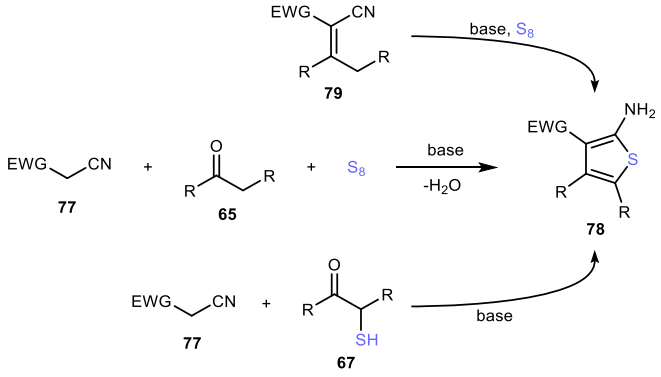
Nguyen et al. reported several Gewald-type syntheses of 5-



Scheme 34. C–N bond coupling reactions and oxidative aromatization reactions reported by the groups of Nguyen and Deng in Refs. [110–114] and schematic representation of the proposed mechanisms.



Scheme 35. General representation of oxidative transformations of activated methylene groups.

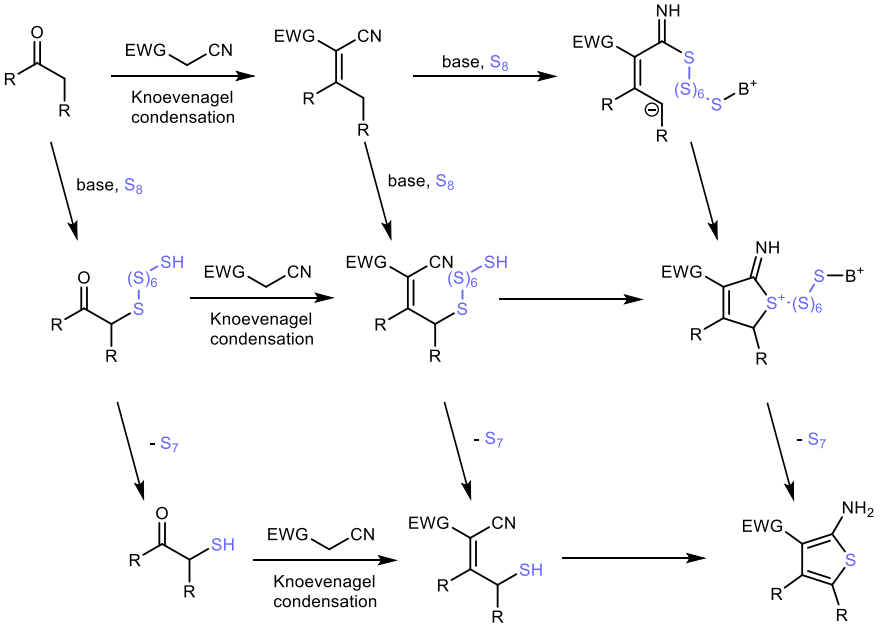


Scheme 36. The different variations of the Gewald reaction.

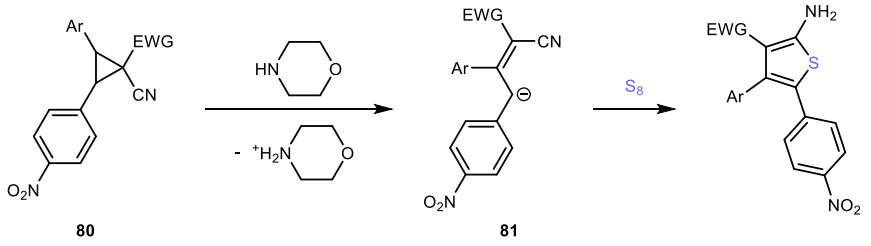
acylsubstituted aminothiophenes using chalcones **83** as replacement for the carbonyl component. In this variation, a Michael addition of the cyano compound **77** is proposed to be the first step of the reaction, yielding a γ-cyanoketone **84**, as identified by control experiments. Variation of the cyano compounds was shown to result in the formation of different products (Scheme 40).

Nguyen et al. have reported several iterations of the reaction with different cyano components, including aryl- and hetarylacetonitriles, cyanoacetates and N-substituted cyanoacetamides [120,121]. In all cases, the reactions required elevated temperatures between 80 and 100 °C and strong bases as catalysts, namely 1,4-diazabicyclo[2.2.2]octane (DABCO) or DBU in loadings between 10 and 20 mol%.

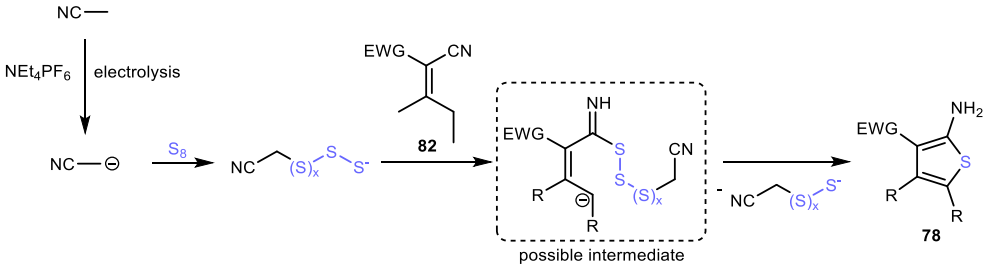
Notably, the Michael addition products **84** obtained in these cases are essentially the α,β-saturated equivalent of a Knoevenagel product obtained during a "regular" Gewald reaction. Still, 2-aminothiophenes **85** are obtained as products, indicating that an additional oxidation



Scheme 37. Schematic representation of the possible orders of the reaction steps of a Gewald-three component reaction.



Scheme 38. Gewald reaction with cyanocyclopropanes **80**, as reported by Yan et al. in Ref. [118].



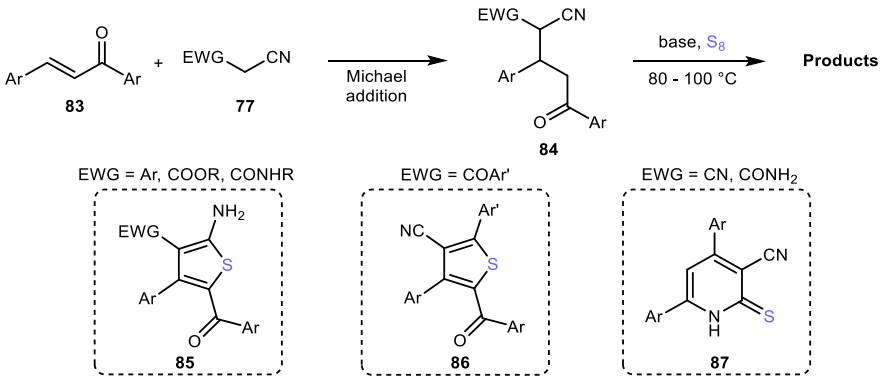
Scheme 39. Gewald reaction with an electrogenerated cyanomethyl anion, reported by Feroci et al. in Ref. [119].

step must take place.

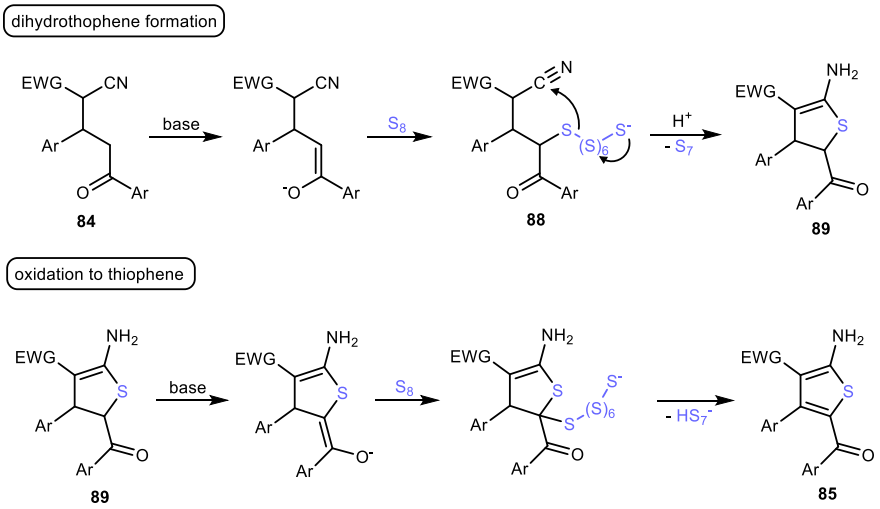
Mechanistically, all reports propose the formation of an enolate by deprotonation of the Michael adduct **84** and its subsequent attack on elemental sulfur, forming an octasulfide in the α-position of the carbonyl group (**88**). This is followed by nucleophilic attack of the polysulfide S^1 position onto the cyano function with concerted extrusion of cyclo-S_7 as in the Gewald reaction, yielding a dihydrothiophene **89**. Oxidation to the final product is postulated via another deprotonation/thiolation sequence at the α-position of the carbonyl function, followed by elimination of a hydrosulfide anion and sulfur, driven by aromatization (Scheme 41).

Interestingly, several other instances of Michael additions to chalcones followed by a sulfur-mediated cyclization have been reported, furnishing different products than Gewald-aminothiophenes.

The groups of Nguyen et al. and Zheng et al. reported essentially the same reaction in 2022, where α-cyanoacetophenones were used as the reactants, both reactions proceeding under similar conditions [122, 123]. The products of the reaction of the Michael adduct with sulfur were 3-cyanothiophenes **86**. The key mechanistic difference here is that the cyclization seems to proceed preferably with the carbonyl group and not the cyano group. Nguyen et al. attributed this to steric repulsion, since the 2-aminothiophenes resulting from cyclization with the nitrile function bear large aromatic substituents at the adjacent 3- and 4-positions. A cyano group hence not being required for successful cyclization, the scope of the reaction was further extended to benzoyl acetate esters. Both groups suggested the same mechanism for the transformation, analogous to the one depicted in Scheme 41. In addition, the group of Zheng excluded the involvement of free radicals in control experiments



Scheme 40. Michael addition of cyano compounds **77** to chalcones **83** and subsequent reactions with sulfur, furnishing different products (**85**–**87**) depending on the nature of the cyano compound.



Scheme 41. Proposed mechanism for the oxidative Gewald reaction of Michael adducts of cyano compounds and chalcones (**84**) (see Refs. [120,121]).

with radical scavengers [123].

Michael adducts of chalcones with other non-cyano–CH–acidic compounds such as 1,3-diketones were also reported to furnish thiophenes under cyclization with elemental sulfur by Adib et al., also including the α-thiolation of the enolate in the mechanistic postulate. In this case however, it was suggested that the unimolecular extrusion of S_7 occurs first, yielding an intermediate thiolate [124].

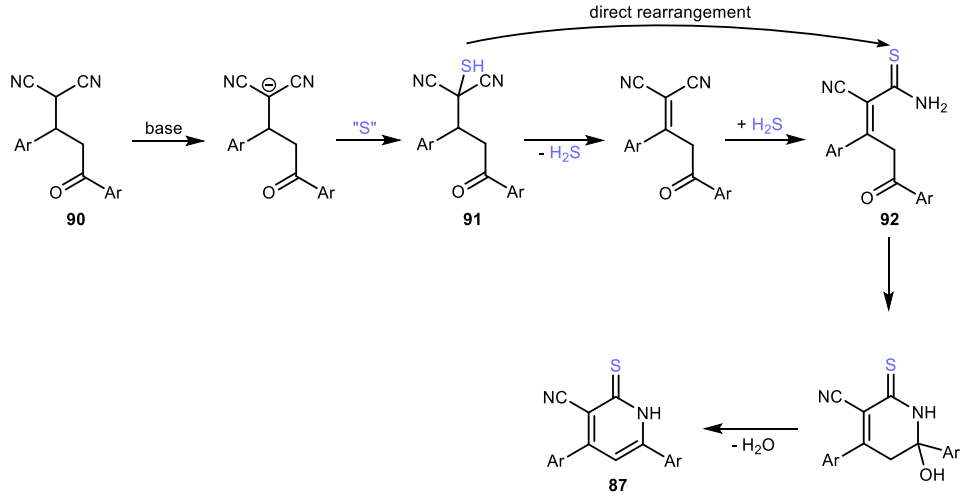
A recurring motif in the proposed pathways of these reactions is that the introduction of sulfur into the molecules is suggested to proceed via enolate formation and subsequent thiolation at the α-position of the carbonyl function. However, for highly activated reactants like cyanoketones, the high C–H acidity of the cyano-substituted carbon in the corresponding Michael adduct **84** likely renders the formation of a carbanion in this position competitive to enolate formation. Indeed, mechanisms entailing thiolation at this position have also been described in the past, leading to different products.

The reaction of the Michael adduct of highly activated dicyanomethane (**90**) with sulfur was investigated by Shestopalov et al., similarly using high temperatures and triethylamine as the basic catalyst. In this case, instead of a Gewald-type cyclization, the formation of a six-membered ring was observed, the isolated product being a pyridinethione **87**. Mechanistically, thiolation of the Michael adduct at the highly acidic cyano-substituted position, yielding **91**, followed by several intramolecular rearrangements and ultimately resulting in the formation of a thioamide **92** was proposed. The product **87** is generated by intramolecular condensation with the carbonyl function (Scheme 42) [125]. Recently, Nguyen et al. reported a synthesis of the corresponding pyridinones by using cyanoacetamide as the reactant instead of dicyanomethane, proposing a similar mechanism [126].

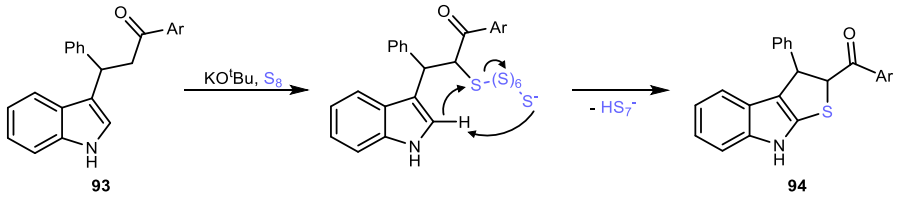
Similar cyclization reactions have also been reported for chalcone Michael adducts with other electron-withdrawing groups in the γ-position, leading to products such as lactones or furans [127,128]. Clearly, a wide variety of Michael adducts of chalcones with electron withdrawing substituents at the γ-position can undergo thermodynamically driven cyclization reactions with elemental sulfur and bases. While in most cases the cyclization is suggested to proceed via thiolation and subsequent intramolecular reaction of the thiolate with an electrophilic group, several instances suggest slightly different pathways.

Liu, Lv and Zhang reported the synthesis of thienoindoles **94** from Michael adducts of indoles and chalcones (**93**), using elemental sulfur and sodium *tert*-butoxide in DMSO at 100 °C. Here it was suggested that the ring closure occurs by nucleophilic attack of the electron-rich C^2-position of the indole at the polysulfide chain during the thiolation step (Scheme 43). In most other cases, it is proposed that the thiolate, resulting as the final monosulfurized product, is the active species in the reaction. A free radical pathway for the reaction was ruled out by the authors in control experiments with the radical scavengers dibutylhydroxytoluene (BHT) and (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) [129].

Several other reactions involving the thiolation of enolates as part of the mechanism have been reported. Adib et al. for instance reported the oxidation of a dihydrofuran **95** to a thiophene **96** by treatment with



Scheme 42. Mechanism for the formation of pyridinethiones **87** from γ-dicyanoketones and base-activated sulfur, proposed by Shestopalov et al. in Ref. [125].



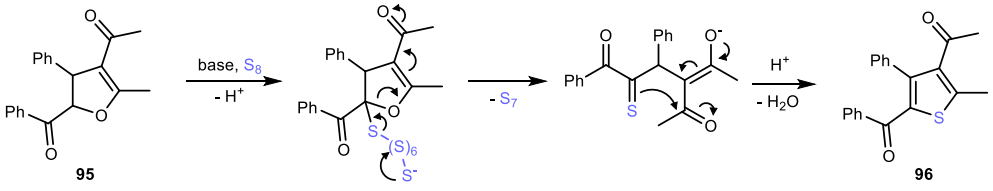
Scheme 43. Oxidative ring closure by intramolecular nucleophilic attack, proposed by Liu, Lv and Zhang in Ref. [129].

sulfur and base in water at 80 °C. Both organic and inorganic bases were effective for this transformation. It was proposed that the reaction proceeds via nucleophilic thiolation of the enolate, opening the furan ring, with subsequent recyclization and water-elimination (Scheme 44). Since the formation of sulfur-centered radicals from elemental sulfur in water is generally not observed, a radical mechanism seems unlikely in this case [130].

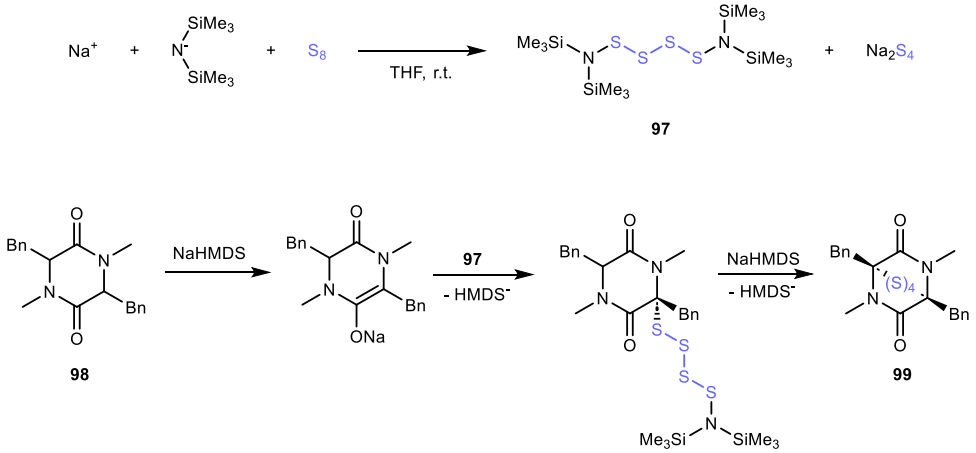
Nicolaou et al. presented a method for the synthesis of 3,6-epidithio-2,5-diketopiperazines in 2012. The first step of this method involved the reaction of 2,5-diketopiperazine **98** with a solution of elemental sulfur and the strong base sodium hexamethyldisilazide (NaHMDS) in THF at room temperature, yielding primarily the epitetrasulfide **99** as the product of the reaction. Control experiments led to the mass-spectrometric identification and isolation of the tetrathiobissilazane **97** in the mixture, which was suggested to be generated from oxidative solvolysis of elemental sulfur and the nitrogen base under simultaneous formation of a tetrasulfide dianion, in accordance with the general mechanism for the interaction of amine bases with sulfur provided in Scheme 3. The corresponding tri- and penta-sulfides were also observed. The presence of polysulfide dianions is further underlined by the observation of a blue color when adding sulfur to the NaHMDS solution. Indeed, substituting elemental sulfur with **97** for the sulfenylation of the diketopiperazine **98** yielded the same product. Hence it was suggested that the tetrathiobissilazane **97** is the active species in the reaction (Scheme 45). The formation of the epitetrathiodiketopiperazine **99** was suggested to take place via initial enolate formation and subsequent substitution of the HMDS groups of the tetrathiodisilazane **97** [59].

Nguyen et al. reported the synthesis of thiocarbonyl compounds from malonic acid derivatives **100**, amines and elemental sulfur, catalyzed by strong organobases such as DABCO (Scheme 46) [131]. The use of unsubstituted malonic acid **100a** resulted in the formation of thioureas **101**, while thioamides **102** were obtained from monosubstituted malonic acids. Disubstituted malonic acid did not react at all, hence it was suggested that C–H deprotonation and subsequent formation of a carbon-centered nucleophile represent the key reactivity. The postulated mechanism entails the formation of a thiocarbonyl function via reaction of trideprotonated malonate **103** with elemental sulfur, followed by elimination of a polysulfide anion. The final product is then generated via successive nucleophilic attack of the amine and oxidative decarboxylation steps. It was found that the reaction is particularly efficient in DMSO, which was attributed to its function as a cooxidant.

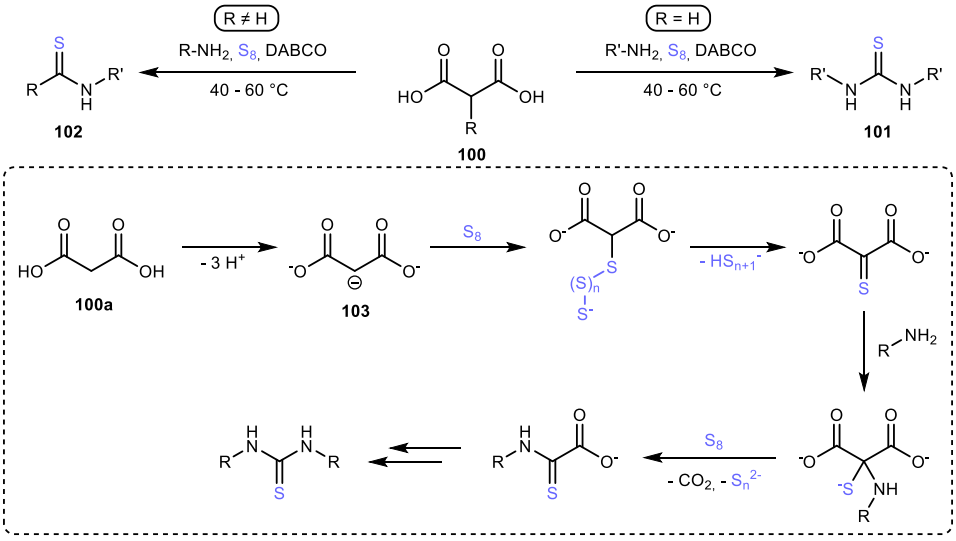
Clearly, all these transformations involve base-assisted thiolation steps at some point in the mechanism. Undoubtedly, the regioselectivity of this thiolation merits further investigation. In this context, the reversibility of the α-thiolation of ketones demonstrated by Asinger et al. described in section 3.2.3, could potentially serve as explanation why it seems that products can only be formed when the α-thiolated position undergoes a follow-up reaction, making it inaccessible towards



Scheme 44. Oxidation of dihydrofurans **95** to thiophenes **96** with elemental sulfur, reported by Adib et al. in Ref. [130].



Scheme 45. Synthesis of epitetrathiopiperazines **99**, reported by Nicolaou et al. in Ref. [59].



Scheme 46. Synthesis of thioamides **102** and thioureas **101** from malonic acid derivatives **100**, reported by Nguyen et al. in Ref. [131].

desulfurization. Steric factors have also been suggested to have great influence on the outcome of such reactions, potentially explaining the large variety of accessible products.

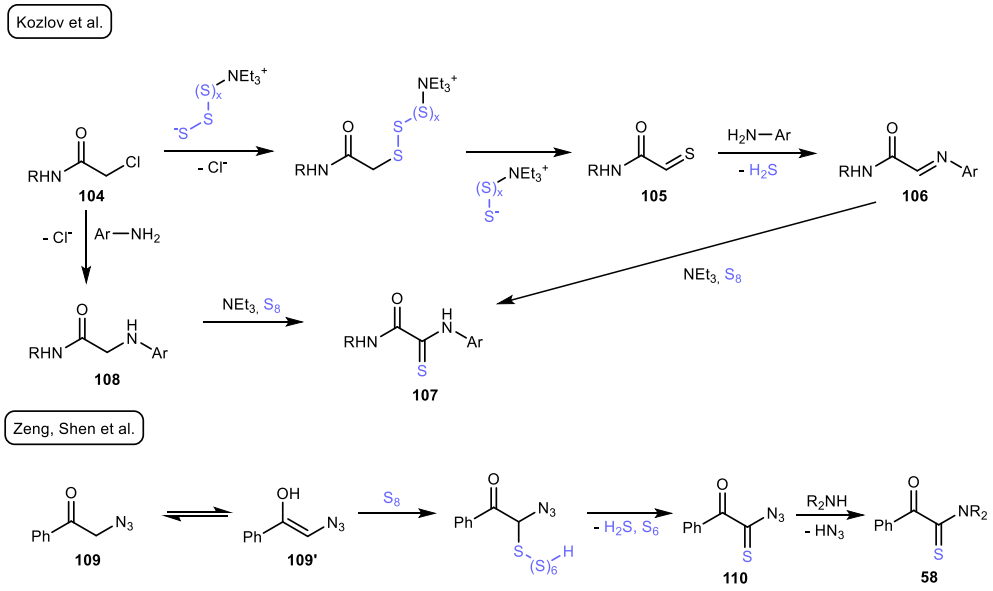
3.3.3. *Carbonyl compounds with α-hetero substituents*

Mayer et al. observed that chloroacetic acid esters and amides react rapidly and exothermically to dithiooxalates when treated with sulfur and triethylamine at room temperature. It was further reported that the resulting dithiooxalates could be further transformed to thioamides by reacting them with amines. No mechanism was proposed for the transformations [132].

Kozlov et al. reported the reaction of *o*-aminophenols and -thiophenols with chloroacetamides **104** and sulfur, yielding benzothiazoles. In their mechanistic postulate, they propose that the chloride is displaced by the nucleophilic, zwitterionic polysulfide generated from NEt_3 and sulfur. Extrusion of a shortened polysulfide and deprotonation yields a thioaldehyde **105**, which condenses with the amino group, yielding an imine **106**. The imine undergoes further oxidation to a thioamide **107**, which condenses with the *o*-thiol substituent, yielding a benzothiazole (Scheme 47, cyclization of thioamide omitted) [133]. However, it was also observed by the authors that the product **108**, resulting from the nucleophilic substitution of the chloride by the amino function, yields the same product upon treatment with sulfur, indicating that this order of reaction is also possible. Furthermore, intermediate formation of a dithiooxalate, which was not considered, is conceivable [132]. Similar transformations were reported by Volkova et al. where biphenylenediamines were reacted with chloroacetamides, yielding diazepines as the products after cyclization [134,135].

Zeng, Shen et al. reported the synthesis of α-ketothioamides **58** from α-azidoketones **109**, sulfur and amines at room temperature, proposing a slightly different mechanism. They propose that the enol form **109'** of the ketone acts as a nucleophile, attacking S_8, followed by concerted release of hydrogen sulfide and cyclo-S_6, yielding a C=S double bond in the α-methylene position (**110**). The final thioamide **58** is then generated by nucleophilic substitution of the azide group with the amine (Scheme 47) [136]. The same transformation has been reported by other groups, instead using α-nitroketones and α-sulfoxonium ylides, under similarly mild conditions, suggesting the same mechanism [137–139].

Viehe et al. reported that methylene groups with a captodative substitution pattern, *i.e.* bearing both an electron-donating and an electron-withdrawing substituent, are especially susceptible to reaction with elemental sulfur. They were able to convert α-acylamines, α-acylhalides and α-acylthioethers to ketothioamides using morpholine and sulfur at room temperature. Although no mechanism was suggested or investigated, captodative substitution patterns are known to stabilize the formation of radicals, potentially indicating the involvement of free



Scheme 47. Different mechanisms for the oxidation of α-(pseudo)halocarbonyl compounds. For the mechanism reported by Kozlov et al. a generic amine is used as representative for the o-aniline derivatives that were used in the report. (see Refs. [133,136]).

radical species [140].

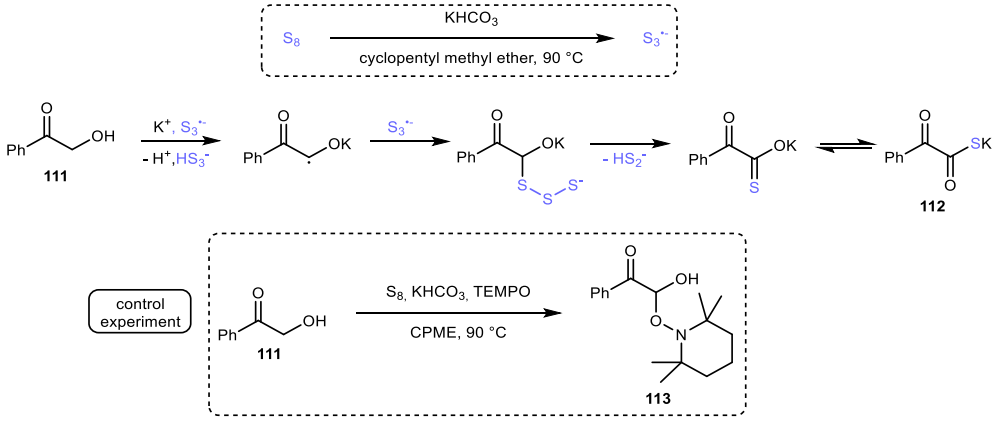
As another example for the oxidation of a captodative methylene compound, the oxidation of α-hydroxyacetophenones **111** with elemental sulfur in the presence of potassium bicarbonate was reported by Wang et al., in 2019 (Scheme 48). In this case, a radical mechanism involving the generation of the trisulfide radical anion was proposed, since a control experiment with TEMPO yielded the coupling product of the supposed α-acyl-radical with TEMPO (**113**). The choices of solvent and base make the generation of $S_3^{\bullet-}$ likely in this case. Hence, it was suggested that the α-methylene-position is oxidized via successive radical H-abstraction and radical recombination with $S_3^{\bullet-}$, finally yielding a thiocarboxylate **112** after elimination of a hydrodisulfide anion. The authors further converted **112** to thioesters via alkylation with alkyl halides [141].

3.3.4. *Benzylic oxidation*

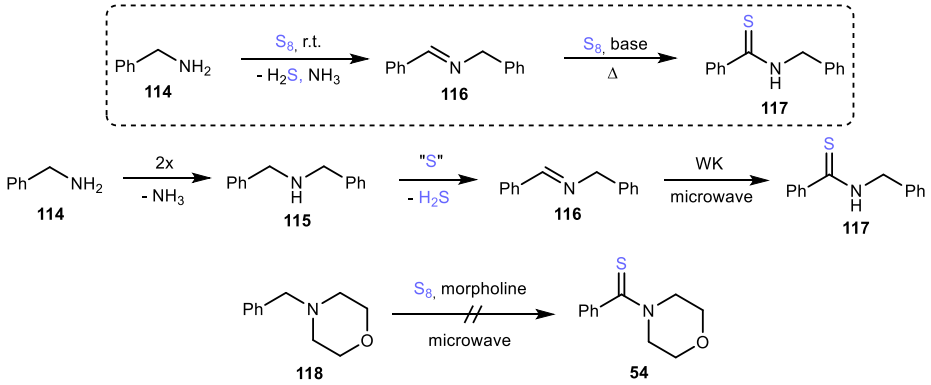
The benzylic position possesses characteristic properties compared to other sp^3-carbon positions due to its increased ability to stabilize radicals, carbocations and carbanions. In many cases, it has been observed that benzylic positions react readily with activated sulfur, resulting in the formation of thiocarbonyl functional groups.

3.3.4.1. Benzylic amines. McMillan et al. observed that benzylamine **114**, when heated with elemental sulfur to 185 °C, selectively forms *N*-benzylthiobenzamide **117** [142]. Aghapoor et al. further investigated these findings and reported that a reaction between benzylamine and sulfur already occurs at room temperature, forming *N*-benzylidenebenzylamine **116** and releasing ammonia and hydrogen sulfide. They proposed that the initial step involves homocondensation of benzylamine to dibenzylamine **115**, which forms the imine **116** after benzylic thiolation and H_2S elimination. They further found that **116** was converted to the thioamide **117** under microwave heating with sulfur, which is equivalent to the final step of the Willgerodt-Kindler reaction (Scheme 49). It was noted by the authors that the formation of an imine seems essential, since *N*-benzylmorpholine **118** did not form the corresponding thioamide **54** under their conditions [143].

Nguyen et al. reported that the oxidative homocoupling of benzylamine **114** to *N*-benzylthiobenzamide **117** was still feasible at temperatures of 110 °C, achieving almost full conversion after 16 h. Using 2-phenethylamine **119**, they also observed formation of the corresponding homocoupled thioamide **121**, although higher temperatures of 150 °C were required, illustrating the particular reactivity of the benzylic position. Due to these different reactivities, a synthetically useful cross-coupling was established between benzylamines and non-



Scheme 48. Radical mechanism for the α-thionation of hydroxyacetophenones **111**, proposed by Wang et al. in Ref. [141].



Scheme 49. Synthesis of thiobenzamide **117** from benzylamine **114** via benzylideneimine **116**, reported by Aghapoor et al. in Ref. [143]. N-benzylmorpholine **118** was not oxidizable to the thioamide.

benzylic amines, yielding a wide range of thioamides. It was noted that benzylic amines bearing electron-withdrawing substituents reacted more efficiently (Scheme 50).

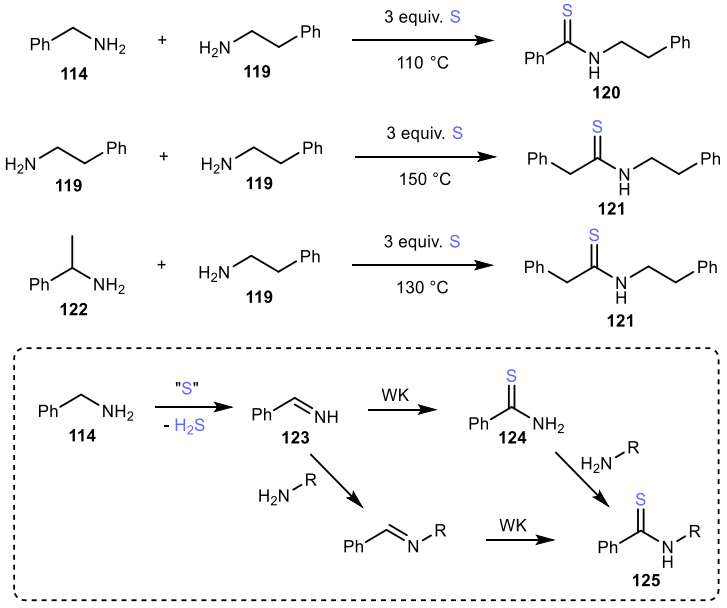
A mechanism was proposed, suggesting oxidation of benzylamine to benzylideneimine **123** as the first step. From the imine, two main pathways to the product were proposed, the first involving oxidation of **123** to thioamide **124**, followed by *trans*-thioamidation, yielding **125**. The second pathway involves alkylation of the imine **123**, followed by oxidation to thioamide **125**. Both pathways are driven to the cross-coupled products by continuous oxidation of the benzylic amine, removing it from the equilibria (Scheme 50) [144]. The involvement of an imine is supported by the fact that 1-phenethylamine **122** yielded 2-phenylthioacetamides **121**, indicating an intermediate Willgerodt-Kindler rearrangement, which requires imines to be formed (Scheme 50). Radical pathways were not considered [144].

Nguyen further expanded the synthetic utility of the reaction by applying aromatic amines bearing nucleophilic *o*-substituents, such as amino, alcohol or thiol groups, resulting in a cyclization of the intermediate thioamide to yield benzazoles. Interestingly, 2-aminothiophenol underwent the characteristic thiol oxidation to a trisulfide. Still, benzothiazoles could be obtained using the trisulfide as the reactant [145].

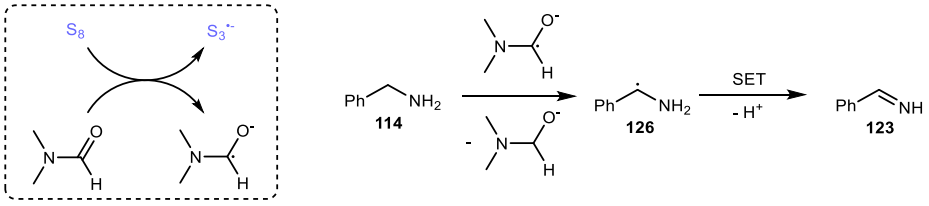
Wang and Wei et al. provided further insight into the oxidation of benzylic amines into imines, suggesting the involvement of radicals when the reaction is carried out in amide-based solvents such as DMF or *N,N*-dimethylpropyleneurea (DMPU). It was reported that radical anions can be formed from the interactions of amide solvents and sulfur or sulfide salts at elevated temperatures of 90 °C, also forming trisulfide radical anions (Scheme 51). The radical pathway was further underlined by control experiments with radical scavengers.

It was suggested that benzylic amines are oxidized to the imine by radical H-abstraction, forming a benzyl radical **126**, followed by single-electron-transfer, yielding the imine. DFT calculations further reinforced the particular character of the benzylic position, indicating that radical H-abstraction is exergonic for benzylic substrates. For non-benzylic positions, it was found that radical formation is both endergonic and kinetically disfavored via a higher activation barrier [146]. Furthermore, the involvement of the $S_3^{\bullet-}$ in the Willgerodt-Kindler oxidation of imines to thioamides was suggested in this report.

3.3.4.2. Benzylic methyl functions. Nguyen et al. reported that picolines **128** undergo oxidation of their benzylic methyl group in their described synthesis of benzothiazoles **129** using *o*-chloronitrobenzene **127** and sulfur at 120 °C [147]. This reaction also involves the reduction of the aromatic nitro group, which will be discussed in more detail in section 3.7. Control experiments under omittance of sulfur or picoline only



Scheme 50. Homo- and cross-couplings of amines with benzylic amines to thioamides, reported by Nguyen et al. in Ref. [144].

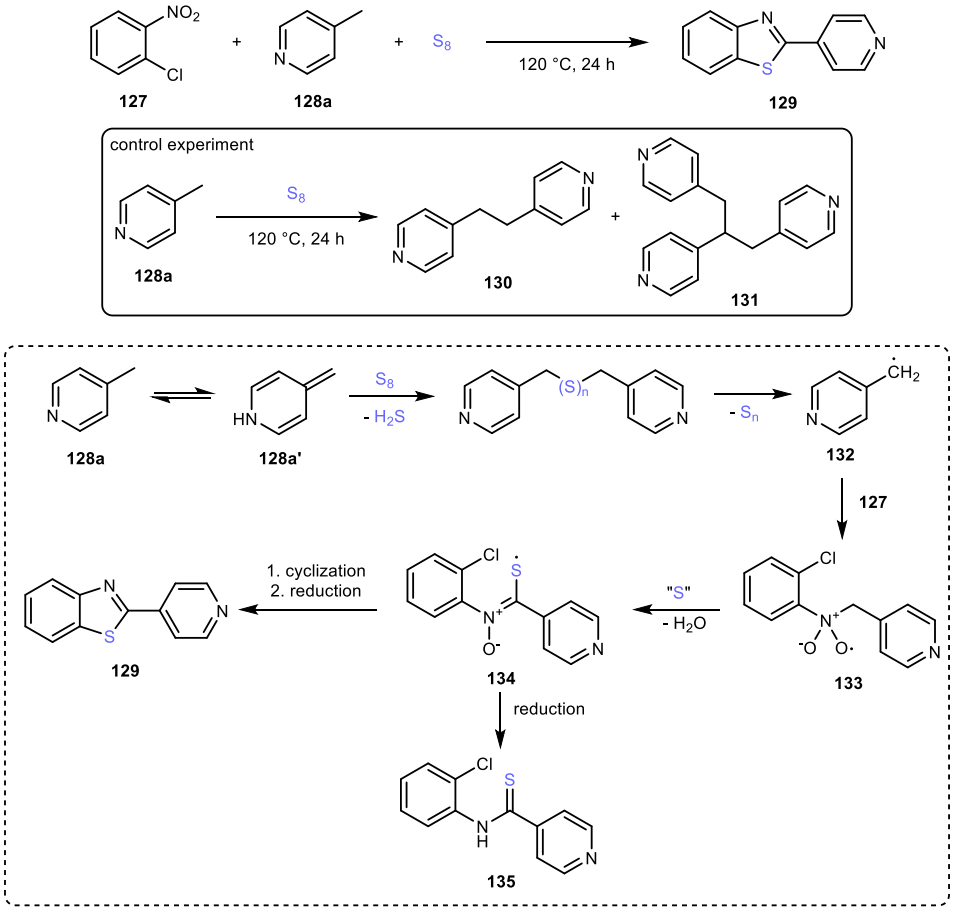


Scheme 51. Radical mechanism for the benzylic oxidation of amines to imines, suggested by Wei et al. in Ref. [146].

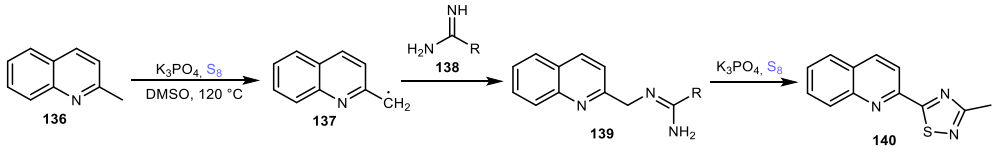
resulted in the recovery of the starting materials. The control experiment of reacting 4-picoline **128a** with sulfur resulted in the formation of oxidative coupling products bis(4-picolyl) **130** or 4-(bis(4-picolyl) methyl)pyridine **131**. Furthermore, using the corresponding *o*-amino-chlorobenzenes did not result in the formation of product, indicating that the nitro group is essential for the coupling. Based on these observations, a radical mechanism was proposed by the authors, entailing the formation of the benzylic radical **132** from the picoline reactant via sulfurization and elimination of hydrogen sulfide. Notably, this reaction was only successful for 2- and 4-picolines, which was attributed to the enamine character of the methyl groups due to conjugation with the nitrogen atom. The benzylic radical **132** was proposed to be trapped by the nitro group, resulting in the formation of **133**. In the next step, the incorporation of another sulfur atom in the benzylic position is proposed, yielding thiyl radical **134**. The product is generated via cyclization with the aromatic halide, followed by reduction of the *N*-oxide function. The formation of a thioamide side product **135**, which results from premature reduction and cannot undergo the cyclization to the benzothiazole, was observed in some cases (Scheme 52) [147].

A radical mechanism was further supported by Huang and Deng et al. in their synthesis of thiadiazoles **140** from methylquinolines **136** and amidines **138**. It was found that the reaction is inhibited by radical scavengers. The authors proposed that their reaction proceeds via oxidative coupling of the quinolyl radical **137** with the amidine, yielding a benzylated amidine **139**, followed by thiolation of the other amidine nitrogen and cyclization (Scheme 53). Although no comment was made about the nature of the involved sulfur species, the reaction conditions are favorable for the formation of sulfur radical anions [148]. Cheng et al. modified the synthesis by employing an aryl halide instead of a methylquinoline, hence generating the intermediate benzylated amidine in an S_N reaction [149].

Nguyen et al. expanded the scope of the sulfur-based reactions of *N*-methylhetarenes by directly coupling them with amines, forming thioamides **142**. In this case however, no radical mechanism was suggested. Instead, it was proposed that a thioaldehyde **141** is formed by successive enamine thiolations. The thioamide **142** is formed via attack of the amine and subsequent oxidation, mediated by either elemental sulfur or DMSO (Scheme 54). Interestingly, it was found that an acidic additive



Scheme 52. Synthesis of benzothiazoles **129** via radical nitro-methyl-coupling, reported by Nguyen et al. in Ref. [147].



Scheme 53. Synthesis of thiadiazoles **140** from methylquinolines **136** and amidines **138** via a proposed radical mechanism.

was required when using aliphatic amines. The less strongly basic aromatic amines formed the thioamides without an acidic additive. However, no suggestions regarding the involvement of the acid in the mechanisms were made [150].

During their investigations on the reduction of aromatic nitro compounds with elemental sulfur to amino groups (see section 3.7), Oae et al. discovered that the reaction of *p*-nitrotoluene **143** with sulfur in liquid ammonia yielded not only the expected *p*-toluidine **144**, but also substantial amounts of *p*-cyanoaniline **145** (Scheme 55) [151]. The cyano group was apparently formed via benzylic oxidation of the methyl group in the presence of ammonia. To our knowledge, no further reports about this reactivity have been made since.

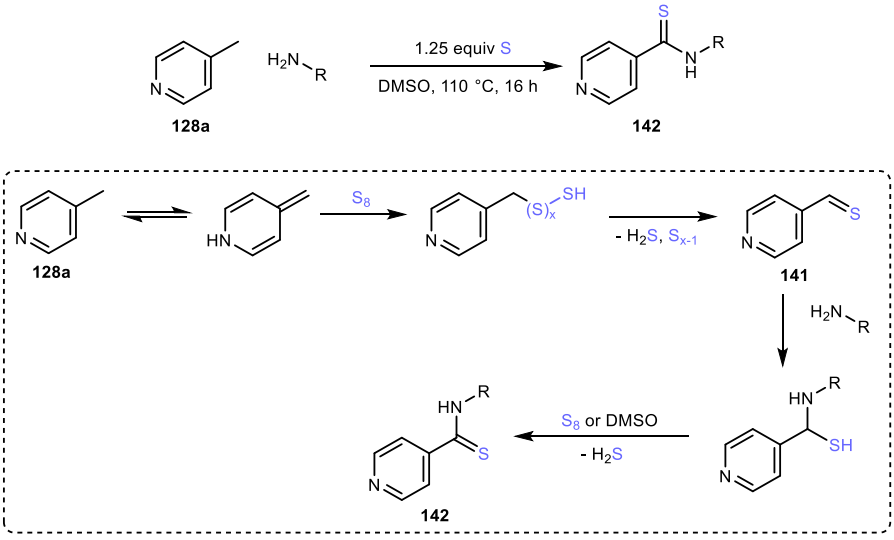
3.3.4.3. Other benzylic substrates. Mayer et al. reported that benzyl chloride readily reacts with sulfur in the presence of triethylamine, forming dithiobenzoates under mild conditions. As a side reaction, alkylation of the dithiobenzoates by unreacted benzyl chloride was observed. It was further observed that the reaction proceeds more efficiently with benzyl chlorides bearing electron-withdrawing substituents. No mechanism was suggested for the transformation [132].

Masson et al. used benzyl sulfones **146** under similar conditions in order to prevent the competing self-alkylation reactions, also obtaining dithiobenzoates **151** as the products [152]. It was found that stronger bases than triethylamine, such as DBU or KO^{t}Bu, mediated the reaction more efficiently, allowing it to proceed at room temperature. Hence, the authors suggested the C–H acidity of the benzylic position as the key factor for this reaction, proposing the formation of a benzyl anion **147** as the first step of the reaction. Subsequent reaction of the benzylic anion with sulfur results in the formation of a polysulfide anion **148**. In a test reaction with methyl iodide, the authors were able to detect the methylthiolated species **149**, supporting this mechanism. Further deprotonation and thiolation results in **150**, which yields the dithiocarboxylate **151** after elimination of a sulfinate (Scheme 56). Alternatively, the elimination of the sulfinate at other points in the mechanism, yielding benzylidene carbenes, was suggested [152].

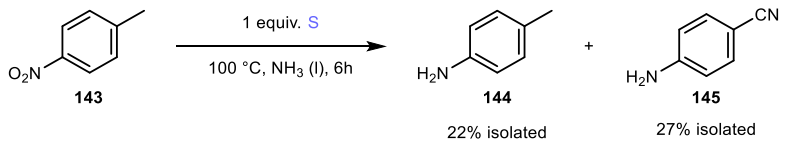
Zhou et al. reported the formation of thioamides **154** from benzylic halides **152** using formamides as the amine source, mediated by overstoichiometric amounts of inorganic bases [153]. The direct use of amines was found to favor the formation of the benzylated amine via S_N2 reaction, which was not further oxidizable to the thioamide under their employed conditions. The authors further stated that the combination of benzyl chloride and NaOH/sulfur did not yield any product, which is unexpected given the earlier reports by Mayer and Masson [132,152]. Backed by quantum chemical calculations, the following mechanism was proposed. Benzyl halide is deprotonated in the benzylic position by the base, followed by the formation of a heptasulfide anion **153** from an "S_7 cluster". The thioamide **154** is generated by subsequent displacement of the chloride by the formamide, followed by elimination of a shortened anionic polysulfide and decarbonylation of the formamide (Scheme 57) [153].

Although the DFT calculations demonstrated this pathway to be energetically favorable, it is in our opinion highly questionable, since it fails to address several critical issues. First, the benzylic position is highly activated towards S_N2 reactions, making benzylic halides susceptible to rapid hydrolysis in the presence of hydroxide ions. The generation of benzyl alcohol from hydroxide and benzyl halide has however not been considered in the described calculations. Secondly, only neutral sulfur clusters of varying sizes were investigated for the pathway. The involvement of polysulfide anions or radicals was not considered. Given the nature of the employed bases and the reaction conditions, the formation of radical species is likely [153].

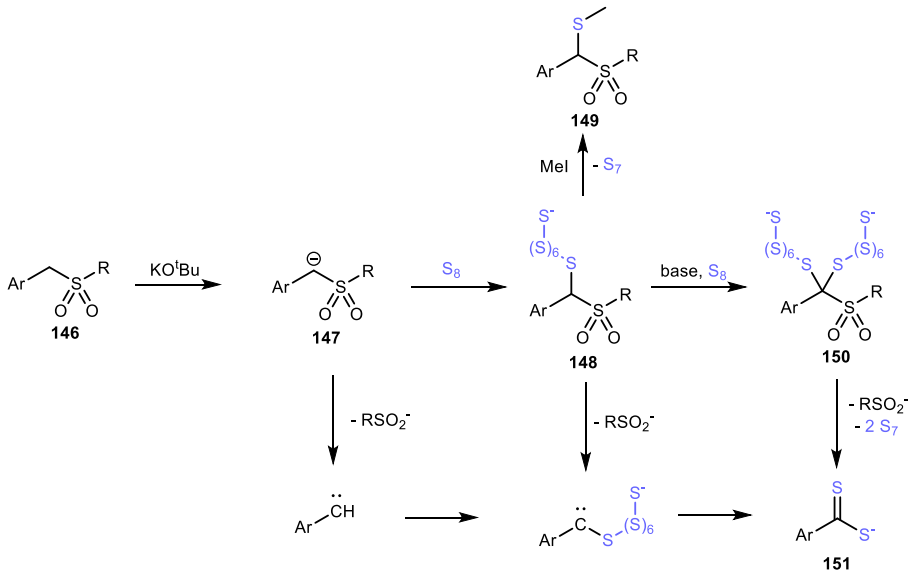
The same group published another report of the synthesis of thioamides, using benzyl alcohols as the substrates. Aliphatic alcohols did not react under these conditions. It was found that benzyl formate could be generated from benzyl alcohol and formamides under the reaction conditions. Indeed, using formate esters as the substrates instead of alcohols, it was possible to expand the scope of the reaction to aliphatic substrates. This suggests the intermediate formation of formate esters from the benzyl alcohols during the pathway. Hence, we propose that



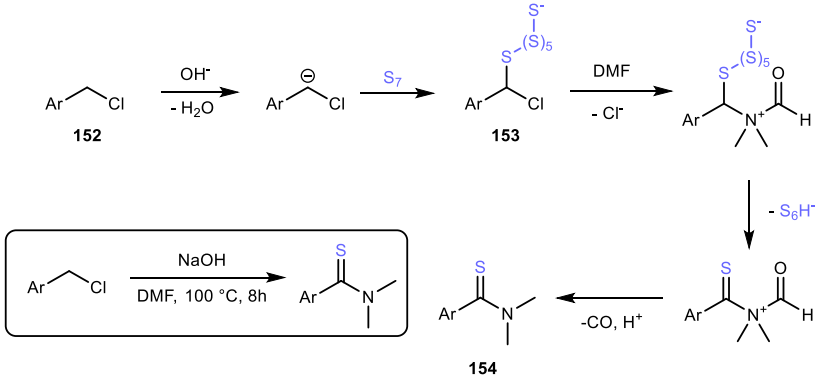
Scheme 54. Proposed non-radical mechanism for the synthesis of thioamides **142** from picolines **128** and amines, reported by Nguyen et al. in Ref. [150].



Scheme 55. Formation of cyanoaniline **145** during the reaction of *p*-nitrotoluene **143** with elemental sulfur via oxidation of the methyl function, reported by Oae et al. in Ref. [151].



Scheme 56. Proposed mechanism for the formation of dithiobenzoates **151** from benzyl sulfones **146**, reported by Masson et al. in Ref. [152].

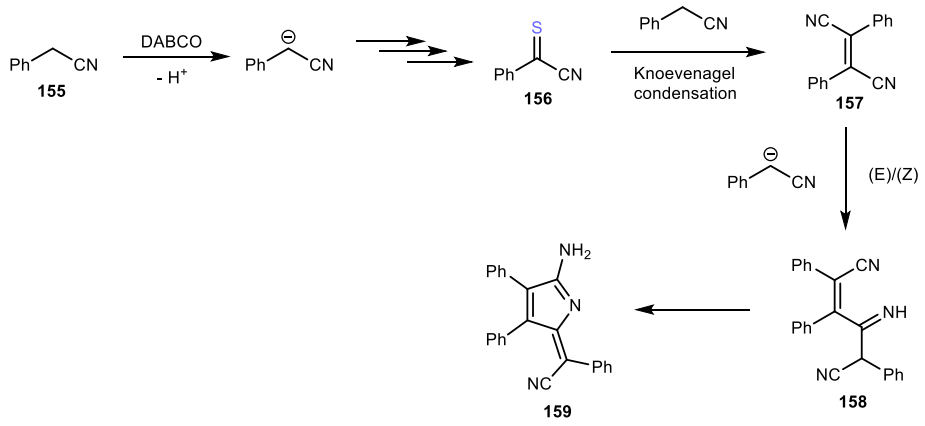


Scheme 57. Proposed mechanism by Zhou et al. for the synthesis of thioamides **154** from benzyl halides **152** and DMF (see Ref. [153]).

the formation of an intermediate formate ester may potentially be involved in the aforementioned synthesis of thioamides from benzyl chlorides (Scheme 57), either via its hydrolysis to the alcohol, or via direct reaction with DMF [154].

While investigating Gewald-type reactions with phenylacetonitriles **155** (compare Scheme 40), Nguyen et al. discovered that they react with elemental sulfur and bases in an oxidative trimerization reaction, catalyzed by DABCO, forming 2-aminopyrroles **159**. Weak bases such as pyridines were not effective in this transformation, also suggesting that the benzylic deprotonation may play a role. Control experiments indicated that this reaction worked exclusively with phenylacetonitriles **155** under the reported conditions. Hence, it was proposed that the methylene group of **155**, highly activated by the benzylic character and the electron-withdrawing cyano function, is oxidized to a thione **156** by successive deprotonation/thiolation (Scheme 58). Subsequent Knoevenagel condensation with another nitrile furnishes **157**. This is followed by nucleophilic attack of a third nitrile anion, yielding **158**, which undergoes intramolecular cyclization to yield the final pyrrole product **159**. The authors suggested a possible involvement of DMSO as cooxidant. The involvement of radicals was not considered or investigated. Interestingly, phenylacetonitriles bearing electron-donating substituents resulted in higher yields, which is slightly unexpected because this would lower the C–H acidity of the methylene function, which seems to play an important role in all suggested mechanistic steps. This indicates that a captodative substitution pattern, which would facilitate radical formation, might potentially be beneficial for the reaction [155].

Aghapoor et al. found that subjecting benzyl thiol to Willgerodt-Kindler conditions with morpholine also resulted in the formation of the corresponding thiobenzamide. However, no mechanism was



Scheme 58. Proposed mechanism for the oxidative trimerization of phenylacetonitriles **155** (see Ref. [155]).

proposed [152]. Nguyen et al. have further elaborated the synthetic utility of this reaction, discovering that both benzylic thiols, as well as the corresponding bis(benzyl) disulfides **160** could be converted to thiobenzamides with a variety of different amines. Weakly basic anilines required the additional use of *N*-methylpiperidine as a basic catalyst. Hence, the oxidation of the thiol to the disulfide, mediated by elemental sulfur, was proposed as the initial step. Aliphatic thiols and disulfides did not react under these conditions. As the second step, it was proposed that the disulfide undergoes oxidative cleavage into thiobenzaldehyde **151**, which reacts to thioamide in a Willgerodt-Kindler type oxidation (Scheme 59). Interestingly, only catalytic amounts of elemental sulfur were required (25 mol%), and the reaction worked exclusively in DMSO. It was suggested that DMSO acts as a cooxidant, reoxidizing the reduced sulfur species to elemental sulfur, simultaneously generating dimethyl sulfide. It is indeed known that DMSO can act as an oxidizer towards sulfide ions, forming oxidized sulfur species, such as the trisulfide radical anion [21]. The involvement of radical species in the benzylic oxidation was not considered [156].

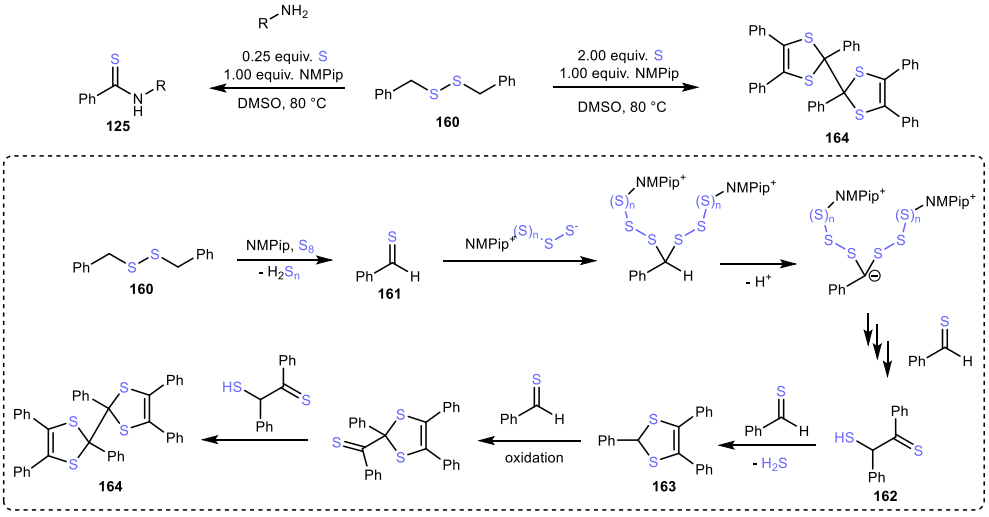
Exposing dibenzyl disulfides **160** to elemental sulfur activated by *N*-methylpiperidine in the absence of an amine coupling partner was found to result in the selective formation of a hexabenzylidyne tetrasulfide **164**. The same product could also be obtained using phenylacetic acids instead of disulfides, suggesting that dibenzyl disulfides are formed *in situ* from phenylacetic acids when exposed to sulfur and base [157]. The suggested mechanism of this transformation similarly involves the *in situ* formation of thiobenzaldehyde **161**. As a possible pathway to the product, it was proposed that dithiobenzoin **162** is formed via a Corey-Seebach type umpolung of a thiobenzaldehyde, effected by nucleophilic attack of an NMP-polysulfide zwitterion and deprotonation. Dithiobenzoin **162** is then suggested to condense with another molecule of thiobenzaldehyde, releasing hydrogen sulfide to yield dithiole **163**. The oxidative dimerization of **163** was suggested to occur via deprotonation and addition to another molecule of thiobenzaldehyde, which after oxidation condenses with another dimer **162**, forming the product **164** (Scheme 59). Alternatively, the involvement of radical species was suggested.

Clearly, methylene groups activated by the presence of electron-withdrawing groups, captodative substitution patterns or aromatic substituents readily react with elemental sulfur in C–H functionalization reactions to a wide range of potential products. There is indication for both nucleophilic and radical mechanisms to be involved in these transformations. The sometimes ambiguous reports regarding the reactivity of certain substrates, such as benzylic halides, warrant further investigations.

3.4. Oxidative transformations of carbon-carbon multiple bonds

3.4.1. Alkynes

3.4.1.1. The Alkyne-Willgerodt-Kindler reaction. Carmack et al. reported



Scheme 59. Proposed mechanism for the benzylic oxidation of dibenzyl disulfides **160**, yielding intermediate thioaldehydes **161**, which react with amines to form thioamides **125**, or undergo homo-hexamerization towards hexabenzylidyne tetrasulfides **164** (see Ref. [157]).

that terminal aliphatic and aromatic alkynes react with morpholine and sulfur under Willgerodt-Kindler conditions, yielding the corresponding terminal thiomorpholides [158,159]. It was proposed that the electron-rich triple bond reacts with morpholine octasulfide, forming the same thiirenium intermediate **167** that is proposed as part of the mechanism of the Willgerodt-Kindler reaction of ketones (compare Scheme 23), thus producing the thioamide in an analogous mechanism (Scheme 60) [92].

Nguyen et al. further elaborated the synthetic methodology, achieving the reaction at significantly lower temperatures of 60 °C for a wide range of primary and secondary amines [160]. Interestingly, also internal aliphatic alkynes were demonstrated to react to terminal thioamides **166** at 100 °C, indicating that a Willgerodt-Kindler isomerization is also possible with alkynes. Control experiments further indicated that in the absence of either reactant, no reaction occurred, suggesting that hydroamination or thiolation of the alkyne are not involved in the pathway. The authors proposed a mechanism involving the nucleophilic attack of an aminopolysulfide formed from amine and sulfur on the terminal alkyne carbon, yielding an enethiol derivative **168**, which undergoes further nucleophilic attack by the amine to yield a thiosemiaminal **169**. The thioamide **166** is formed via proton shift and elimination of a shortened polysulfide (Scheme 61).

Recently, the scope of the synthesis was further expanded to aromatic amines, which require the presence of a strongly basic catalyst such as DBU or DABCO [161]. In this report, a control experiment with alkyne **165** and sulfur in the absence of amine resulted in the formation of a 1,3-dithiole **172** via sulfurative dimerization of the alkyne (*vide infra*). Hence, the proposed mechanism was suggested to involve the formation of an intermediate thioketene **171** via extrusion of a shortened polysulfide in an earlier step (Scheme 62).

Interesting reactivities were observed when *o*-phenylenediamine **59** was used as substrate for the reaction with alkynes. Gan reported that the reaction of *o*-phenylenediamine **59** with sulfur and phenylacetylene **173** in DMF at 110 °C results in the formation of a benzimidazole **176**, which was attributed to the condensation of the *o*-amino substituent with the intermediate thioamide **175** [162]. Nguyen et al. have observed that performing the reaction in DMSO at 80 °C with catalytic amounts of DABCO results in the formation of a quinoxaline-2-thione **60** [163]. It was reported that the use of DMSO was essential for this reaction to occur, otherwise the formation of benzimidazole **176** is observed. It was proposed that the enethiol intermediate **174** of the pathway is stabilized via hydrogen bonding with the *o*-amino substituent, enabling it to be further thionated in the α-position, leading to the favored formation of a six-membered ring. Since it is essential for the reaction, DMSO was proposed to potentially play a role in this oxidation step (Scheme 63).

3.4.1.2. Formation of thio-ynolates from terminal alkynes. Terminal alkynes are readily deprotonated by very strong bases, forming acetylide anions, which are isoelectronic to cyanide anions and can act as nucleophiles. Gewald et al. have reported that lithium acetylides **177**, prepared from the reaction of phenylacetylene **176** with ^{n}BuLi, react with elemental sulfur to form a thio-ynolate **178** [164]. In the presence of acidic compounds, it was found that thio-ynolates rapidly dimerize to a 1,3-dithiol **172**. It was noted that the yne-thiol formed upon protonation exists in equilibrium with its corresponding thioketene **171**, indicating that the cyclization may proceed via nucleophilic attack of the thio-ynolate **178** on the thioketene **171**, followed by nucleophilic 5-*endo*-dig cyclization (Scheme 64).

It was further noted by Gewald et al. that amines react with thio-ynolates to thioamides, rendering the formation of a thio-ynolate another possible pathway for the alkyne-Willgerodt-Kindler reaction (see section 3.4.1.1).

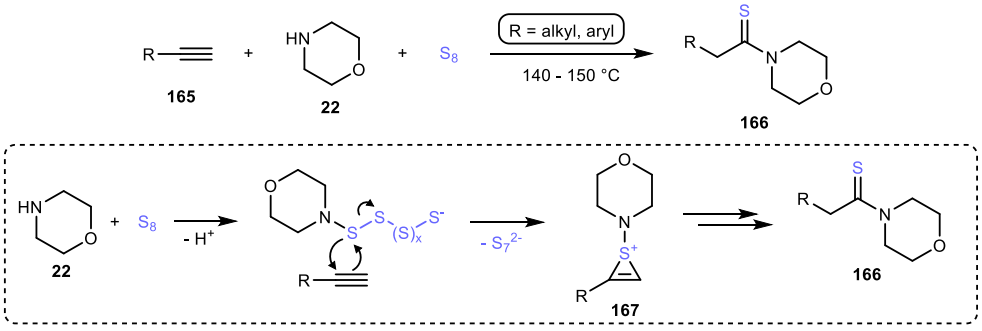
Thio-ynolates formed from acetylides and sulfur with BuLi undergo several reactions which are also known for their oxa-analogues. For instance, they react with ketones or ketimines in a formal [2 + 2]-cycloaddition, yielding β-lactones or lactams, respectively [165–167]. Furthermore, a reaction with carbodiimides is known to result in dihydropyrimidinethiones. The mechanism of this reaction is not clear, however a [2 + 2]-cycloaddition is proposed to be the first step.

Other transformations involving the formation of thio-ynolates involve its *S*-centered nucleophilicity in reactions with various electrophiles, such as alkyl halides, epoxides, or isocyanates, among others [167–169]. In some of these reports, other bases, such as NaH, were used in order to deprotonate the alkyne component [168]. The use of a copper catalyst, which is known to increase the acidity of terminal alkynes, allows the use of weaker bases, such as KO^{t}Bu, to mediate thio-ynolate formation [169].

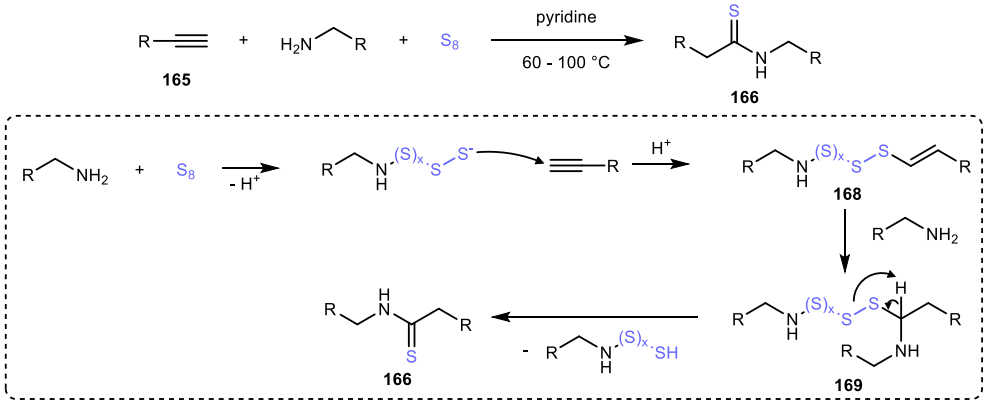
3.4.1.3. Reactions involving internal alkynes and conjugated diynes. Lei et al. reported that conjugated diynes, such as diphenyldiacetylene **179**, react with elemental sulfur and KO^{t}Bu already at room temperature in DMF, forming 2,5-disubstituted thiophenes **180** [170]. It was concluded by the authors that the trisulfide radical anion $S_3^{\bullet-}$ was the key intermediate in this transformation, being detected in EPR studies. The reaction was completely inhibited by TEMPO. The involvement of $S_3^{\bullet-}$ was further evidenced by a similar synthesis using potassium sulfide in DMF as the sulfur source [171].

Experiments with deuterated solvents further confirmed that the hydrogen substituents of the thiophene ring are incorporated via H-abstraction from solvent molecules. Lei et al. proposed a mechanism involving the addition of $S_3^{\bullet-}$ to one of the triple bonds, followed by H-abstraction from the solvent, yielding an enethiolate **181**. This is followed by nucleophilic 5-*endo*-dig ring closure with the other triple bond, yielding a thienyl anion, which is protonated by solvent molecules, yielding the thiophene product (Scheme 65).

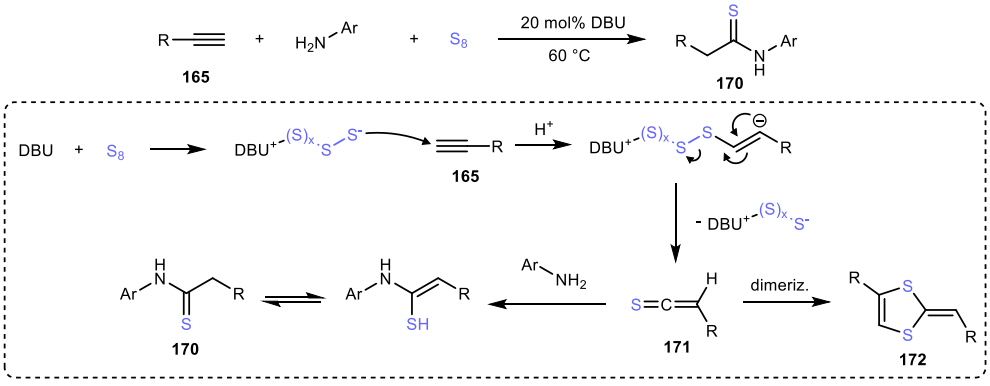
Liu et al. reported a thiophene (**183**) synthesis from electron-poor alkynes, namely propiolate esters **182**, mediated by elemental sulfur and potassium *tert*-butoxide in toluene at 100 °C [172]. Control experiments with TEMPO were also found to completely inhibit the reaction, leading the authors to propose a radical mechanism involving addition of the trisulfide radical anion to the triple bond, followed by Michael addition of the resulting vinyl radical anion **184** to another alkyne and



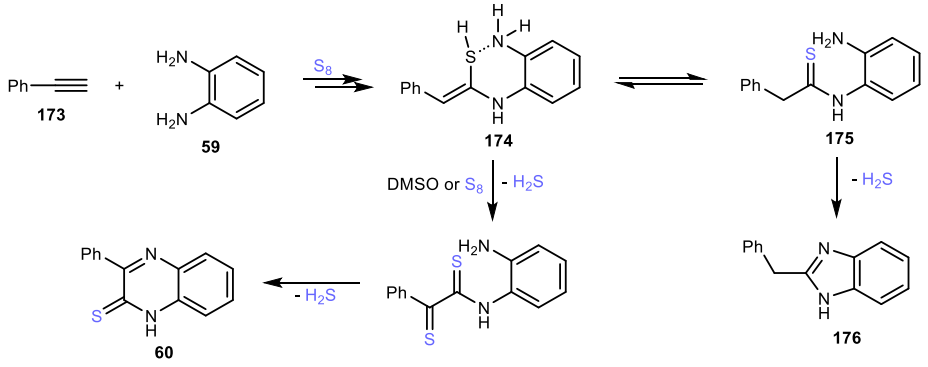
Scheme 60. Mechanism for the synthesis of thioamides **166** from alkynes **165**, proposed by Carmack et al. in Ref. [92].



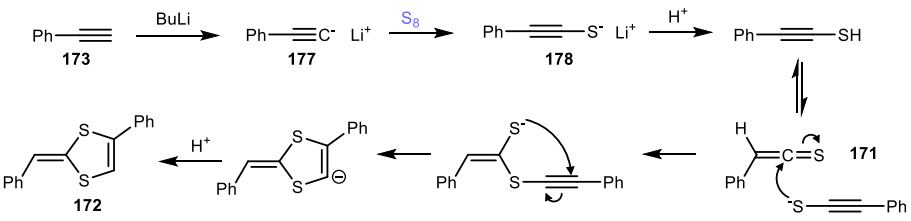
Scheme 61. Mechanism for the synthesis of thioamides **166** from alkynes, proposed by Nguyen in Ref. [160].



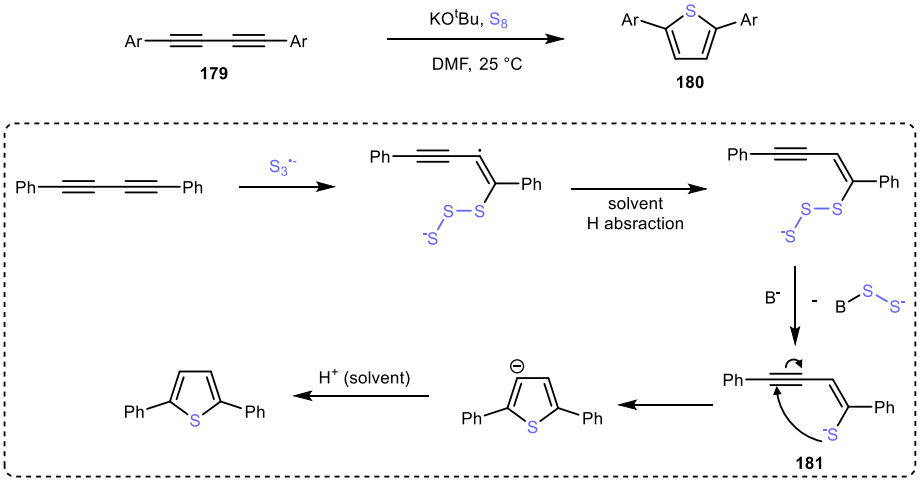
Scheme 62. Mechanism for the DBU-catalyzed synthesis of thioamides **170** from alkynes and aromatic amines, proposed by Nguyen in Ref. [161].



Scheme 63. Pathways for the formation of benzimidazoles **176** and quinoxaline-2-thiones **60** from *o*-phenylenediamine **59** and phenylacetylene **173**, observed and proposed by Gan and Nguyen in Refs. [162,163].



Scheme 64. Formation of thio-ynolates **178** from acetylides **177** and sulfur, and possible mechanism for their acid-induced dimerization to 1,3-dithioles **172** (see. Ref [164]).



Scheme 65. Synthesis of 2,5-disubstituted thiophenes **180** from conjugated diynes **179**, reported by Lei et al. in Ref. [170].

subsequent electrocyclization (Scheme 66).

Previously, Alizadeh et al. reported an ionic mechanism for the synthesis of thiophenes (**187**) from the very electron-deficient diethyl acetylenedicarboxylate **185**, catalyzed by pyridine, which proceeds already at room temperature in DCM [173]. It was proposed that pyridine adds to the triple bond, forming a zwitterion, which is subsequently thiolated by interaction with elemental sulfur (Scheme 67). The resulting zwitterion **186** was proposed to add to another acetylenedicarboxylate, finally undergoing cyclization under elimination of pyridine. This mechanism is further supported by a later report, showing that the thiolated zwitterion **186** is the isolable main product if stoichiometric amounts of pyridine are used [174].

Kong and Li. reported that ynones **188** and propiolates can react with elemental sulfur already at 0 °C, forming 1,4-dithiins **189** [175]. It was observed that both 2,5- and 2,6-homosubstituted isomers **189a-b** were generated, with the 2,5-isomers **189a** being the clear main products, especially when conducting the reaction at low temperatures, producing isomeric ratios up to 10:1. It was found that both inorganic bases, such as potassium carbonates, as well as organic bases such as DABCO, were effective for the transformation. The mechanistic postulate involves the formation of a 1,2-dithiete **190** intermediate via nucleophilic Michael addition of a polysulfide, generated from sulfur and base, to the ynone, followed by further thiolation of the resulting carbanion and ring-closure (Scheme 68).

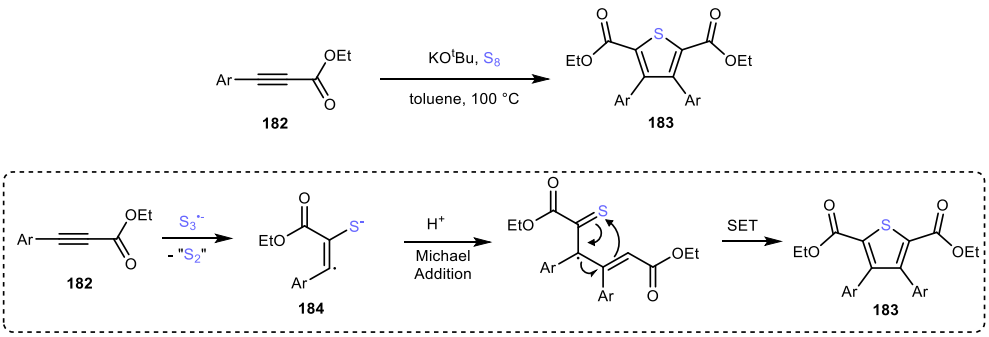
The formation of a dithiete intermediate was evidenced by earlier reports by Nakayama et al. on stable dithietes, formed from sterically hindered alkynes such as bis(*tert*-butyl)acetylene **192** at very high temperatures of 190 °C (Scheme 68) [176,177]. The dithiete intermediate is proposed to be in equilibrium with its open dithione form **191**, which can undergo a hetero-Diels-Alder reaction with another alkyne, yielding a dithiin **189**. The preferred formation of the 2,5-isomer was attributed to electronic reasons.

Zhang and Zhang reported the formation of bis(isothiazolyl)disulfides **195** from ynone ketoxime ethers **194** and elemental sulfur, catalyzed by DBU [178]. A radical pathway was ruled out in control experiments. Furthermore, when isothiazole **196** was subjected to the reaction conditions, no reaction occurred, indicating that the introduction of the sulfur atom to the α-carbon of the ketoxime ester **194** occurs before the cyclization. The authors proposed that disulfide anions are formed *in situ* from DBU and sulfur. The disulfide dianions are then suggested to add to the α-carbon of the ketoxime ethers, followed by thiolation of the resulting β-carbanions. The product is obtained by intramolecular demethoxylative cyclization (Scheme 69). However, ynone ketoxime ethers possess the electronic profile of Michael systems, hence the α-carbon is the least electrophilic, making a nucleophilic attack in this position questionable. In fact, the same group later reported a synthesis of the uncoupled isothiazoles **196**, using sodium sulfide as the sulfur source, proposing a nucleophilic attack at the more electrophilic β-position in this case (Scheme 69) [179].

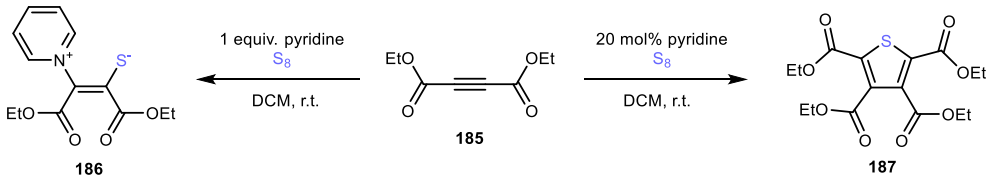
3.4.2. Alkenes

In the context of their studies on the Willgerodt-Kindler reaction, Carmack et al. reported that styrenes **197** can also serve as the reactants, reacting with morpholine and sulfur at 160 °C, furnishing phenylthioacetamides **54**. It was noted that, in contrast to the reaction with alkynes, a strong evolution of hydrogen sulfide was observed due to the additional oxidation step. No mechanism for the Willgerodt-Kindler reaction of styrenes was proposed [158,159].

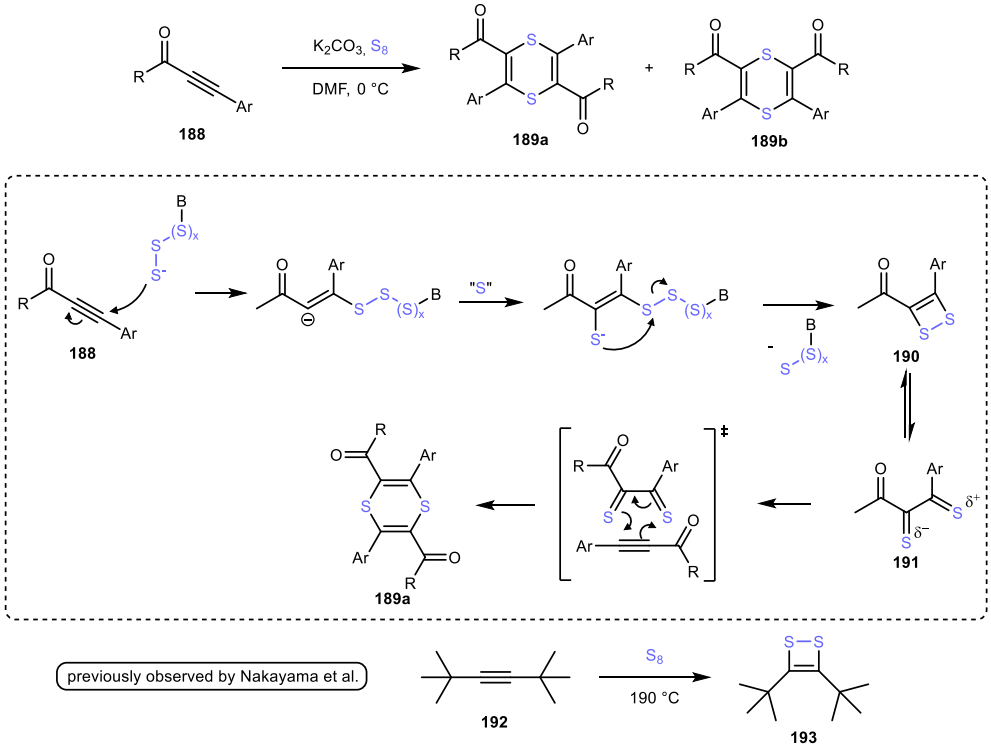
A few more reports of Willgerodt-Kindler reactions of styrenes are available since. Moghaddam et al. reported the synthesis of several



Scheme 66. Proposed mechanism for the radical formation of thiophenes **183** from propiolates **182** and sulfur, proposed by Liu et al. in Ref. [172].



Scheme 67. Formation of a stable zwitterion **186** from diethyl acetylenedicarboxylate **185**, which can further react to a thiophene **187**, reported by Alizadeh et al. in Ref. [173].



Scheme 68. Proposed mechanism for the formation of 1,4-dithiins **189** from ynones **188**, reported by Kong and Li in Ref. [175]. The postulation of dithiete intermediate **190** is based on a previous observation by Nakayama et al. from Ref. [177].

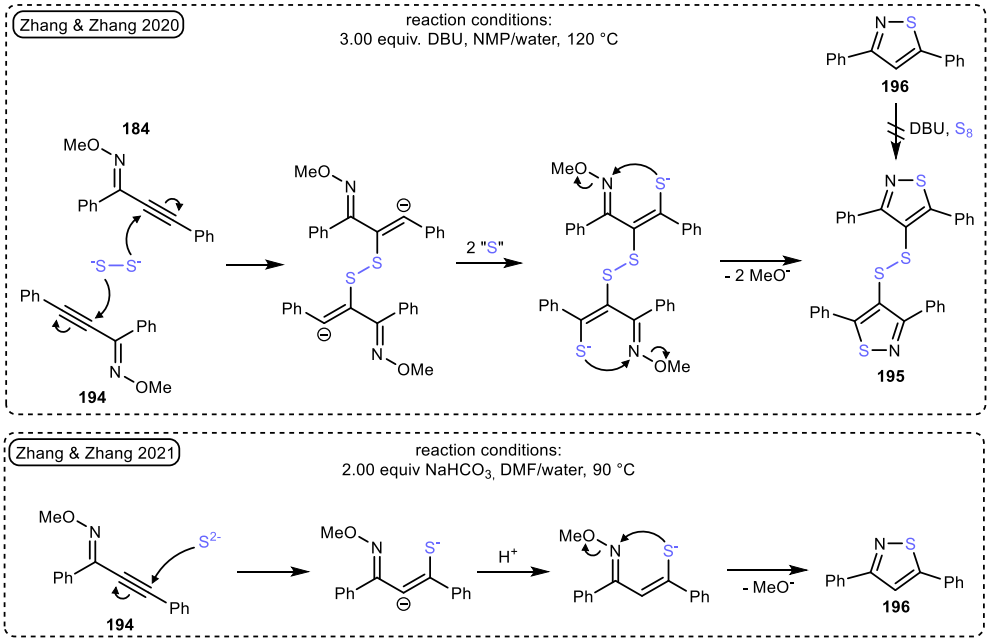
thioamides from differently substituted styrenes under microwave conditions, but no mechanism was proposed [180]. Darabi et al. compared the reactivity of several substrates under Willgerodt-Kindler conditions, and found that styrenes give lower yields than the corresponding alkynes or acetophenones [181].

In 2018, Chen and Wu reported a more detailed study on the synthesis of thioamides **199** from styrenes, amines and sulfur [182]. It was found that using potassium phosphate as basic reagent, phenylthioacetamides **199** could be efficiently formed from styrenes with both aromatic and aliphatic amines. Aliphatic olefins were however completely inactive under the employed reaction conditions. A free radical mechanism was ruled out in control experiments with TEMPO, despite favorable conditions for sulfur radical formation. Furthermore, mass spectrometric investigations of the reaction mixtures led to the identification of the molecular mass of an aminopentasulfide anion **200**, formed from amine and sulfur. It was proposed that this species undergoes an "oxidative coupling" with styrene, yielding enethiol derivative **201**. Other signals in the mass spectra of the reaction mixtures were attributed to pentathiepin **202** and thiosemiaminal derivative **203**, leading the authors to suggest their involvement as possible intermediates (Scheme 70).

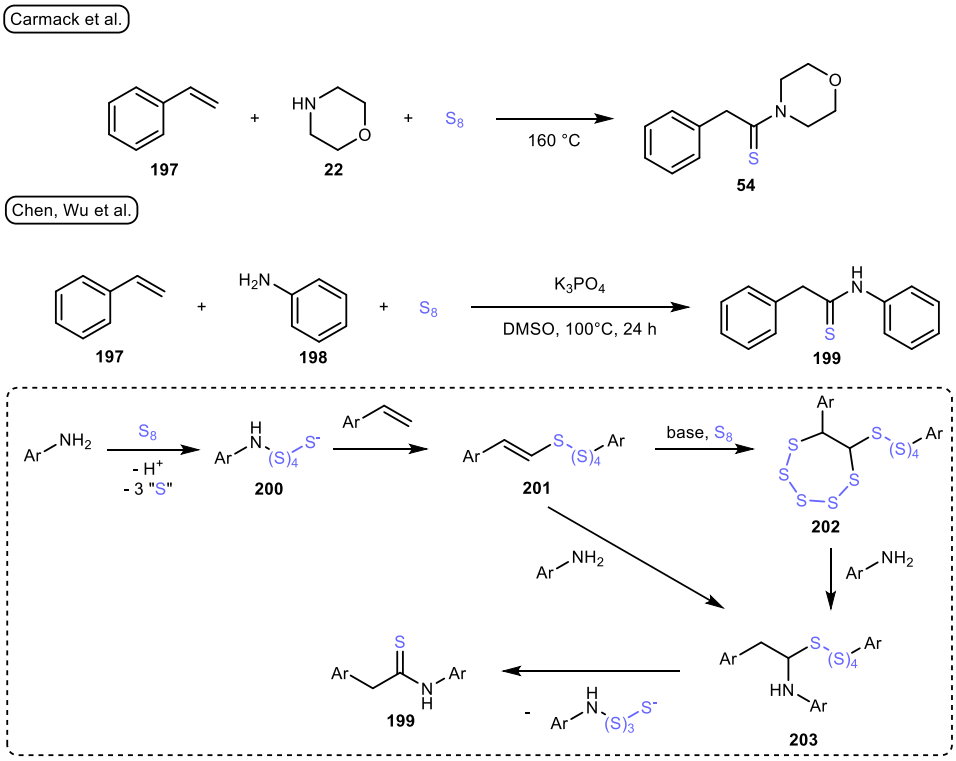
It was proposed that **201** could undergo further reaction with activated sulfur, yielding **202**, followed by reaction with the amine, yielding **203**. Furthermore, it was proposed that the direct reaction of **201** with amine can yield **203**, which reacts to thioamide **199** via polysulfide extrusion [182]. A report by Han, Pan et al. studying *o*-substituted anilines, thus providing a pathway for further cyclization of the product thioamide to a benzazole, also proposes enethiol **201** and thiosemiaminal **203** as intermediates of the reaction [183].

Vankar et al. reported that thioamides **26** could also be generated from *gem*-dibromoalkenes **204**, amines and sulfur in water [184]. It was noted that the presence of water was essential for the success of the reaction, which had also previously been reported by Dalal et al. for the thioamidation of benzaldehydes [100]. Due to the high electron-deficiency of the styrene β-carbon, an ionic mechanism was proposed, entailing successive nucleophilic substitution of the bromide substituents with aminopolysulfide and amine, yielding the thioamide after water-assisted elimination of a shortened polysulfide (Scheme 71).

Nguyen et al. reported that chalcones **83** undergo sulfurative dimerization at room temperature in DMSO in the presence of sulfur and bases, such as DABCO or triethylamine, yielding 1,3-dithioles **205** [185]. A complicated mechanism was suggested, starting with the thia-Michael addition of an NEt_3 polysulfide zwitterion to the chalcone, followed by elimination of triethylamine, yielding chalcone polysulfide **206**. **206** is then proposed to attack another chalcone in a Michael addition, yielding enethiol **207** and another chalcone polysulfide **208**



Scheme 69. Syntheses of bis(isothiazolyl)disulfides **195** and isothiazoles **196** from ynone ketoxime ethers **194**, reported by Zhang and Zhang in Refs. [178,179].

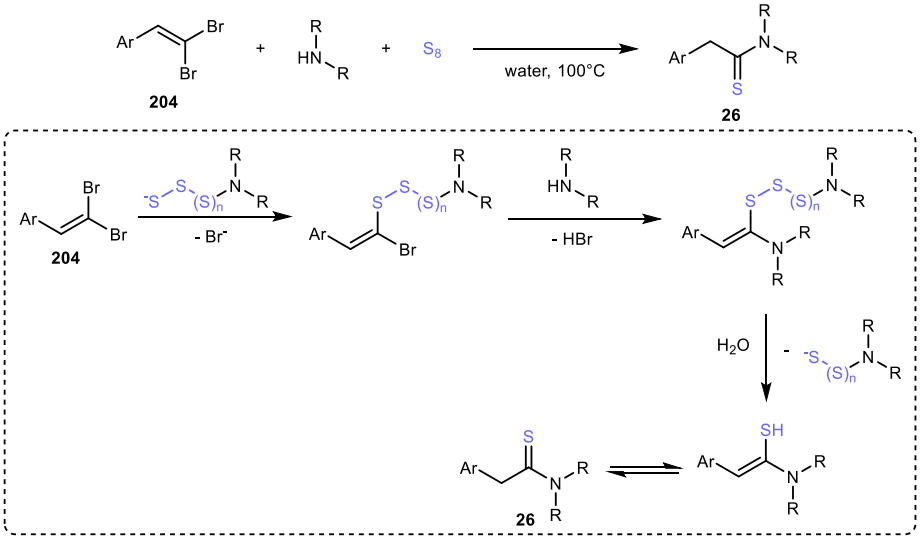


Scheme 70. Syntheses of thioamides from styrenes **197**, reported by Carmack in Ref. [158] and Chen, Wu et al. in Ref. [182], along with proposed intermediates of the reaction.

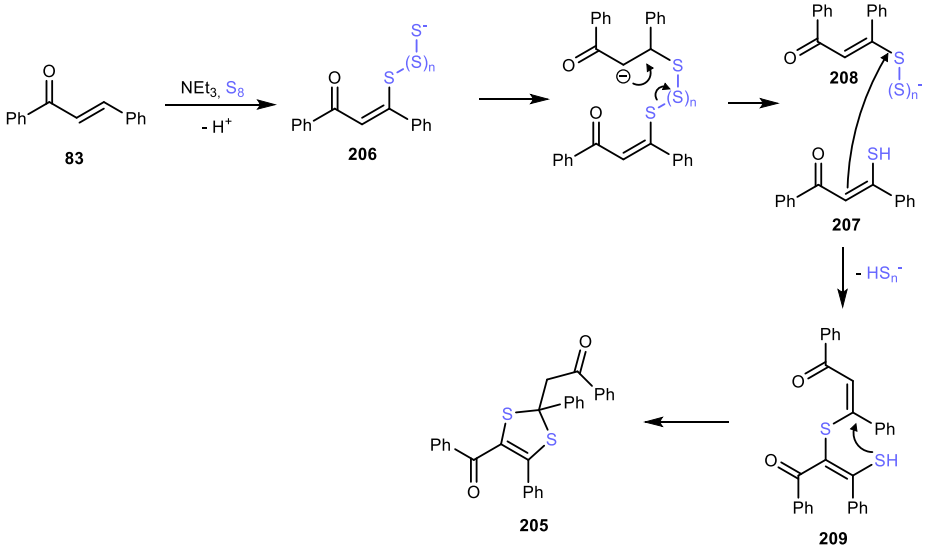
after cleavage of the polysulfide chain. In the next step, enethiol **207** is proposed to act as a nucleophile, attacking **208,** followed by liberation of a hydropolysulfide anion, yielding **209**, which forms the final product in a final intramolecular Michael addition (Scheme 72). The involvement of radical species was not considered.

Wang and Phan et al. reported a radical mechanism for a sulfur mediated amination of chalcones **83**, yielding enaminones **212** [186]. The reaction proceeded in DMSO at temperatures ranging from 40 to 80 °C, and the trisulfide radical anion was detected in the mixture via its characteristic UV/Vis absorption. A pathway was proposed, involving the initial formation of a thiirane **210** from the chalcone via addition of $S_3^{\bullet-}$ and elimination of $S_2^{\bullet-}$. Subsequent nucleophilic attack of the amine yields **211**, which forms the final enaminone by elimination of hydrogen sulfide. DFT calculations demonstrated the viability of this pathway (Scheme 73).

Recently, Zhao et al. confirmed the involvement of a thiirane



Scheme 71. Proposed mechanism for the synthesis of thioamides from gem-dibromoalkenes **204**, reported by Vankar in Ref. [184].

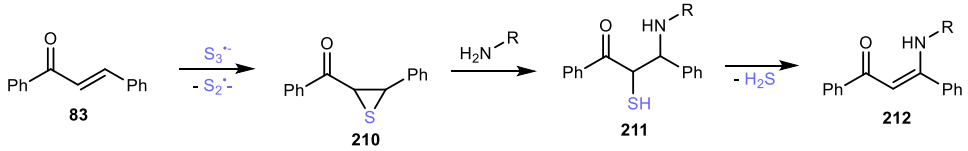


Scheme 72. Proposed mechanism for the formation of 1,3-dithioles **205** from chalcones **83** and sulfur, reported by Nguyen et al. in Ref. [185].

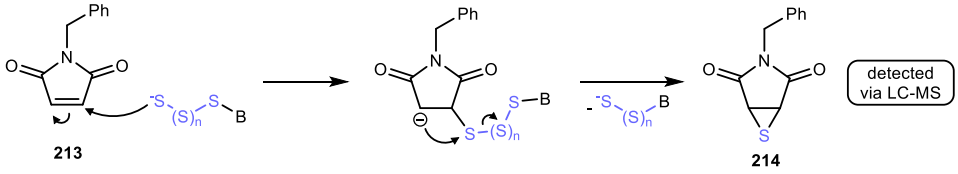
intermediate in the mechanism of their reported multicomponent reaction between maleimides **213**, sulfur and triazinanes, featuring catalytic amounts of sodium bicarbonate as the activating base [187]. It was postulated that a thiirane is formed via Michael addition of an anionic polysulfide, followed by extrusion of a shorter polysulfide species (Scheme 74). The thiirane **214** was detected via liquid chromatography/mass spectrometry (LC-MS). The involvement of radicals in the mechanism was ruled out by the authors, since their reaction also proceeded in the presence of the radical scavengers TEMPO or BHT.

3.4.3. *Cleavage reactions of carbon-carbon multiple bonds*

Xu and Liu et al. found that the reaction of phenylacetylenes **173** with formamides in the presence of a large excess of sulfur and potassium phosphate yielded thiobenzamides **154**, resulting from the cleavage of the alkyne triple bond [188]. It was found that also internal alkynes **215** could undergo the cleavage reaction, yielding thioamides derived from both alkylidyne fragments. Control experiments involving terminal alkynes revealed that using amines instead of formamides did not lead to cleavage and the expected Willgerodt-Kindler product, a phenylthioacetamide, was generated. A free radical pathway was ruled out due to control experiments with TEMPO, despite the reaction



Scheme 73. Radical mechanism for the amination of chalcones **83** via a thiirane intermediate **210**, proposed by Wang and Phan et al. in Ref. [186].



Scheme 74. Thiirane formation from maleimides **213** and activated sulfur, postulated by Zhao et al. in Ref. [187]. The thiirane **214** was detected via LC-MS.

conditions potentially favoring the formation of sulfur-centered radicals. The authors proposed a mechanism involving a nucleophilic attack of the alkyne to the cyclooctasulfur ring to yield a cyclic species (**216**), which tautomerizes to an α-polysulfidothioketone **217** (Scheme 75). Subsequently, the attack of dimethylamine, generated via the thermal base-promoted decomposition of DMF, to the thione carbon is proposed, followed by elimination of a carbene species **218** to yield the thiobenzamide **154**.

The nature of the eliminated species was not commented on, however, due to the observation of thioamide formation of both fragments of internal alkynes, a further pathway towards thioamide formation must exist. If the extruded species is indeed the postulated carbene, it can be expected to react with elemental sulfur, forming a dithiocarboxylate, which could likewise be converted to a thioamide via reaction with amines.

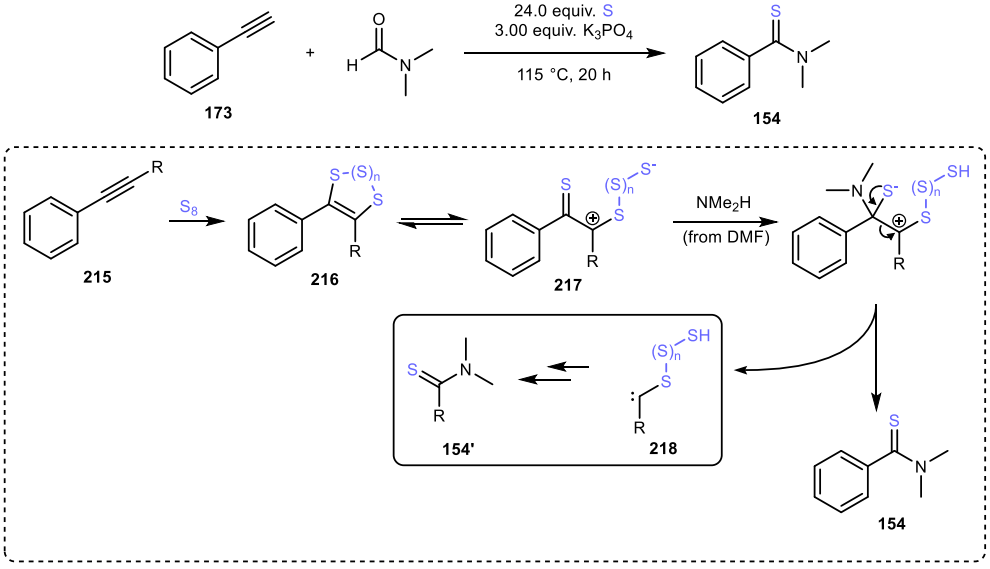
The same group observed a related cleavage reaction for styrenes **197** and cinnamic acids under very similar conditions, merely potassium carbonate yielding better results than potassium phosphate. Similarly, internal alkenes produced the thioamides derived from both alkylidene fragments. The proposed mechanism is essentially equivalent to that proposed for alkynes (Scheme 75).

The cleavage of alkenes was also observed by Chen and Wu et al. in their already mentioned report on the thioamidation of styrenes **197** with amines (compare Scheme 70) [182]. They found that the cleavage reaction competes with the expected thioamide formation, depending on the used base. While using K_3PO_4 resulted in complete selectivity towards the uncleaved product **199**, the use of KF exclusively yielded the cleaved product **102**. Other bases produced mixtures of both products. Supported by mass spectrometric studies, they proposed that cyclic species **219** (detected via ESI-MS) is formed in the course of the mechanism (Scheme 76). Similar to the mechanism proposed for the non-cleaving thioamidation (compare Scheme 70), it was proposed that enethiol derivative **201** is formed, which reacts to **219** upon interaction with base and sulfur. The subsequently proposed pathway to the cleaved thioamide includes the nucleophilic attack of amine, followed by oxidative ring closure and elimination of an unspecified side product. The side product **220** depicted in Scheme 76 is the species theoretically resulting from the electron flow postulated by the authors. No comment on the exact nature of the generated byproduct has been made. Furthermore, the authors noted that the reasons for the chemoselectivity exerted by the bases remained unclear.

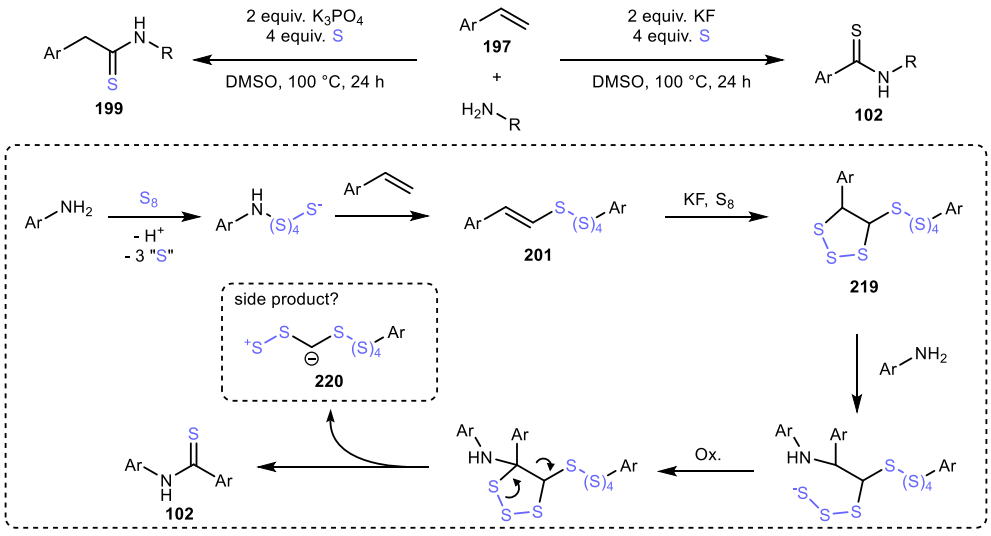
Interestingly, the cleavage reaction reported by Chen and Wu et al. only proceeded with weakly nucleophilic aromatic amines. It thus seems that cleavage is favored if the activity of the nucleophilic species is low, either via weak intrinsic nucleophilicity, or via low concentration of more strongly nucleophilic amines, as is the case for the cleavage reactions reported by Xu and Liu et al. where amines are generated in low concentrations via decomposition of formamides [188,189].

A sulfur-mediated cleavage reaction of enaminones **221**, yielding α-ketothioamides **58**, was reported by Wan et al. [190] Interestingly, only DMAP was found to effect the cleavage reaction, while no reaction was observed with bases such as DABCO or *N*-methylmorpholine. The authors found that air atmosphere was essential for the reaction, indicating that oxygen serves as a co-oxidant. It was proposed that the enaminone is thiolated in the α-position, mediated by DMAP. Subsequent intramolecular cyclization yields a thiirane **222**, which is proposed to be oxidized to an oxathietane **223** by molecular oxygen (Scheme 77). Ring opening and elimination of the amine yields a thioxoaldehyde **224**, which forms the product by attack of amine and elimination of formaldehyde. The generation of formaldehyde as the side product was confirmed via GC-MS.

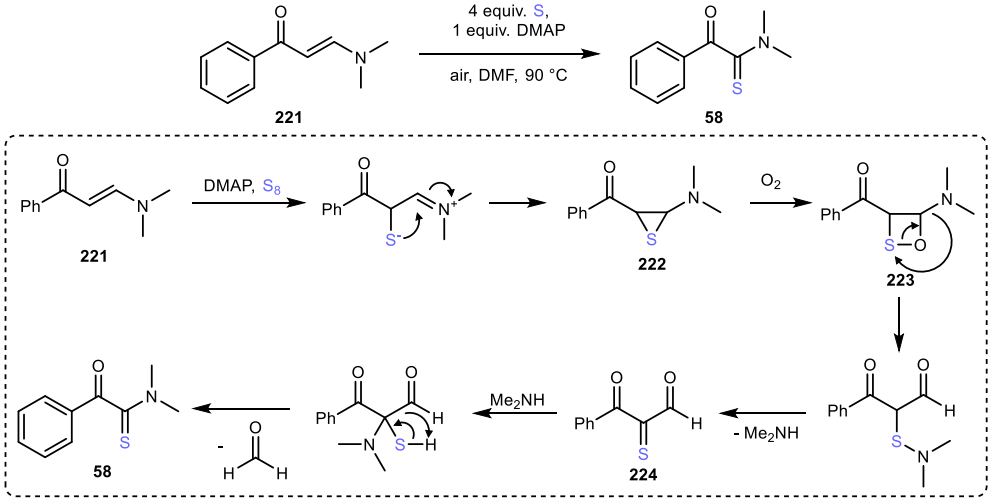
Chen and Zeng et al. reported the formation of thioamides via cleavage of β-nitrostyrenes **225** using potassium *tert*-butoxide in DMF [191]. They propose the formation of a cyclic species via insertion of the olefinic double bond into the S_8 ring, followed by base-induced cleavage, resulting in the formation of a thiobenzaldehyde **226**,



Scheme 75. Cleavage of alkyne triple bonds in the presence of formamides and sulfur, resulting in thiobenzamides **154**, reported by Xu et al. in Ref. [188].



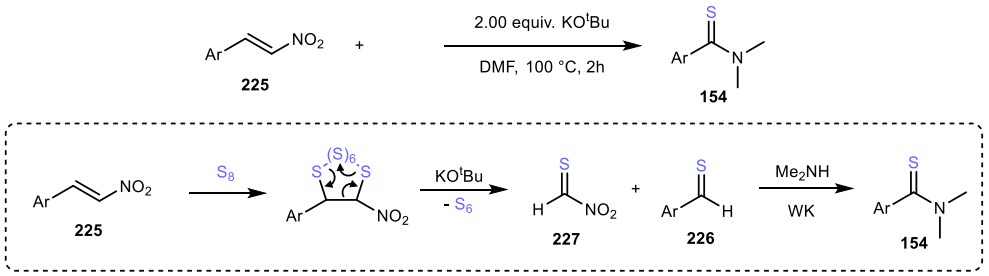
Scheme 76. Chemoselective thioamidation of styrenes **197** with amines and sulfur, yielding cleaved (**102**) or uncleaved (**199**) products depending on the choice of base. The mechanism was proposed by Chen and Wu et al. in Ref. [182]. Intermediate **219** was identified via ESI mass spectrometry.



Scheme 77. Formation of thioamides **58** via cleavage of enaminones **221**, reported by Wan et al. in Ref. [190].

cyclohexasulfur and nitrothioformaldehyde **227** (Scheme 78). The thiobenzaldehyde **226** is suggested to then be converted to the thioamide via a Willgerodt-Kindler reaction with dimethylamine, generated *in situ* via decomposition of DMF. A free radical pathway was ruled out by the authors based on control experiments with TEMPO. No further comments on the side products were made by the authors. To our knowledge, nitrothioformaldehyde **227** has not yet been isolated or characterized. It can be expected to be highly reactive due to its highly electrophilic thiocarbonyl carbon, potentially undergoing further reactions.

The reactions presented in this section are illustrative of the high diversity of the mechanisms proposed for reactions of elemental sulfur with carbon-carbon multiple bonds. In many cases, counterintuitive reactivities are proposed, and the reasons for the observed chemoselectivities between the various types of transformation remain insufficiently clarified.



Scheme 78. Proposed mechanism for the cleavage of β-nitrostyrenes **225**, reported by Chen and Zeng et al. in Ref. [191].

3.5. Aromatic substitution reactions

3.5.1. Aromatic C–H substitution

Several reports describe the C–H-functionalization of aromatic compounds via direct interaction of the aromatic system with elemental sulfur.

Itami et al. reported that alkynyl-substituted polycyclic aromatic hydrocarbons (**228**) react with elemental sulfur at high temperatures of 140 °C in DMF, forming thiophene-fused aromatic systems (**229**). It was proposed that the aromatic system itself acts as a nucleophile, forming a thiolated zwitterion, which undergoes 5-*endo*-dig cyclization (Scheme 79). Radical pathways were ruled out via control experiments with radical scavengers. It is assumed that the enhanced electron density of polycyclic aromatics is essential, since no thiophene formation occurred at the aryl substituents on the other side of the alkynyl functions [192].

Similar interactions with sulfur were also reported for other electron-rich aromatics. Zhang and Yu et al. reported a synthesis of thiazolidinones **231** and dihydrothiazinones **232** from polycyclic aromatic amines **230**, elemental sulfur and carbon dioxide, mediated by a large excess of NaO^{t}Bu [193]. The sulfur atoms were regioselectively incorporated to the most electron-rich positions of the aromatic substrates. Control experiments identified the corresponding aryl isocyanate **233**, formed *in situ* from amine and CO_2, as a likely intermediate of the reaction. Subsequently, two pathways leading to the product were suggested: (i) a direct reaction of the nucleophilic position of the aromatic ring with sulfur, leading to a thiolated species **234**, followed by intramolecular cyclization and (ii) a nucleophilic attack of anionic polysulfide species, generated from sulfur and base, to the electrophilic isocyanate carbon, followed by intramolecular nucleophilic attack of the aromatic ring on the sulfur chain, eliminating a shortened polysulfide (Scheme 80).

Nguyen et al. reported a reaction of 2-naphthols **235** with aromatic isothiocyanates **236**, resulting in 2-imino-1,3-oxathioles **237**, catalyzed by DABCO [194]. Mechanistic control experiments revealed that in the absence of isothiocyanate, the reaction of naphthol with sulfur and DABCO yielded bis(2-hydroxy-1-naphthyl)disulfide **238**. It was further noted that 1-naphthol, as well as monocyclic aromatics, did not react. Based on these observations, it was proposed that 2-napthoxide reacts with elemental sulfur in 1-position, followed by thioacylation of the hydroxide with the isothiocyanate, yielding a thiourethane **239**. Intramolecular cyclization results in the formation of the final product (Scheme 81).

Other reactions involving the formation of a C–S-bond from aromatic C–H bonds are generally proposed to involve the formation of sulfurized species in other parts of the participating compounds, followed by subsequent intramolecular attack on the aromatic system.

For instance, Deng et al. reported a synthesis of thienoindoles **241** from *N*-alkylindoles **240**, alkynes and sulfur in DMF [195]. It is proposed that the alkyne forms a Willgerodt-Kindler thiirenium intermediate **242** via reaction with elemental sulfur and dimethylamine, the latter being generated *in situ* via acid- and temperature-induced decomposition of the solvent DMF. The thiirenium species, which is nucleophilically attacked by the C3-position of the indole, forms the product via intramolecular nucleophilic aromatic substitution at the C2 position with sulfur (Scheme 82).

Radical mechanisms for the C–H substitution at aromatic systems have also been suggested in several instances. Deng et al. published several reports on the synthesis of various benzothienothiazoles using *O*-acylacetophenone oxime **243** as the main building block (Scheme 83). Mechanistically, it was suggested that 3-aminobenzothiophene **245** is generated *in situ* in these reactions as the key intermediate. Due to the low dissociation energy of the N–O bond of the oxime ester, a radical mechanism mediated by the *in situ* generated $S_3^{\bullet-}$ radical anion was proposed [196]. The postulate involves the attack of $S_3^{\bullet-}$ on the oxime nitrogen, forming an iminotrisulfur radical **244**, which undergoes a 1, 3-hydrogen shift, moving the trisulfur moiety to the α-methyl group. Subsequently, a radical attack on the benzene ring, followed by elimination of S_2 and subsequent single-electron oxidation, is proposed, yielding 3-aminobenzothiophene **245**. In a later report, Wu and Jiang et al. performed a similar reaction with free oximes, catalyzed by TBD, detecting the trisulfide radical anion in the reaction mixture using EPR spectroscopy [197].

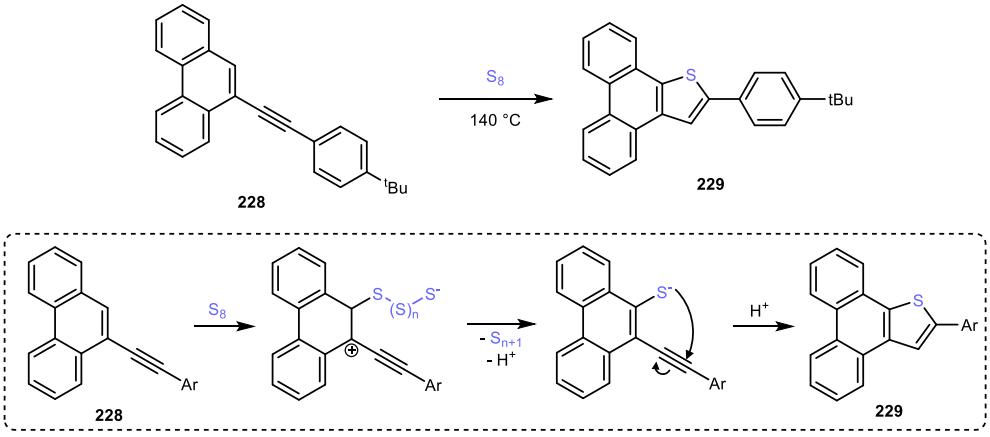
3.5.2. Aromatic C-X substitution

As already described in section 2.4, the highly nucleophilic character of anionic sulfur species enables their participation in nucleophilic aromatic substitution reactions, if good leaving groups such as halides or nitro groups are involved. Both classic S_NAr, as well as radical-nucleophilic aromatic substitution ($S_{RN}Ar$) mechanisms have been postulated for such transformations.

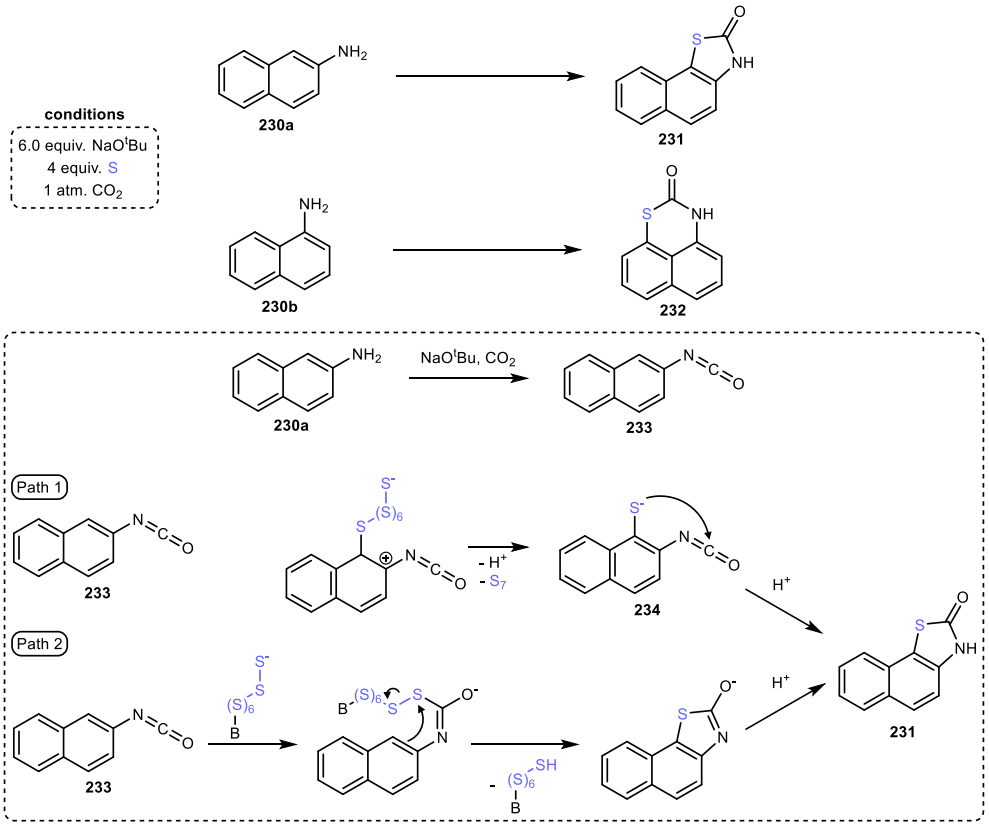
In 1979, Sato et al. reported the nucleophilic aromatic substitution of *p*-chloronitrobenzene by aminopolysulfide species generated *in situ* from elemental sulfur in liquid ammonia. The product consisted of a mixture of the corresponding *p*-nitroaniline, -thiol and bis(*p*-nitrophenyl)disulfide. It was proposed by the authors that polythiosulfenamides are formed as intermediates, since earlier investigations of the degradation of such compounds resulted in similar product mixtures [198,199].

Deng et al. observed the aromatic substitution of *o*-bromobenzaldehyde **246** as part of their reported synthesis of benzothiophenes [200]. It was shown that *o*-bromobenzaldehyde reacts with elemental sulfur to bis(2-formylphenyl) disulfide **247** under the applied reaction conditions. No suggestion on the substitution mechanism was made by the authors. The reaction conditions are potentially beneficial for the formation of sulfur centered radicals (Scheme 84).

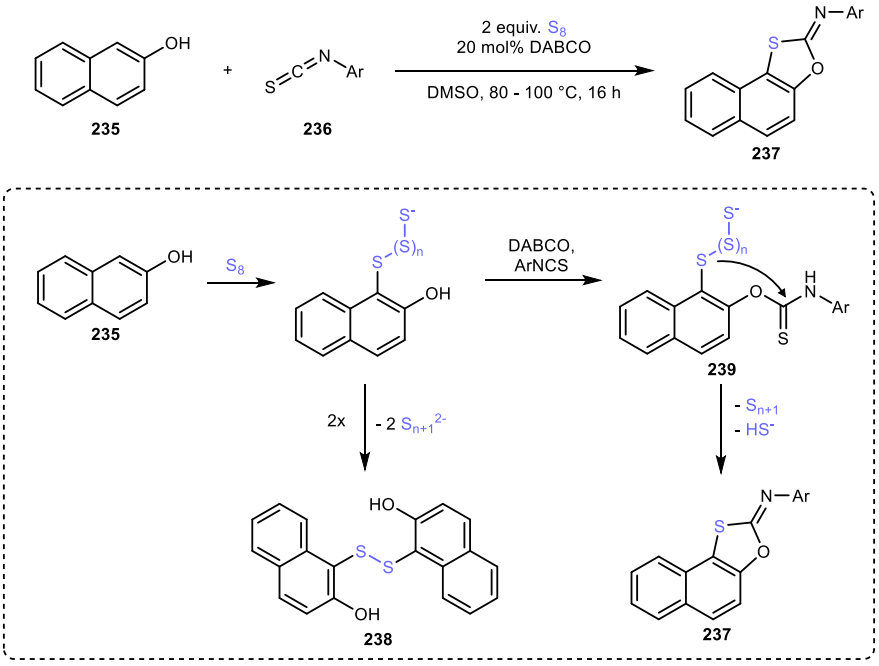
Jiang et al. reported a radical sulfur-iodine exchange reaction of bis



Scheme 79. Proposed mechanism for the synthesis of fused thiophenes **229** from alkynyl-PAHs **228**, reported by Itami et al. in Ref. [192].

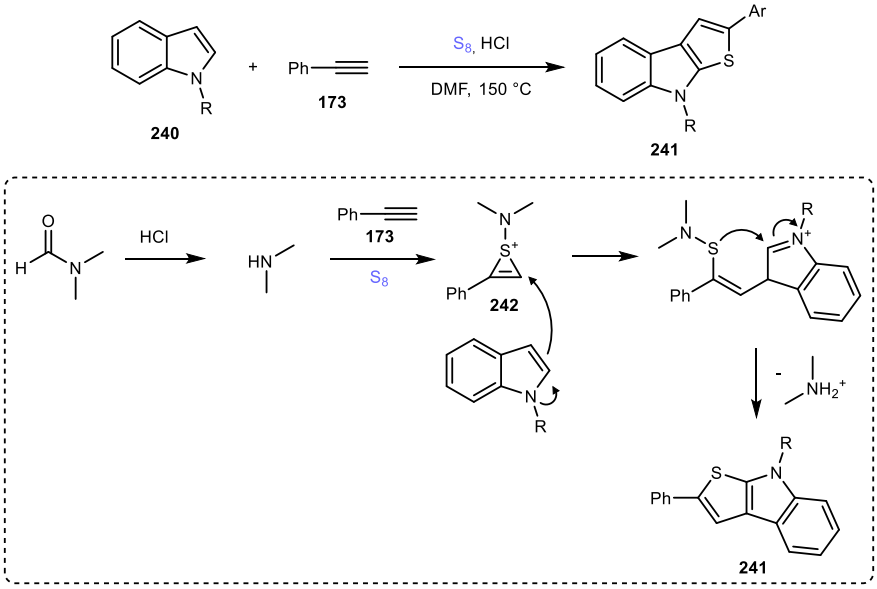


Scheme 80. Proposed mechanism for the formation of thiazolones **231** and dihydrothiazinones **232** from aromatic amines **230** via an intermediate isocyanate **233**, reported by Zhang and Yu et al. in Ref. [193].

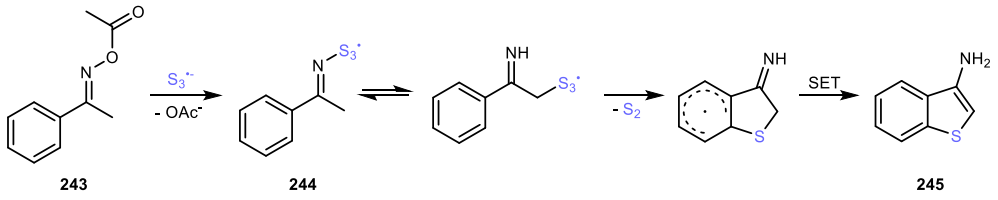


Scheme 81. Formation of iminooxathiazoles **237** from 2-naphthols **235**, sulfur and isothiocyanates **236**, catalyzed by DACBO. Sulfur and naphthol form bis(hydroxynaphthyl)disulfide **238** in the absence of isothiocyanate.

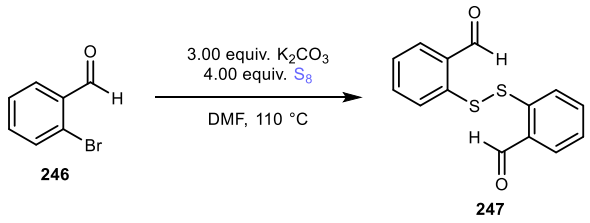
(aryl)iodonium **248** compounds, yielding bis(aryl)sulfides **249** (Scheme 85) [201]. The presence of the $S_3^{\bullet-}$ radical anion was identified under the reaction conditions. The proposed mechanism entails the attack of $S_3^{\bullet-}$ to the iodine, cleaving a C–I bond to form an aryl radical (**250**), which recombines with another $S_3^{\bullet-}$ radical. The resulting aryl trisulfide is suggested to degrade to a thiophenoxide (**251**), which undergoes intramolecular nucleophilic aromatic substitution to generate the final product **249**. The involvement of the aryl radical was evidenced in a



Scheme 82. Synthesis of thienoindoles **241** from indoles **240**, alkynes and sulfur via a Willgerodt-Kindler intermediate **242**, reported by Deng et al. in Ref. [195].



Scheme 83. Proposed radical mechanism for the synthesis of 3-aminobenzothiophene **245**, mediated by the $S_3^{\bullet-}$ radical anion, as suggested in Ref. [196].



Scheme 84. Formation of a disulfide **247** via aromatic substitution of *o*-bromobenzaldehyde **246**, reported by Deng et al. in Ref. [200].

control experiment with the radical scavenger 1,1-diphenylethylene **252**, which resulted in the isolation of the coupled product **253**.

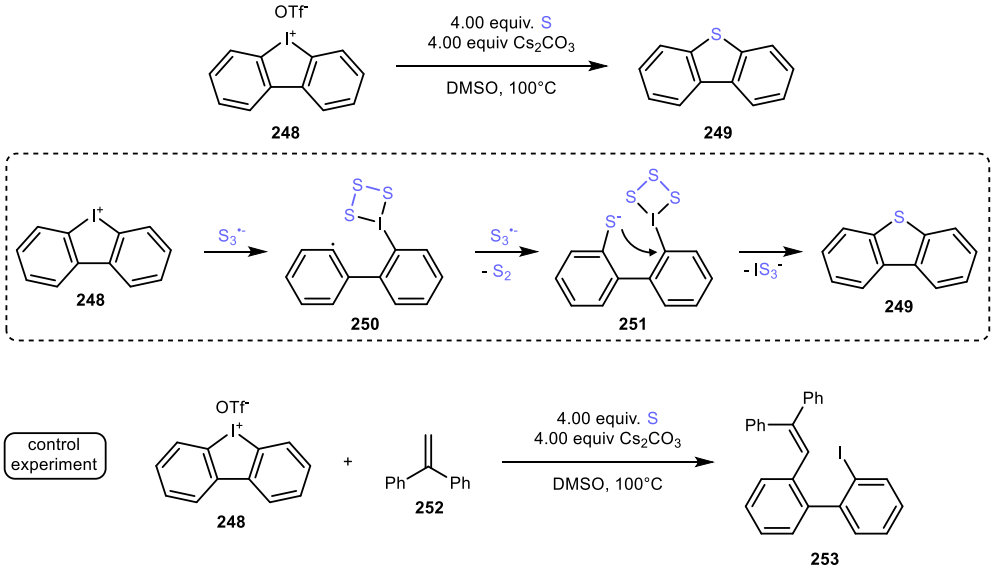
Most other reported instances of aromatic C-X substitutions involve the preceding incorporation of sulfur atoms to other sites of the involved compounds via one of the mechanisms discussed in the previous sections (compare Scheme 27).

Deng et al. reported the synthesis of benzoisothiazoles **255** from *o*-chlorobenzamidines **254** and sulfur, mediated by potassium phosphate. It was proposed that the amidine is thiolated via attack on sulfur and elimination of S_7, followed by an intramolecular S_NAr. Radical mechanisms were ruled out in control experiments with TEMPO (Scheme 86) [202]. Fu and Peng reported a similar reaction involving *N*-acyl-*o*-bromoamidines **256**, proposing a similar mechanism. For the final cyclization step involving the aromatic substitution, they propose an "S_{NR}" mechanism, potentially implying radical involvement (Scheme 86) [203].

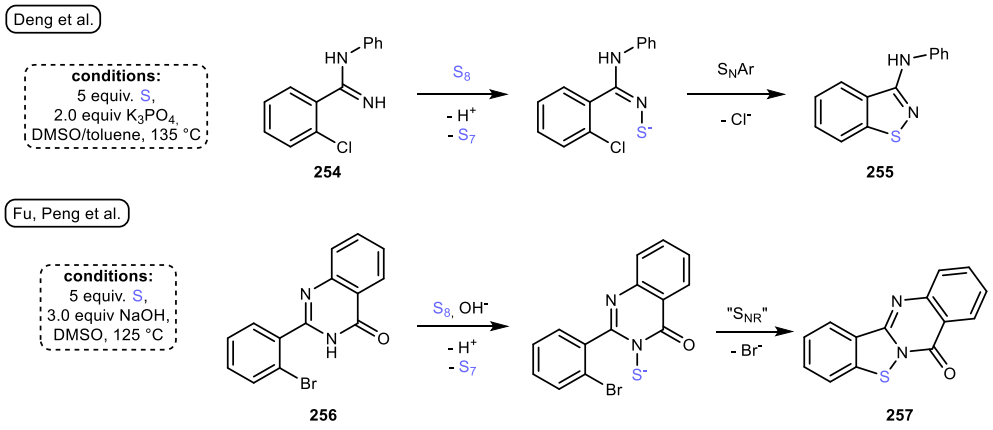
Dyker et al. reported the formation of thienobenzothiophenes **260** as a side reaction of the Willgerodt-Kindler reaction, if the aromatic moiety is sufficiently activated for nucleophilic aromatic substitution (Scheme 87) [204]. For instance, 4-chloropyrid-3-yl-butan-2-one **258** was reported to yield thienobenzothiophene **260** under Willgerodt-Kindler conditions. Mechanistically, α-thiolation of the enamine was proposed (compare section 3.2.2), followed by intramolecular nucleophilic aromatic substitution, yielding benzothiophene **259**. The final product **260** is generated via C3-thiolation of **259** and Willgerodt-Kindler thioamide formation, followed by nucleophilic condensation with H_2S elimination.

Nguyen et al. reported the synthesis of 2-benzoylbenzothiophenes **262** from 2-nitrochalcones **261**. The reaction was enabled by several organobases, DIPEA being the most effective [205]. A later report using the isomeric 2'-nitrochalcones **263**, mediated by triethylamine, states that the use of solvents such as DMSO or DMF allowed the reaction to proceed at room temperature, indicating that the solvent potentially plays a critical role in the reaction. It was suggested that NEt_3 attacks the chalcone β-position, followed by thiolation of the resulting enolate and subsequent intramolecular S_NAr of nitrite (Scheme 88) [206]. Similar reactions involving thiolation of chalcones and subsequent nitro-substitution were reported by Singh et al. who found that TEMPO did not inhibit the reaction and thus ruled out the involvement of radicals, further supporting the S_NAr character of the reaction. It was further found that brominated substrates did not undergo any reaction under the reported conditions, hence the authors emphasized the particular character of the nitro group both as activating group for the thiolation and as leaving group for the subsequent cyclization [207, 208].

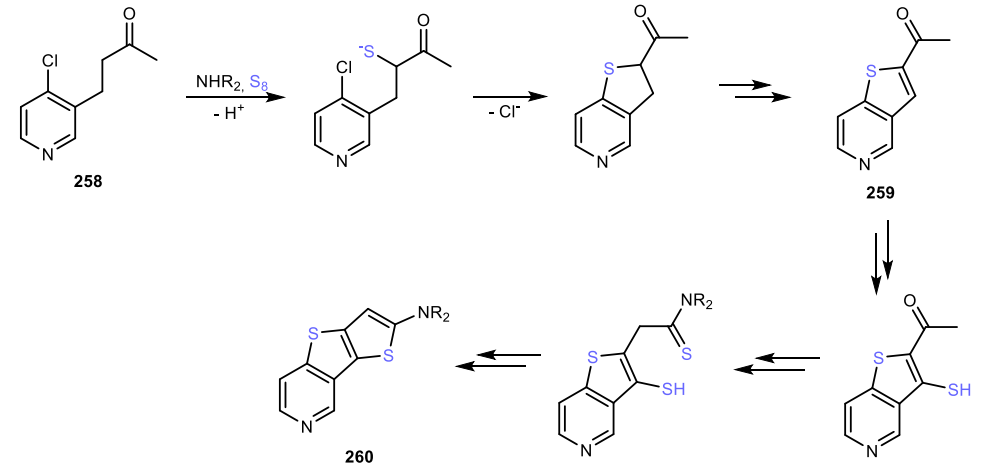
Many other reports employ copper-based catalysts for reactions involving elemental sulfur and aromatic halides, which facilitate the cleavage of the C-halogen bonds. Such reactions are often suggested to involve *in situ* generated copper-sulfur complexes as active species, and



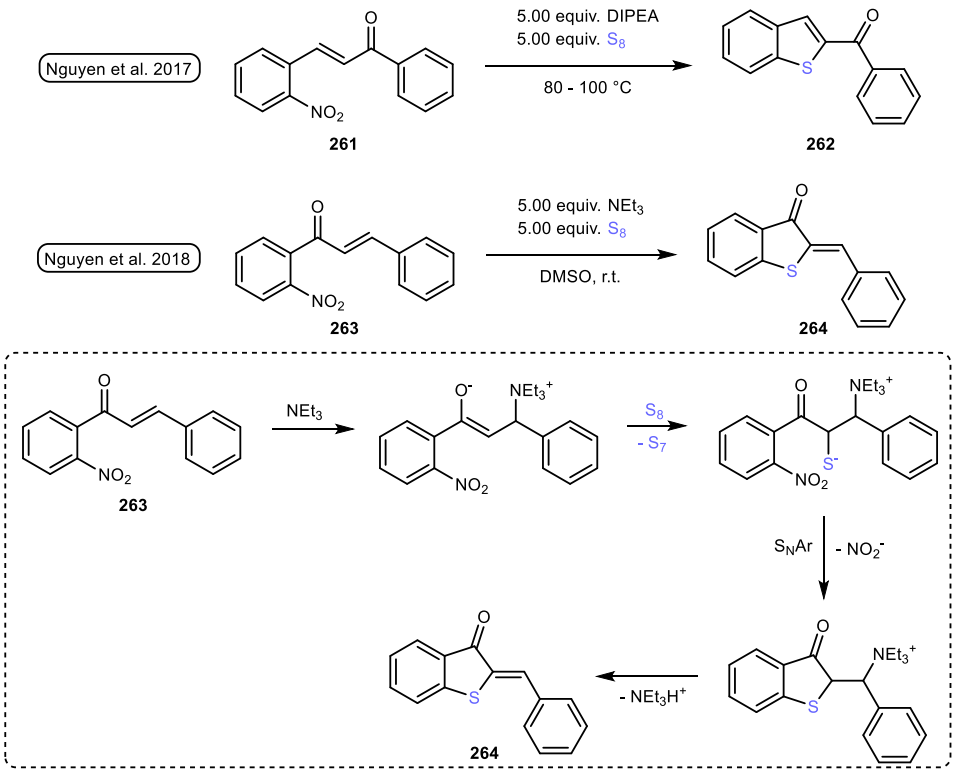
Scheme 85. Radical iodine-sulfur exchange of bis(aryl)iodonium salts **248**, reported by Jiang et al. in Ref. [201].



Scheme 86. Mechanisms for isothiazole formation from *o*-haloamidines, reported by Deng et al. in Ref. [202] and Fu and Peng et al. in Ref. [203].



Scheme 87. Domino-annulation of SNAr-activated substrates under Willgerodt-Kindler conditions, reported by Dyker et al. in Ref. [204].



Scheme 88. Thiolation and intramolecular nucleophilic aromatic substitution of nitrochalcones, reported by Nguyen et al. in Refs. [205,206].

are hence out of the scope of this review (for select examples, see Refs. [209–213]).

3.6. *Thionation of carbenes and carbenoids*

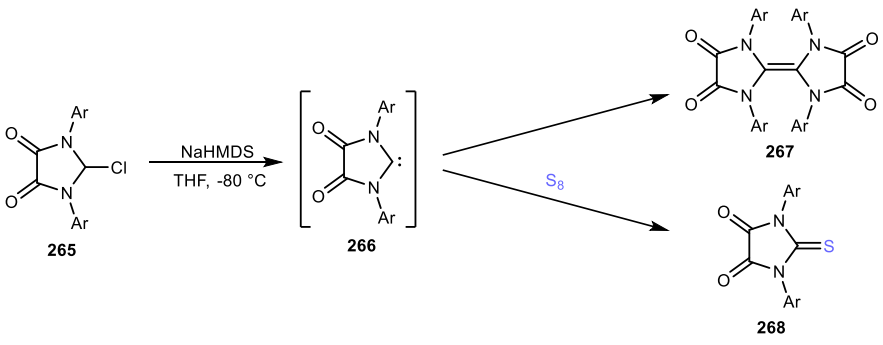
Carbenes are generally transient species with high electrophilic character due to the electron sextet at the carbon center. Reactions of carbenes with elemental sulfur result in the formation of C=S double bonds.

N-heterocyclic carbenes (NHCs) are known to form the corresponding thioureas via reaction with elemental sulfur in a highly exothermic reaction [214]. For instance, the reaction has been used by Ganter et al. in order to verify the *in situ* generation of a carbene **266** from a cyclic chlorooxalamide **265** with strong base. In the absence of sulfur, only the Wanzlick dimer **267** was detected, the addition of sulfur to the reaction mixture resulted in the formation of the corresponding thiourea **268** (Scheme 89) [215]. To our knowledge, no exact mechanism has been suggested for this transformation.

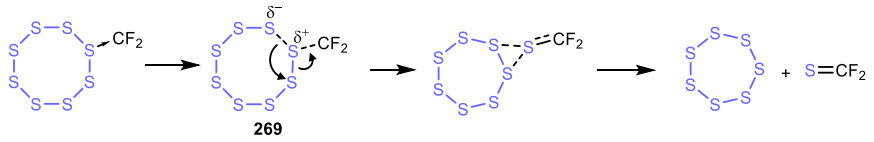
Xiao et al. found that difluorocarbene reacts with sulfur to form thiocarbonyl fluoride *in situ* and suggested a mechanism based on DFT calculations (Scheme 90) [216,217]. It was found that CF_2 and S_8 initially exothermically form a Lewis adduct. Subsequently, the non-bonding electrons of CF_2 are transferred to antibonding orbitals of the S_8 cycle, forming a cyclic intermediate **269** with a strongly polarized S–S bond. This step is essentially equivalent to a nucleophilic attack on S_8, although according to the calculations, the polarized S–S bond is not completely broken, as has been postulated for instance for the nucleophilic attack of amines on S_8. **269** further decomposes into S_7 and thiocarbonyl fluoride. The overall reaction is highly exergonic with a Gibbs free energy of −207 kJ/mol and a total activation barrier of 66 kJ/mol.

Latif et al. found that the reaction of diazo compounds **270** with elemental sulfur at room temperature gave rise to thiiranes **273**, formed through the generation of an intermediate thioketone **272** and subsequent Barton-Kellogg reaction with the reactant diazo compound **270** [218]. It was suggested by the authors that the reaction proceeds via a carbene **271** intermediate, formed *in situ* via spontaneous elimination of molecular nitrogen from diazo compounds (Scheme 91).

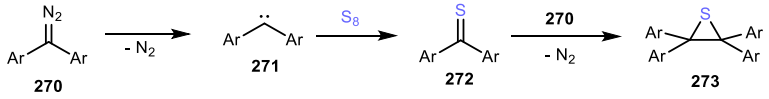
A similar reaction was reported by Meier et al. where diazo compounds **270** were formed *in situ* via the decomposition of benzophenone-derived *N*-tosylhydrazones **274** under basic conditions, similarly



Scheme 89. Formation of a thiourea **268** from an *in situ* generated NHC **266**, reported by Ganter et al. in Ref. [215].



Scheme 90. Proposed mechanism for the formation of thiocarbonyl fluoride from difluorocarbene and sulfur.



Scheme 91. Formation of thiiranes **273** from diazo compounds **270** via reaction with elemental sulfur and subsequent Barton-Kellogg reaction, reported by Latif et al. in Ref. [218].

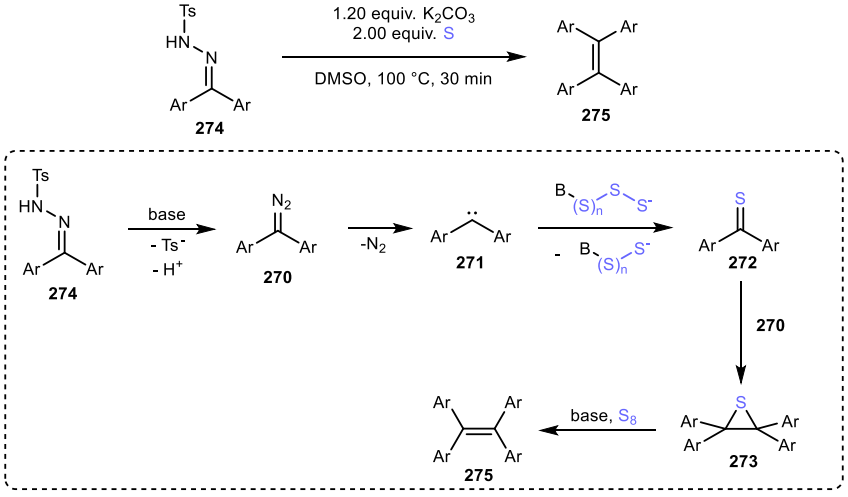
forming thiiranes, which were cleanly reduced to tetraphenylethylenes **275** by base-activated sulfur in a tandem reaction (*vide infra*) [219]. Mechanistic control experiments using a diazo compound **270** under the optimized conditions found that the use of base and sulfur, in contrast to only using sulfur, resulted in an increased selectivity towards the formation of the final tetraphenylethylene product (**275**). It was suggested that the high temperatures and basic conditions of the reaction form nucleophilic sulfur species, which facilitate the reaction of carbene with sulfur (Scheme 92). The reported optimized reaction conditions are also potentially favorable for the involvement of sulfur radical species.

The synthesis of dithiobenzoates **279** from benzyl sulfones **276**, reported by Masson et al. has already been discussed in an earlier section (compare Scheme 56) [152]. The intermediate formation of a benzylidene carbene **277** via deprotonation of the sulfone **276** followed elimination of a sulfinate anion was suggested as a possible pathway by the authors. It was proposed that the reaction of carbene with sulfur involves the insertion of the carbene into the cyclooctasulfur ring, forming an octathionane intermediate **278**, which subsequently eliminates a smaller, cyclic sulfur species (Scheme 93).

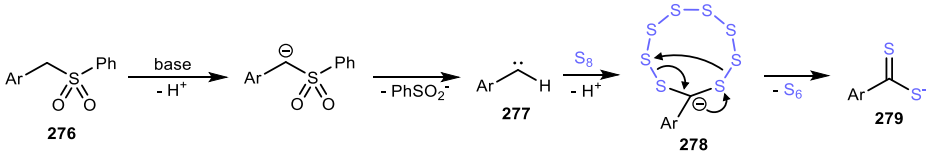
Carbon monoxide possesses carbenoid character at its carbon atom, making it susceptible to nucleophilic attack. Mizuno et al. published a series of reports involving the *in situ* reaction of carbon monoxide with elemental sulfur under basic conditions, forming carbonyl sulfide COS or chemically equivalent species [220–224].

It was reported that primary amines react with sulfur and carbon monoxide, forming ammonium thiocarbamates **280**. It was initially postulated that the aminopolysulfides formed from amine and sulfur attack carbon monoxide, forming COS via extrusion of a shortened polysulfide. COS subsequently reacts with amine, forming the carbamate [220,221]. It was later reported that the presence of DBU also enables secondary amines to react. However, test reactions revealed that no free COS was formed from the reaction of DBU with elemental sulfur and CO, an alcohol or amine being necessary for a reaction. Hence, the postulated mechanism was adapted to involve the concerted formation of the thiocarbamate species after nucleophilic attack of the polysulfide on CO under extrusion of smaller elemental sulfur allotropes (Scheme 94). DBU was only postulated to assist in the reaction steps that require deprotonation [222–224]. Later reports by Wu et al. found that the presence of radical scavengers did not influence the reaction of CO with sulfur and base, ruling out radical mechanisms [225,226].

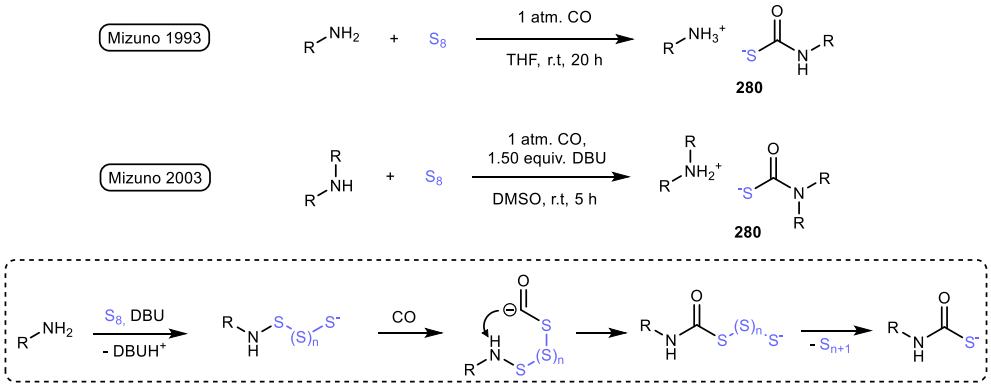
Isocyanides are isoelectronic with carbon monoxide and thus possess the same characteristic amphiphilic character at their carbenoid carbon atoms. Lipp et al. discovered that isocyanides **281** and sulfur react with amines or hydrazines, forming thioureas **101** and thiosemicarbazides, respectively [227]. Al-Mourabit et al. further optimized the reaction and suggested several possible pathways (Scheme 95). It was proposed that the isocyanide could act as a carbon-centered nucleophile, attacking elemental sulfur to form a nitrilium polysulfide species **282**, which is attacked nucleophilically by the amine, yielding the final product under elimination of a sulfur species. A second possible pathway is analogous to those proposed for the reaction of CO with sulfur (compare Scheme 94), involving activation of elemental sulfur by the amine and nucleophilic attack on the isocyanide carbon. The thiourea could either be yielded by a concerted pathway with elimination of a shortened sulfur



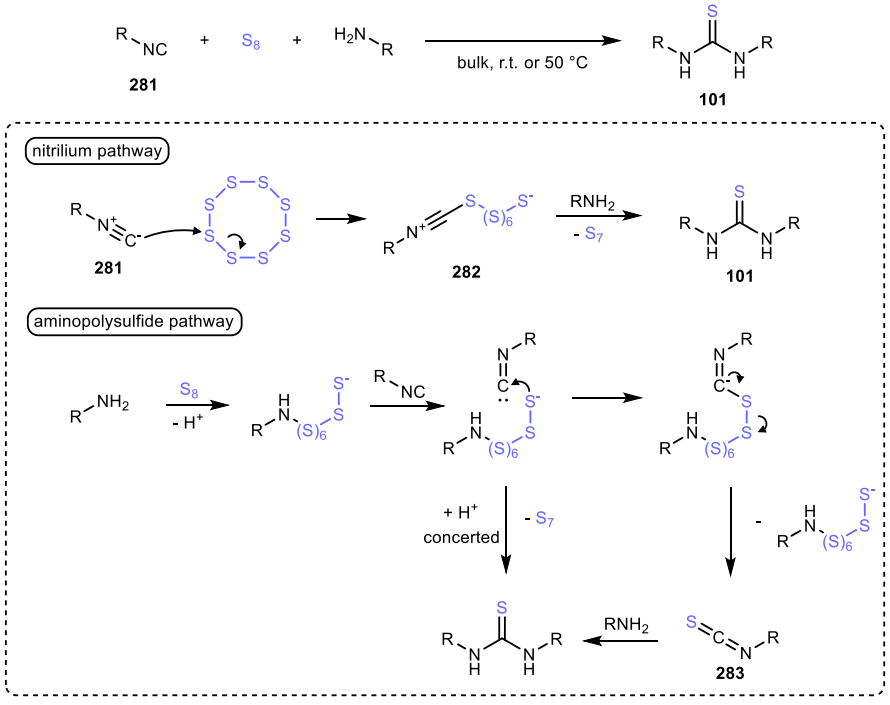
Scheme 92. Synthesis of tetraphenylethylene derivatives **275** via sulfur-mediated olefination, involving carbene thionation via nucleophilic sulfur species, reported by Meier et al. in Ref. [219].



Scheme 93. Pathway for the formation of a dithiobenzoate **279** from a benzyl sulfone **276**, suggested by Masson et al. in Ref. [152].



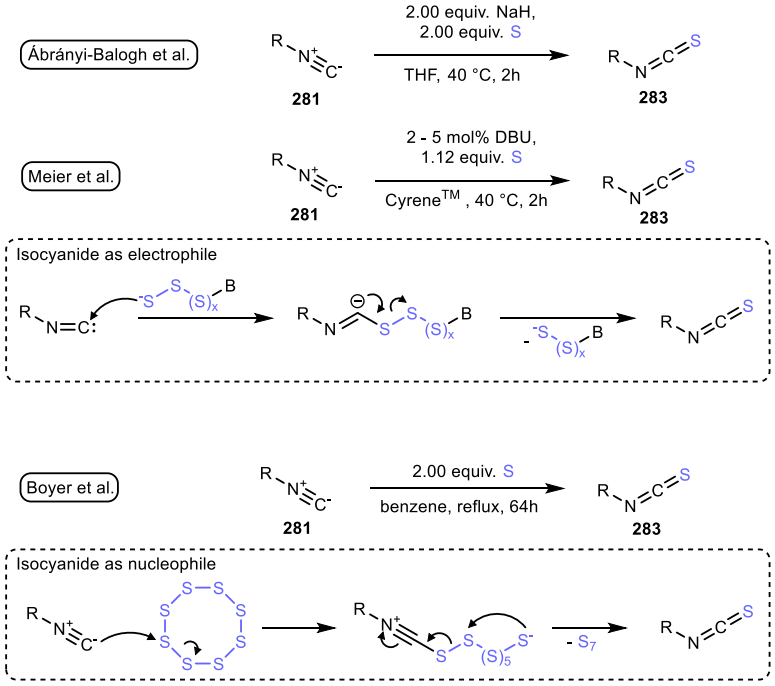
Scheme 94. Postulated mechanism for the formation of thiocarbamates from amines and CO according to Mizuno et al. in Ref. [222].



Scheme 95. Possible pathways for the synthesis of thioureas **101** from isocyanides **281**, amines and sulfur, suggested by al-Mourabit et al. in Ref. [227].

species, or in a multi-step pathway involving the formation of an intermediate isothiocyanate **283**, which undergoes rapid nucleophilic addition with the amine [228].

In a recent review, Ábrányi-Balogh et al. have proposed that the formation of thioureas via sulfur activation using isocyanides and bases involves isothiocyanates as most likely intermediates (Scheme 96) [18]. This is based on several reports involving the isolation of isothiocyanates in reactions of isocyanides and sulfur with non-nucleophilic bases. Ábrányi-Balogh et al. have reported a synthesis of thiourethanes from isocyanides, alcohols and elemental sulfur using sodium hydride as the base. In the absence of alcohol, isothiocyanates were the sole products. No reaction occurred in the additional absence of base [229]. Meier et al. found that isothiocyanates could be efficiently synthesized from isocyanides and sulfur using catalytic amounts of organobases under mild conditions (Scheme 96). It was found that higher basicity correlated with the catalytic effect of the base, DBU being the most effective among the examined catalysts in loadings as low as 2 mol% [230]. These reports indicate that the activation of elemental sulfur with bases is crucial for the formation of isothiocyanates from isocyanides under mild conditions. Still, there have been reports on the synthesis of



Scheme 96. Syntheses of isothiocyanates **283** from isocyanides **281** and elemental sulfur with suggested pathways for both electrophilic and nucleophilic reactivity of isocyanides.

isothiocyanates from isocyanides and sulfur without any basic additives, albeit requiring higher temperatures and longer reaction times [231, 232]. It has been proposed that this reaction proceeds via the nitrilium pathway, where the isocyanide reacts as a nucleophile, indicating that this pathway is also feasible under harsher conditions (Scheme 96).

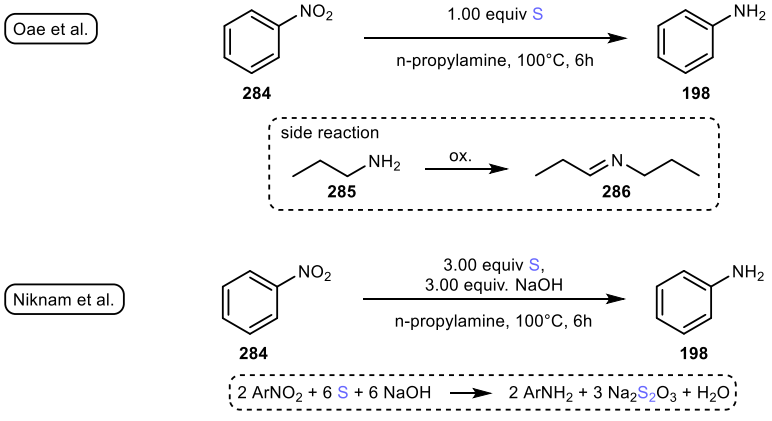
3.7. Sulfur-mediated reductions

3.7.1. Reduction of nitro functions

Nitroarenes can be reduced to aniline derivatives by elemental sulfur in the presence of bases. Oae et al. reduced nitrobenzene **284** and other nitroarenes with elemental sulfur in amine solvents or liquid ammonia [151]. It was found that the reaction proceeds more readily in primary amines such as *n*-propylamine **285** than in secondary amines. Furthermore, it was observed that substrates bearing electron-withdrawing substituents, such as *p*-cyanonitrobenzene, react more efficiently. It was suggested by the authors that the amine solvent acts as a cooxidant, being oxidized to the corresponding imine **286** (Scheme 97). The potential involvement of radicals in the mechanism was suggested.

Niknam et al. reported the reduction of nitroarenes **284** with elemental sulfur, mediated by NaOH, and identified thiosulfate anions as the oxidized sulfur species. They proposed a stoichiometry for the reaction, indicating that a threefold excess of sulfur and hydroxide base is necessary (Scheme 97) [233]. Similar postulates were made by McLaughlin et al., who employed $NaHCO_3$ as the base [234].

The reduction of nitroarenes to anilines with elemental sulfur is presumably closely related to the Zinin reaction, which instead uses sodium sulfide or polysulfides as the reducing agent. The Zinin reduction is proposed to proceed in stepwise fashion via intermediate nitrosoarenes **287** and arylhydroxylamines **288**, with the initial reduction of the nitroarene **284** being the rate-determining step. To our knowledge, the exact mechanism of the Zinin reduction is not yet fully clarified [235]. The similarity of the reduction using elemental sulfur to the Zinin reaction was noted by Romero et al. who performed further studies on the mechanism of elemental sulfur reductions in the presence of hydroxide bases [236]. The disproportionation of elemental sulfur in the basic medium, forming sulfide and thiosulfate species, was confirmed experimentally. Furthermore, using *N,N*-dimethyl-*p*-nitroaniline as the



Scheme 97. Reduction of nitroarenes to anilines reported by Oae and Niknam in Refs. [233,234].

model substance, the corresponding nitroso compound, hydroxylamine and azoxy compound were identified in the reaction mixture, thus confirming the relationship to the Zinin reduction. A mechanism for the reduction of nitroarenes was proposed, involving the formation of thioperoxide anions from the interaction of sulfur and hydroxide as the active species (Scheme 98). The reduction proceeds via nucleophilic attack of HOS^- on the nitro function, eliminating hydroxide, followed by elimination of sulfoxylate anions, yielding the nitroso compound **287**, which reacts in the same fashion to form the hydroxylamine **288**. For further reduction of the nucleophilic hydroxylamines, thiosulfite anions are proposed to be the active species, reacting to thiosulfate, accompanied by formation of the aniline product **198**. The generation of thiosulfite is proposed to occur via the reaction of sulfoxylate with elemental sulfur. The observation of the azoxy compound was attributed to its formation via the condensation of the nitroso intermediate with the hydroxylamine.

The proposed nucleophilic reactions at the nitro group are consistent with the reported higher efficiency of substrates with electron-withdrawing substituents. A notable application for the reaction is the possibility to selectively reduce only one nitro function of arenes bearing multiple nitro substituents due to the deactivating effect of the newly generated amino group for a second reduction [236,237].

In the already mentioned reduction of nitroarenes in amine solvents and ammonia, conducted by Oae et al., no hydroxide ions are present. The authors however noted the known formation of aminothiolate species via the interaction of elemental sulfur and amines. It can hence be expected that these species can react via similar mechanisms [151].

Other synthetic applications of the reduction of nitroarenes involve the combination of this reactivity with other typical reactivities associated with elemental sulfur. The already previously mentioned nitromethyl-redox coupling reported by Nguyen et al. involves the oxidation of the benzylic methyl groups of picolines and simultaneous reduction of the nitro function of *o*-halonitrobenzenes **127**, yielding benzothiazoles **129** (compare Scheme 52) [147].

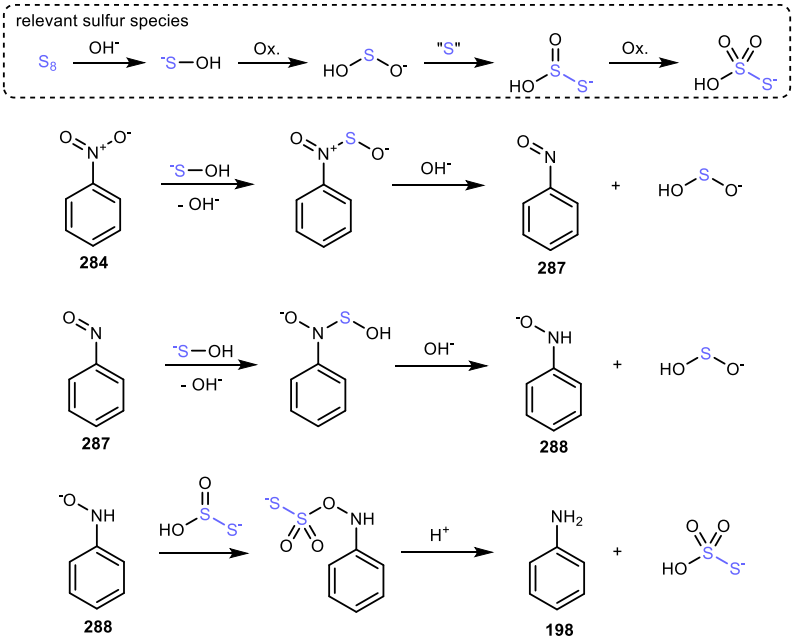
Nguyen et al. further expanded the reductive coupling of *o*-halonitrobenzenes **127** to benzylamines **114** as the coupling partner, also yielding benzothiazoles **289** [238]. Control experiments resulted in the detection of *N*-benzylsulfamate **290** salts as the oxidized sulfur species, further reinforcing the notion that aminothiolates also participate in the nitro reduction as the active species. It was further observed that the use of alkali sulfides as the reducing agent did not yield the benzothiazole, but merely reduced the nitro function, yielding an *o*-chloroaniline.

The authors proposed an exemplary mechanism entailing the formation of an aminothiolate from benzylamine and sulfur, followed by S_NAr of the *o*-chloro substituent of the chloronitrobenzene, yielding **291** (Scheme 99). This is followed by stepwise intramolecular transfer of the oxygen atoms to a sulfur atom, forming intermediate nitroso compound **292** and hydroxylamine **293**. Meanwhile, oxidation of the benzylic position enables nucleophilic coupling with the newly formed hydroxylamine substituent. Further intramolecular oxygen transfer and attack of another benzylamine eventually result in the formation of the product benzothiazole **289** and the byproduct *N*-benzylamidosulfite **294**, which is further oxidized to the sulfamate **290**. The authors noted that all processes could likewise take place with aminothiolates of other chain lengths, and that the exact order of steps is not clear. It is conceivable that also intermolecular redox processes could be involved.

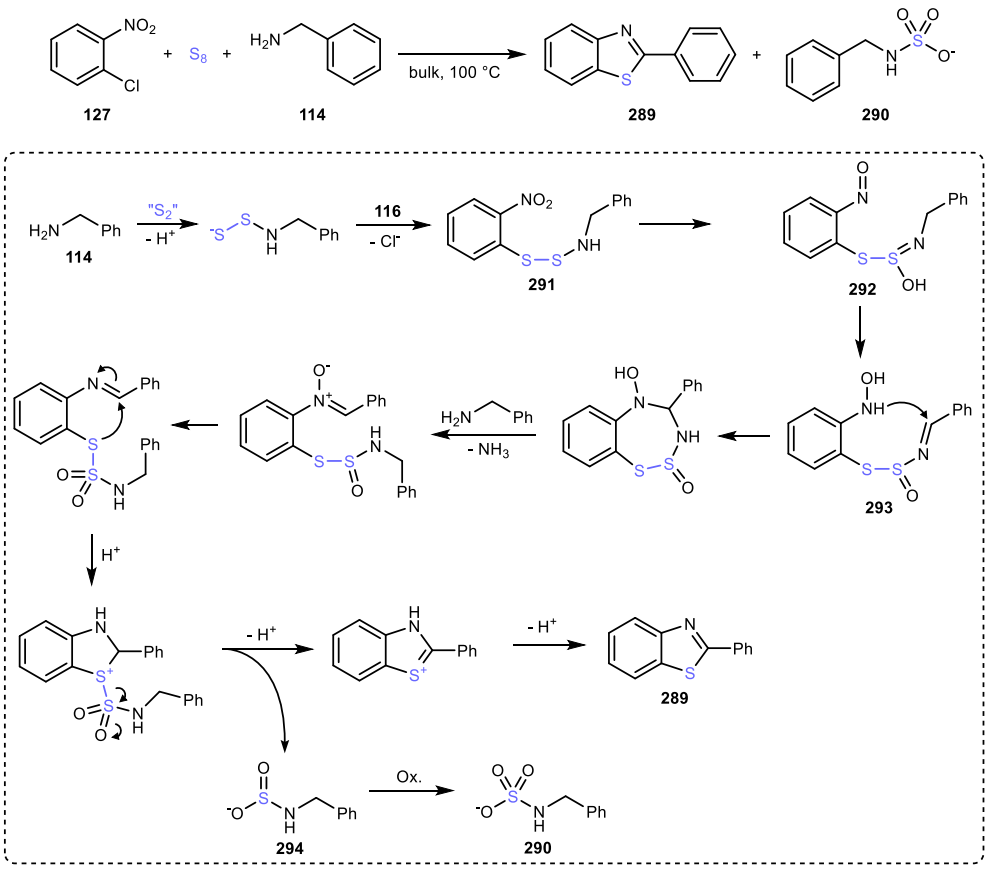
The synthetic scope of such nitro-redox coupling reactions of *o*-chloronitrobenzene has since been further extended to aromatic aldehydes or acetophenones as the coupling partners instead of benzylamines or methylhetarenes [239,240].

The reduction of aliphatic nitro groups has been more scarcely reported. Adib et al. reported the reduction of an aliphatic nitro group as part of the cyclization of 1,3-diaryl-γ-nitroketones **295** to pyrroles **296** with ammonium acetate in the presence of sulfur and morpholine. The proposed mechanism entails the nucleophilic attack of a morpholine polysulfide anion on the carbon atom of the *aci*-nitro tautomer, followed by elimination of an "SO" fragment via a four-membered cyclic intermediate **297**, resulting in an oxime **298** (Scheme 100). The carbonyl group of **298** forms an imine with ammonium acetate, which is suggested to undergo intramolecular nucleophilic cyclization with the oxime, eliminating hydroxylamine. No further evidence for their postulate was provided by the authors [241].

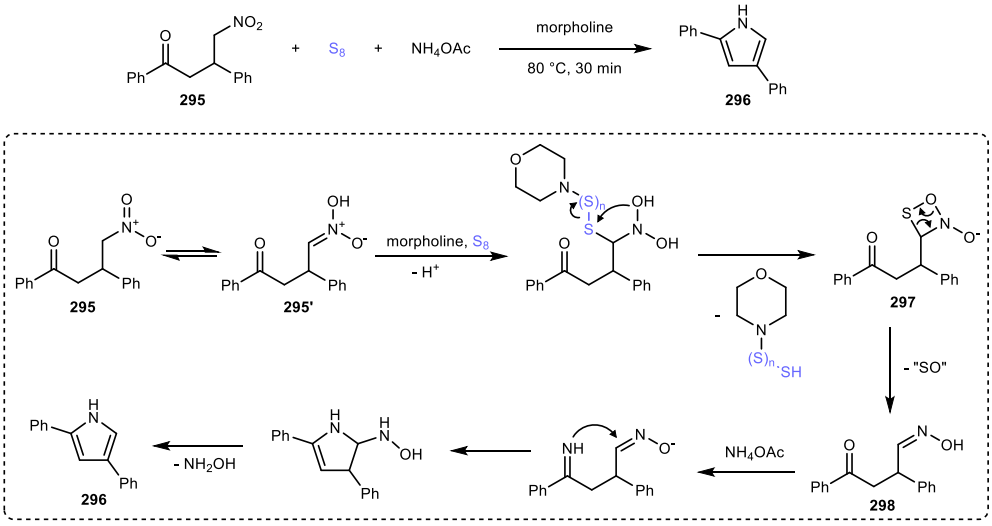
Recently, Nguyen et al. utilized nitromethane **299** as a building block for the synthesis of thioureas **101** together with amines and sulfur, catalyzed by strong organobases such as DABCO or NMPip [242]. When aliphatic amines were used, no activating catalyst was required. Test



Scheme 98. Proposed mechanism for the elemental sulfur-mediated reduction of nitroarenes **284** in the presence of hydroxide anions, reported by Romero et al. in Ref. [236].



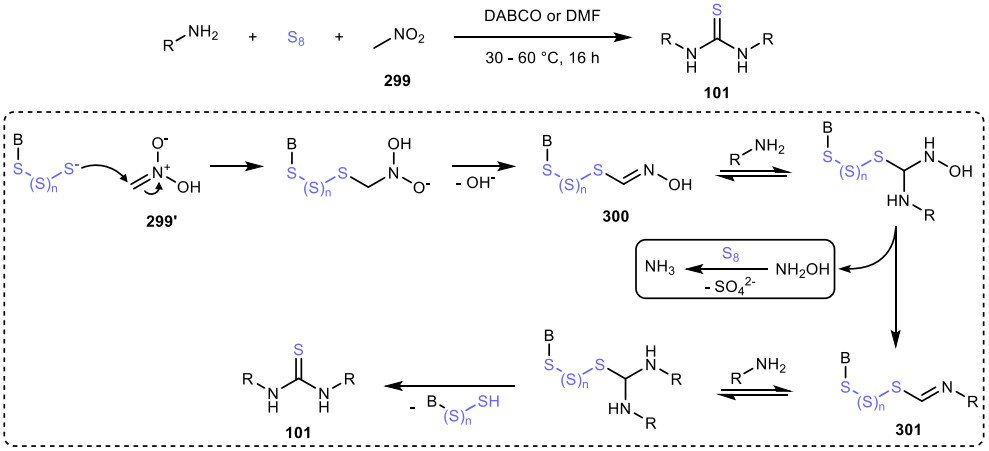
Scheme 99. Proposed mechanism for the synthesis of benzothiazoles **289** from *o*-chloronitrobenzene **127** and benzylamine **114**, reported by Nguyen in Ref. [238].



Scheme 100. Proposed mechanism for the formation of pyrroles **296** from γ-nitroketones **295**, reported by Adib et al. in Ref. [241].

reactions confirmed that the nitro group does not merely act as a leaving group, as in previously discussed S_NAr reactions, but participates in the reaction as a cooxidant. It was suggested by the authors that the reaction initiates with the nucleophilic attack of an anionic polysulfide to *aci*-nitromethane **299'**, which forms oxime derivative **300** after tautomerization and elimination of hydroxide (Scheme 101). **300** is suggested to be in equilibrium with imine derivative **301** by reaction with the amine, with the formed hydroxylamine being removed from the equilibrium by being reduced to ammonia by elemental sulfur. This was underlined by the detection of sulfate ions in the reaction mixture as the oxidized sulfur species. Imine **301** then forms the thiourea product **101** via reaction with another amine, followed by elimination of a shortened polysulfide species.

A highly interesting base-dependent chemoselectivity between nitro reduction and nitro-S_NAr was discovered by Nguyen et al. During their studies on the reaction of 2-nitrochalcones **261** with elemental sulfur and bases, they discovered that depending on the conditions, either benzothiophenes **262** or cyclic sulfonamides (sultams) **302** were



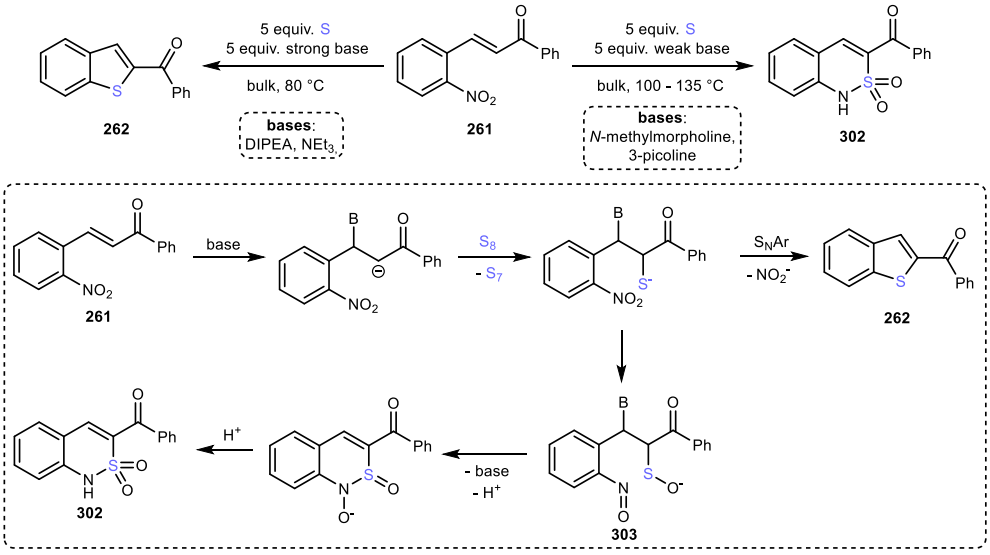
Scheme 101. Synthesis of thioureas **101** from amines, sulfur and nitromethane **299**, reported by Nguyen et al. in Ref. [242].

selectively generated [243,244]. The formation of benzothiophene **262** was already described in Section 3.5.2 and presumably proceeds via nucleophilic thiolation of the chalcone and subsequent intramolecular S_NAr cyclization by elimination of nitrite (compare Scheme 88). Strong organic bases such as triethylamine or DIPEA were required for this transformation. The use of weaker bases such as *N*-methylmorpholine or 3-picoline at higher temperatures was found to selectively generate the sultam **302** instead of the benzothiophene **262** (Scheme 102). The proposed mechanism for the transformation similarly entails the formation of a Michael adduct from base and chalcone, followed by formation of a polysulfide in the α-position. Instead of a subsequent S_NAr reaction, it was proposed that the thiolate attacks the nitro group, yielding a nitroso-sulfenate **303**, which rearranges to the sultam **302**. The underlying reasons for this highly interesting base-dependent chemoselectivity remain unclarified. The synthetic scope of the sultam formation has however since been expanded to other β-(*o*-nitrophenyl)-substituted Michael systems [245].

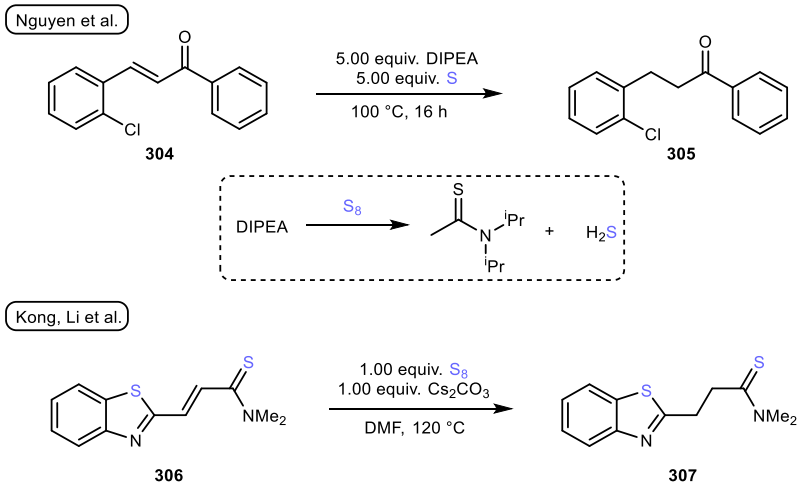
3.7.2. *Other reductions*

Nguyen et al. discovered an interesting behavior of chalcones when investigating potential alternative substrates to 2-nitrochalcones for intramolecular S_NAr reactions. It was found that using 2-halochalcones **304** did not result in intramolecular S_NAr when exposed to DIPEA and elemental sulfur (Scheme 103). Instead, formation of the hydrogenated chalcone **305** was observed. It was postulated that hydrogen sulfide, formed *in situ* via the oxidation of DIPEA, is the responsible species [243]. A similar reactivity has been postulated by Kong, Li et al. as part of the suggested mechanism for their synthesis of thioamides via ring-opening of benzothiazoles. It was suggested that the final product of the reaction, a saturated thioamide **307**, is generated via sulfur-mediated reduction of the corresponding α,β-unsaturated thioamides **306** (Scheme 103) [246]. The exact mechanism of this interesting reduction remains unclarified.

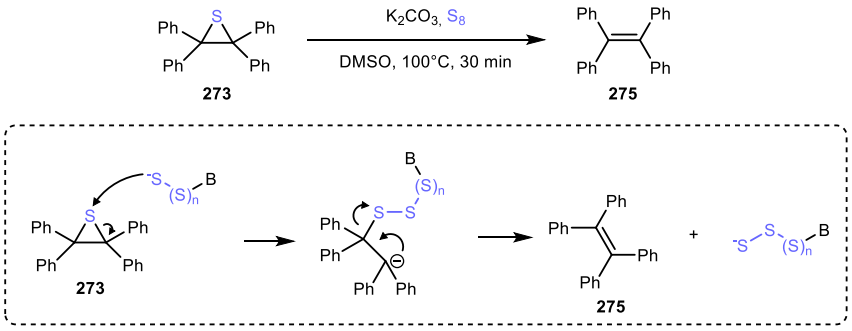
Meier et al. reported a synthesis of tetraphenylethylene derivatives **275** via a sulfur-mediated homocoupling of aromatic *N*-tosylhydrazones, which entails the formation of a thiirane **273** from *in situ* formed diazo compounds and thioketones (compare Scheme 92) [219]. It was found that the thiirane **273** is fully reduced to the corresponding alkene **275** under the optimized reaction conditions. Further control experiments confirmed that the thiirane is thermally stable and that the conversion to the alkene only proceeds in the presence of both potassium carbonate and elemental sulfur. The authors suggested a nucleophilic desulfurization pathway, entailing the nucleophilic attack of a polysulfide species formed from base and sulfur to the thiirane sulfur, followed by extrusion of a longer polysulfide species (Scheme 104). This suggestion was based on earlier reports by Huisgen, stating that



Scheme 102. Base-mediated chemoselective formation of sultams **303** or benzothiophenes **262** from 2-nitrochalcones **261**, reported by Nguyen in Refs. [243,244].



Scheme 103. Observed hydrogenation of chalcones **304** in the presence of DIPEA and elemental sulfur, reported by Nguyen in Ref. [243], and a similar reaction reported by Kong, Li et al. in. Ref. [246].



Scheme 104. Proposed mechanism for the reductive desulfurization of thiiranes with base and sulfur, reported by Meier et al. in Ref. [219].

thiiranes can be reduced to their alkene with a nucleophilic catalyst such as thiophenoxide [247]. It was assumed that the reaction is driven by the π-conjugation gained by the formation of the double bond. The reaction conditions could potentially also enable a radical mechanism for the desulfurization.

4. Conclusion

In this review, we have compiled and discussed typical reactivities that are commonly observed in organic reactions involving elemental sulfur under basic conditions, especially focusing on the suggested but often not unequivocally proven mechanisms. The discussed mechanistic proposals demonstrate the large degree of diversity in the suggested pathways, even for similar transformations, clearly highlighting the need for additional investigations to further understand the highly versatile reactivity of elemental sulfur in organic synthesis. The mechanisms of established reactions, such as the Willgerodt-Kindler or Gewald reactions, which have been known for decades, are still not unambiguously clarified. The underlying reasons for the many interesting and unexpected observations in reactions with elemental sulfur that have been discussed in this manuscript, such as the unexpected chemoselectivities induced by the choice of base or even the mode of heating, remain unexplored. Meanwhile, new synthetic work involving elemental sulfur is continuously published. It is obvious that many aspects concerning the organic chemistry of elemental sulfur remain unknown. We thus hope that this manuscript will serve as an incentive and guideline for future, more fundamental studies on the interactions of elemental sulfur with bases and nucleophiles, as well as the reactivities of the resulting intermediates.

CRediT authorship contribution statement

Peter Conen: Writing – original draft, Methodology, Conceptualization. **Michael A.R. Meier:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MM is an editorial board member and had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Jun Kee Cheng.

Data availability

No data was used for the research described in the article.

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