

# One-Pot Synthesis of Thiocarbamates

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An efficient isocyanide-based synthesis of *S*-thiocarbamates was discovered and thoroughly investigated. The new reaction protocol is a one-pot procedure and allows the direct conversion of *N*-formamides into thiocarbamates by initial dehydration with *p*-toluene sulfonyl chloride to the respective isocyanide and subsequent addition of a sulfoxide component. Contrary to recent literature, which also uses isocyanides as starting material, but with other sulfur reagents than sulfoxides, in this protocol, no isolation and purification of the isocyanide component is necessary, thus significantly decreasing the environmental impact and increasing the efficiency of the

synthesis. The new protocol was applied to synthesize a library of sixteen thiocarbamates, applying four *N*-formamides and four commercially available sulfoxides. Furthermore, experiments were conducted to investigate the reaction mechanism. Finally, four norbornene-based thiocarbamate monomers were prepared and applied in controlled ring-opening metathesis polymerization (ROMP) reactions. The polymers were characterized by size-exclusion chromatography (SEC) and their properties were investigated utilizing differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA).

## Introduction

Thiocarbamates are a well-established substance class within organic chemistry.<sup>[1–16]</sup> Their versatility is partially derived from their isomeric character: *O*-organyl and *S*-organyl thiocarbamates as well as dithiocarbamates are well known. Some are biologically active and hence they have found applications as antifertility agents, antivirals, pesticides and herbicides (e.g. the *S*-organyl thiocarbamates Thiobencarb, Orbencarb, and Molinate).<sup>[4,17–19]</sup>

However, preparation of *S*-organyl thiocarbamates involves toxic starting materials or intermediates.<sup>[10,20,21]</sup> Their synthesis often relies on the conversion of phosgene or its derivatives by subsequent addition of an amine and a thiol or *vice versa* or, alternatively, the conversion of organic isocyanates utilizing thiols.<sup>[1,2,9,10,22,23]</sup> Whereas isocyanates are not as hazardous as phosgene itself, their preparation commonly involves reacting primary amines with phosgene – hence both strategies involve the same starting material, which should generally be omitted in terms of environmental aspects and for safety reasons.<sup>[24,25]</sup>

Alternatively, more sustainable routes to isocyanates were published in the last years and some of them have already been employed in the synthesis of thiocarbamates.<sup>[11,21]</sup> Recently, it was shown that also isothiocyanates can be obtained rather sustainably utilizing isocyanides as starting material,<sup>[26]</sup> which, if applied, would allow for a more benign synthesis of *O*-organyl or dithiocarbamates by functionalization with an alcohol or thiol. On this basis, *S*-organyl thiocarbamates are theoretically accessible through the Newman-Kwart rearrangement by isomerization of the *O*-thiocarbamates,<sup>[27]</sup> yet a direct synthetic route is more favorable. Generally, isocyanides have been recognized as a substance class of remarkable reactivity as they can be applied in a variety of reactions, e.g. in multi-component chemistry,<sup>[28]</sup> insertion reactions<sup>[29–31]</sup> and van Leusen reactions.<sup>[32]</sup>

In the last decade, several new routes toward *S*-thiocarbamates have been published starting with the work of Maes *et al.* in 2016, who employed isocyanides for their synthesis.<sup>[4]</sup> These were converted by thiosulfonates and iodine as catalyst that are, like isocyanides, far easier to handle than either phosgene or isocyanates, especially on laboratory scale (Scheme 1). In the following years, the working groups of Sun, Yang, Wei Wei and Khalaj also exploited this newfound reactivity of isocyanides to access a wide variety of *S*-thiocarbamates in good yields, by utilizing the thermolysis of sulfoxides, a photochemical reaction of thiols, an iodine-catalyzed conversion of sulfinates or in a three-component reaction with elemental sulfur and an aryl iodide.<sup>[5–8]</sup>

All these synthetic strategies involve environmentally benign solvents, reactants, and reaction conditions, yet do not consider the preparation of the isocyanide component. The synthesis of isocyanides, however, also relies on hazardous reagents, like phosphoryl trichloride (POCl<sub>3</sub>) or phosgene and its derivatives and nearly always requires time- and resource-consuming column chromatography in addition to excessive aqueous work-up (quenching with sodium carbonate solution

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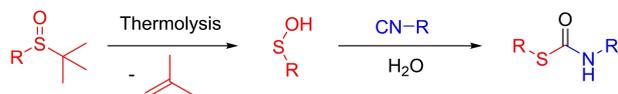
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Previous publications

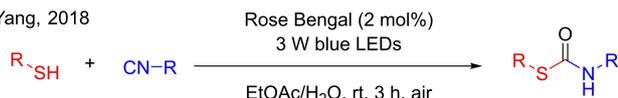
Maes, 2016



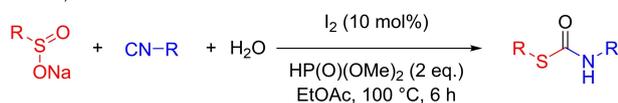
Sun, 2018



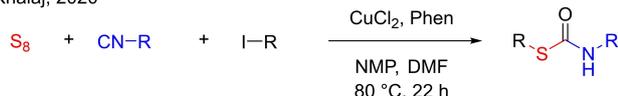
Yang, 2018



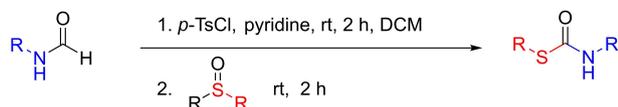
Wei Wei, 2019



Khalaj, 2020



Herein reported procedure



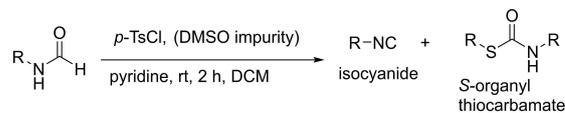
**Scheme 1.** Previous publications of isocyanide-based *S*-organyl thiocarbamate synthesis and the herein reported one-pot approach starting from the *N*-formamide.<sup>[4–8]</sup>

and extraction).<sup>[33,34]</sup> However, also mild conditions have been reported for the synthesis of isocyanides, but are not commonly in use.<sup>[35,36]</sup>

In 2020, Meier *et al.*<sup>[37]</sup> as well as the working group of Dömling<sup>[38]</sup> published an extensive sustainability analysis of isocyanide syntheses. In the first publication, the more sustainable synthesis of aliphatic isocyanides utilizing *p*-toluene sulfonyl chloride (*p*-TsCl) in either dimethyl carbonate (DMC) or dichloromethane (DCM) with pyridine (Pyr) as a base was described. These conditions not only significantly reduced the E-factor of the isocyanide synthesis, but also omitted the toxic phosphoryl chloride (POCl<sub>3</sub>), which is mostly considered as the dehydrating agent of choice by literature – also in the most recent publication by Dömling, in which time expense/efficiency were key foci toward sustainability.

Herein, we report a new one-pot synthesis of *S*-thiocarbamates, which was discovered as side reaction within our studies on a more sustainable route to isocyanides and investigated thereafter (Scheme 2).

Key point of the discovery was a freshly synthesized *N*-formamide that was still contaminated with dimethyl sulfoxide (DMSO) after column chromatography due to the high polarity



**Scheme 2.** Initial discovery of the one-pot *S*-organyl thiocarbamate synthesis.

of the latter. The subsequent dehydration to the respective isocyanide utilizing *p*-TsCl/Pyr in DCM yielded the desired product, but also an unknown side-product, which proved to be the respective *S*-methyl thiocarbamate. It was hypothesized that the sulfoxide had unexpectedly reacted as a sulfur donor (Scheme 2).

## Results and Discussion

In the literature, however, such a one-pot protocol starting from the *N*-formamide directly yielding the *S*-organyl thiocarbamate is not known. The approach that comes closest to the observed reactivity is a publication by Sun *et al.*, which utilizes *tert*-butyl organyl sulfoxides that are thermolyzed at 100 °C in toluene to give a sulfenic acid intermediate.<sup>[5]</sup> Subsequent addition of the isocyanide component and nucleophilic attack of one equivalent of water yielded a variety of *S*-organyl thiocarbamates in up to excellent yields.

However, in our case, we suspected a different mechanism as the sulfoxide and an isocyanide component alone in dichloromethane could not react. Therefore, we started our investigation with the optimization of the reaction protocol. First, we evaluated the time of sulfoxide addition and found that adding it after complete *N*-formamide dehydration (2 h) is beneficial in terms of yield. Therefore, the general protocol featured dissolving *N*-dodecyl formamide in dichloromethane/Pyridine and addition of dehydration agent. After two hours of stirring, dimethyl sulfoxide was added and the solution was allowed to stir for two more hours, upon which strong coloring was observed (turquoise to green). Finally, flash column chromatography of the crude mixture afforded the *S*-organyl thiocarbamate as the desired product.

Initially, the equivalents of dehydration agent (*p*-TsCl) were varied between 1.00 and 1.60 eq., as shown in Table 1 (entries 1–7). Especially with low amounts of *p*-TsCl, mixtures of thiocarbamate and isocyanide were obtained and proved to be inseparable by flash column chromatography, hence the yield was calculated utilizing <sup>1</sup>H NMR spectroscopy of the mixture.

Whereas 1.00 eq. *p*-TsCl yielded only isocyanide, already at 1.30 eq., two thirds of the converted *N*-formamide were thiocarbamate, while at 1.40 eq. 100% conversion was achieved. Increasing the equivalents above 1.50 eq. led to no significant improvement in terms of yield.

Subsequently, the amount of dimethyl sulfoxide was varied between 1.00 and 2.00 eq. In this test series, however, no consistent trend was observed, as already 1.00 eq. of DMSO led to full conversion of the intermediately formed isocyanide and

**Table 1.** Optimization of the thiocarbamate one-pot synthesis starting from *N*-dodecyl formamide. The varied component is marked in blue.

| Entry | Eq. <i>p</i> -TsCl <sup>[a]</sup> | Eq. DMSO | Solvent | Yield (%)             |
|-------|-----------------------------------|----------|---------|-----------------------|
| 1     | 1.00                              | 1.50     | DCM     | / <sup>[b]</sup>      |
| 2     | 1.10                              | "        | "       | 10.2 <sup>[c]</sup>   |
| 3     | 1.20                              | "        | "       | 45.1 <sup>[c]</sup>   |
| 4     | 1.30                              | "        | "       | 68.2 <sup>[c]</sup>   |
| 5     | 1.40                              | "        | "       | 74.8 <sup>[d]</sup>   |
| 6     | 1.50                              | "        | "       | 76.8 <sup>[d]</sup>   |
| 7     | 1.60                              | "        | "       | 76.5 <sup>[d]</sup>   |
| 8     | 1.50                              | 1.00     | DCM     | 81.2 <sup>[d]</sup>   |
| 9     | "                                 | 1.25     | "       | 76.5 <sup>[d]</sup>   |
| 10    | "                                 | 1.40     | "       | 70.0 <sup>[d]</sup>   |
| 11    | "                                 | 1.50     | "       | 76.8 <sup>[d]</sup>   |
| 13    | "                                 | 1.60     | "       | 74.4 <sup>[d]</sup>   |
| 13    | "                                 | 2.00     | "       | 47.0 <sup>[d]</sup>   |
| 14    | 1.50                              | 1.50     | Me-THF  | 55.9 <sup>[d,e]</sup> |
| 15    | 1.50                              | 1.50     | DMC     | 75.5 <sup>[d,e]</sup> |

[a] Amount of pyridine was eq. (*p*-TsCl) × 2. [b] Only isocyanide was obtained. [c] Mixtures of product and isocyanide were obtained and hence the yield was calculated by <sup>1</sup>H NMR spectroscopy. Therefore, the product mixture was purified by flash column chromatography without separating the remaining isocyanide and the thiocarbamate. Then, the CH<sub>2</sub> adjacent to the isocyanide functionality and the NH of the thiocarbamate were integrated and compared. [d] Only product was obtained. [e] Isocyanide synthesis proceeds at lower rate in these solvents, and hence the reaction time of the first step was adjusted to 8 h.

gave the highest yield of thiocarbamate (81.2%). Increasing the amount of DMSO led to a decrease in product yield, but with a local maximum at 1.50 eq. with 76.8%. Later, also sulfoxides other than DMSO, and hence different reactivity, were utilized, which gave higher yield with 1.50 eq. Therefore, it was decided to conduct any further reactions with 1.50 eq. of *p*-TsCl and sulfoxide. Lastly, two alternative solvents, 2-methyl tetrahydrofuran (Me-THF) and DMC, were applied. Whereas for Me-THF a significant decrease in yield was noticed, the batch with DMC gave results quite similar to DCM. Nonetheless, we chose to proceed with DCM as the initial dehydration to the isocyanide progressed much faster (overnight for DMC vs 2 h for DCM).<sup>[37]</sup> It is noted that 8 h of stirring was enough for the one-pot reaction, which is still four times longer than in DCM. However, if sustainability is an important criterion, the dichloromethane can be replaced by the environmentally more benign DMC without significant loss in yield.

The thus optimized conditions (1.50 eq. *p*-TsCl, 3.00 eq. pyridine, 1.50 eq. sulfoxide in DCM) were then applied to synthesize a library of sixteen different thiocarbamates, which were based on four *N*-formamides and four commercially available sulfoxides.

For the *N*-formamides, dodecyl, cyclohexyl, benzyl, and methyl norbornyl substituents were utilized (Table 2). The functionalized norbornenes were later applied in ring-opening metathesis polymerization (ROMP). As sulfoxide, DMSO, butyl sulfoxide, tetrahydrothiophene-1-oxide and benzyl sulfoxide were employed. The respective *S*-organyl thiocarbamates were obtained after flash column chromatography in acceptable to good yields (exception is the *S*-benzyl cyclohexyl thiocarbamate, which could only be isolated in 25% yield) and in good purity. Generally, the benzylic sulfoxide proved to be the least

reactive in the thiocarbamate synthesis, whereas the cyclic tetrahydrothiophene-1-oxide and DMSO gave consistently high yields. Interestingly, the thiocarbamates starting from *N*-benzyl formamide gave higher yields than just the synthesis of benzyl isocyanide in our previous publication (synthesis of benzyl isocyanide in DCM with aqueous work-up and flash column chromatography: 44% vs 46–72% for the resulting thiocarbamates).<sup>[37]</sup> This is possibly a consequence of the hydrolytic instability of benzyl isocyanide or its solubility in water, which leads to a decrease in yield for protocols that use aqueous work up. In the thiocarbamate procedure, however, the benzyl isocyanide is directly converted and hence losses by the aforementioned factors are minimal.

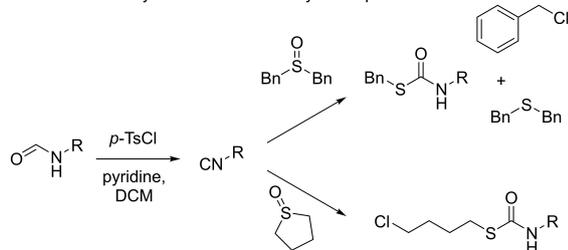
Employment of the cyclic sulfoxide (Table 2, tetrahydrothiophene-1-oxide) was of particular interest as the expected ring-opening was relevant to evaluate the fate of the second sulfoxide substituent, which remained unknown for DMSO and butyl sulfoxide. For tetrahydrothiophene-1-oxide, however, a nucleophilic attack of chloride was observed after initial ring-opening yielding *S*-4-chlorobutyl thiocarbamates as products (Scheme 3, 1.). Likewise, this observation led to the conclusion that also the reaction of other sulfoxides would result in halocarbon species – chloromethane, 1-chlorobutane and benzyl chloride, respectively. However, the first two molecules are highly volatile and could neither be isolated nor detected in gas chromatography paired with mass-spectrometry (GC-MS). Therefore, our focus shifted to the benzyl sulfoxide, or rather benzyl chloride, which was found by GC-MS (Figure S47) as well as by thin-layer chromatography (TLC), further strengthening our hypothesis regarding the retention of the second sulfoxide substituent. Concludingly, the reaction proceeds under formation of an alkyl chloride as byproduct (Figure S47 and Fig-

**Table 2.** Thiocarbamates synthesized through one-pot dehydration and sulfoxide addition.

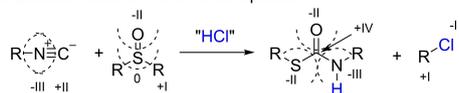
| Entry | <i>N</i> -formamide | Sulfoxide 1<br>yield [%] | Sulfoxide 2<br>yield [%] | Sulfoxide 3<br>yield [%] | Sulfoxide 4<br>yield [%] |
|-------|---------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|       |                     |                          |                          |                          |                          |
| 1     |                     |                          |                          |                          |                          |
| 1     |                     | 77 <sup>[a]</sup>        | 85 <sup>[a]</sup>        | 80 <sup>[a]</sup>        | 53 <sup>[a]</sup>        |
| 2     |                     |                          |                          |                          |                          |
| 2     |                     | 69 <sup>[a]</sup>        | 70 <sup>[a]</sup>        | 70 <sup>[a]</sup>        | 25 <sup>[a]</sup>        |
| 3     |                     |                          |                          |                          |                          |
| 3     |                     | 72 <sup>[a]</sup>        | 59 <sup>[a]</sup>        | 81 <sup>[a]</sup>        | 46 <sup>[a]</sup>        |
| 4     |                     |                          |                          |                          |                          |
| 4     |                     | 60 <sup>[b]</sup>        | 73 <sup>[b]</sup>        | 79 <sup>[b]</sup>        | 50 <sup>[b]</sup>        |

[a] 1.50 eq. *p*-TsCl, 3.00 eq. pyridine 1 M in DCM. 2.50 mmol *N*-formamide. [b] 1.50 eq. *p*-TsCl, 3.00 eq. pyridine 1 M in DCM. 10.0 mmol *N*-formamide.

1. Reaction of benzyl sulfoxide and tetrahydrothiophen-1-oxide



2. Oxidation state of the involved species



**Scheme 3.** 1. Employment of benzyl sulfoxide and tetrahydrothiophene-1-oxide for the synthesis of thiocarbamates. For the first, benzyl chloride and benzyl sulfide were confirmed as side products. For the second, an *S*-4-chlorobutyl thiocarbamate was identified as product, indicating a nucleophilic attack of chloride at the open end of the ring-opened sulfoxide. 2. Oxidation states of the assumed reactants indicating an oxidation of the isocyanide carbon from +II to +IV and a reduction of the sulfoxide sulfur from 0 to -II. The assumed byproduct consisting of a chloride and the second sulfoxide alkyl chain retain their oxidative state of +I/-I, respectively. The necessary proton and chloride (blue), however, cannot stem from the main participants of the reaction (isocyanide and sulfoxide).

ure S48). Surprisingly, alkyl-phenyl substituted sulfoxides, like methylphenyl sulfoxide, which theoretically form *S*-phenyl thiocarbamates with chloromethane as byproduct – as the existence of cationic phenyl moiety can be excluded – did not react at all. As an unsaturated reactant, allyl sulfoxide showed both low conversion and yield and was therefore not utilized in the synthesis of the thiocarbamate library.

Furthermore, it was noticed that the reactions with dimethyl sulfoxide were accompanied by a strong smell of rotten

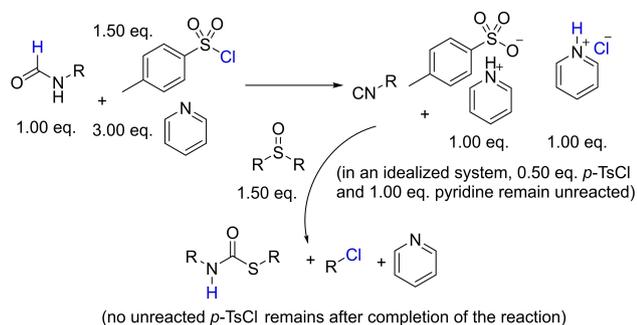
cabbage after addition of the sulfoxide, after the noxious smell of the isocyanide had faded. This characteristic smell was attributed to the formation of dimethyl sulfide, which is a common byproduct in reactions utilizing dimethyl sulfoxide, such as the Swern or the Pfitzner-Moffatt oxidation.<sup>[39–42]</sup> However, dimethyl sulfide was also too volatile to be detected by GC-MS and hence our attention turned to benzyl and butyl sulfoxide to confirm sulfide formation. After careful evaluation of the GC data of both their reaction mixtures, benzyl as well as butyl sulfide could indeed be identified as side products (Scheme 3, 1.).

These findings matched observations by Ganem from 2011, which featured DMSO – activated by trifluoroacetic anhydride – as a selective oxidant of isocyanides to isocyanates.<sup>[43]</sup> In that work, trifluoroacetic anhydride was utilized in catalytic amounts and the reaction was carried out at -60 °C to 0 °C in dichloromethane – a protocol that shows, temperature and the presence of a sulfoxide set aside, distinct similarities to our approach and hence was later reconsidered for a potential mechanism. However, in this one-pot procedure, the dehydration agent cannot be used in just catalytic amounts, but rather with 1.40 eq. or more to ensure full conversion of the isocyanide intermediate (Table 1).

Next, analyzing the oxidation states of the involved species revealed oxidation of the isocyanide carbon from +II to +IV, which is common for this substance class and hence expected.<sup>[44]</sup> On the other hand, the sulfoxide was reduced from 0 to -II in the thiocarbamate, already balancing the redox reaction. Considering the final *S*-thiocarbamate product, addition of one formal equivalent HCl is necessary for a complete stoichiometry (Scheme 3, 2. marked in blue). However, neither the isocyanide nor the sulfoxide component can provide these necessary atoms and hence they must stem from the reaction

mixture. Reconsidering the initial part of the reaction, the dehydration of an *N*-formamide employing *p*-TsCl and pyridine also yields pyridinium tosylate (PPTS) and pyridinium hydrochloride as byproducts in equimolar amounts. Therefore, we assumed that the *in situ* produced pyridinium hydrochloride provides the formal equivalent of HCl and is reconverted to pyridine in the process of thiocarbamate formation (Scheme 4).

As already mentioned, the isocyanide and sulfoxide component alone, dissolved in dichloromethane, could not react and hence it was assumed that the present conditions in the reaction mixture somehow promote thiocarbamate formation. Intrigued by the findings by Ganem in 2011, which postulate DMSO activation by trifluoroacetic anhydride,<sup>[43]</sup> as well as a publication about Swern-Oxidation employing *p*-TsCl instead of oxalyl chloride in 2018,<sup>[45]</sup> our attention was drawn to *p*-TsCl as it is also present in our reaction mixture as dehydration agent. However, these publications feature two distinct reactions in two different scenarios, as the trifluoroacetic anhydride is only necessary in catalytic amounts (5 mol%),<sup>[43]</sup> whereas the *p*-TsCl is necessary in stoichiometric amounts for the Swern-like oxidation of alcohols.<sup>[45]</sup> Yet in our procedure, the *p*-TsCl is neither present only in catalytic nor stoichiometric amounts as is described in the following paragraph.



**Scheme 4.** Idealized dehydration of a formamide yields its respective isocyanide as well as 1.00 eq. of pyridinium tosylate and pyridinium hydrochloride. Theoretically, an excess of 0.50 eq. of *p*-TsCl remains unreacted within the reaction mixture. After sulfoxide addition, the isocyanide is converted to the thiocarbamate formally utilizing one equivalent of HCl. After the reaction, no *p*-TsCl is detectable in the GC or on TLC indicating a certain relevance for conversion.

In the one-pot protocol toward *S*-organyl thiocarbamates, 1.50 eq. of *p*-TsCl are employed, of which 1.00 eq. dehydrate the *N*-formamide (idealized system: water traces and purity of the *p*-TsCl are neglected). Hence, about 0.50 eq. remain in the reaction solution, which coincides with our previously published results on more sustainable isocyanide synthesis (there, also 1.50 eq. of *p*-TsCl were employed in the synthesis and the excess was still visible in TLC analysis after full conversion of the *N*-formamide to its respective isocyanide).<sup>[37]</sup> Therefore, any remaining dehydrating agent had to be quenched utilizing saturated sodium carbonate solution).<sup>[37]</sup> Herein, however, the excess of dehydration agent remains within the reaction mixture and should thus be detectable after thiocarbamate formation. As this is not the case, the *p*-TsCl is neither detectable by TLC nor GC analysis after conversion of the isocyanide and sulfoxide component, the dehydrating agent seems to be involved in the mechanism (Scheme 4).

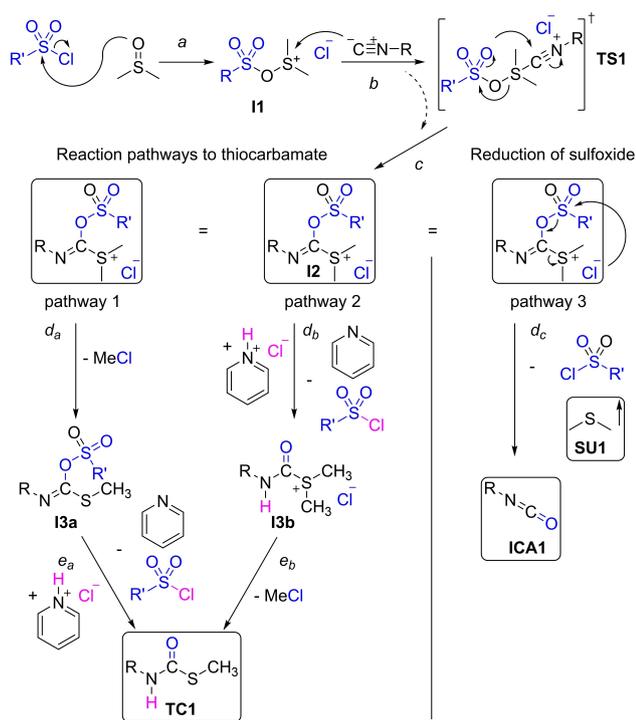
Therefore, a test series was designed in which sulfoxide and isocyanide components were mixed with the byproducts of the isocyanide formation (PPTS and Pyr<sup>+</sup>HCl) to assess whether they promote thiocarbamate formation (Table 3). However, neither *p*-toluene sulfonic acid (*p*-TsOH) nor PPTS in combination with the HCl donor Pyr<sup>+</sup>HCl were able to convert the isocyanide into the *S*-organyl thiocarbamate. For Table 3 (entry 1) decomposition of the isocyanide into the *N*-formamide was observed. For entries 2 and 3, neither decomposition nor conversion were detected. Therefore, the conditions of entries 2 and 3 were reused, however with the theoretical excess of *p*-TsCl and pyridine after complete *N*-formamide dehydration (0.50 eq. *p*-TsCl/1.00 eq. pyridine). Following these reactions by GC revealed conversion to the respective thiocarbamate within 24 h. Therefore, it was concluded that the *p*-TsCl, similarly to the findings of Ganem, acts as activator for the DMSO, possibly in a similar manner as in the *p*-TsCl based Swern-oxidation, as is later shown (Scheme 5).<sup>[43]</sup>

Furthermore, an experiment was conducted to exclude a radical-based mechanism, as isocyanides are also known to support such mechanisms. Therefore, the standard protocol was employed, but prior to the sulfoxide addition, 1.50 eq. of benzophenone were added as radical scavenger. However, as the reaction proceeded as expected, a radical-based mechanism

**Table 3.** Reaction conditions of the evaluation of the role of *p*-TsCl in the thiocarbamate formation.

| Entry              | Eq. <i>p</i> -TsOH | Eq. PPTS | Eq. <i>p</i> -TsCl | Eq. Pyr | Thiocarbamate signal in GC |
|--------------------|--------------------|----------|--------------------|---------|----------------------------|
| 1 <sup>[a]</sup>   | 0.50               | /        | /                  |         | None                       |
| 2 <sup>[a]</sup>   | /                  | 1.50     | /                  |         | None                       |
| 3 <sup>[a]</sup>   | /                  | /        | /                  |         | None                       |
| 4 <sup>[a,b]</sup> | /                  | 1.50     | 0.50               | 1.00    | Found                      |
| 5 <sup>[a,b]</sup> | /                  | /        | 0.50               | 1.00    | Found                      |

[a] Monitored with TLC and ASAP-APCI-MS. [b] These entries feature the same conditions as entries 2 and 3, yet also contain the theoretical excess of dehydrating agent and pyridine from the isocyanide dehydration.



**Scheme 5.** Proposed mechanism of thiocarbamate formation utilizing DMSO and an isocyanide by *p*-TsCl activation. *a* DMSO and *p*-TsCl react to form a Swern-like intermediate I1. *b* The isocyanide component (nucleophile) attacks I1 to form the hypothetical transition state TS1, *c* which rearranges to I2. From here, the reaction continues in three potential pathways: *d*<sub>a</sub> and *d*<sub>b</sub> lead to the expected product, whereas *d*<sub>c</sub> targets the sulfoxide reduction to sulfide SU1 also yielding the isocyanate ICA1.

was deemed highly unlikely and was excluded in further investigations.

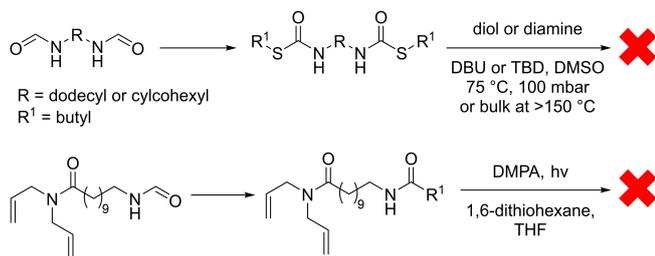
Finally, the reaction was conducted with phosphoryl trichloride as dehydration agent, which is often the reagent of choice in isocyanide synthesis due to its broad substrate tolerance (aliphatic and aromatic *N*-formamides), to evaluate if this altered protocol also allows for the synthesis of *S*-organyl thiocarbamates. However, the reaction was accompanied by a pungent smell after sulfoxide addition and neither isocyanide nor thiocarbamate were isolated after flash-column chromatography of the crude mixture. Regarding the smell, a complete decomposition of the sulfoxide to the sulfide was assumed, however not further investigated.

Based on all described results and control experiments, a possible mechanism is proposed as depicted in Scheme 5. The crucial reaction steps are marked with letters, while important intermediates carry the notion I+number. Note that after the dehydration of the *N*-formamide, excess *p*-TsCl (theoretically 0.50 eq.) as well as the dehydration byproducts PPTS and pyridinium hydrochloride are present (see discussion above and Scheme 4), the latter being important for complete stoichiometry. In reaction step *a* (Scheme 5), the remaining *p*-TsCl reacts with DMSO to form I1 in a Swern-like reaction. This is backed by recent literature, which proposed that *p*-TsCl is indeed capable of replacing oxalyl chloride, which is utilized in the standard

protocol of a Swern oxidation.<sup>[45]</sup> As the sulfoxide is now activated, the isocyanide component acts as nucleophile (step *b*), yielding the hypothetical and rather unstable transition state TS1. After rearrangement in step *c* to form intermediate I2, the reaction proceeds in three different pathways. However, pathways 1 and 2 featuring steps *d*<sub>a</sub>+*e*<sub>a</sub>/*d*<sub>b</sub>+*e*<sub>b</sub> are basically the same, yet in inverted order and, finally, both lead to the expected thiocarbamate. Step *d*<sub>a</sub> features the separation of the alkyl chloride (methyl chloride in this case) yielding I3a, whereas in *d*<sub>b</sub> the *p*-TsCl species is recovered, and the isocyanide nitrogen subtracts the proton from pyridinium hydrochloride giving I3b. After step *e*<sub>a</sub>/*e*<sub>b</sub>, the product TC1 is obtained, respectively. These pathways are confirmed by the presence of benzyl chloride in the GC measurement for the reaction utilizing benzyl sulfoxide as reagent. Furthermore, even in an idealized reaction, only 0.50 eq. *p*-TsCl remain after the dehydration to the isocyanide, yet the reaction proceeds to full conversion. This suggests the recovery of the activating *p*-TsCl species. However, it remains unclear if indeed chloride attacks as a nucleophile or rather the conjugated base of *p*-TsOH (leading to the symmetric anhydride of *p*-TsOH, which should also allow for activation), as they both are weak nucleophiles. In the remaining pathway 3, step *d*<sub>c</sub> targets the side reaction leading to the respective sulfide. Herein, the tosyl species is eliminated from I2 without any further reaction, yielding the sulfide SU1 (in this case dimethyl sulfide, which evaporates due to its low boiling point) as well as an isocyanate ICA1. The oxidation of isocyanides utilizing DMSO and the detection of butyl sulfide/benzyl sulfide as well as the isolation of benzyl sulfide confirm the assumed pathway. However, the respective isocyanate compound was only detected in small amounts by GC and could not be isolated. It is likely that it decomposes under the applied conditions.

After having concluded our investigations into the potential acting mechanism, possible applications for the reaction were considered. Given the interesting properties arising from (thio) carbamate moieties in polymers,<sup>[46–48]</sup> mostly owed to hydrogen bonding in bulk, we decided to study the synthesis of suitable monomers. Furthermore, only few examples of *S*-organyl thiocarbamate polymers are known in literature,<sup>[49]</sup> while *O*-organyl thiocarbamate-bearing polymers are mainly synthesized by post-polymerization modification,<sup>[50,51]</sup> or step-growth polymerization techniques.<sup>[52]</sup> First experiments featured the synthesis of bithiocarbamates as the necessary di-*N*-formamides are easily accessible *via* their diamines. Afterwards, several pathways for step-growth polymerization were investigated, however, the employed protocols (transesterification/thiol-ene) only led to low yields/molecular weight (Scheme 6), most likely due to solubility challenges.<sup>[53]</sup>

A both pathways were challenging and did not lead to promising results, we instead sought to exploit a chain-growth protocol, namely ring-opening metathesis polymerization (ROMP), as it allows for control over the polymerization process. ROMP has shown excellent tolerance towards a range of functional groups,<sup>[54,55]</sup> while our fundamental interest in the coupling of multicomponent reactions with polymer synthesis has found this approach versatile and highly efficient.<sup>[56,57]</sup> It is



**Scheme 6.** Top: Polymerization by trans- amidation and -esterification or in bulk. Bottom: Thiol-ene polymerization with 1,6-dithiohexane. All three approaches did not meet the targeted expectations.

noted that sulfur-bearing monomers are known to be particularly challenging in several chain-growth polymerizations, e.g. in radical processes. However, with ROMP this difficulty can be overcome, e.g. recently dithiocarbamate-functional norbornene monomers were polymerized by ROMP in a controlled way, obtaining macroinitiators capable of initiating reversible-addition-fragmentation chain-transfer (RAFT) polymerization.<sup>[58]</sup>

Here, we synthesized four norbornene-based monomers bearing different *S*-organyl thiocarbamate moieties to evaluate their polymerization behavior by ROMP. The polymerizations were performed under an argon atmosphere, at ambient temperature, in degassed DCM (Table 4). The third generation Grubbs (G3) catalyst was used, owing to its broad tolerance of functional groups and its high initiation rates.<sup>[59,60]</sup> The degree of polymerization was predefined by the monomer to catalyst (M:C) ratio and was chosen to be 50:1. After 15 minutes of polymerization, the monomer was fully converted and the reaction was quenched with an excess of ethyl vinyl ether.

After purification, the obtained polymers were analyzed by <sup>1</sup>H NMR spectroscopy and size exclusion chromatography (SEC). <sup>1</sup>H NMR spectra for all polymers (Figures S35, S37, S39 and S41) confirmed the presence of the respective side chain, indicating that the thiocarbamate moiety was stable throughout the polymerization process. SEC traces for **P1**, **P2** and **P3** (Figur-

es S36, S38 and S40) exhibited narrow unimodal molecular weight distributions, indicating good polymerization control. **P4** exhibited a narrow, unimodal molecular weight distribution before purification, but a bimodal distribution after (Figure S42), attributed to polymer-polymer coupling during purification. Interestingly, a similar behavior was observed for **P2** and **P3** when the quenched reaction mixture was stored in solution for more than a day before further purification. We hypothesize that the cleaved unreactive Fischer carbene derivative was reactivated by the coordinative thiocarbamate units, resulting in polymer-polymer side reactions, and thus leading to the appearance of a second distribution at twice the original molecular weight. Hence, it is important to remove the cleaved Fischer carbene derivative immediately after the quenching process. Further research to support this observation was out of the scope of this publication and was thus not conducted. It is noted that in all cases the polymerization was very fast, reaching > 50% conversion after a few seconds (determined by <sup>1</sup>H NMR spectroscopy).

Thermal properties of the polymers, namely the glass transition temperature (*T<sub>g</sub>*) and the decomposition temperature (*T<sub>d</sub>*), were determined using differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA), respectively. The *T<sub>g</sub>* values of the polymers unsurprisingly varied according to the different R groups, with a maximum of 67 °C for the methyl-functionalized **P1** and a minimum of 45 °C for the chlorobutyl-functionalized **P4**. Comparing **P1** (R = methyl, *T<sub>g</sub>* = 67 °C) and **P3** (R = butyl, *T<sub>g</sub>* = 58 °C), the longer aliphatic chains led to a decrease in *T<sub>g</sub>*. The additional chloride end-groups in **P4** (*T<sub>g</sub>* = 45 °C) led to a decrease in *T<sub>g</sub>* compared to **P3**. Interestingly, the aromatic **P2** (*T<sub>g</sub>* = 57 °C) exhibited a *T<sub>g</sub>* similar to that of the aliphatic **P3** (Figure S43).

For all polymers, the thermal decomposition was found to be a two-step process (Figure S44). The first decomposition step, described as *T<sub>d,1</sub>*, was found to vary with functional groups and was hypothesized to result from the cleavage of the thiocarbamate, yielding free thiols and forming isocyanate functionalities attached to the polymeric backbone. The

**Table 4.** Schematic: Ring-opening polymerization (ROMP) of thiocarbamate functional norbornene monomers using G3 catalyst. Table: Conversion, molecular weight, dispersity, and thermal characteristics of the synthesized polymers.

| Entry | Polymer <sup>[a]</sup> | Conversion (%) <sup>[b]</sup> | <i>M<sub>n,theo</sub></i> [g mol <sup>-1</sup> ] <sup>[c]</sup> | <i>M<sub>n</sub></i> [g mol <sup>-1</sup> ] <sup>[c]</sup> | <i>Đ<sub>M</sub></i> <sup>[d]</sup> | <i>T<sub>g</sub></i> [°C] <sup>[f]</sup> | <i>T<sub>d,1</sub></i> [°C] <sup>[g]</sup> | <i>T<sub>d,2</sub></i> [°C] <sup>[g]</sup> |
|-------|------------------------|-------------------------------|---|--|-------------------------------------|--|--|--|
| 1     | P1                     | > 99                          | 9,900   | 18,400   | 1.11                                | 67                                       | 228  | 417  |
| 2     | P2                     | > 99                          | 12,000  | 22,300   | 1.10                                | 57                                       | 219  | 421  |
| 3     | P3                     | > 99                          | 13,700  | 22,600   | 1.10                                | 58                                       | 221  | 419  |
| 4     | P4                     | > 99                          | 13,700  | 24,900   | 1.25 (1.10) <sup>[e]</sup>          | 45                                       | 163  | 422  |

[a] Reaction conditions: 0.10 M monomer in DCM with 2 mol% G3 for 15 minutes at ambient temperature. [b] Determined by <sup>1</sup>H NMR spectroscopy. [c] Calculated by the conversion. [d] Determined by size exclusion chromatography (SEC) in THF with 2 vol% triethylamine against poly(methyl methacrylate) standards. [e] Before purification. [f] Midpoint, determined by differential scanning calorimetry (DSC). [g] Temperature at 10% weight loss regarding each decomposition step, determined by thermogravimetric analysis (TGA).

obtained thermogravimetric data supports this hypothesis through comparison of the measured weight loss with the calculated weight percentage of the cleaved thiol of the corresponding repeat unit (Table S1). Furthermore, to confirm this decomposition path, we compared the infrared (IR) spectra of P3 before and after heating to 300 °C (Figure S45). After heating, an intense signal appeared at 2250 cm<sup>-1</sup>, which was assigned to the N=C=O stretching frequency of isocyanates. Additionally, a significant reduction of the signal at 3300 cm<sup>-1</sup> was observed, which was assigned to the carbamyl N–H stretching frequency.<sup>[61]</sup> To further confirm this thermal decomposition to isocyanates, the monomers were analyzed by gas chromatography coupled with mass spectrometry (GC-MS) applying a peak temperature of 300 °C (Figure S46). Due to partial decomposition, the chromatograms exhibited a mixture of products including the intact monomers as well as decomposition species. The signals at 4.76 minutes (148.9 m/z) can be assigned to the norbornene functional isocyanate, which is identical for all monomers. Furthermore, the chromatogram of the benzyl monomer exhibited an additional signal at 4.09 minutes (123.8 m/z), which can be assigned to the cleaved benzyl thiol (Table S2). The other cleaved thiols were not detected using this method, but their absence can be explained by their relatively low boiling points. The second decomposition step seen in the TGA graph (Figure S44), described as  $T_{d,2}$ , was consistently at about 420 °C for P1–P4 and was thus ascribed to further decomposition of the polymer.<sup>[62]</sup> Therefore, the thermal properties of the functional polymers were readily tuned by the moiety introduced to the monomer through the thiocarbamate-forming reaction.

## Conclusion

A one-pot synthesis of *S*-organyl thiocarbamates was discovered and investigated, featuring direct conversion of *N*-formamides *via* intermediate dehydration to their respective isocyanide and subsequent reaction with sulfoxides. In this study, the reaction parameters were optimized and a library of sixteen different thiocarbamates (including four norbornene monomers for ROMP) originating from four *N*-formamides and four commercially available sulfoxides were synthesized. The compounds were obtained in mediocre to good yields and characterized.

Furthermore, the underlying mechanism was postulated based on dedicated control experiments. Alkyl chlorides were identified as byproducts, whereas the reduction of the sulfoxide to a sulfide was observed as a side reaction. It was also confirmed that the dehydrating agent *p*-TsCl is crucial for the conversion of the isocyanide into the thiocarbamate. It was proposed that it serves as activating species for the sulfoxide component.

To show possible applications of this new synthetic procedure, four norbornene-based thiocarbamate bearing monomers were synthesized and employed in ring-opening metathesis polymerizations. The obtained homopolymers were purified, characterized and their properties were evaluated by

TGA and DSC. Crucially, the thiocarbamate functionality was retained and the polymer properties corresponded to the pendant groups.

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## Conflict of Interest

The authors declare no conflict of interest.

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